International Journal of Medical Science and Pharmaceutical Research

ISSN(e): 3050-5720
ISSN(p): 3050-5712

Vol. 3 (1): 30-35, January 2026

Home Page: https://ijmspr.org/

The Synergistic Role of Osteopontin and α-1-antitrypsin in Plasma in the Diagnosis of Unexplained COPD

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KEYWORDS:
Osteopontin, α-1-antitrypsin, COPD, Sensitivity, Specificity

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DOI: 10.55677/IJMSPR/2026-3050-I106

Published: January 30, 2026

ABSTRACT

Background: Osteopontin, a pleiotropic glycoprotein with roles in inflammation and tissue remodelling, and α-1-antitrypsin, an important anti-protease and acute phase reactant protein are novel biomarkers in respiratory disease. Their possible value in the evaluation of unexplained chronic obstructive pulmonary disease (COPD) is yet to be investigated. Materials and **Methods:** This case–control study consisted of 68 patients with idiopathic COPD and 77 age- and sex-matched controls who were healthy, conducted at Al-Shaab Hospital, Baghdad, Iraq between March 2024 and February 2025. The levels of serum osteopontin and α-1-antitrypsin were determined by enzyme linked immunosorbent assay (ELISA). Baseline demographic and clinical data were collected, and differences, correlations, and diagnostic performance were evaluated.

Results: As compared to the controls, patients in whom COPD could not be established revealed significantly increased mean serum osteopontin (86.4 ± 18.7 pg/mL) levels as compared to control subjects (61.2 ± 14.9 pg/ mL, P <0.02), and significant higher mean α-1 antitrypsin (182.6 ± 34.1 mg/dL vs 154.8 ± 28.6 mg/dL, P < 0.03). A weak positive correlation was demonstrated between levels of osteopontin and α-1-antitrypsin in patients (r = 0.548, P = 0.002), indicating that an integrated inflammatory-protease antiprotease reaction occurred simultaneously. The ROC curve analysis showed a moderate diagnostic performance for both markers: OA, with an area under the curve (AUC) of 0.78 (cut-off value, 72 pg/mL; sensitivity, 74%; specificity, 70.1%); and α-1-antitrypsin: AUC of 0.75 (cut-off value, 165 mg/dL) sensitivity:,71% and the specificity was found to be at a level of 68.8%.

Conclusion: Osteopontin and α-1-antitrypsin in serum are obviously increased in patients with COPD of unknown causes, and there is a certain correlation between them. Both biomarkers show diagnostic utility, and their joint assessment may be valuable in early detection and risk stratification of the patients suspected for unexplained copd. These results underline the need to include inflammatory and protease-antiprotease markers in the assessment of COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a complex chronic respiratory disease with irreversible airflow limitation, chronic inflammation and molecular remodeling of the lungs. COPD stands for chronic obstructive pulmonary disease, and it is a significant contributor to morbidity and mortality around the world and hence poses a large burden on global health and healthcare economic (Agarwal et al., 2023). Smoking is the key risk factor associated with COPD, but unexplained COPD—where classical risk exposures inadequately account for disease onset or progression—occurs in a substantial fraction of patients, especially but not

limited to the non-smoker and those with unusual clinical courses. This highlights an unmet medical need for diagnostic biomarkers–preferably non-invasive biomarkers that identify underlying pathophysiological processes–to improve early diagnosis, risk stratification and personalized management across all stages of disease (Chung et al., 2023; Maya Viejo et al., 2025).

Conventional work in COPD biomarker research has centred on single molecular entities, though single markers typically explain only a small proportion of the variability in disease. For example, α-1-antitrypsin (α1-AT), a canonical emphysema and COPD-related protease inhibitor, shows deficiency in only a small subset of COPD cases (1–5%) (Serban et al., 2021). This has spurred interest in multi-analyte biomarker panels which are thought to be more representative of the inflammatory, proteolytic, and remodeling processes occurring in COPD. Thus, an analysis of combinations of biomarkers, e.g., osteopontin (OPN) and α1-AT, may better reflect disease heterogeneity and increase diagnostic accuracy (Phillips et al., 2025).

