

RESEARCH

Open Access



Blood cell ratio biomarkers of systemic inflammation in chronic obstructive pulmonary disease

Kaman So¹, Aabida Saferali¹, Jeong H. Yun¹ , Min Hyung Ryu² , Enrico Schiavi³ , Peter J. Castaldi¹, Lisa Ruvuna⁴ , Russell P. Bowler⁴ , Jeffrey L. Curtis⁵ and Craig P. Hersh^{1*}

Abstract

Background Blood eosinophil count is an accepted biomarker for type 2 inflammation in COPD. However, the majority of COPD patients are characterized by non-type 2 inflammation. We aimed to test readily obtainable immune cell ratios as biomarkers for clinical phenotypes in the broad COPD population and to determine pathways represented by these ratios using multi-omics data.

Methods Using complete blood counts with differential collected at the Phase 2 (5-year) visit in the COPDGene Study, we calculated three immune cell ratios previously described in COPD and other diseases: the neutrophil–lymphocyte ratio (NLR), the platelet–lymphocyte ratio (PLR), and the Systemic Immune-Inflammation Index (SII = $\text{NLR} \times \text{platelets}$). We tested for associations with COPD outcomes, including lung function, chest CT scan phenotypes, and exacerbations. Blood RNA-sequencing and proteomics data were used to identify genes, proteins and pathways associated with the ratios.

Results In univariate analyses, the three biomarkers were associated with COPD severity measures. In zero inflated Poisson regression models, all three were associated with increased odds of having an exacerbation but were not associated with exacerbation counts. Conversely, the three biomarkers were generally associated with prospective exacerbation counts, but not the zero-inflation term. In logistic regression models, the three biomarkers were significantly associated with having two or more exacerbations in the prior year; however, receiver operating characteristic analyses did not lead to clear cutoff values. Complement and PI3K signaling pathways were enriched across more than one ratio in both the RNA-sequencing and proteomics results. Other inflammatory pathways relevant in COPD appeared in different enrichment sets in either omics data type.

Conclusions Higher levels of three easily obtained blood cell ratios were associated with COPD severity and exacerbations outcomes; however, there are not clear thresholds which would be required for clinical application. Blood RNA-sequencing and proteomics identified inflammatory pathways associated with the three biomarkers, including targets for COPD therapies currently in human trials.

Keywords COPD exacerbation, Lymphocytes, Neutrophils, Platelets, Proteomics, RNA-sequencing

*Correspondence:

Craig P. Hersh
craig.hersh@channing.harvard.edu

Full list of author information is available at the end of the article



© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

Background

Chronic obstructive pulmonary disease is a heterogeneous condition, involving multiple cellular and molecular features, [1, 2] yet there are limited biomarkers available to define the different inflammatory pathways [3]. Blood eosinophil count, a biomarker for type 2 inflammation, is associated with exacerbation risk [4] and response to inhaled corticosteroids, [5] and has been used as an entry criteria into clinical trials of biologic therapies targeting type 2 inflammation in COPD [6, 7]. Fractional exhaled nitric oxide and immunoglobulin E levels are other biomarkers of type 2 inflammation that are used in clinical care for asthma and have been applied in research studies of COPD [7, 8]. Despite the clinical relevance of type 2 inflammation in COPD, this mechanism is likely important only in a minority of COPD patients. Studies have shown that 20–40% of COPD patients have evidence of type 2 inflammation, indicated by elevated blood eosinophil counts [4, 9]. There are no available biomarkers for other inflammatory pathways in the full COPD population.

Complete blood count with white blood cell differential is a commonly obtained clinical laboratory measurement. Both blood neutrophil counts and platelet counts are elevated in inflammatory states and are associated with COPD severity [10, 11]. Several blood cell ratios have been developed to capture systemic inflammation, including the neutrophil to lymphocyte ratio (NLR), the platelet to lymphocyte ratio (PLR) and the systemic inflammatory-immune index ($SII = NLR * platelets$). These ratios have been predominantly applied in cancer studies, but are increasingly shown to be relevant for COPD outcomes including exacerbations and mortality [12–15]. These indices are purported to reflect systemic inflammation, but the specific inflammatory pathways represented are unknown.

Our hypothesis is that these blood cell ratios can serve as biomarkers of non-type 2 inflammation. We executed two aims to test this hypothesis. First, we sought to confirm the associations with respiratory outcomes, especially exacerbations, in a large population of current and former smokers with and without COPD in the Genetic Epidemiology of COPD Study (COPDGene). Second, we aimed to identify the biological pathways represented by the indices using blood RNA-sequencing and proteomics data in COPDGene.

Methods

The genetic epidemiology of COPD study (COPDGene)

COPDGene is an observational study of over 10,000 current and former smokers (at least 10 pack years) with and without COPD, along with additional non-smoking controls; [16] however, non-smokers were excluded from this analysis. One-third of COPDGene subjects are African

Americans. Subjects were ages 45–80 at the initial visit. Subjects with cancer within the last 5 years and with other lung diseases except asthma were excluded. The baseline study visit included questionnaires, spirometry, a 6-min walk test, and a high-resolution chest computed tomography (CT) scan with computerized analysis for emphysema and airway disease. Five- and ten-year follow-up visits (Phases 2 and 3) used similar phenotype assessments, with the addition of a complete blood count (CBC) with differential, which was assayed in each center's clinical laboratory. COPD exacerbations in the past year are queried at each study visit, and prospective exacerbations are recorded using web or telephone-based longitudinal follow-up questionnaires every 6 months [17]. COPD exacerbations were defined by use of antibiotics and/or systemic steroids. Severe exacerbations required emergency department visits or hospitalization. Frequent exacerbators were defined as two or more exacerbations in the prior year. All subjects gave written informed consent. COPDGene was approved by the Institutional Review Boards at all participating centers.

RNA-sequencing and proteomics

At the Phase 2 visit, blood samples were collected for RNA-sequencing and proteomics; methods have been previously published [18, 19]. Briefly, whole blood was collected in PaxGene RNA tubes (BD Biosciences). RNA was extracted and used to generate stranded total RNA libraries with ribosomal reduction. Illumina sequencing used 75 bp paired-end reads. Blood proteomics was generated using SomaScan v4.0 which uses aptamers to quantify approximately 5000 proteins. Whole genome sequencing is available through the NHLBI Trans-Omics in Precision Medicine (TOPMed) program [20]. Duffy null phenotype was determined by minor allele homozygosity for a single nucleotide polymorphism in the atypical chemokine receptor 1 gene (*ACKR1*; rs2814778) [21].

