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Original Article



# Characteristics of Severe Asthma in the Elderly: Observations From the Korean Severe Asthma Registry (KoSAR)

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## ABSTRACT

**Purpose:** Few studies have compared the clinical characteristics of severe asthma (SA) in elderly patients compared to that in nonelderly patients.
**Methods:** We analyzed data from the Korean SA Registry, a nationwide, real-world observational study of SA in Korea. The baseline clinical characteristics, disease control status, and medication use of the patients were compared between elderly (≥ 65 years) and nonelderly groups.
**Results:** Of the 864 patients with SA, 260 (30.1%) were in the elderly group. The elderly group had lower atopy rate, but had higher prevalence of chronic obstructive pulmonary disease (COPD), hypertension, and osteoporosis than did the nonelderly group. The elderly group had a lower rate of type 2 inflammation and lower levels of forced expiratory

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volume in 1 second (FEV1) (% predicted) and FEV1/forced vital capacity ratio than did the nonelderly group ($P < 0.05$ for all). However, asthma symptom scores and the frequency of asthma exacerbation were not significantly different between the 2 groups. Of controller medications, biologics were less frequently used in the elderly group ($P < 0.05$ for all). **Conclusions:** SA in the elderly is characterized by lower lung function, less type 2-low airway inflammation, and comorbidity with COPD. These findings are being taken into consideration in the management of elderly patients with SA in real-world clinical practice.

**Keywords:** Asthma; character; elderly

## INTRODUCTION

According to the World Health Organization, in 2007, approximately 334 million people were diagnosed with asthma worldwide.[1] Population studies on adult asthma showed higher incidence in women than in men,[2,3] and there was a trend toward a higher incidence with age over 50 years.[4-6] The prevalence of asthma in elderly patients (≥ 65 years) has also been increasing in Korea (5.88% in 2002; 8.7% in 2012).[7] Asthma in the elderly is associated with higher morbidity and mortality than those in younger populations.[3,8,9] After adjustment for comorbidities, the elderly with asthma had a 5-time higher risk of mortality (odds ratio [OR], 5.2; 95% confidence interval [CI], 4.0–6.9) than do the younger population with asthma.[8] In addition, elderly women with asthma had a 1.87-fold higher risk of asthma exacerbation (AE) than non-elderly men with asthma (95% CI, 1.19–2.93; $P = 0.006$).[7] The reasons for the higher disease burden are multifactorial, including age-related immunosenescence, changes in lung physiology, comorbidity, under-perception of asthma symptoms, and medication underuse.[10-13] Therefore, a more comprehensive assessment and a multidimensional approach is necessary for asthma in the elderly.[14,15]

Severe asthma (SA) is defined as uncontrolled asthma despite use of high dose inhaled corticosteroid (ICS) or a requirement for high intensity treatment to maintain asthma control.[16,17] The prevalence of SA is estimated at 5%–10% among adults with asthma.[18] SA is associated with frequent hospitalization and higher economic costs owing to uncontrolled symptoms and frequent AEs.[18-20] Although the incidence, clinical phenotypes, and characteristics of elderly with asthma have been widely studied, those in elderly patients with SA are not well characterized.[11,15]

The present study aimed to compare the clinical characteristics, comorbidities, control status, and medication use in elderly patients with SA compared to those in non-elderly patients by analyzing data from the Korean Severe Asthma Registry (KoSAR).

## MATERIALS AND METHODS

### Data collection and study design

The KoSAR is a nationwide, multicenter prospective observational study organized by the Working Group on SA, in the Korean Academy of Asthma, Allergy and Clinical Immunology.[21] Currently, allergy or pulmonology specialists from 39 hospitals in South Korea are participating in this study.[22] The inclusion criteria and diagnosis of SA are either as follows: 1) asthmatics who had been treated for longer than one year but did not consistently reach


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a well-controlled status despite Global Initiative for Asthma (GINA) treatment step 4 or 5 or 2) they have a well-controlled asthma after GINA treatment step 4 or 5, but have a history of more than one unscheduled urgent visit or ≥ 3 administrations of systemic corticosteroids in the previous year, they have ever had a near-fatal asthma attack or worsening symptoms when oral corticosteroid (OCS) or ICS was reduced to 25%.[22-24]