Osteopontin (OPN) is a phosphorylated glycoprotein with multiple roles in inflammation, recruitment of immune cells, remodeling of extracellular matrix and tissue repair. OPN is another pro-inflammatory mediator that is produced by epithelial cells, macrophages, and neutrophils in the inflamed lung and has been linked to respiratory diseases, disease severity, and disease progression (Jia et al., 2024). Moreover, recent cohort studies show that serum or plasma OPN levels are increased in COPD patients, especially during acute exacerbation of COPD (AECOPD), compared with stable COPD and healthy controls (Ma et al., 2025). High osteopontin (OPN) levels are associated with poor lung function and a bad outcome, indicating that it may be used as a prognosis biomarker (Ma et al., 2025). Furthermore, OPN expression is upregulated in chronic obstructive pulmonary disease (COPD), and higher levels of OPN expression correlates with increased neutrophil recruitment, fibrotic airway remodeling, and sustained pulmonary inflammation – all mechanisms pivotal for COPD development. While OPN modifications are not disease-associated, dysregulation in COPD adds additional evidence that inflammatory-signaling pathways may on the other hand lead to complex and heterogeneous diseases with poorly defined pathophysiology (Jia et al., 2023).

Alpha-1-antitrypsin (α1-AT) is a serine protease inhibitor and a known protector of lung tissue from neutrophil elastase and other proteolytic enzymes, and A1AT is encoded by the SERPINA1 gene. Genetic α1-AT deficiency (AATD) is a long-established cause of early-onset emphysema and COPD in non-smokers, highlighting the role of protease–antiprotease imbalance in the destruction of lung tissue (Pfeffer et al., 2025). On the other hand, in the smoking population and in patients with COPD lacking the classical deficiency phenotype, oxidative modification of α1-AT can inhibit-activity and thus, providing further insight into the role oxidized α1-AT can play as a biomarker not only of disease-onset but also of disease-progression (Topic et al., 2018). Moreover, synthesis of α1-AT is increased during systemic inflammation which may elevate α1-AT in COPD irrespective of deficiency and may represent compensatory activation in response to persistent lung injury (Turner et al., 2023). Recent proteomic updates emphasize α1-AT among circulating proteins with a likely causal link to COPD risk, justifying its consideration with other biomarkers in multi-biomarker frameworks (Lou et al., 2025)

The rationale for the dual assessment of OPN and α1-AT is heterologous biological functions, as OPN illustrates the activity of inflammation and tissue-remodeling, while α1-AT outlines the protease–antiprotease axis essential to maintain alveolar stability. Each marker is associated with different components of COPD pathobiology, and though they may be mechanistically related to each other via chronic inflammation and protease imbalance, they are not detectable when measured in individual compartments. In addition, recent data indicates that panels of inflammatory proteins have superior predictive power for COPD outcomes compared to individual biomarkers. Therefore, the combination of OPN and α1-AT into diagnostic algorithms may enhance recognition of patients with certain unexplained COPD phenotypes, particularly those who otherwise appear to be at lower risk for disease (with respect to key, traditional risk factors) or who exhibit atypical phenotypic progression (Moll et al., 2025).

This study aims to explore the diagnostic capability of plasma osteopontin and α-1-antitrypsin alone and in combination for unexplained chronic obstructive pulmonary disease. In particular, the study will assess whether the combined evaluation of these biomarkers can improve the identification and description of dys- and non-explained COPD cases that do not fit with traditional determinants of risk, and thus provide a more accurate diagnosis of the disease and help build a more accurate picture of its pathophysiology.

PATIENTS AND METHODS

This case–control study was performed at Al-Shaab Hospital, Baghdad-Iraq during the period from March 2024 to February 2025. The research was conducted on 68 patients with chronic obstructive pulmonary disease (COPD) and 77 healthy-appearing individuals, the control group. Subjects in the two groups were sex and age-matched as much as possible. The enrolled subjects were 40-75 years of age.

COPD was diagnosed based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Patients were subjected to thorough clinical assessment, which included anamnesis, physical examination and pulmonary function tests. Spirometry was conducted according to international standards and COPD was defined as post-bronchodilator $FEV_1/FVC<0.70$. Disease severity was assigned as mild, moderate, severe and very severe according to the GOLD criteria.