Statistical analysis

All statistical analyses were performed in R (v.4.3.2) in R Studio Pro Server (v2025.05.1+513). Unless otherwise stated, to test the univariate associations of NLR, PLR, and SII with clinical variables, we used the 2-tailed unpaired Student's t test for categorical variables, and correlation for quantitative variables. To test the association between three immune cell ratios and exacerbations counts, zero-inflated Poisson regression analyses were performed using the *pscl* (v.1.5.9) package in R. Zero-inflated Poisson models were adjusted for age, sex, race, current smoking status (vs. former), pack-years, FEV₁ percent predicted and Duffy null phenotype, the major determinant of neutrophil count primarily in populations of African descent [22]. Scale function was applied to the predictors, which generally improves model stability and

convergence, especially for predictors with large values or different scales. To test the association between the three immune cell ratios and binary exacerbation outcomes, logistic regression analyses were performed using stats (v.4.2.0) package in R. Logistic models adjusted for age, sex, race, smoking status (vs. former), pack-years, FEV₁ percent predicted and Duffy null phenotype. Models for prospective exacerbations were additionally adjusted for the number of exacerbations in the prior year.

Table 1 COPDGene Phase 2 subject characteristics. N(%) or mean (SD) are shown

	All Subjects (n = 5652)	COPD GOLD 2–4 (n = 1970)
Female sex	2799 (49.5%)	898 (45.6%)
Non-Hispanic white	3930 (69.5%)	1493 (75.5%)
African American	1722 (30.5%)	477 (24.2%)
Current smoker	2194 (38.8%)	677 (34.4%)
Age, years	65.26 (8.66)	67.76 (8.24)
Pack-years of smoking	43.70 (24.09)	51.66 (25.06)
FEV ₁ % predicted, post-bronchodilator	77.81 (24.54)	52.27 (17.22)
GOLD stage		
0	2423 (42.9%)	NA
1	542 (9.6%)	NA
2	1131 (20.0%)	1131 (57.4%)
3	590 (10.4%)	590 (29.9%)
4	249 (4.4%)	249 (12.6%)
PRISM	717 (12.7)	NA
SGRQ total score	23.47 (21.31)	36.32 (21.03)
6 min walk distance, ft	1290.99 (436.86)	1113.35 (434.12)
BODE score	1.68 (2.15)	3.32 (2.48)
BMI (kg/m ²)	28.99 (6.40)	28.27 (6.45)
% emphysema (LAA950)	5.42 (9.02)	11.86 (12.43)
Perc15	84.81 (30.36)	66.18 (29.25)
Pi10	2.28 (0.58)	2.69 (0.56)
Airway wall thickness of segmental airways	1.04 (0.22)	1.13 (0.23)
Wall area % of segmental airways	50.29 (8.43)	54.77 (7.98)
White blood cell count	7.18 (2.34)	7.56 (2.31)
Neutrophil count	4.33 (1.80)	4.76 (1.95)
Lymphocyte count	2.06 (1.12)	1.95 (0.87)
Monocyte count	0.56 (0.21)	0.6 (0.22)
Eosinophil count	0.19 (0.15)	0.2 (0.16)
Exacerbations in the prior year		
0	4652 (82.3%)	1336 (67.8%)
1	581 (10.3%)	350 (17.8%)
2 or more	419 (7.4%)	284 (14.4%)
Severe exacerbation in the prior year	532 (9.4%)	361 (18.3%)

Abbreviations: BODE Body mass index, Obstruction, Dyspnea, Exercise Capacity, BMI Body mass index, FEV₁ Forced expiratory volume in 1 s, GOLD Global Initiative for Chronic Obstructive Lung Disease, LAA950 Low attenuation area at −950 Hounsfield Units, Perc15 15th percentile of lung density histogram, Pi10 Square root wall area of hypothetical airway with 10 mm internal perimeter, PRISM Preserved Ratio Impaired Spirometry (FEV₁ < 80% predicted with FEV₁/FVC ≥ 0.7) [27], SGRQ St. George's Respiratory Questionnaire

We performed differential gene expression and proteomic analysis using Limma (v3.54.2) in R. Linear models were adjusted for age, sex, race, smoking status (current vs former), pack-years, and FEV₁ percent predicted. As per previous COPDGene analyses, proteomics were additionally adjusted for clinical center, [19] and RNA-seq was also adjusted for library batch [18]. We used Sigora (v3.1.1) to identify the underlying function of gene sets. Four annotated gene sets – hallmark gene sets, [23] KEGG, [24] Gene Ontology [25] and Reactome [26] v2025.1 – were chosen for the reference gene sets. An FDR adjusted *p*-value < 0.05 was set as the cutoff criteria. Volcano plots were drawn with the EnhancedVolcano package.

Results

Neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) were derived from Phase 2 CBC data for 5,652 current and former smoking subjects, including 1,970 with COPD, defined as post-bronchodilator FEV₁/FVC < 0.7 and FEV₁ < 80% predicted, corresponding to Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 2–4 (Table 1). Even within the COPD subjects, there is heterogeneity in phenotypes, such as exacerbation history. The three measures were highly correlated: NLR–PLR (Pearson) *r* = 0.66, NLR–SII *r* = 0.89, SII–PLR *r* = 0.76, in all subjects.

In univariate analyses, all three biomarkers were significantly associated with demographic and clinical variables such as sex, race, smoking status, age, lung function (FEV₁% predicted), disease-related quality of life (St. George's Respiratory Questionnaire [SGRQ] total score), exercise capacity (6-min walk distance), and chest CT scan emphysema measures in all subjects and in COPD only (Tables 2 and 3); overall, the correlations were weak. NLR and SII, but not PLR, were associated with chest CT scan airway metrics, in all subjects and in COPD only. Weak negative correlations were found between blood eosinophil counts and NLR (*r* = −0.03) and PLR (*r* = −0.07); SII was not significantly correlated (*r* = −0.009). Moderate repeated measures correlations were observed between Phase 2 and Phase 3 values for NLR (*r* = 0.34, *n* = 2844), PLR (*r* = 0.53, *n* = 2826), and SII (*r* = 0.35, *n* = 2826).

