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ORIGINAL RESEARCH

Predictive Role of White Blood Cell Differential Count for the Development of Acute Exacerbation in Korean Chronic Obstructive Pulmonary Disease

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Purpose: Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterized by chronic inflammation. Acute exacerbation of COPD (AECOPD) manifests as acute worsening of respiratory symptoms and is associated with high morbidity and mortality. The aim of the present study was to evaluate the predictive value of white blood count (WBC) and its derived inflammatory biomarkers for AECOPD.

Methods: From the Korean COPD Subgroup Study cohort, a prospective and multicenter observational study, 826 patients who had baseline complete blood count (CBC) and 3-year AECOPD data were included. Follow-up CBC data at 1 (n = 385), 2 (n = 294), and 3 (n = 231) years were collected for available patients. The primary outcome was the occurrence of AECOPD at 3 years. The risk of AECOPD was evaluated using a binary logistic analysis.

Results: The cumulative incidences of 12-, 24-, and 36-month AECOPD were 47.6%, 60.5%, and 67.6%, respectively. Patients with AECOPD at 3 years had higher baseline WBC counts, neutrophil counts, neutrophil/lymphocyte ratio (NLR), and neutrophil/monocyte ratio than those without AECOPD. Higher WBC count, neutrophil count, and NLR were associated with the 3-year occurrence of AECOPD in the univariate analysis, but only the higher neutrophil count was a significant risk factor (odds ratio [OR] = 1.468; 95% confidence interval [CI]: 1.024–2.104) in the covariates-adjusted analysis. In the analysis of changes in inflammatory parameters, a decrease in the platelet count (OR = 0.502; 95% CI: 0.280–0.902) and NLR (OR = 0.535; 95% CI: 0.294–0.974) at 2 years and an increase in the eosinophil count (OR = 2.130; 95% CI: 1.027–4.416) at 3 years were significantly associated with AECOPD in the adjusted analysis.

Conclusion: Our data suggest that a high baseline WBC count, particularly neutrophil count, was associated with a higher incidence of long-term AECOPD.

Keywords: blood cell count, blood platelets, eosinophils, lymphocytes, neutrophils, pulmonary disease, chronic obstructive

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent, often progressive airflow obstruction and tissue destruction.[1] It is a leading cause of death and disability worldwide, estimated to affect nearly 400 million people globally.[2] Long-term exposure to tobacco smoke is the most significant risk factor of COPD, and air pollution, genetic factors, and respiratory infections can also contribute to the development of COPD.[2,3] Acute exacerbation of COPD

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(AECOPD) manifests as sudden worsening of COPD symptoms, including dyspnea, coughing, and sputum production. Various factors, including respiratory infections, air pollution, and exposure to allergens, can trigger AECOPD.[4,5] The prognosis of AECOPD depends on the severity of the exacerbation and the patient's comorbidities. AECOPD can be severe and associated with significant morbidity and mortality, particularly in patients with more impaired lung function or multiple comorbidities, such as cardiovascular disease or diabetes.[6,7] Therefore, identifying predictive markers to screen high-risk populations is important.

Systemic inflammation causes the progression or worsens the outcomes of COPD.[8] The complete blood count (CBC) can measure various components of inflammation, including the white blood cell (WBC) count, to assess the presence and severity of systemic inflammation. In patients with COPD, WBC may show increased/decreased neutrophil and monocyte counts, depending on the stage and severity of COPD.[9,10] Additionally, the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio, and monocyte/lymphocyte ratio (MLR) are composite inflammatory biomarkers that can be calculated using values obtained from CBC. These WBC-related biomarkers reflect the overall inflammation status of the body and are associated with the severity and prognosis of COPD.[11–19] However, the association between the long-term prognosis, particularly the risk of AECOPD, and WBC differential count and WBC-derived inflammatory markers is poorly understood. Therefore, the aim of the present study was to evaluate the predictive value of WBC differential count and WBC-derived inflammatory biomarkers for the long-term occurrence of AECOPD in Korean patients with COPD.

Materials and Methods

Study Population

We screened 3478 patients with COPD registered in the Korean COPD Subtype Study (KOCOSS) cohort from 2012 to 2017 (Figure 1). The KOCOSS cohort is a prospective, multicenter observational cohort consisting of patients with COPD from 52 participating referral centers across Korea.[20]

Inclusion criteria of KOCOSS were: 1) Korean adults with COPD over 40 years of age; and 2) a ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC) < 0.7 after bronchodilator use. After excluding patients without baseline CBC data (n = 478) and those without 3-year follow-up data for the occurrence of AECOPD (n = 2174), we included 826 patients with COPD.

Ethics

This study was conducted in accordance with the Declaration of Helsinki. All patients provided informed consent for the use of clinical data. Ethics approval was obtained from all medical institutions, including the Institutional Review Board of the Soonchunhyang University Seoul Hospital (2022-03-019).

