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Characteristics of Severe Asthma Patients and Predictors of Asthma Control in the Swiss Severe Asthma Registry

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Keywords
Severe asthma · Asthma control · Predictors · Cohort

Abstract

Background: Asthma is a chronic airway disease, affecting over 300 million people worldwide. 5–10% of patients suffer from severe asthma and account for 50% of asthma-related financial burden. Availability of real-life data about the clinical course of severe asthma is insufficient. ***Objectives:*** The aims of this study were to characterize patients with severe asthma in Switzerland, enrolled in the Swiss Severe Asthma Registry (SSAR), and evaluate predictors for asthma control. ***Method:*** A descriptive characterisation of 278 patients was performed, who were prospectively enrolled in the registry until January 2022. Socio-demographic variables, comorbidities, diagnostic values, asthma treatment, and healthcare utilisation were evaluated. Groups of controlled and uncontrolled asthma according to the asthma control test were compared. ***Results:*** Forty-eight percent of patients were female and the mean age was 55.8 years (range 13–87). The mean body mass index (BMI) was 27.4 kg/m^2 (±6). 10.8% of patients were current smokers. Allergic

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comorbidities occurred in 54.3% of patients, followed by chronic rhinosinusitis (46.4%) and nasal polyps (34.1%). According to the ACT score, 54.7% had well controlled, 16.2% partly controlled and 25.9% uncontrolled asthma. The most common inhalation therapy was combined inhaled corticosteroids/long-acting β_2-agonists (78.8%). Biologics were administered to 81.7% of patients and 19.1% received oral steroids. The multivariable analysis indicated that treatment with biologics was positively associated with asthma control whereas higher BMI, oral steroids, exacerbations, and COPD were negative predictors for asthma control. ***Conclusion:*** Biologics are associated with improved control in severe asthma. Further studies are required to complete the picture of severe asthma in order to provide improved care for those patients.

Introduction

Asthma is a respiratory disorder characterised by chronic airway inflammation with respiratory symptoms such as cough, shortness of breath, wheezing, chest tightness, and airflow limitation that vary over time [1]. Asthma is one of the most common chronic diseases worldwide, affecting around 339 million people and accounting for 23.7 million Disability Adjusted Life Years globally in 2016 [2]. An estimated 5–10% of asthmatics suffer from severe asthma [3–5]. Although patients with severe asthma represent only a small proportion of the overall asthma population, this group constituted about 50% of the medical costs related to asthma and carried a high disease burden [6–8].

In 2014, an international European Respiratory Society and American Thoracic Society (ERS/ATS) taskforce published new guidelines about the definition and treatment of severe asthma [7]. They defined severe asthma as being treated with high-dose inhaled corticosteroids (ICS) and an additional controller medication (and/or systemic corticosteroids) to prevent asthma from becoming uncontrolled or which remains uncontrolled despite this therapy [7]. As adequate controller medication, long-acting β_2-agonists (LABA), leukotriene receptor antagonists (LTRA), and theophylline are recommended [7]. In 2020, the ERS/ATS taskforce formulated recommendations about the use of monoclonal antibody treatments in severe asthma [9], which are equivalent to the Global Initiative for Asthma (GINA) guidelines steps 4–5, on which the Swiss guidelines are based on [10, 11].

Despite precise definitions of severe asthma and treatment recommendations, little is known about the real-life situation of patients with severe asthma. Patients enrolled in randomised controlled trials with biologics are not representative of the severe asthma population [12]. The pathogenesis, clinical course, therapy, and prognosis are not well known, which makes severe asthma challenging to treat [7]. To close this knowledge gap, several countries have initiated severe asthma registries that aim to collect information about individuals with severe asthma and have so far provided interesting findings such as the presence of different severe asthma phenotypes, enabling a more personalised therapy [13–16].

In Switzerland, data on patients affected by severe asthma are sparse and the prevalence of patients can only be estimated. In 2017, around 4.8% of the Swiss population aged 15 or older was self-diagnosed with asthma, whereas women (5.3%) were more often affected than men (4.2%) [17]. The prevalence of severe asthma in Switzerland is estimated to be around 5% of the asthmatic population [18, 19]. However, there might still be a substantial number of patients wrongly diagnosed with severe asthma due to factors such as inadequate inhaler technique, untreated comorbidities or non-adherence to therapy [10, 20–23]. The Swiss Severe Asthma Registry (SSAR) was established to obtain more comprehensive information regarding patients with severe asthma in Switzerland.

The SSAR aims to collect baseline and follow-up data for up to 15 years, in order to optimise diagnostic workup and treatment of patients with severe asthma. The analysis and interpretation of this dataset aim to provide reliable information about disease phenotypes and their treatments in Switzerland and to improve the understanding of asthma's clinical course and health-related quality of life. This paper describes the characteristics of the severe asthma population in Switzerland.

Secondary aim was to identify characteristics associated with asthma control which is important to improve care of severe asthma patients and reduce the burden of disease due to symptoms and exacerbations. Previous studies have identified several variables associated with poor asthma control, such as smoking, obesity, and socioeconomic status [24–27]. However, predictors of asthma control in severe asthma may differ between populations and registries of severe asthmatics. Therefore, we aimed to evaluate differences in characteristics between controlled and uncontrolled asthma according to patients' scores in the asthma control test (ACT).

Table 1. Enrolment criteria for the registry

Enrolment criteria
Asthma diagnosed by a respiratory physician In- and outpatients Age ≥6 years Informed consent as documented by signature
High-level therapy (presence of at least one) 1. High-dose inhaled corticosteroids (ICS) in combination with long-acting β_2-agonist (LABA) or leukotriene modifier/theophylline for the previous year 2. Daily long-term therapy with systemic corticosteroids (CS) for ≥50% of the previous year to prevent asthma from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy 3. Therapy with monoclonal antibodies independent from the co-therapy 4. Daily long-term therapy with medium- to high-dose ICS in combination with LABA or leukotriene modifier/theophylline for the previous year
Symptom control (presence of at least one in addition to the criteria) 1. Poor symptom control: ACQ consistently >1.5 or ACT <20 (or "not well controlled" by NAEPP/GINA guidelines) despite maximal optimised therapy and treatment of contributory factors 2. Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year 3. Severe exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year 4. Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the presence of reduced FEV_1/FVC defined as less than the lower limit of normal) 5. Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

ACT, asthma control test; ACQ, asthma control questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GINA, global initiative for asthma; ICU, intensive care unit; LABA, long-acting β_2-agonist; NAEPP, National Asthma Education and Prevention Program.

