Journal of Asthma and Allergy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

The Effect of Comorbidities on Asthma-Related Outcomes Over a Two-Year Period: A Prospective Analysis of Swiss Severe Asthma Registry (SSAR)

Fabienne Jaun[1,2], Mathivannan Kanagarasa[1,2], Maria Boesing[1,2], Giorgia Lüthi-Corridori[1,2], Pierre-Olivier Bridevaux[3], Florian Charbonnier[4], Christian F Clarenbach[5], Pietro Gianella[6], Anja Jochmann[7], Lukas Kern[8], Nikolay Pavlov[9], Thomas Rothe[10], Tsogyal Daniela Latshang[10], Christophe Von Garnier[11], Joerg D Leuppi[1,2]

[1]University Institute of Internal Medicine, Cantonal Hospital Baselland, Liestal, Switzerland; [2]Medical Faculty, University of Basel, Basel, Switzerland; [3]Centre Hospitalier du Valais Romand, Sion, Switzerland; [4]University Clinic of Pneumology, University Hospital Geneva, Geneva, Switzerland; [5]Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland; [6]Pneumology Department, Ente Ospedaliero Cantonale, Lugano, Switzerland; [7]Department of Pneumology, University Children Hospital Basel, Basel, Switzerland; [8]Center for Lung Diseases, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; [9]Department of Pulmonary Medicine, Allergology, and Clinical Immunology Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [10]Pneumology Department, Cantonal Hospital Grisons, Chur, Switzerland; [11]Division of Pulmonology, Department of Medicine, Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland

Correspondence: Fabienne Jaun, Kantonsspital Baselland, Universitäres Institut für Innere Medizin, Mühlemattstrasse 26, Liestal, CH-4410, Switzerland, Tel + 41 61 400 37 55, Email fabienne.jaun@unibas.ch; fabienne.jaun@ksbl.ch

Purpose: Severe asthma is frequently accompanied by comorbidities such as chronic rhinosinusitis, nasal polyps, allergies, and gastroesophageal reflux disease (GERD). With increasing age, non-communicable conditions such as cardiovascular diseases and multimorbidity become more prevalent. This study aimed to analyze the prevalence of comorbidities and their impact on asthma-related outcomes over a two-year period using data from the Swiss Severe Asthma Registry (SSAR).

Patients and Methods: We included 234 patients with baseline data and 2 years of follow-up visits from the SSAR. Patient's asthma control (ACT), quality of life (QoL), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), diffusing capacity of the lungs for carbon monoxide (DLCO) and fraction expiratory nitric oxide (FeNO) and their association to comorbidities were analyzed longitudinally using general estimation equations (GEEs) with log link function.

Results: Over the study period, ACT and QoL scores significantly improved, and the frequency of exacerbations declined. The prevalence of the examined comorbidities remained stable. However, the presence of chronic obstructive pulmonary disease (COPD) was significantly associated with lower ACT scores, reduced QoL, and impaired pulmonary function (all $p < 0.05$). GERD was also linked to lower ACT and QoL ($p < 0.05$), while depression was associated with a significant decrease in DLCO ($p < 0.05$).

Conclusion: Our findings underscore the strong impact of comorbidities—particularly COPD, GERD, and depression—on asthma control, quality of life, and lung function in patients with severe asthma. These results highlight the need for integrated, multi-disciplinary management strategies targeting comorbid conditions to improve overall asthma outcomes. Further research should explore these subgroups in more detail to guide personalized treatment approaches.

Keywords: severe asthma, real world evidence, asthma control, asthma-related quality of life, observational study

Introduction

Asthma is a chronic inflammatory condition of the airways, marked by increased sensitivity and airway obstruction. The severity and occurrence of symptoms, as well as airflow restrictions, can fluctuate over time, influenced by various

Received: 12 February 2025
Accepted: 10 June 2025
Published: 15 July 2025

external factors, including physical activity, allergens, weather changes, and respiratory infections, or comorbid conditions.[1]

Asthma affects over 300 million people globally, making it one of the most prevalent chronic non-communicable diseases (NCDs), driven by factors such as urbanization and lifestyle changes.[2,3]

Severe asthma (SA) is a distinct, high-burden asthma phenotype that requires a high level of therapy and is characterized by persistent symptoms and frequent exacerbations despite. It is defined as asthma that requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller with or without oral corticosteroids (OCS) for 50% of the previous year to prevent the disease to become uncontrolled or the disease remains uncontrolled despite a high level of therapy.[1,4] According to estimates 5% to 10% of asthma patients are affected by severe asthma.[3] Despite affecting only a small proportion of asthma patients, severe asthma accounts for a disproportionate share of asthma-related healthcare utilization and costs.[5] SA impacts not only daily life by its high disease burden, but often leads to long-term use of oral OCS and its associated side effects such as obesity, diabetes, osteoporosis, hypertension, adrenal suppression, or psychological issues like depression and anxiety.[6]

Comorbidities play a significant role in both the clinical course but also the management of SA. Comorbid conditions, can both exacerbate respiratory symptoms and reduce the quality of life.[7,8] Certain comorbidities are linked to more frequent or SA exacerbations and can affect the severity and course of the disease.[7,9] These conditions, which are more common in patients with SA, include allergic rhinitis, chronic sinusitis, nasal polyps, sleep apnea, gastroesophageal reflux disease (GERD), diabetes, dyslipidemia, cardiovascular diseases (CVDs), osteoporosis and depression.[9–11] SA may contribute to worsening of these conditions, through factors like corticosteroid use, reduced physical activity, or poor sleep.[10,11]

Diseases of the upper airways, including allergic and nonallergic rhinitis or sinusitis are described to be moderately to strongly associated with asthma outcomes.[9,12] Chronic Rhinosinusitis with or without nasal polyps is associated with type 2 inflammation pathways, which also plays an important role in severe asthma.[6,13] GERD affects around 40 to up to 60% of individuals with SA, which may be facilitated by an abnormal respiratory physiology, and is described to be associated with worse symptom control and poorer quality of life.[14,15] The common co-occurrence of depression, diabetes mellitus, obesity, and asthma is particularly notable in clinical practice.[16] Obesity is commonly co-occurring with asthma and is associated with a higher use of asthma medication, reduced lung function and worse disease control and quality of life.[17]

Previous studies have shown that patients with asthma have a higher risk for CVDs including arterial hypertension compared to individuals without asthma, requiring an integrated management due to overlapping risk factors like obesity or smoking.[12,18,19] The co-existence of asthma and chronic obstructive pulmonary disease (COPD) results in worse outcomes such as higher exacerbation rates and a lower quality of life and a faster decline in lung function.[20]

The presence of multiple comorbidities (multimorbidity) becomes more common with age and is associated with worse clinical outcomes, increased mortality, and higher medical costs. However, multimorbidity remains inconsistently defined in asthma research, often referring to the coexistence of two or more chronic conditions.[14,21,22] Despite its clinical importance, there are limited longitudinal data on the evolution and impact of comorbidities in patients with SA, especially within structured care pathways.

