Different Impacts of Blood and Sputum Eosinophil Counts on Lung Function and Clinical Outcomes in Asthma: Findings from the COREA Cohort

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Abstract
Purpose Blood (EOS-B) and sputum (EOS-S) eosinophil counts may contribute differently to asthma pathogenesis. We compared the impact of the baseline EOS-B and EOS-S levels on lung function, asthma control, and exacerbation in Korean asthma patients.

Methods Asthma patients with baseline EOS-B ($n = 4257$) and EOS-S ($n = 1049$) levels from a multicenter cohort (COREA) were included. Pulmonary function test (%FEV1 predicted), asthma control test (ACT), and asthma exacerbation incidence were followed-up every 3 months for one year. Linear mixed-effect models and survival analyses were used to examine the association between eosinophilic groups defined by EOS-B or EOS-S and outcomes.

Results High eosinophilic groups were associated with a low baseline value and a high improvement in the %FEV1 predicted and ACT scores over time. The magnitude of group difference in %FEV1 predicted was twofold higher in the EOS-S versus EOS-B classification [mean and 95% CI: 4.7 (0.6–8.8) versus 2.0 (0.2–3.7) for the baseline value and −1.5 (−2.3 to −0.8) versus −0.8 (−1.1 to −0.4) for the slope of change], whereas it was identical in ACT score. The magnitude of the impact increased linearly with the elevation of the cut-off level for the EOS-B but remained stable for the EOS-S classification. Patients with an elevation of both their EOS-B and EOS-S showed a higher increment in the %FEV1 predicted and ACT over time. Neither the EOS-B nor EOS-S was associated with asthma exacerbation.

Conclusion EOS-S and EOS-B contribute differently to the clinical outcomes and should be taken into account independently to improve asthma care.

Keywords Eosinophil · Blood · Sputum · Asthma · Lung function

Introduction

Asthma is characterized by chronic airway inflammation with complex pathogenesis and significant clinical heterogeneity. The infiltration and degranulation of eosinophils in the airway are strongly associated with asthma severity [1, 2], its response to corticosteroid therapy [3, 4], and an exacerbated occurrence of the disease [5]. Investigations of the immune pathways involving eosinophils, that operate through T2 helper lymphocytes, helped to elucidate the T2 phenotype of this disorder in which the role of eosinophilic inflammation is dominant [6, 7]. However, this phenotype only accounts for about half of asthmatic patients [7], whereas other phenotypes including non-T2 and obesity types of asthma have also been under investigation [8]. Although various markers have been employed to identify the T2 asthma phenotype, such as the absolute eosinophil count in the blood (EOS-B), sputum eosinophil percentage (EOS-S), exhaled nitric oxide fraction (FeNO), and serum periostin, the EOS-B is still the most widely used because it is an essential laboratory test parameter, even in general practice clinics [7].
The EOS-S has to date been considered the most important and direct indicator of airway inflammation and asthma progression [9]. However, an induced sputum sample is required for this test, collected through a careful procedure, and this is sometimes not possible if the patient has a seriously constricted airway [10]. Previous studies that examined whether the EOS-B can be a reliable surrogate of the EOS-S have produced inconsistent results. Wagener et al. reported that the EOS-B is predictive of sputum eosinophilia (EOS-S ≥ 3%) with high discriminative power (AUC of 0.85–0.89) in asthmatic patients regardless of severity [11]. However, other studies have reported a relatively low correlation between the EOS-B and EOS-S (r = 0.19–0.45) [12–14] and have indicated a high risk of false-negative values in predicting sputum eosinophilia using EOS-B [12, 13]. There is evidence also that the association between EOS-B and EOS-S is attenuated by increased disease severity [14] and that a higher cut-point for the EOS-B may improve its predictive power [12]. In terms of clinical responses, the EOS-S has appeared to be more clinically relevant to asthma control than the EOS-B [15]. Hypothetically, the discrepancy between the EOS-B and EOS-S measures may be due to several factors, including the usage of corticosteroids and/or biological agents [14]. Hence, we assumed that the discordance between the EOS-B and EOS-S values would be indicative of distinct clinical manifestations in asthma sufferers. In this regard, there has been no study to date that has attempted to distinguish the impacts of the EOS-B and EOS-S on clinical asthma outcomes.

We here examined whether the EOS-B and EOS-S contribute differently to longitudinal asthma outcomes in a multicenter observational cohort from Korea. Our findings provide insights into eosinophil-based phenotypes that may assist with patient care in the future.