Clinical Data Collection

At the time of enrollment, baseline data were collected from a self-reported questionnaire, including demographics, smoking status, body mass index (BMI), comorbidities including history of asthma, chronic respiratory symptoms such

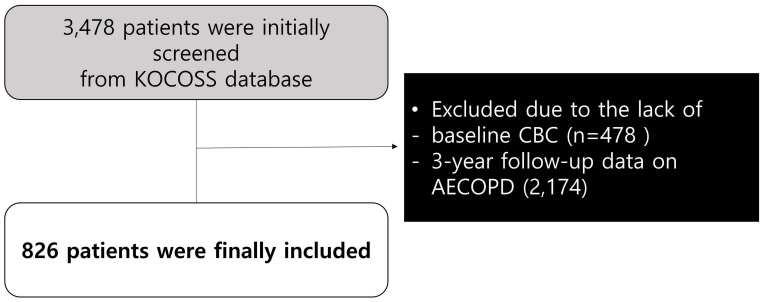

Figure 1 Enrollment of patients. This figure showed the flowchart of patient enrollment in the study. A total of 3478 patients with COPD were screened for eligibility, and 826 patients were included in the final analysis after exclusion criteria were applied.
Abbreviations: KOCOSS, Korean COPD Subtype Study; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CBC, complete blood count.

as cough or sputum lasting over 3 months, and previous history of exacerbations during the 1 year before enrollment. An abnormal finding on the baseline chest X-ray was reviewed. In addition, our study assessed all respiratory medications, including inhalers, using multiple selection at the time of registration.

To measure the quality of life in patients with COPD, St. George's respiratory questionnaire (SGRQ), symptom scores from the COPD assessment test (CAT) and modified Medical Research Council (mMRC) dyspnea grade were obtained. Spirometry and body plethysmography were performed based on the European Respiratory Society (ERS)/American Thoracic Society (ATS) guideline.[21,22] Diffusing capacity for carbon monoxide (DLco) was also measured using the single-breath method following the ERS/ATS guideline.[23] The predicted percentage values were calculated using an equation developed for the Korean population.[24,25] According to the 2023 Global Initiative for Chronic Obstructive Lung Disease guidelines (GOLD),[1] patients were classified based on FEV_1: GOLD 1, $FEV_1 \geq 80\%$ predicted; GOLD 2, $FEV_1 \geq 50\%$ and $< 80\%$ predicted; GOLD 3, $FEV_1 \geq 30\%$ and $< 50\%$ predicted; and GOLD 4, $FEV_1 < 30\%$ predicted. A six-minute walk test (6MWT) was performed based on the ATS guidelines.[26] Over 3 years, prospective clinical data were collected using a study design that followed-up participants at regular intervals of 1 year.

WBC Differential Count and Derived Parameters

At each participating center, the total WBC, neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts were measured at the time of enrollment, with the majority of participants in a stable condition. Using the initial CBC test, the following WBC-derived composite parameters were calculated: NLR, derived neutrophil/lymphocyte ratio (dNLR, calculated as the absolute neutrophil count/WBC – absolute neutrophil count), neutrophil/monocyte ratio, platelet/lymphocyte ratio, MLR, and eosinophil/basophil ratio (EBR).

For patients with available follow-up CBC data at 1 (n = 385), 2 (n = 294), and 3 (n = 231) years, changes in WBC differential parameters were determined by calculating differences between baseline and follow-up CBC values for each patient.

Clinical Outcomes

The study protocol was designed to track the incidence and frequency of moderate to severe exacerbations over a 3-year period, starting from the time of enrollment. The occurrence of AECOPD was documented through self-reporting questionnaires and medical chart reviews conducted at yearly intervals. A moderate AECOPD was defined as a deterioration in symptoms, such as increased sputum production or worsened breathlessness, resulting in the administration of antibiotics or steroids during outpatient visits. A severe AECOPD, on the other hand, was characterized by a significant exacerbation of respiratory symptoms necessitating urgent medical attention or hospitalization. The primary outcome was the occurrence of AECOPD at 3 years, and the secondary outcome was the cumulative occurrence of AECOPD over the 3-year period.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range), while categorical variables are expressed as frequency (percentage). Since WBC derived parameters were skewed, they were log-transformed before analyses and treated as continuous variables. The inflammatory markers were analyzed as categorical variables by dividing them into higher and lower groups based on the median values. To analyze serial changes in inflammatory parameters, we categorized parameters that remained stable or increased during the follow-up compared to baseline as "increased" and used them in the analyses.

To compare the two groups, Student's *t*-test or Mann–Whitney *U*-test were used for continuous variables and chi-square test or Fisher's exact test for categorical variables. The cumulative incidence of AECOPD during the follow-up was estimated by using the Kaplan–Meier method. The binary logistic analysis was used to identify the risk factors of 3-year cumulative AECOPD, presented as odds ratio (OR) with 95% confidence interval (CI). The univariate and covariates-adjusted multivariable analyses (age, sex, smoking status, BMI, previous AECOPD history, FEV_1, FVC, CAT total score, use of a long-acting muscarinic antagonist [LAMA], inhaled corticosteroid/long-acting beta-agonist

combination [ICS/LABA]) were performed. Statistical analyses were conducted using SPSS software version 23.0 (IBM, Armonk, NY, USA). A p-value < 0.05 was considered to indicate statistical significance.

Results

Comparison of Clinical Parameters Between the AE and Non-AE Patients

We enrolled 826 patients, including 758 (91.8%) men and 68 (8.2%) women, with a mean age of 68.6 years. Of all patients, 90.9% were ever-smokers (Table 1). The most common comorbidity was asthma (36.9%), followed by hypertension (36.6%) and a history of tuberculosis (27.9%). Over the 3-year follow-up, 558 patients experienced moderate to severe AECOPD, with cumulative incidence rates of 47.6% at 12 months, 60.5% at 24 months, and 67.6% at 36 months (Figure 2a). The cumulative incidences of moderate AECOPD at 12, 24, and 36 months were 47.7%, 56.5%, and 63.2%, respectively (Figure 2b), while those of severe AECOPD were 13.1%, 20.2%, and 26.6%, respectively (Figure 2c).

