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Epidemiological, clinical and economic burden of severe eosinophilic asthma: Results from a large tertiary care hospital

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Abstract

Background: Burden of severe eosinophilic asthma (SEA) data in Asia are limited.

Objective: This retrospective, observational study characterized SEA epidemiology, healthcare resource use (HCRU) and costs for adult patients in Taiwan.

Methods: Data from Taichung Veterans General Hospital electronic medical record database, between 2013 to 2016, were extracted. Eligible general asthma patients were ≥ 18 years at index date, with ≥ 1 medical claim with an asthma diagnosis after the index date. Patients with SEA (meeting additional criteria: Global Initiative for Asthma Step 4/5 treatment guidelines [within 3 months preceding index date], ≥ 2 clinically significant exacerbations, and eosinophil counts ≥ 300 cells/μL [within 12 months preceding index date] or ≥ 150 cells/μL [on index date]) and SEA patients using high-dose inhaled corticosteroids (HD ICS) were also identified. Twelve months' pre-index data were used to evaluate exacerbation frequency, treatment patterns, HCRU, and costs (2016 US Dollars).

Results: Of 2,601 eligible general asthmatic patients, 162 (6.2%) met predefined criteria for SEA; of SEA patients, 72/162 (44.4%) had used HD ICS. SEA and HD ICS SEA patients experienced more clinically significant exacerbations than general asthma patients (1.6 ± 3.3 and 1.5 ± 2.6 vs 0.6 ± 2.0, $p < 0.01$). HD ICS SEA and SEA patients incurred at least 2–2.5-fold higher total asthma-related and all-cause costs than general asthma patients and had significantly greater HCRU.

Conclusions: Of eligible Taiwanese general asthma patients, 6.2% met predefined SEA criteria. Compared with general asthma patients, SEA and HD ICS SEA patients used more respiratory medications, experienced more exacerbations, and incurred greater HCRU and higher costs.

Key words: severe eosinophilic asthma, high-dose inhaled corticosteroids, Taiwan, epidemiology, health care costs

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Introduction

Most asthma cases are controlled with available medication or stepped up if they remain uncontrolled. For patients with Severe Asthma (SA), however, most still have poor asthma control, persistent airflow limitation, and frequent severe exacerbations.[1,2]

Estimates, predominantly from Western countries, indicate low prevalence of SA (5–10%),[1] however, this group contributes to disproportionally high health-care resource use (HCRU, ~50%) due to treatment of frequent acute exacerbations.[3] Compared with controlled asthma, uncontrolled disease imposes substantial direct and indirect costs through lost working days,[4] increased total and asthma-related health-care costs,[5,6] decreased health-related quality of life,[7,8] and increased risk of death.[9] As current therapies do not adequately control symptoms for all patients with SA, there is an unmet need for therapeutic options to reduce SA-related morbidity and mortality.

Severe eosinophilic asthma (SEA), associated with elevated blood and sputum eosinophil counts,[1,10,11] and severe allergic (immunoglobulin [Ig]E-mediated) asthma (SAA), are SA phenotypes that can overlap leading to overlap in treatment eligibility.[12] Clinical characterization of SEA patients, and examination of their associated HCRU, has been conducted in Western countries but are poorly described in Asia. This study aimed to characterize the epidemiology and clinical characteristics of adult patients with SEA in Taiwan, to describe dispensed medications, HCRU and associated asthma-related and all-cause costs.

Methods

Objectives

To estimate the prevalence of asthmatic patients in Taiwan meeting SEA criteria, describe patient demographics, clinical characteristics, respiratory medication use, and quantify HCRU and costs (all-cause and asthma-related) over 12-months.

Study design

This retrospective population study utilized data from July 1st, 2013 through June 30th, 2016, obtained from the Taichung Veterans General Hospital (VGHTC) electronic medical record (EMR) database. The VGHTC is a large tertiary center with up to 190 million outpatient visits annually and a high proportion of returning patients. Exacerbation frequency, treatment patterns and HCRU/costs were assessed post-index period (index was defined as the date with the first confirmed diagnosis of asthma after July 1st, 2014).

Patient Cohort Identification

Included patients were: ≥ 18 years at index date, with a record of ≥ 1 medical claim with an asthma diagnosis (International Classification of Diseases-9: 493.xx; -10: J45 or J46) after July 1st, 2014, minimum of 12 months' medical data available before (baseline) and after (follow-up) the index date for a total of 24 months. Patients with chronic obstructive pulmonary disease (COPD) and smokers were not excluded.

Patients were further classified as having SEA if they: met the criteria for GINA Step 4 or 5 treatment guidelines[13] in the 3 months prior to index date, had ≥ 2 clinically significant exacerbations in the 12 months prior to index date, and had ≥ 1 blood eosinophil count (BEC) result of ≥ 300 cells/μL (steady state or exacerbated state) in the 12 months prior to index date, OR ≥ 150 cells/μL measured on index date. Patients meeting SEA criteria were stratified by the following BEC ranges: < 150, 150–300, > 300–400, and > 400 cells/μL. As there is currently no gold standard for defining eosinophilic asthma severity,[14] different cut-offs were explored to define SEA and to determine the corresponding effect on the prevalence.

A subset of SEA population who had ever been treated with HD ICS was also extracted and analyzed.

Patients meeting the SEA criteria were additionally classified based on the number of exacerbations and their use of oral corticosteroid (OCS).