Methods and Materials

Study Design

The SSAR is a multicentre, prospective, open cohort study of patients suffering from severe asthma. Forty-five centres were initiated to recruit patients, 30 centres did actively recruit patients (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000533474). Participating centres include primary, secondary, and tertiary pulmonary care facilities across all regions of Switzerland. The range of included patients per centre was from 1 patient to 40 patients (median: 5 patients). Recruitment of patients is ongoing.

This study aims to characterise the patients (n = 278) enrolled in the SSAR between April 2019 to January 2022 and investigate which variables are associated with poor asthma control. Investigators were encouraged to recruit all patients with severe asthma irrespective of comorbidities and treatment to reflect the true clinical situation in Switzerland.

Ethics

All seven Local Ethics Committees in Switzerland approved the SSAR and use of the collected data for analysis (BASEC ID 2018-01553). The SSAR is registered on clinicalTrials.gov (NCT03984253).

Participants and Data Collection

For the enrolment in the SSAR, all patients diagnosed with severe asthma, aged 6 years or older, who fulfil the ERS/ATS definition for severe asthma, respectively, require treatment according to the GINA guidelines steps 4–5 are eligible for participation (Table 1) [7, 9, 10]. Exclusion criteria were a life expectancy below 6 months or insufficient knowledge of one of the registry languages (German, French, or Italian). For children and adolescents, the inclusion criteria were slightly adapted. The patients have to be followed up by a respiratory specialist for at least 6 months and differential diagnoses must have been excluded by fulfilling diagnostic features of asthma. Furthermore, they must have a high level of therapy for over a year to prevent asthma from becoming uncontrolled or which was uncontrolled despite this therapy was required.

The eligible patients were asked to participate in the SSAR by their treating respiratory specialist and enrolled after giving their written informed consent. At the baseline visit, socio-demographic information as well as medical data were collected and entered in a non-public electronic register provided by the German Asthma Net e.V., located in Mainz, Germany [28]. The follow-up visits take place annually, or as treatment evaluation after 4 months after initiating a monoclonal antibody treatment. At the follow-up visits, routine diagnostics are collected if performed and questionnaires about symptoms, treatment, healthcare utilisation, and comorbidities are filled out. No requested sample size has been defined for the cohort.

Variables

Pulmonary function testing (PFT) values are obtained by performing spirometry or body plethysmography. The forced expiratory volume in 1 s (FEV_1), the ratio between FEV_1 and

forced vital capacity (FVC) (FEV_1/FVC) as well as the total lung capacity (TLC) were analysed [29].

The focus of the current study is the following variables documented at the baseline visit:

- Socio-demographic: sex, age, age at asthma onset, body mass index (BMI), smoking status and pack-years, asthma type according to the international classification of disease 10th version, chapter J45.0 to J45.8 (ICD-10) [30] March 25, 2023, 14: 18:00, asthma in relatives
- Comorbidities
- Diagnostic values: FEV_1% predicted, FEV_1 l, FEV_1/FVC %, TLC % predicted, TLC l, GINA asthma control, asthma control test score (ACT), common asthma biomarkers (blood eosinophil count, immunoglobulin E (IgE), fractional exhaled nitric oxide)
- Asthma treatment: medication, rehabilitation, asthma training, inhaler technique education
- Healthcare utilisation within the last 12 months: unplanned outpatient visits, number of exacerbations, emergency department visits, hospital admissions, inability to work due to asthma

Asthma Control

Asthma control according to GINA is evaluated by physicians using four questions. Asthma is considered well controlled if all questions are answered with no, partly controlled if 1–2 questions are answered with yes and uncontrolled when 3–4 questions are answered with yes [1]. The questions are:

1. Daytime asthma symptoms more than twice/week?
2. Any night awakening due to asthma?
3. SABA reliever for symptoms more than twice/week?
4. Any activity limitation due to asthma?

The asthma control test (ACT) is composed of five questions with the possibility of 1–5 points per question. One equals maximum impairment and five means no impairment at all. The points of the five questions are then summarised for the ACT score. ACT score ≥20 reflects well-controlled asthma; ACT score 16–19 reflects partly controlled asthma; ACT score 5–15 reflects poorly controlled asthma [1, 31, 32]. The questions of the ACT refer to the past 4 weeks and involve working impairment due to asthma, shortness of breath, night time awakening due to asthma symptoms, use of rescue medication, and a rating of asthma control [31]. The ACT has proven to be useful as an objective measure for asthma control [33].

Statistical Analyses

In the descriptive analysis, median values and range were calculated for continuous variables. For categorical variables, absolute numbers and percentages were evaluated. We checked for outliers and normal distribution, by visual inspection of boxplots and histogram of the continuous data. Unrealistic or implausible values were replaced by a missing value.

For the analysis of variables associated with asthma control, two groups were created depending on the ACT score. Controlled asthma was defined as an ACT score of 20–25 and uncontrolled asthma as ACT score of 5–19 [1]. We show median values and range across controlled and uncontrolled asthma patients for continuous variables as well as absolute numbers and percentages across controlled and uncontrolled asthma patients.

