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Predictors of persistent poor control and validation of ASSESS score: Longitudinal 5-year follow-up of severe asthma cohort



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Background: Longitudinal predictors of persistent poor asthma control in severe asthma (SA) cohort remain scarce. The predictive value of the asthma severity scoring system (ASSESS) in the SA cohort outside the original study and in the Asian population is unknown.

Objective: We sought to determine the 5-year longitudinal outcome of patients with SA and validate the use of ASSESS score in predicting future outcomes in SA.

Methods: A prospective longitudinal observational study of patients with SA attending the multidisciplinary specialist SA clinic of the Singapore General Hospital from 2011 to 2021 was conducted. The number of exacerbations and asthma control test results were recorded yearly for 5 consecutive years. The ASSESS score was computed at baseline, and the area under the receiver-operating characteristic curve for predicting persistent poor asthma control was generated.

Results: Of the 489 patients recruited into the study, 306 patients with 5-year follow-up data were analyzed. Seventy-three percent had type 2 inflammation with increased overall exacerbations over 5 years (rate ratio, 2.55; 95% CI, 1.31-4.96; $P = .006$) relative to non-type 2 SA. In the multivariate model, bronchiectasis, gastroesophageal reflux disease, and an asthma control test score of less than 20 were significantly associated with persistent poor asthma control over 5 years. ASSESS scores were good at predicting persistent poor asthma control with an area under the receiver-operating characteristic curve of 0.71 (95% CI, 0.57-0.84).

Conclusions: Bronchiectasis and gastroesophageal reflux disease are predictors for persistent poor asthma control and targeted traits for precision medicine in SA. The ASSESS score has a good prediction for persistent poor asthma control over 5 years. (J Allergy Clin Immunol Global 2024;3:100188.)

Key words: Severe asthma, ASSESS score, type 2 asthma, Singapore, Asian

Severe asthma (SA) accounts for 3% to 4% of patients with asthma and is associated with poor quality of life, increased health care utilization, and socioeconomic burden.¹⁻⁵ As a complex and heterogeneous disease, it has different clinical courses, treatment responses, and airway inflammation. SA can be classified into 2 important endotypes on the basis of underlying inflammation: type 2 (T2) and non-T2 asthma. T2 asthma accounts for approximately 80% of SA, is often steroid-responsive, and is the target for biologic treatment (anti-IgE, anti-IL-5, anti-IL-5R, anti-IL-4R, and anti-thymic stromal lymphopoietin).⁶⁻¹⁰ Conversely, non-T2 asthma is characterized by pauci-immune or neutrophilic inflammation and is generally refractory to corticosteroid treatment and most of the currently available biologic treatments except for anti-thymic stromal lymphopoietin.¹¹ Nonetheless, the availability of biologic therapies allows a precision medicine approach with targeted treatment based on underlying inflammatory endotype in SA. However, biologic therapy is not widely available, and cost remains a significant barrier in many countries with substantial variation in licensing and reimbursement criteria.^{12,13}

Studies from several countries have shown that comprehensive assessment and multidisciplinary management in SA clinics improve asthma outcomes independent of biologic treatment.¹⁴⁻¹⁹ However, longitudinal outcomes beyond 1 year remain scarce, and findings are diverse. Investigators from the Severe Asthma Research Program III followed up 206 patients with SA over a period of 3 years and performed annual sputum differential cell counts. They reported that the group with the mixed inflammatory phenotype (neutrophilic and eosinophilic) was associated with greater lung function decline and patients with variable sputum eosinophil had increased health care utilization.²⁰ In a 10-year follow-up study, Lee et al²¹ reported lower lung function and higher basophil and platelet counts in the highly exacerbation-prone SA group with 4 or more severe exacerbations per year, and Soremekun et al²² reported that exacerbations (≥ 2 exacerbations per year) and lung function declined. Kimura et al²³ followed up 105 patients with SA over 3 years and found that high fractional exhaled nitric oxide (FENO) predicted future exacerbation events. These findings highlight the heterogeneity of patients

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Abbreviations used

| | |
|---------|--|
| ACT: | Asthma control test |
| ASSESS: | Asthma severity scoring system |
| AUC: | Area under the receiver-operating characteristic curve |
| BMI: | Body mass index |
| FENO: | Fractional exhaled nitric oxide |
| GERD: | Gastroesophageal reflux disease |
| GINA: | Global INitiative for Asthma |
| HRCT: | High-resolution computed tomography |
| IQR: | Interquartile range |
| RR: | Rate ratio |
| SA: | Severe asthma |
| T2: | Type 2 |

with SA and relatively scarce data on predictor and long-term outcomes, particularly in Asian SA involving a multiethnic population. In addition, the variations in health care systems, local practices, policies, funding structure, and accessibility to biologic therapies may significantly influence the outcomes of patients with SA. Longer follow-up data are required to better understand the heterogeneity and outcomes of the diverse population and treatment approach.

There is a lack of objective measurement of asthma severity, with discrepancies in the assessment by both primary care and respiratory physicians.^{24,25} The asthma severity scoring system (ASSESS) is a multidimensional tool incorporating various measurements, including asthma control, lung function, medications used, and exacerbation rate, intending to provide continuous assessment of asthma severity.²⁶ It has also been shown to predict treatment response in SA. A 2-point decrease in the ASSESS score is associated with improved quality of life. However, this is not validated in the Asian cohort, and the correlation between baseline ASSESS score and long-term SA outcomes is uncertain.

We sought to evaluate the longitudinal outcomes of patients with SA over a period of 5 years and the predictors for persistent poor asthma control. In addition, we aimed to validate the ASSESS score and its use as a predictor of persistent poor asthma control.

METHODS**Study participants**

Patients with SA attending the Singapore General Hospital's multidisciplinary SA clinic were recruited to a prospective longitudinal observational study from 2011 to 2021. Patients who fulfilled the International Severe Asthma Registry criteria for SA and those with complete 5-year follow-up data were included in the analysis.⁶ A patient with SA is defined as one being on Global INitiative for Asthma (GINA) 2018 step 5 treatment or GINA step 4 treatment with any of the following: an asthma control test (ACT) score of less than 20, 1 or more emergency department visits or hospitalizations, 2 or more steroid bursts per year, or postbronchodilator FEV₁ of less than 80%.^{3,6} The diagnosis of asthma was based on the GINA guidelines (ie, variable symptoms and documented expiratory flow limitation).³ A frequent exacerbator was defined as one who had 2 or more exacerbations requiring systemic corticosteroids, emergency department visits, or hospitalization. As per the International Severe Asthma Registry criteria, T2-high asthma is when blood eosinophil count is

