Received: 22 February 2023 | Revised: 23 May 2023 | Accepted: 5 June 2023

DOI: 10.1111/cea.14362

ORIGINAL ARTICLE

WILEY

Long-term clinical outcomes of aspirin-exacerbated respiratory disease: Real-world data from an adult asthma cohort

Youngsoo Lee[1] | Chungsoo Kim[2] | Eunyoung Lee[3,4] | Hyun Young Lee[5] | Seong-Dae Woo[6] | Seng Chan You[7] | Rae Woong Park[2,3] | Hae-Sim Park[1]

[1]Department of Allergy & Clinical Immunology, Ajou University School of Medicine, Suwon, South Korea

[2]Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Suwon, South Korea

[3]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, South Korea

[4]Office of Biostatistics, Ajou Research Institute for Innovative Medicine, Ajou University Medical Center, Suwon, South Korea

[5]Department of Statistics, Clinical Trial Center, Ajou University Medical Center, Suwon, South Korea

[6]Division of Pulmonology and Allergy, Chungnam National University School of Medicine, Daejeon, South Korea

[7]Department of Biomedicine System Informatics, Yonsei University College of Medicine, Seoul, South Korea

Correspondence
Hae-Sim Park, Department of Allergy & Clinical Immunology, Ajou University School of Medicine, 164 Worldcup-ro, Yeongtong-gu, Suwon 16499, South Korea.
Email: hspark@ajou.ac.kr

Funding information
Korea Health Industry Development Institute, Grant/Award Number: HR16C0001

Abstract

Background: Aspirin-exacerbated respiratory disease (AERD) is a phenotype of severe asthma, but its disease course has not been well documented compared with that of aspirin-tolerant asthma (ATA).

Objectives: This study aimed to investigate the long-term clinical outcomes between AERD and ATA.

Methods: AERD patients were identified by the diagnostic code and positive bronchoprovocation test in a real-world database. Longitudinal changes in lung function, blood eosinophil/neutrophil counts, and annual numbers of severe asthma exacerbations (AEx) were compared between the AERD and the ATA groups. Within a year after baseline, two or more severe AEx events indicated severe AERD, whereas less than two AEx events indicated nonsevere AERD.

Results: Among asthmatics, 353 had AERD in which 166 and 187 patients had severe and nonsevere AERD, respectively, and 717 had ATA. AERD patients had significantly lower FEV1%, higher blood neutrophil counts, and higher sputum eosinophils (%) (all $p < .05$) as well as higher levels of urinary LTE4 and serum periostin, and lower levels of serum myeloperoxidase and surfactant protein D (all $p < .01$) than those with ATA. In a 10-year follow-up, the severe AERD group maintained lower FEV1% with more severe AEs than the nonsevere AERD group.

Conclusion and Clinical Relevance: We demonstrated that AERD patients presented poorer long-term clinical outcomes than ATA patients in real-world data analyses.

KEYWORDS
aspirin-exacerbated respiratory disease, asthma exacerbations, biomarker, eosinophilic inflammation, lung function

Youngsoo Lee and Chungsoo Kim contributed equally as co-first authors.

Rae Woong Park and Hae-Sim Park contributed equally as co-senior authors.

1 | INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) is characterized by asthma, chronic rhinosinusitis with/without nasal polyposis, and aspirin or nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity. Its prevalence in adult patients with asthma is approximately 7%–10%.[1–3] In AERD, chronic eosinophilic airway inflammation persists despite avoiding NSAIDs, and therefore many patients require high doses of inhaled or systemic corticosteroids (CS).[4] Thus, patients with AERD are more likely to have frequent asthma exacerbations (AEx) and unscheduled hospital visits than those with aspirin-tolerant asthma (ATA).[5]

AERD has many heterogeneous clinical features.[6–10] It is heterogeneous in inflammatory profiles and clinical outcomes and is divided into several distinct clinical subtypes. A recent study analysing a large AERD cohort identified three potential AERD subtypes showing different demographic and clinical characteristics as well as blood/sputum inflammatory signatures.[11] However, data describing the long-term clinical outcomes of AERD remain scarce compared with those of ATA, although patients with AERD could have diverse clinical courses.

Given the higher severity of AERD and disease burden, documenting clinical heterogeneity by demonstrating differences in AERD's long-term outcomes is necessary. Patients with AERD with frequent AEx (severe AERD group) might have worse long-term clinical outcomes and persistent type 2 inflammation than those with AERD showing fewer AEx (nonsevere AERD group). To our knowledge, this study is the first evidence to compare clinical outcomes (lung function, severe AEx, inflammatory markers, and systemic CS) between patients with AERD and those with ATA, and between severe and nonsevere AERD groups in a large-scale, long-term, and real-world cohort of adult patients with asthma.

Key messages

- Patients with AERD have poorer long-term clinical outcomes compared to those with ATA.
- Lower lung function and frequent asthma exacerbations were shown in AERD patients compared to ATA patients.
- Patients with AERD can be classified into subtypes according to those clinical/inflammatory phenotypes.

2 | METHODS

2.1 | Study design and data source

This study is an observational cohort study to compare clinical and laboratory findings of patients with AERD with those of patients with ATA to demonstrate the long-term clinical outcomes of AERD endotypes in real-world clinical practice. We used a single database from Ajou University Medical Center in Korea. The Department of Allergy and Clinical Immunology of this institution has continuously collected clinical and laboratory data (applied to monitor patients with asthma in daily clinical practice) of patient with asthma taking antiasthmatic medications such as inhaled CS (ICS) with/ without long-acting β2-agonist (LABA), leukotriene modifiers, and systemic CS. Data on biomarkers including serum eosinophilic-derived neurotoxin (EDN), surfactant protein D (SPD), myeloperoxidase (MPO), periostin, and transforming growth factor-β1 (TGF-β1), urinary LTE4 and extensive electronic medical records were also collected and measured at baseline. Patients in the current study were collected prospectively for retrospective analyses. Moreover, we developed a longitudinal database named Immune/Inflammatory Disease Common Data Model Augmentation for Research Union System (ICARUS) to analyse in detail the clinical characteristics and clinical outcomes of various inflammatory diseases; ICARUS also included electronic medical records, biomarkers, and lung function measurements. This database was structured in a format of the Observational Medical Outcome Partnership Common Data Model (OMOP CDM) version 5.3.[12,13] and approved by our institutional review board (AJOUIRB-MBD-2019-100). The informed consent was waived due to the use of de-identified data.