The study population was aged ≥ 18 years, and elderly patients were defined as those aged ≥ 65 years at the time of registration. To avoid any controversy about [surrounding] the definition of elderly age, we conducted a thorough review of literature and selected a cutoff of 65 years as in previous studies. The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regiments study,[25] Australasian Severe Asthma network,[26] Korea Cohort for Reality and Evolution of adult Asthma,[27] and another nationwide multicenter elderly asthma cohort in Korea,[28-30] defined the elderly using the 65 years or more cut-off. The KoSAR database included the baseline characteristics of the patients, such as age, sex, smoking history, body mass index (BMI), underlying medical diseases, and history of asthma (age of symptom onset/diagnosis and duration of treatment). In addition, laboratory and lung function test results, including complete blood count, induced sputum cell counts, serum total immunoglobulin E (IgE), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio and fractional exhaled nitric oxide (FeNO) levels were collected. Atopy was defined when a skin prick test or serum specific IgE test showed positive results to at least one inhalant allergen. Type 2 airway inflammation was determined on the basis of the blood/sputum eosinophil counts, FeNO levels, and skin test positivity.[17,22] When patients were either eosinophilic (blood eosinophils ≥ 150 cells/μL, FeNO ≥ 20 ppb, or sputum eosinophil ≥ 2%) or allergic (positive skin test to aeroallergens), they were determined to have type 2 inflammation.

Asthma control status was assessed according to the GINA control level[17] and Asthma Control Test (ACT) score. Quality of Life was measured using the Questionnaire in Adult Korean Asthmatics (QLQAKA).[31] Information about asthma medication prescription, including ICSs, long-acting β2 agonists (LABAs), leukotriene receptor antagonists (LTRAs), long-acting antimuscarinic antagonists (LAMAs), short-acting β2 agonists (SABAs), OCSs, macrolides, phosphodiesterase 4 (PDE4) inhibitors, immunosuppressants, and biologics, was collected. Patients were surveyed for histories of OCS burst treatment and unscheduled hospital visits in the previous year. An OCS burst was defined as the short-term use of OCS lasting at least 3 consecutive days. We analyzed patient data collected between February 2010 and January 2022. This study was approved by the Institutional Review Board (IRB) of each hospital, and informed consent was obtained from all study participants (IRB number: AMC 2017-1382).

## Statistical analyses

For continuous variables, mean and standard deviation were calculated for normally distributed variables, whereas median and interquartile range (IQR, 25th–75th) were used for non-normally distributed data. Proportions were used as categorical variables. Analysis of the differences between the elderly and non-elderly asthma groups was performed using the Student's *t*-test for continuous variables and the $\chi^2$ or Fisher's exact test for categorical variables. The Mann–Whitney *U* test was performed because the values of the 2 groups categorized according to median values did not follow a normal distribution. ORs and their 95% CIs were computed. All tests were two-sided, and a *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA).


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# RESULTS

## Clinical characteristics and comorbidities

Of the 864 enrolled patients with SA, 260 (30.1%) were in the elderly group. The mean age was significantly higher in the elderly group than in the non-elderly group (71.8 ± 5.0 vs. 49.2 ± 10.9 years, $P < 0.001$). Forty-five percent of the patients were male in the elderly group, which was similar to that in the non-elderly group. There were no significant differences in median BMI or obesity rate between the two groups. Smoking history showed differences: the proportion of never-smokers was similar; however, the median smoking pack-years was higher in the elderly group (**Table 1**). Interestingly, age at symptom onset (55.4 ± 16.4 vs. 36.5 ± 13.9 years) and asthma diagnosis (59.4 ± 13.2 vs. 38.5 ± 13.3 years) were significantly higher in the elderly group than in the non-elderly group ($P < 0.001$) (**Fig. 1**). Moreover, treatment durations were similar between the two groups (10.6 ± 12.1 vs. 10.4 ± 10.9 years, $P = 0.856$) (**Fig. 1**). Asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) was determined by the attending specialists of the institute at the time of enrollment based on smoking history, bronchodilator response, and the presence of fixed airway obstruction.[22] The elderly group had a higher prevalence of ACO than the nonelderly group did (44.8% vs. 23.4%, $P < 0.001$). In addition, the elderly group had a higher prevalence of hypertension (52.6% vs. 21.3%, $P < 0.001$) and osteoporosis (19.6% vs. 5.7%, $P < 0.001$) than did the nonelderly group. However, percentages of allergic comorbidities, such as allergic rhinitis (41.4% vs. 72.9%, $P < 0.001$), allergic conjunctivitis (2.7% vs. 13.3%, $P < 0.001$), and atopic dermatitis (3.1% vs. 10.7%, $P < 0.001$), were significantly lower in the elderly group than in the nonelderly group. The prevalence of gastroesophageal reflux (14.3% vs. 28.4%, $P < 0.001$), aspirin-intolerant asthma (1.3% vs. 11.0%, $P < 0.001$), depression (3.9% vs. 8.2%,