Table 2. Baseline characteristics of the enrolled patients in the Swiss severe asthma registry

Baseline characteristics	Overall (*n* = 278)
Female, *n* (%)	134 (48.2)
Age, median (range), years	57 (13–87)
Age at diagnosis	
Age, median (range), years	45.5 (1–83)
Unknown, *n* (%)	100 (36)
<18 years, *n* (%)	22 (7.9)
18–40 years, *n* (%)	48 (17.3)
>40 years, *n* (%)	108 (38.8)
Relatives with asthma, *n* (%)	88 (31.7)
Asthma type	
Allergic asthma, *n* (%)	128 (46)
Non-allergic asthma, *n* (%)	95 (34.2)
Mixed asthma, *n* (%)	52 (18.7)
BMI	
BMI, median (range)	26.35 (16.7–63.3)
<18.5, *n* (%)	7 (2.5)
≥18.5–<25, *n* (%)	95 (34.2)
≥25–>30, *n* (%)	97 (34.9)
≥30, *n* (%)	77 (27.7)
Smoking status	
Non-smoker, *n* (%)	145 (52.2)
Active Smoker, *n* (%)	30 (10.8)
Ex-smoker, *n* (%)	102 (36.7)
Pack-years, median (range)	12.5 (0.05–80)
PFT pre-bronchodilation, *n* (%)	231 (83.1)
FEV_1% predicted, median (range)	78 (27.9–124)
FEV_1 l, median (range)	2.31 (0.32–4.73)
FEV_1/FVC %, median (range)	71 (26–106)
TLC %, median (range)	103 (61–140)
TLC l, median (range)	6.5 (3.31–14.6)
GINA control	
Controlled, *n* (%)	150 (54)
Partially controlled, *n* (%)	69 (24.8)
Uncontrolled, *n* (%)	58 (20.9)
ACT score, median (range)	20 (5–25)
20–25, *n* (%)	152 (54.7)
16–19, *n* (%)	45 (16.2)
5–15, *n* (%)	72 (25.9)

ACT, asthma control test; BMI, body mass index (kg/m^2); PFT, pulmonary function test; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; GINA, Global Initiative for Asthma.

To prepare data for multivariable analysis, predictive variables with more than 20% missing values were removed. Variables with fewer than 20% missing values were imputed with $k = 10$ neighbours using the median for continuous variables or mode for discrete variables. For sensitivity analysis, we show results of the

complete cases and the imputed dataset. Most important predictors from literature [34] were used for the multivariable analysis and encompassed: age, smoking status, ICD-10 asthma type, number of unplanned physician visits, BMI, number of exacerbations in the last year, relatives with asthma, asthma medication and treatment, comorbidities, pulmonary function, and rehabilitation. To evaluate predictive factors for asthma control, a multivariable logistic regression model was built using a generalised linear model of the binomial family (1 = asthma control, zero = no asthma control).

For the statistical analyses, we used R version 4.0.3 [35]. All tests were two-tailored. A p value <0.05 was defined as statistically significant.

Results

Demographic

The initial dataset comprised in total 278 patients, which were analysed for the baseline characteristics (Table 2). There were more male patients (51.8%) enrolled and the overall mean age was 55.8 years (range 13–87). Late onset asthma (37.8%) was more common than early onset (20.9%) in the enrolled patients. The majority of patients were overweight or obese (BMI 25–29.99 kg/m^2, 34.9%, BMI ≥30 kg/m^2, 27.7%) and only a small proportion of 2.5% was underweight (BMI <18.5 kg/m^2). Roughly, half of the patients reported a history of smoking (former and current smokers) with a mean pack-year amount of 18.5. For 2 patients, the BMI was not available. One patient was entered in the database, but no data were filled in.

Asthma Control

Data on asthma control according to GINA were available for 277 patients of which 54% were reported having controlled asthma, 25% partly controlled asthma and 21% uncontrolled asthma. According to ACT, 55% of patients had controlled asthma (ACT ≥20), 16.2% partly controlled asthma (ACT 16–19), and 26% uncontrolled asthma (ACT 5–15). Asthma control test (ACT) values were available only in 269 patients, and their distribution is shown in Figure 1.

Comorbidities

The most frequent comorbidities were allergic comorbidities (56.1%), chronic rhinosinusitis (47.96%), nasal polyps (35.3%), gastroesophageal reflux disease (GERD, 26.4%), and arterial hypertension (20.4%) (Table 3). 34.2% of patients suffered from allergic rhinitis, 8.6% from food allergy, 8.6% from atopic eczema, and 16.4% from another kind of allergy.

Lung Function and Blood Eosinophil Count

Pulmonary function testing (PFT) prior to bronchodilation was available for 83% (n = 231) (Table 2; Fig. 2) fractional exhaled nitric oxide was available for 161 patients (58%). From the patients with an available blood eosinophil count (n = 138), 44% showed an elevated value over 150 cells/uL. In 29%, an IgE level above 500 Ul/mL was observed, but only the IgE values for 112 patients were available (online suppl. Table 2).

Asthma Treatment

In our cohort, 78.8% of patients received a combined inhaler that contain ICS/LABA (Fig. 3), 19.4% received inhaled corticosteroids (ICS) as single inhalers. The mean dose for ICS was 1,416 μg beclomethasone equivalent daily. The majority (81.7%) received treatment with a monoclonal antibody with a median treatment duration of 16 months (range: 0–120). Mepolizumab was used in 30.2%, which was the most frequent biologic in the Swiss study population. The distribution of the applied monoclonal antibodies is presented in Figure 4, the treatment duration for each available monoclonal antibody is shown in the online supplementary Figures 1, 2. 19.1% were treated with continuous oral steroids with a mean prednisolone equivalent dose of 12.5 mg daily. Two patients received theophylline and immunotherapy (sublingual or subcutaneous) respectively. No patient that was treated by bronchial thermoplasty was enrolled. Medication was not available for 4 patients. Absolute numbers of patients for each treatment and for each treatment combination can be found in the online supplementary Table 3.

In addition, we observed statistically significant differences between patients who were treated with biologics compared to those who were not on the following variables: FEV_1% predicted (p = 0.003) and FEV_1 l (p = 0.001). There was no statistically significant difference in achieving asthma remission (according to [36]) in both groups (biologics: 33.6% vs. no biologics 25.5%, p = 0.244) (online suppl. Table 4).

