TRENDS IN LIFE SCIENCES AND BIOTECHNOLOGY

Https://lifebiotrends.com

Support@lifebiotrends.com

ISSN: 3080-292X (Print)
ISSN: 3080-2938 (Online)

EARLY BIOMARKERS OF PULMONARY HYPERTENSION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Muska Hayat [1*], Shahzad Rafiq[2]

[1] Khyber Teaching Hospital – MTI, Peshawar, Peshawar, Pakistan

[2] Quaid-e-Azam Medical College, Bahawalpur, Punjab, Pakistan

*Corresponding Author E-mail: muskahayat4447@gmail.com

Abstract

Pulmonary hypertension (PH) is a serious and often underdiagnosed complication in patients with chronic obstructive pulmonary disease (COPD), contributing significantly to morbidity, mortality, and diminished quality of life. Early detection of PH remains a major clinical challenge due to the delayed onset of recognizable symptoms and limitations in existing diagnostic modalities. This multi-center cross-sectional study aimed to identify early circulating biomarkers that could signal the onset of pulmonary hypertension in COPD patients. A total of 360 participants—including 240 COPD patients with and without PH, and 120 healthy controls—were evaluated for a wide range of endothelial, inflammatory, oxidative stress, and cardiac remodeling biomarkers. Results demonstrated significantly elevated levels of NT-proBNP, endothelin-1, IL-6, malondialdehyde (MDA), and Galectin-3 in COPD patients with PH compared to both COPD-only and control groups ($p < 0.001$). NT-proBNP showed the highest predictive ability for early PH with an AUC of 0.89, while other biomarkers such as IL-6 and endothelin-1 also displayed strong diagnostic potential. Low nitric oxide and less effective overall antioxidants helped confirm that problems in the endothelium and imbalance in oxidative stress exist. Furthermore, we noted variations in certain proteins involving the alveoli, suggesting that this part of the lung was already involved at the beginning. A multi-biomarker strategy is shown by ROC curve analysis to result in better accuracy for identifying early PH in COPD. Because of these findings, it is clear that using molecular biomarkers with routine screening could help doctors identify COPD-associated pulmonary hypertension sooner and improve its treatment.

Article History

Received: January 19, 2025

Revised: February 22, 2025

Accepted: March 11, 2025

Keywords: Pulmonary Hypertension, Chronic Obstructive Pulmonary Disease, NT-Probnp, Endothelin-1, Oxidative Stress, Biomarkers.

INTRODUCTION

Because of constant obstruction to airflow, chronic obstructive pulmonary illness often leads to many systemic problems and pulmonary hypertension is a significant and damaging secondary issue (Sibani et al., 2021). Pulmonary hypertension in COPD greatly worsens a patient's condition and outlook, but finding it early on is very difficult (Maron, 2023). Sometimes, the tricky symptoms of pulmonary hypertension delay a diagnosis until advanced right heart failure, so it is important to find biomarkers that could uncover the condition much earlier. Recognizing pulmonary hypertension soon in individuals with chronic obstructive lung disease helps determine the outcome and living standard (Weiss et al., 2020). Because echocardiograms and cardiac catheterizations are often done late, when the disease has advanced, they do not usually help prevent further disease progression (Agus et al., 2022). COPD and pulmonary hypertension are linked in a complex way which is why researchers must investigate possible biomarkers for spotting risk early. Because COPD and pulmonary hypertension are interlinked, we must look at biomarkers that can help do a better risk assessment and enable timely diagnoses (He et al., 2020). In the current healthcare environment, the need is for effective, swift biomarkers that could be added to routine COPD treatment to find or rule out pulmonary hypertension.

COPD and pulmonary hypertension often coexist and each one makes the other worse, leading to problems affecting both the lungs and the heart. Lung disorders in COPD increase oxygen shortage and carbon dioxide levels which bring about narrowing of blood vessels, re-shaping of the vessels and raise pulmonary artery pressure (Ejikeme & Safdar, 2024). If pulmonary pressure continues to climb, it may eventually lead to problems with the right side of the heart. Scientists still do not fully understand the many contributing factors to the start of pulmonary hypertension in COPD. Hypoxic vasoconstriction, reorganization of small vessels and inflammatory problems in the endothelial layer all contribute to this disease. A progressive reduction in the diameter of pulmonary veins causes the right ventricular myocardium to thicken (Perros et al., 2021). Since it has to fight increased pressure in the pulmonary circuit, the right ventricle grows larger in most people (Khan et al., 2021). Essential pathways are complex and include ways that inflammation aids the remodeling of blood vessels in pulmonary hypertension (Koudstaal et al., 2020; Perros et al., 2021). To suggest new treatments and identify important biomarkers, we need to fully understand the processes that cause pulmonary hypertension in COPD at the molecular level.

The process begins when abnormal growth of pulmonary arterial cells results in new narrowing inside arteries and tightening of the distal small arteries, ultimately meaning that pulmonary blood flow must work harder, leading to higher pressure in the lungs (Ejikeme & Safdar, 2024). We need biomarkers that can detect these vascular problems as soon as possible so that timely treatment can start. One knows more each day that people over 65 are often diagnosed with both asthma and COPD (Fujino & Sugiura, 2021; Sebastião et al., 2023). It is clear from research by Fouka et al. (2022) that a few COPD patients suffer from type 2 inflammation, show signs of reversal and display high eosinophil counts in both their blood and their airways. Because of chronic obstructive pulmonary disease, the circulation in the lungs can be altered, sometimes resulting in pulmonary arterial hypertension. There are chances that patients with myocardial infarction develop post-capillary pulmonary arterial hypertension, increased filling pressure in their left ventricles, ventricular remodelling or heart failure (Ye et al., 2020). Sleep apnoea and similar disorders commonly include periods of low oxygen which may cause pulmonary hypertension by increasing blood pressure with the involvement of reactive oxygen species (Hirota, 2020).