Study procedures and evaluations

Demographics and clinical characteristics

These were described for patients at study index date.

Exacerbations

Clinically significant asthma exacerbations were recorded during the 12-month follow-up period (inclusive of index date) and were defined as an asthma-related ED visitor hospital admission, or an exacerbation treated with OCS.

Asthma medication

Asthma medication exposure, including pattern of medication use, adherence, and OCS average daily dose, were defined as:

Medication use: The distribution of patients prescribed ≥ 1 asthma medications over the 12-month index period were summarized.

Medication adherence: Adherence to controller therapy at index date was assessed over 365 days using proportion of days covered (PDC).

OCS average daily dose: The average daily dose for OCS was described for OCS episodes (defined as a sequence of OCS claims that occurred ≤ 7 days apart.

Healthcare resource use

Asthma-related HCRU data (encompassing medical claims with an asthma diagnosis in the primary position) were examined during the 12-month follow-up period (inclusive of index date). Frequency of out-patient department (OPD) visits, ED visits, hospitalizations (≥ 1 day to distinguish from patients who received diagnostic services or procedures), average length of stay, and intensive care unit (ICU) admission (Yes/No) were analyzed.

All-cause and asthma-related healthcare costs

Healthcare costs comprised all medical fees (medication, examination, surgeries, inpatient hospital admissions, OPD, ER, wards, etc.) charged to the patient.

Statistical analysis

For medication adherence, PDC was multiplied by 100 to yield a percentage and categorized as high (> 80%), medium (80% ≥ PDC ≥ 50%), low (50% > PDC ≥ 30%), and very low (< 30%) based on published literature.[15,16]

For HCRU, frequency rates (number of events/person/year) were evaluated. For economic endpoints, asthma-related healthcare costs paid to providers were computed per patient annually and applied to costs of hospitalization, OPD visits, and ED visits. Costs were standardized and reported in 2016 US dollars using the Medical Care Consumer Price Index. A non-parametric bootstrap procedure was used to carry out statistical inference and determine *p*-values for the cost difference between exposure groups.

Economic outcomes, demographics and clinical characteristics were summarized by descriptive statistics (n and mean ± standard deviation (SD) for continuous parameters, and frequency and percentage for categorical parameters).

Statistical analyses were performed for SEA, and HD ICS SEA, vs general asthma populations; $p < 0.05$ was considered statistically significant. Continuous variables were analyzed using *t*-test and categorical variables using Chi-square test. All analyses were conducted using SAS version 9.4. This was a descriptive epidemiologic study therefore no controlling for confounding, sample size or power/precision calculations were performed. Missing values were not imputed. Data cleaning methods were not required.

Ethics Approval and Consent to Participate

This observational study complied with the principles laid down by the 64th World Medical Assembly (Helsinki, 2013). The study was conducted in accordance with legal and regulatory requirements/guidelines, as well as with scientific purpose, value and rigor; and followed generally accepted research practices.

Informed consent was not required in this retrospective study using the VGHTC database since these anonymized data were approved for the use in observational research and the study did not involve the contact with patients. This study complied with all applicable laws regarding subject privacy. The study posed minimal privacy risk for patients and had been approved by the Institutional Review Board of VGHTC (IRB code: SF16245B).

Results

Baseline patient demographics and clinical characteristics

Of 9,455 patients with asthma diagnosis codes, 2,601/9,455 (27.5%) met the inclusion criteria; 162/2,601 (6.2%) met SEA criteria and among these, 72/162 patients (44.4%) had used HD ICS (**Figure 1**). Mean age was comparable between the populations, and most patients were aged ≥ 50 years. SEA and general asthma patients had comparable BMI scores, while HD ICS SEA patients had a significantly higher BMI compared with general asthma patients ($p < 0.05$). Most patients from all populations had total IgE levels of > 30 and < 1300 IU/mL (**Table 1**).

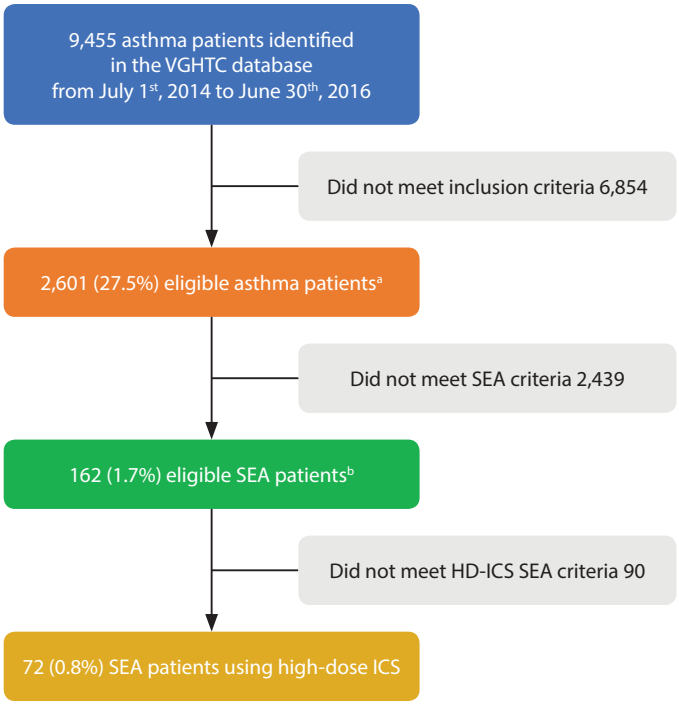

Figure 1. Patient flow diagram.