To our knowledge, longitudinal data on the specific population of patients with severe asthma and other diseases, with and without associated clinical pathways, are scarce. For Switzerland, no such data are available.

Due to the lack of thorough data, the Swiss Severe Asthma Registry (SSAR) was started to obtain comprehensive, longitudinal information regarding patients with severe asthma in Switzerland to optimize the diagnostic evaluation, treatment of patients with severe asthma and better understanding influencing factors.[23] The aim of the current study is to take a closer look at comorbidities and severe asthma, especially their prevalence over a period of three years. Furthermore, we want to investigate if there are associations between comorbidities and asthma control, asthma-related quality of life, and FEV1.

Materials and Methods

For this analysis, we used data from the SSAR. The SSAR is an ongoing multicenter, longitudinal, prospective cohort study that includes patients with SA in Switzerland.[23] This study is conducted in accordance with the ethical principles

outlined in the Declaration of Helsinki and was approved by all seven ethics committees in Switzerland under the lead of the ethics committee of northwestern and central Switzerland (EKNZ) with the BASEC (Business Administration System for Ethics Committees) 2018–01553.

Participants and Data Collection

Patients with severe asthma aged 6 years or older who fulfill the definition of SA according to ERS/ATS guidelines can be included in the registry after giving their written informed consent, in children under the age of 14 the parents had to give their consent.[4] In this study, we analyzed the data of 234 patients who were included in the registry from May 2019 to July 2022 and had completed at least two years of follow-up.

Socio-demographic information and medical data are collected both at inclusion visit and in the annual follow up visit. In addition, self-reported asthma-related quality of life (Mini-AQLQ) and self-reported asthma control (ACT) are assessed. The data are recorded in a non-public electronic database.

Outcomes

Our study aimed to investigate how asthma-related outcomes change over time in the study population and in individuals with certain comorbidities. The comorbidities were chosen according to their prevalence (<10% at time of inclusion) in our cohort as well as the current literature. Asthma-related outcomes were defined as the asthma control test score (ACT), the Mini AQLQ (disease-specific health-related quality of life questionnaire), the presence of acute exacerbations (AE) and pulmonary function parameters (FEV1, FVC, DLCO and FeNO).[24–27]

The minimal clinically important differences (MCID) for the outcomes were 3 points for the ACT, and 0.5 points for the MiniAQLQ.[28,29]

For the airway parameter, FEV1, FVC and DLCO, no MICD values have been established so far, due to multiple limitations, for FeNO a change of 20% in either direction is considered as MCID.[29]

Statistical Analysis

R version 4.3.1 was used for all statistical analyses. All tests were two-tailed and a p value <0.05 was defined as statistically significant, missing data were noted but not imputed.[30] For continuous variables, the mean and standard deviation (SD) were calculated across all included patients per visit. For categorical variables, absolute and relative frequencies were evaluated. A t-test for dependent samples was used to evaluate the mean change of continuous variables between follow-up visits. The X^2 test was used to compare the change of categorical variables between follow-up visits. To estimate the association of comorbidities with the expected change in the outcome variables over the two years, we used a generalized estimating equation (GEE) model. The GEE accounts for repeated measures, especially the within-subject correlation and non-independence of the variables.[31,32]

Results

Descriptive Analysis

Baseline characteristics, asthma-related outcomes, and treatment patterns were described and compared over the two-year follow-up period. This section summarizes the temporal changes in patient demographics, clinical parameters, and management approaches observed during the study. At time of inclusion, the mean age was 56.1 years, and 47.9% of patients were female. 22.2% of patients had their asthma diagnosed in childhood. In terms of asthma type, 46.2% of patients were reported to have an allergic form of asthma, 37.6% have a non-allergic type of asthma and 16.2% have a mixed form of asthma (Table 1).

Longitudinal Assessment of Patient Characteristic and Asthma-Related Outcomes

Changes of patient characteristics, asthma-related outcomes and treatment over the follow-up period are summarized in Table 2. At time of inclusion, 9.8% of patients were current smokers at time of inclusion in the registry and 7.7% at visit 2, respectively.

Table 1 Patient Characteristics

Baseline Characteristics	V0 (n = 234)
Age, mean (±SD)	56.1 (15.3)
Female, n (%)	112 (47.9)
Male, n (%)	122 (52.1)
Childhood onset[a], n (%)	52 (22.2)
Asthma in Relatives[b], n (%)	106 (45.3)
Asthma Type	
Allergic asthma, n (%)	108 (46.2)
Non-allergic asthma, n (%)	88 (37.6)
Mixed form, n (%)	38 (16.2)

Notes: [a]Age of onset before the age of 12 [b]Asthma in first degree relatives (mother, father, siblings, own children).

Table 2 Patient Characteristics Over Time

Patient Characteristics	V0	V1	V2	p-value
Smoking Status				
Non-smoker, n (%)	211 (90.17)	213 (91.02)	213 (91.02	0.491
Active Smoker, n (%)	23 (9.8)	19 (8.1)	18 (7.7)	
Missing, n (%)	0.00	2 (0.8)	3 (1.3)	
BMI				
BMI, mean (±SD)	27.3 (5.9)	27.1 (5.6)	27.2 (5.8)	0.916
Exacerbations				
None	110 (47.0)	163 (69.7)	172 (73.5)	< 0.001
1x year	51 (21.8)	41 (17.5)	30 (12.8)	
More than 1 x/ year	67 (28.7)	23 (9.8)	28 (12)	
Asthma Control				
ACT, mean (±SD)	18.9 (4.9)	20.3 (4.4)	19.9 (4.6)	0.009
ACT ≥ 20, n (%)	127 (54.3)	134 (57.3)	134 (57.3)	< 0.001
Asthma Related Quality of Life				
Mini AQLQ, mean (±SD)	74.1 (20.2)	83.4 (16.6)	82.9 (16.6)	< 0.001
Mean response per question (range)	4.9 (1.3)	5.6 (1.1)	5.5 (1.1)	< 0.001
Pulmonary Function Tests				
FEV1 l, mean (±SD)	2.37 (0.85)	2.34 (0.80)	2.36 (0.82)	0.925
FEV1% predicted, mean (±SD)	76.6 (20.6)	76.4 (20.3)	77.2 (20.6)	0.912
FVC l, mean (±SD)	3.55 (0.99)	3.46 (0.98)	3.55 (0.95)	0.514
FVC % predicted, mean (±SD)	90.9 (16.2)	89.7 (16.1)	92.3 (16.3)	0.266
DLCO mmol/min/kPa, mean (±SD)	7.56 (2.36)	7.59 (3.18)	7.89 (3.00)	0.699
DLCO % predicted, mean (±SD)	86.6 (20.9)	85.3 (22.5)	91.9 (28.3)	0.181
FeNO ppb, mean (±SD)	42.4 (39.9)	40.6 (50.8)	39.5 (39.9)	0.834

(*Continued*)

Table 2 (Continued).