**Table 1.** Demographics and clinical characteristics between the elderly and nonelderly groups in 864 severe asthmatics

| Characteristics | Total (n = 864) | Elderly (n = 260) | Nonelderly (n = 604) | *P* value |
|---|---|---|---|---|
| Age (yr) | 56.0 ± 14.0 | 71.8 ± 5.0 | 49.2 ± 10.9 | < 0.001 |
| Male | 388 (44.9) | 117 (45.0) | 271 (44.9) | 0.971 |
| BMI (kg/m$^2$) | 24 (21.9–26.5) | 24.4 (22.4–26.7) | 23.9 (21.7–26.3) | 0.078 |
| < 25 | 533 (61.8) | 151 (58.2) | 382 (63.4) | |
| ≥ 25 | 330 (38.2) | 109 (41.9) | 221 (36.7) | 0.430 |
| Smoking history (n = 861) | | | | 0.034 |
| Never smoker | 491 (57.0) | 148 (56.9) | 343 (57.1) | |
| Ever smoker | 370 (42.9) | 175 (43.1) | 272 (43.0) | |
| Smoking (pack-years) (n = 355) | 17.0 (6.8–33.3) | 32.8 (15.1–48.3) | 14.0 (5.5–26.0) | < 0.001 |
| Asthma/COPD overlap (n = 798) | 240 (30.1) | 112 (44.8) | 128 (23.4) | < 0.001 |
| Comorbidities | | | | |
| Allergic rhinitis (n = 849) | 538 (63.4) | 106 (41.4) | 432 (72.9) | < 0.001 |
| Hypertension (n = 856) | 262 (30.6) | 134 (52.6) | 128 (21.3) | < 0.001 |
| Chronic sinusitis (n = 793) | 243 (30.6) | 38 (16.0) | 205 (36.9) | < 0.001 |
| Gastroesophageal reflux (n = 857) | 207 (24.2) | 37 (14.3) | 170 (28.4) | < 0.001 |
| Allergic conjunctivitis (n = 854) | 86 (10.1) | 7 (2.7) | 79 (13.3) | < 0.001 |
| Osteoporosis (n = 852) | 84 (9.9) | 50 (19.6) | 34 (5.7) | < 0.001 |
| Atopic dermatitis (n = 860) | 72 (8.4) | 8 (3.1) | 64 (10.7) | < 0.001 |
| AERD (n = 760) | 61 (8.0) | 3 (1.3) | 58 (11.0) | < 0.001 |
| History of pulmonary tuberculosis (n = 858) | 62 (7.2) | 23 (8.9) | 39 (6.5) | 0.210 |
| Depression (n = 857) | 59 (6.9) | 10 (3.9) | 49 (8.2) | 0.022 |
| Arrhythmia (n = 855) | 26 (3.0) | 9 (3.5) | 17 (2.8) | 0.587 |
| Anxiety disorder (n = 858) | 28 (3.3) | 3 (1.2) | 25 (4.2) | 0.023 |
| Sleep apnea (n = 859) | 26 (3.0) | 5 (1.9) | 21 (3.5) | 0.222 |
| Heart failure (n = 856) | 14 (1.6) | 6 (2.4) | 8 (1.3) | 0.375 |

Values are presented as mean ± standard deviation, median (interquartile range), or number (%).
BMI, body mass index; COPD, chronic obstructive lung disease; AERD, aspirin exacerbated respiratory disease.


