



Characteristics and asthma control status in the Korean Severe Asthma Registry-2: a real-world analysis

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About half of patients with severe asthma in Korea had poor asthma control at baseline. Low socioeconomic status was linked to poor control, while T2 inflammation was associated with better control, highlighting the need for clinical and social support. <https://bit.ly/4hiElPQ>

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Abstract

Background Severe asthma is associated with poor asthma control, leading to poor outcomes. However, few studies have evaluated asthma control status in patients with severe asthma in the biologic era. This study aimed to evaluate baseline asthma control in patients with severe asthma using phase 2 of the Korean Severe Asthma Registry (KoSAR-2).

Methods Adult subjects meeting the international consensus definition of severe asthma were prospectively enrolled from 41 hospitals in Korea (March 2022 to June 2023). Data on demographics, comorbidities, lung function, inflammation and healthcare utilisation were collected. Using asthma control test (ACT) scores, patients were classified into a well-controlled asthma group (ACT ≥20) and poorly controlled asthma group (ACT <20).

Results Among 594 severe asthma patients, 51.9% had poorly controlled asthma. Multivariable analysis showed that medical aid (adjusted odds ratio (aOR)=5.515, 95% confidence interval (CI) 2.614–13.110,

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$p < 0.001$), being underweight (aOR=4.129, 95% CI 1.081–20.192), forced expiratory volume in 1 s $< 60\%$ predicted (aOR=1.854, 95% CI 1.090–3.175) and prior exacerbations (aOR=3.400, 95% CI 1.987–6.012) were associated with poorly controlled asthma, while T2 inflammation was associated with well-controlled asthma (aOR=0.560, 95% CI 0.316–0.977). However, biologic use was not associated with asthma control status.

Conclusions About half of patients with severe asthma in KoSAR-2 had poorly controlled asthma at baseline. While poor socioeconomic status reflected by medical aid was a key factor underlying poor asthma control, T2 inflammation was associated with better asthma control in severe asthma. These findings underscore the importance of both clinical management and socioeconomic support to improve asthma control outcomes.

Introduction

Severe asthma is defined as asthma that remains uncontrolled despite high levels of treatment or that requires intensive therapy to maintain good symptom control and reduce exacerbations [1]. It affects ~5–10% of the total asthma population; however, its impacts on individual quality of life and public healthcare cost are significant compared to mild to moderate asthma [2]. In Korea, the prevalence of severe asthma has been reported to range from 1.6% to 6.1%, and healthcare utilisation and asthma-related costs are increasing more over time for those with severe asthma than those with non-severe asthma [3, 4]. Given the substantial burden of severe asthma, a better understanding of its epidemiology, disease mechanisms and the effectiveness of novel biologics is highly needed in clinical practice. As guidelines are evidence-based and rely on randomised controlled trial data that may not fully reflect real-world settings, each country has organised national registries for severe asthma. Registry data have provided insights into country-specific epidemiological characteristics, risk factors and treatment patterns, which are important for translational research as well as healthcare policy development [5].

In Korea, a national registry of severe asthma was established in 2011 by the Korean Academy of Asthma, Allergy and Clinical Immunology (KAAACI) Working Group on Severe Asthma and named the Korean Severe Asthma Registry (KoSAR). This registry was established to estimate the burden and treatment status of patients with severe asthma and to develop better strategies for management of this condition [6]. During the past decade, novel biologics targeting type 2 (T2) inflammation became available in clinical practice, and the concept of severe asthma evolved from an umbrella term to a heterogeneous clinical syndrome. Phase 2 of the Korean Severe Asthma Registry (KoSAR-2) was initiated in 2022 to assess longitudinal outcomes in patients with severe asthma in Korea [2, 7].

Asthma control is a core concept in asthma management and is considered a critical outcome as it reflects the effectiveness of current treatment regimens and provides insights into patients' daily functioning and well-being [5]. In addition, asthma control is an important predictor of future outcomes such as exacerbations, lung function decline, oral corticosteroid use and economic costs [8]. Although T2 biologics enable better asthma control and reduce the risk of exacerbations, decreased lung function and oral corticosteroid use, a significant number of patients on biologics still have uncontrolled severe asthma [9]. The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) II cohort study reported 58.1% of subjects had very poorly controlled asthma, while only 7.7% of patients achieved well-controlled asthma, according to the National Heart, Lung and Blood Institute asthma guidelines [10]. A multinational, observational and real-world study of patients with severe asthma reported that 81% of severe asthmatic patients had uncontrolled asthma (based on an Asthma Control Questionnaire-5 (ACQ-5) score of ≥ 1.5) [11]. Previous studies have identified several variables associated with poor asthma control, including smoking, comorbidities such as psychological problems or obesity, and socioeconomic status [12, 13]. Thus, in this era of recent advances in biologics for asthma control, registry-based studies are valuable for identifying real-world determinants of asthma control and can improve severe asthma management strategies.

This study aims to describe the demographic and clinical characteristics of patients with severe asthma in Korea based on asthma control status and to identify factors associated with poor asthma control.