[a]asthma patients meeting criteria 1–3; [b]SEA patients meeting criteria 1–6; ICS, inhaled corticosteroids; SEA, severe eosinophilic asthma; VGHTC, Taichung Veterans General Hospital.

A significantly greater proportion of HD ICS SEA and SEA patients were female compared with general asthma patients (56.9% and 51.9%, respectively vs 40.8%; $p < 0.01$), had atopy and had more comorbidities; HD ICS SEA and SEA populations also included higher proportions of patients who were current or had ever been smokers. On the index date, BECs of ≥ 300 cells/μL were recorded for 58.0% of SEA patients vs 52.7% HD ICS SEA patients vs 14.7% general asthma patients (**Table 1**).

Table 1. Baseline patient demographics and clinical characteristics.

Items		General asthma n = 2439	HD-ICS SEA n = 72	SEA n = 162	SEA population by eosinophil level (cells/μL) n = 162				*P* value[a] vs General asthma	
					< 150 n = 29	150-300 n = 39	> 300-400 n = 35	> 400 n = 59	HD ICS SEA	SEA
Age (years), mean ± SD		61.9 ± 16.42	64.6 ± 17.97	62.9 ± 17.88	66.0 ± 16.53	60.4 ± 19.19	64.3 ± 15.42	62.2 ± 19.08	0.18	0.47
Age groups (years),	18 to < 30	101 (4.1)	3 (4.2)	7 (4.3)	0 (--.-)	4 (10.3)	0 (--.-)	3 (5.1)		
n (%)	30 to < 50	444 (18.2)	13 (18.1)	34 (21.0)	7 (24.1)	6 (15.4)	7 (20.0)	14 (23.7)		
	50 to < 70	1021 (41.9)	27 (37.5)	62 (38.3)	10 (34.5)	18 (46.2)	13 (37.1)	21 (35.6)	1.00	0.66
	≥ 70	873 (35.8)	29 (40.3)	59 (36.4)	12 (41.4)	11 (28.2)	15 (42.9)	21 (35.6)		
Gender, female, n (%)		995 (40.8)	41 (56.9)	84 (51.9)	11 (37.9)	22 (56.4)	17 (48.6)	34 (57.6)	0.006*	0.006*
BMI (kg/m^2)	Missing	1209	7	30	4	4	6	16	0.05*	0.47
	Mean ± SD	25.0 ± 4.77	26.6 ± 6.53	25.3 ± 5.60	27.2 ± 8.28	25.7 ± 6.16	25.2 ± 4.18	24.0 ± 3.54		
Smoking status, n (%)	Missing	7	0	0	0	0	0	0		
	Non-smokers	2043 (84.0)	52 (72.2)	124 (76.5)	22 (75.9)	25 (64.1)	28 (80.0)	49 (83.1)	0.002*	0.03*
	Ex-smokers	252 (10.4)	17 (23.6)	27 (16.7)	5 (17.2)	8 (20.5)	6 (17.1)	8 (13.6)		
	Smokers	137 (5.6)	3 (4.2)	11 (6.8)	2 (6.9)	6 (15.4)	1 (2.9)	2 (3.4)		
Total IgE (IU/mL),	Missing	2135	52	127	23	31	26	47		
n (%)	≤ 30	69 (22.7)	2 (10.0)	5 (14.3)	2 (33.3)	1 (12.5)	1 (11.1)	1 (8.3)	0.41	0.25
	> 30 to < 1300	212 (69.7)	16 (80.0)	25 (71.4)	3 (50.0)	6 (75.0)	7 (77.8)	9 (75.0)		
	≥ 1300	23 (7.6)	2 (10.0)	5 (14.3)	1 (16.7)	1 (12.5)	1 (11.1)	2 (16.7)		
Eosinophil level	Missing	1163	0	0	0	0	0	0		
(cells/μL)	Mean ± SD, median (IQR)	167.3 ±172.86, 120.0 (56.8–214.8)	475.5 ± 574.81, 310.2 (210.3–509.4)	467.5 ± 504.17, 326.4, (210.0–518.4)	78.0 ± 43.95, 81.9 (41.0–121.6)	236.6 ± 42.70, 241.2 (202.8– 277.2)	344.9 ± 30.64, 340.0 (319.3–377.4)	884.3 ± 636.74, 644.8 (500.5–1004.8)	< 0.001*	< 0.001*
Eosinophil level	Missing	1163	0	0	-	-	-	-		
(cells/μL), n (%)	< 100	534 (41.8)	12 (16.7)	18 (11.1)	-	-	-	-		
	100 to < 150	246 (19.3)	3 (4.2)	11 (6.8)	-	-	-	-		
	150 to < 200	138 (10.8)	2 (2.8)	9 (5.6)	-	-	-	-	< 0.001*	< 0.001*
	200 to < 250	105 (8.2)	8 (11.1)	13 (8.0)	-	-	-	-		
	250 to < 300	66 (5.2)	9 (12.5)	17 (10.5)	-	-	-	-		
	300 to < 400	71 (5.6)	15 (20.8)	35 (21.6)	-	-	-	-		
	≥ 400	116 (9.1)	23 (31.9)	59 (36.4)	-	-	-	-		

Table 1. (Continued)