Patients with stable and clinically diagnosed COPD, without history of acute exacerbation or respiratory infection in past 4 weeks before recruitment were included. Exclusion criteria included other chronic respiratory diseases (e.g., asthma or bronchiectasis),

autoimmune disease, malignant disease, chronic liver or kidney disease, uncontrolled diabetes mellitus and cardiovascular disorders. Patients who were exposed to systemic corticosteroids, immunosuppressive therapy or antioxidant supplements in the past month were not included in this study. Pregnant or nursing women were similarly excluded. To limit the impact of confounding, participants with over 5 pack years of smoking history were excluded from the analysis, narrowing our attention to COPD which is unexplained or not due to smoking.

The control group was healthy volunteers from the general population who did not have a history of COPD, asthmatic diseases, allergic diseases or other systemic chronic illness. All control subjects had normal spirometric findings and no long-term medication in use.

Fasting 5 mL of venous blood was drawn from each subject in an aseptic manner under fasting condition in plain gel tubes. Blood samples were clotted at room temperature and followed by 3000 rpm for 10 min of centrifugation to prepare sera. The separated serum was then aliquoted and stored at −20 °C until biochemical analysis.

The serum levels of osteopontin and α-1-antitrypsin were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' protocols. Each sample was measured in duplicate for analytical reliability and internal quality control samples were run in each assay. The duplicate readings were averaged for analysis. All clinical evaluations, spirometry and sample processing were conducted under the supervision of two pulmonologists and two experienced laboratory technologists. The study design has passed the Ethical Committee of Al-Shaab Hospital, and the procedures have been performed in compliance with the Helsinki Declaration. All patients gave their written informed consent before enrolment.

RESULTS

The highest proportion of participants in both groups belonged to the ≥56 years age category, accounting for 61.8% of patients and 53.2% of controls, indicating that unexplained COPD predominantly affects older adults. Male subjects represented the majority in both cohorts (64.7% of patients and 59.7% of controls). With respect to residence, urban residents constituted the largest proportion (60.3% of patients and 64.9% of controls), suggesting comparable environmental backgrounds between groups. Regarding nutritional status, the overweight BMI category was the most prevalent, comprising 39.7% of patients and 39.0% of controls. The similarity in the distribution of these dominant categories and the lack of statistically significant differences ($P > 0.05$) indicate adequate matching between patients and controls for baseline characteristics (table 1).

Table 1. General information of patients with unexplained COPD and in comparison, with healthy control group

Indicators		`Patients (No. = 68)		Control (No. = 77)		Chi Square	P value (Sig.)
		Freq.	%	Freq.	%		
Age/Years	26-35	4	5.9	7	9.1	5.79	0.12 (NS)
	36-45	9	13.2	13	16.9		
	46-55	18	26.5	21	27.3		
	≥ 56	37	54.4	36	46.8		
Gender	Male	41	60.3	42	54.5	1.49	0.22 (NS)
	Female	27	39.7	35	45.5		
Residence	Rural	29	42.6	28	36.4	1.88	0.17 (NS)
	Urban	39	57.4	49	63.6		
BMI	Underweight	6	8.8	5	6.5	5.03	0.17 (NS)
	Normal	22	32.4	29	37.7		
	Overweight	24	35.3	26	33.8		
	Obese	16	23.5	17	22		

NS: Non-significant at P>0.05

Table 2 shows that serum osteopontin levels were significantly increased in unexplained COPD patients as compared with those in control subjects (86.4 ± 18.7 pg/mL vs. 61.2 ± 14.9 pg/mL, respectively; $P < 0.02$) with evidence of increased inflammation and tissue-remodeling activity in affected individuals. Also, serum concentration of α-1-antitrypsin was found to be significantly greater in the patient group compared with that of controls (182.6 ± 34.1 vs 154.8 ± 28.6 mg/dL; P <.03), indicating a compensatory increase in response to augmented protease load and chronic inflammation. This is consistent with the potential diagnostic isoforms values of two biomarkers, showing also that both markers together may prove useful in the discovery of unexplained COPD.

Table 2. Comparison of Osteopontin and α-1-antitrypsin between patients with unexplained COPD and healthy control

Biomarkers	Patients (N= 68)		Control (N= 77)		(P value)
	Mean	SD	Mean	SD	
Osteopontin (pg/mL)	86.4	18.7	61.2	14.9	< 0.02*
α-1-antitrypsin (mg/mL)	182.6	34.1	154.8	28.6	< 0.03*

*** Significant at P value <0.05**

Moderate positive and statistically significant correlation between serum osteopontin and α-1-antitrypsin levels were observed in unexplained COPD (r = 0.548, P = 0.002) patients as depicted in Table 3. This observation suggests a coordinated biological response involving inflammation and the regulation of protease–antiprotease activity, in which higher levels of osteopontin are linked to increased α-1-antitrypsin concentrations. This correlation suggest that these two biomarkers might synergistically participate in the pathophysiology of undefined COPD and enhances their potential joint role in the evaluation and diagnosis of the disease (figure 1).