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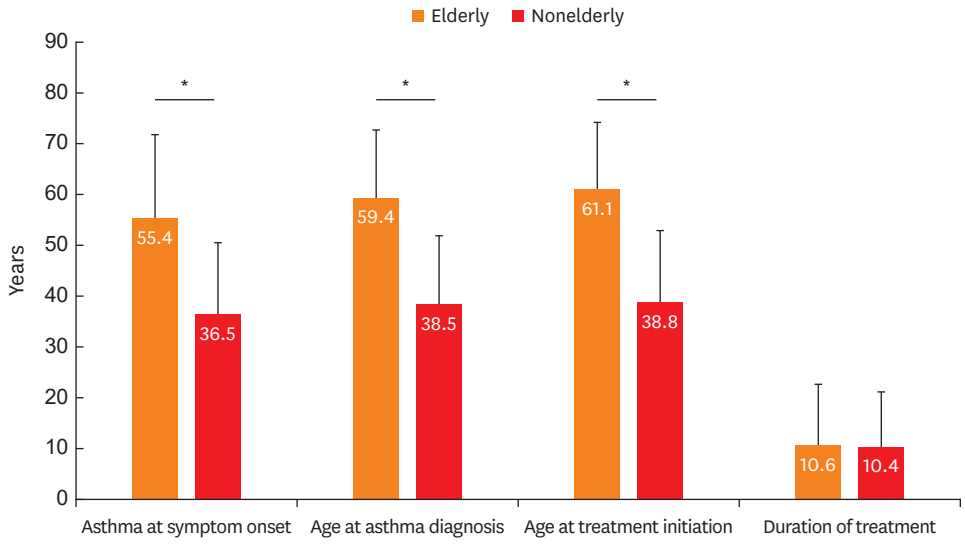


**Fig. 1.** Comparison of asthma history between the elderly and nonelderly groups. The values are expressed as the mean ± standard deviation.
*$P$ < 0.001 compared between the elderly and nonelderly groups.

$P$ = 0.022), and anxiety disorders (1.2% vs. 4.2%, $P$ = 0.023) was also lower in the elderly group than in the nonelderly group. There were no significant differences in the histories of pulmonary tuberculosis, arrhythmia, heart failure, or sleep apnea between the 2 groups.

**Table 2** shows the laboratory findings and pulmonary function test results for both groups. Blood and sputum eosinophils were higher in the nonelderly group than in the elderly group (blood: 2.3% [1%–5.3%] vs. 3.8% [1.4%–8%], $P$ < 0.001; sputum: 3.0% [0%–13%] vs. 5.0% [1%–45%], $P$ = 0.004). FeNO and total IgE levels were lower in the elderly group than in the non-elderly group (FeNO: 28.0 [15.0–49.0] vs. 40.0 [22.0–66.0], $P$ = 0.006, IgE: 134.0 [45.3–312.6] vs. 242.9 [93.6–667.0], $P$ = 0.005). Moreover, the number of patients with type 2 inflammation was significantly lower in the elderly group than in the non-elderly group

**Table 2.** Comparisons of laboratory findings and lung function between the elderly and nonelderly groups in 864 severe asthmatics

| Variables | Total (n = 864) | Elderly (n = 260) | Nonelderly (n = 604) | *P* value |
|---|---|---|---|---|
| Laboratory tests | | | | |
| WBC (/μL) (n = 785) | 7.8 (6.4–9.6) | 7.9 (6.4–10.0) | 7.7 (6.4–9.5) | 0.483 |
| Blood eosinophils (/mL) (n = 777) | 241.4 (98.8–540.2) | 172 (72.0–389.2) | 283.1 (110.2–585.3) | < 0.001 |
| Blood eosinophils (%) (n = 777) | 3.2 (1.2–7.2) | 2.3 (1.0–5.3) | 3.8 (1.4–8.0) | < 0.001 |
| Sputum Neutrophils (%) (n = 239) | 50.0 (15.3–85) | 56.5 (18.0–82.0) | 44 (14.7–85.0) | 0.822 |
| Sputum Eosinophils (%) (n = 232) | 4.8 (1.0–27.5) | 3.0 (0–13.0) | 5.0 (1.0–45.0) | 0.004 |
| FeNO (ppb) (n = 318) | 35.0 (20.0–62.0) | 28.0 (15.0–49.0) | 40.0 (22.0–66.0) | 0.006 |
| Total IgE (IU/mL) (n = 251) | 199.7 (81.3–547.9) | 134.0 (45.3–312.6) | 242.9 (93.6–667.0) | 0.005 |
| Pulmonary function test | | | | |
| FVC (% predicted) (n = 835) | 79.5 (69.8–89.0) | 76.0 (65.0–87.5) | 80.9 (71.0–89.8) | < 0.001 |
| FEV1 (% predicted) (n = 836) | 67.8 (55.3–78.0) | 65.1 (50.8–77.0) | 68.4 (57.0–78.5) | 0.013 |
| FEV1/FVC (n = 841) | 68.2 (59.3–76.5) | 64.7 (55.1–73.4) | 69.3 (61.1–78.3) | < 0.001 |
| Type 2 inflammation | 656 (75.9) | 168 (64.6) | 488 (80.8) | < 0.001 |
| Blood eosinophils ≥ 150 cells/μL | 498 (64.1) | 131 (56.7) | 367 (67.2) | 0.005 |
| FeNO ≥ 20 ppb | 241 (75.8) | 50 (64.9) | 191 (79.3) | 0.011 |
| Sputum eosinophil ≥ 2% | 154 (66.4) | 42 (58.3) | 112 (70.0) | 0.082 |
| Skin test positivity | 196 (46.9) | 28 (28.9) | 168 (52.3) | < 0.001 |