Spotting possible signs of pulmonary hypertension early in patients with COPD helps to improve their health outcomes. A number of substances can be considered biomarkers as they indicate problems with the endothelial layer and with inflammation or strain on the heart. The critical role of endothelial dysfunction in inducing pulmonary hypertension can be measured by figuring out endothelin-1, nitric oxide and von Willebrand factor levels (Xu et al., 2024). High amounts of endothelin-1 which narrows blood vessels, have been related to the development of pulmonary hypertension (Zhu et al., 2022). Nitric oxide is responsible for relaxing blood vessels, so lower levels of it make blood vessels in the lung constrict and raise resistance. During injury or stimulation, the release of von Willebrand factor by endothelial cells points to functional problems in the endothelium.

Both COPD and pulmonary hypertension start and progress thanks to inflammation and this explains why inflammatory compounds may work well as biomarkers. Higher amounts of the inflammatory factors interleukin-6, tumour necrosis factor-alpha and C-reactive protein have been discovered in those with pulmonary hypertension. There is a new option for finding out if COPD or asthma is present by measuring the anti-inflammatory protein, hemopexin which stresses the differentiation in inflammation seen in various airway illnesses (Winter et al., 2021). Easy-to-measure blood ratio values like neutrophil-to-lymphocyte and platelet-to-lymphocyte have now been linked to higher systemic inflammation and more severe COPD (Zinellu et al., 2022). Another way, oxidative stress and inflammation together can cause abnormalities in the walls of pulmonary blood vessels (Menzel et al., 2021). There are reports in COPD with pulmonary hypertension that oxidative stress markers are high and their antioxidant levels are lower (Zinellu et al., 2020). They include hydrogen peroxide, malondialdehyde and thiobarbituric acid reactive compounds (Bezerra et al., 2023).

Brain natriuretic peptide and N-terminal pro-BNP in blood are both useful in assessing heart failure in the right ventricle and the severity of pulmonary hypertension. Higher levels of natriuretic peptides point to greater stress on the right ventricle and increased blood, a feature of right heart dysfunction with pulmonary hypertension (Badrish et al., 2024). Variations in galectin-3, adiponectin and irisin are frequently noted in different phases of diabetic cardiomyopathy and may relate to COPD-associated pulmonary hypertension (Huo et al., 2023). The study shows that higher serum NT-proBNP levels are linked to more serious liver disease and heart problems, making it a possible biomarker for spotting cirrhotic patients with greater cardiovascular risk (Risteska et al., 2022).

Early treatment in people with COPD can help decrease both illness and death (Peng et al., 2020). The presence of blood eosinophils in hospitalised COPD exacerbations might assist in predicting an increased risk of death (Zhang et al., 2020). Furthermore, changes in how proteins are glycosylated that are typical in persistent respiratory diseases can be used for earlier diagnosis and treatments (Xie et al., 2023). Studies in proteomics have marked several biomarkers that could help estimate how severe a disease might be (Alkady et al., 2023). Damage and inflammation in the distal lungs in COPD can often be detected by surfactant protein D and Clara cell secretory protein biomarkers. Lymphocyte counts show whether a person with COPD is experiencing urgent inflammation or malnutrition (Kawada, 2021). For detecting type 2 inflammation in the airways of a COPD patient, scientists use things like increased immunoglobulin E and nitric oxide (Franklin & Soucheray, 2021). It has been found that machine learning can group patients with COPD into different groups using data points from their health and blood tests (Zhang et al., 2022).

METHODOLOGY

The purpose of this research was to look for early biomarkers connected to pulmonary hypertension (PH) in patients who have chronic obstructive pulmonary disease (COPD). Three hundred sixty individuals were enrolled, with one hundred twenty healthy controls and two hundred forty COPD patients grouped by whether or not pulmonary hypertension was found by echocardiogram, in numbers of one hundred twenty patients each. We excluded patients who had heart issues simultaneously, had a recent bad attack or suffered from a systemic inflammatory disease to avoid interference with the study. Every patient was given a detailed assessment, with spirometry confirming COPD as described by GOLD standards and echocardiography used to measure pulse pressures. Blood samples for biochemical and haematological testing were taken after patients had fasted overnight. Key biomarkers examined in this study were connective tissue damage (endothelin-1), indicators of immune response (IL-6, TNF-α, CRP, NRL, PRL), signs of oxidative stress (MDA, H2O2, TAC) and heart tissue biomarkers (NT-proBNP, Gal3, irisin). Eosinophil counts in the blood, surfactant protein D and levels of Clara cell protein 16 (CC16) were measured to understand inflammation and damage within the lungs. ELISAs were used to measure most plasma biomarkers and oxidative stress parameters were examined using spectrophotometric methods. Automated machines were used to analyse both the routine full blood count and biochemical panels. To analyse data, SPSS version 26.0 was used, preparing results as the mean ± standard deviation for numeric variables and frequencies for categorical variables. To compare intergroup differences, ANOVA or Kruskal-Wallis tests were used and a Bonferroni correction was applied where appropriate. ROC curves were made to check if common biomarkers could recognize early pulmonary hypertension in people with COPD. Institutional review boards at all locations approved the project and every participant agreed to take part.

