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Integrative analysis of serum inflammatory biomarkers reveals a PCA-derived composite factor associated with COPD status

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Abstract

Background

Chronic obstructive pulmonary disease (COPD) is increasingly viewed as a heterogeneous disorder with systemic inflammatory features that may emerge before overt airflow limitation. However, individual circulating biomarkers often show substantial variability and limited clinical consistency.

Methods

A total of 87 participants were included in this exploratory cross-sectional study: patients with COPD (n = 48), smokers without airflow limitation (n = 24), and healthy never-smokers (n = 15). Serum interleukin-8 (IL-8), interleukin-18 (IL-18), matrix metalloproteinase-9 (MMP-9), and soluble receptor for advanced glycation end products (sRAGE) were measured via ELISA. Between-group comparisons were performed via analysis of covariance adjusted for age, sex, and body mass index. Associations with clinical variables were assessed via correlation analysis. Principal component analysis (PCA) was used to derive an integrated biomarker factor, and logistic regression with receiver operating characteristic (ROC) analysis was applied to evaluate its association with COPD status.

Results

After covariate adjustment, only MMP-9 remained significantly different between the groups ($p = 0.007$). IL-18 was associated with age, IL-8 with sex, and sRAGE with body mass index. MMP-9 showed the most consistent associations with symptom burden and lung function. PCA identified a single component explaining 39.0% of the total variance, with positive loadings for IL-8, IL-18, and MMP-9 and a negative loading for sRAGE. This composite biomarker factor was independently associated with COPD status (OR = 8.11, $p = 0.009$) and showed acceptable discriminative ability (AUC = 0.813).

Conclusions

Individual circulating biomarkers showed limited and covariate-dependent associations with COPD, whereas an integrated biomarker profile suggested a more consistent association with disease status. These findings support multivariate biomarker approaches for characterising systemic inflammatory processes in COPD patients.

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition characterised by persistent airflow limitation and chronic inflammation of the airways and lung parenchyma. In addition to local pathological processes in the respiratory system, COPD is increasingly recognised as a disorder with a systemic inflammatory component, reflecting its complex, multifactorial pathogenesis [1–3]. Despite advances in management, COPD remains a leading cause of morbidity and mortality worldwide and contributes substantially to the global burden of disease [4, 5].

Traditionally, COPD has been diagnosed based on spirometric evidence of airflow obstruction. However, this approach primarily captures relatively advanced stages of the disease. Growing evidence indicates that structural, inflammatory, and immunological changes may develop long before a measurable decline in the FEV_1/FVC ratio occurs. This has led to the concept of “pre-COPD”, which considers the disease as a continuum beginning at subclinical stages [6, 7].

Large cohort studies have demonstrated that smokers with preserved spirometry may already exhibit respiratory symptoms, functional impairment, and structural lung abnormalities associated with an increased risk of adverse outcomes [8, 9]. These observations highlight the need for biomarkers that can detect early biological alterations associated with COPD susceptibility, particularly before the onset of overt airflow limitation.

In this context, circulating inflammatory biomarkers have attracted considerable attention. Interleukin-8 (IL-8) plays a key role in neutrophil recruitment and activation and is considered a central mediator of airway inflammation [10]. Interleukin-18 (IL-18) is involved in innate immune regulation and may contribute to the persistence of chronic lung inflammation [11]. Matrix metalloproteinase-9 (MMP-9) participates in extracellular matrix degradation and tissue remodelling [12], while soluble receptor for advanced glycation end products (sRAGE) has been proposed as a marker of alveolar injury and emphysema-related changes [13].

Although these biomarkers reflect distinct but interconnected biological pathways, their clinical utility remains limited when they are assessed individually. Evidence from large observational studies indicates that circulating biomarkers demonstrate substantial variability and limited reproducibility, and their associations with clinical and functional outcomes are often inconsistent [14, 15].

These limitations have led to increasing interest in integrative approaches that consider multiple biomarkers simultaneously. Multivariate methods may capture latent biological signals that are not apparent when markers are analysed separately, thereby providing a more comprehensive representation of underlying disease processes [16–19]. While such approaches have been used for phenotyping in established COPD, their application to the identification of early or subclinical inflammatory profiles across the disease continuum remains limited.