Patient Characteristics	V0	V1	V2	p-value
Current Treatment				
ICS, n (%)	45 (19.2)	39 (16.7)	38 (16.2)	0.204
LABA, n (%)	12 (5.1)	8 (3.4)	7 (2.9)	0.146
ICS/LABA, n (%)	195 (83.3)	192 (82.1)	183 (78.2)	0.158
LAMA, n (%)	109 (46.6)	102 (43.6)	99 (42.3)	0.205
LTRA, n (%)	49 (20.9)	42 (17.9)	37 (15.8)	0.123
ICS/LABA/LAMA, n (%)	6 (2.6)	12 (5.1)	18 (7.7)	0.049
OCS, n (%)	54 (23.1)	38 (16.2)	32 (13.7)	0.010
Beclomethasone equivalent in µg/day, mean (±SD)	1502 (1003)	1303 (832)	1239 (701)	0.003
Prednisone equivalent in mg/day, mean (±SD)	11.7 (14.5)	10.8 (11.5)	9.2 (10.3)	0.682
Biologics				
Patients treated with a biologics, n (%)	191 (81.6)	194 (82.9)	191 (81.6)	0.946
Benralizumab, n (%)	55 (23.5)	58(24.8)	54(23.1)	0.265
Dupilumab, n (%)	21 (8.9)	38 (16.2)	45 (19.2)	0.002
Mepolizumab, n (%)	74 (31.6)	62 (26.5)	57 (24.4)	0.082
Omalizumab, n (%)	39 (16.7)	33(14.1)	31 (13.2)	0.181
Reslizumab, n (%)	4 (1.7)	3 (1.3)	3 (1.3)	0.307
Tezepelumab, n (%)	NA	2 (0.9)	3 (1.3)	< 0.001

Abbreviations: ACT, Asthma control test; BMI, Body mass index; DLCO, Diffusing capacity for carbon monoxide; FEV1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; FeNO, Fractional exhaled nitric oxide; ICS, Inhaled corticosteroids; LABA, Long-acting beta agonist; LAMA, Long-acting muscarinic antagonist; LTRA, Leukotriene receptor antagonist; Mini AQLQ, Asthma quality of life questionnaire, short version; OCS, Oral corticosteroids.

The mean BMI remained stable in the overweight range at all three visits (27.3 kg/m^2 vs 27.1 kg/m^2 vs 27.2 kg/m^2 respectively, p = 0.916). The proportion of patients with no exacerbation in the previous 12 months increased over the observational period from 47% at time of inclusion to 73.5% after two years (p < 0.001). The mean ACT score increased significantly from 18.9 to 19.9 (p = 0.009), but did not reach the MCID of three points. The Mini-AQLQ increased significantly from a mean per question of 4.9 to 5.5 (p < 0.001), which is above the MCID of 0.5 points. There was no significant change in pulmonary function as measured by FEV1, FVC, DLCO or FeNO.

Longitudinal Assessment of Treatment

Most patients received a fix combination of inhaled corticosteroids with a long-acting beta agonist (ICS- LABA) as maintenance therapy. At the end of the follow-up period, significantly more patients received a triple therapy compared to the inclusion visit (7.7% vs 2.6% respectively. p = 0.049). In addition, significantly less patients received maintenance OCS (23.1% vs 13.7%, p = 0.010) at the end of the follow-up period, with no significant decrease in the mean dose of daily OCS (11.7 mg/day vs 9.2 mg/day prednisone equivalent, p = 0.682). However, there was a significant decrease in the mean daily dose of inhaled corticosteroids at the end of the follow-up period (1502 µg/day 1239 µg/day, beclomethasone equivalent; p = 0.003).

Most of the included patients have been treated with monoclonal antibodies during the observational period (81.6% at inclusion vs 81.6% at visit 2, p = 0.946). A significantly higher number of patients were treated with dupilumab at the second follow-up visit, compared to inclusion (19.2% vs 8.9% respectively, p = 0.002). There was no significant change in the usage frequency of the other biologics.

Longitudinal Assessment of Comorbidities

The most prevalent comorbidity at the time of inclusion were allergies (55.1%), followed by CRS (48.3%) and nasal polyps (35%). None of the comorbidities showed statistically significant differences in prevalence during the observational period (Table 3).

Table 3 Comorbidities Over Time

Comorbidities	V0	V1	V2	p-value
Allergies, n (%)	129 (55.1)	134 (57.3)	136 (58.1)	0.832
CRS, n (%)	113 (48.3)	106 (45.3)	109 (46.6)	0.364
Nasal polyps n (%)	82 (35.0)	86 (36.8)	84 (36.3)	0.382
GERD, n (%)	68 (29.1)	66 (28.2)	67(28.7)	0.423
Arterial hypertension, n (%)	50 (21.4)	52 (22.2)	51(21.8)	0.244
Other CVDs, n (%)	27 (11.5)	32 (13.7)	37 (15.8)	0.101
COPD, n (%)	27 (11.5)	24 (10.3)	25 (10.7)	0.232
Depression, n (%)	24 (10.3)	21 (8.9)	26 (11.1)	0.184
Obesity, n (%)	64 (27.3)	59 (25.2)	62 (26.5)	0.107
Multimorbidity, n (%)	148 (63.3)	148 (63.3)	148 (63.3)	1.00
OCS induced side effects				
None	173 (73.9)	173 (73.9)	167 (71.4)	0.262
Diabetes	13 (5.6)	10 (4.3)	11 (4.7)	0.391
Skin lesions	15 (6.4)	13 (5.6)	19 (8.1)	0.302
Weight gain	9 (3.8)	8 (3.4)	11 (4.7)	0.496

Abbreviations: COPD, Chronic obstructive pulmonary disease; CRS, Chronic rhinosinusitis; CVDs, cardiovascular diseases; GERD, Gastroesophageal reflux disease.

Most of the patients had no reported steroid induced side effects or associated long-term complications at all three visits (73.9% vs, 73.9% vs, 71.4%, p = 0.262). Diabetes skin lesions and weight gain were the most frequently reported OCS induced side effects (5.6%, 6.4% and 3.8% respectively).

Comorbidities and Asthma-Related Outcomes

To investigate the association between comorbidities and longitudinal changes in clinical and physiological outcomes over the two-year follow-up period, GEE models were conducted. Outcome variables included the ACT, the Mini-AQLQ, FEV_1, FVC, DLCO, and FeNO.

An overall time effect was found for both the 1-year and 2-year follow-up in the ACT and the Mini-AQLQ and Exacerbations. Our model showed significant positive associations between time and ACT (1 year: *b2* = 1.06; 95% CI: 1.02–1.10; p < 0.001; 2 years: *b2* = 1.06; 95% CI: 1.06–1.09; p < 0.001) (Figure 1), Mini-AQLQ (1 year: *b2* = 1.10; 95% CI: 1.06–1.14; p < 0.001; 2 years: *b2* = 1.11; 95% CI: 1.08–1.15; p < 0.001) (Figure 2), as well as exacerbations (1 year: OR = 0.43 95% CI: 0.22–0.83); p = 0.012, 2 years OR = 0.30; 95% CI: 0.16–0.57; p < 0.001) (Figure 3). The time-based changes are also shown in the Supplementary Figures 1–4. For the other outcome variables, no time effect was shown.