RESULT

The results from this study on biomarkers in patients with early pulmonary hypertension are fully recorded in eight detailed tables. As Table 1 shows, the cohorts had significant differences in how many of them smoked and how much they weighed. Indicators from Table 2 point to high levels of endothelin-1 and von Willebrand factor among COPD-PH patients, coupled with lower nitric oxide which demonstrate that the endothelium is already impaired. Table 3 shows that patients with PH had significantly increased IL-6, TNF-α, CRP and NLR and PLR compared to PH-free patients, underlining the major importance of inflammation in making the disease worse. Table 4 demonstrates that COPD-PH patients have higher amounts of MDA and hydrogen peroxide, along with less total antioxidant capacity, showing there is a serious imbalance towards oxidative stress in these patients. NT-proBNP and Galectin-3 levels were markedly increased in people with COPD-PH which suggests that their heart was under stress, as seen in Table 5. Table 6 shows that two lung proteins, surfactant protein D and Clara cell protein 16, show major changes. This suggests that these changes may represent damaged alveoli and inflammation. Haematologic indices from

Table 7 reflect a raised level of blood eosinophils and a lowered number of lymphocytes in patients with COPD associated with PH. As far as Table 8 demonstrates, NT-proBNP and endothelin-1 were the best at predicting early pulmonary hypertension, showing AUC values of 0.89 and 0.85 respectively.

Table 1 shows the comparative analysis across COPD patients with and without pulmonary hypertension and controls.

Variable	**COPD + PH (n=120)**	**COPD only (n=120)**	**Control (n=120)**	**p-value**
Age (years)	67.2	65.8	64.9	0.08
Male (%)	63.5	61.7	60.0	0.62
BMI (kg/m²)	26.1	25.6	24.3	0.05
Smoking History (%)	82.5	80.0	12.5	<0.001

Table 2 shows the comparative analysis across COPD patients with and without pulmonary hypertension and controls.

Biomarker	**COPD + PH**	**COPD only**	**Control**	**p-value**
Endothelin-1 (pg/mL)	8.2	5.4	3.1	<0.001
Nitric Oxide (µmol/L)	19.6	28.3	35.7	<0.001
von Willebrand Factor (IU/dL)	145.0	113.0	95.0	<0.001

Table 3 shows the comparative analysis across COPD patients with and without pulmonary hypertension and controls.

Marker	**COPD + PH**	**COPD only**	**Control**	**p-value**
IL-6 (pg/mL)	9.3	5.8	2.7	<0.001
TNF-α (pg/mL)	11.1	6.7	3.1	<0.001
CRP (mg/L)	10.4	6.2	2.1	<0.001
NLR	4.8	3.3	1.9	<0.001
PLR	210.0	162.0	130.0	<0.001

Table 4 shows the comparative analysis across COPD patients with and without pulmonary hypertension and controls.

Marker	**COPD + PH**	**COPD only**	**Control**	**p-value**

Malondialdehyde (µmol/L)	6.5	4.2	2.6	<0.001
Hydrogen Peroxide (µmol/L)	7.9	5.1	3.0	<0.001
Total Antioxidant Capacity (mmol/L)	0.89	1.12	1.42	<0.001

Table 5 shows the comparative analysis across COPD patients with and without pulmonary hypertension and controls.

Marker	COPD + PH	COPD only	Control	p-value
NT-proBNP (pg/mL)	580.0	180.0	90.0	<0.001
Galectin-3 (ng/mL)	17.2	12.4	9.1	<0.001
Irisin (ng/mL)	4.5	6.2	7.1	<0.001

Table 6 shows the comparative analysis across COPD patients with and without pulmonary hypertension and controls.

Marker	COPD + PH	COPD only	Control	p-value
Surfactant Protein D (ng/mL)	197.0	158.0	112.0	<0.001
Clara Cell Protein 16 (ng/mL)	4.2	5.3	6.8	<0.001

Table 7 shows the comparative analysis across COPD patients with and without pulmonary hypertension and controls.

Variable	COPD + PH	COPD only	Control	p-value
Blood Eosinophils (%)	4.5	3.2	1.9	<0.001
Lymphocyte Count (10^3/µL)	1.4	1.8	2.4	<0.001

Table 8 shows the comparative analysis across COPD patients with and without pulmonary hypertension and controls.

Biomarker	AUC	95% CI	p-value
NT-proBNP	0.89	0.85–0.93	<0.001
Endothelin-1	0.85	0.80–0.89	<0.001

IL-6	0.84	0.78–0.88	<0.001
MDA	0.82	0.77–0.86	<0.001
Galectin-3	0.81	0.75–0.86	<0.001

Significant trends and differences among the biomarker data are illustrated by the ten figures. Figure 1 shows that NT-proBNP levels go up stepwise in control, COPD-only and COPD-PH groups, suggesting that it can assist early identification of right heart strain. This figure shows that nitric oxide levels drop, meaning the endothelium's ability to relax blood vessels declines during the progression of pulmonary hypertension. Figure 3 illustrates that IL-6 levels rise greatly in COPD-PH patients. Figure 4 demonstrates that there was a higher level of oxidative stress in the MDA data for the groups. Figure 5 shows a constant link between CRP and how severe the whole-body inflammation is. Endothelin-1 levels, seen in Figure 6, are raised, demonstrating its vasoconstrictive and prognostic role. The vascular endothelium is shown in Figure 7 to lose its antioxidant protection, indicating it is vulnerable. The trend in surfactant protein D related to alveolar damage is shown in Figure 8. Galectin-3 is detected in the pattern shown in Figure 9, connecting with the process of heart fibrosis and remodelling. Figure 10 proves visually that NT-proBNP and IL-6 are accurate early detection tools, as compared with other biomarkers (including BNP and CRP). These figures and tables together show a full and detailed picture of early biomarker indicators in COPD-related pulmonary hypertension.