In this exploratory study, we aimed to investigate whether an integrated serum inflammatory profile based on IL-8, IL-18, MMP-9, and sRAGE could identify a composite biomarker signal associated with COPD status across the continuum from never-smokers to smokers without airflow limitation and patients with COPD. Using principal component analysis, we sought to derive a composite biomarker factor reflecting coordinated biological processes and to evaluate its clinical relevance [19].

Methods

Study design and setting

This cross-sectional observational study was conducted between 2025 and 2026 at the Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan (Tashkent, Uzbekistan) in collaboration with the Republican Specialised Scientific and Practical Medical Centre of Phthisiology and Pulmonology (Ministry of Health of Uzbekistan).

Study population

A total of 87 participants aged ≥ 20 years were included and stratified into three groups: patients with COPD (n = 48), smokers without airflow limitation (n = 24), and healthy never-smokers (n = 15).

Patients with COPD were recruited in a hospital setting and were clinically stable at the time of inclusion. COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria based on the presence of chronic respiratory symptoms and persistent airflow limitation, defined as a post-bronchodilator FEV_1/FVC ratio < 0.70 [4]. Blood samples were collected at admission prior to any modification of ongoing therapy.

Smokers without airflow limitation had a current or former smoking history with preserved spirometry (FEV_1/FVC ≥ 0.70) and no prior diagnosis of COPD.

Healthy never-smokers without chronic respiratory disease or clinically significant symptoms were included as a control group and served as an internal reference for interpreting biomarker levels across the continuum from health to smoking exposure and established COPD.

The exclusion criteria for all groups included acute infectious diseases, bronchial asthma, interstitial lung disease, active systemic autoimmune disorders, malignancy, and severe comorbid conditions likely to affect systemic inflammatory markers. In patients with COPD, stable cardiovascular diseases were not considered exclusion criteria.

Clinical and functional assessment

All participants underwent standardised clinical evaluations, including demographic characteristics, smoking history, occupational exposure, and comorbidities. Smoking exposure was quantified in pack-years based on smoking duration and average daily cigarette consumption.

In patients with COPD, the frequency of exacerbations over the previous year was assessed using medical records and patient interviews. Symptom burden was evaluated using the COPD Assessment Test (CAT) and the modified Medical Research Council (mMRC) dyspnoea scale [20, 21].

Spirometry was performed in accordance with international ATS/ERS standards [22]. The following parameters were recorded: forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), the FEV_1/FVC ratio, and forced expiratory flow between 25% and 75% of forced vital capacity (FEF25–75).

Laboratory analysis

Venous blood samples were processed according to a standardised protocol. To minimise pre-analytical variability, all the samples were handled under uniform conditions and were not subjected to repeated freeze–thaw cycles.

Serum concentrations of IL-8 and IL-18 were measured using commercially available ELISA kits (Vector-Best, Russia), MMP-9 using a research-grade kit (Cloud-Clone Corp., Wuhan, China), and sRAGE using a commercially available kit (Bio-Techne / R&D Systems, USA). All assays were performed according to the manufacturer's instructions.

Statistical analysis

Statistical analyses were performed using JASP (version 0.19.3; University of Amsterdam, The Netherlands). The normality of continuous variables was assessed via the Shapiro–Wilk test. Data are presented as mean ± standard deviations or median (interquartile range). Categorical variables were analysed with the chi-squared test, as appropriate, and reported as counts and percentages.

Between-group differences in biomarker levels were analysed using analysis of covariance (ANCOVA), with study group as a fixed factor and age, sex, and body mass index (BMI) as covariates. Effect sizes were estimated using omega squared (ω^2). Associations between biomarkers and clinical or functional parameters were evaluated using partial Spearman correlations adjusted for age, sex, and BMI.

To assess the integrated behaviour of serum biomarkers (IL-8, IL-18, MMP-9, and sRAGE), principal component analysis (PCA) was performed based on the correlation matrix. Sampling adequacy was evaluated via the Kaiser–Meyer–Olkin measure and Bartlett's test of sphericity. The components were retained based on eigenvalues and inspection of the scree plot. The first principal component was interpreted as a composite biomarker factor reflecting the shared variance of inflammatory and remodelling markers.