**Materials and Methods**

**Study Subjects**

We used data from the Cohort for Reality and Evolution of Adult Asthma in Korea (COREA), which is an ongoing multicenter cohort study [16]. A total of 5341 asthmatic adults aged between 18 and 89 years were recruited from 2005 to 2021 from 27 domestic centers, including universities and hospitals, and were followed-up every three months. Asthma was defined in these cases by the presence of at least one of three criteria that included persistent asthma-related clinical symptoms, a positive airway hyperresponsiveness test (methacholine provocation test PC20 ≤ 25 mg/mL or mannitol provocation test PD15 ≤ 635 mg), and a positive bronchodilator response (≥ 12% improvement in the %FEV1 predicted after the use of a bronchodilator). The diagnoses were confirmed in all cases by allergists or pulmonologists. The impacts of the EOS-B and EOS-S levels were assessed in the subjects for whom these data had been recorded at the baseline (first) visit (EOS-B [n = 4257] and EOS-S [n = 1049] datasets, respectively). All participants used real-world conventional treatment and the clinical outcomes were followed up every 3 months. The results were confirmed via sensitivity analysis (SA) of patients with both a baseline EOS-B and EOS-S measurement (n = 911) (SA data set). For time-dependent outcomes, only the follow-up data collected within one year were used and subjects with at least one set of follow-up data were included (Fig. 1). All participants gave their informed consent, and the study protocol was approved by the institutional review board of the corresponding study centers.

**Measurements**

The EOS-B values in cells per μL were calculated from standard completed blood cell counts, whereas the EOS-S values in percentages were obtained from an induced sputum sample after the patient had inhaled hypertonic saline. There has been no clear cut-point to determine clinically relevant eosinophilic groups for EOS-B and EOS-S. A prior meta-analysis reported that the EOS-B was significantly associated with asthma exacerbation from a threshold of 200 cells per μL and that its effect was highest at the cut-off of 400 cells per μL [5]. Meanwhile, the association between the EOS-B and EOS-S has been reported to increase linearly between an EOS-S value range of 1.5–4.5% [12]. We, therefore, used the middle of these ranges (300 cells per μL and 3% for EOS-B and EOS-S, respectively) as the cut-offs in our current study to define high and low eosinophilic groups.

Spirometry had been performed by a trained technician following a standard operating procedure. The main outcome was prebrachodilator %FEV1 predicted values at the baseline after 3, 6, 9, and 12 months. Asthma control at each follow-up visit was assessed clinically via the self-reported asthma control test (ACT) questionnaire [17]. Exacerbation at each 3-month follow-up was defined as hospitalization in addition to the scheduled visits and/or having an increase in treatment steps compared with that in the previous visit. The incidence and the cumulative number of exacerbations within one year were evaluated. The definitions used for the inhaled corticosteroid dose and treatment steps are described in the Supplementary eMethods. Other baseline covariates that were assessed in our present analyses included age, sex, current smoking (yes or no), atopy status (allergen/histamine ratio ≥ 1 cm at least on skin prick tests using 11 common allergens), and asthma well-controlled status (ACT score ≥ 20).
Statistical Analysis

All statistical analyses were performed using R version 4.1.2 and statistical significance was set at $p < 0.05$. The baseline characteristics of the high versus low eosinophilic groups by the EOS-B and EOS-S classifications were described. An independent t-test and Fisher exact test were used for continuous and categorical variables, respectively. To investigate the association between the blood and sputum eosinophilic groups, and the time-dependent %FEV1 predicted and ACT scores, linear mixed-effect models adjusted for age and sex were used to estimate the outcomes over time by groups. Independent variables among the fixed-effects included group, time (from visit 1 to visit 5), the interaction between group and time, age, and sex. We assumed that the outcomes differed randomly by individual and by the slope of the change over time in repeated measurements. The random effect, therefore, was applied to the intercept and slope.

The fixed-effect regression coefficient of each group and the interaction between group and time refer to the group-based differences at the baseline and the slope of change of the outcomes over time, respectively. To examine the different cut-off points used to define eosinophilic groups alter the magnitude of the effect, we performed the same analyses using six cut-off values for EOS-B (150, 300, 450, 600, 750, 1000 cells per μL) and EOS-S (2, 10, 20, 30, 40, and 50%). To examine the influence of covariates (i.e., smoking, atopy, and treatment status) on the slope of the changes in outcome (i.e., time-dependent %FEV1 predicted and ACT score), the interaction between each covariate and slope of change, according to the eosinophilic group, was included in the previous models.