Patients with AECOPD at 3 years had a higher rate of osteoporosis, chronic cough and sputum, emphysema on chest X-ray and previous history of AE in the past year than those without (Table 1). In addition, patients with AECOPD had

Table 1 Comparison of Baseline Characteristics Between Patients with and without 3-Year AECOPD

Variables	AE	Non-AE	Total	*p*-value
No.	328	498	826	
Age (years)	69.1 ± 7.4	68.3 ± 7.6	68.6 ± 7.6	0.107
Men	297 (90.5%)	461 (92.6%)	758 (91.8%)	0.366
Ever-smokers	295 (89.9%)	454 (91.2%)	749 (90.9%)	0.638
Smoking pack-years	40.0 ± 28.9	40.7 ± 25.7	40.4 ± 27.0	0.745
BMI (kg/m^2)	22.7 ± 3.4	23.0 ± 3.4	22.9 ± 3.4	0.282
Comorbidities				
Asthma	127 (39.2%)	175 (35.4%)	302 (36.9%)	0.298
Hypertension	122 (37.2%)	180 (36.1%)	302 (36.6%)	0.816
Tuberculosis	92 (28.4%)	137 (27.6%)	229 (27.9%)	0.871
Diabetes mellitus	66 (20.2%)	97 (19.5%)	163 (19.8%)	0.873
GERD	38 (11.7%)	42 (8.5%)	80 (9.7%)	0.162
Allergic rhinitis	43 (13.2%)	43 (8.7%)	86 (10.5%)	0.050
Hyperlipidemia	37 (11.5%)	57 (11.4%)	94 (11.4%)	1.000
Osteoporosis	27 (8.3%)	23 (4.6%)	50 (6.1%)	0.048
Atopic dermatitis	12 (3.7%)	16 (3.2%)	28 (3.4%)	0.870
Dementia	10 (3.1%)	11 (2.2%)	21 (2.6%)	0.592
Peripheral vascular disease	9 (2.8%)	6 (1.2%)	15 (1.8%)	0.177
Cerebrovascular attack	2 (2.4%)	6 (3.2%)	8 (2.9%)	1.000
Thyroid disease	9 (2.8%)	10 (2.0%)	19 (2.3%)	0.647
Liver disease	1 (1.2%)	2 (1.1%)	3 (1.1%)	1.000

(*Continued*)

Table 1 (Continued).

Variables	AE	Non-AE	Total	*p*-value
Chronic respiratory symptoms (≥3 months)				
Cough	94 (28.7%)	105 (21.2%)	199 (24.2%)	0.018
Duration, median [IQR]	5.0 [1.5–10.0]	4.0 [2.0–10.0]	5.0 [2.0–10.0]	0.834
Sputum	116 (35.4%)	138 (27.8%)	254 (30.8%)	0.027
Duration, median [IQR]	4.5 [1.5–10.0]	3.0 [2.0–10.0]	3.0 [2.0–10.0]	0.358
Chest X-ray				
Normal	109 (40.8%)	181 (48.5%)	290 (45.3%)	0.064
TB-destroyed lung	16 (6.0%)	30 (8.0%)	46 (7.2%)	0.404
Emphysema	113 (42.3%)	115 (30.8%)	228 (35.6%)	0.004
Fibrosis	4 (2.2%)	3 (1.1%)	7 (1.5%)	0.553
Bronchiectasis	18 (6.7%)	30 (8.0%)	48 (7.5%)	0.643
Previous AE history over the past year	99 (30.3%)	100 (20.4%)	199 (24.4%)	0.002

Note: Data are expressed as mean ± standard deviation or number (%), unless otherwise indicated.
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AE, acute exacerbation; BMI, body mass index; GERD, gastroesophageal reflux disease; IQR, interquartile range; TB, tuberculosis.

impaired lung function, with lower pre- and post-bronchodilator FEV_1, FVC and lower DLco than those without AECOPD. Patients with AECOPD also had lower distance in 6MWT, higher CAT total score, SGRQ score, and mMRC grade than those without AECOPD (Table 2). Patients with AECOPD were more likely to be treated with inhalers, including LAMA monotherapy, ICS/LABA, ICS/LABA/LAMA, and methylxanthine, than those without AECOPD (Table 3).

Patients with AECOPD had higher WBC count, neutrophil counts and NLR than those without AECOPD. Conversely, hemoglobin levels were lower in patients with AECOPD than in those without AECOPD (Table 4).