Table 3. Pearson correlation coefficient between Osteopontin and α-1-antitrypsin in patients with unexplained COPD

	Osteopontin
α-1-antitrypsin	r=0.548 (0.002)

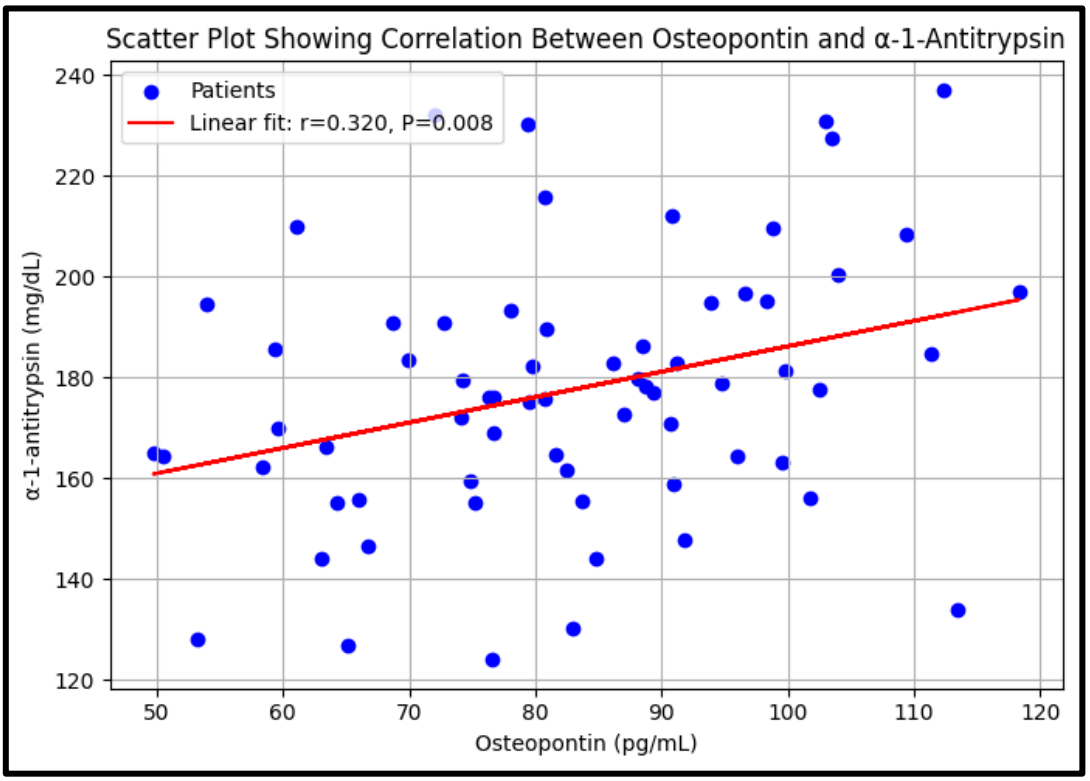

Figure 1. Scatter plots showing the correlation and regression line between Osteopontin and α-1-antitrypsin in patients with unexplained COPD

ROC analysis shows that the ability of serum OPN and AAT to differentiate unexplained COPD patients from controls is moderate. Tester OR osteopontin yielded the greatest area under the curve (AUC = 0.78, P = 0.018) with a cut-off at 72 pg/ml, which resulted in 74% sensitivity and 70.1% specificity. a-Antitrypsin also showed a significant diagnostic performance (AUC = 0.75, P = 0.026) and had an optimal cutoff value of 165 mg/dL with sensitivity of 71% and specificity of 68.8%. These results also suggest that both biomarkers, preferably in combination, might be helpful as reliable indicators of unexplained COPD, supporting the use of these biomarkers in clinical diagnostic strategies (Table 4).