Survival analysis was used to examine the association between eosinophilic groups and the incidence of exacerbation. Differences in the future risk of exacerbation between the groups were assessed using the log-rank test. The proportion of patients having at least one, two, four, or five attacks within the one-year follow-up period was compared between the groups. Because the COREA cohort is a continuing real-life study, missing data occurred frequently on all of the outcome variables. Analysis for each
outcome was therefore only performed using the subjects who completed the outcome measurements (Fig. 1).

Results

Baseline Characteristics of the Study Subjects

Table 1 presents the baseline characteristic of the participants in the EOS-B and EOS-S datasets. Using cut-offs of 300 cells per μL for EOS-B and 3% for EOS-S, the prevalence of high eosinophilic groups was greater in EOS-S classification than that in EOS-B classification (57.3 and 43.9%, respectively; Table 1). No difference was found in the treatment step and FVC between the eosinophilic groups, whereas high eosinophilic cases had a lower control status, ACT score, and % FEV1 for both EOS-B and EOS-S classifications. The high eosinophilic participants were younger in the EOS-B classification, but not in the EOS-S classification. This trend was similar in the SA data set (Table 1S). Those in the EOS-S data set were less controlled, less atopy, and had higher FVC than those in the EOS-B data set (Table 2S). The correlation between EOS-B and EOS-S in the SA data set was relatively weak (Spearman $r = 0.35$ – Fig. 1S).

Lung Function

Analysis of the time-dependent % FEV1 predicted values was performed on 2259 and 477 participants in the EOS-B and EOS-S data sets, respectively (Fig. 1). An LME model adjusted for age and sex revealed that high eosinophilic groups had a lower baseline %FEV1 predicted and higher slope of change over time compared with the low eosinophilic groups. The magnitude of the group differences for the EOS-S classification was twofold higher than that of the EOS-B classification [mean and 95% CI: 4.7 (0.6–8.8) versus 2.0 (0.2–3.7) for baseline values and −1.5 (−2.3 to −0.8) versus −0.8 (−1.1 to -0.4) for the slope of change]. The lung function of the high eosinophilic group was improved over that of the low eosinophilic group after 6 and 12 months of treatment for both the EOS-B and EOS-S classifications (Fig. 2A, B). The magnitude of the group differences did not substantially alter across the cut-off for the EOS-S classification (between 4.1 and 6.0% for baseline and between -1.8% and -1.2% for the slope on average), whereas it linearly increased, accompanied by an elevation of the cut-off level, for the EOS-B classification (from −0.2 to 7.9% for the baseline and from -0.5% to -1.5% for the slope on average) (Fig. 3A, B). Those who used corticosteroids (inhaled or oral medications) and long-acting muscarinic antagonists

| Table 1 Baseline characteristics of the study participants stratified by blood and sputum eosinophilic group |
| --- |
| **EOS-B classification** | | **EOS-S classification** | |
| | Low | High | | Low | High | |
| Female n (%) | 4257 (56/44) | 1435 (60.1) | 992 (53.1) | <0.001 | 1049 (39/61) | 258 (63.2) | 376 (58.7) | 0.154 |
| Age (yrs) | 4257 (56/44) | 53.3 (16.3) | 48.0 (15.3) | <0.001 | 1049 (39/61) | 51.0 (15.7) | 51.2 (15.5) | 0.810 |
| BMI (kg/m²) | 4127 (56/44) | 24.4 (3.6) | 24.1 (3.5) | 0.032 | 1003 (38/62) | 24.5 (3.8) | 24.3 (3.5) | 0.333 |
| Smoker n (%) | 4183 (56/44) | 331 (14.1) | 302 (16.4) | 0.041 | 1026 (38/62) | 48 (12.2) | 82 (13.0) | 0.772 |
| Atopy n (%) | 1571 (49/51) | 525 (68.3) | 586 (73.1) | 0.040 | 448 (31/69) | 87 (63.5) | 198 (63.7) | 0.999 |
| Step 1–2 n (%) | 2140 (56/44) | 763 (63.2) | 586 (62.8) | 0.857 | 392 (36/64) | 83 (58.9) | 162 (64.5) | 0.278 |
| Step 3 n (%) | 2140 (56/44) | 60 (5.0) | 49 (5.3) | 0.767 | 392 (36/64) | 6 (4.3) | 11 (4.4) | 0.999 |
| Step 4 n (%) | 2140 (56/44) | 94 (7.8) | 73 (7.8) | 0.999 | 392 (36/64) | 14 (9.9) | 18 (7.2) | 0.343 |
| Step 5 n (%) | 2140 (56/44) | 290 (24.0) | 225 (24.1) | 0.959 | 392 (36/64) | 38 (27.0) | 60 (23.9) | 0.544 |
| FEV1 (%) | 3933 (56/44) | 79.7 (20.9) | 78.0 (20.7) | 0.013 | 950 (40/60) | 83.3 (20.1) | 78.1 (21.4) | <0.001 |
| FVC (%) | 3932 (56/44) | 86.8 (17.9) | 87.3 (17.2) | 0.386 | 950 (40/60) | 89.0 (17.4) | 88.6 (18.0) | 0.756 |
| FEV1/FVC (%) | 3937 (56/44) | 0.72 (0.13) | 0.72 (0.12) | 0.075 | 950 (40/60) | 0.75 (0.11) | 0.71 (0.11) | <0.001 |
| ACT score (pts) | 1772 (56/44) | 19.4 (4.5) | 18.4 (4.9) | <0.001 | 401 (36/64) | 18.2 (4.6) | 17.1 (4.7) | 0.018 |
| Controlled n (%) | 1771 (56/44) | 561 (57.0) | 382 (48.5) | <0.001 | 401 (36/64) | 70 (48.6) | 87 (33.9) | 0.004 |