Type 2 inflammation was defined when the patients were either eosinophilic phenotype (blood eosinophils ≥ 150 cells/μL, FeNO ≥ 20 ppb, or sputum eosinophil ≥ 2%) or allergic (positive skin test to aeroallergens). Values are presented as median (interquartile range) or number (%).
WBC, white blood cell; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second.


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**Table 3.** Comparisons of asthma control, symptom exacerbation and quality of life between the elderly and nonelderly groups in 864 severe asthmatics

| Variables | Total (n = 864) | Elderly (n = 260) | Nonelderly (n = 604) | *P* value |
|---|---|---|---|---|
| ACT score (n = 840) | 19.0 (14.0–22.0) | 19.0 (15.0–23.0) | 19.0 (14.0–22.0) | 0.129 |
| QLQAKA (n = 841) | 62.0 (50.0–73.0) | 64.0 (53.0–73.0) | 62.0 (49.0–72.0) | 0.219 |
| Steroid burst treatment for at least 3 days in the previous year (n = 698) | 173 (22.0) | 69 (28.3) | 104 (19.1) | 0.065 |
| Number of steroid burst treatment in the previous year (n = 682) | | | | |
| ≥ 2 times in the previous year | 212 (31.1) | 53 (26.8) | 159 (32.9) | 0.119 |
| Presence of unscheduled visit in the previous year | | | | |
| Outpatient department visit (n = 860) | 211 (24.5) | 55 (21.2) | 156 (26.0) | 0.129 |
| Emergency department visit (n = 859) | 143 (16.7) | 35 (13.5) | 108 (18.0) | 0.099 |
| Hospitalization (n = 861) | 181 (21.0) | 53 (20.4) | 128 (21.3) | 0.763 |
| Intensive care unit admission (n = 859) | 10 (1.2) | 2 (0.8) | 8 (1.3) | 0.732 |

Values are presented as median (interquartile range) or number (%).
ACT, asthma control test; QLQAKA, Quality of Life Questionnaire for Adult Korean Asthmatics.

(64.6% vs. 80.8%, $P < 0.001$). The baseline FEV1 (% predicted) and FEV1/FVC ratio (65.1% [50.8%–77%] vs. 68.4% [57%–78.5%], $P = 0.013$; 64.7 [55.1–73.4] vs. 69.3 [61.1–78.3], $P < 0.001$) were significantly lower in the elderly group than in the nonelderly group.

## Symptom control, AE, and quality of life

**Table 3** compares asthma control status, AE rate and quality of life scores between the elderly and non-elderly groups. There were no significant differences in the median ACT and QLQAKA scores between the two groups. When analyzing the prevalence of steroid burst treatment in the previous year based on patient recall, 173 (22.0%) patients experienced OCS burst treatment, a rate that was higher in the elderly group than in the non-elderly group without statistical significance (28.3% vs. 19.1%, $P = 0.065$). Among the 682 patients, 31.1% experienced 2 or more OCS burst treatments in the previous year, and the AE rates were similar (26.8% vs. 32.9%, $P = 0.119$) between the 2 groups. No significant differences were noted in the frequencies of unscheduled hospital visits in the previous year, including outpatient/inpatient clinics, emergency departments, and hospitalizations, between the 2 groups.

## Asthma medications

**Table 4** and **Fig. 2** summarize medication prescriptions for asthma in the enrolled patients. Most patients had used ICS-LABAs and LTRAs, with no statistical differences between the