greater than or equal to $0.3 \times 10^9/L$, IgE is greater than or equal to 75 IU/mL, or FENO is greater than or equal to 25 ppb.⁶ Clinical data were collected at recruitment, including demographic characteristics, smoking history, comorbidities, ACT score, pulmonary function test result, blood or sputum eosinophil count, IgE level, allergy sensitization test to common aeroallergens (by either skin prick test or serum specific IgE), the number of exacerbations requiring systemic corticosteroid treatment, emergency visits and hospitalizations, high-resolution computed tomography (HRCT) result, and treatment received. ASSESS score was computed using baseline ACT score, lung function, exacerbations in the past year, controller medications, oral corticosteroids, and biologics used.²⁶ Follow-up records for ACT and exacerbation frequency were obtained through the electronic medical record and verified with the patients. Bronchiectasis was defined as bronchoarterial ratio of more than 1, lack of tapering, or visibility of the airway within 1 cm of pleural surface on HRCT.^{27,28} Exacerbation was defined as worsening of asthma requiring systemic corticosteroid for 3 or more days, emergency department visit, or hospitalization.²⁹ Gastroesophageal reflux disease (GERD) was diagnosed on the basis of patient-reported symptoms, gastroenterology assessment, and response to treatment. Anxiety and depression were diagnosed by formal psychiatric assessment. Obstructive sleep apnea was based on polysomnography results. Allergic rhinitis was defined on the basis of 1 or more symptoms of sneezing, rhinorrhea, itching, nasal congestion, or being on allergic rhinitis treatment.³⁰ We defined uncontrolled asthma as an ACT score of less than 20 and/or frequent exacerbations (≥ 2 exacerbations per year) and persistent poor asthma control as 4 or more years of uncontrolled asthma.

The Singhealth Centralised Institutional Review Board approved this study (CIRB 2018/2486; 2010/810/C), and written informed consent was obtained from all participants.

Statistical analysis

The statistical analysis was performed using R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria). Continuous data were compared using the *t* test for normally distributed data and the Mann-Whitney *U* test for nonnormally distributed data. The chi-square test and the Fisher exact test were used for categorical variables as appropriate. The logistic regression model was used with persistent poor asthma control over 5 years as the dependent variable, and baseline variables with a *P* value of less than .05 in univariate analysis were selected for inclusion in the model. The goodness of fit was assessed by the Hosmer-Lemeshow test. The exacerbations rate ratio (RR) was determined with negative binomial regression controlling for potential confounding effects of age, sex, body mass index (BMI), and treatment received. The receiver-operating characteristic curve was generated to evaluate the model discrimination, and the area under the receiver-operating characteristic curve (AUC) was calculated. An AUC value of 1.0 indicates a perfect model, and a value of 0.5 indicates a model that performs almost at random. The Sankey plot was used to demonstrate a longitudinal trend for categorical variables. A significant level was defined as a *P* value of less than .05.

RESULTS**Characteristics of T2-high versus T2-low SA**

Of the 486 patients with SA, 306 patients with complete 5-year follow-up data were included in the analysis. The baseline

TABLE I. Characteristics of overall cohort, T2-high and T2-low SA

| SA | Overall | T2-low | T2-high | P value |
|---|-----------------------------|------------------------------|-----------------------------|-----------------|
| No. of patients | 306 | 83 | 223 | |
| Age (y), median (Q1, Q3) | 59.0 (44.3, 71.0) | 56.5 (33.0, 71.5) | 60.0 (47.0, 71.0) | .457 |
| Age of onset (y), median (Q1, Q3) | 27.0 (10.0, 46.0) | 20.0 (10.0, 47.0) | 29.0 (10.0, 46.0) | .378 |
| Sex, n (%) | | | | .694 |
| Female | 178 (58.2) | 45 (54.2) | 133 (59.6) | |
| Male | 128 (41.8) | 38 (45.8) | 90 (40.4) | |
| Race, n (%) | | | | .356 |
| Chinese | 179 (58.5) | 53 (63.9) | 126 (56.5) | |
| Indian | 54 (17.6) | 15 (18.1) | 39 (17.5) | |
| Malay | 55 (18.0) | 13 (15.7) | 42 (18.8) | |
| Others* | 18 (5.9) | 2 (2.4) | 16 (7.2) | |
| Smoker, n (%) | | | | .964 |
| Ex-smoker | 33 (10.8) | 6 (7.2) | 27 (12.1) | |
| Never | 232 (75.8) | 65 (78.3) | 167 (74.9) | |
| Current | 41 (13.4) | 12 (14.5) | 29 (13.0) | |
| BMI (kg/m ²), median (Q1, Q3) | 25.3 (22.1, 29.4) | 23.8 (21.1, 27.8) | 26.0 (22.5, 29.8) | .039 |
| BMI, n (%) | | | | .047 |
| Underweight (BMI < 18.5 kg/m ²) | 21 (6.9) | 5 (6.0) | 16 (7.2) | |
| Normal (BMI = 18.5-22.9 kg/m ²) | 79 (25.8) | 31 (37.3) | 48 (21.5) | |
| Overweight (BMI = 23-27.5 kg/m ²) | 103 (33.7) | 24 (28.9) | 79 (35.4) | |
| Obese (BMI > 27.5 kg/m ²) | 103 (33.7) | 23 (27.7) | 80 (35.9) | |
| Pre-BD FEV ₁ , % predicted, median (Q1, Q3) | 72.0 (57.0, 87.0) | 73.0 (57.0, 88.0) | 71.0 (57.0, 85.0) | .925 |
| ACT score, median (Q1, Q3) | 19.0 (15.0, 21.0) | 19.0 (17.0, 21.0) | 18.0 (15.0, 21.0) | .424 |
| ACT score < 20, n (%) | 170 (55.6) | 42 (50.6) | 128 (57.4) | .228 |
| Frequent exacerbator past year, n (%) | 158 (51.6) | 37 (44.6%) | 121 (54.3%) | .321 |
| Hospitalization in the past year, n (%) | 141 (46.1) | 28 (33.7) | 113 (50.7) | .012 |
| Blood eosinophil count (×10 ⁹ /L), median (Q1, Q3) | 0.440 (0.220, 0.690) | 0.140 (0.0900, 0.210) | 0.510 (0.360, 0.810) | <.001 |
| Blood eosinophil group (×10 ⁹ /L), n (%) | | | | <.001 |
| <0.15 | 90 (29.4) | 54 (65.1) | 36 (16.1) | |
| 0.15-0.29 | 47 (15.4) | 29 (34.9) | 18 (8.1) | |
| ≥0.30 | 169 (55.2) | 0 (0) | 169 (75.8) | |
| IgE (IU/mL), median (Q1, Q3) | 299 (116, 683) | 21.0 (14.1, 24.7) | 310 (127, 693) | .002 |
| FENO (ppb), median (Q1, Q3) | 25.0 (16.0, 47.0) | 16.0 (13.3, 20.3) | 32.0 (21.0, 48.0) | .015 |
| Near-fatal asthma, n (%) | 25 (8.2) | 6 (7.2) | 19 (8.5) | .895 |
| HRCT, n (%) | 146 (48) | 24 (29) | 122 (55) | <.001 |
| Bronchiectasis, n (%) | 15 (10.3) | 4 (16.7) | 11 (9.0) | .447 |
| Anxiety, n (%) | 13 (4.2) | 3 (4.8) | 10 (4.6) | .945 |
| Depression, n (%) | 14 (4.6) | 2 (2.4) | 12 (5.4) | .542 |
| Eczema, n (%) | 23 (7.5) | 5 (6.0) | 18 (8.1) | .719 |
| Allergic rhinitis, n (%) | 184 (60.1) | 41 (49.4) | 143 (64.1) | .027 |
| GERD, n (%) | 66 (21.6) | 9 (10.8) | 57 (25.6) | .021 |
| Obstructive sleep apnea, n (%) | 8 (2.6) | 0 (0%) | 8 (3.6) | .217 |
| GINA, n (%) | | | | .079 |
| Step 4 | 199 (65.0) | 61 (73.5) | 138 (61.9) | |
| Step 5 | 107 (35.0) | 22 (26.5) | 85 (38.1) | |
| Long-term oral steroids, n (%) | 13 (4.2) | 3 (3.6) | 10 (4.5) | .945 |
| Biologics, n (%) | 3 (1.0) | 0 (0) | 3 (1.3) | .682 |
| Baseline inhaled corticosteroid dose (μg/d fluticasone-equivalent), median (Q1, Q3) | 500 (320, 1000) | 500 (400, 1000) | 500 (320, 1000) | .731 |
| Anticholinergic, n (%) | 24 (7.8) | 0 (0) | 24 (10.8) | .004 |
| Leukotriene receptor antagonist, n (%) | 156 (51.0) | 33 (39.8) | 123 (55.2) | .023 |
| Theophylline, n (%) | 55 (18.0) | 12 (14.5) | 43 (19.5) | .620 |