2.2 | Participants

We included adult patients with asthma (>18 years old) with an antiasthmatic medication prescription and a diagnosis code for asthma or its subtypes (Korean Classification of Diseases 10th Revision; J45–J46). In this study, a baseline was the time at which a diagnosis code for asthma was first registered for each patient. Patients were those who had been prescribed antiasthmatic medications for over 3 months in a year after baseline. Patients taking type 2 biologics (omalizumab, mepolizumab, reslizumab, and dupilumab) were excluded to ensure comparability of patient severity between the study groups. Furthermore, patients with AERD were classified if those with the diagnosis code for AERD (J45.81 Aspirin induced asthma), which was registered in patients having recurrent clinical exacerbation histories after taking aspirin/NSAIDs and/or having a positive lysine-aspirin bronchoprovocation test as previously described.[14–16] We further classified patients with AERD into the severe AERD (≥2 AEx) and nonsevere AERD group (<2 AEx) within a year after baseline. Patients were considered to have a severe AEx if they were taking systemic CS (oral prednisolone ≥15 mg/day or its equivalent dose) for 3 consecutive days or visited the emergency department or underwent hospitalization for worsened asthmatic symptoms; short-acting β_2-agonist (SABA) use was not considered as an AEx event.

2.3 | Demographic and clinical data

The presence of nasal polyps and chronic rhinosinusitis were determined by paranasal sinus series, computed tomography, endoscopic exam, or nasal polyp operation histories. All patients underwent pulmonary function tests using the same device and method, as previously described.[17,18] Complete blood cell count with differentials (eosinophil/neutrophil counts), sputum eosinophil/neutrophil (%), renal/liver function tests, electrolytes, uric acid, albumin, erythrocyte sedimentation rate, and urine analysis were collected at baseline. In addition, the serum levels of total immunoglobulin E (IgE), specific IgE to house dust mites, and environmental pollens were measured using ImmunoCAP® (Thermo Fisher, Waltham, MA, USA).

Antiasthmatic medications were as follows: ICS plus LABA, SABA, and systemic CS. Medium-to-high-dose ICS was defined according to the Global Initiative for Asthma guidelines (e.g., >250 mcg for fluticasone); otherwise, it was defined as low-dose ICS. High-dose CS user was defined as ≥40 mg/day of prednisolone or its equivalent dose.[19]

2.4 | Measurement of metabolic and serum biomarkers

Serum and urine samples of patients with asthma were collected at the initial visit, stored at −80°C, and thawed before measurement. Prior to serum and urine collection, patients were informed to discontinue systemic CS for at least 2 weeks and leukotriene modifiers for at least 7 days. The serum SPD, MPO, and TGF-β1 levels were measured by enzyme-linked immunosorbent assay (ELISA) (Quantikine, R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Serum periostin level was measured using a proprietary sandwich ELISA kit (Shino-test, Kanagawa, Japan), as previously mentioned.[20] Furthermore, we measured the urinary LTE_4 levels by using an ultra-high-performance liquid chromatography system, as previously described.[21]

2.5 | Statistical analysis

Baseline demographic and clinical characteristics, inflammatory profiles, and comorbidities were compared between patients with AERD and those with ATA by cross-sectional analysis. We also compared their demographic characteristics such as age, sex, body mass index (BMI), asthma onset age, and smoking history. Clinical characteristics included the lung function test, forced expiratory volume in one second (FEV1) %, FEV1 per forced vital capacity (FEV1/FVC), and provocative concentration of methacholine inducing a 20% decline in FEV1 (PC_{20}). Regarding inflammatory profiles, we assessed eosinophil/neutrophil counts in serum and sputum samples, total and specific levels of IgE, and serum levels of novel biomarkers.

Continuous variables were assessed using a Student's *t*-test or Wilcoxon-signed rank test after testing for data normality with the Shapiro–Wilk test. For comparing categorical variables, we used the χ^2 test. A p value of <.05 was considered statistically significant. The differences in long-term changes in lung function and inflammatory markers (e.g., serum eosinophil/neutrophil count) were identified using the linear mixed model (LMM). LMM is suitable for real-world studies because it accounts for irregularly dispersed longitudinal data with different time points. Random intercept and slope were calculated for the study participants and observation time, respectively. All statistical data were analysed using R (version 3.5.1, R Project for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Demographic and clinical characteristics

We enrolled 353 patients with AERD (166 and 187 in the severe and nonsevere AERD groups, respectively) and 717 patients with ATA from the ICARUS database. Table 1 presents the comparison of baseline characteristics between patients with AERD and ATA and between the severe and nonsevere AERD groups. Age ($p=.426$), onset age of asthma ($p=.885$), female sex ($p=.088$), and BMI ($p=.064$) were not significantly different between the AERD and ATA groups. However, the AERD group had a longer follow-up duration of asthma ($p=.030$), a higher BMI ($p=.039$), and a significantly lower proportion of current or ex-smokers ($p<.001$) than the ATA group. Baseline FEV1% ($p=.038$), FEV1/FVC ($p=.008$), and PC_{20} methacholine ($p<.001$) were also significantly lower in the AERD group. The severe AERD group was older ($p=.009$) and had later asthma onset ($p=.036$) and lower baseline FEV1% ($p=.001$) than the nonsevere AERD group. The nonsevere AERD group differed from the ATA group only by lower BMI ($p=.024$) and a lower proportion of current or ex-smokers ($p<.001$).

3.2 | Laboratory parameters

Table 2 shows the comparison of the baseline laboratory parameters between the AERD and ATA groups and between the severe and nonsevere AERD groups. The AERD group had significantly higher blood neutrophil counts ($p=.002$) and sputum eosinophils ($p=.038$) and lower blood basophils ($p=.041$) than ATA patients. The total IgE levels ($p=.573$), specific IgE levels to *Dermatophagoides pteronyssinus* ($p=.064$) and *Dermatophagoides farinae* ($p=.053$), and blood eosinophil counts ($p=.942$) showed no difference between these groups. Only specific IgE levels to *D. farinae* ($p=.025$) were significantly lower in the severe AERD group than in the nonsevere AERD group. All baseline laboratory findings of the nonsevere AERD group were comparable to those of ATA patients ($p>.05$).

TABLE 1 Baseline demographic and clinical characteristics of patients with AERD (the severe AERD group and the nonsevere AERD group) and patients with ATA.