Exacerbations were assessed both retrospectively and prospectively. Subjects were followed for an average of 7.05 (± 2.65) years. In zero inflated Poisson regression models for exacerbations in the past year, adjusted for clinical covariates and Duffy null genotype, higher values for all three biomarkers were associated with reduced odds for being a non-exacerbator (zero inflation term in Table 4) – i.e. higher odds of having an exacerbation – but were not associated with exacerbation counts.

Table 2 Univariate associations of NLR, PLR, and SII with clinical variables. Categorical variables (mean values are shown)

Variable	All subjects			COPD (GOLD 2–4)		
	NLR	PLR	SII	NLR	PLR	SII
Male	2.63**	132.1	594.1	3.12**	141.9	715.9
Female	2.29	134.0	590.7	2.66	142.9	967.8
White race	2.70**	136.9**	648.6**	3.12**	145.2*	763.0**
African American race	1.90	124.0	461.7	2.24	133.3	533.1
Current smoker	2.19**	121.9**	539.4**	2.49**	126.8**	614.3**
Former smoker	2.63	140.1	625.8	3.12	150.4	756.1

Abbreviations: GOLD Global Initiative for Chronic Obstructive Lung Disease, NLR neutrophil to lymphocytes ratio, PLR platelet to lymphocyte ratio, SII systemic immune-inflammation index

* $p < 0.05$ ** $p < 0.001$. P -values are for t-test

Table 3 Univariate associations of NLR, PLR, and SII with clinical variables. Quantitative variables (correlation coefficients are shown)

Variable	All subjects			COPD (GOLD 2–4)		
	NLR	PLR	SII	NLR	PLR	SII
Age	0.20**	0.12**	0.14**	0.17**	0.10**	0.11**
Pack-years	0.12**	0.02	0.08**	0.08**	0.02	0.06*
FEV ₁ % predicted, post-bronchodilator	−0.19**	−0.09**	−0.17**	−0.16**	−0.12**	−0.14**
SGRQ total score	0.17**	0.08**	0.16**	0.15**	0.11**	0.16**
6 min walk distance	−0.16**	−0.08**	−0.15**	−0.18**	−0.14**	−0.17**
BODE index	0.21**	0.13**	0.20**	0.19**	0.15**	0.18**
% emphysema (LAA950)	0.21**	0.14**	0.19**	0.15**	0.15**	0.15**
Perc15	−0.19**	−0.17**	−0.17**	−0.15**	−0.16**	−0.15**
Pi10	0.12**	0.01	0.11**	0.09**	0.03	0.08**
Airway wall thickness	0.14**	−0.01	0.09**	0.10**	0.01	0.06*
Wall area %	0.13**	−0.01	0.10**	0.08*	0.01	0.06*

Abbreviations: BODE Body mass index, Obstruction, Dyspnea, Exercise Capacity, FEV₁ forced expiratory volume in 1 s, GOLD Global Initiative for Chronic Obstructive Lung Disease, LAA950 Low attenuation area at −950 Hounsfield Units, NLR Neutrophil to lymphocytes ratio, Perc15 15th percentile of lung density histogram, Pi10 Square root wall area of hypothetical airway with 10 mm internal perimeter, PLR Platelet to lymphocyte ratio, SGRQ St. George's Respiratory Questionnaire, SII Systemic immune-inflammation index

* $p < 0.05$ ** $p < 0.001$, P -values are for correlation test

Table 4 Associations with exacerbation outcomes. Zero inflated Poisson regression models for exacerbations counts (beta (SE) are shown)

Outcome	Term	All subjects			COPD (GOLD 2–4)		
		NLR	PLR	SII	NLR	PLR	SII
Exacerbations in past year	Zero inflation	−0.22 (0.05)**	−0.22 (0.05)***	−0.25 (0.05)***	−0.18 (0.07)**	−0.21 (0.07)**	−0.24 (0.09)**
	Count	0.001 (0.018)	−0.001 (0.018)	0.002 (0.016)	0.02 (0.03)	−0.004 (0.03)	0.003 (0.02)
Prospective exacerbations	Zero inflation	0.14 (0.09)	0.28 (0.08)***	0.13 (0.08)	0.32 (0.21)	0.28 (0.17)	0.38 (0.21)
	Count	0.43 (0.01)***	0.37 (0.01)***	0.39 (0.01)***	0.65 (0.01)***	0.42 (0.02)***	0.54 (0.01)***

Abbreviations: GOLD Global Initiative for Chronic Obstructive Lung Disease, NLR neutrophil to lymphocytes ratio, PLR platelet to lymphocyte ratio, SII systemic immune-inflammation index

** $p < 0.01$, *** $p < 0.001$. P -values are for regression coefficients

Conversely, the three biomarkers were generally associated with prospective exacerbation counts, but not the zero inflation term. Similar results were found for prospective severe exacerbation counts (data not shown). In logistic regression models adjusted for covariates, the three biomarkers were significantly associated with having frequent exacerbations, defined as two or more in the prior year (Table 5). All three were associated with having a severe exacerbation in the past year; however only NLR and SII were associated with having a severe exacerbation in the prospective follow-up.

To assess the discrimination of frequent exacerbation status (two or more in the prior year), we next constructed receiver operating characteristic (ROC) analyses. When combined with clinical covariates, all three biomarkers showed small but significantly increased area under the ROC curve (AUROC) values compared to covariates alone in all subjects (Fig. 1, Table 6). In COPD subjects, AUROCs were slightly lower than in all subjects (Supplemental Fig. 1, Table 6); NLR and SII showed significant improvement compared to covariates alone. We examined various cutoffs to dichotomize the

Table 5 Associations with exacerbation outcomes. Logistic regression models for frequent exacerbations (2 or more in the prior year) and severe exacerbations (beta (SE) shown)

Outcome	All subjects			COPD (GOLD 2–4)		
	NLR	PLR	SII	NLR	PLR	SII
Frequent exacerbations	0.11 (0.02)***	0.003 (7e-4)***	4.6e-4 (9e-5)***	0.07 (0.03)**	0.002 (8e-4)**	3e-4 (1e-4)**
Retrospective severe exacerbation	0.09 (0.02)***	0.002 (6e-4)***	3e-4 (8e-5)***	0.08 (0.02)**	0.002 (4e-4)**	3e-4 (9e-5)***
Prospective severe exacerbation	0.06 (0.02)***	5.6e-4 (5.3e-4)	1.5e-4 (7.4e-5)*	0.07 (0.03)**	0.001 (6.6e-4)	1.8e-4 (9.1e-5)*