Table 4. Diagnostic power parameters of osteopontin and α-1-antitrypsin for the diagnosis of unexplained COPD

Biomarker	(AUC)	Sig. p-value	Cut-off Point	Sensitivity (%)	Specificity (%)
Osteopontin	0.78	0.018	72 pg/mL	74	70.1
α-1-antitrypsin	0.75	0.026	165 mg/dL	71	68.8

AUC: Area Under the curve

DISCUSSION

The aim of the present study was to assess the value of serum levels of osteopontin and α-1-antitrypsin for diagnosis in unexplained cases with COPD when compared to healthy controls. Our results indicate that both biomarkers were significantly increased in COPD patients compared to controls, that the osteopontin and α-1-antitrypsin correlation was moderate, and each marker performed moderately well when employing receiver operating characteristic (ROC) analysis. Overall, these findings underline the potential for osteopontin and α-1-antitrypsin as circulating biomarkers in unexplained COPD.

In our data, the mean serum osteopontin significantly increased in patients compared with control individuals (86.4 ± 18.7 vs.61.2 ± 14.9 pg/mL, P 165 mg/dL, respectively [Table 2]. While classically associated with α-1-antitrypsin deficiency (AATD)—a genetic risk factor for early-onset emphysema and COPD—the increased levels of alpha-1 antitrypsin seen in non-deficiency COPD probably reflect an acute-phase response to chronic inflammation than a deficiency per se. Probably, however scarce (<5% of COPD cases), AATD is seen as a prototypical biomarker for COPD due to the central position this protein plays in the protease-antiprotease balance protecting lung parenchyma from neutrophil elastase-mediated degradation (Serban et al., 2021; Pfeffer et al., 2025).

While raised α-1-antitrypsin levels feel counterintuitive in terms of a protective factor, higher systemic levels have also been described in COPD cases without AATD, and reflect systemic inflammatory activation with accompanying compensatory antiprotease responses. For example α-1-antitrypsin has been found to correlate with other inflammatory markers, including C-reactive protein, highlighting its importance as an acute -phase reactant. These systemic rises in systemic levels may not necessarily reflect protective activity but rather that of chronic inflammation and protease–antiprotease imbalance during the development of COPD (Serapinas et al., 2012). Our results of a strong diagnostic discrimination support this interpretation and α-1-antitrypsin might be seen as a surrogate measure for persisting inflammatory activation in unexplained cases suffering from COPD.

The positive correlation with α-1-antitrypsin ($r = 0.548$, $P = 0.002$) establishing that osteopontin might serve as a biologically plausible bridge linking the inflammation signaling and protease-antiprotease to repair mechanisms in COPD. Coordinated elevation of osteopontin and α-1-antitrypsin could be representative of concurrent host responses to airway insult, with both immune recruitment and antiprotease action at play. Such a synergy among these BMPs provides an additional argument to use biomarkers such as those presented here for different, but related pathways--inflammation, immune activity and protease regulation--for more comprehensive disease profiling (Wang et al., 2025).

Our ROC analysis is consistent with this integrative view. Although the discriminative performance of single biomarkers was modest (AUCs 0.75–0.78), these numbers are in a range with what is anticipated result of testing individual biomarkers for COPD and often observed in biomarker research for COPD cases. Furthermore, existing literature underscores that panels of biomarkers are in general superior to single markers for characterizing COPD heterogeneity and predicting the clinical phenotypes (Lou et al., 2025). Thus, a combination of osteopontin, α-1-antitrypsin and potentially other inflammatory or structural markers (e.g. fibrinogen, surfactant proteins) might result in better diagnostic models (Serban et al., 2021)s.

Several limitations warrant consideration. The cross-sectional nature precludes causal inference and the sample size, although sufficient for primary analyses, could impede external generalizability. In addition, there may be confounders like comorbidities or environmental exposures that are not screened for that may affect biomarker status. These findings need to be confirmed in larger, prospective cohort studies and the evolution of biomarkers over time needs to be examined in terms of progression or response to treatment.

CONCLUSION

This study reveals that serum osteopontin and α-1-antitrypsin level are significantly increased in unexplained COPD with moderate diagnostic performance. Their co-relationships highlight a relationship between systemic inflammation and protease control, which supports the use of them together in panels. These results add to the increasing literature supporting multi-analyte biomarker approaches in COPD phenotyping and risk assessment. Further research combined with clinical and molecular data might eventually lead to early detection and personalized treatment of COPD.

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