Pre-BD, Prebronchodilator. Bold indicates variables with *P* < .05.

*Other races include Sikh, Bangladeshi, Arabian, and Eurasian.

characteristics of the patients are provided in [Table I](#) (see also [Table E1](#) in this article's Online Repository at www.jaci-global.org). The patients with SA had a median age of 59 years (interquartile range [IQR], 44-71 years), female predominance (58.2%), and a median ACT score of 19 (IQR, 15-21); 55.6% had an ACT score of less than 20, 51.6% had frequent exacerbations in the past year, 13 (4.2%) patients were on long-

term oral corticosteroids, and only 3 (1%) patients were on biologic treatment. Most patients were T2-high (n = 223; 73%) with median blood eosinophil count of 0.51 (0.36-0.81 × 10⁹/L), IgE level of 310 (127-693 IU/mL), and FENO value of 32 (21-48 ppb). Compared with T2-low SA, T2-high SA had higher BMI (median, 26 vs 23.8; *P* = .039), higher proportion with hospitalizations in the past 1 year (50.7% vs 33.7%; *P* = .012),

allergic rhinitis (64.1% vs 49.4%; $P = .027$), and GERD (25.6% vs 10.8%; $P = .021$).

Longitudinal asthma outcomes for patients with T2-high and T2-low SA

We next assessed the longitudinal outcomes over 5 years in patients with T2-low and T2-high SA. The T2-high SA group had increased overall annual exacerbations over 5 years (RR, 2.55; 95% CI, 1.31-4.96; $P = .006$) compared with the T2-low SA group, but had no significant difference in ACT score over 5 years. The number of exacerbations was significantly higher in the first 3 years of follow-up (see Fig E1 in this article's Online Repository at www.jaci-global.org) (Fig 1), adjusted for age, sex, BMI, and treatment received (inhaled corticosteroid strength, anticholinergic, long-term oral corticosteroid, leukotriene receptor antagonist, and biologics). The RRs for exacerbations in the T2-high SA group compared with the T2-low SA group are as follows (Fig 1): first year, 3.11 (95% CI, 1.28-7.57; $P = .01$); second year, 4.00 (95% CI, 1.49-10.72; $P = .01$); third year, 2.93 (95% CI, 1.11-7.70; $P = .03$); fourth year, 1.59 (95% CI, 0.58-4.31; $P = .36$); and fifth year, 1.43 (95% CI, 0.51-3.99; $P = .50$). There were higher exacerbations at years 1 and 2, with a subsequent decrease in exacerbations from year 3 onward. This is likely contributed by ongoing systematic assessment and multidisciplinary care of SA at specialist asthma clinics.

Predictors for persistent poor asthma control over 5 years

Having identified the poor outcomes in T2-high SA, we next sought to determine other predictors of persistent poor asthma control over 5 years. Overall, 26% ($n = 58$) of patients with T2-high SA and 10% ($n = 8$) of those with T2-low SA had persistent poor asthma control over 5 years. There was an overall decrease in the proportion of patients with uncontrolled asthma at follow-up (year 1: $n = 133$ [43%]; year 2: $n = 109$ [36%]; year 3: $n = 97$ [32%]; year 4: $n = 104$ [34%]; and year 5: $n = 96$ [31%]) compared with baseline ($n = 246$ [80%]) (Fig 2, A). A trend toward a reduction in the proportion of patients with an ACT score of less than 20 was observed from baseline to year 5 of follow-up, but the number of frequent exacerbations remained similar from year 1 to year 5, after an initial decrease from baseline (Fig 2, A and B). High BMI, low baseline ACT score, depression, and GERD were associated with persistent low ACT score (<20 for ≥ 4 years), whereas frequent exacerbation and high eosinophil count at baseline were associated with persistent exacerbations (≥ 2 exacerbations per year for ≥ 4 years) over 5 years (see Tables E2 and E3 in this article's Online Repository at www.jaci-global.org).

Table II provides the predictors of persistent poor asthma control over 5 years. On univariate analysis, high BMI and exacerbation frequency, lower baseline ACT score, high eosinophil count, bronchiectasis, GERD, and biologic and anticholinergic treatment were associated with persistent poor asthma control over 5 years. The multivariate logistic regression model for predicting poor asthma control over 5 years was generated on the basis of the variables with a P value of less than .05 in the univariate analysis. The Hosmer-Lemeshow goodness-of-fit test suggests that the model was well fitted ($\chi^2 = 27.11$; degree of freedom = 8; $P = .167$). The presence of bronchiectasis and GERD and an

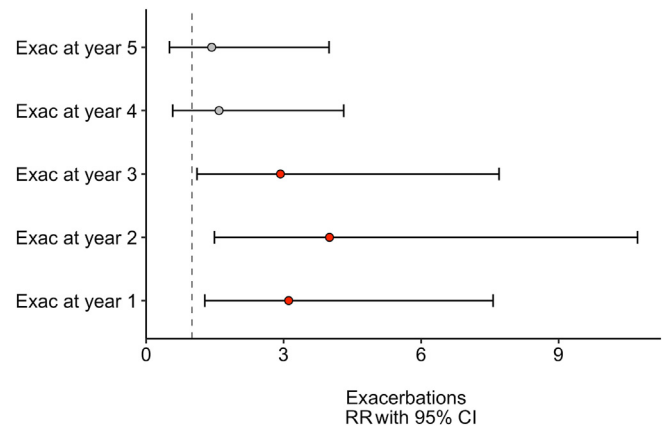


FIG 1. Increased exacerbations with T2-high SA. Forest plot illustrating the RR (circles) with 95% CI (error bars) for exacerbations (Exac) at each follow-up year in T2-high SA relative to T2-low SA. Colors correspond to significant levels: red ($P < .05$) and gray (not significant).