Variables	AERD			ATA ($n=717$)	p value[a]	p value[b]	p value[c]
	Total ($n=353$)	Severe AERD ($n=166$)	Nonsevere AERD ($n=187$)				
Age, years	40.6 ± 13.4	42.6 ± 13.7	38.9 ± 13.0	41.5 ± 14.6	.426	.009	.032
Asthma onset age, years	33.3 ± 19.3	34.3 ± 23.7	32.3 ± 14.0	33.8 ± 15.2	.885	.036	.341
Follow-up duration, years	7.9 ± 6.1	8.2 ± 6.1	7.6 ± 6.1	7.1 ± 5.9	.030	.286	.297
Female, *n* (%)	231 (65.4)	106 (63.9)	125 (66.8)	429 (59.8)	.088	.633	.095
Body mass index, kg/m^2	23.77 ± 3.84	24.01 ± 4.18	23.46 ± 3.42	24.29 ± 3.71	.039	.386	.024
Smoking history, *n*	267	126	141	328			
Current or ex-smoker, *n* (%)	100 (37.5)	50 (39.7)	50 (35.5)	450 (62.8)	<.001	.559	<.001
Baseline FEV1, %	87.2 ± 18.5	82.6 ± 19.3	92.1 ± 16.2	90.4 ± 19.1	.038	.001	.648
Baseline FEV1/FVC, %	78.5 ± 10.4	76.3 ± 10.6	80.7 ± 9.8	81.7 ± 10.3	.008	.057	.372
Baseline PC_{20}, mg/mL	8.6 ± 24.6	5.2 ± 10.2	11.4 ± 31.7	10.8 ± 13.7	<.001	<.001	.095
Chronic rhinosinusitis/nasal polyp	246 (69.7)	129 (77.7)	117 (62.6)	305 (42.5)	<.001	.003	<.001

Note: Continuous values are presented as mean ± SD, and categorical variables are presented as number (%).

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PC_{20}, provocative concentration of methacholine inducing a fall of 20% decline in FEV1.

[a]AERD versus ATA.

[b]Severe AERD versus nonsevere AERD.

[c]Nonsevere AERD versus ATA.

3.3 | Biomarkers

Table 3 lists the candidate biomarkers for AERD. Compared with the ATA group, the AERD group and nonsevere AERD group showed significantly higher urinary LTE_4 levels ($p<.001$ and $p=.007$, respectively). Serum periostin levels were significantly higher in the AERD group than in the ATA group ($p=.002$), however, they were comparable between the severe and nonsevere AERD groups ($p=.386$), and between the nonsevere AERD and ATA groups ($p=.060$). Serum EDN levels showed no significant differences between the AERD and ATA groups ($p=.127$) and between the severe and nonsevere AERD groups ($p=.163$). In addition, the AERD group showed significantly lower serum levels of SPD than the ATA group ($p=.003$); the severe AERD group tended to show lower SPD levels than the nonsevere AERD group, although the difference was not statistically significant ($p=.066$). Conversely, serum TGF-β_1 levels were significantly higher in the AERD group than in ATA patients ($p=.003$) and were comparable between the AERD subgroups ($p=.839$). Moreover, serum MPO levels were significantly lower in the AERD group than in ATA patients ($p<.001$), but not in the severe AERD group compared with the nonsevere AERD group ($p=.918$). Serum MPO levels were also significantly lower in the nonsevere AERD group than in the ATA group ($p<.001$).

3.4 | Trajectory analysis

Longitudinal changes in FEV1%, blood eosinophil/neutrophil counts, and sputum eosinophil count (%) for up to 10 years of follow-up are shown in Figure 1. Although baseline FEV1% was significantly lower in patients with AERD than in those with ATA, FEV1% declined in both throughout the follow-up, showing persistently lower FEV1% levels in the AERD group than in the ATA group (Table S1). Blood eosinophil count was comparable between the AERD and ATA groups at baseline and declined progressively throughout the follow-up period. Blood neutrophil counts were significantly higher in the AERD group than in ATA group at baseline and declined progressively in both, showing persistently higher neutrophil counts in patients with AERD than in those with ATA throughout the follow-up period (Table S1).

Longitudinal changes in the parameters were compared between the severe and nonsevere AERD groups (Figure 2). FEV1% decreased faster in the severe AERD group than in the nonsevere AERD group, whereas blood eosinophil count decrements were comparable between these groups. Furthermore, blood neutrophil counts declined more rapidly in the severe AERD group than in the nonsevere AERD group. However, according to the LMM model analyses, patients with AERD had significant associations with FEV1% decrease and blood neutrophil increase, despite the overall decrease throughout the follow-up period ($p<.05$; Table S1). Similarly, the severe AERD group was an independent factor contributing to the FEV1% decrease and blood eosinophil increase ($p<.05$; Table S1).

3.5 | Severe AEx

Annual numbers of severe AEx were compared between the AERD and ATA groups and between the severe and nonsevere AERD

TABLE 2 Baseline laboratory parameters of patients with AERD (the severe AERD group and the nonsevere AERD group) and patients with ATA.

	AERD					
	Total ($n=353$)	Severe AERD ($n=166$)	Nonsevere AERD ($n=187$)	ATA ($n=717$)	*p* value[a]	*p* value[b]	*p* value[c]
Total IgE, kU/L	337.5 ± 453.9	387.9 ± 534.4	290.2 ± 358.4	372.2 ± 590.2	.573	.079	.575
Der p-specific IgE, kU/L	7.7 ± 17.3	6.3 ± 17.4	8.9 ± 17.3	12.1 ± 22.9	.064	.103	.644
Der f-specific IgE, kU/L	10.4 ± 21.0	5.8 ± 15.0	14.7 ± 24.7	15.5 ± 26.6	.053	.025	.978
Blood eosinophil counts, /μL	377.2 ± 460.4	433.4 ± 576.5	328.8 ± 320.8	381.1 ± 507.3	.942	.143	.307
Blood neutrophil counts, /μL	4809.6 ± 2579.4	5090.0 ± 2637.4	4600.1 ± 2529.1	4362.5 ± 2199.3	.002	.178	.117
Sputum eosinophils, %	46.5 ± 36.0	47.0 ± 36.8	45.9 ± 35.4	37.2 ± 32.9	.038	.840	.166
Sputum neutrophils, %	57.5 ± 34.3	56.7 ± 34.7	58.5 ± 34.1	63.4 ± 31.0	.096	.817	.269
Blood basophils, %	0.57 ± 0.32	0.55 ± 0.30	0.60 ± 0.34	0.63 ± 0.36	.041	.298	.330

Note: Continuous values are presented as mean ± SD.