Healthcare Utilisation

The majority of patients (66.2%) with severe asthma did not have unplanned outpatient visits related to asthma during the year prior to enrolment (Table 4). Exacerbations occurred once per year in 18.7% and 2–11 times per year in 28.8% of the patients. Almost half of the patients (48.6%) did not have an exacerbation in the previous year. About one-third presented to the emergency department and 15% were hospitalised due to their asthma in the previous year. 18.3% of the enrolled

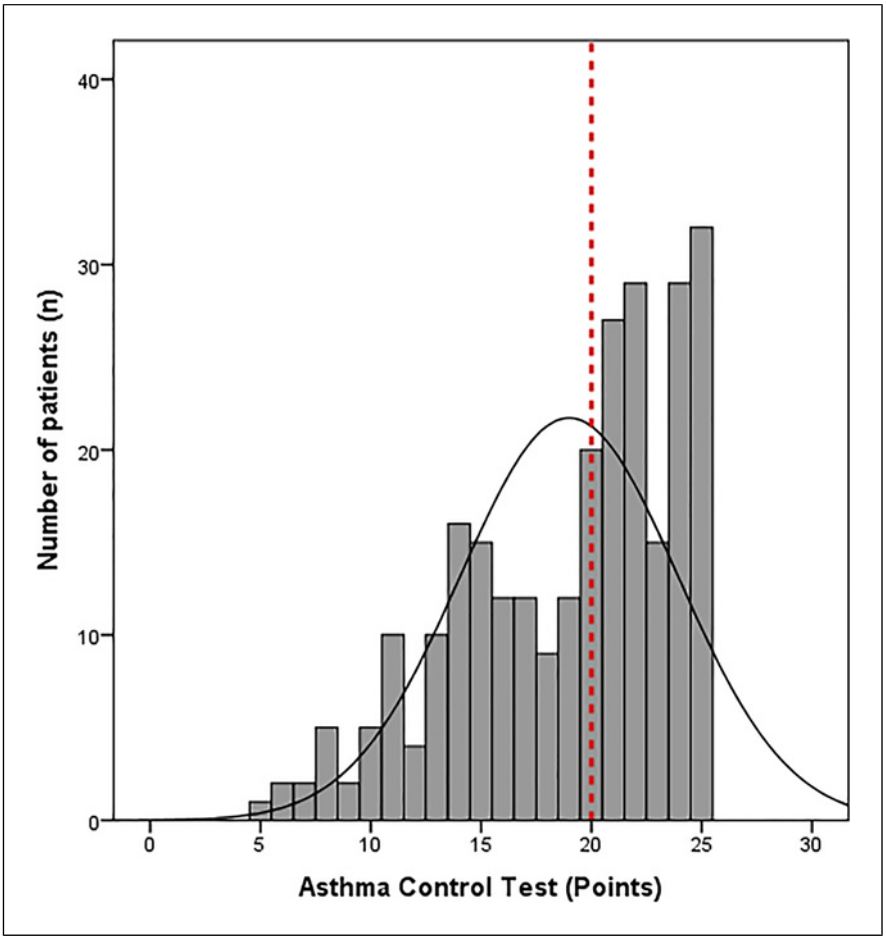

Fig. 1. Distribution of the asthma control test (ACT) scores. Black line – normal distribution curve. Red dotted line – cut-off for good asthma control (20 points).

patients had at least 1 day of absence at work or school due to their asthma (not including patients who were retired) (Table 4). The number of emergency department visits and hospitalisations in the last 12 months before enrolment was not available for 10 patients. The number of exacerbations was not reported for 20 patients.

Predictors of Asthma Control

There were 2 patients with more than 70% missing values in the remaining dataset and were excluded from the uni- and multivariable analyses. Statistically significant differences between controlled (ACT 20–25) and uncontrolled asthma (ACT 5–19) were found in the univariable logistic regression analysis for 18 of the analysed variables (online suppl. Table 5).

A statistically significant result was found for BMI, which was on average higher in the group with uncontrolled asthma (p = 0.007). Statistically significant differences were found in surgery of nasal polyps (p = 0.048) and surgery of chronic sinusitis (p < 0.001), which had occurred more often in the group with good asthma control. However, chronic obstructive pulmonary disease (COPD, p = 0.003), depression (p = 0.001) and inducible laryngeal obstruction (p = 0.037) were more frequent in the group with uncontrolled asthma. An overview of the frequency of comorbidities in each group is shown in Table 3 and in the online supplementary Table 6.

For the diagnostic variables, statistically significant results were found for mean FEV_1% predicted (p < 0.001) and FEV_1 in l (p = 0.006), which were higher in the controlled group. Furthermore, mean TLC % (p = 0.038) and number of eosinophil blood count above 150 cells/uL (p = 0.006) were lower in the controlled group (online suppl. Table 5).

For the asthma treatment, statistically significant differences existed for the use of mepolizumab (p = 0.009), oral corticosteroids (OCS) (p = 0.001), long-acting anticholinergic (p = 0.008), and LTRA (p = 0.005). Except for mepolizumab, all these treatments were more often used in the group with uncontrolled asthma (online

Table 3. Overall occurrence of comorbidities and comparison between the ACT groups