Material and methods

Study participants

We analysed baseline data from KoSAR-2, a nationwide, multicentre prospective registry initiated in 2022 with support from the Korea National Institute of Health. KoSAR-2 is an expansion of the original KoSAR, established in 2011, and was renamed to reflect updated data collection protocols, the inclusion of new clinical variables, and broader participation from tertiary and secondary hospitals. The registry collects a more comprehensive range of data, including patient-reported outcomes, biomarker profiles and detailed

treatment information. Patients are followed longitudinally at regular intervals to assess their clinical characteristics and long-term outcomes in severe asthma [6]. Patients aged ≥ 18 years with a diagnosis of severe asthma according to the European Respiratory Society (ERS)/American Thoracic Society (ATS) criteria were eligible for enrolment in this registry (supplementary figure S1) [1]. Briefly, asthma patients who required treatment for Global Initiative for Asthma (GINA) steps 4–5 asthma or who used systemic corticosteroids for $\geq 50\%$ of the previous year to prevent their asthma becoming “uncontrolled” or who had “uncontrolled” asthma despite this therapy were considered to have severe asthma. Uncontrolled asthma is referred to as: 1) an asthma control test (ACT) score < 20 or uncontrolled state based on GINA guidelines, 2) frequent severe exacerbations (≥ 2 bursts of systemic corticosteroid for ≥ 3 days), 3) serious exacerbations such as at least one hospitalisation, intensive care unit stay or mechanical ventilation, and 4) persistent airflow limitations. Exclusion criteria included other respiratory diseases (e.g., severe bronchiectasis, tuberculosis-destroyed lung, interstitial lung disease), serious mental illness, major comorbidities (e.g., severe heart, renal or liver disease) and chronic oral corticosteroid use for non-asthma-related conditions. The study protocol was approved by the institutional review board (IRB) of each participating hospital, and informed consent was obtained from all study participants (IRB number: HALLYM 2022-04-020).

Data collection

Patients’ demographic information (age, sex, body mass index (BMI), smoking history), asthma history (symptom onset, asthma duration, asthma medications) and comorbidities (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, chronic rhinosinusitis, osteoporosis, anxiety disorders) were collected using online structured questionnaires and items. The insurance type was categorised into national health insurance, medical aid type 1, medical aid type 2 and others according to the Korean National Health Insurance (NHI) System [14]. Laboratory parameters (complete blood cell counts with differential and total IgE), allergen sensitisation evaluation using skin-prick tests, the multiple allergen simultaneous test, or the immunoCAP assay for common inhalant allergens, and lung function (pre-bronchodilator forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC and forced expiratory flow (FEF) at 25–75% of FVC (FEF_{25-75})), and fraction of exhaled nitric oxide (F_{ENO}) were also collected. Lung function tests and F_{ENO} measurements were performed at each institution in accordance with the ATS/ERS guidelines [15, 16].

Asthma control questionnaires

Standardised questionnaires including the ACT, severe asthma questionnaire (SAQ), SAQ-visual analogue scale (VAS), and EuroQoL 5-Dimension 5-Level (EQ-5D-5L) were measured at baseline. The ACT assesses asthma control over the past 4 weeks using five items (score range: 5–25); scores ≥ 20 indicate well-controlled asthma, while those < 20 indicate poor control [13, 17]. The SAQ consists of 16 items rated on a 7-point scale, averaged for a total score [18, 19]. The EQ-5D-5L consists of two parts: a descriptive system (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a visual analogue scale (EQ-VAS) [20]. The EQ-5D-5L includes a descriptive system (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a VAS. The index score ranges from < 0 to 1 (1=perfect health), and the EQ-VAS from 0 to 100 (higher scores=better health). Symptom severity (cough, sputum, wheezing, throat discomfort, breathlessness) over the past week was assessed using self-reported VAS scores ranging from 0 to 100, with higher scores indicating greater severity [21].

Statistical analysis

Categorical variables are presented as counts and percentages, while continuous variables are presented as mean $\pm$ SD or medians with interquartile ranges (Q1–Q3), as appropriate. Group differences were assessed using the χ^2 test or Fisher’s exact test for categorical variables, and the independent t-test or Mann–Whitney U-test for continuous variables, depending on normality. FEV_1 (% pred), F_{ENO} , blood eosinophil count (BEC), sputum eosinophils and BMI were categorised based on clinically relevant thresholds. $FEV_1\%$ was classified as $< 60\%$ or 60–80%, reflecting the severity of airflow obstruction. Markers of T2 inflammation were categorised based on GINA guidelines: $BEC \geq 150$ cells μL^{-1} , $F_{ENO} \geq 20$ ppb and sputum eosinophils $\geq 2\%$ [22]. BMI was classified according to standard categories for the Asian population: underweight (< 18.5 kg $\cdot m^{-2}$), normal weight (18.5–22.9 kg $\cdot m^{-2}$), overweight (23.0–24.9 kg $\cdot m^{-2}$) and obese (≥ 25.0 kg $\cdot m^{-2}$) [23].