Allergies

Allergic comorbidities occur in more than 55% of the investigated population, with a non-significant increase over the observational period (Table 3). When looking at the effect of allergies on asthma-related outcomes our models showed that Allergies have a significant negative association on the Mini AQLQ score (*b2* = 0.95; 95% CI: 0.90–0.99; p = 0.036) (Figure 2). In the other outcome variables, no significant association was found with the ACT (Figure 1), Exacerbations (Figure 3), FEV1 (Figure 4), FVC, DLCO or FeNO (Supplementary Figures 5–7).

CRS and Nasal Polyps

In our population, around 50% of the patients suffer from CRS, and more than a third of the patients has nasal polyps, without relevant changes in the prevalence over the observational period (Table 3). CRS was not associated with a change in either direction in the outcome variables investigated (Figures 1–4). The same was observed for nasal polyps, our models did not show any significant associations, with either the patient reported outcome variables (ACT and Mini AQLQ and exacerbations; Figures 1–3) or the physiological outcome measures (FEV1, FVC, DLCO and FeNO; Figure 4; Supplementary Figures 5–7).

Forest Plot of GEE Model Parameters for the ACT

Variable	b^2	95% Confidence Interval		p-value
1 Year	1.06	[1.02	1.10]	**0.001**
2 Years	1.06	[1.02	1.09]	**0.001**
Allergies	0.97	[0.93	1.03]	0.391
Sinusitis	0.98	[0.94	1.03]	0.392
Nasal Polyps	1.04	[0.99	1.10]	0.067
COPD	0.83	[0.76	0.92]	**< 0.001**
GERD	0.91	[0.87	0.98]	**0.009**
Depression	0.95	[0.88	1.04]	0.269
Arterial Hypertension	1.00	[0.94	1.09]	0.666
CVDs	0.94	[0.89	1.01]	0.087
Obesity	0.96	[0.90	1.02]	0.170
Multimorbidity	0.97	[0.92	1.03]	0.146

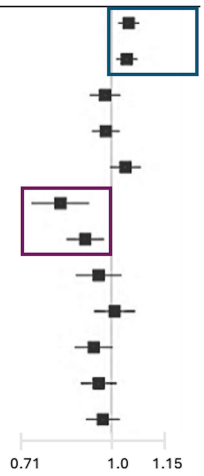

Figure 1 GEE Model Estimates and forest plot for the ACT Score. Model estimate: generalized estimating equations with Gamma Distribution and Log Link function. Dependent Variable: ACT, Controller Variable: Age (b2= 1.00, 95% CI: 0.99–1.00, p = 0.173), Biologic Treatment (b2= 1.12, 95% CI1.05–1.18, p < 0.001). Multimorbidity defined as 2 or more additional chronic diseases.
Abbreviations: COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; CVDs, cardiovascular disease.

Forest Plot of GEE Model Parameters for the MiniAQLQ

Variable	b^2	95% Confidence Interval		p-value
1 Year	1.10	[1.06	1.14]	**<0.001**
2 Years	1.11	[1.08	1.15]	**< 0.001**
Allergies	0.95	[0.90	0.99]	**0.036**
Sinusitis	0.99	[0.94	1.04]	0.742
Nasal Polyps	1.04	[0.99	1.11]	0.138
COPD	0.88	[0.80	0.97]	**0.007**
GERD	0.92	[0.86	0.98]	**0.006**
Depression	1.00	[0.92	1.09]	0.959
Arterial Hypertension	0.98	[0.91	1.04]	0.451
CVDs	1.00	[0.94	1.09]	0.787
Obesity	0.93	[0.88	0.99]	**0.016**
Multimorbidity	0.98	[0.93	1.05]	0.622

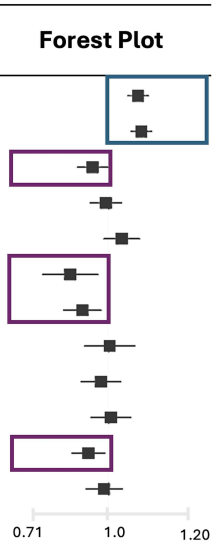

Figure 2 GEE Model Estimates and forest plot for the Mini AQLQ Score. Model estimate: generalized estimating equations with Gamma Distribution and Log Link function. Dependent Variable: MiniAQLQ, Controller Variable: Age (b2= 1.00, 95% CI: 1.00–1.00, p = 0.088), Biologic Treatment (b2= 1.11, 95% CI1.06–1.17, p < 0.001). Multimorbidity defined as 2 or more additional chronic diseases.
Abbreviations: COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; CVDs, cardiovascular disease.

COPD

Around 10% of our population were reported to have a coexisting COPD (Table 3). Over the observational period, no significant change in the prevalence was observed. Our models found a significant negative association with the patient reported outcomes ACT (*b2* = 0.83, 95% CI: 0.76–0.92, p < 0.001; Figure 1) and Mini AQLQ (*b2* = 0.88; 95% CI: 0.80–0.97; p = 0.012; Figure 2) but not with exacerbations (OR = 1.75; 95% CI: 0.65–4.68; p = 0.266). In the ACT model, patients with

https://doi.org/10.2147/JAA.S521005

Forest Plot of GEE Model Parameters for Exacerbations

Variable	*OR*	95% Confidence Interval		p-value
1 Year	0.43	[0.22	0.83]	**0.012**
2 Years	0.30	[0.16	0.57]	**< 0.001**
Allergies	0.64	[0.33	1.23]	0.187
Sinusitis	1.07	[0.53	2.12]	0.844
Nasal Polyps	0.49	[0.23	1.07]	0.074
COPD	1.74	[0.65	4.67]	0.266
GERD	2.51	[1.20	5.22]	**0.014**
Depression	0.36	[0.09	1.40]	0.141
Arterial Hypertension	0.88	[0.35	2.15]	0.779
CVDs	1.00	[0.34	2.91]	0.991
Obesity	1.37	[0.69	2.73]	0.364
Multimorbidity	4.17	[1.60	10.90]	**0.003**

Forest Plot

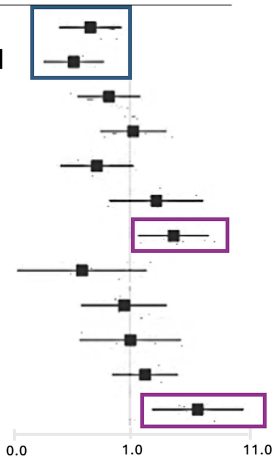

Figure 3 GEE Model Estimates and forest plot for Exacerbations. Model estimate: generalized estimating equations (binominal family). Dependent Variable: Minimum of 1 exacerbation, Controller Variable: Age (OR= 0.96, 95% CI 0.94–0.99, p= 0.018), Biologic Treatment (OR 0.60, 95% CI 0.26–1.41, p= 0.249). Multimorbidity defined as 2 or more additional chronic diseases.
Abbreviations: COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; CVDs, cardiovascular disease.