Items		General asthma n = 2439	HD-ICS SEA n = 72	SEA n = 162	SEA population by eosinophil level (cells/μL) n = 162				*P* value[#] vs General asthma	
					< 150 n = 29	150-300 n = 39	> 300-400 n = 35	> 400 n = 59	HD ICS SEA	SEA
Comorbidities[¥], n (%)	None	593 (24.3)	13 (18.1)	32 (19.8)	1 (3.4)	15 (38.5)	4 (11.4)	12 (20.3)		
	1–2	1505 (61.7)	34 (47.2)	86 (53.1)	15 (51.7)	18 (46.2)	20 (57.1)	33 (55.9)		
	3–5	317 (13.0)	24 (33.3)	40 (24.7)	11 (37.9)	5 (12.8)	10 (28.6)	14 (23.7)	< 0.001*	< 0.001*
	> 5	24 (1.0)	1 (1.4)	4 (2.5)	2 (6.9)	1 (2.6)	1 (2.9)	0 (--.-)		
Atopy, n (%)		209 (8.6)	12 (16.7)	22 (13.6)	2 (6.9)	6 (15.4)	6 (17.1)	8 (13.6)	0.03*	0.04*

[¥]Comorbidities include nasal polyps, rhinitis allergic, rhinitis chronic, tachycardia, dysrhythmias, atrial fibrillation, cardiac dysrhythmias, myocardial infarction, angina pectoris, unstable angina, transient ischemic attack, other forms of chronic ischemic heart disease, cardiac failure congestive, atrioventricular block, bundle branch block right, conduction disorder, palpitations, pericardial effusion, ventricular extra-systoles, hypertension, pulmonary hypertension, cerebrovascular disorders, ischemic stroke, hemorrhagic stroke, pulmonary embolism, hypotension, and thrombophlebitis.
[#]Between-group comparison by *t* test for continuous data and Chi-square test for categorical data. *Denotes statistical significance. BMI, body mass index; CI, confidence interval; HD ICS, high-dose inhaled corticosteroid; IgE, immunoglobulin E; IQR, interquartile range; SD, standard deviation; SEA, severe eosinophilic asthma

Table 2. Asthma exacerbations during the 12-month follow-up period.

Items		General asthma n = 2439	HD ICS SEA n = 72	All SEA n = 162	SEA population by eosinophil level (cells/μL) n = 162				*P*-value[#] vs General asthma	
					< 150 n = 29	150-300 n = 39	> 300-400 n = 35	> 400 n = 59	HD ICS SEA	All SEA
Exacerbations (times/patient-year), mean ± SD, median (IQR)		0.6 ± 2.02, 0.0 (0.0–0.0)	1.5 ± 2.59, 0.0 (0.0–2.0)	1.6 ± 3.32, 0.0 (0.0–1.0)	1.6 ± 3.19, 0.0 (0.0–1.0)	1.5 ± 3.47, 0.0 (0.0–1.0)	1.2 ± 1.77, 0.0 (0.0–2.0)	1.9 ± 3.96, 1.0 (0.0–2.0)	0.006*	< 0.001*
Number of exacerbations	None	1974 (80.9)	38 (52.8)	85 (52.5)	18 (62.1)	21 (53.8)	18 (51.4)	28 (47.5)		
(times/year), n (%)	1-2	323 (13.2)	20 (27.8)	50 (30.9)	4 (13.8)	14 (35.9)	11 (31.4)	21 (35.6)	< 0.001*	< 0.001*
	3	33 (1.4)	4 (5.6)	6 (3.7)	2 (6.9)	1 (2.6)	2 (5.7)	1 (1.7)		
	≥ 4	109 (4.5)	10 (13.9)	21 (13.0)	5 (17.2)	3 (7.7)	4 (11.4)	9 (15.3)		
Led to ED, n (%)		245 (52.7)	20 (58.8)	42 (54.5)	6 (54.5)	6 (33.3)	10 (58.8)	20 (64.5)	0.49	0.76
Led to hospitalization, n (%)		217 (46.7)	19 (55.9)	36 (46.8)	5 (45.5)	12 (66.7)	10 (58.8)	9 (29.0)	0.30	0.99
Used OCS, n (%)		97 (20.9)	5 (14.7)	14 (18.2)	3 (27.3)	3 (16.7)	2 (11.8)	6 (19.4)	0.39	0.59
OCS dose (mg/day), mean ± SD, median (IQR)		11.4 ± 13.50, 7.2 (4.0–16.0)	17.8 ± 13.69, 17.7 (6.0–24.0)	11.2 ± 9.85, 8.0 (4.0–17.7)	4.9 ± 1.03, 4.6 (4.0–6.0)	16.4 ± 18.27, 8.0 (3.8–37.3)	13.5 ± 14.85, 13.5 (3.0–24.0)	11.0 ± 5.63, 9.2 (8.0–17.7)	0.30	0.96

[#]Between-group comparison by *t* test for continuous data and Chi-square test for categorical data. *Denotes statistical significance. ED, emergency department; HD ICS, high-dose inhaled corticosteroid; IQR, interquartile range; OCS, oral corticosteroids, SEA, severe eosinophilic asthma; SD, standard deviation.

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Table 3. Overall respiratory medication adherence and utilization during the 12-month follow-up period.