Variables that showed statistically significant differences in demographic and clinical characteristics between groups based on an ACT score of 20 were included in univariable and multivariable logistic regression analyses to identify factors associated with poor asthma control. Variables with $p < 0.1$ in univariable analysis were included in the multivariable model. All analyses were conducted using SAS

TABLE 1 Comparison of baseline characteristics of severe asthmatic patients with control asthma *versus* those with uncontrolled asthma based on ACT score

	Total	Controlled status (ACT score ≥ 20)	Uncontrolled status (ACT score < 20)	p-value
Patients, n	594	286	308	
Age, years, mean$\pm$SD	57.3 $\pm$ 13.3	58 $\pm$ 12.2	56.6 $\pm$ 14.2	0.275
Male sex, n (%)	241 (40.6)	126 (44.1)	115 (37.3)	0.096
BMI, kg·m⁻², mean$\pm$SD (n=593)	25.1 $\pm$ 4.3	24.8 $\pm$ 3.7	25.5 $\pm$ 4.8	0.129
<18.5, n (%)	15 (2.5)	3 (1.1)	12 (3.9)	0.027
18.5 to 23, n (%)	177 (29.9)	93 (32.5)	84 (27.4)	
23 to 25, n (%)	141 (23.8)	75 (26.2)	66 (21.5)	
≥ 25 , n (%)	260 (43.8)	115 (40.2)	145 (47.2)	
Smoking history, n (%)				0.620
Never-smoker	362 (60.9)	170 (59.3)	192 (62.3)	
Ex-smoker	186 (31.3)	95 (33.2)	91 (29.6)	
Current smoker	46 (7.8)	21 (7.3)	25 (8.1)	
Asthma history				
Age at symptom onset, years, mean $\pm$ SD	41.1 $\pm$ 16.5	41.6 $\pm$ 15.6	40.7 $\pm$ 17.4	0.554
Age at asthma diagnosis, years, mean $\pm$ SD	43.4 $\pm$ 15.6	43.4 $\pm$ 15	43.3 $\pm$ 16.1	0.767
Duration of diagnosis, years, mean $\pm$ SD	13.9 $\pm$ 11.2	14.6 $\pm$ 11.4	13.3 $\pm$ 10.9	0.100
Presence of unscheduled visit in the previous year, n (%)	96 (16.2)	25 (8.7)	71 (23.1)	<0.001
Emergency department visits	63 (10.6)	17 (5.9)	46 (15.0)	<0.001
Hospitalisation	69 (11.6)	18 (6.3)	51 (16.6)	<0.001
Intensive care unit admission	6 (1.0)	1 (0.4)	5 (1.6)	0.218
Comorbidities, n (%)				
Allergic rhinitis	381 (64.6)	187 (65.6)	194 (63.6)	0.610
Chronic sinusitis	196 (33.2)	100 (35.1)	96 (31.5)	0.352
Hypertension	184 (31.2)	82 (28.8)	102 (33.4)	0.221
Gastroesophageal reflux	148 (25.1)	64 (22.5)	84 (27.5)	0.155
COPD	81 (13.7)	41 (14.4)	40 (13.1)	0.654
Osteoporosis	71 (12.0)	40 (14.0)	31 (10.2)	0.149
Depression or anxiety disorder	50 (8.5)	17 (6.0)	33 (10.8)	0.034
Allergic conjunctivitis	45 (7.6)	19 (6.7)	26 (8.5)	0.396
Atopic dermatitis	42 (7.1)	17 (6.0)	25 (8.2)	0.292
History of pulmonary tuberculosis	38 (6.4)	12 (4.2)	26 (8.5)	0.033
Arrhythmia	19 (3.2)	9 (3.2)	10 (3.3)	0.934
Sleep apnoea	19 (3.2)	7 (2.5)	12 (3.9)	0.309
Heart failure	8 (1.4)	4 (1.4)	4 (1.3)	>0.999
Insurance type, n (%)				<0.001
National health	525 (88.4)	276 (96.4)	249 (80.8)	
Medical aid type 1	43 (7.2)	5 (1.8)	38 (12.3)	
Medical aid type 2	15 (2.5)	4 (1.4)	11 (3.6)	
Others	11 (1.9)	1 (0.4)	10 (3.3)	
Private health insurers	363 (61.1)	175 (61.2)	188 (61.0)	0.970

Bold for p-values denotes statistical significance. ACT: asthma control test; BMI: body mass index.

version 9.4 (SAS Institute Inc., Cary, NC, USA), and a two-sided p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study subjects

A total of 594 patients were enrolled (table 1), with a mean age of 57.3 $\pm$ 13.3 years and a female predominance (M:F=1:1.46). Of the participants, 60.9% were never-smokers, and the mean age of asthma onset was 41.1 $\pm$ 16.5 years. Common comorbidities were allergic rhinitis (64.6%), chronic rhinosinusitis (33.2%), hypertension (31.2%) and gastroesophageal reflux (25.1%).