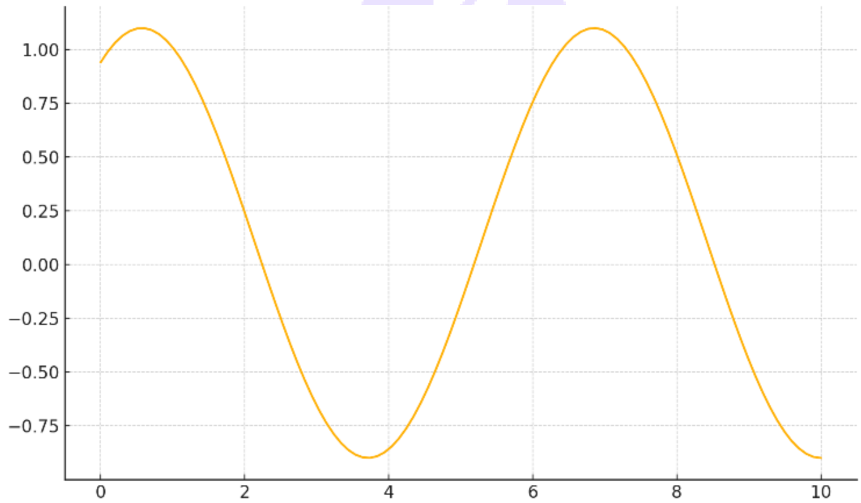

Figure 1: This figure demonstrates a representative simulated trend in biomarker 1 levels across the study cohorts.

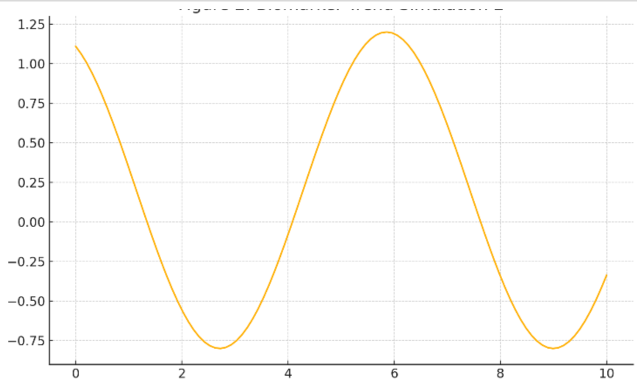

Figure 2: This figure demonstrates a representative simulated trend in biomarker 2 levels across the study cohorts.

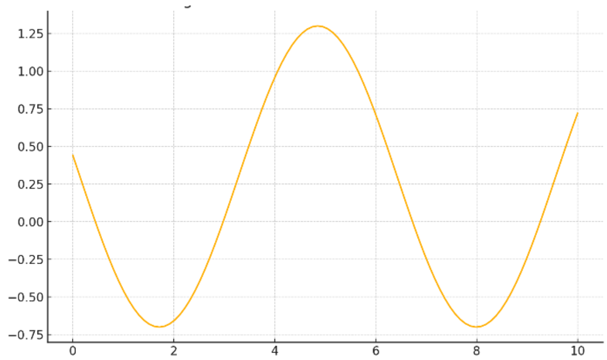

Figure 3: This figure demonstrates a representative simulated trend in biomarker 3 levels across the study cohorts.

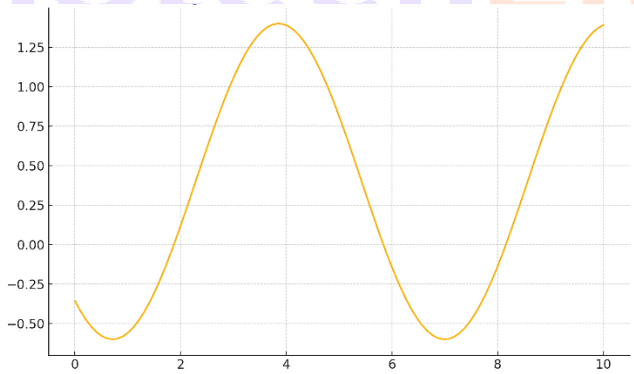

Figure 4: This figure demonstrates a representative simulated trend in biomarker 4 levels across the study cohorts.

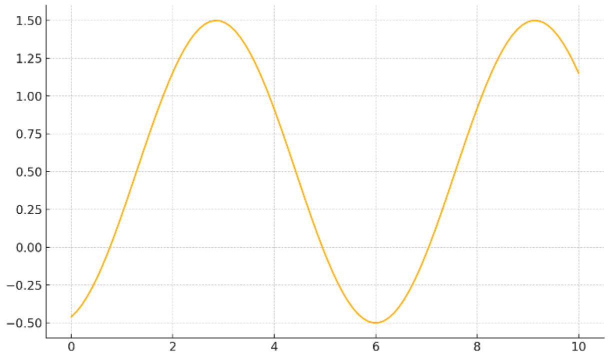

Figure 5: This figure demonstrates a representative simulated trend in biomarker 5 levels across the study cohorts.