Comorbidities	Overall (n = 269)	ACT ≤19 (n = 117)	ACT ≥20 (n = 152)	p value[a]
Allergic comorbidities, n (%)	151 (56.1)	57 (48.7)	89 (58.6)	0.107
Allergic rhinitis, n (%)	92 (34.2)	39 (33.3)	52 (34.2)	0.440
Food allergy, n (%)	23 (8.6)	9 (7.7)	15 (9.9)	0.530
Other allergies, n (%)	44 (16.4)	13 (11.1)	28 (18.4)	0.088
Atopic eczema, n (%)	23 (8.6)	8 (6.8)	16 (10.5)	0.280
Chronic sinusitis, n (%)	129 (47.96)	51 (43.6)	75 (49.3)	0.347
Sinusitis surgery, n (%)	55 (20.4)	13 (11.1)	41 (27)	**0.001****
Nasal polyps, n (%)	95 (35.3)	35 (29.9)	57 (37.5)	0.189
Nasal polyp surgery, n (%)	62 (23.0)	20 (17.1)	41 (27)	**0.049***
GERD, n (%)	71 (26.4)	35 (29.9)	34 (22.4)	0.164
Cardiovascular disease				
Arterial hypertension, n (%)	55 (20.4)	25 (21.4)	29 (19.1)	0.644
Other cardiovascular disease, n (%)	32 (11.9)	14 (12)	18 (11.8)	0.975
Frequent lower respiratory tract infections (>2 x/y), n (%)	38 (14.1)	22 (18.8)	15 (9.9)	0.980
COPD, n (%)	33 (12.3)	22 (18.8)	10 (6.6)	**0.003****
Depression, n (%)	30 (11.2)	19 (16.2)	10 (6.6)	**0.001****
Aspirin intolerance, n (%)	27 (10.0)	9 (7.7)	17 (11.2)	0.325
SARS-CoV-2-infection, n (%)	18 (6.7)	10 (8.5)	8 (5.3)	0.300
Urticaria, n (%)	17 (6.3)	9 (7.7)	8 (5.3)	0.430
Bronchiectasis of unknown origin, n (%)	14 (5.2)	7 (6)	7 (4.6)	0.620
EGPA, n (%)	8 (3)	3 (2.6)	5 (3.3)	0.724
Neuromuscular disease, n (%)	7 (2.6)	3 (2.6)	4 (2.6)	0.970
Inducible laryngeal obstruction, n (%)	7 (2.6)	6 (5.1)	1 (0.7)	**0.037***
Hyperventilation syndrome and panic disorder, n (%)	6 (2.2)	4 (3.4)	2 (1.3)	0.27
Eosinophilic pneumonia, n (%)	6 (2.2)	3 (2.6)	3 (2)	0.75
Other comorbidities, n (%)[b]	10 (3.7)	8 (6.8)	12 (7.9)	0.71

COPD, chronic obstructive lung disease; EPGA, eosinophilic granulomatosis with polyangiitis; GERD, gastroesophageal reflux disease; SARS-CoV-2, severe acute respiratory syndrome with coronavirus-2. Level of significance: * <0.05, ** <0.01, *** <0.001. [a]Significance based on χ^2 test. [b]Other comorbidities include all those that are present in <2% in the overall population.

suppl. Table 7). The number of exacerbations ($p < 0.001$), visits to the emergency department ($p < 0.001$), hospitalisations ($p = 0.004$) and inability to work due to asthma ($p = 0.007$) were negatively associated with asthma control (online suppl. Table 8).

Independent factors associated with asthma control are presented in Table 5 and Figure 5. The area under the curve was 0.80 for the multivariable logistic regression model. The optimal threshold was at a predicted probability of 0.57 with an accuracy of 0.75, a specificity of 0.72, and a sensitivity of 0.77 (online suppl. Fig. 3–6).

Discussion

The SSAR included 278 patients from all regions of Switzerland and from different care facilities ranging from primary to tertiary asthma care. This means that despite the small sample size, it is likely that the collected data give a representative insight in the care of severe asthma patients in Switzerland.

The observations of the SSAR should not only be seen independently but also in an international context, therefore a comparison of our data to the registries in the UK (n = 2,225), Germany (n = 1,317 and n = 2,011), Italy (n = 437), Belgium (n = 350), Denmark (n = 621), Japan (n = 154), Latin America (n = 594) as well as the international severe asthma registry (ISAR) (n = 4,990) was made, whenever the analysed variables overlap [13–16, 36–40]. The differences, respectively, the similarities between the registries might be partly explained by the differences in sample size, national diagnostic, and treatment standards or different time points of inclusion, such as before or after the market authorisation of certain treatment approaches such as monoclonal antibodies.

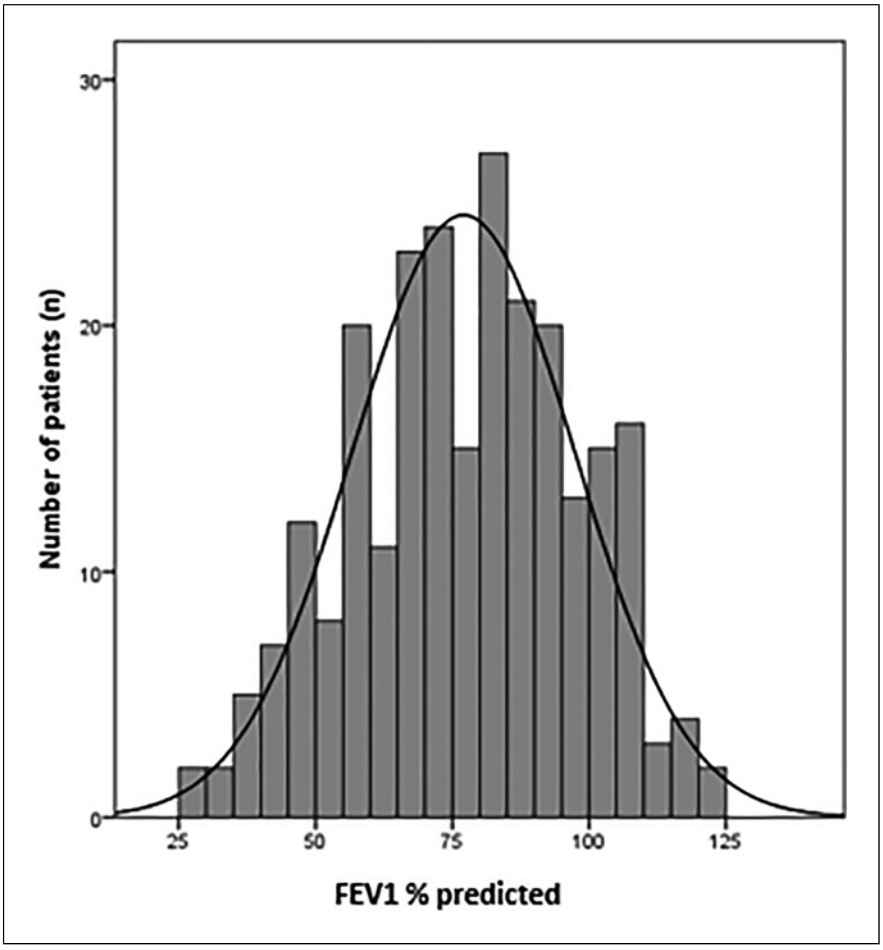

Fig. 2. Distribution of the FEV_1 values. Black line–normal distribution curve.