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; *Der p*, *Dermatophagoides pteronyssinus*; *Der f*, *Dermatophagoides farinae*.

[a]AERD versus ATA.

[b]Severe AERD versus nonsevere AERD.

[c]Nonsevere AERD versus ATA.

groups (Figure 3). The numbers were higher in the AERD group than in the ATA group at baseline, and they decreased in the first year of follow-up and became comparable to those of the ATA group (approximately 1 AEx annually) (Figure 3A). The annual numbers in the severe AERD group decreased throughout the follow-up period but persisted at over 1 AEx per year, whereas those in the nonsevere AERD group remained lower than that (Figure 3B).

3.6 | Antiasthmatic medication

Table S2 summarizes the use of antiasthmatic medications for patients in the AERD and ATA groups within a year after baseline. Significantly higher proportions of patients with AERD were treated by systemic CS at least once ($p<.001$), high-dose systemic CS (≥ 40 mg of prednisolone or its equivalent dose; $p<.001$), and SABA ($p=.001$) during the follow-up period. Compared to the nonsevere AERD group, the severe AERD group had significantly higher proportions of patients using systemic CS at least once ($p<.001$), high-dose systemic CS ($p<.001$), and SABA ($p<.001$) during the follow-up period. Additionally, the annual dose of systemic CS was higher in the AERD group than in the ATA ($p<.001$) and in the severe AERD group than in the nonsevere AERD group ($p<.001$).

4 | DISCUSSION

The present study demonstrated real-world evidence of the distinct clinical outcomes of patients with AERD in comparison with those with ATA. The AERD group showed worse clinical parameters at baseline, such as lower FEV1%, increased airway hyperresponsiveness, higher sputum eosinophils (%), and blood neutrophil counts in the cross-sectional model. Furthermore, the longitudinal model showed persistently lower FEV1% with higher sputum eosinophils/blood neutrophils, and more frequent AEx in the AERD group than in the ATA group for up to 10 years of follow-up. Thus, the AERD group (even taking antiasthmatic medications following the clinical guidelines) was likely to present worse clinical outcomes than the ATA group. Taken together, AERD exhibited poor clinical outcomes compared with ATA in both cross-sectional and longitudinal outcome models in a real-world clinical setting.

AERD is a clinical phenotype of severe asthma and a heterogeneous disease that could be classified into several clinical/inflammatory phenotypes.[15,22] However, previous studies insufficiently described the long-term clinical course and heterogeneity of AERD. We hypothesized that the longitudinal clinical course of AERD is variable and that patients with frequent AEx in the first few years of treatment would have persisting AEx, rapid lung function declines, and severe airway inflammation. The present study demonstrated not only persistently lower and declining FEV1% with more frequent AEx in the AERD group than in the ATA group, but also the severe/nonsevere AERD groups with longitudinal outcome models. In the trajectory analyses, the most notable was the FEV1% changes

TABLE 3 Baseline serum and urinary biomarkers of patients with AERD (the severe AERD group and the nonsevere AERD group) and patients with ATA.

	AERD						
	Total ($n=353$)	Severe AERD ($n=166$)	Nonsevere AERD ($n=187$)	ATA ($n=717$)	*p* value[a]	*p* value[b]	*p* value[c]
Urinary LTE_4, pg/mg Cr	553.1 ± 86.2/35	736.3 ± 1029.9/19	335.5 ± 327.6/16	229.1 ± 380.3/32	<.001	.208	.007
Serum EDN, ng/mL	64.4 ± 36.5/107	67.8 ± 34.1/53	61.0 ± 38.6/54	59.5 ± 37.4/243	.127	.163	.836
Serum SPD, pg/mL	2725.9 ± 3134.9/142	2136.2 ± 2131.7/73	3349.8 ± 3846.8/69	3171.0 ± 2785.5/366	.003	.066	.305
Serum TGF-β_1, ng/mL	33.0 ± 14.3/187	32.7 ± 14.6/96	33.3 ± 14.1/91	28.4 ± 15.8/292	.003	.839	.012
Serum periostin, ng/mL	88.9 ± 44.6/197	91.4 ± 45.1/98	86.3 ± 44.1/99	76.8 ± 38.8/370	.002	.386	.060
Serum MPO, ng/mL	186.7 ± 215.0/180	184.2 ± 180.7/85	189.0 ± 242.6/95	290.7 ± 275.0/318	<.001	.918	<.001

Note: Continuous values are presented as mean ± SD. The number of patients measured for each biomarker is also presented.

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; EDN, eosinophil-derived neurotoxin; LTE_4, leukotriene E_4; MPO, myeloperoxidase; SPD, surfactant protein D; TGF-β_1, transforming growth factor-β_1.

[a]AERD versus ATA.

[b]Severe AERD versus nonsevere AERD.

[c]Nonsevere AERD versus ATA.