At baseline, 48.1% of patients had well-controlled asthma (ACT ≥ 20), whereas 51.8% had poorly controlled asthma (ACT < 20). BMI distribution varied significantly between the two groups ($p=0.027$). The patients with ACT < 20 had a higher rate of previous pulmonary tuberculosis (TB) and depression/

TABLE 2 Comparison of asthma medication use based on ACT score

	Total	Controlled status (ACT score ≥ 20)	Uncontrolled status (ACT score < 20)	p-value
Patients, n	594	286	308	
GINA treatment step, n (%) (n=590)				0.341
Step 4	208 (35.3)	106 (37.2)	102 (33.4)	
Step 5	382 (64.8)	179 (62.8)	203 (66.6)	
ICS/LABA, n (%)	571 (96.1)	274 (95.8)	297 (96.4)	0.694
ICS/LAMA, n (%)	335 (56.4)	150 (52.5)	185 (60.1)	0.061
ICS/LABA/LAMA, n (%)	324 (54.6)	147 (51.4)	177 (57.5)	0.138
LTRA, n (%)	471 (79.3)	225 (78.7)	246 (79.9)	0.719
Macrolides, n (%)	45 (7.6)	16 (5.6)	29 (9.4)	0.078
Phosphodiesterase 4 inhibitors, n (%)	15 (2.5)	5 (1.8)	10 (3.3)	0.245
Immunosuppressants, n (%)	6 (1.0)	2 (0.7)	4 (1.3)	0.687
Biologics, n (%)	162 (27.3)	85 (29.7)	77 (25.1)	0.205
Mepolizumab	13 (2.2)	11 (3.9)	2 (0.7)	0.008
Reslizumab	49 (8.3)	24 (8.4)	25 (8.1)	0.903
Omalizumab	41 (6.9)	23 (8)	18 (5.8)	0.291
Dupilumab	53 (8.9)	25 (8.7)	28 (9.1)	0.881
Benralizumab	11 (1.9)	5 (1.8)	6 (2.0)	0.857
Tezepelumab	1 (0.2)	0 (0.0)	1 (0.3)	>0.999
Systemic steroid[#] use as maintenance dose, n (%) (n=323)	106 (32.8)	44 (33.9)	62 (32.1)	0.747
Dose, mg·day ⁻¹ , median (IQR) (n=106)	9.48 (5–20)	6.75 (5–18)	10 (5–20)	0.346

Bold for p-values denotes statistical significance. ACT: asthma control test; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; LABA: long-acting β_2 agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist. [#]: systemic steroid was calculated as the prednisolone equivalent dose.

anxiety disorders than those with ACT ≥ 20 ($p=0.033$ and $p=0.034$, respectively). Insurance type was also significantly different between groups, with medical aid more common in those with ACT < 20 ($p<0.001$). The incidence of unscheduled visits in the previous year was also significantly higher in patients with ACT < 20 than in those with ACT ≥ 20 ($p<0.001$, respectively).

There was no difference between the two groups in GINA step classifications (table 2). Use of inhaled corticosteroid (ICS)/long-acting β_2 -agonist (LABAs), ICS/LABA/long-acting muscarinic antagonists (LAMAs) and other controller medications was similar between groups. Biologics were prescribed to 27.3% of all patients, with no significant differences between groups except for mepolizumab. While 32.8% of patients were on maintenance oral steroids, the median dose was higher among those with ACT < 20 than those with ACT ≥ 20 , though this difference did not reach statistical significance.

Comparison of lung function and inflammatory markers based on ACT score

Mean FEV₁ of all subjects was $66.9 \pm 18.2\%$ predicted, the FEV₁/FVC ratio was 66.6 ± 13.9 , and FEF₂₅₋₇₅ was $1.5 \pm 1.1 \text{ L} \cdot \text{s}^{-1}$ (table 3). Patients with ACT < 20 exhibited significantly lower mean FEV₁, FVC and FEF₂₅₋₇₅ values than those with ACT ≥ 20 ($64.3 \pm 18.6\%$ pred versus $69.6 \pm 17.3\%$ pred for FEV₁, $76.2 \pm 15.5\%$ pred versus $80.2 \pm 14.6\%$ pred for FVC and $1.4 \pm 1.1 \text{ L} \cdot \text{s}^{-1}$ versus $1.6 \pm 1.1 \text{ L} \cdot \text{s}^{-1}$ for FEF₂₅₋₇₅, $p<0.001$, $p=0.001$ and $p=0.026$, respectively).

Total blood eosinophil level, and the percentages of blood eosinophils and sputum eosinophils were significantly higher in patients with ACT ≥ 20 than in those with ACT < 20 ($p=0.015$ for blood eosinophil count, $p=0.002$ for blood eosinophils (%), $p=0.001$ for sputum eosinophils (%)). When defining T2 inflammation as blood eosinophils $\geq 150 \text{ cells} \cdot \mu\text{L}^{-1}$, $F_{\text{ENO}} \geq 20 \text{ ppb}$ or sputum eosinophil percentage $\geq 2\%$ or a positive skin test to aeroallergens, 86.2% of all subjects had T2 inflammation; however, the T2 phenotype was more prevalent in patients with ACT ≥ 20 than in those with ACT < 20 (89.7% in patients with ACT ≥ 20 versus 83.0% in those with ACT < 20 , $p=0.022$).