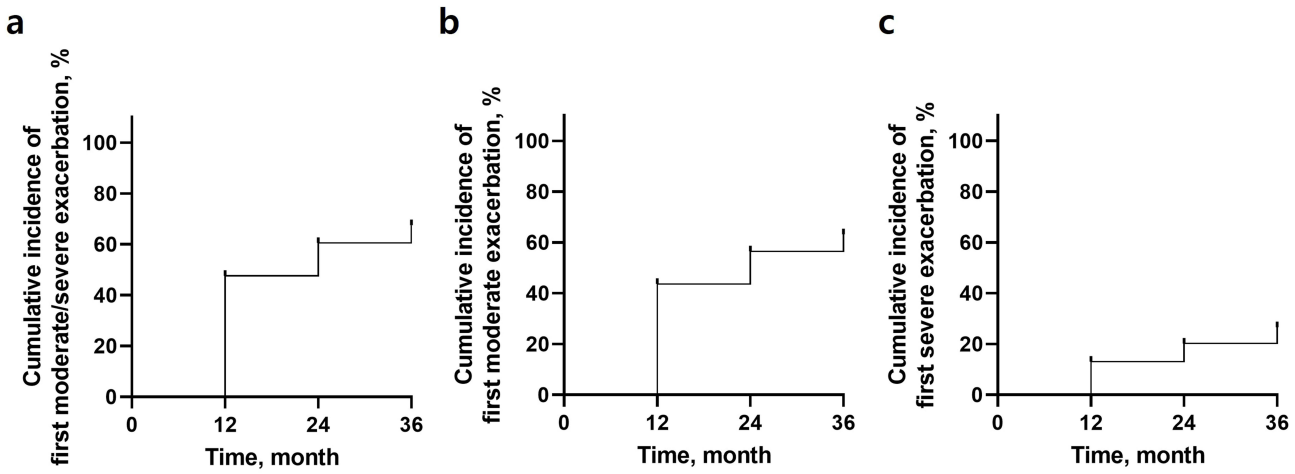

Figure 2 Kaplan–Meier curve for the time of onset of AECOPD by severity. (**a**) Moderate to severe, (**b**) moderate and (**c**) severe.
Abbreviation: AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

Table 2 Comparison of Lung Function, Exercise Capacity, Life Quality Between Patients with and without 3-Year AECOPD

Variables	AE	Non-AE	Total	*p*-value
No.	328	498	826	
Pre-BD FEV_1, % predicted	48.3 ± 16.1	55.2 ± 16.6	52.5 ± 16.8	< 0.001
Pre-BD FVC, % predicted	72.5 ± 16.1	77.3 ± 16.4	75.4 ± 16.4	< 0.001
Post-BD FEV_1, % predicted	50.8 ± 16.1	58.0 ± 16.8	55.1 ± 16.9	< 0.001
Post-BD FVC, % predicted	75.5 ± 16.0	79.5 ± 16.0	77.9 ± 16.1	< 0.001
DLco, % predicted (n=673)	61.0 ± 20.3	66.0 ± 21.6	64.1 ± 21.2	0.003
TLC, % predicted (n=526)	101.5 ± 19.2	102.2 ± 25.5	101.9 ± 23.1	0.752
IC, % predicted	73.6 ± 27.8	76.1 ± 23.1	75.1 ± 25.2	0.294
RV/TLC, % predicted	40.8 ± 3.0	40.4 ± 3.0	40.6 ± 3.0	0.162
GOLD				<0.001
1	39 (11.9%)	144 (29.3%)	182 (22.3%)	
2	239 (73.1%)	303 (61.7%)	542 (66.3%)	
3	4 (1.2%)	6 (1.2%)	10 (1.2%)	
4	45 (13.8%)	38 (7.7%)	83 (10.2%)	
mMRC grade				<0.001
0	21 (6.4%)	62 (12.5%)	83 (10.1%)	
1	136 (41.7%)	289 (58.1%)	425 (51.6%)	
2	108 (33.1%)	105 (21.1%)	213 (25.9%)	
3	55 (16.9%)	38 (7.6%)	93 (11.3%)	
4	6 (1.8%)	3 (0.6%)	9 (1.1%)	
Total CAT score	17.9 ± 7.7	14.0 ± 7.6	15.6 ± 7.9	< 0.001
Cough	2.1 ±1.4	1.7 ±1.4	1.9 ±1.4	<0.001
Phlegm	2.4 ± 1.4	2.0 ±1.4	2.2 ±1.4	<0.001
Chest tightness	1.9 ±1.4	1.5 ±1.4	1.6 ±1.4	<0.001
Breathlessness	3.7 ±1.2	3.2 ±1.4	3.4 ±1.4	<0.001
Activities	1.9 ±1.5	1.2 ±1.4	1.5 ±1.5	<0.001
Confidence	1.7 ±1.5	1.1 ±1.4	1.4 ±1.5	<0.001
Sleep	1.7 ±1.5	1.2 ±1.4	1.4 ±1.5	<0.001
Energy	2.6 ±1.2	2.2 ±1.3	2.3 ±1.3	<0.001
SGRQ Total	43.5 ± 22.0	30.8 ± 19.6	35.9 ± 21.5	< 0.001
SGRQ Symptoms	51.0 ± 20.8	40.9 ± 19.9	44.9 ± 20.8	< 0.001

(*Continued*)

Table 2 (Continued).

Variables	AE	Non-AE	Total	*p*-value
SGRQ Activity	55.8 ± 27.3	40.0 ± 25.5	46.2 ± 27.3	< 0.001
SGRQ Impacts	33.4 ± 23.7	22.1 ± 21.0	26.6 ± 22.8	< 0.001
Six-minute walk test (Distance)	356.6 ± 109.3	382.7 ± 116.7	372.2 ± 114.4	0.004

Note: Data are expressed as mean ± standard deviation or number (%), unless otherwise indicated.
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AE, acute exacerbation; BD, bronchodilator; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; TLC, total lung capacity; IC, inspiratory capacity; RV, residual volume; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; SGRQ, St. George's Respiratory Questionnaire.