ACT score of less than 20 were predictors for the persistence of poor asthma control over 5 years on multivariate logistic regression (Table III).

Relationship between baseline ASSESS score and longitudinal asthma outcomes

Asthma severity was measured using the ASSESS score, a multidimensional tool that incorporates various components of asthma control, including symptoms, lung function, treatment, and exacerbations²⁶ (Table IV). The T2-high SA group had an overall higher ASSESS score (median, 10 [IQR, 8-12] vs 9 [IQR, 8-11]; $P = .018$) at baseline compared with the T2-low SA group. This was mainly driven by a higher proportion of patients with T2-high SA with asthma exacerbations (Table IV).

We next evaluated the association between baseline ASSESS score and 5-year longitudinal outcome. Patients with uncontrolled asthma at follow-up years 1 to 5 (Fig 3, A-E) and those with persistent poor asthma control over 5 years had higher baseline ASSESS scores (median, 11 [IQR, 9-12] vs 9 [IQR, 8-11]; $P < .001$) (Fig 3, F). The AUC for ASSESS score in predicting persistent poor asthma control over 5 years was 0.71 (95% CI, 0.57-0.84) (Fig 4), and the threshold for ASSESS score on the basis of the Youden index was 10.5 (sensitivity, 53%; specificity, 66%).

DISCUSSION

The prevalence of T2-high SA was 73% in our cohort. Patients with T2-high SA were more likely to be overweight and obese with a greater frequency of severe exacerbations and comorbid allergic rhinitis and GERD at baseline (Table I). On longitudinal assessment, the T2-high SA group demonstrated higher overall exacerbations over 5 years, with a greater number of exacerbations occurring in the first 3 years of follow-up. There was an overall improvement in symptoms and exacerbations during the follow-up period relative to baseline, suggesting benefit after multidisciplinary SA clinic management. However, there remained a substantial proportion of patients (24%) with poor asthma control over 5 years. Of those with persistent poor asthma

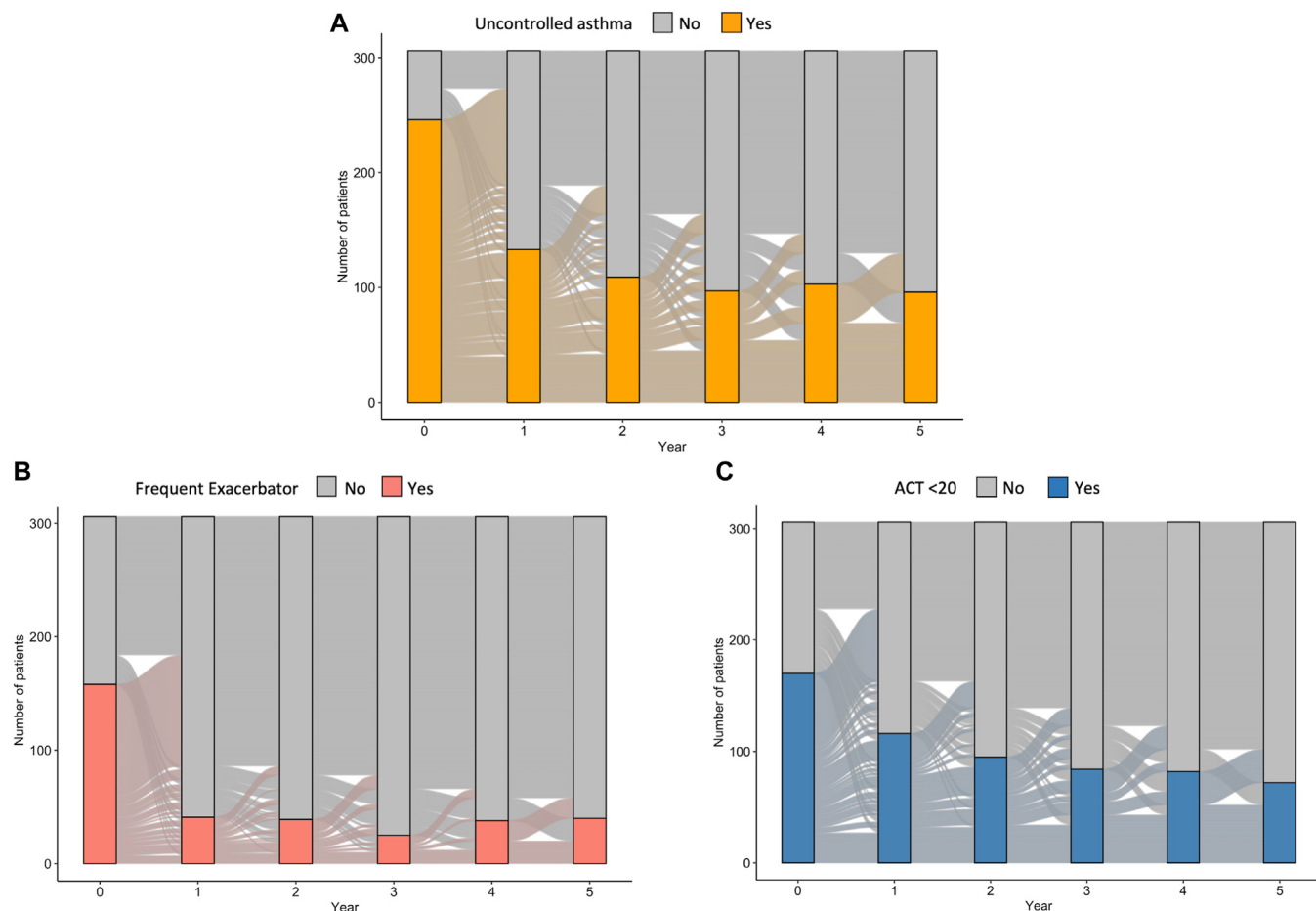


FIG 2. A-C, Sankey plots illustrating the changes in the proportion of patients with uncontrolled asthma (Fig 2, A), frequent exacerbator (Fig 2, B), and an ACT score of less than 20 (Fig 2, C), from baseline (year 0) to year 5 of follow-up.

control (n = 66), only 18 (3 at baseline and 15 during follow-up) patients were on biologic treatment. Bronchiectasis and GERD at baseline predicted persistent poor asthma control. The ASSESS score was validated in our SA cohort with good performance in predicting persistent poor asthma control (ACT score < 20 and/or ≥ 2 exacerbations per year for ≥ 4 years) over 5 years. The ability to predict patients with poor outcomes is vital for clinical decision making, allowing early identification of “high-risk” patients for targeted therapy (eg, biologic therapy), early control of disease, and prevention of complications arising from poor asthma control or frequent corticosteroid exposures.