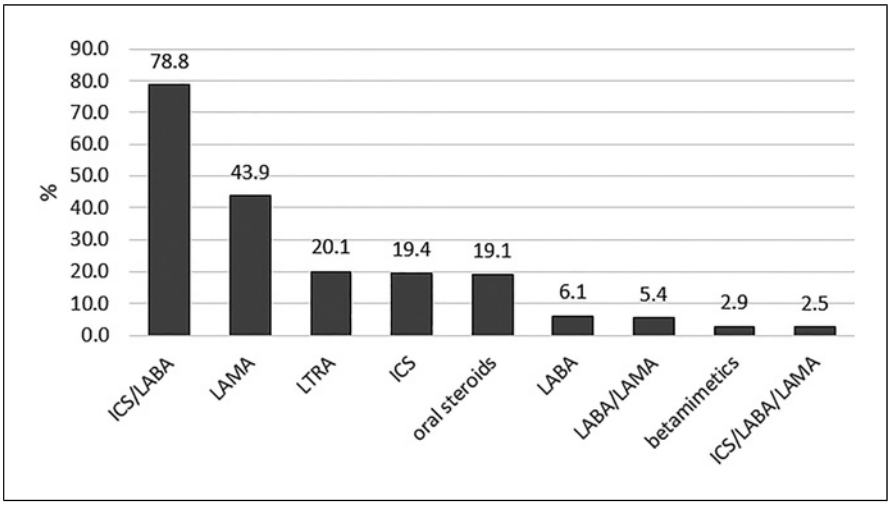

Fig. 3. Maintenance therapy used in the Swiss severe asthma registry.

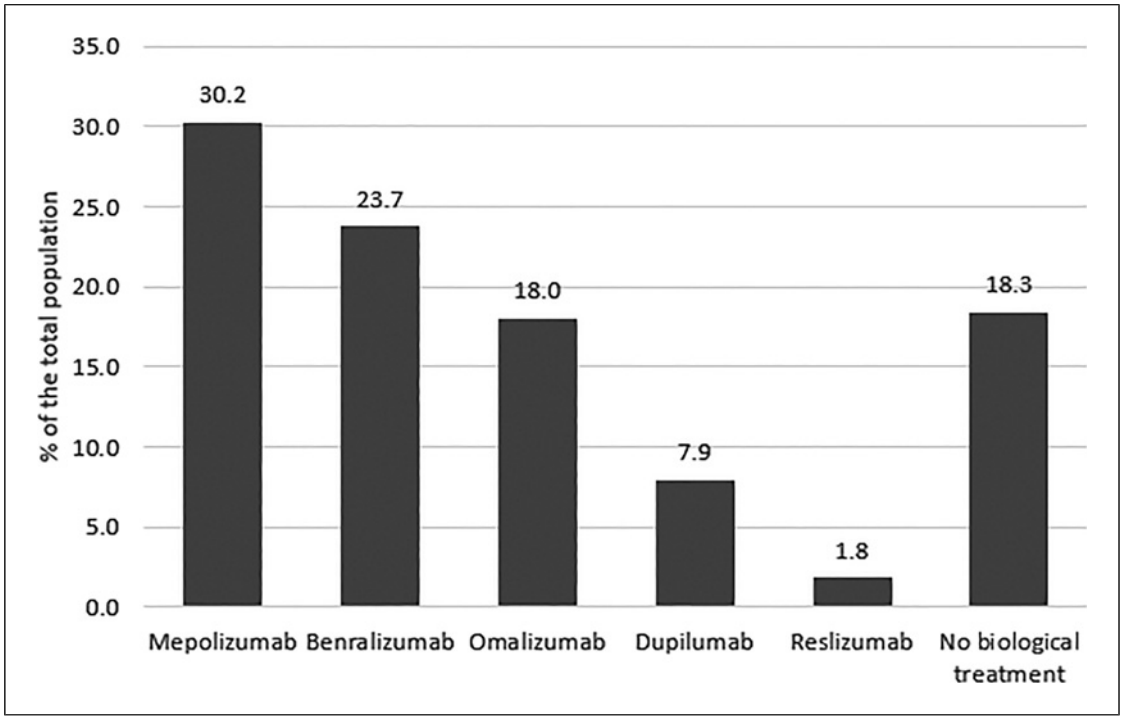

Fig. 4. Use of monoclonal antibody therapies in per cent.

Table 4. Healthcare utilisation within 12 months prior to enrolment

Healthcare utilisation	Overall (*n* = 278)	ACT ≤19 (*n* = 117)	ACT ≥20 (*n* = 152)	*p* value
Unplanned outpatient visits				
1–3, *n* (%)	60 (21.6)	28 (18.4)	31 (26.5)	0.117[a]
>3, *n* (%)	30 (10.8)	14 (9.2)	13 (11.1)	0.61[a]
0, *n* (%)	184 (66.2)	107 (70.4)	73 (62.4)	0.169[a]
Inability to work due to asthma, *n* (%)	51 (18.3)	30 (26)	19 (12.5)	**0.003****[a]
Exacerbations, mean (SD)	1.2 (1.8)	1.9 (2.2)	0.7 (1.3)	<**0.001*****
0, *n* (%)	135 (48.6)	39 (33.3)	90 (59.2)	<**0.001***[a]
1 x/y, *n* (%)	52 (18.7)	27 (17.8)	24 (20.5)	0.57[a]
>1 x/y but <1 x/month, *n* (%)	80 (28.8)	50 (42.7)	30 (19.7)	<**0.001***[a]
≥1 x/month, *n* (%)	1 (0.4)	1 (0.9)	0 (0)	0.32[a]
Emergency department visits, *n* (%)	74 (26.6)	47 (40.2)	26 (17.1)	<**0.001***[a]
Hospitalizations, *n* (%)	42 (15.1)	27 (23.1)	15 (9.9)	**0.004****[a]
Rehabilitation ever, *n* (%)	57 (20.5)	29 (24.8)	27 (17.8)	0.165[a]
Asthma training, *n* (%)	96 (34.5)	47 (30.9)	47 (40.2)	0.116[a]
Inhaler technique education, *n* (%)	243 (87.4)	102 (87.2)	134 (88.2)	0.81[a]

Level of significance: * <0.05, ** <0.01, *** <0.001. [a]Significance based on χ^2 test.