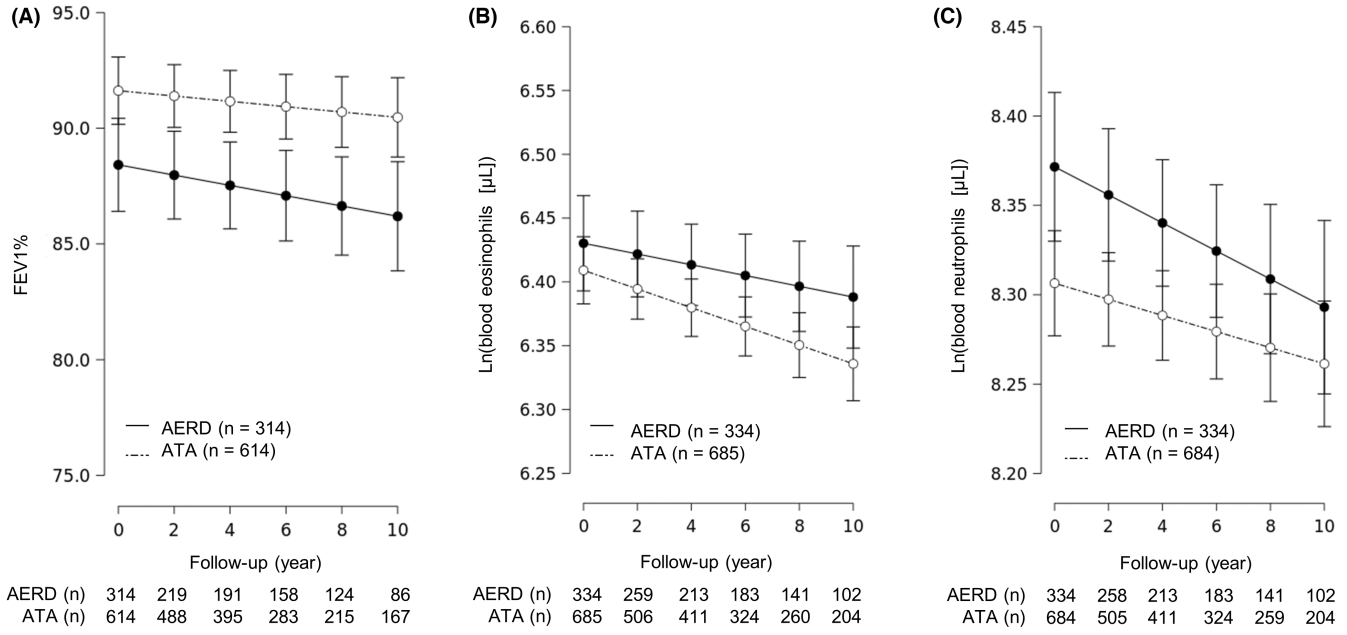

FIGURE 1 Longitudinal changes in lung function and inflammatory parameters in patients with AERD (solid line with closed circle) and ATA (dashed line with open circle). (A) FEV1%, (B) blood eosinophil counts, (C) blood neutrophil counts. Error bars indicate 95% confidence interval. AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma. Ln, log-transformed values.

between the severe and nonsevere AERD groups. On the other hand, blood eosinophils and neutrophils converged during the follow-up period, implying that other pathophysiologic changes than eosinophilic/neutrophilic inflammation, such as airway epithelial cells and airway remodelling, could be involved. The impact of epithelial damage on AERD severity needs to be clarified to prevent lung function declines in AERD.

LTE_4 overproduction is the inflammatory hallmark of AERD pathogenesis.[6,23] In AERD, excessive amounts of cysteinyl LTs (cysLTs) are released from mast cells and eosinophils. LTE_4 (the terminal metabolite of cysLT synthesis) is an important biomarker of AERD for activating eosinophilic inflammation.[24] Furthermore, cysLTs contribute to bronchoconstriction after aspirin/NSAID exposures in AERD.[25,26] In our study, urinary LTE_4 levels effectively differentiated the AERD and nonsevere AERD groups from the ATA group. Although not statistically significant, they tended to be higher in the severe AERD group than in the nonsevere AERD group; thus, cysLT overproduction could be a key mediator for AERD phenotype and severity.

AERD is also characterized by severe and persistent type 2 airway inflammation with extensive eosinophilic infiltration.[27] Compared with ATA, AERD shows extensive eosinophilic

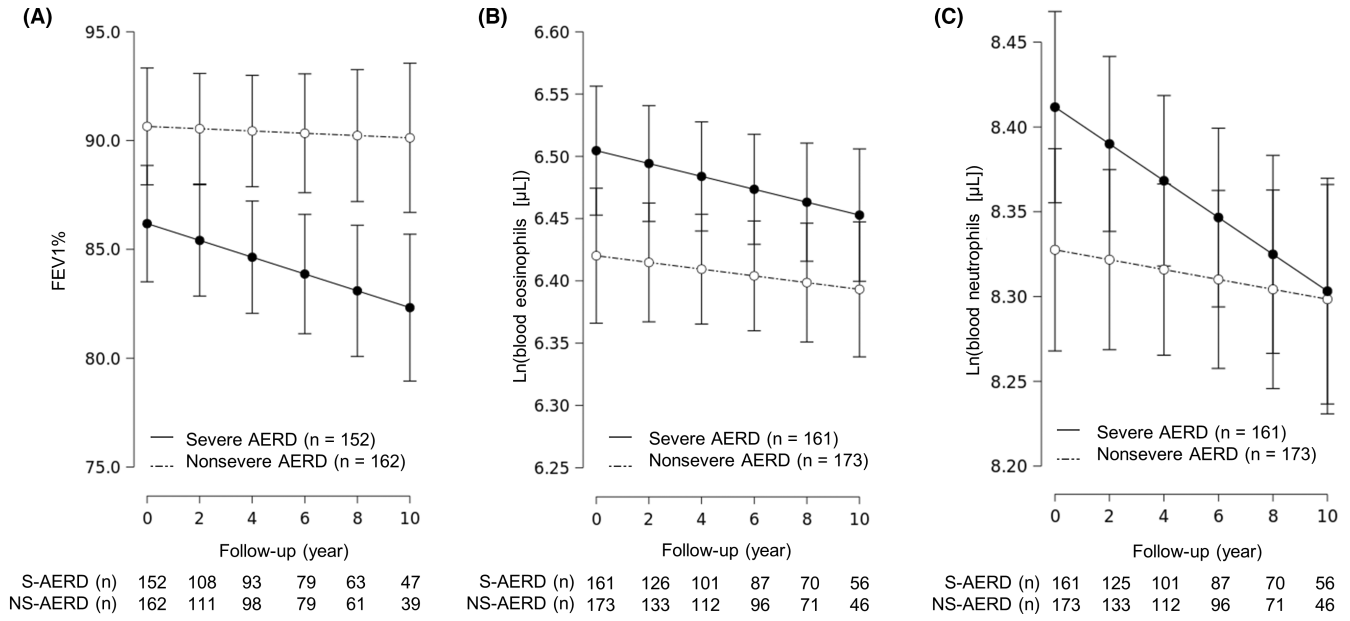

FIGURE 2 Longitudinal changes in lung function and inflammatory parameters in the severe AERD group (solid line with closed circle) and the nonsevere AERD group (dashed line with open circle). (A) FEV1%, (B) blood eosinophil counts, (C) blood neutrophil counts. Error bars indicate a 95% confidence interval. AERD, aspirin–exacerbated respiratory disease; Ln, log-transformed values.