**Table 4.** Use of biologics and maintenance OCS in the study subjects

| Variables | Total (n = 864) | Elderly (n = 260) | Nonelderly (n = 604) | *P* value |
|---|---|---|---|---|
| ICS-LABA | 809 (93.6) | 240 (92.3) | 569 (94.2) | 0.295 |
| LTRA | 655 (75.8) | 193 (74.2) | 462 (76.5) | 0.477 |
| LAMA | 368 (42.6) | 122 (46.9) | 246 (40.7) | 0.091 |
| Macrolides | 30 (3.5) | 8 (3.1) | 22 (3.6) | 0.677 |
| Phosphodiesterase 4 inhibitor | 20 (2.3) | 5 (1.9) | 15 (2.5) | 0.615 |
| Immunosuppressants | 12 (1.4) | 1 (0.4) | 11 (1.8) | 0.121 |
| Biologics (n = 135) | | | | |
| Any biologics | 107 (12.4) | 19 (7.3) | 88 (14.6) | 0.003 |
| Mepolizumab | 43 (5.0) | 9 (3.5) | 34 (5.6) | 0.179 |
| Reslizumab | 43 (5.0) | 9 (3.5) | 34 (5.6) | 0.179 |
| Omalizumab | 22 (2.6) | 1 (0.4) | 21 (3.5) | 0.008 |
| Dupilumab | 11 (1.3) | 0 (0.0) | 11 (1.8) | 0.040 |
| Benralizumab | 2 (0.2) | 0 (0.0) | 2 (0.3) | 1.000 |
| OCS dependency | 166 (30.3) | 53 (33.5) | 113 (29) | 0.292 |
| Total OCS dose for 6 months (mg) (n = 510) | 420 (200–900) | 420 (210–900) | 420 (200–900) | 0.746 |
| Daily maintenance OCS dose (mg) (n = 166) | 6.1 (3.3–8.8) | 5.0 (4.4–7.5) | 6.2 (2.7–9.8) | 0.488 |

OCS dependency was determined at enrollment when the maintenance OCS treatment lasted more than 6 months during the previous year. Values are presented as median (interquartile range) or number (%).
OCS, oral corticosteroid; ICS, inhaled corticosteroid; LABA, long-acting β2 agonist; LTRA, leukotriene receptor antagonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β2 agonist.


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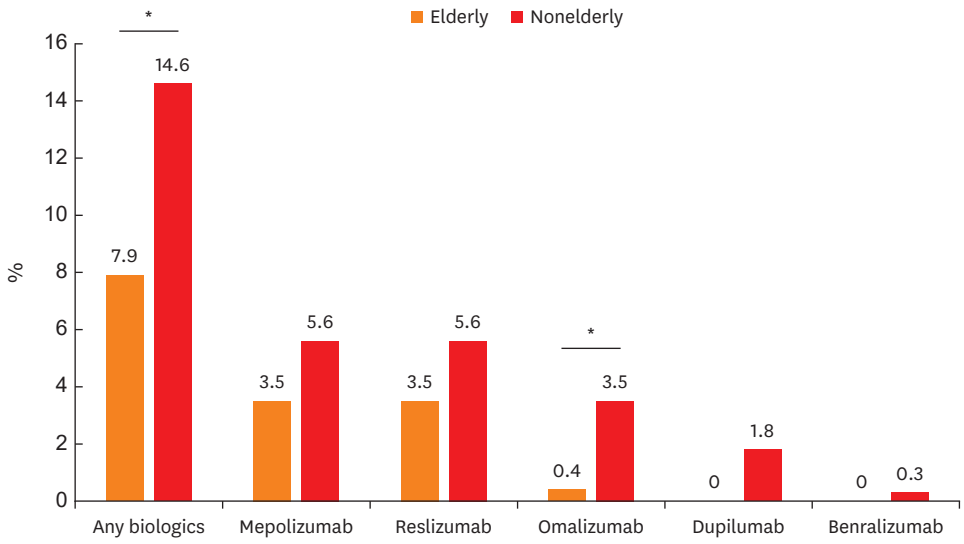


**Fig. 2.** Use of biologics between the elderly and nonelderly groups. The values are expressed as percentage (%).
*$P$ < 0.01 compared between the elderly and nonelderly groups.

two groups. The percentage of LAMA use tended to be higher in the elderly group than in the non-elderly group without statistical significance ($P$ = 0.091). Some patients had used macrolides, PDE4 inhibitors, or immunosuppressants; however, the percentages were similar between the 2 groups. Among the 864 patients, 107 (12.4%) had used biologics; the percentage of patients who had used biologics was significantly lower in the elderly group than in the nonelderly group (7.3% vs. 14.6%, $P$ = 0.003). The elderly group had used omalizumab and dupilumab less frequently compared to what the non-elderly group used ($P$ = 0.008 and $P$ = 0.040, respectively). The frequency of anti-interleukin (IL)-5 inhibitor use, including mepolizumab, reslizumab, and benralizumab, was not different between the 2 groups. Finally, we analyzed whether the patients had an OCS dependency, which was defined at enrollment as maintenance OCS treatment lasting for > 6 months during the previous year.[22] Of total patients, 166 (30.3%) had OCS dependency, and these proportions were not different between the elderly and non-elderly groups; the total and daily maintenance OCS doses were not significantly different between the 2 groups.