Comparison of asthma questionnaires based on ACT score

Mean EQ-VAS and EQ-5D scores for all patients were 62.4 ± 19.4 and 0.82 ± 0.15 , respectively. When comparing scores based on ACT score, EQ-VAS was significantly lower in patients with ACT < 20 than

TABLE 3 Comparison of lung function and inflammatory markers based on ACT score

	Total	Controlled status (ACT score ≥ 20)	Uncontrolled status (ACT score < 20)	p-value
Patients, n	594	286	308	
Pulmonary function tests, mean$\pm$sd				
FVC, L (n=590)	3.0 $\pm$ 0.9	3.1 $\pm$ 0.9	2.9 $\pm$ 0.9	0.001
FVC % predicted (n=544)	78.1 $\pm$ 15.2	80.2 $\pm$ 14.6	76.2 $\pm$ 15.5	0.002
FEV ₁ , L (n=544) (n=590)	2.0 $\pm$ 0.7	2.1 $\pm$ 0.7	1.9 $\pm$ 0.7	<0.001
FEV ₁ % predicted (n=544)	66.9 $\pm$ 18.2	69.6 $\pm$ 17.3	64.3 $\pm$ 18.6	<0.001
FEV ₁ /FVC (n=590)	66.6 $\pm$ 13.9	67.7 $\pm$ 12.9	65.6 $\pm$ 14.8	0.157
FEF _{25–75} , L·s ⁻¹ (n=588)	1.5 $\pm$ 1.1	1.6 $\pm$ 1.1	1.4 $\pm$ 1.1	0.026
FEF _{25–75} % predicted (n=359)	17.4 $\pm$ 23.0	15.9 $\pm$ 20.9	18.9 $\pm$ 24.8	0.225
Laboratory tests, median (IQR)				
WBC per μ L (n=521)	7.5 (6.1–9.2)	7.4 (6–9.1)	7.6 (6.2–9.3)	0.280
Blood eosinophils per μ L (n=480)	247.3 (56.8–590.0)	300.0 (84.0–637.4)	210.6 (45.1–500.0)	0.015
Blood eosinophils % (n=516)	4.9 (2–10.0)	5.9 (2.6–11.4)	4.0 (1.7–8.2)	0.002
Sputum eosinophils % (n=126)	3 (1–5)	3 (2–6)	1 (0–3)	0.001
F _{ENO} , ppb (n=367)	47 (26–82)	51 (30–90)	43 (24–76)	0.011
Total IgE, IU·mL ⁻¹ (n=491)	256.0 (89.7–571.0)	263.0 (100.9–599.0)	243.9 (71.0–551.0)	0.133
Type 2 inflammation[#], n (%)	473 (86.2)	235 (89.7)	238 (83.0)	0.022
Blood eosinophils ≥ 150 cells μ L ⁻¹	299 (62.3)	158 (68.1)	141 (56.9)	0.011
F _{ENO} ≥ 20 ppb	310 (84.5)	154 (89.5)	156 (80.0)	0.012
Sputum eosinophil $\geq 2\%$	83 (65.9)	59 (78.7)	24 (47.1)	<0.001
Skin test positivity	150 (66.1)	74 (71.8)	76 (61.3)	0.095

Bold for p-values denotes statistical significance. ACT: asthma control test; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; FEF_{25–75}: forced expiratory flow at 25–75% of FVC; WBC: white blood cells; F_{ENO}: fractional exhaled nitric oxide. #: type 2 inflammation was defined as blood eosinophils ≥ 150 cells· μ L⁻¹, F_{ENO} ≥ 20 ppb, sputum eosinophil percentage $\geq 2\%$ or a positive skin test to aeroallergens; the percentage was calculated among patients with available data for at least one of these type 2 inflammation markers.

those with ACT ≥ 20 ($p < 0.001$, table 4). The EQ-5D index score, as well as SAQ score, was significantly lower in patients with ACT < 20 than in those with ACT ≥ 20 ($p < 0.001$, respectively). VAS scores for cough, sputum, throat discomfort, breathlessness and wheezing were lower in those with ACT < 20 than in those with ACT ≥ 20 ($p < 0.001$, respectively).

Factors associated with uncontrolled asthma

In univariable analysis, being underweight, a history of tuberculosis or depression/anxiety disorder, insurance type, lower lung function and presence of unscheduled visit in the previous year were associated with uncontrolled asthma (ACT < 20) (table 5). Conversely, the presence of T2 inflammation was linked to a decreased risk of uncontrolled asthma.