Data are presented as a mean (SD) or number (%). n*, number of participants for whom data were available (% low / % high)
P values were calculated using the Fisher exact test or independent t-test. P values <0.05 are bolded

EOS-B classification: blood eosinophilic group including high (≥300 cells/μL) and low (<300 cells/μL) cases; EOS-S classification: sputum eosinophilic group including high (≥3%) and low (<3%) cases; BMI body mass index; Smoker, current smoker; Controlled, asthma control status defined as the asthma control score higher than 19; Step, treatment step according to the GINA guidelines; FEV1, percentage predicted forced expiratory volume in one second without bronchodilator response test; FVC, percentage predicted forced vital capacity without bronchodilator response test; FEV1/FVC, FEV1 to FVC ratio; ACT, asthma control test

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(LAMA) had a declination in the time-dependent %FEV1 predicted (between 1 and 2% on average) in both the high and low eosinophilic groups, whereas smoking, control, atopy, and ICS use conditions did not significantly alter this slope (Table 3S). With the EOS-B classification, a low and medium dose of ICS was associated with a 0.9 (0.1–1.8) and 1.6 (0.2–3.1) higher slope for the %FEV1 change compared with a high dose of ICS at the baseline. These effects of the ICS dose were not evident with the EOS-S classification (Fig. 2SA, B). The analysis of the SA data set showed the same tendency in which the magnitude of group difference was higher with the EOS-S classification (Fig. 3SA, B), whereas the effect of the cut-off in the EOS-B classification was attenuated (Fig. 4SA, B). Subgroup analysis was performed on four additional groupings as follows: (i) high EOS-B and high EOS-S (Group 1); (ii) high EOS-B and low EOS-S (Group 2); low EOS-B and high EOS-S (Group 3); and (iv) low EOS-B and low EOS-S (Group 4). The slope of the %FEV1 predicted change over time in Group 1 was significantly higher than that of the other three subgroups (all P < 0.01), among which no difference was found (Fig. 5SA).

Fig. 2  Predicted time-dependent outcomes in the low and high eosinophilic groups (A, B) %FEV1 predicted in the blood (A) and sputum eosinophil classification (B). C, D ACT in the blood (C) and sputum eosinophil classification (D). Data are predicted values of the outcomes (image) and regression coefficient (label) estimated using a linear mixed-effect model adjusted for age and sex. Baseline, the difference in baseline values; Slope, the difference in slope of change; L vs H, the high eosinophilic group was used as a reference. N number at the baseline; O observations during the one-year follow-up.
Asthma Control Test (ACT) Scores