Table 3 Comparison of the Treatment Status Between Patients with and without 3-Year AECOPD

Variables	AE	Non-AE	Total	*p*-value
No.	328	498	826	
Treatment	300 (91.5%)	434 (87.2%)	734 (88.9%)	0.069
Inhalers	284 (86.6%)	409 (82.1%)	693 (83.9%)	0.108
ICS	0 (0.0%)	1 (0.2%)	1 (0.1%)	1.000
LABA	45 (15.0%)	86 (19.8%)	131 (17.8%)	0.115
LAMA	223 (74.3%)	265 (61.1%)	488 (66.5%)	< 0.001
LABA/LAMA	3 (1.0%)	31 (7.1%)	34 (4.6%)	< 0.001
ICS/LABA	174 (58.0%)	169 (38.9%)	343 (46.7%)	< 0.001
ICS/LABA/LAMA	133 (44.3%)	100 (23.0%)	233 (31.7%)	< 0.001
PDE4 Inhibitor	15 (5.0%)	16 (3.7%)	31 (4.2%)	0.495
Methylxanthine	130 (43.3%)	145 (33.4%)	275 (37.5%)	0.008
Erdosteine	1 (0.3%)	2 (0.5%)	3 (0.4%)	1.000
Acetylcysteine	1 (0.3%)	0 (0.0%)	1 (0.1%)	0.853
Macrolide	1 (0.3%)	0 (0.0%)	1 (0.1%)	0.853
LTRA	23 (7.7%)	20 (4.6%)	43 (5.9%)	0.115

Note: Data are expressed as number (%), unless otherwise indicated.
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AE, acute exacerbation; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; PDE4 inhibitor, phosphodiesterase-4 inhibitor; LTRA, leukotriene receptor antagonist.

Baseline Risk Factors for 3-Year AECOPD

The univariate analysis revealed that both continuous and high WBC and neutrophil counts and continuous NLR were associated with the development of AECOPD at the 3-year follow-up (Table 5). However, in the covariate-adjusted multivariable models, only a higher neutrophil count was associated with the occurrence of AECOPD in patients with COPD (OR = 1.468; 95% CI: 1.024–2.104; $p = 0.036$).

The univariate analysis showed that both continuous and higher WBC and neutrophil counts, NLR, dNLR, and continuous MLR were associated with the 3-year cumulative AECOPD (Supplementary Table 1). However, in

Table 4 Comparison of Laboratory Findings Between Patients with and without 3-Year AECOPD

Variables	AE	Non-AE	Total	*p*-value
No.	328	498	826	
Total WBC, /mm^3	7400.0 [6200.0–9200.0]	7100.0 [6000.0–8600.0]	7200.0 [6100.0–8800.0]	0.006
Neutrophil, /mm^3	4416.1 [3568.2–5961.3]	4022.4 [3181.5–5313.2]	4159.5 [3274.8–5556.6]	0.001
Lymphocyte, /mm^3	1923.8 [1506.9–2483.9]	1961.3 [1474.0–2504.3]	1947.1 [1480.7–2504.0]	0.871
Monocyte, /mm^3	510.5 [411.2–661.9]	504.0 [396.0–646.8]	507.4 [401.2–655.7]	0.309
Eosinophil, /mm^3	171.1 [97.7–311.4]	155.8 [91.8–264.6]	159.9 [93.8–285.0]	0.106
Basophil, /mm^3	34.4 [21.3–54.6]	37.0 [22.6–56.0]	36.0 [22.2–55.3]	0.603
NLR	2.3 [1.6–3.2]	2.0 [1.4–3.0]	2.1 [1.5–3.1]	0.016
NMR	8.7 [6.8–11.3]	8.1 [6.3–10.3]	8.3 [6.4–10.8]	0.018
dNLR	1.5 [1.1–2.1]	1.5 [1.1–2.0]	1.5 [1.1–2.0]	0.051
PLR	121.1 [92.7–162.0]	118.7 [91.8–161.7]	119.7 [92.2–161.7]	0.656
MLR	0.250 [0.190–0.350]	0.260 [0.200–0.365]	0.260 [0.190–0.350]	0.164
EBR	5.0 [2.5–8.6]	4.3 [2.4–7.7]	4.6 [2.5–8.0]	0.118
Hemoglobin, mg/dL	14.1 [13.1–15.0]	14.3 [13.3–15.2]	14.2 [13.3–15.1]	0.042
Hematocrit, %	42.0 [39.0–45.0]	42.0 [40.0–45.0]	42.0 [40.0–45.0]	0.102
Platelet, 10^3/μL	238.0 [196.5–290.0]	237.0 [196.5–285.5]	237.0 [196.0–288.0]	0.587
ESR, mm/hr	17.0 [8.0–33.0]	13.0 [7.0–25.0]	14.0 [7.0–27.0]	0.097

Note: Data are expressed as median [interquartile range], unless otherwise indicated.
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AE, acute exacerbation; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; dNLR, derived neutrophil/lymphocyte ratio; NMR, neutrophil/monocyte ratio; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; EBR, eosinophil/basophil ratio; ESR, erythrocyte sedimentation rate.

multivariable models adjusted for other covariates, only continuous WBC (OR = 2.366; 95% CI: 1.211–4.623; $p = 0.012$) and high neutrophil counts (OR = 1.703; 95% CI: 1.153–2.517; $p = 0.008$) were independently associated with the development of 3-year cumulative AECOPD.

Changes in Risk Factors for 3-Year AECOPD

A subgroup analysis was conducted to identify the risk factors for AECOPD in patients with CBC data available during 1 (n = 385), 2 (n = 294), and 3 (n = 231) years of follow-up (Table 6). In the univariate analysis, an increase in basophils during the first year was associated with the occurrence of AECOPD at 3 years. However, no significant factor was identified in patients with 1-year follow-up CBC data in the multivariable analysis. Among patients whose CBC data were available for 2 years, the univariate analysis showed that increased lymphocyte and reduced platelet counts and NLR were significantly associated with AECOPD. In the multivariable analysis, reduced platelet count (OR = 0.502; 95% CI: 0.280–0.902; $p = 0.021$) and NLR (OR = 0.535; 95% CI: 0.294–0.974; $p = 0.041$) remained significantly associated with the occurrence of AECOPD. In the univariate analysis including 3-year changes in CBC data, an increase in lymphocyte, eosinophil counts and EBR during the 3 years was associated with AECOPD. However, in the multivariable analysis after adjusting for other covariates, only increased eosinophil count (OR = 2.130; 95% CI: 1.027–4.416; $p = 0.042$) and EBR (OR = 3.276; 95% CI: 1.463–7.336; $p = 0.004$) were significantly associated with the occurrence of AECOPD.