The association between the PCA-derived composite biomarker factor and COPD status was evaluated using logistic regression analysis. Its discriminative performance was further assessed using receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) was calculated.

All statistical tests were two-sided, and p-values < 0.05 were considered statistically significant.

Handling of missing data

Serum biomarker measurements were not available for all participants because laboratory analyses were performed in stages and were limited by the availability of biological material and laboratory reagents. Statistical analyses were therefore conducted via complete-case analysis without imputation. Missingness was considered primarily operational, related to sample/reagent availability.

Results

Study population characteristics

A total of 87 participants were included in the study: patients with COPD (n = 48), smokers without airflow limitation (n = 24), and healthy never-smokers serving as the reference group (n = 15). Patients with COPD were characterised by substantially older age, more severe impairment of lung function, greater symptom burden, and a greater frequency of exacerbations than smokers without airflow limitation and healthy never-smokers. Smoking exposure, expressed in pack-years, was highest among patients with COPD, intermediate among smokers without airflow limitation, and absent among never-smokers (Table 1).

Table 1
Baseline characteristics of the study population

Characteristic	Never-smokers n = 15	Smokers without airflow limitation (n = 24)	COPD patients n = 48
Age, years	45.9 ± 8.5	46.3 ± 12.8	69.4 ± 6.8
Male sex, n (%)	14 (93.3)	16 (66.7)	46 (95.8)
BMI, kg/m²	24.2 ± 2.6	26.9 ± 4.4	24.4 ± 5.0
Current smokers, n (%)	—	20 (83.3)	20 (41.7)
Smoking exposure, pack-years	0 (0–0)	14.5 (6.9–19.0)	45.0 (20.8–65.6)
CAT score	—	8 (4–9)	28 (22–32)
mMRC grade	—	0 (0–1)	3 (2–3)
FEV_1, % predicted	105.7 ± 6.9	86.6 ± 18.1	26.3 ± 10.1
FEV_1/FVC, %	91.8 ± 6.8	81.2 ± 6.7	49.8 ± 14.8
FVC, % predicted	98.9 ± 5.4	88.1 ± 18.7	33.8 ± 12.2
Exacerbations per year	0 (0–0)	0 (0–0)	2 (2–2)

Note. Values are presented as mean ± standard deviation (SD) or median (interquartile range, IQR), as appropriate. Groups were not matched for age or smoking exposure by design. Symptom scores (CAT and mMRC) were assessed in smokers and patients with COPD only. Abbreviations: BMI — body mass index; CAT — COPD Assessment Test; FEV_1 — forced expiratory volume in one second; FVC — forced vital capacity; mMRC — modified Medical Research Council dyspnoea scale.

Serum biomarker levels and their clinical correlations

Group differences in serum biomarker levels were assessed using ANCOVA adjusted for age, sex, and BMI. Serum biomarker measurements were available for a subset of participants: never-smokers (n = 8),

smokers without airflow limitation (n = 20), and COPD patients (n = 20) (Table 2).

Table 2
Serum biomarker levels in never-smokers, smokers without airflow limitation, and COPD patients

Biomarker	Never-smokers (n = 8)	Smokers without airflow limitation (n = 20)	COPD patients (n = 20)	ANCOVA p-value
IL-8, pg/mL	3.55 (2.59–4.86)	4.34 (3.36–4.65)	4.53 (4.08–5.87)	0.256
IL-18, pg/mL	124.2 (99.6–166.9)	115.2 (90.7–126.6)	185.1 (134.6–230.0)	0.91
MMP-9, ng/mL	5.50 (4.13–7.19)	3.40 (2.09–5.16)	2.43 (2.09–6.98)	0.007*
sRAGE, pg/mL	1061 (851.9–1277)	1040 (761.6–1361)	715.9 (431.7–974.2)	0.517

Note. Values are presented as median (interquartile range, IQR). Group differences were assessed using ANCOVA adjusted for age, sex, and BMI. *p < 0.05. Abbreviations: IL-8 — interleukin-8; IL-18 — interleukin-18; MMP-9 — matrix metalloproteinase-9; sRAGE — soluble receptor for advanced glycation end products.