Abbreviations: GOLD Global Initiative for Chronic Obstructive Lung Disease, NLR Neutrophil to lymphocyte ratio, PLR Platelet to lymphocyte ratio, SII Systemic immune-inflammation index

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. P -values are for regression coefficients

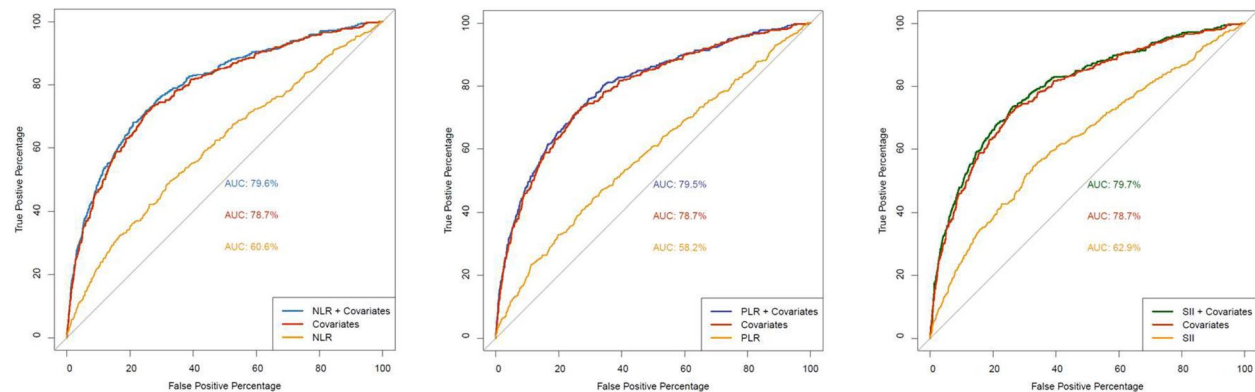


Fig. 1 Receiver operating characteristic curves for frequent exacerbations outcome (2 or more in the prior year)

Table 6 Area under the receiver operating characteristic curve, frequent exacerbation outcome (2 or more in the prior year)

	Covariates only	NLR	NLR + covariates	PLR	PLR + covariates	SII	SII + covariates
All subjects	78.7	60.6	79.6 ^{a,b}	58.2	79.5 ^{a,b}	62.9	79.7 ^{a,b}
COPD (GOLD 2–4)	74.6	57.1	75.4 ^{a,b}	57.7	75.4 ^b	59.7	75.6 ^{a,b}

Abbreviations: GOLD Global Initiative for Chronic Obstructive Lung Disease, NLR Neutrophil to lymphocyte ratio, PLR Platelet to lymphocyte ratio, SII Systemic immune-inflammation index

^a $p < 0.05$ for comparison vs covariates only by Delong test

^b $p < 0.0001$ for comparison with biomarker only (e.g. NLR) by Delong test

three biomarkers, using the 1st, 2nd or 3rd quartile of each. ROC curve analyses did not show an optimal cutoff in all subjects or in COPD subjects only (Supplemental Table 1).

We performed a sensitivity analysis to assess whether blood eosinophil counts affected these associations in all subjects and in COPD only. The results of zero inflated Poisson regression models for exacerbations in the past year and logistic regression models for frequent exacerbations (2 or more in the prior year) and severe exacerbations in the past year did not change appreciably when adjusted for blood eosinophil counts, nor did the area under the ROC curves for the frequent exacerbations outcome (data not shown).

Blood RNA-sequencing and proteomics

Using whole blood RNA-sequencing data we found that the majority of the expressed transcripts were significantly associated (false discovery rate < 0.05) with each of the three blood cell ratios: NLR 13,458 transcripts, PLR 13,380, SII 13,307 (Supplemental Tables 2– 4, Supplemental Fig. 2). A large number of plasma proteins were also significantly associated with each ratio, although these represented a lower fraction of the total proteins assayed: NLR, 1429 proteins; PLR, 1602; SII, 1807 (Supplemental Tables 5– 7, Supplemental Fig. 3). Pathway enrichment analysis of the top 300 genes in each analysis (ranked by adjusted p -value) was performed using several databases including Gene Ontology, KEGG, Reactome, and Hallmark gene sets (Table 7, Supplemental Tables 8–13). As positive controls, we employed pathways related to neutrophil degranulation (NLR and SII

Table 7 Selected results from pathway analysis of RNA-sequencing and proteomics data. Full results are available in Supplemental Tables 7–13

Pathway	RNA-sequencing			Proteomics		
	NLR	PLR	SII	NLR	PLR	SII
Complement		**	**	**	**	**
PI3K signaling			**	**		**
Apoptosis	**		**			
RhoGTPase	*	**	*			
Epithelial-mesenchymal transition				**	**	**
Collagen/extracellular matrix				**	**	**
IL6/JAK/STAT3 signaling	**		**	**		
IL2/STAT5 signaling			*			**
TNF-alpha signaling			**			
WNT signaling				**		
IL4/IL13 signaling			**	**		

*Bonferroni adjusted $p < 0.05$ ** Bonferroni adjusted $p < 0.001$. P -values are for pathway enrichment

RNA-seq and proteomics) and platelet activation (PLR RNA-seq and proteomics). In the RNA-seq analysis, there was enrichment across more than one cell ratio in several pathways, including apoptosis, Rho GTPase, complement, and IL6/JAK/STAT3 signaling. Similarly, in the proteomics data, there was enrichment across more than one ratio in pathways related to collagen and extracellular matrix, epithelial-mesenchymal transition, interleukin signaling, complement, and PI3K signaling. Thus, the latter two pathways appeared in both RNA-seq and proteomics analyses. Other inflammatory pathways relevant in COPD appeared in different enrichment sets, including signaling pathways such as TNF-alpha, WNT, and IL-2/STAT5. Interestingly, IL-4/IL-13 signaling, relevant for T2 inflammation, was enriched in the SII RNA-seq and NLR proteomics results. A number of targets for COPD therapies currently in human trials appeared in the enriched proteomics pathways, such as neutrophil elastase, alpha-1 antitrypsin, and IL1RL1 (ST2 protein) [28, 29].