Items		General asthma n = 2439	HD-ICS SEA n = 72	SEA n = 162	SEA population by eosinophil level (cells/μL) n = 162				*P* value# vs General asthma	
					< 150 n = 29	150-300 n = 39	> 300-400 n = 35	> 400 n = 59	HD ICS SEA	SEA
Adherence, PDC (%)	Overall, mean ± SD, median (IQR)	66.8 ± 36.17, 84.7 (32.3–100.0)	73.7 ± 31.66, 89.5 (53.8–100.0)	67.2 ± 34.13, 83.0 (40.0–99.7)	65.8 ± 34.63, 80.5 (38.4–95.9)	61.8 ± 36.57, 61.9 (27.7–100.0)	72.2 ± 34.21, 91.0 (46.3–100.0)	68.5 ± 32.59, 82.7 (46.8–99.7)	0.11	0.89
PDC level, n (%)	High (> 80)	988 (52.1)	44 (61.1)	83 (52.2)	15 (51.7)	18 (48.6)	20 (58.8)	30 (50.8)		
	Medium (50 to < 80)	256 (13.5)	11 (15.3)	24 (15.1)	4 (13.8)	6 (16.2)	3 (8.8)	11 (18.6)		
	Low (30 to < 50)	207 (10.9)	6 (8.3)	20 (12.6)	4 (13.8)	3 (8.1)	6 (17.6)	7 (11.9)	0.30	0.71
	Very low (< 30)	445 (23.5)	11 (15.3)	32 (20.1)	6 (20.7)	10 (27.0)	5 (14.7)	11 (18.6)		
	Missing†	543	0	3	0	2	1	0		
Medications, n (%)										
LAMA		182 (7.5)	14 (19.4)	21 (13.0)	4 (13.8)	7 (17.9)	4 (11.4)	6 (10.2)	< 0.001*	0.01*
LABA		56 (2.3)	2 (2.8)	6 (3.7)	0 (--.-)	1 (2.6)	1 (2.9)	4 (6.8)	1.00	0.38
ICS		219 (9.0)	6 (8.3)	13 (8.0)	0 (--.-)	6 (15.4)	4 (11.4)	3 (5.1)	0.85	0.68
SAMA		0 (--.-)	0 (--.-)	0 (--.-)	0 (--.-)	0 (--.-)	0 (--.-)	0 (--.-)	NA	NA
SABA		719 (29.5)	38 (52.8)	77 (47.5)	19 (65.5)	16 (41.0)	17 (48.6)	25 (42.4)	< 0.001*	< 0.001*
Theophylline		349 (14.3)	32 (44.4)	52 (32.1)	12 (41.4)	13 (33.3)	9 (25.7)	18 (30.5)	< 0.001*	< 0.001*
LTRA		621 (25.5)	22 (30.6)	51 (31.5)	8 (27.6)	7 (17.9)	16 (45.7)	20 (33.9)	0.33	0.09
Systemic corticosteroids		155 (6.4)	12 (16.7)	24 (14.8)	6 (20.7)	5 (12.8)	4 (11.4)	9 (15.3)	0.001*	< 0.001*
Systemic β agonists		114 (4.7)	6 (8.3)	13 (8.0)	3 (10.3)	3 (7.7)	3 (8.6)	4 (6.8)	0.25	0.06
Omalizumab (Xolair)		56 (2.3)	7 (9.7)	10 (6.2)	1 (3.4)	1 (2.6)	3 (8.6)	5 (8.5)	< 0.001*	0.005*
Tiotropium		167 (6.8)	12 (16.7)	19 (11.7)	3 (10.3)	7 (17.9)	3 (8.6)	6 (10.2)	0.001*	0.02*
ICS + LABA (free-dose)		11 (0.5)	0 (--.-)	1 (0.6)	0 (--.-)	0 (--.-)	0 (--.-)	1 (1.7)	0.57	1.00
ICS + Theophylline (free-dose)		25 (1.0)	3 (4.2)	3 (1.9)	0 (--.-)	1 (2.6)	0 (--.-)	2 (3.4)	0.05	0.55
ICS + LTRA (free-dose)		59 (2.4)	2 (2.8)	5 (3.1)	0 (--.-)	1 (2.6)	2 (5.7)	2 (3.4)	1.00	0.79
LABA + LAMA (fixed-dose)		9 (0.4)	0 (--.-)	1 (0.6)	0 (--.-)	0 (--.-)	0 (--.-)	1 (1.7)	0.61	1.00
SABA + SAMA (fixed-dose)		285 (11.7)	31 (43.1)	46 (28.4)	10 (34.5)	14 (35.9)	8 (22.9)	14 (23.7)	< 0.001*	< 0.001*
ICS + LABA (fixed-dose)		1404 (57.6)	72 (100)	153 (94.4)	29 (100)	36 (92.3)	31 (88.6)	57 (96.6)	< 0.001*	< 0.001*

#Between-group comparison by Chi-square test. *Denotes statistical significance. †Indicates non-users of medication. ICS, inhaled corticosteroid; HD ICS, high-dose inhaled corticosteroids; IQR, interquartile range; LABA, long-acting β2-agonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonist; NA, not applicable; SABA, short-acting β2-agonists; SAMA, short-acting muscarinic antagonists; SEA, severe eosinophilic asthma.

Table 4. Healthcare resource use in the 12-month follow-up period.