T2-high asthma represents the main endotype, forming up to 80% of the SA cohort.⁶ T2-high asthma is assessed clinically with raised blood or sputum eosinophil count, total and specific IgE, and FENO.^{3,6} It is associated with increased comorbidity, exacerbations, and asthma severity.^{5,31,32} Although T2-high asthma is corticosteroid-responsive, frequent systemic corticosteroid use has resulted in significant morbidity and mortality.^{33,34} Cumulative exposure of 0.5 g to less than 1 g, equivalent to 4 lifetime courses of corticosteroid used, has been shown to increase the risk of adverse consequences, including osteoporosis, pneumonia, weight gain, and diabetes.³³ Therefore, approaches to optimizing asthma control and reducing the use of systemic corticosteroids are paramount in asthma management. The advanced

understanding of T2 inflammation has led to the development of various biologic therapies targeting different T2 pathways in SA. Currently, 4 approved biologics are available in Singapore for T2-high SA: omalizumab for allergic asthma; benralizumab anti-IL-5R and mepolizumab anti-IL-5 for eosinophilic asthma; and dupilumab anti-IL-4 and anti-IL-13 for eosinophilic, allergic, and oral corticosteroid-dependent asthma. In agreement with previous studies, we found a high prevalence of T2-high SA associated with greater exacerbations, comorbidity, and persistent poor asthma control.^{5,31,32} During the 5-year follow-up, 8% of patients with T2-high SA and 1% of those with T2-low SA remained as frequent exacerbators; however, only 17% of the T2-high frequent exacerbators received biologic therapy. The use of biologic therapies remains low in Singapore, contributed by the high cost and lack of reimbursement from the government, patient attitude, and perception of injection therapy.⁴

The benefits of specialist SA management were proven consistently in previous studies, with improved overall outcomes, including symptoms score and lung function, reduced unscheduled health care visits, and oral corticosteroid use.¹⁴ Multidisciplinary and systemic approaches in managing SA with targeted comorbidity treatment, adherence assessment, education, and personalized management are important parts of SA management, with improvement in long-term outcomes independent of

TABLE II. Predictors for persistent poor asthma control over 5 y

| Persistent poor asthma control over 5 y | No | Yes | P value |
|--|-----------------------------|-----------------------------|-----------------|
| No. of patients | 240 | 66 | |
| Age (y), median (Q1, Q3) | 59.0 (36.5, 71.0) | 60.5 (48.8, 72.0) | .315 |
| Age of onset (y), median (Q1, Q3) | 25.5 (10.0, 46.0) | 33.5 (15.0, 44.8) | .491 |
| Sex, n (%) | | | .150 |
| Female | 134 (55.8) | 44 (66.7) | |
| Male | 106 (44.2) | 22 (33.3) | |
| Race, n (%) | | | .744 |
| Chinese | 140 (58.3) | 39 (59.1) | |
| Indian | 40 (16.7) | 14 (21.2) | |
| Malay | 45 (18.8) | 10 (15.2) | |
| Others | 15 (6.3) | 3 (4.5) | |
| Smoker, n (%) | | | .428 |
| Ex-smoker | 23 (9.6) | 10 (15.2) | |
| Never | 184 (76.7) | 48 (72.7) | |
| Current | 33 (13.8) | 8 (12.1) | |
| BMI (kg/m ²), median (Q1, Q3) | 24.8 (22.1, 28.8) | 26.8 (23.7, 31.8) | .022 |
| Pre-BD FEV ₁ % predicted, median (Q1, Q3) | 72.0 (57.0, 87.0) | 69.5 (54.3, 84.0) | .747 |
| ACT score, median (Q1, Q3) | 19.0 (16.0, 21.0) | 17.0 (15.0, 20.0) | .010 |
| Frequent exacerbator past year, n (%) | 116 (48.3) | 42 (63.6) | .039 |
| Eosinophil count (×10 ⁹ /L), median (Q1, Q3) | 0.400 (0.205, 0.675) | 0.500 (0.330, 0.780) | .029 |
| IgE (IU/mL), median (Q1, Q3) | 287 (93.5, 691) | 335 (164, 645) | .648 |
| FENO (ppb), median (Q1, Q3) | 24.5 (13.8, 47.3) | 27.0 (21.5, 39.5) | .99 |
| T2-high SA, n (%) | 165 (68.8) | 58 (87.9) | .003 |
| Near-fatal asthma, n (%) | 19 (7.9) | 6 (9.1) | .956 |
| HRCT, n (%) | 97 (40.4) | 49 (74.2) | <.001 |
| Bronchiectasis, n (%) | 7 (7.2) | 8 (16.3) | .006 |
| Anxiety, n (%) | 8 (3.3) | 5 (7.6) | .318 |
| Depression, n (%) | 8 (3.3) | 6 (9.1) | .140 |
| Eczema, n (%) | 19 (7.9) | 4 (6.1) | .808 |
| GERD, n (%) | 37 (15.4) | 29 (43.9) | <.001 |
| Allergic rhinitis, n (%) | 143 (59.6) | 41 (62.1) | .933 |
| Obstructive sleep apnea, n (%) | 4 (1.7) | 4 (6.1) | .140 |
| GINA treatment, n (%) | | | .226 |
| Step 4 | 162 (67.5) | 37 (56.1) | |
| Step 5 | 78 (32.5) | 29 (43.9) | |
| Long-term oral steroids, n (%) | 8 (3.3) | 5 (7.6) | .318 |
| Biologics, n (%) | 0 (0) | 3 (4.5) | .004 |
| Baseline inhaled corticosteroid dose (μg/d fluticasone-equivalent) | 500 (320, 1000) | 570 (360, 1000) | .527 |
| Anticholinergic, n (%) | 14 (5.8) | 10 (15.2) | .045 |
| Leukotriene receptor antagonist, n (%) | 125 (52.1) | 31 (47.0) | .763 |
| Theophylline, n (%) | 40 (16.7) | 15 (22.7) | .525 |
| ASSESS score | 9.00 (8.00, 11.0) | 11.0 (9.00, 12.0) | .007 |

Pre-BD, Prebronchodilator. Bold indicates variables with $P < .05$.