Discussion

We examined three blood cell ratios – neutrophil–lymphocyte ratio, platelet–lymphocyte ratio, and systemic immune-inflammatory index – in a large study of current and former smokers with and without spirometry-defined COPD. We found that these ratios were either weakly negatively correlated or uncorrelated with blood eosinophil count, a currently used biomarker in COPD management. They were weakly associated with almost all COPD severity outcomes, including retrospective and prospective exacerbations, though it is not clear whether they add substantially to clinical risk factors for exacerbations. We did not find clear threshold levels which would be required for use as a clinical biomarker in COPD management. Using RNA-sequencing and proteomics obtained at the same blood draw, we showed that these

ratios were associated with multiple biologic pathways, including inflammatory pathways relevant for COPD.

The three ratios, especially the NLR, have been extensively studied in multiple chronic diseases in addition to COPD. Previous studies have demonstrated associations with COPD outcomes, including acute exacerbations. Studies of NLR and PLR have been reviewed elsewhere [12, 30, 31]. Despite the multiple studies, no clear consensus has emerged on an optimal cut-off which would be required to use a ratio as a clinical biomarker. Our study largely confirmed that higher levels of these biomarkers are associated with exacerbations and similarly did not find an optimal threshold value for any of the three ratios. We controlled for multiple clinical covariates including lung function, and found a statistically significant, but unlikely clinically relevant, improvement in discriminative ability in the ROC curve analyses. Even when adjusting for lung function, we AUROCs were higher in the entire cohort than in the subset with COPD. Prior studies in COPDGene have shown that current and former smokers without airflow obstruction may also experience respiratory exacerbations, [32] which may be related to systemic inflammation.

The SPIROMICS study, another large observational study of COPD in the US, has recently reported associations between NLR and outcomes in current and former smokers with and without COPD, as well as non-smokers [33]. They found stability in NLR values at 6 weeks and 1 year (intraclass correlations 0.74 and 0.62, respectively). Subjects with NLR in the highest quartile had increased odds of an exacerbation within the following year and higher mortality. They found no difference in mortality for quartiles 1–3, but did not examine these thresholds for associations with exacerbations, as we did. Similar to our study, the SPIROMICS analyses were adjusted for Duffy null phenotype.

Our study addressed three easily obtained blood cell ratios in a large sample with and without COPD, finding consistent results regardless of disease status. The novelty of our study is the assessment of two different omics data types, blood RNA-sequencing and proteomics, allowing us to determine the biological pathways that may be indicated by these biomarkers. Reassuringly, we found strong enrichment for neutrophil and platelet-related pathways. Several inflammatory pathways were found in one of the two omics datasets. Complement and phosphatidylinositol 3-kinase (PI3K) signaling were shared by more than one biomarker in each of the two omics data types.

Proteins in the complement pathway are known to be altered in COPD [34]. Proteomics analysis of blood and bronchoalveolar lavage fluid found enrichment for proteins in the complement pathway in subjects with rapid lung function decline [35, 36]. Markers of complement activation are elevated in sputum during COPD exacerbations [37]. Hypocomplementemic urticarial vasculitis, a rare small vessel vasculitis, has been associated with COPD [38]. Furthermore, components of cigarette smoke may cause dysregulation of the complement system [39].

PI3K signaling is involved in fundamental cellular processes such as growth and proliferation. Several PI3K inhibitors are FDA-approved for use in different types of cancer [40]. PI3K activation leads to secretion of inflammatory cytokines and generation of reactive oxygen species by several immune cell types in COPD, including neutrophils [41]. PI3K is a potential target for COPD therapies [42]. Nemiralisib, a PI3K delta inhibitor, has shown mixed results thus far regarding efficacy, though it appears to be safe [43].

Our study has several limitations. In COPDGene, CBC with differential were obtained starting at the Phase 2 (5-year) visit, not at the baseline visit. Despite this, we still have a large sample size with an average of 7 years follow-up time. Furthermore, the RNA-seq and proteomics data were collected concurrently at Phase 2. The blood cell ratios may not fully reflect lung inflammation; bronchoalveolar lavage or sputum samples would be required for comparison and were not included in COPDGene.

Conclusions

GOLD recommends measurement of blood eosinophil count as part of the initial assessment of a person with COPD [3]. The three ratios we analyzed can be derived from the same CBC with differential that is used to measure the blood eosinophil count. Currently, COPD patients are dichotomized into type 2 and non-type 2 inflammation subtypes using the blood eosinophil count. However, COPD is a heterogeneous condition, and it is likely that both pathways, and other inflammatory pathways, are active to varying degrees in individual patients. Further studies will be needed to determine how these

biomarkers can be used to determine response to existing anti-inflammatory therapies as well as novel therapies targeting other inflammatory mechanisms and how they relate to other measures of COPD progression such as lung function decline.

Abbreviations

AUROC	Area under the ROC curve
BODE	Body mass index, Obstruction, Dyspnea, Exercise Capacity
CBC	Complete blood count
CT	Computed tomography
FEV ₁	Forced expiratory volume in 1 s
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
LAA950	Low attenuation area at -950 Hounsfield Units
NLR	Neutrophil to lymphocyte ratio
Perc15	15 th percentile of lung density histogram
PI10	Square root wall area of hypothetical airway with 10 mm internal perimeter
PLR	Platelet to lymphocyte ratio
ROC	Receiver operating characteristic
SGRQ	St. George's Respiratory Questionnaire
SII	Systemic immune-inflammation index

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12931-026-03632-3>.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Acknowledgements