Items (times/patient-year)	General asthma (n = 1000#)	HD ICS SEA (n = 1000#)	All SEA (n = 1000#)	SEA population by eosinophil level (cells/μL) (n = 1000#)				*P*-value vs General asthma	
				< 150	150-300	> 300-400	> 400	HD ICS SEA	All SEA
OPD	4.2 ± 0.11	4.5 ± 0.76	4.7 ± 0.48	5.0 ± 1.38	2.6 ± 0.65	5.0 ± 0.93	5.9 ± 0.91	0.63	0.20
ED	0.0 ± 0.01	0.2 ± 0.07	0.2 ± 0.08	0.1 ± 0.08	0.3 ± 0.29	0.1 ± 0.04	0.2 ± 0.09	0.005*	0.001*
Hospitalization	0.0 ± 0.00	0.1 ± 0.03	0.0 ± 0.01	0.0 ± 0.03	0.1 ± 0.04	0.0 ± 0.03	0.0 ± 0.02	< 0.001*	0.003*
Length of stay (all-cause, days)	2.8 ± 0.20	13.7 ± 2.23	9.2 ± 1.30	10.8 ± 3.20	12.8 ± 2.78	8.1 ± 2.65	6.7 ± 1.90	0.001*	< 0.001*
Length of stay (asthma-related, days)	0.1 ± 0.02	0.6 ± 0.33	0.3 ± 0.14	0.4 ± 0.38	0.2 ± 0.11	0.5 ± 0.53	0.1 ± 0.14	0.002*	0.03*
ICU	0.0 ± 0.00	0.0 ± 0.02	0.0 ± 0.01	0.0 ± 0.00	0.0 ± 0.00	0.1 ± 0.04	0.0 ± 0.00	0.008*	0.03*

#Frequency was estimated by bootstrapping method using 1000 replicates. *Denotes statistical significance. ED, emergency department; ICU, intensive care unit; HRU, healthcare resource utilization; OPD, outpatient department; SEA, severe eosinophilic asthma; SD, standard deviation.

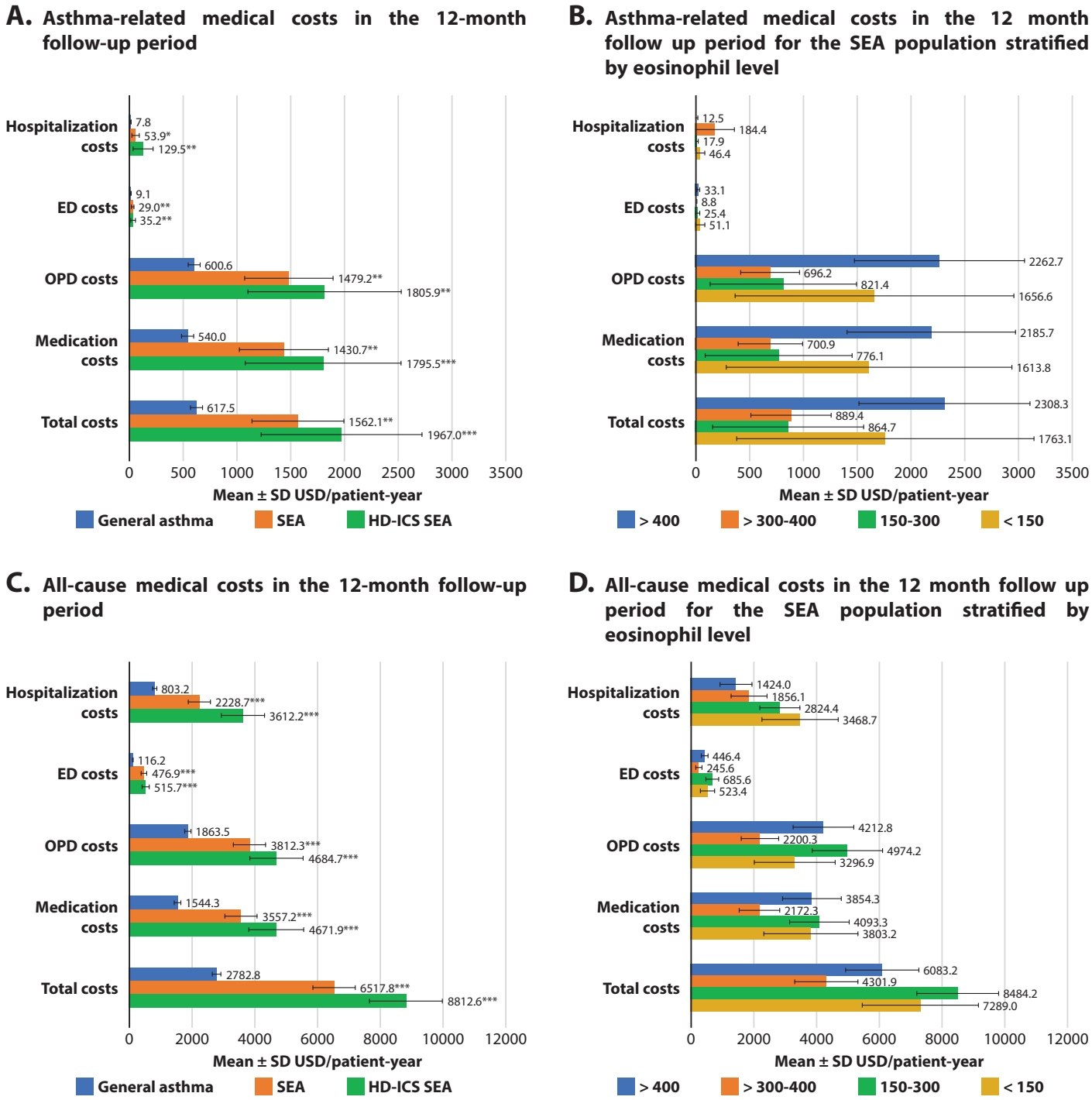

Figure 2. Asthma-related and all-cause medical costs in the 12-month follow-up period