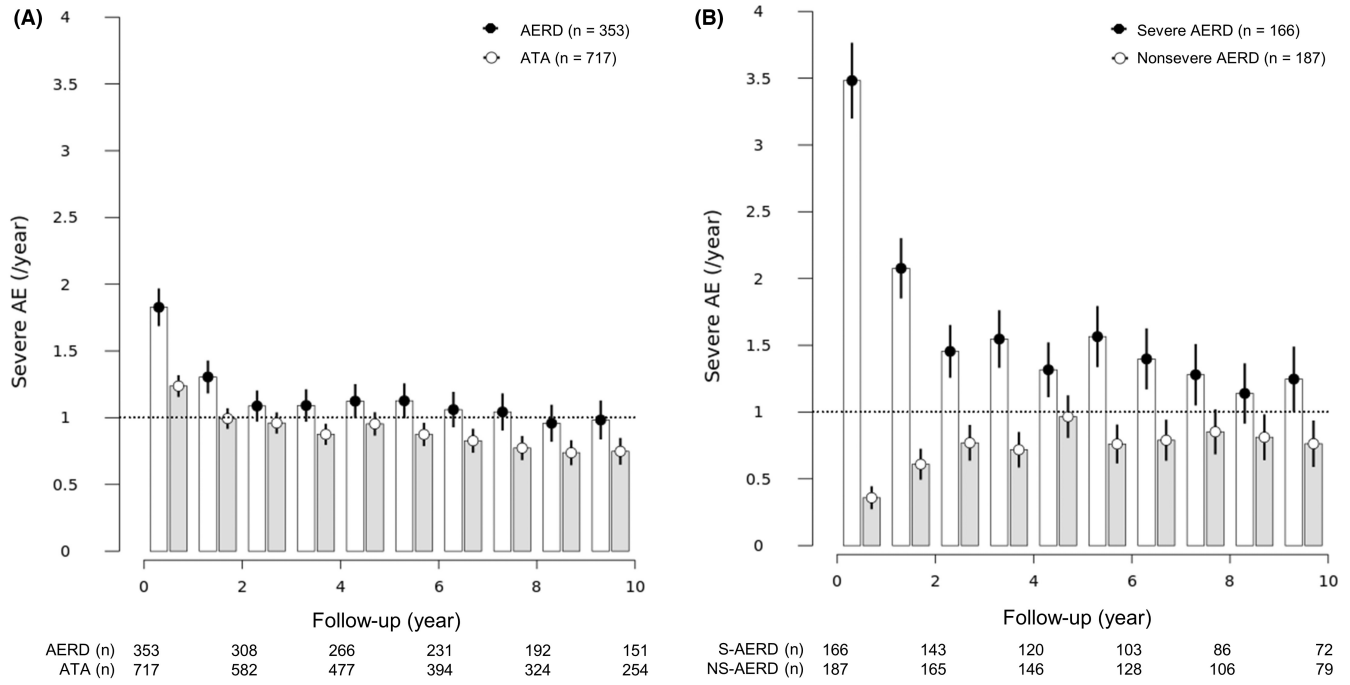

FIGURE 3 Annual number of severe asthma exacerbations compared (A) between patients with AERD (white bar with closed circle) and ATA (grey bar with open circle) and (B) between the severe AERD (white bar with closed circle) and nonsevere AERD groups (white bar with open triangle). Error bars indicate a 95% confidence interval. AE, asthma exacerbation; AERD, aspirin–exacerbated respiratory disease; ATA, aspirin–tolerant asthma.

infiltration in the upper and lower airways.[28] In our study, increased sputum eosinophil count effectively distinguished the AERD group from the ATA group, but was comparable between the severe and nonsevere AERD groups. In the trajectory analyses, blood eosinophil counts decreased similarly between the AERD and ATA groups and between the severe and nonsevere AERD groups, consistent with previous observations that eosinophilic inflammation is a key pathogenetic factor. However, blood/sputum eosinophils do not effectively measure eosinophilic airway inflammation because of eosinophil variability by ICS or systemic CS.[29–31] Instead,

the levels of eosinophil granular proteins increased in AERD than in healthy controls.[32] For example, EDN was reported as a serum biomarker for eosinophilic inflammation in severe eosinophilic asthma.[18,33–35] In our study, serum EDN levels tended to be higher in the AERD and severe AERD groups than in the ATA and nonsevere AERD groups, respectively. Periostin is released from airway epithelial cells stimulated by type 2 inflammatory cytokines (e.g., IL-13), as well as TGF-β1 and our study showed higher serum periostin levels in the AERD group than in the ATA group, as was shown in previous studies,[20,36,37] suggesting that TGF-β may contribute to the production of periostin in AERD patients. Increased serum periostin levels might be a potential biomarker for predicting severe AERD if measured in a sufficient number of patients. Changes in the level of these biomarkers with pharmacologic or biologic treatment and their relationships to AEx must be further investigated in larger AERD cohorts.

AERD pathogenesis is also complicated by other various inflammatory cells, including ILC2 cells, epithelial cells, plasma cells, and platelets, which have rarely been investigated.[38,39] The novel biomarkers for neutrophilic inflammation and airway remodelling in severe asthma should be investigated in AERD as a distinct phenotype of severe asthma.[40,41] In our study, the AERD group had significantly lower serum SPD/MPO levels and higher serum TGF-β_1 levels than the ATA group. Notably, serum SPD level was the only biomarker differentiating severe AERD from nonsevere AERD, and lower serum SPD level and increased serum TGF-β1/periostin levels were the predictive markers for severe AERD. SPD is a pattern recognition molecule released by airway epithelial cells to mediate the innate immune responses in the airways, especially phagocytosis. SPD reportedly alleviates type 2 airway inflammation by inhibiting mast cells and eosinophils, and decreased SPD is associated with epithelial damage in the airways of patients with severe asthma.[42–45] SPD levels decrease in BAL fluid and increase in the sera of patients with asthma, possibly resulting from increased SPD synthesis and air–blood barrier integrity loss.[46–49] In addition, we previously reported the protective functions of SPD in AERD pathogenesis; SPD could attenuate type 2 airway inflammation/remodelling by an interplay with TGF-β1/periostin.[50] MPO (secreted by activated neutrophils) is another biomarker that may contribute to neutrophilic inflammation in asthma. The AERD group had higher blood neutrophil counts but lower serum MPO levels than the ATA group. Given that blood/sputum neutrophils are easily varied by systemic CS, the exact roles of MPO as a reliable biomarker reflecting neutrophilic inflammation should be elucidated. Furthermore, the insight into whether less neutrophilic inflammation contributes to AERD pathogenesis should also be investigated.