TABLE III. Multivariate logistic regression table for the predictor of persistent poor asthma control (ACT score < 20 and/or ≥2 exacerbations per year for 4 y or more) over 5 y

| Characteristics | Odds ratio | 95% CI | P value |
|----------------------|-------------|-------------------|-----------------|
| BMI | 1.01 | 0.95-1.08 | .69 |
| T2-high asthma | 2.31 | 0.71-7.53 | .17 |
| Frequent exacerbator | 1.27 | 0.57-2.82 | .76 |
| ACT score < 20 | 2.57 | 1.14-5.80 | .02 |
| Bronchiectasis | 4.16 | 1.19-14.59 | .03 |
| GERD | 3.92 | 1.67-9.20 | <.001 |
| Anticholinergic | 2.02 | 0.64-6.36 | .23 |

Bold indicates variables with $P < .05$.

biologic treatment.^{15,16,35} The SA clinic in Singapore General Hospital is a multidisciplinary clinic run by SA respiratory specialists, asthma specialist nurses, and pharmacists, supported by

pulmonary function laboratories and allied health professionals, including physiotherapists, social workers, and psychologists. Our results have shown the effectiveness of our SA clinic, with significant improvement in the overall outcome: 17% reduction in patients with an ACT score of less than 20 and 38% reduction in frequent exacerbators at first year of follow-up compared with baseline. This highlights the importance of structured and multidisciplinary assessment of SA. Despite the comprehensive management, patients with comorbid GERD and bronchiectasis are associated with persistent poor asthma control, particularly persistent poor ACT score over 5 years. Bronchiectasis and GERD have been associated with poor asthma control, and a higher prevalence of bronchiectasis was reported in the SA cohort.³⁵⁻⁴¹ These comorbidities are important, and early screening and treatment may affect asthma outcomes. A recent small retrospective study has described improvement in outcomes of patients given T2-targeted biologics with asthma and

TABLE IV. Component of ASSESS score in T2-low and T2-high SA

| ASSESS score components | Overall (N = 306) | T2-low (n = 83) | T2-high (n = 223) | P value* |
|--|-------------------|-------------------|-------------------|-------------|
| ACT score, n (%) | | | | .742 |
| 0 point: ACT score 23-25 | 52 (17.0) | 13 (15.7) | 39 (17.5) | |
| 1 point: ACT score 20-22 | 84 (27.5) | 28 (33.7) | 56 (25.1) | |
| 2 points: ACT score 17-19 | 78 (25.5) | 22 (26.5) | 56 (25.1) | |
| 3 points: ACT score 14-16 | 51 (16.7) | 12 (14.5) | 39 (17.5) | |
| 4 points: ACT score 11-13 | 28 (9.2) | 6 (7.2) | 22 (9.9) | |
| 5 points: ACT score 8-10 | 7 (2.3) | 1 (1.2) | 6 (2.7) | |
| 6 points: ACT score 5-7 | 6 (2.0) | 1 (1.2) | 5 (2.2) | |
| ASSESS ACT score, median (Q1, Q3) | 2 (1, 3) | 2 (1, 2) | 2 (1, 3) | .276 |
| Lung function, n (%) | | | | .703 |
| 0 point: FEV ₁ ≥ 80% predicted | 103 (33.7) | 28 (33.7) | 75 (33.6) | |
| 1 point: FEV ₁ 70%-80% predicted | 69 (22.5) | 22 (26.5) | 47 (21.1) | |
| 2 points: FEV ₁ 60%-70% predicted | 45 (14.7) | 10 (12.0) | 35 (15.7) | |
| 3 points: FEV ₁ < 60% predicted | 89 (29.1) | 23 (27.7) | 66 (29.6) | |
| ASSESS lung function score, median (Q1, Q3) | 1 (0, 3) | 1 (0, 3) | 1 (0, 3) | .680 |
| Controller medications, n (%) | | | | .079 |
| 4 points: step 4: medium-dose ICS + ≥1 controllers or high-dose ICS + ≥1 controllers | 199 (65.0) | 61 (73.5) | 138 (61.9) | |
| 5 points: step 5: high-dose ICS + ≥2 or more controllers | 107 (35.0) | 22 (26.5) | 85 (38.1) | |
| ASSESS controller medications score, median (Q1, Q3) | 4 (4, 4) | 4 (4, 4) | 4 (4, 4) | .068 |
| Oral corticosteroid, n (%) | | | | .945 |
| 0 point: No | 293 (95.8) | 80 (96.4) | 213 (95.5) | |
| 1 point: Yes | 13 (4.2) | 3 (3.6) | 10 (4.5) | |
| ASSESS oral corticosteroid score, median (Q1, Q3) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | .738 |
| Biologics, n (%) | | | | .682 |
| 0 point: No | 303 (99.0) | 83 (100) | 220 (98.7) | |
| 1 point: Yes | 3 (1.0) | 0 (0) | 3 (1.3) | |
| ASSESS biologic score, median (Q1, Q3) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | .289 |
| Asthma exacerbations, n (%) | | | | .019 |
| 0 point: None | 107 (35.0) | 33 (39.8) | 74 (33.2) | |
| 2 points: Prednisone burst | 58 (19.0) | 22 (26.5) | 36 (16.1) | |
| 4 points: Prednisone burst + hospitalization | 141 (46.1) | 28 (33.7) | 113 (50.7) | |
| ASSESS asthma exacerbations score, median (Q1, Q3) | 2 (0, 4) | 2 (0, 4) | 4 (0, 4) | .034 |
| Total ASSESS score, median (Q1, Q3) | 9.00 (8.00, 11.0) | 9.00 (8.00, 11.0) | 10.0 (8.00, 12.0) | .018 |

ICS, Inhaled corticosteroid. Bold indicates variables with $P < .05$.

*P value corresponds to comparison between non-T2 and T2 asthma using the χ^2 test for categorical variables and the Mann-Whitney U test for continuous variables.

bronchiectasis, which may be a promising treatment to address the unmet needs in this group of patients.⁴² However, these findings have not been validated in randomized controlled trials, and hence we await future studies to validate these findings (NCT05189613). Interestingly, factors influencing persistent poor ACT score differ from persistent frequent exacerbations; nonetheless, these are important outcomes, and targeted treatments addressing these factors are required to reduce both symptoms and exacerbations.

The ASSESS score is a composite score developed as an objective measurement of asthma severity. A 2-point decrease in ASSESS score was associated with increased quality of life and predictor of treatment response.²⁶ It was reported to have good specificity but poor sensitivity to detect outcome improvement, including exacerbations, hospitalization, number of controller medications, and quality-of-life score. However, the ASSESS score has not been validated outside the original study and in the SA cohort in Asia.²⁶ This is the first study validating the use of ASSESS scores in the multiethnic Asian SA population. Our study showed an association between ASSESS score and the long-term outcome of asthma control. This is contributed by the inclusion of symptoms and exacerbation frequency in the ASSESS score, whereby control at baseline predicts future

outcomes in SA. The ASSESS score had good performance in predicting persistent poor outcomes over 5 years in our cohort of patients with SA with an AUC of 0.71. With the high prediction for persistent poor asthma control, the ASSESS score may be used as a monitoring tool for patients with SA on biologic treatment.