Forest Plot of GEE Model Parameters for the FEV_1 % predicted

Variable	b^2	95% Confidence Interval		p-value
1 Year	1.00	[0.97	1.02]	0.778
2 Years	1.00	[0.97	1.03]	0.820
Allergies	1.02	[0.97	1.08]	0.398
Sinusitis	1.00	[0.96	1.04]	0.955
Nasal Polyps	1.02	[0.96	1.08]	0.577
COPD	0.79	[0.67	0.93]	**0.006**
GERD	0.99	[0.93	1.05]	0.699
Depression	0.93	[0.83	1.04]	0.218
Arterial Hypertension	1.01	[0.95	1.08]	0.693
CVDs	1.04	[0.99	1.10]	0.102
Obesity	0.97	[0.93	1.03]	0.316
Multimorbidity	1.00	[0.95	1.05]	0.941

Forest Plot

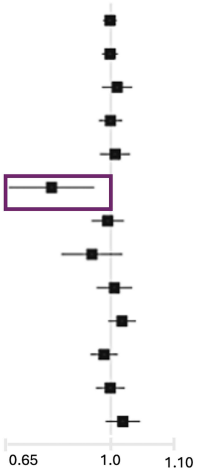

Figure 4 GEE Model Estimates and forest plot for the FEV 1% predicted. Model estimate: generalized estimating equations with Gamma Distribution and Log Link function. Dependent Variable: FEV1, Controller Variable: Biologic Treatment (b2= 1.05, 95% CI 0.98–1.12, p= 0.163). Multimorbidity defined as 2 or more additional chronic diseases.
Abbreviations: COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; CVDs, cardiovascular disease.

COPD showed a persistent lower ACT score despite an overall improvement of the score over time (Figure 1, Supplementary Figure 4). The same effect is observed for the Mini AQLQ, that patients with COPD showed a persistent lower Mini AQLQ compared to patients with no COPD (Figure 2; Supplementary Figure 2). In addition to the patient reported outcomes, we observed negative associations of COPD with physiological parameters. Concomitant COPD was associated with lower FEV_1 and persistent lower FEV_1 over the observational period (*b2* = 0.79; 95% CI: 0.67–0.93; p = 0.006, Figure 4, Supplementary Figure 3) and FVC (*b2*= 0.90; 95% CI: 0.83–0.99, p = 0.028, Supplementary Figures 4 and 5). Our analysis also showed

a negative association of COPD on FeNO, meaning that patients with COPD having a lower FeNO (*b2* = 0.51; 95% CI: 0.37–0.70; p < 0.001, Supplementary Figure 7). No association was found for COPD and DLCO (Supplementary Figure 6).

GERD

Around 30% of our study population were reported to have GERD, with slightly less in the follow-up period (Table 3). For GERD our analyses revealed significant associations with both ACT score (*b2* = 0.91, 95% CI: 0.87–0.97, p = 0.009) and the Mini AQLQ *(b2*= 0.92; 95% CI: 0.86–0.98; p = 0.006), which is shown in Figures 1 and 3. Further, we observed that patients with GERD are 2.51 times more likely to experience exacerbations compared to patients without GERD (OR = 2.51; 95% CI 1.20–5.23; p = 0.014, Figure 3). The analysis did not reveal a significant association with the physiological outcome variables and GERD (Figure 4 and Supplementary Figures 5–7).

Depression

Depression was observed in around 10% of our severe asthma population with a minimal reduction to 8.9% at the one year follow-up (Table 3). Our GEE models did not show any significant association with patient reported outcomes ACT Score (*b2*= 0.95; 95% CI: 0.88–0.102; p = 0.192), Mini AQLQ (*b2*= 1.00; 95% CI: 0.94–0.1.09; p = 0.959) or exacerbations (OR = 0.36; 95% CI 0.09–1.40; p = 0.141) (Figures 1–3). When looking at the physiological parameters, we could not detect an association between depression, FEV1 (Figure 4), FVC or FeNo (Supplementary Figures 5 and 6). However, the GEE Model revealed a significant negative association between depression and DLCO (*b2*= 0.74; 95% CI: 0.64–0.85; p < 0.001) (Supplementary Figure 7).

Arterial Hypertension and Cardiovascular Diseases

More than 20% of our population was reported to have arterial hypertension, with no changes in the prevalence (Table 3). Other CVD's where present in 11.5% of the patients with a non-significant increase up to 15.8% at follow-up two (Table 3).

We could not observe any significant associations in our analyses of either arterial hypertension or CVD's with the patient reported outcomes ACT score, Mini AQLQ or exacerbations (Figure 1–3). When looking in the physiological parameters, we detected no significant associations between arterial hypertension and FEV1 (Figure 4), FVC, DLCO or FeNO (Supplementary Figures 5–7). In CVDs, a significant positive association between with FVC % predicted (*b2*= 1.09; 95% CI: 1.05–1.14, p < 0.001) compared to patients without CVDs was detected (Supplementary Figure 1). For the other outcome variables, we did not detect any significant associations.

Obesity

Obesity was defined as having a BMI ≥ 30 kg/$m^{2.}$ In our population, 27.3% of the patients were considered as obese with a minimal decrease over time (Table 3).

When looking at the patient reported outcomes, we found no association between obesity and the ACT score (Figure 1), or exacerbations (OR = 1.37; 95% CI 0.69–2.73; p = 0.364) (Figure 3), but a significant negative association between obesity and the Mini AQLQ score (*b2*= 0.93; 95% CI: 0.88–0.99; p = 0.016). For the physiological outcome measures, we only found a significant association between obesity and a higher DLCO % predicted (*b2* = 1.12; 95% CI: 1.03–1.21; p = 0.005) (Supplementary Figure 7).

Multimorbidity

In our population, more than 60% of patients were affected by multimorbidity, meaning to have more than 2 other conditions (Table 3). In the patient reported outcomes, we could not find an association between multimorbidity and the ACT Score or the Mini AQLQ (Figures 1 and 2). But we observed, that patients with multimorbidity were four times more likely to experience at least one exacerbation (OR = 4.18; 95% CI 1.60–10.91; p = 0.003) (Figure 3). When looking at the physiological parameters, our models did not show any significant associations between multimorbidity and any of the outcome variables (Figure 4, Supplementary Figures 5–7).

Discussion

This study presents a comprehensive characterization of patients with SA in Switzerland enrolled in a real-world registry, focusing on demographic features, clinical outcomes, treatment patterns, and comorbidities over a two-year observational period. Our findings showed notable improvements in asthma control and health-related quality of life, as reflected by increased ACT and Mini AQLQ scores, as well as a reduction of exacerbations. These trends suggest enhanced disease management despite the absence of significant changes in pulmonary function test parameters. While our results are broadly consistent with those reported in previous cohorts, careful interpretation is essential. The absence of formal assessment of adherence or diagnostic variability may limit internal consistency of the findings, which should be considered when contextualizing the nuances of SA management in real-world clinical settings.