COPDGene® Investigators – Core Units

Administrative Center: James D. Crapo, MD (PI); Edwin K. Silverman, MD, PhD (PI); Barry J. Make, MD; Elizabeth A. Regan, MD, PhD Genetic Analysis Center: Terri H. Beaty, PhD; Peter J. Castaldi, MD, MSc; Michael H. Cho, MD, MPH; Dawn L. DeMeo, MD, MPH; Adel El Boueiz, MD, MMSc; Marilyn G. Foreman, MD, MS; Auyon Ghosh, MD; Lystra P. Hayden, MD, MMSc; Craig P. Hersh, MD, MPH; Jacqueline Hetmanski, MS; Brian D. Hobbs, MD, MMSc; John E. Hokanson, MPH, PhD; Wonji Kim, PhD; Nan Laird, PhD; Christoph Lange, PhD; Sharon M. Lutz, PhD; Merry-Lynn McDonald, PhD; Dmitry Prokopenko, PhD; Matthew Moll, MD, MPH; Jarrett Morrow, PhD; Dandi Qiao, PhD; Elizabeth A. Regan, MD, PhD; Aabida Saferali, PhD; Phuwanat Sakornsakolpat, MD; Edwin K. Silverman, MD, PhD; Emily S. Wan, MD; Jeong Yun, MD, MPH Imaging Center: Juan Pablo Centeno; Jean-Paul Charbonnier, PhD; Harvey O. Coxson, PhD; Craig J. Galban, PhD; Meilan K. Han, MD, MS; Eric A. Hoffman, Stephen Humphries, PhD; Francine L. Jacobson, MD, MPH; Philip F. Judy, PhD; Ella A. Kazerooni, MD; Alex Klueber; David A. Lynch, MB; Pietro Nardelli, PhD; John D. Newell, Jr., MD; Aleena Notary; Andrea Oh, MD; Elizabeth A. Regan, MD, PhD; James C. Ross, PhD; Raul San Jose Estepar, PhD; Joyce Schroeder, MD; Jered Sieren; Berend C. Stoel, PhD; Juerg Tschirren, PhD; Edwin Van Beek, MD, PhD; Bram van Ginneken, PhD; Eva van Rikxoort, PhD; Gonzalo Vegas Sanchez-Ferrero, PhD; Lucas Veitel; George R. Washko, MD; Carla G. Wilson, MS; PFT QA Center, Salt Lake City, UT: Robert Jensen, PhD Data Coordinating Center and Biostatistics, National Jewish Health, Denver, CO: Douglas Everett, PhD; Jim Crooks, PhD; Katherine Pratte, PhD; Matt Strand, PhD; Carla G. Wilson, MS Epidemiology Core, University of Colorado Anschutz Medical Campus, Aurora, CO: John E. Hokanson, MPH, PhD; Erin Austin, PhD; Gregory Kinney, MPH, PhD; Sharon M. Lutz, PhD; Kendra A. Young, PhD Mortality Adjudication Core: Surya P. Bhatt, MD; Jessica Bon, MD; Alejandro A. Diaz, MD, MPH; Meilan K. Han, MD, MS; Barry Make, MD; Susan Murray, ScD; Elizabeth Regan, MD; Xavier Soler, MD; Carla G. Wilson, MS Biomarker Core: Russell P. Bowler, MD, PhD; Katerina Kechris, PhD; Farnoush Banaei-Kashani, PhD
COPDGene® Investigators – Clinical Centers

Ann Arbor VA: Jeffrey L. Curtis, MD; Perry G. Pernicano, MD Baylor College of Medicine, Houston, TX: Nicola Hanania, MD, MS; Mustafa Atik, MD; Aladin Boriek, PhD; Kalpatha Guntupalli, MD; Elizabeth Guy, MD; Amit Parulekar, MD; Brigham and Women's Hospital, Boston, MA: Dawn L. DeMeo, MD, MPH; Craig Hersh, MD, MPH; Francine L. Jacobson, MD, MPH; George Washko, MD Columbia University, New York, NY: R. Graham Barr, MD, DrPH; John Austin, MD; Belinda D'Souza, MD; Byron Thomashow, MD Duke University Medical Center, Durham, NC: Neil MacIntyre, Jr., MD; H. Page McAdams, MD; Lacey Washington, MD HealthPartners Research Institute, Minneapolis, MN: Charlene McEvoy, MD, MPH; Joseph Tashjian, MD Johns Hopkins University, Baltimore, MD: Robert Wise, MD; Robert Brown, MD; Nadia N. Hansel, MD, MPH; Karen Horton, MD; Allison Lambert, MD, MHS; Nirupama Putcha, MD, MHS Lundquist Institute for Biomedical Innovation at Harbor UCLA Medical Center, Torrance, CA: Richard Casaburi, PhD, MD; Alessandra Adami, PhD; Matthew Budoff, MD; Hans Fischer, MD; Janos Porszaz, MD, PhD; Harry Rossiter, PhD; William Stringer, MD Michael E. DeBakey VAMC, Houston, TX: Amir Sharafkhan, MD, PhD; Charlie Lan, DO Minneapolis VA: Christine Wendt, MD; Brian Bell, MD; Ken M. Kunisaki, MD, MS Morehouse School of Medicine, Atlanta, GA: Eric L. Flanagan, MD; Hirut Gebrekristos, PhD; Mario Ponce, MD; Silanath Terpenning, MD; Gloria Westney, MD, MS National Jewish Health, Denver, CO: Russell Bowler, MD, PhD; David A. Lynch, MB Reliant Medical Group, Worcester, MA: Richard Rosiello, MD; David Pace, MD Temple University, Philadelphia, PA: Gerard Criner, MD; David Ciccolella, MD; Francis Cordova, MD; Chandra Dass, MD; Gilbert D'Alonzo, DO; Parag Desai, MD; Michael Jacobs, PharmD; Steven Kelsen, MD, PhD; Victor Kim, MD; A. James Mamary, MD; Nathaniel Marchetti, DO; Aditi Satti, MD; Kartik Shenoy, MD; Robert M. Steiner, MD; Alex Swift, MD; Irene Swift, MD; Maria Elena Vega-Sanchez, MD University of Alabama, Birmingham, AL: Mark Dransfield, MD; William Bailey, MD; Surya P. Bhatt, MD; Anand Iyer, MD; Hrudaya Nath, MD; J. Michael Wells, MD University of California, San Diego, CA: Douglas Conrad, MD; Xavier Soler, MD, PhD; Andrew Yen, MD University of Iowa, Iowa City, IA: Alejandro P. Comellas, MD; Karin F. Hoth, PhD; John Newell, Jr., MD; Brad Thompson, MD University of Michigan, Ann Arbor, MI: Meilan K. Han, MD MS; Ella Kazerooni, MD MS; Wassim Labaki, MD MS; Craig Galban, PhD; Dharshan Vummidi, MD University of Minnesota, Minneapolis, MN: Joanne Billings, MD; Abbie Begnaud, MD; Tadashi Allen, MD University of Pittsburgh, Pittsburgh, PA: Frank Sciruba, MD; Jessica Bon, MD; Divay Chandra, MD, MSc; Joel Weissfeld, MD, MPH University of Texas Health, San Antonio, San Antonio, TX: Antonio Anzueto, MD; Sandra Adams, MD; Diego Maselli-Caceres, MD; Mario E. Ruiz, MD; Harjinder Singh

Artificial intelligence declaration

During the preparation of this work the authors used Microsoft Copilot to write an initial draft of the Results section. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Authors' contributions

Concept and design: KS, JLC, CPH Data collection: PJC, RPB, CPH Data analysis: KS Statistical support: AS, JHY, MHR, LR Manuscript writing and editing: KS, AS, JHY, MHR, ES, PJC, LR, PRB, JLC, CPH Funding: CPH, RPB.