Demographic

The sex distribution in the Swiss registry is similar to the Danish cohort, where more male patients are included [36]. However, the majority of patients are female in other severe asthma registries [13–16]. The mean age of 55.8 years is also comparable to other registries in Europe. In the Swiss registry, we observed a relatively late asthma onset in the early 1940s, compared to registries across Europe. The mean BMI shows a tendency to overweight, which is similar to other countries. The

Table 5. Results of the multivariable logistic regression model with dependent variable asthma control (ACT scores 20–25) and 23 predictors, imputed dataset from 267 observations

Multivariable regression for predictors of the ACT score	Frequency, controlled/ uncontrolled, *n* (%)	OR	Lower 95% CI	Upper 95% CI	*p* value
(Intercept)		0.89	0.06	14.27	0.935
Age, mean (per 10 years)	See supplementary Table 3	1.14	0.92	1.42	0.224
Active smoker	14 (9.2)/15 (12.8)	1.56	0.58	4.29	0.38
Non-allergic asthma	57 (37.5)/35 (29.9)	1.62	0.73	3.67	0.237
Mixed asthma form	23 (15.1)/26 (22.2)	0.94	0.39	2.24	0.885
Unplanned physician visits, *n*	See Table 5	1.28	0.76	2.21	0.358
BMI, mean (per 10 kg/m^2)	See supplementary Table 3	0.62	0.37	1.01	0.06
Exacerbations, *n*	See Table 5	0.63	0.5	0.78	<**0.001*****
Relatives with asthma	41 (27)/44 (37.6)	0.54	0.28	1.02	0.059
Sex (female)	83 (54.6)/55 (47)	0.71	0.38	1.31	0.271
LAMA/LABA add-on		0.77	0.4	1.5	0.445
ICS/LABA	121 (79.6)/92 (78.6)	1.01	0.47	2.14	0.976
LTRA	24 (15.8)/30 (25.6)	0.93	0.44	2	0.856
Oral corticosteroids	21 (13.8)/31 (26.5)	0.47	0.21	1.05	0.065
Monoclonal antibody	134 (88.2)/86 (73.5)	2.62	1.19	5.89	**0.018****
Rehabilitation	See table 5	0.87	0.46	1.64	0.665
Allergies	89 (58.6)/57 (48.7)	1.78	0.88	3.64	0.111
Chronic rhinosinusitis with or without nasal polyps		1.52	0.83	2.77	0.174
COPD	10 (6.6)/22 (18.8)	0.33	0.11	0.95	**0.044***
GERD	34 (22.4)/35 (29.9)	0.76	0.37	1.54	0.439
Depression	10 (6.6)/19 (16.2)	0.57	0.19	1.58	0.284
FEV_1% predicted (per 10)	See supplementary Table 3	1.18	0.95	1.47	0.139
FEV_1/FVC % (per 10)	See supplementary Table 3	0.9	0.66	1.22	0.482
Equivalent dose beclomethason in µg (per 1,000)	See supplementary Table 3	1.08	0.78	1.48	0.63

LAMA, acting anticholinergic. Dependent variable was asthma control (ACT scores 20–25). Results are expressed in odds ratios (OR) and 95% confidence interval (CI) with values above 1 indicating higher likelihood of asthma control whereas values below 1 indicate that the variable is associated with poorer asthma control level of significance: * <0.05, ** <0.01, *** <0.001.

percentage of active and former smokers in the Swiss cohort is higher than in Italy and the UK [14, 16], but similar to Belgium [13].

Asthma Control

Asthma control according to GINA criteria is good in 54% of patients, enrolled in the registry, which is higher than in the Japanese (43.5%) and German (13.3%) registries [39, 40]. A higher mean ACT score than in other registries (Italy, Belgium, Denmark, and Germany) shows a better asthma control in the Swiss cohort [13–15, 36]. However, more patients achieve an ACT score ≥20 (well-controlled asthma) in the Italian registry than in the Swiss one (64% vs. 55%, respectively).

Comorbidities

In this cohort, 56.1% of patients have an allergic comorbidity. This is less than reported in other European registries like Italy (71%), Belgium (70%), Germany (63.5%), and the UK (63%) [13–16]. Chronic rhinosinusitis occurred in 47.96% of patients in the Swiss cohort, which is comparable to other European countries [13, 14, 38]. Nasal polyps were much more common in our cohort (35.3%) than in other registries [13, 16, 37, 38]. The frequency of GERD (26.4%) was comparable to the numbers in Latin America (27.2%) and lower than in Belgium (36%) or Germany (35.4%) [13, 15, 37]. However, the UK registry showed a lower rate of GERD (16.9%) [16]. Our cohort had more cases of COPD (12.3% vs. 6%) and inducible laryngeal obstruction (2.6% vs. 1%) than in Germany and Latin America [15, 38]. Bronchiectasis was found in 5.2% of patients in our cohort, which is similar to Germany (3%) but lower than Italy and Belgium (both 16%) [13–15]. Comorbidities in the Latin American cohort were patient reported and therefore might be inaccurate. Overall, our population has a high proportion of comorbidities, which has been shown in registries of