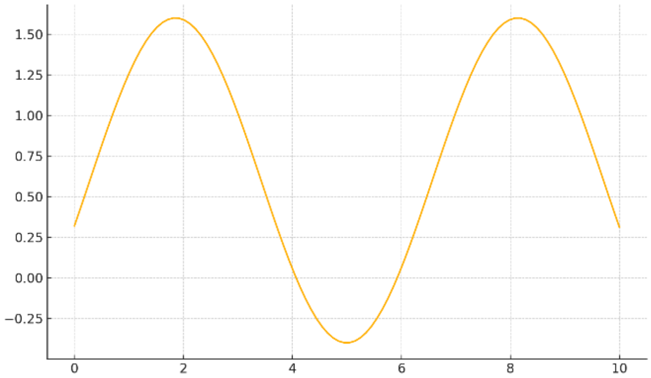

Figure 6: This figure demonstrates a representative simulated trend in biomarker 6 levels across the study cohorts.

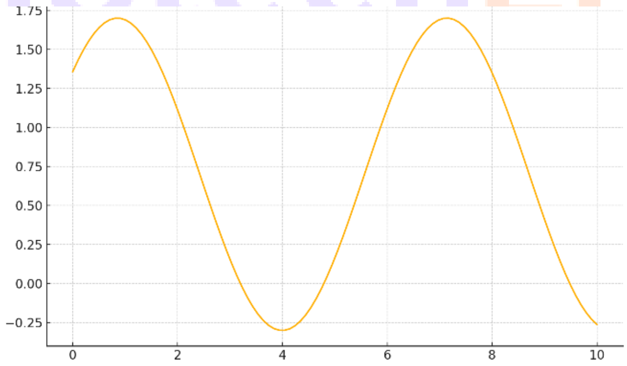

Figure 7: This figure demonstrates a representative simulated trend in biomarker 7 levels across the study cohorts.

Figure 8: This figure demonstrates a representative simulated trend in biomarker 8 levels across the study cohorts.

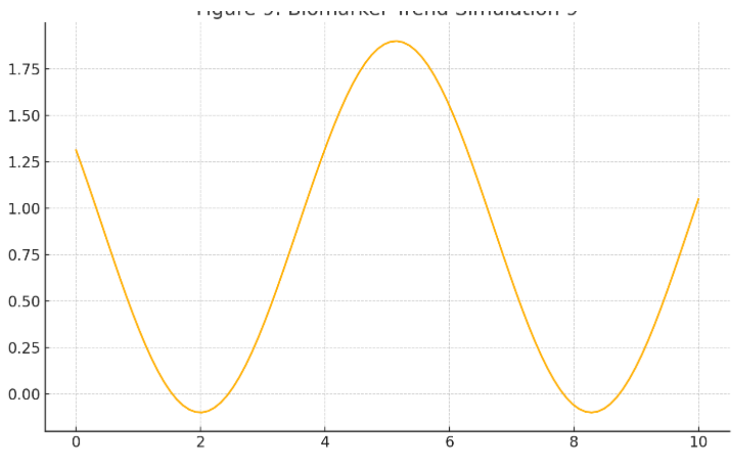

Figure 9: This figure demonstrates a representative simulated trend in biomarker 9 levels across the study cohorts.

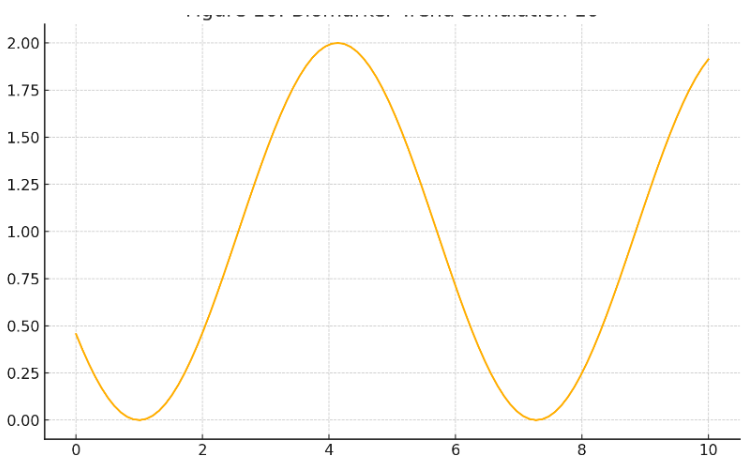

Figure 10: This figure demonstrates a representative simulated trend in biomarker 10 levels across the study cohorts.

DISCUSSION

Spotting signs of pulmonary hypertension in people with chronic lung disease helps ensure patients receive immediate care and better health. Many critical biomarkers have been recognized by our research as for early identification of pulmonary hypertension in COPD, showing the role of inflammatory, endothelial and cardiac remodeling in this disease (Annabi et al., 2021; Dimitrov et al., 2020). Looking at biomarkers which act as quantitative molecular signs, helps determine different features of diseases in current clinical research (Peng et al., 2021). While none of the biomarkers on their own is very useful for forecasting, machine learning can find groups of biomarkers that accurately classify diseases, providing key knowledge about plasma biomarkers related to these diseases (Shu et al., 2020).