TABLE 4 Comparison of EQ-VAS and EQ-5D index scores between patients with severe asthma with or without controlled asthma

	Total	Controlled status (ACT score ≥ 20)	Uncontrolled status (ACT score < 20)	p-value
Patients, n	594	286	308	
EQ-VAS	62.4 $\pm$ 19.4	72.1 $\pm$ 15.9	53.4 $\pm$ 18.1	<0.001
EQ-5D-5L index score	0.82 $\pm$ 0.15	0.90 $\pm$ 0.10	0.75 $\pm$ 0.16	<0.001
SAQ score (n=593)	85.5 $\pm$ 22.0	97.7 $\pm$ 14.1	74.1 $\pm$ 22.0	<0.001
Cough VAS	35.7 $\pm$ 27.6	23.3 $\pm$ 23.0	47.3 $\pm$ 26.4	<0.001
Sputum VAS	40.3 $\pm$ 28.5	29.8 $\pm$ 25.9	50.1 $\pm$ 27.2	<0.001
Throat discomfort VAS	36.6 $\pm$ 28.6	25.0 $\pm$ 24.8	47.4 $\pm$ 27.7	<0.001
Breathlessness VAS	32.9 $\pm$ 29.6	15.9 $\pm$ 21.6	48.7 $\pm$ 27.3	<0.001
Wheezing VAS	30.0 $\pm$ 29.6	13.7 $\pm$ 20.5	45.2 $\pm$ 28.6	<0.001

Data are presented as mean $\pm$ sd unless stated otherwise. Bold for p-values denotes statistical significance. EQ-VAS: EuroQol visual analogue scale; EQ-5D-5L: European Quality of Life 5-Dimension 5-Level; ACT: asthma control test; SAQ: severe asthma questionnaire; VAS: visual analogue scale.

TABLE 5 Factors associated with uncontrolled asthma (ACT score <20)

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Sex (<i>versus</i> female)	0.757 (0.544–1.050)	0.096		
Obesity (<i>versus</i> 18.5 to 23 kg·m ⁻²)				
<18.5 kg·m ⁻²	4.428 (1.352–19.920)	0.025	4.129 (1.081–20.192)	0.050
23 to 25 kg·m ⁻²	0.974 (0.625–1.518)	0.908	0.993 (0.592–1.664)	0.979
≥ 25 kg·m ⁻²	1.396 (0.952–2.051)	0.088	1.328 (0.847–2.086)	0.217
History of pulmonary tuberculosis	2.120 (1.071–4.435)	0.037	1.697 (0.735–4.084)	0.222
Depression or anxiety disorder	1.912 (1.054–3.591)	0.037	1.405 (0.696–2.905)	0.347
National health insurance (<i>versus</i> yes)				
Medical aid type 1/2/others	6.537 (3.419–13.838)	<0.001	5.515 (2.614–13.110)	<0.001
FEV ₁ % predicted (<i>versus</i> ≥80)				
<60	1.937 (1.224–3.081)	0.005	1.854 (1.090–3.175)	0.023
60 to 80	1.383 (0.895–2.146)	0.145	1.471 (0.906–2.404)	0.121
Type 2 inflammation	0.558 (0.334–0.916)	0.023	0.560 (0.316–0.977)	0.043
Blood eosinophils ≥150 cells·μL ⁻¹	0.617 (0.424–0.895)	0.011		
F _{ENO} ≥20 ppb	0.468 (0.251–0.842)	0.013		
Sputum eosinophil ≥2%	0.241 (0.108–0.519)	<0.001		
Skin test positivity	0.620 (0.351–1.083)	0.096		
Presence of unscheduled visits in the previous year	3.128 (1.943–5.182)	<0.001	3.400 (1.987–6.012)	<0.001
Emergency department visits	2.789 (1.588–5.118)	<0.001		
Hospitalisations	2.955 (1.711–5.320)	<0.001		
ICS/LAMA	1.364 (0.985–1.890)	0.062	1.098 (0.734–1.641)	0.647
Macrolides	1.754 (0.943–3.374)	0.082	1.484 (0.735–3.074)	0.276
Biologics use	0.788 (0.548–1.131)	0.197		

Bold for p-values denotes statistical significance. ACT: asthma control test; FEV₁: forced expiratory volume in 1 s; F_{ENO}: fractional exhaled nitric oxide; ICS: inhaled corticosteroid; LAMA: long-acting muscarinic antagonist.

As shown in table 5 and figure 1, multivariable analysis revealed that receiving medical aid from the government was the strongest factor associated with uncontrolled asthma (adjusted odds ratio (aOR) 5.515; 95% confidence interval (95% CI) 2.614–13.110, $p<0.001$), followed by being underweight (aOR 4.129, 95% CI 1.081–20.192, $p=0.050$) and having an FEV₁ <60% predicted (aOR 1.854, 95% CI 1.090–3.175, $p=0.023$). Meanwhile, the presence of T2 inflammation was related to well-controlled asthma (aOR 0.560,