Among the analysed biomarkers, significant between-group differences were observed only for MMP-9 (p = 0.007). No statistically significant group differences were detected for IL-8, IL-18, or sRAGE after adjustment for age, sex and BMI. These findings prompted further analysis of combined biomarker behaviour.

Among the covariates, age was independently associated with the MMP-9 and IL-18 levels, whereas sex was associated with the IL-8 and IL-18 levels. BMI was associated with sRAGE levels.

Partial Spearman correlation analysis adjusted for age, sex and BMI revealed several associations between biomarker levels and clinical or functional characteristics (Table 3).

Table 3
Correlations between serum biomarkers and clinical and functional parameters

Biomarker	Parameter	Spearman ρ	p-value
MMP-9	CAT score	0.467	0.006
MMP-9	mMRC grade	0.497	0.003
MMP-9	FEV_1 (% predicted)	−0.353	0.034
MMP-9	FEF25 (% predicted)	−0.486	0.003
MMP-9	FEF50 (% predicted)	−0.390	0.019
MMP-9	FEF25–75 (% predicted)	−0.396	0.019
IL-18	FVC (% predicted)	−0.321	0.049
sRAGE	mMRC grade	−0.405	0.020

Note. Data are presented as partial Spearman correlations adjusted for age, sex, and BMI. Abbreviations: CAT — COPD Assessment Test; mMRC — modified Medical Research Council dyspnoea scale; FVC — forced vital capacity; FEV_1 — forced expiratory volume in one second; FEF25–75 — forced expiratory flow between 25% and 75% of forced vital capacity.

Table 4
Principal component loadings of serum biomarkers

Biomarker	Loading (PC1)
IL-8, pg/mL	0.737
MMP-9, ng/mL	0.645
IL-18, pg/mL	0.545
sRAGE, pg/mL	−0.554
Eigenvalue = 1.562; explained variance = 39.0%	

Note. Loadings represent correlations between individual biomarkers and the first principal component (PC1). Negative loading of sRAGE indicates an inverse contribution to the composite inflammatory–remodelling profile.

Among the analysed biomarkers, MMP-9 demonstrated the most consistent associations with clinical and functional parameters. It was positively correlated with symptom burden (CAT, mMRC) and inversely associated with lung function indices. IL-18 showed a modest inverse association with FVC, whereas sRAGE was negatively associated with mMRC grade.

Principal component analysis of serum biomarkers

Principal component analysis (PCA) was performed to explore the underlying structure of the relationships among the serum biomarkers (IL-8, IL-18, MMP-9, and sRAGE) (Table 4; Figs. 1, 2).

The sampling adequacy was acceptable (KMO = 0.620), and Bartlett's test of sphericity was significant ($\chi^2 = 16.485$, df = 6, p = 0.011).

Eigenvalues across principal components are shown. Only one component with an eigenvalue > 1 was retained, explaining 39.0% of the total variance.

IL-8, IL-18, and MMP-9 showed positive loadings, whereas sRAGE showed a negative loading, indicating an inverse relationship with the composite inflammatory–remodelling profile.

A single principal component was retained based on eigenvalue and scree plot criteria (eigenvalue = 1.562), explaining 39.0% of the total variance. It showed positive loadings for IL-8 (0.737), MMP-9 (0.645), and IL-18 (0.545), and a negative loading for sRAGE (− 0.554), indicating an integrated inflammatory–remodelling biomarker profile. Factor scores were calculated for each participant and used in subsequent analyses.

Clinical and diagnostic relevance of the composite biomarker factor

The clinical relevance of the composite biomarker factor was evaluated in relation to COPD status. In logistic regression analysis, inclusion of the biomarker factor significantly improved model fit compared with the null model ($\Delta\chi^2 = 15.11$, $p < 0.001$). This factor was independently associated with COPD (OR = 8.11, p = 0.009). The model demonstrated moderate explanatory power (Nagelkerke $R^2 = 0.447$) and classification performance (accuracy = 70.3%). ROC analysis revealed acceptable discriminative ability, with an AUC of 0.813. The sensitivity and specificity were 66.7% and 73.7%, respectively. (Fig. 3).