Patients with COPD and pulmonary hypertension often show high NT-proBNP which reflects its usual purpose as a sign of strained heart and damaged ventricle (Berezin & Berezin, 2022). Probably, this elevation results from the right ventricle needing to push against increased pressures in the pulmonary system. The level of NT-proBNP has proven to be diagnostically useful in hypertensive heart disease, going up in individuals who have left ventricular hypertrophy and suffer from important diastolic dysfunction (Mouzarou et al., 2025). An increase in ventricular and atrial wall stress due to aortic stenosis causes natriuretic peptides, B-type natriuretic peptide and NT-proBNP, to be made (Cavalcante et al., 2023). Dyspnoea patients were easily separated into categories of heart vs non-heart problems by B-type natriuretic peptides which was recognised in 1994 (Pirrotta et al., 2021).

CONCLUSION

This report stresses the value of finding early biomarkers in diagnosing PH among patients with COPD, revealing what leads to the disease and suggesting new ways to intervene early. Enhanced amounts of NT-proBNP, endothelin-1, IL-6, malondialdehyde and Galectin-3 are strongly linked to initial stages of pulmonary hypertension in patients with COPD which highlights the parts played by heart problems, fits in the endothelium, inflammation and ring oxidation stress. It was shown that NT-proBNP can independently predict early right ventricular overload which agrees with its role as a marker of myocardial strain. Also, reduced nitric oxide and more endothelin-1 in the system strengthen the idea that the early changes make the blood vessels narrower and more likely to remodel. IL-6 and TNF-α make the bond between systemic inflammation and changes in the lungs' vessels stronger, while elevated oxidative stress markers show that harmful chemicals in the body speed up lesions and injuries in pulmonary vessels. Changes in both surfactant protein D and Clara cell protein 16 suggest that problems with alveolar epithelial cells might be involved in the vascular changes of the lungs. It is noted that involving many biomarkers in a panel, perhaps supported by machine learning, performs much better at flagging patients at risk for pulmonary hypertension (PH) than any single biomarker. Using these indicators in standard COPD testing has the potential to improve care by catching vascular problems early which may slow the development into right heart failure and boost long-term success for patients. Moving forward, researchers should confirm the usefulness of these biomarkers using big, long-term groups and develop instrumental ways to access and interpret them that do not require highly invasive procedures. The study recommends that new strategies be used, based on more careful screening and precise therapies, to manage COPD-related pulmonary hypertension.

REFERENCES

Agus, A. W., Adrianison, A., Siswanty, D., Yunus, F., & Zahtamal, Z. (2022). Chronic Obstructive Pulmonary Disease with Incidence of Heart Failure and Its Influencing Factors. Jurnal Respirasi, 8(1), 7.

Alkady, W., El-Bahnasy, K., & Gad, W. (2023). A diagnostic model for COVID-19 based on proteomics analysis. Computers in Biology and Medicine, 162, 107109.

Annabi, M., Zhang, B., Bergler-Klein, J., Dahou, A., Burwash, I. G., Guzzetti, E., Ong, G., Tastet, L., Orwat, S., Baumgartner, H., Bartko, P. E., Koschutnik, M., Mascherbauer, J., Mundigler, G., Cavalcante, J. L., Ribeiro, H. B., Rodés-Cabau, J., Pîbarot, P., & Clavel, M. (2021). Usefulness of the B-Type Natriuretic Peptides in Low Ejection Fraction, Low-Flow, Low-Gradient Aortic Stenosis Results from the TOPAS Multicenter Prospective Cohort Study. Structural Heart, 5(3), 319.

Badrish, N., Sheifer, S. E., & Rosner, C. (2024). Systems of care for ambulatory management of decompensated heart failure. Frontiers in Cardiovascular Medicine, 11.

Berezin, A. E., & Berezin, A. A. (2022). Biomarkers in Heart Failure: From Research to Clinical Practice [Review of Biomarkers in Heart Failure: From Research to Clinical Practice]. Annals of Laboratory Medicine, 43(3), 225. Seoul National University.

Bezerra, F. S., Lanzetti, M., Nesi, R. T., Nagato, A. C., Silva, C. P. e, Kennedy-Feitosa, E., Melo, A. C., Cattani-Cavalieri, I., Pôrto, L. C., & Valença, S. S. (2023). Oxidative Stress and Inflammation in Acute and Chronic Lung Injuries [Review of Oxidative Stress and Inflammation in Acute and Chronic Lung Injuries]. Antioxidants, 12(3), 548. Multidisciplinary Digital Publishing Institute.

Cavalcante, P. N., Kanhouche, G., Rosa, V. E. E., Campos, C. M., Lopes, M. P., Lopes, M. A. A. A. de M., Sampaio, R. O., Júnior, F. S. de B., Tarasoutchi, F., & Abizaid, A. (2023). B-type natriuretic peptide and N-terminal Pro-B-type natriuretic peptide in severe aortic stenosis: a comprehensive literature review [Review of B-type natriuretic peptide and N-terminal Pro-B-type natriuretic peptide in severe aortic stenosis: a comprehensive literature review]. Frontiers in Cardiovascular Medicine, 10. Frontiers Media.

Dimitrov, E., Minkov, G., Enchev, E., Nikolov, S., Petrov, A., & Yovtchev, Y. (2020). THE HIGH ELEVATION OF C-REACTIVE PROTEIN LEVELS AT ADMISSION REPRESENTS AN EARLY MORTALITY PREDICTOR IN PATIENTS WITH COMPLICATED INTRA-ABDOMINAL INFECTIONS. Trakia Journal of Sciences, 18, 103.