This is the first study that validates the use of the ASSESS score outside the original study, demonstrating its potential to predict 5-year asthma control. Although our study is a longitudinal prospective study with a large number of well-phenotype patients with SA with complete 5 years of follow-up data, it has limitations. First, because this is a single-center study, our result is not generalizable to all patients with SA. Nevertheless, our SA clinic is the largest SA service in Singapore and receives referrals from primary care, respiratory, and internal medicine physicians, and serves the Singaporean population from the southern and eastern parts. Second, yearly lung function and biomarker testing were not performed in all patients, and therefore, we could not evaluate lung function changes or biomarker fluctuation, including T2-high SA and low status over time, or compare ASSESS score longitudinally. This is a limitation of real-world observational study. Third, there were relatively few patients on biologic treatment, and hence we could not evaluate biologic response, the association with exacerbations, or use of ASSESS

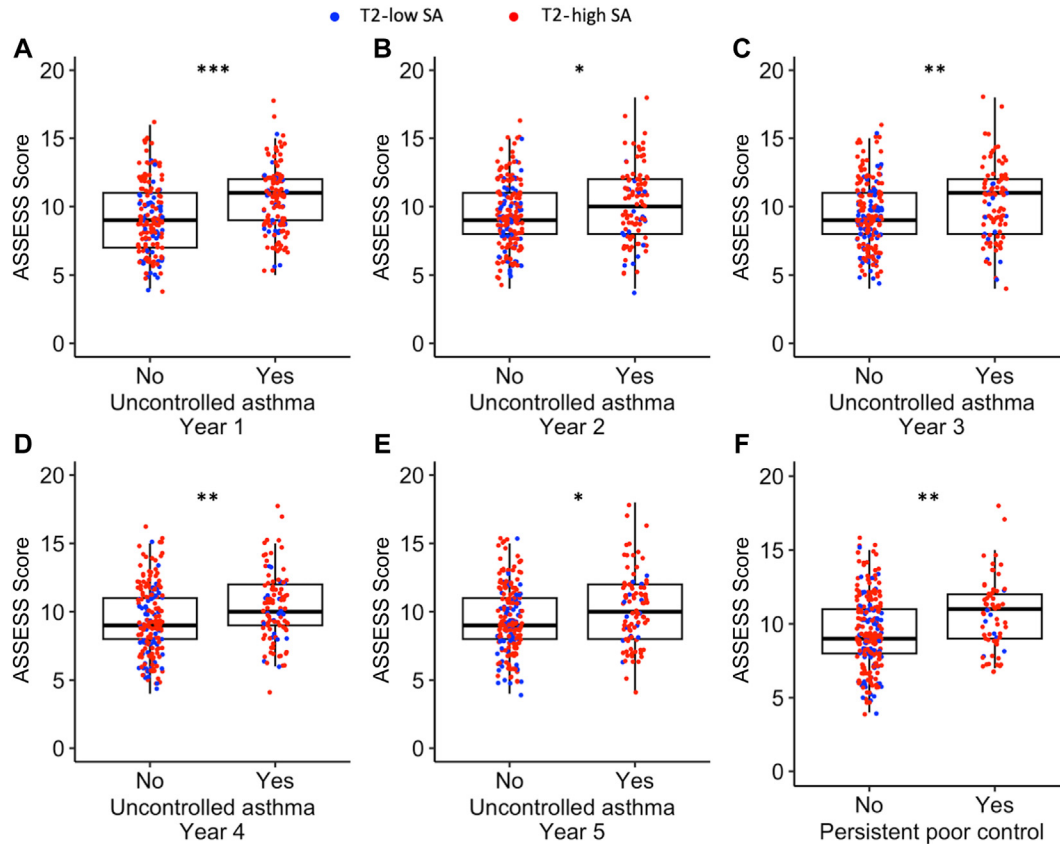


FIG 3. A-F, Scattered boxplots showing the baseline ASSESS score in the presence (Yes) or absence (No) of uncontrolled asthma at year 1 to year 5 (Fig 3, A-E) and persistent poor asthma control (≥ 4 years of uncontrolled asthma) over 5 years (Fig 3, F). Uncontrolled asthma is defined as an ACT score of less than 20 and/or frequent exacerbations (≥ 2 exacerbations per year). Colors correspond to T2-low (blue) and T2-high (red) SA. Boxplots illustrate the median and IQR and the largest and smallest values above or below the 75th and 25th percentile, respectively. * $P < .05$; ** $P < .01$; *** $P < .001$.

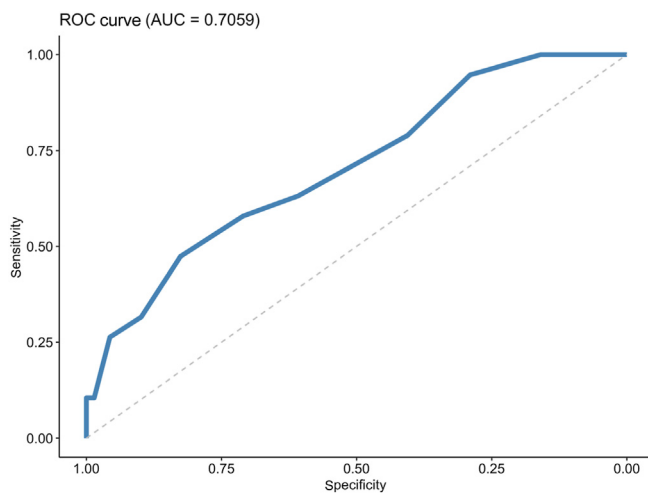


FIG 4. Receiver-operating characteristic (ROC) curve for ASSESS score in predicting persistent poor asthma control over 5 years.

score to predict biologic response. HRCT results were not available for half of the cohort; therefore, the number of bronchiectasis may be underdiagnosed despite having a normal chest radiograph. Furthermore, the severity of bronchiectasis was

not quantified. Nonetheless, with the large cohort and 5 years of follow-up data, this study has the potential to guide clinical decision making and inform policy decisions.

Bronchiectasis and GERD were associated with poor asthma control over 5 years among patients with SA. Comprehensive assessment and management of SA in specialist clinics improved overall SA outcomes. The ASSESS score can be used to identify patients with poor asthma control. Future study is required to evaluate the use of ASSESS as a monitoring tool for biologic treatment response.

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Clinical implications: The ASSESS score predicts persistent poor asthma control over 5 years, and bronchiectasis and GERD are treatable traits with significant contributions to persistent poor asthma control in a multiethnic Asian SA cohort.