The PCA-derived composite biomarker factor showed acceptable discriminative ability (AUC = 0.813). Sensitivity and specificity were 66.7% and 73.7%, respectively.

Discussion

In this exploratory study, we examined serum inflammatory biomarkers across the continuum from never-smokers to smokers without airflow limitation and patients with COPD, with a particular focus on their integrated behaviour. The main finding is that individual biomarkers showed limited robustness after adjustment for key covariates, whereas a composite biomarker factor derived from principal component analysis retained a stable association with COPD status. These findings suggest that coordinated inflammatory and remodelling signals may be more informative than isolated circulating markers.

Our results are consistent with the current understanding of COPD as a heterogeneous disease with a systemic inflammatory component [1–3, 15, 18]. At the same time, they highlight an important limitation

of single biomarker approaches. After adjustment for age, sex and BMI, only MMP-9 remained significantly different between groups, whereas IL-8, IL-18 and sRAGE did not show independent group effects. This pattern underscores the influence of demographic and metabolic factors on circulating biomarker levels and may partly explain the inconsistent findings reported in previous studies [14, 15].

Among the analysed markers, MMP-9 demonstrated the most consistent associations with clinical and functional parameters, including symptom burden and lung function, supporting its relevance to disease severity. This is in line with its established role in extracellular matrix degradation and tissue remodelling [12, 23]. However, the observed heterogeneity in MMP-9 levels suggests that it may reflect specific biological processes present in certain COPD phenotypes rather than serving as a universal marker of the disease [16–18].

In contrast, IL-18 and IL-8 did not show independent between-group differences after adjustment but were instead associated with age and sex, respectively, consistent with the concepts of immune ageing ("inflammaging") and sex-related differences in innate immune responses [24–26]. Similarly, sRAGE did not demonstrate independent group differences but was associated with BMI, suggesting an influence of metabolic factors. Although sRAGE has been proposed as a marker of alveolar injury and emphysema [13, 27–29], its relationship with adiposity may complicate its interpretation in cross-sectional settings [30, 31].

Taken together, these findings support the value of an integrated approach to biomarker analysis. The identified composite factor captured a coordinated inflammatory–remodelling profile, characterised by increased IL-8, IL-18, and MMP-9 levels and reduced sRAGE, suggesting a shared underlying biological process. This is in line with previous studies applying multivariate techniques to COPD phenotyping [16–19].

Importantly, while most prior work has focused on patients with established disease, the present study extends this approach across the continuum from health to smoking exposure and clinically overt COPD. The absence of substantial differences in individual biomarkers may therefore reflect overlapping systemic inflammatory signals, particularly at earlier or subclinical stages of disease [7–9].

In this context, the concept of pre-COPD provides a useful framework for interpreting our findings [7]. Structural and inflammatory alterations have been described in smokers with preserved spirometry [8, 9], suggesting that pathological processes begin before airflow limitation becomes detectable. The composite biomarker factor identified in this study may reflect these early systemic changes, capturing subtle shifts in the inflammatory balance that are not apparent when markers are considered separately.

From a clinical perspective, these findings support the potential value of integrative biomarker strategies, which may provide a more stable and biologically meaningful representation of disease-related processes. This approach aligns with the broader move toward multidimensional phenotyping and systems-level analysis in chronic respiratory diseases [16–18].

Despite these findings, several limitations should be considered. Biomarker analyses were performed in a subset of participants due to resource constraints, resulting in reduced and variable sample sizes across analyses; therefore, the findings should be interpreted as exploratory. The cross-sectional design precludes causal inference and prevents assessment of the predictive value of the identified biomarker patterns. Although adjustments were made for age, sex, and BMI, residual confounding cannot be excluded, particularly given the imbalance in sex distribution between groups. In addition, the proportion of variance explained by the principal component was moderate, reflecting biological heterogeneity rather than a single dominant pathway. Finally, the observed diagnostic performance may be influenced by the limited sample size and requires validation in independent cohorts.