Funding

NIH grants R01HL166231 and K24HL173667 (CPH). COPDGene was supported by NHLBI grants U01HL089897 and U01HL089856 and by NIH contract 75N92023D00011. Proteomics data generation was supported by R01HL137995. The COPDGene study (NCT00608764) has also been supported by the COPD Foundation through contributions made to an Industry Advisory Committee that has included AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Novartis, Pfizer, and Sunovion.

Data availability

COPDGene data are available on the NCBI's Database of Genotypes and Phenotypes (dbGaP), accessions phs000179, phs000765, phs000951.

Declarations

Ethics approval and consent to participate

COPDGene was approved by the Institutional Review Board at Mass General Brigham and all participating centers. The research was conducted in accordance with the Belmont Report.

Consent for publication

Not applicable.

Competing interests

JHY reports consulting fees from Bridge BioTherapeutics and serving on an Advisory Board for Genentech. PJC reports grants from Sanofi and Bayer, and consulting fees from Verona Pharma and Genentech. JLC reports grants from the COPD Foundation, consulting fees from AstraZeneca and participation on Data Safety Monitoring Board or Advisory Board for Novartis and Genentech. CPH reports grants from the Alpha-1 Foundation and Bayer, and consulting fees from Apogee Therapeutics, AstraZeneca, Chiesi, Genentech, Ono Pharma, Sanofi, Takeda, and Verona Pharma. None of the other authors report any conflicts of interest.

Author details

¹Channing Division of Network Medicine, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, USA

²Division of Respiratory Medicine, University of British Columbia, Vancouver, BC, Canada

³Sapienza University of Rome, Rome, Italy

⁴Department of Systems Biology and Genome Sciences, Cleveland Clinic, Cleveland, OH, USA

⁵Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA

Received: 12 January 2026 / Accepted: 12 March 2026

Published online: 18 March 2026

References

1. Barnes PJ. Cellular and molecular mechanisms of asthma and COPD. *Clin Sci*. 2017;131(13):1541–58.
2. Brightling CE, Bafadhel M, Han MK, Papon JF, Rabe KF, Rogliani P, et al. A translational view of airway epithelial dysfunction in COPD. *Eur Respir Rev Off J Eur Respir Soc*. 2025;34(178):250110.
3. Agusti A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, et al. Global initiative for chronic obstructive lung disease 2023 report: GOLD executive summary. *Am J Respir Crit Care Med*. 2023;207(7):819–37.
4. Yun JH, Lamb A, Chase R, Singh D, Parker MM, Saferali A, et al. Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol*. 2018;141(6):2037–2047 e10.
5. Bafadhel M, Peterson S, De Blas MA, Calverley PM, Rennard SI, Richter K, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med*. 2018;6(2):117–26.
6. Sciruba FC, Criner GJ, Christenson SA, Martinez FJ, Papi A, Roche N, et al. Mepolizumab to prevent exacerbations of COPD with an eosinophilic phenotype. *N Engl J Med*. 2025;392(17):1710–20.
7. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M, et al. Dupilumab for COPD with Type 2 inflammation indicated by eosinophil counts. *N Engl J Med*. 2023;389(3):205–14.
8. Hersh CP, Zacharia S, Prakash Arivu Chelvan R, Hayden LP, Mirtar A, Zarei S, et al. Immunoglobulin E as a biomarker for the overlap of atopic asthma and chronic obstructive pulmonary disease. *Chronic Obstr Pulm Dis*. 2020;7(1):1–12.
9. Oishi K, Matsunaga K, Shirai T, Hirai K, Gon Y. Role of Type2 inflammatory biomarkers in chronic obstructive pulmonary disease. *J Clin Med*. 2020;9(8):2670.
10. Halper-Stromberg E, Yun JH, Parker MM, Singer RT, Gaggar A, Silverman EK, et al. Systemic markers of adaptive and innate immunity are associated with chronic obstructive pulmonary disease severity and spirometric disease progression. *Am J Respir Cell Mol Biol*. 2018;58(4):500–9.
11. Fawzy A, Putcha N, Paulin LM, Aaron CP, Labaki WW, Han MK, et al. Association of thrombocytosis with COPD morbidity: the SPIROMICS and COPDGene cohorts. *Respir Res*. 2018;19(1):20.
12. Zinellu A, Zinellu E, Mangoni AA, Pau MC, Carru C, Pirina P, et al. Clinical significance of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in acute exacerbations of COPD: present and future. *Eur Respir Rev*. 2022. <https://doi.org/10.1183/16000617.0095-2022>.