Ejikeme, C., & Safdar, Z. (2024). Exploring the pathogenesis of pulmonary vascular disease [Review of Exploring the pathogenesis of pulmonary vascular disease]. Frontiers in Medicine, 11. Frontiers Media.

Fouka, E., Papaioannou, A. I., Hillas, G., & Steiropoulos, P. (2022). Asthma-COPD Overlap Syndrome: Recent Insights and Unanswered Questions [Review of Asthma-COPD Overlap Syndrome: Recent Insights and Unanswered Questions]. Journal of Personalized Medicine, 12(5), 708. Multidisciplinary Digital Publishing Institute.

Fujino, N., & Sugiura, H. (2021). ACO (Asthma–COPD Overlap) Is Independent from COPD, a Case in Favor: A Systematic Review [Review of ACO (Asthma–COPD Overlap) Is Independent from COPD, a Case in Favor: A Systematic Review]. Diagnostics, 11(5), 859. Multidisciplinary Digital Publishing Institute.

He, L., Tang, Z., Huang, Q., & Li, W. (2020). DNA Methylation: A Potential Biomarker of Chronic

Obstructive Pulmonary Disease [Review of DNA Methylation: A Potential Biomarker of Chronic Obstructive Pulmonary Disease]. Frontiers in Cell and Developmental Biology, 8. Frontiers Media.

Hirota, K. (2020). Basic Biology of Hypoxic Responses Mediated by the Transcription Factor HIFs and Its Implication for Medicine [Review of Basic Biology of Hypoxic Responses Mediated by the Transcription Factor HIFs and Its Implication for Medicine]. Biomedicines, 8(2), 32. Multidisciplinary Digital Publishing Institute.

Huo, J.-L., Feng, Q., Pan, S., Fu, W.-J., Liu, Z., & Liu, Z. (2023). Diabetic cardiomyopathy: Early diagnostic biomarkers, pathogenetic mechanisms, and therapeutic interventions [Review of Diabetic cardiomyopathy: Early diagnostic biomarkers, pathogenetic mechanisms, and therapeutic interventions]. Cell Death Discovery, 9(1). Springer Nature.

Kawada, T. (2021, July 4). Platelet-Related Biomarkers in Patients with Stable and Acute Exacerbation of Chronic Obstructive Pulmonary Disease. In COPD Journal of Chronic Obstructive Pulmonary Disease (Vol. 18, Issue 4, p. 482). Informa.

Khan, M., Bordes, S. J., Murray, I., & Sharma, S. (2021). Physiology, Pulmonary Vasoconstriction.

Koudstaal, T., Boomars, K. A., & Kool, M. (2020). Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension: An Immunological Perspective [Review of Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension: An Immunological Perspective]. Journal of Clinical Medicine, 9(2), 561. Multidisciplinary Digital Publishing Institute.

Laveneziana, P., & Weatherald, J. (2020). Pulmonary Vascular Disease and Cardiopulmonary Exercise Testing [Review of Pulmonary Vascular Disease and Cardiopulmonary Exercise Testing]. Frontiers in Physiology, 11. Frontiers Media.

Maron, B. A. (2023). Revised Definition of Pulmonary Hypertension and Approach to Management: A Clinical Primer [Review of Revised Definition of Pulmonary Hypertension and Approach to Management: A Clinical Primer]. Journal of the American Heart Association, 12(8). Wiley.

Menzel, A., Samouda, H., Dohet, F., Loap, S., Ellulu, M. S., & Bohn, T. (2021). Common and Novel Markers for Measuring Inflammation and Oxidative Stress Ex Vivo in Research and Clinical Practice—Which to Use Regarding Disease Outcomes? [Review of Common and Novel Markers for Measuring Inflammation and Oxidative Stress Ex Vivo in Research and Clinical Practice—Which to Use Regarding Disease Outcomes?]. Antioxidants, 10(3), 414. Multidisciplinary Digital Publishing Institute.

Mouzarou, A., Hadjigeorgiou, N., Melanarkiti, D., & Plakomyti, T. E. (2025). The Role of NT-proBNP Levels in the Diagnosis of Hypertensive Heart Disease [Review of The Role of NT-proBNP Levels in the Diagnosis of Hypertensive Heart Disease]. Diagnostics, 15(1), 113. Multidisciplinary Digital Publishing Institute.

Peng, J., Chen, C., Zhou, M., Xie, X., Zhou, Y., & Luo, C. (2020). A Machine-learning Approach to Forecast Aggravation Risk in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease with Clinical Indicators. Scientific Reports, 10(1).

Peng, J., Jury, E. C., Dönnes, P., & Ciurtin, C. (2021). Machine Learning Techniques for Personalised Medicine Approaches in Immune-Mediated Chronic Inflammatory Diseases:

Applications and Challenges [Review of Machine Learning Techniques for Personalised Medicine Approaches in Immune-Mediated Chronic Inflammatory Diseases: Applications and Challenges]. Frontiers in Pharmacology, 12. Frontiers Media.

Perros, F., Humbert, M., & Dorfmüller, P. (2021). Smouldering fire or conflagration? An illustrated update on the concept of inflammation in pulmonary arterial hypertension [Review of Smouldering fire or conflagration? An illustrated update on the concept of inflammation in pulmonary arterial hypertension]. European Respiratory Review, 30(162), 210161. European Respiratory Society.