Table 5 Univariate and Multivariable Logistic Analysis for the Risk Factors of 3-Year AECOPD Among Baseline WBC

Variables	Unadjusted			Adjusted*		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
WBC	1.830	1.168–2.869	0.008	1.159	0.897–2.843	0.111
Median	1.334	1.008–1.764	0.044	1.194	0.837–1.705	0.328
Neutrophil	1.579	1.164–2.142	0.003	1.442	0.989–2.103	0.057
Median	1.538	1.162–2.039	0.003	1.468	1.024–2.104	0.036
Lymphocyte	0.934	0.675–1.292	0.680	1.056	0.697–1.601	0.797
Median	0.922	0.698–1.219	0.569	0.969	0.676–1.390	0.865
Monocyte	1.219	0.864–1.720	0.259	1.136	0.728–1.774	0.573
Median	1.098	0.831–1.451	0.513	0.986	0.691–1.407	0.938
Platelet	1.055	0.680–1.636	0.811	1.096	0.642–1.872	0.737
Median	1.027	0.777–1.358	0.852	0.953	0.671–1.355	0.789
NLR	1.307	1.053–1.622	0.015	1.188	0.904–1.5561	0.217
Median	1.300	0.984–1.721	0.065	1.272	0.886–1.827	0.192
PLR	1.068	0803–1.422	0.650	0.999	0.698–1.431	0.997
Median	1.147	0.868–1.516	0.334	1.165	0.813–1.669	0.404
dNLR	1.248	0.993–1.567	0.057	1.138	0.863–1.502	0.360
Median	1.138	0.861–1.504	0.363	1.060	0.743–1.513	0.748
MLR	1.211	0.909–1.614	0.190	1.052	0.712–1.554	0.800
Median	1.152	0.872–1.53	0.320	0.977	0.681–1.404	0.901
EBR	1.148	0.984–1.340	0.080	1.128	0.931–1.366	0.218
Median	1.170	0.85–1.547	0.269	1.084	0.765–1.537	0.649

Notes: *Adjusted OR was calculated after adjusting for age, sex, smoking status, BMI, previous AECOPD history, FEV_1, FVC, CAT total score, long-acting muscarinic antagonist use, and inhaled corticosteroid/bronchodilator combination use. WBC differential count and derived parameters were log-transformed before the analysis and used as both continuous and categorical variables based on values above/below the median.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; WBC, white blood cell; OR, odd ratio; CI, confidence interval; NLR, neutrophil/lymphocyte ratio; dNLR, derived neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; EBR, eosinophil/basophil ratio; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; CAT, COPD Assessment Test.

Table 6 Univariate and Multivariable Logistic Analysis for the Risk Factors of 3-Year AECOPD in WBC Changes

Variables	Unadjusted			Adjusted*		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
1-year (n = 385)						
WBC	1.268	0.853–1.884	0.241	1.150	0.705–1.875	0.576
Neutrophil	1.142	0.769–1.695	0.510	1.183	0.721–1.941	0.507
Lymphocyte	1.059	0.741–1.571	0.777	0.927	0.567–1.514	0.761
Monocyte	1.152	0.777–1.710	0.481	0.859	0.523–1.411	0.549

(*Continued*)

Table 6 (Continued).

Variables	Unadjusted			Adjusted*		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Eosinophil	0.980	0.661–1.454	0.920	1.083	0.665–1.763	0.748
Basophil	1.515	1.019–2.254	0.040	1.430	0.869–2.352	0.159
Platelet	0.710	0.478–1.054	0.089	0.685	0.419–1.117	0.130
NLR	1.152	0.770–1.710	0.481	1.359	0.831–2.222	0.222
NMR	1.834	0.165–20.393	0.622	1.780	0.127–24.916	0.669
PLR	0.913	0.057–14.694	0.949	0.766	0.038–15.246	0.861
dNLR	1.032	0.695–1.532	0.876	1.136	0.697–1.853	0.609
MLR	0.999	0.673–1.482	0.996	1.003	0.610–1.648	0.991
EBR	0.787	0.529–1.170	0.237	0.815	0.495–1342	0.422
2-year (n = 294)						
WBC	0.739	0.468–1.169	0.196	0.827	0.462–1.480	0.523
Neutrophil	0.879	0.557–1.385	0.577	0.951	0.536–1.687	0.863
Lymphocyte	1.760	1.110–2.788	0.016	1.585	0.878–2.860	0.126
Monocyte	0.655	0.415–1.035	0.070	0.640	0.353–1.159	0.141
Eosinophil	1.025	0.651–1.614	0.915	1.067	0.588–1.934	0.831
Basophil	0.861	0.546–1.357	0.519	0.777	0.432–1.395	0.398
Platelet	0.592	0.374–0.936	0.025	0.502	0.280–0.902	0.021
NLR	0.590	0.373–0.933	0.024	0.535	0.294–0.974	0.041
NMR	NC			NC		
PLR	NC			NC		
dNLR	0.669	0.424–1.056	0.084	0.701	0.390–1.260	0.235
MLR	0.695	0.440–1.096	0.118	0.584	0.317–1.077	0.085
EBR	0.771	0.489–1.215	0.262	0.821	0.454–1.485	0.514
3-year (n = 231)						
WBC	1.140	0.667–1.948	0.632	1.334	0.666–2.671	0.416
Neutrophil	1.183	0.693–2.020	0.537	1.418	0.706–2.847	0.326
Lymphocyte	1.756	1.038–2.973	0.036	1.308	0.658–2.598	0.444
Monocyte	1.141	0.655–1.987	0.641	1.158	0.555–2.417	0.696
Eosinophil	1.918	1.119–3.287	0.018	2.130	1.027–4.416	0.042
Basophil	1.368	0.807–2.320	0.245	1.097	0.552–2.179	0.792
Platelet	0.843	0.492–1.445	0.534	1.013	0.502–2.043	0.972