Conclusions

In conclusion, individual circulating biomarkers showed limited and covariate-dependent associations with COPD status, whereas an integrated biomarker profile derived from multivariate analysis demonstrated a more consistent relationship with the disease. These findings support the use of integrative approaches to better capture systemic inflammatory processes in COPD and provide a rationale for further investigation in larger, longitudinal studies.

Abbreviations

COPD
Chronic obstructive pulmonary disease
IL
8—Interleukin—8
IL
18—Interleukin—18
MMP
9—Matrix metalloproteinase—9
sRAGE
Soluble receptor for advanced glycation end products
PCA
Principal component analysis
ROC
Receiver operating characteristic
AUC
Area under the curve
BMI
Body mass index
CAT
COPD Assessment Test
mMRC

Modified Medical Research Council dyspnoea scale
FEV_1
Forced expiratory volume in one second
FVC
Forced vital capacity
FEF25
75—forced expiratory flow between 25% and 75% of forced vital capacity

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan, in accordance with the Bioethics and Safety Act (IRB No. 2025-004, approved on September 15, 2025). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before inclusion.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

NK conceived and conducted the study. SZ, ST, and NK collected the data. ST and ST performed laboratory analysis. NK and ON performed statistical analysis and drafted the manuscript. TA, SM, AI, SZ, and NR contributed to revising and critical revision of the manuscript. TA supervised the study. All authors reviewed and approved the final manuscript and agreed to be accountable for all aspects of the work.

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Data Availability

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request, in accordance with institutional policies. The data are not publicly available due to privacy and institutional restrictions.