## DISCUSSION

This study demonstrated a high rate of elderly patients (30%) among patients with severe asthma and compared clinical characteristics between the elderly and nonelderly groups in this real-world, multicenter SA cohort. SA in the elderly was characterized by lower lung function and lower type 2-low inflammation with higher ACO rate, while no differences were noted in asthma control status or AE rate compared to those in the non-elderly. Considering these different characteristics between elderly and non-elderly groups is necessary to determine treatment strategies and predict outcomes. Physicians should be aware of these characteristics in managing elderly patients with SA.

Studies on the prevalence of SA in the elderly are limited. The probability of severe asthma increased by 7% annually up to the age of 45, according to the Severe Asthma Research Program (SARP).[32] The British Thoracic Society (BTS) Severe Asthma Registry found that


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elderly patients (aged ≥ 65 years) were 16.2% among the 896 patients with SA.[33] The present study demonstrated a higher rate (30%) of elderly patients in those with SA, which was remarkably higher than that of the BTS registry. A previous study based on a cohort of elderly patients with asthma in Korea reported a high prevalence (31.3%) of SA, when SA was defined using the European Respiratory Society/American Thoracic Society criteria.[16,34] In addition, the mean age of SA patients in the present study was older than that in the International Registry (based on data from Western countries).[35] The reason for this older age in SA patients could be the higher prevalence of late-onset asthma in this cohort, and a rapidly aging population in this region.[15,35] Also, given that the mean age of SA patients from the Japanese Severe Asthma Registry (KEIO-SARP) was even higher than that of our cohort (60.1 ± 14.9 vs. 56.0 ± 14.0),[36] there appears to be a higher rate of elderly patients among those who have SA in Asian countries than in Western countries. Taken together, considering an increasing prevalence of SA in the elderly and their different characteristics in Asian countries, additional investigations are needed for optimized treatment for elderly patients with SA according to region.

When phenotyping asthma patients based on age, the age of asthma onset might be clinically more relevant than the current age. This is supported by the previous literature that clustered data from large multicenter asthma cohorts.[37-39] Another study described that a long duration of the disease contributed to accelerated lung function decline and frequent acute exacerbations in elderly asthma.[30] In the elderly group, 229 (88.1%) patients were at late onset (onset age of ≥ 40 years), with an older asthma-onset age and shorter disease duration compared to results from the BTS registry.[33] The phenotype of late-onset asthma was characterized by lower atopy rate, obesity, female predominance, and higher smoking rate.[10,40] The elderly group in our cohort had lower atopy rate and higher smoking pack-years than did the non-elderly group, with no statistically significant differences between the patients with late-onset and those without (data not shown). This suggests that the late-onset phenotype might contribute to the development of SA in the elderly. Moreover, when defining treatment strategies, it might be beneficial to consider onset age or disease duration, along with other clinical characteristics, including allergic comorbidities and airway eosinophil inflammation. The asthma-onset age may be related to responses to biologics. Patients with late-onset asthma tended to respond to anti-IL-5 or anti-IL-5 receptor antibody rather than anti-IgE antibody,[41] which was consistent with a lower prescription rate of omalizumab in our cohort.

In addition, the present study demonstrated lower blood/sputum eosinophils as well as lower FeNO/total IgE levels in the elderly group compared to the non-elderly group, which were comparable to those in the BTS registry.[33] Moreover, the elderly group showed lower type 2 inflammation features than did the non-elderly group, resulting in lower prescription rates of type 2 biologics in our cohort. Although additional studies are needed, strategies targeting non-type 2 inflammation are required for the management of elderly patients with SA.

The present study demonstrated lower lung function parameters (lower FEV1%, FEV1/FVC ratio) and higher smoking pack-years in the elderly group than in the nonelderly group, which is associated with high prevalence of ACO. The previous study reported that adults with asthma with ACO were old and had low FEV1% and FEV1/FVC ratio.[23] Another study found the prevalence of ACOS among primary health care asthmatics to be high (27.4%) in patients with a positive smoking history.[42] Altogether, in real-world practice, SA in the elderly is frequently associated with ACO as well as late-onset asthma, leading to progressive lung function decline and poor clinical outcomes.