REFERENCES

- Hekking PW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015;135:896-902.
- Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;9:24.
- Global Initiative for Asthma. Global strategy for asthma management and prevention. 2018. Available at: <https://ginasthma.org/wp-content/uploads/2019/01/2018-GINA.pdf>.
- Lim GN, Allen JC, Tiew PY, Chen W, Koh MS. Healthcare utilization and health-related quality of life of severe asthma patients in Singapore. *J Asthma* 2023;60:969-80.
- Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J* 2015;46:1308-21.
- Denton E, Price DB, Tran TN, Canonica GW, Menzies-Gow A, FitzGerald JM, et al. Cluster analysis of inflammatory biomarker expression in the International Severe Asthma Registry. *J Allergy Clin Immunol Pract* 2021;9:2680-8.e7.
- Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;378:2486-96.
- Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371:1198-207.
- Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017;376:2448-58.
- Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med* 2021;384:1800-9.
- Hudey SN, Ledford DK, Cardet JC. Mechanisms of non-type 2 asthma. *Curr Opin Immunol* 2020;66:123-8.
- Caminati M, Morais-Almeida M, Bleecker E, Ansotegui I, Canonica GW, Bovo C, et al. Biologics and global burden of asthma: a worldwide portrait and a call for action. *World Allergy Organ J* 2021;14:100502.
- Porsbjerg CM, Menzies-Gow AN, Tran TN, Murray RB, Unni B, Audrey Ang SL, et al. Global variability in administrative approval prescription criteria for biologic therapy in severe asthma. *J Allergy Clin Immunol Pract* 2022;10:1202-16.e23.
- Redmond C, Heaney LG, Chaudhuri R, Jackson DJ, Menzies-Gow A, Pfeffer P, et al. Benefits of specialist severe asthma management: demographic and geographic disparities. *Eur Respir J* 2022;60:2200660.
- Tay TR, Lee J, Radhakrishna N, Hore-Lacy F, Stirling R, Hoy R, et al. A structured approach to specialist-referred difficult asthma patients improves control of comorbidities and enhances asthma outcomes. *J Allergy Clin Immunol Pract* 2017;5:956-64.e3.
- van der Meer AN, Pasma H, Kempenaar-Okkema W, Pelinck JA, Schutten M, Storm H, et al. A 1-day visit in a severe asthma centre: effect on asthma control, quality of life and healthcare use. *Eur Respir J* 2016;48:726-33.
- Bratton DL, Price M, Gavin L, Glenn K, Brenner M, Gelfand EW, et al. Impact of a multidisciplinary day program on disease and healthcare costs in children and adolescents with severe asthma: a two-year follow-up study. *Pediatr Pulmonol* 2001;31:177-89.
- Begne C, Justet A, Dupin C, Taille C. Evaluation in a severe asthma expert center improves asthma outcomes regardless of step-up in asthma therapy. *J Allergy Clin Immunol Pract* 2020;8:1439-42.e2.
- Denton E, Lee J, Tay T, Radhakrishna N, Hore-Lacy F, Mackay A, et al. Systematic assessment for difficult and severe asthma improves outcomes and halves oral corticosteroid burden independent of monoclonal biologic use. *J Allergy Clin Immunol Pract* 2020;8:1616-24.
- Hastie AT, Mauger DT, Denlinger LC, Coverstone A, Castro M, Erzurum S, et al. Mixed sputum granulocyte longitudinal impact on lung function in the severe asthma research program. *Am J Respir Crit Care Med* 2021;203:882-92.
- Lee Y, Park Y, Kim C, Lee E, Lee HY, Woo SD, et al. Longitudinal outcomes of severe asthma: real-world evidence of multidimensional analyses. *J Allergy Clin Immunol Pract* 2021;9:1285-94.e6.
- Soremekun S, Heaney LG, Skinner D, Bulathsinhala L, Carter V, Chaudhry I, et al. Asthma exacerbations are associated with a decline in lung function: a longitudinal population-based study. *Thorax* 2023;78:643-52.
- Kimura H, Konno S, Makita H, Taniguchi N, Shimizu K, Suzuki M, et al. Prospective predictors of exacerbation status in severe asthma over a 3-year follow-up. *Clin Exp Allergy* 2018;48:1137-46.
- Gillis RME, van Litsenburg W, van Balkom RH, Muris JW, Smeenk FW. The contribution of an asthma diagnostic consultation service in obtaining an accurate asthma diagnosis for primary care patients: results of a real-life study. *NPJ Prim Care Respir Med* 2017;27:35.
- Braido F, Baiardini I, Alleri P, Bacci E, Barbetta C, Bellocchia M, et al. Asthma management in a specialist setting: results of an Italian Respiratory Society survey. *Pulm Pharmacol Ther* 2017;44:83-7.
- Fitzpatrick AM, Szeffler SJ, Mauger DT, Phillips BR, Denlinger LC, Moore WC, et al. Development and initial validation of the Asthma Severity Scoring System (ASSESS). *J Allergy Clin Immunol* 2020;145:127-39.

27. Hill AT, Sullivan AL, Chalmers JD, De Soyza A, Elborn SJ, Floto AR, et al. British Thoracic Society guideline for bronchiectasis in adults. *Thorax* 2019;74:1-69.
28. Chalmers JD, Aliberti S, Polverino E, Vendrell M, Crichton M, Loebinger M, et al. The EMBARC European Bronchiectasis Registry: protocol for an international observational study. *ERJ Open Res* 2016;2:00081-2015.
29. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59-99.
30. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 2001;108:S2-8.
31. Kerkhof M, Tran TN, Allehebi R, Canonica GW, Heaney LG, Hew M, et al. Asthma phenotyping in primary care: applying the International Severe Asthma Registry eosinophil phenotype algorithm across all asthma severities. *J Allergy Clin Immunol Pract* 2021;9:4353-70.
32. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015;3:849-58.
33. Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Ling Zhi Jie J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy* 2018;11:193-204.
34. Skov IR, Madsen H, Henriksen DP, Andersen JH, Pottegard A, Davidsen JR. Low-dose oral corticosteroids in asthma associates with increased morbidity and mortality. *Eur Respir J* 2022;60:2103054.
35. Yii ACA, Tan JHY, Lapperre TS, Chan AKW, Low SY, Ong TH, et al. Long-term future risk of severe exacerbations: distinct 5-year trajectories of problematic asthma. *Allergy* 2017;72:1398-405.
36. Padilla-Galo A, Olveira C, Fernandez de Rota-Garcia L, Marco-Galve I, Plata AJ, Alvarez A, et al. Factors associated with bronchiectasis in patients with uncontrolled asthma; the NOPES score: a study in 398 patients. *Respir Res* 2018;19:43.
37. Crimi C, Campisi R, Nolasco S, Ferri S, Cacopardo G, Impellizzeri P, et al. Type 2-high severe asthma with and without bronchiectasis: a prospective observational multicentre study. *J Asthma Allergy* 2021;14:1441-52.
38. Mao B, Yang JW, Lu HW, Xu JF. Asthma and bronchiectasis exacerbation. *Eur Respir J* 2016;47:1680-6.
39. Kang HR, Choi GS, Park SJ, Song YK, Kim JM, Ha J, et al. The effects of bronchiectasis on asthma exacerbation. *Tuberc Respir Dis (Seoul)* 2014;77:209-14.
40. Liang B, Yi Q, Feng Y. Association of gastroesophageal reflux disease with asthma control. *Dis Esophagus* 2013;26:794-8.
41. Richter JE. Gastroesophageal reflux disease and asthma: the two are directly related. *Am J Med* 2000;108:153S-8S.
42. Kudlaty E, Patel GB, Prickett ML, Yeh C, Peters AT. Efficacy of type 2-targeted biologics in patients with asthma and bronchiectasis. *Ann Allergy Asthma Immunol* 2021;126:302-4.