(*Continued*)

Table 6 (Continued).

Variables	Unadjusted			Adjusted*		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
NLR	0.760	0.434–1.332	0.338	1.452	0.693–3.042	0.324
NMR	1.812	0.992–3.310	0.053	2.113	0.937–4.765	0.071
PLR	NC			NC		
dNLR	0.854	0.485–1.504	0.585	1.321	0.629–2.774	0.461
MLR	0.665	0.367–1.207	0.180	0.622	0.281–1.376	0.241
EBR	2.190	1.241–3.865	0.007	3.276	1.463–7.336	0.004

Notes: *Adjusted OR was calculated after adjusting for age, sex, smoking status, BMI, previous AECOPD history, FEV_1, FVC, CAT total score, long-acting muscarinic antagonist use, and inhaled corticosteroid/long-acting beta agonist combination use. WBC differential count and derived parameters were log-transformed before the analysis and used as both continuous variables and categorical variables based on values above/below the median.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; WBC, white blood cell; OR, odd ratio; CI, confidence interval; NLR, neutrophil/lymphocyte ratio; dNLR, derived neutrophil/lymphocyte ratio; NMR, neutrophil/monocyte ratio; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; EBR, eosinophil/basophil ratio; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; CAT, COPD Assessment Test; NC, not calculated.

In the univariate analysis, reduced platelet count over 1 year, reduced monocyte count and MLR over 2 years, and reduced NLR and dNLR over 3 years were associated with the development of 3-year cumulative AECOPD (Supplementary Table 2). However, after adjusting for covariates, only reduced platelet count (OR = 0.484; 95% CI: 0.262–0.896; $p = 0.021$) and MLR (OR = 0.525; 95% CI: 0.282–0.978; $p = 0.042$) for 1 year were significant risk factors for the development of cumulative AECOPD over 3 years.

Discussion

We investigated the predictive value of WBC differential count and its derived parameters for 3-year AECOPD in a large, multicenter Korean study. Our findings showed that patients with AECOPD at 3 years had a higher WBC differential count, particularly neutrophil count, and derived parameters compared to those without AECOPD. Among various WBC parameters, a higher neutrophil count was associated with an increased incidence of long-term AECOPD. Additionally, 3-year AECOPD was associated with high eosinophil count during the follow-up and reduced platelet count and NLR.

In the present study, an increased baseline neutrophil count was associated with the occurrence of 3-year AECOPD, consistent with a previous study demonstrating the link between the neutrophil and the prognosis of COPD.[10] In a large population-based COPD registry from East Scotland (n = 7220), patients with a high blood neutrophil count (6000–15,000 cells/μL) had more impaired lung function and a higher average rate of AECOPD (2.3/year [higher] vs 1.3/year [normal], $p < 0.001$), including severe exacerbations (13% vs 5%, $p < 0.001$) in the year following the CBC measurement compared to those with a normal neutrophil count (2000–6000 cells/μL).[10] Another Chinese study by Yan et al demonstrated that a high neutrophil count based on a median value (> 86%) was associated with an increased risk of severe AE (adjusted OR = 1.68; 95% CI:1.09–2.62) during a 1-year follow-up in a prospective COPD cohort (n=521).[27] Moreover, NLR, a composite biomarker of neutrophils and lymphocytes, was effective in predicting AECOPD in several previous studies.[28] Lee et al reported that baseline NLR was significantly associated with acute exacerbations at the 1-year follow-up (adjusted OR = 1.16; 95% CI: 1.04–1.29) in our cohort (n = 855).[19] However, in the present study, NLR was associated with 3-year AECOPD in the univariate analysis but lost statistical significance after adjusting for other covariates in the multivariable analysis. These results suggest that neutrophils, rather than lymphocytes, may have a more significant impact on long-term AECOPD by reflecting the chronic systemic inflammatory status.

Possible mechanisms through which neutrophils contribute to long-term AECOPD are as follows: Elevated levels of neutrophils in the airways can cause chronic inflammation, leading to long-term exacerbations of COPD. A study by Day et al found an increased bronchoalveolar lavage median neutrophil count in frequent exacerbators (n=13, 9.4%)

compared to infrequent exacerbators (n=17, 3.1%) in patients with COPD,[29] which supports the role of airway neutrophils in AECOPD. Additionally, the release of proteases and oxidative stress by neutrophils can cause persistent damage to lung tissues, leading to AECOPD.[30,31] The release of cytokines and proteases by neutrophils, such as neutrophil elastase, matrix metalloproteinase, and myeloperoxidase, can lead to airway remodeling,[32] resulting in long-term changes in the airway structure and function, contributing to AECOPD.[33] Furthermore, Yang et al found that increased sputum neutrophil proportions were associated with a higher risk of severe AE only in the presence of air trapping in patients with COPD.[27] The process of tissue remodeling that occurs in response to high levels of airway neutrophil inflammation may involve repairing damaged tissue, as well as the loss and thickening of small airways. These changes can also contribute to the development of air trapping, which can lead to further damage to the lung structure and function.[34] Day et al also showed that acinar ventilation heterogeneity, a surrogate parameter for small airway disease, was significantly higher in the frequent exacerbator group compared to the infrequent exacerbator group ($p = 0.027$).[29] However, the mechanisms linking neutrophils and AECOPD in patients with COPD are poorly understood and require further research.