A. Asthma-related costs in HD ICS SEA, SEA and general asthma populations

B. Asthma-related costs in SEA population stratified by eosinophil level

C. All-cause medical costs in HD ICS SEA, SEA and general asthma populations

D. All-cause medical costs in SEA population stratified by eosinophil level

Costs were estimated by bootstrapping method using 1000 replicates. * p value < 0.05, ** < 0.01 and *** < 0.001. ED, emergency department; HD ICS, high-dose inhaled corticosteroids; OPD, outpatient department; SD, standard deviation; SEA, severe eosinophilic asthma; USD, United States Dollars

Exacerbations

In the 12-month follow-up period, the mean number of exacerbations was significantly higher for HD ICS SEA and SEA vs general asthma patients: 1.5 ± 2.59 and 1.6 ± 3.32 vs 0.6 ± 2.02, respectively (**Table 2**).

Proportions of SEA and HD ICS SEA patients experiencing 1–2, 3, or ≥ 4 exacerbations were at least 2-fold greater compared with general asthma patients ($p < 0.0001$; **Table 2**). Proportions of patients who experienced exacerbations requiring hospitalization or an ED visit were highest for HD ICS SEA patients, while those who used OCS was highest for the general asthma population (**Table 2**).

Utilization of respiratory medications

The respiratory medications coverage rate in the 12-month follow-up period was significantly higher for HD ICS SEA and SEA vs general asthma patients, with 2- to 3-fold greater use for many medication classes, including LAMA, SABA, theophylline and tiotropium (**Table 3**). Overall, a fixed-dose ICS + LABA combination was the most commonly used medication, and was used by all HD ICS SEA, 94.4% of SEA vs 57.6% of general asthma patients (**Table 3**).

In the SEA and HD ICS SEA populations, proportions of patients receiving omalizumab was low, but significantly greater than for general asthma patients (6.2% and 9.7% vs 2.3%, respectively). At least 2-fold more SEA and HD ICS SEA patients than general asthma patients used systemic corticosteroids (14.8% vs 16.7% vs 6.4%, respectively, **Table 3**).

When classified based on exacerbations and OCS use, the number of SEA patients with 6 months' continuous use of OCS was low across subpopulations.

Adherence to respiratory medications

Mean overall PDC, for aggregated respiratory medications, and for most specific medications, was comparable between SEA and general asthma patients and higher for HD ICS SEA patients in the 12-month follow up period (**Table 3**). The greatest proportion of patients with a PDC level ≥ 80%, was observed in HD ICS SEA patients (HD ICS SEA vs SEA vs general asthma: 61.1% vs 52.2% vs 52.1%; **Table 3**).

Healthcare resource use and costs

There were significantly more asthma-related ED visits, but not OPD visits, for both SEA and HD ICS SEA populations vs the general asthma population in the 12-month follow up period ($p < 0.01$). SEA and HD ICS SEA patients also had significantly higher asthma-related hospitalizations and ICU admissions. Asthma-related length of stay, and all-cause length of stay was significantly longer by at least 3-fold for these patients vs general asthma patients ($p < 0.05$; **Table 4**).

Asthma-related and all-cause costs

The HD ICS SEA and SEA populations incurred significantly greater asthma-related costs for each healthcare category vs the general asthma population; total asthma-related costs were also higher by at least 2.5-fold for these patient populations. OPD costs were the primary driver of total costs (**Figure 2A**). Significantly greater all-cause costs (2–3 fold) across all healthcare categories were also incurred by HD ICS SEA and SEA populations vs the general asthma population; total all-cause costs were $8812.6 and $6517.8 vs $2782.8, respectively. OPD costs were the primary driver of total costs (**Figure 2C**).

There was variation in HCRU and costs between the BEC subgroups of SEA patients.

Discussion

Real-world evidence describing patients with SEA and their associated HCRU is limited in Asia. We found 6.2% of patients met predefined criteria for SEA; 44.4% of these had used HD ICS therapy. SEA and HD ICS SEA patients experienced a higher number of exacerbations than general asthma patients despite greater medication usage, and accounted for higher asthma-related and all-cause HCRU and costs.

HD ICS SEA and SEA patients in Taiwan were similar in age to general asthma patients and more likely to be female, contrasting with a UK SEA population who were more likely to be older than the main study population and for which similar proportions of female patients were found.[17] In the SA Research Program however, female patients were also more likely to have SEA.[18] Consistent with the UK study, Taiwanese SEA and HD ICS SEA patients had more comorbidities and atopy.[17]