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Figures

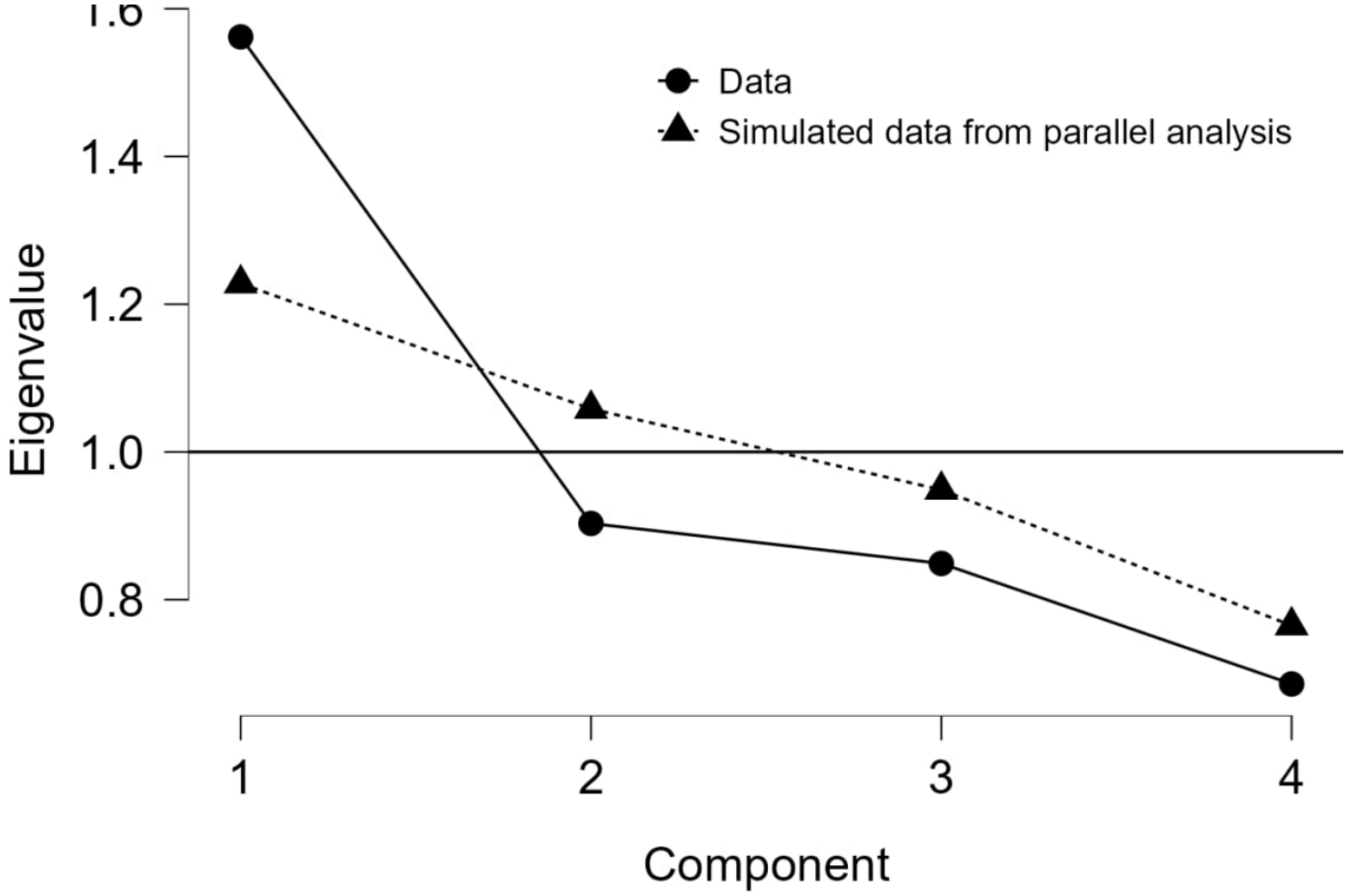


Figure 1

Scree plot from PCA of serum biomarkers.

Eigenvalues across principal components are shown. Only one component with an eigenvalue >1 was retained, explaining 39.0% of the total variance.

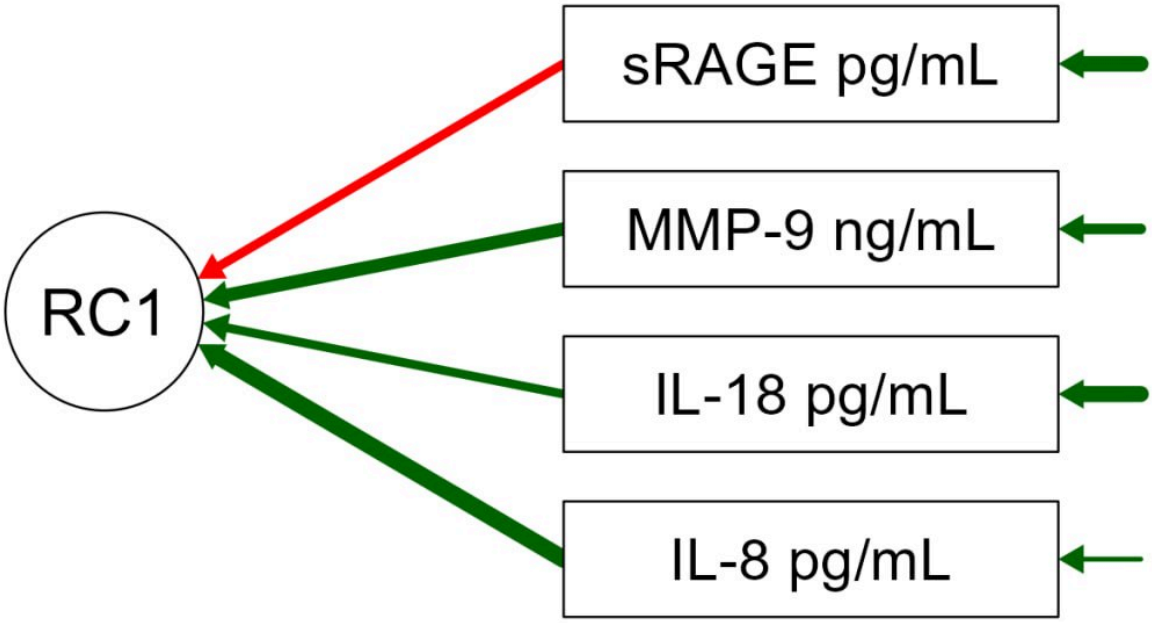


Figure 2

Loadings of individual biomarkers on the first principal component (PC1; labelled as RC1 in the figure).

IL-8, IL-18, and MMP-9 showed positive loadings, whereas sRAGE showed a negative loading, indicating an inverse relationship with the composite inflammatory–remodelling profile.