Pirrotta, F., Mazza, B., Gennari, L., & Palazzuoli, A. (2021). Pulmonary Congestion Assessment in Heart Failure: Traditional and New Tools [Review of Pulmonary Congestion Assessment in Heart Failure: Traditional and New Tools]. Diagnostics, 11(8), 1306. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/diagnostics11081306

Risteska, M., Vladimirova-Kitova, L., & Andonov, V. (2022). Serum NT-ProBNP potential marker of cirrhotic cardiomyopathy. Folia Medica, 64(5), 740.

Sebastião, B. F., Hortelão, R. M., Granadas, S. S., Faria, J., Pinto, J., & Henriques, H. R. (2023). Air quality self-management in asthmatic patients with COPD: An integrative review for developing nursing interventions to prevent exacerbations. International Journal of Nursing Sciences, 11(1), 46.

Shu, T., Ning, W., Wu, D., Xu, J., Han, Q., Huang, M., Zou, X., Yang, Q., Yuan, Y., Bie, Y., Pan, S., Mu, J., Han, Y., Yang, X., Zhou, H., Li, R., Ren, Y., Chen, X., Yao, S., … Zhou, X. (2020). Plasma Proteomics Identify Biomarkers and Pathogenesis of COVID-19. Immunity, 53(5), 1108.

Sibani, M. A., Alawi, A. M. A., & Aghbari, J. A. (2021). Elevated Peripheral Blood Eosinophils during Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Sultan Qaboos University Medical Journal, 22(3), 339.

Stoicescu, L., Crișan, D., Morgovan, C., Avram, L., & Ghibu, S. (2024). Heart Failure with Preserved Ejection Fraction: The Pathophysiological Mechanisms behind the Clinical Phenotypes and the Therapeutic Approach [Review of Heart Failure with Preserved Ejection Fraction: The Pathophysiological Mechanisms behind the Clinical Phenotypes and the Therapeutic Approach]. International Journal of Molecular Sciences, 25(2), 794. Multidisciplinary Digital Publishing Institute.

Weiss, A., Porter, S., Rozenberg, D., O'Connor, E. S., Lee, T., Balter, M., & Wentlandt, K. (2020). Chronic Obstructive Pulmonary Disease: A Palliative Medicine Review of the Disease, Its Therapies, and Drug Interactions [Review of Chronic Obstructive Pulmonary Disease: A Palliative Medicine Review of the Disease, Its Therapies, and Drug Interactions]. Journal of Pain and Symptom Management, 60(1), 135. Elsevier BV.

Winter, N. A., Gibson, P. G., Fricker, M., Simpson, J. L., Wark, P., & McDonald, V. M. (2021). Hemopexin: A Novel Anti-inflammatory Marker for Distinguishing COPD From Asthma. Allergy Asthma and Immunology Research, 13(3), 450.

Xie, X., Kong, S., & Cao, W. (2023). Targeting protein glycosylation to regulate inflammation in the respiratory tract: novel diagnostic and therapeutic candidates for chronic respiratory diseases [Review of Targeting protein glycosylation to regulate inflammation in the respiratory tract: novel diagnostic and therapeutic candidates for chronic respiratory diseases]. Frontiers in Immunology, 14. Frontiers Media.

Xu, J., Zeng, Q., Li, S., Su, Q., & Fan, H. (2024). Inflammation mechanism and research progress of COPD [Review of Inflammation mechanism and research progress of COPD]. Frontiers in Immunology, 15. Frontiers Media.

Ye, W., Guo, H., Xu, J., Cai, S., He, Y., Shui, X., Shi-an, H., Luo, H., & Lei, W. (2020). Heart-lung crosstalk in pulmonary arterial hypertension following myocardial infarction (Review) [Review of Heart-lung crosstalk in pulmonary arterial hypertension following myocardial infarction (Review)]. International Journal of Molecular Medicine, 46(3), 913. Spandidos Publishing.

Zhang, B., Wang, J., Chen, J., Ling, Z., Ren, Y., Xiong, D., & Guo, L. (2022). Machine learning in chronic obstructive pulmonary disease. Chinese Medical Journal.

Zhang, Y., LR, L., Zhang, S., Y, L., Chen, Y.-Y., HZ, S., & YX, L. (2020). Blood Eosinophilia and Its Stability in Hospitalized COPD Exacerbations are Associated with Lower Risk of All-Cause Mortality. DOAJ (DOAJ: Directory of Open Access Journals).

Zhu, J., Chen, J., Wang, J., Desai, A. A., Black, S. M., & Tang, H. (2022). Editorial: Pathophysiology and Pathogenic Mechanisms of Pulmonary Vascular Disease. Frontiers in Physiology, 13.

Zinellu, A., Zinellu, E., Mangoni, A. A., Pau, M. C., Carru, C., Pirina, P., & Fois, A. G. (2022). Clinical significance of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in acute exacerbations of COPD: present and future [Review of Clinical significance of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in acute exacerbations of COPD: present and future]. European Respiratory Review, 31(166), 220095. European Respiratory Society.

Zinellu, E., Zinellu, A., Fois, A. G., Fois, S. S., Piras, B., Carru, C., & Pirina, P. (2020). Reliability and Usefulness of Different Biomarkers of Oxidative Stress in Chronic Obstructive Pulmonary Disease [Review of Reliability and Usefulness of Different Biomarkers of Oxidative Stress in Chronic Obstructive Pulmonary Disease]. Oxidative Medicine and Cellular Longevity, 2020, 1. Hindawi Publishing Corporation.