In the present study, elevated eosinophil count during the 3-year period was associated with the development of AECOPD at 3 years. The association between the eosinophil count and recurrence of AECOPD has been demonstrated in patients with AECOPD.[35,36] However, the association between the eosinophil count and AECOPD in a stable patient remains controversial.[37–40] A post-hoc analysis of 11 clinical trials (n = 22,125) revealed that the rate of annual exacerbation did not vary significantly with the eosinophil count (0.62 [≤ 150 cells/μL] vs 0.65 [151– 300 cells/μL] vs 0.67 [> 300 cells/μL]), regardless of the ICS use or previous AECOPD rate.[37] Kerkhof et al also exhibited that a high baseline eosinophil count (≥ 450 cells/μL) might be a predictor for 1-year AECOPD only in ex-smokers (adjusted relative risk = 1.32; 95% CI: 1.15–1.51) in 8318 patients with stable COPD.[38] However, another small retrospective study (n = 247) showed that a high blood eosinophil count (≥ 2%) was a significant risk factor for the occurrence of AECOPD during 12 months (covariates-adjusted OR = 2.98; 95% CI: 1.42–6.25).[39] Eosinophil-associated proinflammatory factors have been detected in the airways and blood of COPD patients, implying a possible contribution of eosinophils to the development of AECOPD in these patients.[41] However, a post-hoc analysis of the ECLIPSE study found that only 37.4% of patients with COPD had persistently elevated blood eosinophil counts (≥ 2% at baseline and 1, 2, and 3 years), while 49% had intermittent elevation.[42] In the present study, an increased eosinophil count at 3 years was significantly associated with 3-year AECOPD, but an increased baseline eosinophil count was not. These findings suggest that sustained eosinophil inflammation is a factor predicting AECOPD, underscoring the significance of monitoring the eosinophil count as a potential biomarker for AECOPD.

Furthermore, reduced platelet count and NLR were associated with 3-year AECOPD in the present study. This is contrary to most previous studies, which have reported increased platelet count or NLR being associated with a poor prognosis of COPD.[28,43] However, the present study had a relatively small sample size of patients with available CBC data during the 3-year follow-up (385 at 1 year, 294 at 2 years, and 231 at 3 years), which may have introduced potential bias. Therefore, these results should be interpreted cautiously, and further research with larger sample sizes and longer follow-up periods is required to validate these findings.

The present study has some limitations. First, the study design was retrospective. Therefore, the study was based on pre-existing data and limited by the accuracy and completeness of the recorded data. Consequently, only 826 of the 3478 patients registered in the cohort could be included. Notably, the reasons for patient dropout, which could include the possibility of mortality, remain unknown, potentially introducing selection bias. Second, the study was conducted at multiple centers, which may have introduced inter-center variability in patient selection and management. Thirdly, we collected several clinical data, such as comorbid conditions and medication history, via self-administered questionnaires, which may introduce biases as it relies on subjective patient responses rather than mandatory medical record reviews. Nonetheless, data were collected in a uniform format at each institution, and most included institutions were secondary or tertiary, with proper quality control of tests, including CBC. Finally, we could not establish causality between the identified factors and the occurrence of AECOPD. Further prospective studies are required to confirm these findings and explore the underlying mechanisms. Despite these limitations, the present study provided valuable insights into the

predictive value of WBC differential count and derived parameters for the incidence of 3-year AECOPD in the Korean population.

Conclusion

We evaluated the predictive value of WBC differential count and its derived parameters for 3-year AECOPD in this large-scale, multicenter Korean study. Our findings suggest that a high WBC differential count, particularly neutrophil count, was associated with an increased incidence of long-term AECOPD. These results indicate that WBC differential count and WBC derived parameters may serve as useful predictive markers for AECOPD. Further prospective studies are required to confirm these results and explore the underlying mechanisms.

Abbreviations

COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AE, acute exacerbation; BMI, body mass index; GERD, gastroesophageal reflux disease; IQR, interquartile range; TB, tuberculosis; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEF25-75, forced expiratory flow between 25–75% of vital capacity; DLco, diffusing capacity for carbon monoxide; DL/VA, diffusing capacity for carbon monoxide/alveolar volume; Hb, hemoglobin; TLC, total lung capacity; VC, vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; SGRQ, St. George's Respiratory Questionnaire; SpO2, oxygen saturation; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, a long-acting muscarinic antagonist; PDE4 inhibitor, phosphodiesterase-4 inhibitor; LTRA, leukotriene receptor antagonist; CBC, complete blood count; OR, odds ratio; CI, confidence interval; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; dNLR, derived neutrophil/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; EBR, eosinophil/basophil ratio; KOCOSS, Korean COPD Subtype Study.

Data Sharing Statement

Data generated and/or analyzed during the study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

All patients signed an informed consent form for the use of clinical data, and ethics approval was obtained from all medical institutions, including the Institutional Review Board of the Soonchunhyang University Seoul Hospital (2022-03-019).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interests.

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