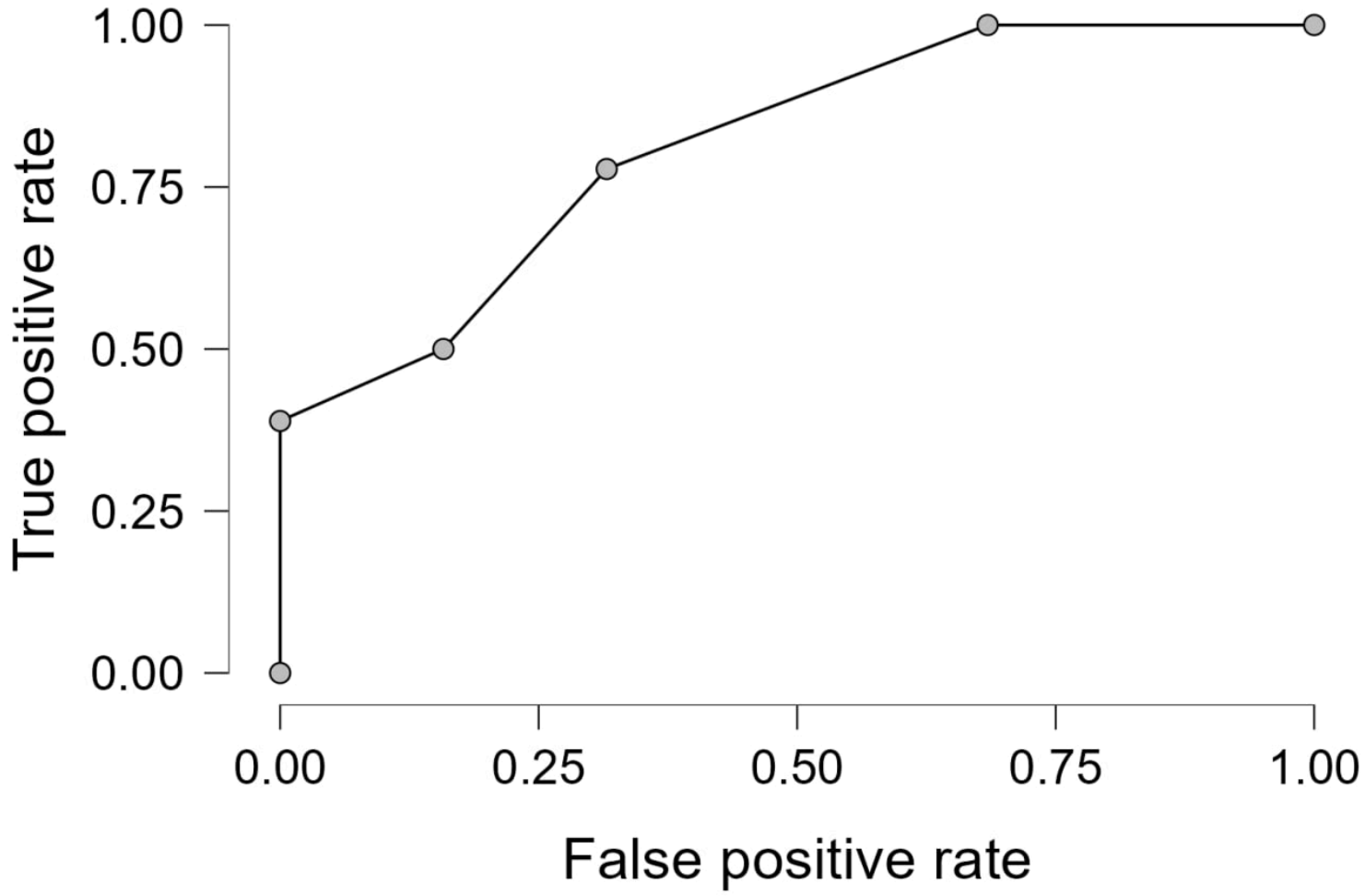


Figure 3

ROC curve of the composite biomarker factor for discriminating COPD.

The PCA-derived composite biomarker factor showed acceptable discriminative ability (AUC = 0.813). Sensitivity and specificity were 66.7% and 73.7%, respectively.