Overall, our results are in line with previous observations on SA patients. The demographic profile with a mean age of 56.1, as well as the proportion of asthma types (46.2% allergic, 37.6% non-allergic, and 16.2% mixed) aligns with the characteristics of adults with moderate-to-severe asthma observed in other studies and cohorts. However, our cohort showed a more equal gender distribution, whereas other studies reported a higher number of female patients.[33–35]

Univariate analysis revealed significant improvements in asthma control (measured by ACT scores) and quality of life (measured by Mini AQLQ scores) over the observational period. Despite not reaching the MCID of 3 points for the mean ACT score and the number of patients with score ≥20 increased, reflecting better asthma control, fewer exacerbations, and improved quality of life, which is in line with previous findings.[36,37] The mean answer per question in the mini AQLQ score, increased by 1.6 points, which is three times more than the MICD of 0.5 points. This finding indicates not only a statistical but also a clinical important difference of the quality of life in our population over the observational period. Reduced quality of life.

However, no significant changes were observed in pulmonary function test parameters, suggesting that ACT and Mini AQLQ improvements may not directly correlate with pulmonary function.

Improvement of asthma control and quality of life is often associated with optimized management, such as biologic treatment or lifestyle modifications.[36] While there was no increased use of biologics over the observational period, reductions in daily ICS doses and OCS use confirm a positive long-term effect of biologic treatment, already found by previous studies.[37–40] Improved treatment adherence, better monitoring or guideline adherence since inclusion in the registry could be other contributing factors, however those factors were not systematically assessed.[41]

Prevalence of comorbidities was similar to prior studies.[7,15] No significant increase in comorbidities, multimorbidity, or steroid-induced side effects was observed during the 2-years follow-up. The prevalence of allergies, CRS, nasal polyps and GERD was notably higher in SA patients (55.1% for Allergies, 48.3% for CRS, 35% for nasal polyps, 29.1% for GERD) compared to the general population (1–20%, for CRS, 1–4% or nasal polyps, 20–30% respectively).[14,15,42] Hypertension and CVD rates (22% and 16% respectively) were lower compared to global averages (30–50%), possibly due to reporting gaps, highlighting the need for better cross-disciplinary data sharing.[43] COPD prevalence (10–12%) was slightly lower compared to global prevalence (12–14%), likely due to lower smoking rates in patients with asthma or diagnostic overlap of both diseases.[44] The identification of COPD in severe asthma is challenging, due to heterogenous clinical presentations or the lack of established definition criteria.[45]

About 27% of patients were obese (BMI > 30 kg/m²), which is nearly double the global prevalence (13%), likely due to OCS use, reduced physical activity, and disability linked to SA.[46,47] Furthermore, obesity worsens asthma severity and control and complicates asthma management. Multimorbidity was higher in the study population (63%) compared to the general population over the age of 45 (30%), and multimorbidity increased with age.[48]

Prevalence of steroid induced side effects was lower in our study compared to other cohorts. Treatment for SA in our study did not differ from other cohorts. Thus, this finding is less likely to be associated with a better asthma management and could be due to potential underreporting or misclassification.[49]

We found several associations between comorbidities and asthma-related outcomes which should be highlighted:

- 11% of the patients with SA were reported to have a comorbid COPD with a significant negative association with pulmonary function, asthma control and quality of life, as described in previous studies.[50] This finding highlights

the importance of early detection, diagnosis and treatment of both disease in a personalized manner in order to improve patients outcomes.[51]

- Second, GERD was associated with poorer asthma control and quality of life, as described in previous studies.[14,15] However, the prevalence of GERD was significantly lower in our study (30%) compared to other cohorts (60%).[14] GERD may have been underdiagnosed or underreported in our registry. Thus, special attention should be paid to the assessment of GERD in the management of patients with SA.[6]
- Finally, we found a strong association between depression and a reduction of DLCO over time. DLCO was found to be a predictor for sleep onset latency and other sleep disorders, especially insomnia and nighttime awakening, which are also common in patients with depression. Therefore, patients with SA and especially those with reduced DLCO might benefit if regularly assessed for depression and sleep disorders. Further studies are needed to investigate the impact of sleep on asthma-related outcomes.

Limitations

Data on socioeconomic status, medication adherence, and incorrect inhalation technique that might also influence asthma-related outcomes are not collected in the SSAR and could not be included in the models used. Due to study design, reporting errors cannot be excluded and therefore the results have to be interpreted with regards to the limitations.

In addition, we must assume a selection bias of recruited patients, as preferably patients treated with biologics were included due to the regular follow-ups. Last, the reporting on comorbidities has its limitations. Due to the structure of the database only the prevalence of certain comorbidities was assessed in our population. Diabetes was only assessed as secondary to OCS use, and we do not have information about diagnostic procedures. In addition, the registry data does not allow a systematic evaluation (including treatment) of comorbidities.

Conclusion

Management of Comorbidities

Given the strong associations between comorbidities such as, GERD and obesity, as well as COPD and lower quality of life, asthma control, exacerbations or pulmonary function, an integrated and personalized approach to asthma care that addresses these comorbid conditions should be adopted.

Future Research

Further studies should investigate the outcomes of multidisciplinary management in the subgroups of patients with SA and GERD or depression as well as the clinical entity of the co-existence of asthma and COPD.

Abbreviations

ACT, Asthma Control Test; ATS, American Thoracic Society; BMI, Body Mass Index; CI, Confidence Interval; COPD, Chronic Obstructive Pulmonary Disease; CRS, Chronic Rhinosinusitis; CVDs, Cardiovascular Disease; DLCO, Diffusing Capacity for Carbon Monoxide; EKNZ, Ethical Committee of Northwestern and Central Switzerland; ERS, European Respiratory Society; FeNO, Fractional Exhaled Nitric Oxide; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GERD, Gastroesophageal Reflux Disease; GEE, Generalized Estimation Equations; ICS, Inhaled Corticosteroids; LABA, Long-Acting Beta-Agonists; LAMA, Long-Acting Muscarinic Antagonist; LTRA, Leukotriene Receptor Antagonist; NCD, Non-communicable diseases; MCID, Minimal clinical important difference; OCS, Oral corticosteroids; SA, Severe Asthma; SSAR, Swiss Severe Asthma Registry.

Acknowledgments

The authors would like to thank all our participating centers and pneumologists for their engagement in this research. The inclusion of patients is tremendously important for this research and the Swiss Severe Asthma Registry in General. Namely: Rehaklinik Heiligenschwendi (Dr. med. P. Brun), Bürgerspital Solothurn, GZO Spital Wetzikon (Dr. med. M. Huber), Gesundheitszentrum Unterengadin (Dr. med. M. Nemec), Kantonsspital Frauenfeld (Dr.med. I. Thüer),

Kanronsspital Münsterlingen (Dr. med. I. Schlecht), Lungenpraxis Morgenthal (Dr. med. C. Eich), Lungenpraxis Wohlen (Dr. med. L. Schlatter), Medizin Stollturm (Dr. med. J. Rüdiger), Praxis Quartier Bleu (Dr. med. D. Schilter, Dr. med R. Fischer), Pneumologie Nordwest (Dr. med. A. Tschacher), Spital Thun (Dr. med. L. Junker), Spital Uster (Prof. Dr. med. D. Franzen, Dr. med. V. Popov), Stadtspital Triemli (KD Dr. med. I Laube, KD. Dr. med. D. Scholtze). In addition, we highly appreciate the work of all the study nurses working for the registry.