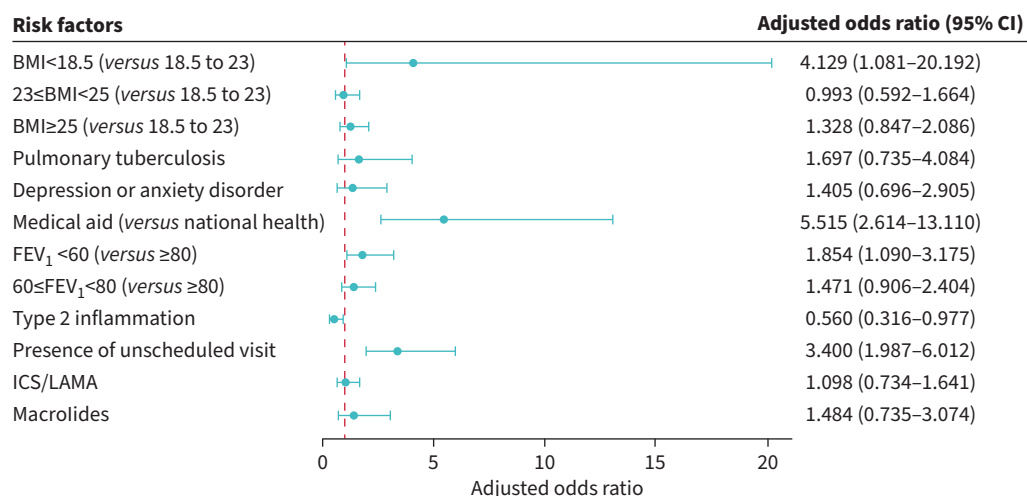


FIGURE 1 Korean Severe Asthma Registry baseline predictors of an uncontrolled state in the multivariable logistic regression model. BMI: body mass index; FEV₁: forced end expiratory volume in 1 s; ICS: inhaled corticosteroid; LAMA: long-acting muscarinic antagonist.

95% CI 0.316–0.977, $p=0.043$). However, biologics use was not associated with asthma control status (OR 0.788, 95% CI 0.548–1.131, $p=0.197$).

Discussion

In this study, we found that 51.9% of patients with severe asthma had uncontrolled asthma despite receiving care at referral centres in this country. Low socioeconomic status reflected by medical aid, being underweight, lower lung function and prior exacerbations was associated with poor asthma control, while T2 inflammation was associated with better control. However, biologic use was not associated with asthma control status.

Asthma control is a key feature when determining the optimal asthma treatment required, and current asthma control can predict future clinical outcomes of asthma patients [8]. Its significance is amplified in severe asthma due to the greater risk of future events such as frequent exacerbations, accelerated lung function decline and potential consequences like increased side-effects from medications, particularly systemic corticosteroids. Accordingly, knowing the prevalence and factors associated with uncontrolled asthma is very important for its appropriate management.

In the KoSAR-2, 51.9% of patients with severe asthma had uncontrolled asthma (ACT <20), comparable to data from Japan (56.5%) but higher than data reported for Italy (36.2%) and Switzerland (42.1%) [24–26]. However, studies of multinational severe asthma registries such as the ERS Severe Heterogeneous Asthma Research collaboration, Patient-Centered (SHARP) (54.6–100%) or International Severe Asthma Registry (ISAR) (75% among patients with biologics and 56% among patients without biologic use) have reported a higher prevalence of uncontrolled asthma than national registries, based on ACQ or ACT [9, 27]. In the current study, patients with uncontrolled asthma had significantly lower SAQ scores than those with well-controlled asthma. Mean EQ-5D index and EQ-VAS scores for all patients were 0.82 and 62.14, respectively. These values are comparable to those reported for other chronic diseases, such as cardiovascular disease, cancer or chronic kidney disease [28]. Patients with uncontrolled asthma had a remarkably low mean EQ-VAS score (mean 53.1), similar to those reported in end-stage renal disease (59.4), rare genetic diseases such as Prader–Willi syndrome (51.3–62.6) and Parkinson disease (57.6) [28]. Our findings suggest that being in uncontrolled asthma significantly impacts the quality of life of severe asthma patients.

Our study revealed that those patients with poor economic status, as reflected by medical aid use, had the highest odds of having uncontrolled severe asthma. Korea operates a two-tiered universal health security system consisting of the National Health Insurance (NHI) programme and the medical aid programme. The NHI is a wage-based, contributory system that covers the majority of the population, while the medical aid programme is a government-subsidised public assistance scheme for individuals who are economically disadvantaged or medically indigent. ~3–4% of the entire population receives medical aid [14]. Similar disparities in asthma outcomes have been observed in other countries. In the USA, several studies have consistently reported higher healthcare utilisation, including emergency department visits or hospitalisation as well as mortality, among patients with lower socioeconomic status (SES) [29, 30]. In countries such as Sweden, Canada and the UK that have universal healthcare coverage, low SES was associated with poorer asthma outcomes and mortality in disadvantaged populations [31–33]. SES may be subject to a multitude of confounders, including occupational exposure, smoking, dietary habits and obesity; thus, individual risk factors should be carefully reviewed. As healthcare systems vary considerably across countries, the observed association between medical aid and poor asthma control (ACT <20) in this study may have limited generalisability. However, limited access to specialised care and financial barriers to appropriate therapy, especially for severe asthma patients with low SES, constitute missed opportunities to improve health outcomes. These findings suggest that healthcare systems and policies should be adjusted to support the management of severe asthma better.