This study has limitations, considering the retrospective collection of clinical data. First, the sample size was small, given that only one database was used. However, only a few institutions routinely differentiate AERD from ATA in clinical practice. Therefore, a large database of patients treated by asthma specialists in a single institution following the same treatment strategy should be analysed. Additionally, our analyses used a common data model database, which allows for easy cooperation with other institutions. Secondly, the data collection period and follow-up were not controlled. Although considered as an inevitable limitation of observational studies, the real-world clinical course should be investigated using real-world data. To mitigate this, we need to analyse repeatedly measured data by using a statistical model such as the LMM. Thirdly, the present study defined AERD patients by the diagnosis code of AERD registered in our EMR, and the prevalence of CRS/NPs, a key clinical feature of AERD, is slightly low. Although some AERD patients do not have CRS/NPs as published previously.[15] Additional studies are required to clarify these points.

In conclusion, AERD exhibited a more severe disease course than ATA despite having antiasthmatic medication as maintenance for up to 10 years of follow-up, as evidenced by persistently lower FEV1% and more frequent AEx, where persistent type 2 inflammation and LTE_4 overproduction are involved. Since AERD is an important clinical phenotype of severe asthma, it should be confirmed by provocation test if an asthmatic has a suspicious clinical history or clinical features of AERD (severe asthma, nasal polyposis). Additional controllers, including biologics, are needed to prevent AEx and achieve better controls, improving long-term clinical outcomes of AERD, especially in severe AERD.

AUTHOR CONTRIBUTIONS

HS Park, RW Park, and SC You involved in study design. Y Lee, C Kim analysed the data. C Kim, E Lee, HY Lee, and SC You conducted statistical interpretation. Y Lee, SD Woo, and HS Park involved in literature search. Y Lee and C Kim wrote the draft of the manuscript. All authors reviewed and gave a critical revision for the article.

FUNDING INFORMATION

This research was funded a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HR16C0001).

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Youngsoo Lee https://orcid.org/0000-0001-8918-9353
Chungsoo Kim https://orcid.org/0000-0003-1802-1777
Eunyoung Lee https://orcid.org/0000-0002-9440-9119
Hyun Young Lee https://orcid.org/0000-0003-4169-8284
Seong-Dae Woo https://orcid.org/0000-0003-2506-7407
Seng Chan You https://orcid.org/0000-0002-5052-6399
Rae Woong Park https://orcid.org/0000-0003-4989-3287
Hae-Sim Park https://orcid.org/0000-0003-2614-0303

REFERENCES

1. Weber RW, Hoffman M, Raine DA Jr, Nelson HS. Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perennial asthmatics. *J Allergy Clin Immunol*. 1979;64(1):32-37.
2. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature. *J Allergy Clin Immunol*. 2015;135(3):676-681.e1.
3. Dursun AB, Woessner KA, Simon RA, Karasoy D, Stevenson DD. Predicting outcomes of oral aspirin challengesin patients with asthma, nasal polyps, andchronic sinusitis. *Ann Allergy Asthma Immunol*. 2008;100(5):420-425.
4. Teran LM, Holgate ST, Park H-S, Sampson AP. Aspirin exacerbated respiratory disease. *J Allergy*. 2012;2012:473863.
5. Mascia K, Haselkorn T, Deniz YM, et al. Aspirin sensitivity and severity of asthma: evidence for irreversible airway obstruction in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol*. 2005;116(5):970-975.
6. White AA, Stevenson DD. Aspirin-exacerbated respiratory disease. *N Engl J Med*. 2018;379(11):1060-1070.
7. Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2002;89(5):474-478.
8. Palikhe NS, Kim J-H, Park H-S. Update on recent advances in the management of aspirin exacerbated respiratory disease. *Yonsei Med J*. 2009;50(6):744-750.
9. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE investigators. European network on aspirin-induced asthma. *Eur Respir J*. 2000;16(3):432-436.
10. Cardet JC, White AA, Barrett NA, et al. Alcohol-induced respiratory symptoms are common in patients with aspirin exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2014;2(2):208-213.e2.
11. Celejewska-Wójcik N, Wójcik K, Ignacak-Popiel M, et al. Subphenotypes of nonsteroidal antiinflammatory disease-exacerbated respiratory disease identified by latent class analysis. *Allergy*. 2020;75(4):831-840.
12. Stang PE, Ryan PB, Racoosin JA, et al. Advancing the science for active surveillance: rationale and design for the observational medical outcomes partnership. *Ann Intern Med*. 2010;153(9):600-606.
13. Hripcsak G, Duke JD, Shah NH, et al. Observational health data sciences and informatics (OHDSI): opportunities for observational researchers. *Stud Health Technol Inform*. 2015;216:574-578.
14. Park HS. Early and late onset asthmatic responses following lysine-aspirin inhalation in aspirin-sensitive asthmatic patients. *Clin Exp Allergy*. 1995;25(1):38-40.
15. Lee H, Ye Y, Kim S, et al. Identification of phenotypic clusters of nonsteroidal anti-inflammatory drugs exacerbated respiratory disease. *Allergy*. 2017;72(4):616-626.
16. Ban GY, Kim SH, Park HS. Persistent eosinophilic inflammation in adult asthmatics with high serum and urine levels of leukotriene E(4). *J Asthma Allergy*. 2021;14:1219-1230.
17. Kim SH, Yang EM, Lee HN, Choi GS, Ye YM, Park HS. Association of the CCR3 gene polymorphism with aspirin exacerbated respiratory disease. *Respir Med*. 2010;104(5):626-632.
18. Lee Y, Lee JH, Yang EM, et al. Serum levels of eosinophil-derived neurotoxin: a biomarker for asthma severity in adult asthmatics. *Allergy Asthma Immunol Res*. 2019;11(3):394-405.
19. Global Strategy for Asthma Management and Prevention; 2022. www.ginasthma.org
20. Kim MA, Yoon MK, Lee YS, et al. Clinical implication of the serum periostin level for differentiating phenotypes of NSAID hypersensitivity. *Allergol Int*. 2016;65(4):492-494.
21. Ban GY, Cho K, Kim SH, et al. Metabolomic analysis identifies potential diagnostic biomarkers for aspirin-exacerbated respiratory disease. *Clin Exp Allergy*. 2017;47(1):37-47.
22. Bochenek G, Kuschill-Dziurda J, Szafraniec K, Plutecka H, Szczeklik A, Nizankowska-Mogilnicka E. Certain subphenotypes of aspirin-exacerbated respiratory disease distinguished by latent class analysis. *J Allergy Clin Immunol*. 2014;133(1):98-103.e6.
23. Gaber F, Daham K, Higashi A, et al. Increased levels of cysteinyl-leukotrienes in saliva, induced sputum, urine and blood from patients with aspirin-intolerant asthma. *Thorax*. 2008;63(12):1076-1082.
24. Martin HC, Derakhshan T, Dwyer DF. Insights into mast cell hyperplasia in aspirin-exacerbated respiratory disease from transcriptional profiling of polyp mast cells. *Ann Allergy Asthma Immunol*. 2021;126(2):120-121.
25. Christie PE, Tagari P, Ford-Hutchinson AW, et al. Urinary leukotriene E4 concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. *Am Rev Respir Dis*. 1991;143(5 Pt 1):1025-1029.
26. Steinke JW, Payne SC, Borish L. Eosinophils and mast cells in aspirin-exacerbated respiratory disease. *Immunol Allergy Clin North Am*. 2016;36(4):719-734.
27. Mullol J, Boyce J, Dahlén SE, Dahlén B, Picado C, Bobolea I. Eicosanoid dysregulation and type 2 inflammation in AERD. *J Allergy Clin Immunol*. 2021;148(5):1157-1160.
28. Payne SC, Early SB, Huyett P, Han JK, Borish L, Steinke JW. Evidence for distinct histologic profile of nasal polyps with and without eosinophilia. *Laryngoscope*. 2011;121(10):2262-2267.
29. Park HS, Nahm DH, Park K, Suh KS, Yim HE. Immunohistochemical characterization of cellular infiltrate in nasal polyp from aspirin-sensitive asthmatic patients. *Ann Allergy Asthma Immunol*. 1998;81(3):219-224.
30. Nasser SM, Pfister R, Christie PE, et al. Inflammatory cell populations in bronchial biopsies from aspirin-sensitive asthmatic subjects. *Am J Respir Crit Care Med*. 1996;153(1):90-96.
31. Lee Y, Park Y, Kim C, et al. Longitudinal outcomes of severe asthma: real-world evidence of multidimensional analyses. *J Allergy Clin Immunol Pract*. 2021;9(3):1285-1294.e6.
32. Stevens WW, Ocampo CJ, Berdnikovs S, et al. Cytokines in chronic rhinosinusitis. Role in eosinophilia and aspirin-exacerbated respiratory disease. *Am J Respir Crit Care Med*. 2015;192(6):682-694.
33. Rutten B, Young S, Rhedin M, et al. Eosinophil-derived neurotoxin: a biologically and analytically attractive asthma biomarker. *PLoS ONE*. 2021;16(2):e0246627.
34. An J, Lee JH, Sim JH, et al. Serum eosinophil-derived neurotoxin better reflect asthma control status than blood eosinophil counts. *J Allergy Clin Immunol Pract*. 2020;8(8):2681-2688.e1.
35. Howarth P, Quirce S, Papi A, et al. Eosinophil-derived neurotoxin and clinical outcomes with mepolizumab in severe eosinophilic asthma. *Allergy*. 2020;75(8):2085-2088.
36. Takayama G, Arima K, Kanaji T, et al. Periostin: a novel component of subepithelial fibrosis of bronchial asthma downstream of IL-4 and IL-13 signals. *J Allergy Clin Immunol*. 2006;118(1):98-104.
37. Kim MA, Izuhara K, Ohta S, et al. Association of serum periostin with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2014;113(3):314-320.
38. Eid R, Yan CH, Stevens W, Doherty TA, Borish L. Innate immune cell dysregulation drives inflammation and disease in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2021;148(2):309-318.
39. Rhyou HI, Nam YH, Park HS. Emerging biomarkers beyond leukotrienes for the management of nonsteroidal anti-inflammatory drug (NSAID)—exacerbated respiratory disease. *Allergy Asthma Immunol Res*. 2022;14(2):153-167.