Funding

The Swiss Severe Asthma Registry has received or is currently receiving project funding from the following sources: Astra Zeneca, GSK, Sanofi Mundipharma, Novartis, Teva Pharma, Vifor, Lungenliga Schweiz, Lunge Zürich, Lungneliga Bern, Lungenliga St.-Gallen Appenzell, Lungenliga Graubünden, Lungenliga beider Basel.

Disclosure

Dr Nikolay Pavlov reports personal fees for lectures and consulting fees from AstraZeneca, CSL Behring, GlaxoSmithKline, OM Pharma, and Sanofi, outside the submitted work. Prof. Dr. Christophe Von Garnier reports grants and/or personal fees from OM Pharma, Astra Zeneca, GSK, Boehringer Ingelheim, Sanofi, Pfizer, MSD, Mundipharma, Novartis, Pulmonx, PneumRx, Swiss Cancer Research, Swiss Lung League, and Vaud Lung League, during the conduct of the study. Prof. Dr. Joerg Leuppi reports grants from AstraZeneca AG Switzerland, GSK AG Switzerland, and OM Pharma AG Switzerland, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Global Initiative for Asthma. Diagnosis and management of difficult-to-treat & severe asthma. diagnosis and management. A short GINA guide for health professionals. Global Initiative for Asthma; 2023. Available from: https://ginasthma.org/severeasthma/. Accessed October 3, 2023.
2. Bousquet J, Akdis CA, Grattan C, et al. Highlights and recent developments in airway diseases in EAACI journals (2017). *Clin Transl Allergy*. 2018;8(1):49. doi:10.1186/s13601-018-0238-3
3. Hekking PPW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol*. 2015;135(4):896–902. doi:10.1016/j.jaci.2014.08.042
4. Chung KF, Wenzel S. International European Respiratory Society/American Thoracic Society guidelines on severe asthma. *Eur Respir J*. 2014;44 (5):1378. doi:10.1183/09031936.00120714
5. Szucs T, Anderhub H, Rutishauser M. The economic burden of asthma: direct and indirect costs in Switzerland. *Eur Respir J*. 1999;13(2):281. doi:10.1034/j.1399-3003.1999.13b10.x
6. McDonald VM, Hamada Y, Agusti A, Gibson PG. Treatable traits in asthma: the importance of extrapulmonary traits—GERD, CRSwNP, atopic dermatitis, and depression/anxiety. *J Allergy Clin Immunol*. 2024;12(4):824–837. doi:10.1016/j.jaip.2024.01.020
7. Tomisa G, Horváth A, Sánta B, Keglevich A, Tamási L. Epidemiology of comorbidities and their association with asthma control. *Allergy Asthma Clin Immunol*. 2021;17(1):95. doi:10.1186/s13223-021-00598-3
8. Patel GB, Peters AT. Comorbidities associated with severe asthma. *J Precision Respir Med*. 2019;2(1):5–9. doi:10.2500/jprm.2019.190006
9. Boulet L. Influence of comorbid conditions on asthma. *Eur Respir J*. 2009;33(4):897–906. doi:10.1183/09031936.00121308
10. Racine G, Forget A, Moullec G, Jiao T, Blais L, Lemiere C. Predictors of asthma control and exacerbations: a real-world study. *J Allergy Clin Immunol*. 2021;9(7):2802–2811.e2. doi:10.1016/j.jaip.2021.04.049
11. Tomisa G, Horváth A, Szalai Z, Müller V, Tamási L. Prevalence and impact of risk factors for poor asthma outcomes in a large, specialist-managed patient cohort: a real-life study. *J Asthma Allergy*. 2019;12:297–307. doi:10.2147/JAA.S211246
12. Rogliani P, Laitano R, Ora J, Beasley R, Calzetta L. Strength of association between comorbidities and asthma: a meta-analysis. *Eur Respir Rev*. 2023;32(167):220202. doi:10.1183/16000617.0202-2022
13. Castillo JA, Plaza V, Rodrigo G, et al. Chronic rhinosinusitis with nasal polyps and allergic rhinitis as different multimorbid treatable traits in asthma. *J Allergy Clin Immunol*. 2023;2(4). doi:10.1016/j.jacig.2023.100134
14. Honkamäki J, Ilmarinen P, Hisinger-Mölkänen H, et al. Nonrespiratory diseases in adults without and with asthma by age at asthma diagnosis. *J Allergy Clin Immunol*. 2023;11(2):555–563.e4. doi:10.1016/j.jaip.2022.10.024
15. Cazzola M, Rogliani P, Ora J, Calzetta L, Matera MG. Asthma and comorbidities: recent advances. *Polish Arch Internal Med*. 2022;132(4):16250. doi:10.20452/pamw.16250
16. von Boetticher D, Meyer T. Somatisches Krankheitsrisiko bei psychischen Erkrankungen unter besonderer Berücksichtigung depressiver Syndrome. *Zeitschrift für Psychosomatische Medizin und Psychotherapie*. 2019;65(2):129–143. doi:10.13109/zptm.2019.65.2.129
17. Bal C, Pohl W, Milger K, et al. Characterization of obesity in severe asthma in the German asthma net. *J Allergy Clin Immunol*. 2023;11(11):3417–3424.e3. doi:10.1016/j.jaip.2023.06.049
18. Granda P, Villamañán E, Laorden D, et al. Cardiovascular events in patients with severe asthma—a retrospective study of two cohorts: asthma type T2 treated with biologics and non-type T2. *J Clin Med*. 2024;13(15):4299. doi:10.3390/jcm13154299
19. Cazzola M, Page CP, Hanania NA, Calzetta L, Matera MG, Rogliani P. Asthma and cardiovascular diseases: navigating mutual pharmacological interferences. *Drugs*. 2024;84(10):1251–1273. doi:10.1007/s40265-024-02086-5
20. Lázár Z, Horváth A, Tomisa G, Tamási L, Müller V. Impact of clinical factors on generic and disease-specific quality of life in COPD and asthma-COPD overlap with exacerbations. *Pulmon Med*. 2020;2020(1):6164343. doi:10.1155/2020/6164343