Epidemiological and HCRU data on SEA patients is available from Western studies. Kerkhof et al (2018) reported that 10% of UK patients with active asthma were prescribed HD ICS/LABA - greater than the proportion we identified. Patients with SEA (defined similarly to our study as ≥ 2 exacerbations in the baseline year and a BEC of ≥ 0.3×10^9/L at index date; n = 2940, 0.8%) also accounted for 2.5–7.6-times greater mean HCRU and direct asthma-related costs for each HCRU-related category vs the main active-asthma population. In the US, higher asthma-related costs have also been associated with elevated eosinophil levels.[19] In our study we found asthma-related costs, for all HCRU categories, were substantially higher (over 2-fold) for the HD ICS SEA and SEA patient populations, vs the general asthma population, but we did not see trends in increasing HCRU and associated costs with increasing eosinophil level within the SEA population, in contrast to other data.[17] A comparison of absolute asthma-related costs is difficult to make between countries due to socioeconomic differences and differences in healthcare systems. However, regarding relative costs,

a systematic literature review of economic burden of asthma in 68 studies found hospitalization and medication costs were the most important drivers of direct costs,[20] while we found OPD costs to be the main driver. In our study, there were limited episodes of asthma-related hospitalization occurring during the 12-month follow-up period (SEA patients had 0.3 ± 0.14 days/patient-year of hospitalization due to asthma, as shown in **Table 4**). This is in-line with our expectation as patients treated at tertiary medical centres are given specialized and intensive care to keep symptoms under control; this was reflected in the greater utilization of OPD services (4.7 ± 0.48 times/patient-year for SEA patients) which resulted in greater healthcare resource use on OPD visits and medication.

Respiratory medication coverage rates were higher for SEA vs general asthma patients by 2- to 3-fold; however, adherence to overall respiratory medications was comparable (~67%), and higher in HD ICS SEA patients (73.7%); these values are considered high based on studies examining the compliance rate of asthma patients (55%)[15] and the adherence rate of patients with SA (28–67%).[21] Of note, our overall medication adherence for SEA and HD ICS SEA patients based on PDC ≥ 80% was broadly similar to that demonstrated previously for long-term oral and inhaled controller medication in a patient population with SA (58.3%).[22] Despite high medication coverage rates, we found approximately half of SEA and HD ICS SEA patients continued to experience exacerbations. Considering the high overall medication adherence results, the likelihood that the asthma of SEA or HD ICS SEA patients in our study would be categorized as difficult-to-treat rather than refractory[7] due to poor adherence is therefore low. We also assessed comorbidities and modifiable risk factors in the study and found that this was higher in SEA vs. general asthma population. Though SEA patients were more frequently prescribed with SABA vs. general asthma patients (**Table 3**), the rate of PDC was not different between SEA and general asthma patients. The persistence of exacerbations in these patient populations is therefore more likely indicative of suboptimal disease control with current treatments. As per GINA guidelines for the diagnosis and management of asthma, severe asthma is asthma that is poorly controlled despite being managed with GINA Step 4–5 treatment, good adherence and good inhaler techniques.[23] As patients in our study fulfilled these criteria, and the majority of the patients had access to inhaler training, we believed most of the patients we recruited had severe asthma rather than difficult-to-treat asthma.

We found few SEA patients were using omalizumab. A retrospective, population-based cohort study using Taiwan National Health Insurance data also reported low coverage of omalizumab (0.4% SAA patients in 2011), despite associated reductions in number of asthma medications, exacerbations and ED visits.[24] In Korean SA patients, omalizumab was found to be used in just 1.8%, although this only represents private use.[25] Low biologic utilization may be due to healthcare reimbursement factors,[25] associated costs that may hinder prescription of biologics by physicians, reservation of omalizumab for patients specifically with SAA, or to patients' treatment with multiple non-biologic medications and/or non-evident clinical benefits over contemporary maintenance inhaler treatments.[26]

This is the first study in Taiwan assessing epidemiology and burden of SEA and provides needed real-world, and ethnic data on SEA in an adult, Chinese population. Although clinical databases can be associated with data quality issues and missing variables, the use of the VGHTC research-ready database[27] may minimize this as it contains a combination of EMR and claims data. Our study has some limitations. Patients with COPD were not excluded, limiting homogeneity of the study population, and patient numbers in the subgroups of SEA patients stratified by BEC were small, limiting comparisons between groups. This research was conducted in a single, though large medical center in Central Taiwan, which could limit external generalizability. However, cost data are expected to be broadly representative of other centers in Taiwan, as prescription patterns and quality of care should be standardized between centers. A further limitation is immortal-time bias, as data for patients who may have died within 12 months after the index date would have been excluded from the study. Lastly, because data from the VGHTC EMR database were not originally collected to answer research questions, misclassification bias can occur.

Conclusion

Our results indicate an unmet need for effective treatments for patients classified with SEA in Taiwan; these patients account for substantially greater asthma-related HCRU and all-cause medical costs than general asthma patients.

Consent for Publication

Not applicable

Availability of Data and Materials

GSK makes available anonymized individual participant data and associated documents from interventional clinical studies which evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com. To access data for other types of GSK sponsored research, for study documents without patient-level data and for clinical studies not listed, please submit an enquiry via the website.

Competing Interests

- SS and Y-FH are employees of and holds stocks with GlaxoSmithKline.
- L-WT and T-ML reports no competing interests.
- Y-HC: reports grant payment and consulting fees or honoraria from GlaxoSmithKline.

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Author Contributions

- Y-HC had full review access to the database population used to create the study population.
- SS, Y-FH, L-WT and T-ML were provided with the full clinical study report for review as part of this analysis.
- SS, Y-FH, L-WT, T-ML and Y-HC contributed to the conception, design, execution or analysis, and interpretation of these data.
- All authors approved the final version to be published after critically revising the manuscript/publication for important intellectual content.

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