Our study revealed that being underweight is associated with poor asthma control in patients with severe asthma. Although the proportion of obese individuals was higher in the ACT <20 group, which is consistent with existing literature that links obesity to poor asthma outcomes, we did not observe a statistically significant association between obesity and asthma control in multivariable analysis. One possible explanation is that the mean BMI in Korean patients with severe asthma is relatively low compared to Western cohorts such as the Severe Asthma Research Program (SARP) and the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) [34]. This trend has also been observed in other East Asian countries, including Japan and China [35, 36]. FURUKAWA *et al.* [37] reported that asthma control status was worse in those patients who were underweight than in those in the normal weight group, even after adjusting for confounding factors. Furthermore, in patients with asthma,

being underweight is associated with decreased FEV₁ and enhanced airway responsiveness [38]. In addition, previous research demonstrated a U-shaped relationship between BMI and asthma incidence [39]. Expanding on this finding, our study is the first to identify an association between underweight and asthma control status in patients with severe asthma. This finding warrants further investigation to better understand the epidemiological patterns and underlying mechanisms, particularly in Asian populations.

Consistent with previous findings [12, 40], our study showed that poor asthma control in severe asthmatics was strongly associated with low FEV₁ and a history of previous exacerbations. Low FEV₁ is a reliable indicator of poor asthma control and is linked to an increased likelihood of future exacerbations [12]. Additionally, a history of recent exacerbations is a strong predictor of future exacerbations, with the frequency of exacerbations increasing as asthma severity worsens [41]. As low lung function and exacerbations may cause a vicious cycle where one condition exacerbates the other, clinicians should pay more attention to providing appropriate strategies to disconnect these associations. In addition, the mean FEF₂₅₋₇₅ value in the current study was significantly lower in patients with uncontrolled state compared to those with controlled. This finding aligns with prior reports showing that small airway dysfunction is associated with lower ACT scores and increased risk of exacerbation, and is often prevalent in severe asthma [42, 43].

In KoSAR-2, 84.2% of patients exhibited a T2 phenotype at baseline, and a similar prevalence of T2 inflammation has been reported across different registries [25, 44–46], confirming that the T2-high phenotype predominates among severe asthma patients. Our study showed that the absence of T2 inflammation was significantly associated with poor asthma control. This may be partly explained by the well-established responsiveness of T2 inflammation to ICS, and other step 4 or step 5 controller therapies such as high-dose ICS-LABA, LAMA or macrolides [47–49]. Although T2-targeted biologics showed efficacy in clinical trials and real-world studies [9, 45], their use in our registry was not associated with better asthma control. This may reflect the poorer baseline control status at the time of biologic initiation, as also noted in the ISAR study [9], and could be influenced by the relatively low proportion of biologic users (27.3%) in our registry. Moreover, the cross-sectional design of our study limits the ability to infer causal relationships between T2 inflammation and asthma control status. These findings highlight the unmet clinical needs of patients with T2-low severe asthma and underscore the importance of identifying effective strategies to improve asthma control in this population.

The strength of this study lies in its use of well-characterised data from the KoSAR-2, which includes nationwide data collected by allergy and pulmonology specialists from 41 hospitals, reflecting real-world clinical practice. This dataset provides comprehensive demographic and clinical profiles of patients with severe asthma in Korea and enables international comparisons. However, several limitations must be considered when interpreting these findings. First, sputum granulocyte data were missing from some institutions, as induced sputum testing was limited. Instead, T2 phenotype was determined based on blood eosinophil count, F_{ENO} and atopy, as recommended by GINA [46]. Second, blood eosinophils and F_{ENO} may fluctuate and be suppressed by systemic or high-dose ICS; 32.3% of patients received systemic corticosteroids, potentially affecting T2 phenotype accuracy. Third, the cross-sectional design precludes causal inference regarding asthma control and related factors. Fourth, only 27.3% of patients in this study received biologics, which is a relatively lower figure than that reported in other countries such as the UK (68.9%), Italy (68.2%) and Germany (47.4%) [50]. This discrepancy may be due to limited insurance coverage in Korea at the time of enrolment, when only omalizumab was reimbursed. Since November 2023, national healthcare insurance coverage has expanded to partially cover anti-IL-4R and anti-IL-5 or 5R antibodies, thus subsequent studies might overcome this limitation. Finally, we used ACT to assess asthma control. Although ACT is a widely used, patient-centred tool and a foundational component of asthma management, it may not fully capture the clinical complexity of the severe asthma cases, and discrepancies exist between symptom control, lung function decline and exacerbation risk [51]. Nevertheless, ACT remains a practical and validated tool for assessing control in both clinical and research settings.

In conclusion, 51.9% of severe asthmatic patients had poorly controlled asthma in the KoSAR-2. Low socioeconomic status reflected by medical aid was the most significant factor affecting poor asthma control, followed by being underweight and having unscheduled hospital visits, whereas the presence of T2 inflammation was associated with good asthma control. Biologics use was not associated with asthma control status. This study provides valuable insights into managing severe asthma and highlights the unmet needs of patients with severe asthma in Korea.

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