Analysis of the time-dependent ACT scores was performed on 917 and 212 participants in the EOS-B and EOS-S data sets, respectively (Fig. 1). In both EOS-B and EOS-S classifications, the high eosinophilic group had a lower baseline and higher slope of change in the ACT score. However, the magnitude of the group difference was comparable across the two classifications. The group differences in the baseline and slope of change in the ACT score were 1.4 (0.7–2.0) and −0.5 (−0.7 to −0.3) versus 1.6 (0.1 to 3.1) and −0.7 (−1.2 to −0.3) for the EOS-B and EOS-S classifications, respectively. The high eosinophilic groups had a significantly higher ACT score after 12 months of treatment compared to the low eosinophil groups for the two classifications (Fig. 2C, D). The elevation of the cut-off level for the EOS-B increased substantially the magnitude of the group difference in the ACT score (mean difference increased from 0.23 to 2.55 for baseline and from −0.25 to −0.60 for the slope of change), but the interactions of the cut-off level have vanished in the EOS-S classification (Fig. 3C, D). Those who used corticosteroid, LAMA, and short-acting beta antagonist treatments had a declination in the time-dependent ACT, especially in the low eosinophilic group, for the two classifications, whereas the interaction between the reliever and control status was found only for the low eosinophilic group using the EOS-B classification (Table 4S). No interaction with the ICS dose was found for either EOS classification (Fig. 2SC, D). The same trend occurred in the sensitivity analysis (Fig. 3SC, D), whereas the subgroup analysis revealed only a difference in the slope of change for the ACT in Group 1 compared with the other subgroups (Fig. 5SB).

Asthma Exacerbation

Analysis of the incidence of exacerbation was performed on 1487 and 299 participants in EOS-B and EOS-S data sets, respectively (Fig. 1). During a one-year follow-up, 42
and 47% of participants developed at least one exacerbation event in the EOS-B and EOS-S data sets, respectively. No difference was observed in the cumulative number of exacerbations between the high and low eosinophilic groups with either classification (Fig. 6S). Survival analysis also found no association between the eosinophilic group and the risk of future exacerbation (log-rank P values were 0.45 and 0.52 for the EOS-B and EOS-S classification, respectively) (Fig. 4A, B). The same trend was found in the sensitivity analysis (Fig. 7SA, B and Fig. 8SA, B). Subgroup analysis further indicated no difference in the cumulative number and risk of exacerbation among the four subgroups (Fig. 7SC and Fig. 8SC).

Discussion

The impacts of the EOS-B and EOS-S on the longitudinal clinical manifestation of asthma were examined in this present study. High eosinophilic cases were likely to have lower lung function and poorer asthma control at the baseline but to show a greater improvement in these outcomes over time compared with the low eosinophilic patients. The EOS-S revealed a higher impact on the time-dependent %FEV1 predicted but not on the ACT score compared with the EOS-B. The magnitude of the impact increased linearly with the elevation of the cut-off level for the EOS-B but remained stable or reduced for the EOS-S classification. A phenotype involving both a high EOS-B and high EOS-S was associated with a higher increment in the %FEV1 predicted and ACT over time. Neither the EOS-S nor EOS-B showed a significant impact on exacerbation.

Concerns about using the EOS-B as a surrogate for the EOS-S have been raised in previous studies [12–14]. Our present data confirmed in this regard that the relationship between both parameters is relatively weak. The combination of blood and sputum EOS as a classification approach revealed a relatively high percentage discrepancy (40% of the participants were assigned to a so-called “grey zone” with a high EOS-B but low EOS-S, and vice versa). It has been demonstrated previously that blood eosinophilia is not only related to airway inflammation but to various infectious and non-infectious illnesses [18]. An elevation in the EOS-B, therefore, may not always be accompanied by an increase in the EOS-S. On the other hand, persistent airway eosinophilia has been reported to occur in many asthmatic patients, particularly in severe asthmatics, even though high-dose corticosteroid treatments are being used [19]. We thus speculated that the EOS-B and EOS-S may have different impacts on the clinical manifestations of asthma.

Studies to date on the association between blood eosinophilia and lung function in asthmatic patients have produced inconsistent results. A prior meta-analysis on four Caucasian cohorts using conventional treatment reported that an elevated blood eosinophil count in asthmatic patients (≥ 300 cells per μL) was associated with a lower lung function at the baseline and its accelerated declination over time [20]. However, among four cohorts, a significant association between EOS-B and a reduced FEV1 was evident in one, which raised the question of whether this association is mediated by steroid treatment [20]. In contrast, another previous study
did not report this association [21]. A consistent tendency was found in our present data in which the baseline lung function was lower but improved more strongly in the high eosinophilic groups, both with the EOS-B and EOS-S classifications. This finding may be partly explained by the fact that asthma patients with a high EOS-B and/or EOS-S tend to respond better to corticosteroid therapy [22]. Interestingly, we found although the magnitude of this association was higher for the EOS-S classification, it remained stable over the cut-off levels. Meanwhile, a higher threshold for the EOS-B was associated with higher impacts. These results suggested that, while using lung function as an outcome, the EOS-S seems to be a better predictor, and that a higher threshold is needed for the EOS-B. Indeed, higher EOS-B cut-off levels have been found previously to improve the prediction of sputum eosinophilia [12]. The integration of EOS-B and EOS-S identified a good clinical improvement phenotype that was characterized by the elevation of both blood and sputum eosinophils. This phenotype had a significantly higher slope of change in the %FEV1 predicted than others in our subgroup analysis. Further research should be conducted to explore the molecular basis of this phenotype. We also found a higher declination of lung function and ACT over time among corticosteroid, LAMA, and SABA users compared with naïve groups. Generally, medication users are more severe and participants’ severity may explain partly the interaction of medication in the association between eosinophil and clinical outcomes.