13. Fang L, Zhu J, Fu D. Predictive value of neutrophil-lymphocyte ratio for all-cause mortality in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *BMC Pulm Med*. 2025;25(1):206.
14. El-Gazzar AG, Kamel MH, Elbahnasy OKM, El-Naggar MES. Prognostic value of platelet and neutrophil to lymphocyte ratio in COPD patients. *Expert Rev Respir Med*. 2020;14(1):111–6.
15. Fu Y, Wang Y, Wang Y, Mou T, He X, Wang J, et al. Biomarkers (NLR, PLR, SII) for frequent COPD exacerbations: diagnostic and clinical management implications in a retrospective study. *Int J Chron Obstruct Pulmon Dis*. 2025;20:987–98.
16. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, et al. Genetic epidemiology of COPD (COPDGene) study design. *COPD: J Chron Obstruct Pulmon Dis*. 2010;7(1):32–43.
17. Stewart JI, Moyle S, Criner GJ, Wilson C, Tanner R, Bowler RP, et al. Automated telecommunication to obtain longitudinal follow-up in a multicenter cross-sectional COPD study. *COPD*. 2012;9(5):466–72.
18. Ryu MH, Yun JH, Morrow JD, Saferali A, Castaldi P, Chase R, et al. Blood gene expression and immune cell subtypes associated with chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med*. 2023;208(3):247–55.
19. Serban KA, Pratte KA, Strange C, Sandhaus RA, Turner AM, Beiko T, et al. Unique and shared systemic biomarkers for emphysema in Alpha-1 Antitrypsin deficiency and chronic obstructive pulmonary disease. *eBioMedicine*. 2022;84:104262.
20. Taliun D, Harris DN, Kessler MD, Carlson J, Szpiech ZA, Torres R, et al. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. *Nature*. 2021;590(7845):290–9.
21. Reich D, Nalls MA, Kao WHL, Akyzbekova EL, Tandon A, Patterson N, et al. Reduced neutrophil count in people of african descent is due to a regulatory variant in the duffy antigen receptor for chemokines gene. *Visscher PM, editor. PLoS Genet*. 2009;5(1):e1000360.
22. Merz LE, Osei MA, Story CM, Freedman RY, Smeland-Wagman R, Kaufman RM, et al. Development of Duffy Null-specific absolute neutrophil count reference ranges. *JAMA*. 2023;329(23):2088–9.
23. Liberzon A, Subramanian A, Pinchback R, Thorvaldsdottir H, Tamayo P, Mesirov JP. Molecular signatures database (MSigDB) 3.0. *Bioinformatics*. 2011;27(12):1739–40.
24. Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res*. 2000;28(1):27–30.
25. Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, et al. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium Nat Genet. 2000;25(1):25–9.
26. Croft D, O’Kelly G, Wu G, Haw R, Gillespie M, Matthews L, et al. Reactome: a database of reactions, pathways and biological processes. *Nucleic Acids Res*. 2011;39(Database issue):D691–7.
27. Wan ES, Castaldi PJ, Cho MH, Hokanson JE, Regan EA, Make BJ, et al. Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry (PRISm) in COPDGene. *Respir Res*. 2014;15(1):89.
28. De Soyza J, Pye A, Turner AM. Are clinical trials into emerging drugs for the treatment of alpha-1 antitrypsin deficiency providing promising results? *Expert Opin Emerg Drugs*. 2023;28(4):227–31.
29. Yousuf AJ, Mohammed S, Carr L, Yavari Ramsheh M, Micieli C, Mistry V, et al. Astegolimab, an anti-ST2, in chronic obstructive pulmonary disease (COPD-ST2OP): a phase 2a, placebo-controlled trial. *Lancet Respir Med*. 2022;10(5):469–77.
30. Paliogiannis P, Fois AG, Sotgia S, Mangoni AA, Zinellu E, Pirina P, et al. Neutrophil to lymphocyte ratio and clinical outcomes in COPD: recent evidence and future perspectives. *Eur Respir Rev*. 2018. <https://doi.org/10.1183/16000617.0113-2017>.
31. Zinellu A, Paliogiannis P, Sotgia E, Mellino S, Fois AG, Carru C, et al. Platelet count and platelet indices in patients with stable and acute exacerbation of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *COPD: J Chron Obstruct Pulmon Dis*. 2021;18(2):231–45.
32. Bowler RP, Kim V, Regan E, Williams A, Santorico SA, Make BJ, et al. Prediction of acute respiratory disease in current and former smokers with and without COPD. *Chest*. 2014;146(4):941–50.
33. Hoesterey DT, Dang H, Markovic D, Buhr RG, Tashkin DP, Barr RG, et al. Neutrophil-to-Lymphocyte Ratio (NLR) as a Biomarker in clinically stable chronic obstructive pulmonary disease: SPIROMICS cohort. *Ann Am Thorac Soc*. 2025;[online ahead of print].
34. Miller RD, Kueppers F, Offord KP. Serum concentrations of C3 and C4 of the complement system in patients with chronic obstructive pulmonary disease. *J Lab Clin Med*. 1980;95(2):266–71.
35. DiLillo KM, Norman KC, Freeman CM, Christenson SA, Alexis NE, Anderson WH, et al. A blood and bronchoalveolar lavage protein signature of rapid FEV1 decline in smoking-associated COPD. *Sci Rep*. 2023;13(1):8228.
36. DiLillo KM, Ruvuna L, Pratte KA, Serban KA, Labaki WW, Han MK, et al. Validation of systemic complement signatures in the progression of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2024;210(10):1269–72.
37. Westwood JP, Mackay AJ, Donaldson G, Machin SJ, Wedzicha JA, Scully M. The role of complement activation in COPD exacerbation recovery. *ERJ Open Res*. 2016;2(4):00027–2016.
38. David C, Jachiet M, Pineton De Chambrun M, Gamez AS, Mehdaoui A, Zenone T, et al. Chronic obstructive pulmonary disease associated with hypocomplementemic urticarial vasculitis. *J Allergy Clin Immunol Pract*. 2020;8(9):3222–3224.e1.
39. Alarabi AB, Alshbool FZ, Khasawneh FT. Impact of smoking on the complement system: a narrative review. *Front Immunol*. 2025;16:1619835.
40. Yu M, Chen J, Xu Z, Yang B, He Q, Luo P, et al. Development and safety of PI3K inhibitors in cancer. *Arch Toxicol*. 2023;97(3):635–50.
41. Liu Y, Kong H, Cai H, Chen G, Chen H, Ruan W. Progression of the PI3K/Akt signaling pathway in chronic obstructive pulmonary disease. *Front Pharmacol*. 2023. <https://doi.org/10.3389/fphar.2023.1238782>.
42. Fagone E, Fruciano M, Gili E, Sambataro G, Vancheri C. Developing PI3K Inhibitors for Respiratory Diseases. In: Dominguez-Villar M, editor. *PI3K and AKT Isoforms in Immunity: Mechanisms and Therapeutic Opportunities*. Cham: Springer International Publishing; 2022. p. 437–66.
43. Yang H, He S, Liang L, Pan J. Efficacy of nemiralisib in chronic obstructive pulmonary disease: a systematic review. *Clin Ther*. 2024;46(4):360–7.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.