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Given that the lung function parameters decrease with age and that FEV1 is one of the parameters defining asthma severity, characterization of the elderly with SA by lower FEV1 and comorbidity with COPD may be controversial. However, the FEV1 (% predicted) used in this analysis was an age-adjusted value and the difference in FEV1% between the elderly and nonelderly groups was statistically significant (**Table 2**). Moreover, based on a recent longitudinal population study, frequent AEs rather than age were associated with rapid FEV1 decline in asthma.[43] Smoking, atopy, airway hyperreactivity and medication adherence were risk factors for accelerated FEV1 decline in asthma patients.[44-46] Moreover, asthma patients, later in life (> 35 years), had the most reduced FEV1 at baseline and accelerated FEV1 decline (< 35 years 11.0 mL/year, 35–64 years 18.2 mL/year, and > 64 years 30.8 mL/year) than those diagnosed before age 35 years.[47] Our study result showed that the elderly patients with SA had decreased FEV1 despite similar asthma control status and histories of AE compared to non-elderly severe asthmatics. These results may be explained by their late-onset characteristic whereas heavy smoking history might contribute to decreased lung function in the elderly population.

Despite these lower lung function test results, asthma control status, AE frequency and quality of life scores as well as OCS uses were not different between the elderly and non-elderly groups, which were comparable to the results of the BTS registry.[33] Although these findings are not fully explained, one possibility is that the elderly with asthma are less aware of bronchoconstriction despite lower FEV1%[12]; the lower rate of current smokers and less occupational exposure may be factors in this explanation. Additionally, close observation by asthma specialists through the National Medical Insurance system could decrease unscheduled visits in this cohort. Considering that asthma severity is frequently determined retrospectively based on the level of symptom control and exacerbation frequencies, the severity in the two groups was similar except for the lung function criterion and current age of the patient with SA, which in itself does not explain the disease severity in our analysis. However, lower FEV1% is a major risk factor that may predict AEs in elderly asthma patients.[28] Physicians' efforts for preventing AEs are needed in the management of SA in elderly.

The management of comorbidities is essential in the management of SA, especially in elderly patients. Among comorbidities, chronic rhinosinusitis (CRS) and/or nasal polyps, obesity, and depression were associated with poor asthma outcomes in elderly with asthma.[48-50] The prevalence of CRS and nasal polyps increased with aging in adults,[51] and airway inflammatory phenotypes in upper airways may be similar to those in lower airways among patients with asthma comorbid with CRS.[52] The present study demonstrated that prevalence of hypertension and osteoporosis as well as COPD was higher in the elderly group than in the nonelderly group, but allergic rhinitis, allergic conjunctivitis, CRS, and atopic dermatitis were less frequently observed in the elderly group, which may be associated with less atopy in the elderly group. It was suggested that CRS and obesity affect asthma development or severity in the elderly.[29,53] Some previous studies have shown greater decline of annual FEV1%[47] and reduced responses to methacholine in the elderly with asthma than in the non-elderly with asthma.[54] IgE sensitization to Staphylococcus enterotoxins was associated with the severity of asthma in elderly patients.[55] Further investigations are needed to evaluate different effects of comorbid conditions on elderly patients with SA.

This study has several limitations. First, this is a cross-sectional study with a lack of prospective observation on future risk of AE and changes in symptom scores. Further longitudinal outcome studies on SA are needed to validate these findings. Secondly, the age of symptom onset and disease duration were self-reported by the patients, which might


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have resulted in recall bias. Information on asthma onset time was based on the response of the participants to the question without objective medical records. We were unable to determine whether the difference between the two groups could be explained simply by the current age or the onset time of asthma based on our findings. Therefore, the results should be interpreted with caution. The present study is based on a single-nation cohort (a homogenous Korean population) and has limitations in identifying racial differences. Thirdly, the results of inflammatory biomarkers, including blood/sputum eosinophils and FeNO levels, could be biased due to medication effects or missing values. Finally, the diagnosis of comorbidities was established mainly by patients' recall, which could have caused a recall bias. However, the present study reflects the real-world clinical practice of asthma specialists with a nationwide multicenter approach in Korea. Most clinical trials of biologics frequently excluded elderly patients with SA because of smoking history, comorbidity, or COPD features, and the effect of biologics targeting type 2 inflammation needs real-world evidence in elderly patients. Our study result could provide valuable data in the era of biologic use for better control of elderly patients with SA.

In conclusion, SA in the elderly is characterized by low lung function, less type 2-low airway inflammation, and high prevalence of ACO, results that are being taken into consideration for the optimized management of elderly patients with SA in real-world clinical practice.

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