21. Sasseville M, Smith SM, Freyne L, et al. Predicting poorer health outcomes in older community-dwelling patients with multimorbidity: prospective cohort study assessing the accuracy of different multimorbidity definitions. *BMJ Open*. 2019;9(1):e023919. doi:10.1136/bmjopen-2018-023919
22. Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: prevalence and trend over the last 20 years. *Eur J Gener Pract*. 2008;14 (sup1):28–32. doi:10.1080/13814780802436093
23. Jaun F, Tröster LM, Giezendanne S, et al. Characteristics of severe asthma patients and predictors of asthma control in the Swiss Severe Asthma Registry. *Respiration*. 2023:1–16. doi:10.1159/000533474
24. Juniper E, Guyatt G, Cox F, Ferrie P, King D. Development and validation of the mini asthma quality of life questionnaire. *Eur Respir J*. 1999;14 (1):32. doi:10.1034/j.1399-3003.1999.14a08.x
25. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59–65. doi:10.1016/j.jaci.2003.09.008
26. Sparling JL, Melo MFV. Chapter 05 - pulmonary pathophysiology and lung mechanics in anesthesiology. In: Cohen E, editor. *Cohen's Comprehensive Thoracic Anesthesia*. Elsevier; 2022:66–87. doi:10.1016/B978-0-323-71301-6.00005-6
27. Ontario Health (Quality). Fractional exhaled nitric oxide testing for the diagnosis and management of asthma: a health technology assessment. *Health Technol Assess Ser*. 2024:1–225.
28. Juniper EF, Price DB, Stampone PA, Creemers JPHM, Mol SJM, Fireman P. Clinically important improvements in asthma-specific quality of life, but no difference in conventional clinical indexes in patients changed from conventional beclomethasone dipropionate to approximately half the dose of extrafine beclomethasone dipropionate. *Chest*. 2002;121(6):1824–1832. doi:10.1378/chest.121.6.1824
29. Bonini M, Di Paolo M, Bagnasco D, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. *Eur Respir Rev*. 2020;29(156):190137. doi:10.1183/16000617.0137-2019
30. R Core Team. *A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2020.
31. Schober P, Vetter TR. Repeated measures designs and analysis of longitudinal data: if at first you do not succeed—try, try again. *Anesthesia Analg*. 2018;127(2):569–575. doi:10.1213/ANE.0000000000003511
32. Burton P, Gurrin L, Sly P. Extending the simple linear regression model to account for correlated responses: an introduction to generalized estimating equations and multi-level mixed modelling. *Stat Med*. 1998;17(11):1261–1291. doi:10.1002/(SICI)1097-0258(19980615)17:11<1261::AID-SIM846>3.0.CO;2-Z
33. Denton E, Hew M, Peters MJ, et al. Real-world biologics response and super-response in the International Severe Asthma Registry cohort. *Allergy*. 2024;79(10):2700–2716. doi:10.1111/all.16178
34. Zhang S, Zhang X, Wei C, Zhang L, Li Z. Causality between 91 circulating inflammatory proteins and various asthma phenotypes: a Mendelian randomization study. *ImmunoTargets Ther*. 2024;13:617–629. doi:10.2147/ITT.S486676
35. Sundbom F, Malinovschi A, Lindberg E, Alving K, Janson C. Effects of poor asthma control, insomnia, anxiety and depression on quality of life in young asthmatics. *J Asthma*. 2016;53(4):398–403. doi:10.3109/02770903.2015.1126846
36. Lanario JW, Hyland ME, Wei Y, Jones RC, Masoli M. Comparison of the effects of pulmonary and extra-pulmonary symptoms on health-related quality of life in patients with severe asthma. *Respir Med*. 2020;162:105870. doi:10.1016/j.rmed.2020.105870
37. Bjerrum AS, Skjold T, Schmid JM. Oral corticosteroid sparing effects of anti-IL5/anti-IL5 receptor treatment after 2 years of treatment. *Respir Med*. 2021;176:106260. doi:10.1016/j.rmed.2020.106260
38. Calzetta L, Aiello M, Frizzelli A, Bertorelli G, Rogliani P, Chetta A. Oral corticosteroids dependence and biologic drugs in severe asthma: myths or facts? A systematic review of real-world evidence. *Int J Mol Sci*. 2021;22(13):7132. doi:10.3390/ijms22137132
39. Guilleminault L, Camus C, Raherison-Semjen C, et al. Improvement in severe asthma patients receiving biologics and factors associated with persistent insufficient control: a real-life national study. *Ther Adv Respir Dis*. 2023;17:17534666231202749. doi:10.1177/17534666231202749
40. Kroes JA, Alfonso-Cristancho R, Bansal AT, et al. Evaluation of real-world mepolizumab use in severe asthma across Europe: the SHARP experience with privacy-preserving federated analysis. *ERJ Open Res*. 2023;9(2):00745–02022. doi:10.1183/23120541.00745-2022
41. Hoque DME, Kumari V, Hoque M, Ruseckaite R, Romero L, Evans SM. Impact of clinical registries on quality of patient care and clinical outcomes: a systematic review. *PLoS One*. 2017;12(9):e0183667. doi:10.1371/journal.pone.0183667
42. Wu D, Chandra RK, Conley DB, Kern RC. Epidemiology of nasal polyps. In: Önerci Celebi Ö, Önerci TM, editors. *Nasal Polyposis and Its Management: Pathogenesis, Medical and Surgical Treatment*. Springer International Publishing; 2024:7–15. doi:10.1007/978-3-031-33199-2_2
43. Richardson LC, Vaughan AS, Wright JS, Coronado F. Examining the hypertension control cascade in adults with uncontrolled hypertension in the US. *JAMA Network Open*. 2024;7(9):e2431997–e2431997. doi:10.1001/jamanetworkopen.2024.31997
44. Al Wachami N, Guennouni M, Iderdar Y, et al. Estimating the global prevalence of chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *BMC Public Health*. 2024;24(1):297. doi:10.1186/s12889-024-17686-9
45. Alsayed AR, Abu-Samak MS, Alkhatib M. Asthma-COPD overlap in clinical practice (ACO_CP 2023): toward precision medicine. *J Personal Med*. 2023;13(4):677. doi:10.3390/jpm13040677
46. Islam AS, Sultana H, Refat MNH, Farhana Z, Kamil AA, Rahman MM. The global burden of overweight-obesity and its association with economic status, benefiting from STEPs survey of WHO member states: a meta-analysis. *Prevent Med Rep*. 2024;46:102882. doi:10.1016/j.pmedr.2024.102882
47. Volmer T, Effenberger T, Trautner C, Buh R. Consequences of long-term OCS therapy and its side effects in severe asthma in adults – a focused review of the impact data in the literature. *Eur Respir J*. 2018;52:1800703. doi:10.1183/13993003.00703-2018
48. Chowdhury SR, Das DC, Sunna TC, Beyene J, Hossain A. Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis. *EClinicalMedicine*. 2023;57.
49. Rubinger L, Ekhtiari S, Gazendam A, Bhandari M. Registries: big data, bigger problems? *Injury*. 2023;54:S39–S42.
50. Hashimoto S, Sorimachi R, Jinnai T, Ichinose M. Asthma and chronic obstructive pulmonary disease overlap according to the Japanese Respiratory Society Diagnostic Criteria: the prospective, observational ACO Japan Cohort Study. *Adv Ther*. 2021;38(2):1168–1184. doi:10.1007/s12325-020-01573-x
51. Shim JS, Kim H, Kwon JW, et al. A comparison of treatment response to biologics in asthma-COPD overlap and pure asthma: findings from the PRISM study. *World Allergy Organ J*. 2023;16(12):100848. doi:10.1016/j.waojou.2023.100848