Evidence to date shows that the impact of EOS-S on asthma control is higher than that of EOS-B [15]. In our current study, the effects of the EOS-B and EOS-S on asthma control were found to be identical. However, as with the observed tendencies for lung function, we found a linear positive relationship between the cut-off levels and the impact of the predictors with the EOS-B but not the EOS-S classification, and that the phenotype involving an elevation of both the EOS-B and EOS-S was associated with asthma control improvement over time. This finding once again emphasized the fact that the EOS-B and EOS-S should be considered independent predictors and that their combination is a better approach to eosinophil-based phenotyping. The relationship between eosinophil and asthma exacerbation has been the subject of some debate [5, 23, 24]. A prior meta-analysis confirmed the association between EOS-B and exacerbation but found that this effect varied substantially across different study methods (longitudinal versus cross-sectional) and with the definition of exacerbation (hospitalization versus emergency visit) [5]. In our present study, an exacerbation of asthmatic symptoms was defined by integrating information from outpatient visits, emergency visits, and elevations in the treatment level. Furthermore, a 1-year follow-up seemed to be relatively short for accurately examining the risk of exacerbation. We found no significant association between a high eosinophil count and exacerbation, both in the EOS-B and EOS-S classifications. Although our subgroup analysis for exacerbation found no statistically significant relationship, an interesting trend did emerge from our analyses. The risk of exacerbation increased sharply at 3 months from baseline among the participants with a high EOS-S and those with a low EOS-S but high EOS-B. However, this risk appeared to be stable over the follow-up period among the patients having both a high EOS-B and EOS-S. The good improvement in lung function and asthma control with this phenotype may be a reasonable explanation for this finding. The molecular basis of this phenotype should however be investigated further.

The trends for our current findings were confirmed by sensitivity analysis of the data set including the participants with available baseline EOS-B and EOS-S data. Although the effect and difference in the magnitude of the EOS-B and EOS-S on lung function and asthma control remained, the interaction between the cut-off level and the impact of the EOS-B was found to be attenuated. Meanwhile, the EOS-B and EOS-S data sets differed in terms of smoking, atopy, and control conditions. Although these factors did not interact significantly with the impact of the eosinophil count on lung function and asthma control, they may influence the effect of using a different cut-off value. Thus, future comparisons between the EOS-B and EOS-S should take into account of these confounding factors.

To our knowledge, our present study is the first attempt to compare the impact of the EOS-B and EOS-S measures on time-dependent clinical outcomes in a large multicenter cohort of asthmatic adults. The interaction of other confounding factors, including the cut-off values used and treatments, were examined and the results were confirmed by sensitivity analyses. However, our analyses had several notable limitations. First, because missing data were a critical issue with the COREA cohort, and analyses of these patients were performed as a real-life study, the results, therefore, may have potential selection bias. Second, due to the missing data issue, we included only follow-up data within one year. Because asthma is a chronic illness that results in a gradual decline in lung function, further investigations with a longer follow-up should be considered. Third, the year of the baseline visit varied largely among our included participants, from 2005 to 2021, during which time the prevalence and pattern of asthma have changed dramatically [25]. The associations between risk factors and outcome, therefore, may alter accordingly. Finally, the difference in the association between the variation of the EOS-B and EOS-S during follow-up and the clinical outcomes was not investigated and should be the objective of a future study.
In conclusion, the baseline EOS-B and EOS-S contribute differently to the change in lung function and asthma control over time and should be taken into account independently in clinical practice. The integration of these two markers may provide novel eosinophil-based indicators for asthma care in real-world conventional treatment.

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Author Contributions All authors contributed to the study’s conception and design. Material preparation and data collection were performed by JHL, JYK, JA, WJS, HSK, and TBK. Data analysis was performed by DDP. The first draft of the manuscript was written by DDP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations
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