40. Lee Y, Quoc QL, Park HS. Biomarkers for severe asthma: lessons from longitudinal cohort studies. *Allergy Asthma Immunol Res*. 2021;13(3):375-389.
41. Choi Y, Sim S, Lee DH, et al. Effect of TGF-β1 on eosinophils to induce cysteinyl leukotriene E4 production in aspirin-exacerbated respiratory disease. *PLoS ONE*. 2021;16(8):e0256237.
42. Deb R, Shakib F, Reid K, Clark H. Major house dust mite allergens dermatophagoides pteronyssinus 1 and dermatophagoides farinae 1 degrade and inactivate lung surfactant proteins A and D. *J Biol Chem*. 2007;282(51):36808-36819.
43. von Bredow C, Hartl D, Schmid K, et al. Surfactant protein D regulates chemotaxis and degranulation of human eosinophils. *Clin Exp Allergy*. 2006;36(12):1566-1574.
44. Qaseem AS, Sonar S, Mahajan L, et al. Linking surfactant protein SP-D and IL-13: implications in asthma and allergy. *Mol Immunol*. 2013;54(1):98-107.
45. Mackay RM, Grainge CL, Lau LC, Barber C, Clark HW, Howarth PH. Airway surfactant protein D deficiency in adults with severe asthma. *Chest*. 2016;149(5):1165-1172.
46. Xu J, Singhera GK, Dorscheid DR. Expression of surfactant protein D in airways of asthmatics and interleukin-13 modulation of surfactant protein D in human models of airway epithelium. *Respir Res*. 2015;16(1):26.
47. Cheng G, Ueda T, Numao T, et al. Increased levels of surfactant protein A and D in bronchoalveolar lavage fluids in patients with bronchial asthma. *Eur Respir J*. 2000;16(5):831-835.
48. Atochina-Vasserman EN, Winkler C, Abramova H, et al. Segmental allergen challenge alters multimeric structure and function of surfactant protein D in humans. *Am J Respir Crit Care Med*. 2011;183(7):856-864.
49. Koopmans JG, van der Zee JS, Krop EJ, Lopuhaä CE, Jansen HM, Batenburg JJ. Serum surfactant protein D is elevated in allergic patients. *Clin Exp Allergy*. 2004;34(12):1827-1833.
50. Choi Y, Lee DH, Trinh HKT, et al. Surfactant protein D alleviates eosinophil-mediated airway inflammation and remodeling in patients with aspirin-exacerbated respiratory disease. *Allergy*. 2019;74(1):78-88.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lee Y, Kim C, Lee E, et al. Long-term clinical outcomes of aspirin-exacerbated respiratory disease: Real-world data from an adult asthma cohort. *Clin Exp Allergy*. 2023;53:941-950. doi:10.1111/cea.14362