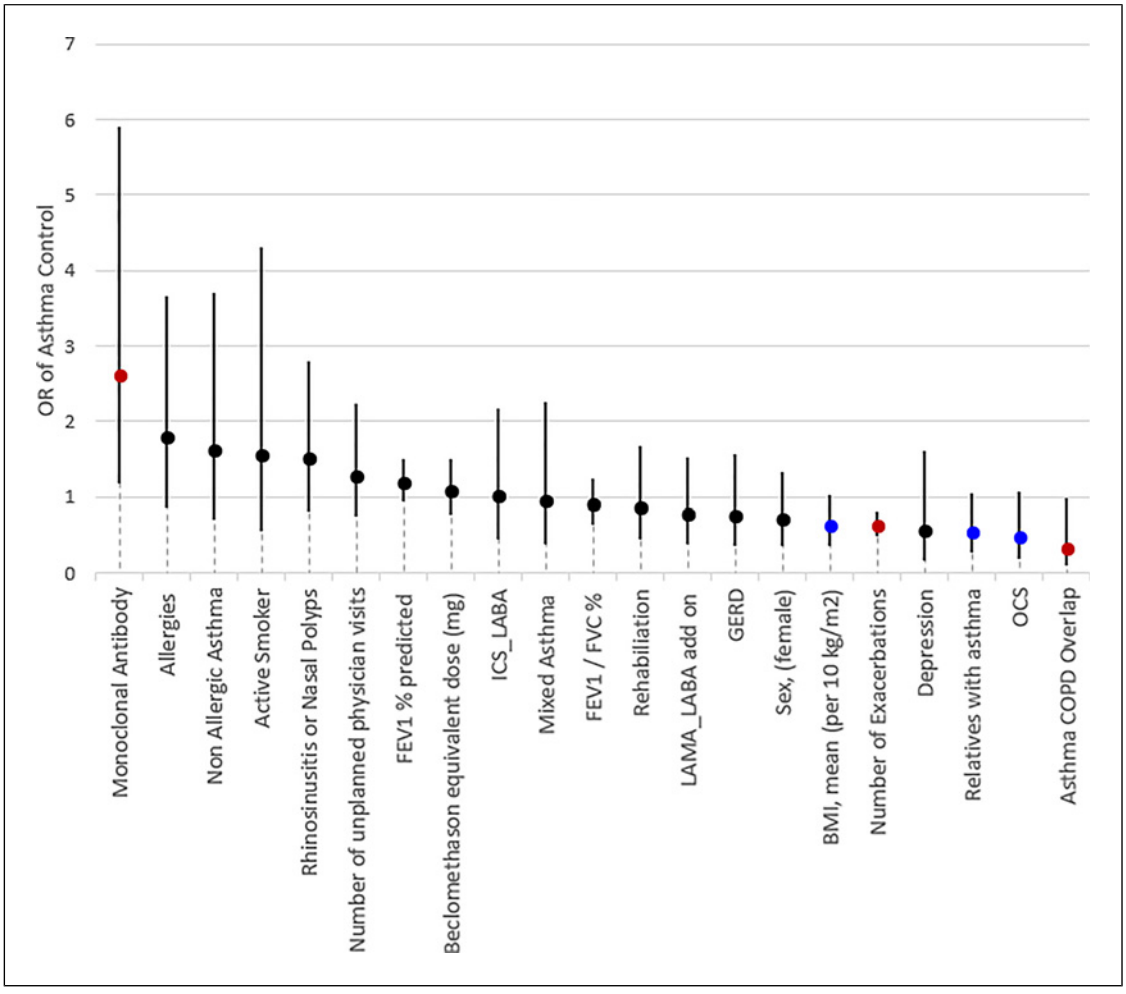

Fig. 5. Forest plot with OR and 95% CI of the multivariable results of logistic regression model on asthma control (ACT scores 20–25) with 23 predictors on the imputed dataset with 267 observations.

severe asthma many times. It is important to diagnose and treat comorbidities as they can aggravate symptoms and lead to more uncontrolled asthma and thus increase the financial and socioeconomic burden of this disease [1]. A higher proportion of well-treated comorbidities could partially explain the observed differences in asthma control compared to other countries.

Lung Function and Blood Eosinophil Count

Our cohort showed better values of FEV_1% predicted and FEV_1/FVC than in Italy, Belgium, Germany, the UK, and Denmark [13–16, 36]. The Japanese cohort showed a similar FEV_1% predicted values [39]. The TLC % predicted value of our cohort was in the same range as in Belgium and Denmark [13, 36].

Type 2 biomarker levels are most comparable to Denmark, which might be explained by the high ratio of patients already on biologics in both cohorts [36]. However, most of our patients were on biologic treatment before being enrolled in the registry, which might lead to lower type 2 biomarkers.

Asthma Treatment

The most frequent inhalation therapy in our cohort was a fixed ICS/LABA combination, which was used in 78.8% of patients. Compared to other registries, Germany had a similar amount (77%), whereas the cohorts in Italy, Belgium, and the UK registered a 100% rate of fixed ICS/LABA combination as would be expected in a severe asthma population [13–16]. Additionally, the beclomethasone (ICS) equivalent daily dose was lower in our cohort compared to other countries except for Japan [39].

81.4% of our patients received a biologic treatment, mepolizumab (30.2%) is the most common biologic used in our cohort. A higher rate of treatment with monoclonal antibodies has only been achieved in the Danish cohort (98%), as it is mandatory to include all patients receiving a monoclonal antibody in the registry [36]. Thus, the Swiss registry has the second highest rate of biologic treatment for severe asthma in Europe. The use of OCS was considerably lower in our population compared to Italy, Germany, and the UK [14–16]. In Latin America, the use of OCS was lower than in our cohort [37]. The impact of single versus multiple inhaler use and of other treatment combinations in the Swiss registry population was not analysed in this article. However, the medication in Latin America was patient reported and might have a reporting bias. At the time of data analysis of our study, five biologic agents were authorised for severe asthma in Switzerland whereas in Belgium only omalizumab was available at the time of the study. Nevertheless, Belgium showed only slightly higher rates of OCS use (24% vs. 19%) than Switzerland [13]. Although in Germany all these biologic agents were available, only 40% of patients received any and 36% were still on OCS. A recent publication from the German cohort showed a slight increase of biologic use (48.5%) but even higher numbers of OCS use than earlier [40]. The UK has 51.7% of patients on OCS despite having a rate of 68.9% on biologics [16]. Those results are surprising, as biologics have shown to reduce the need for OCS [41–43]. Unfortunately, data on OCS are not available for the Danish cohort so far which has the highest rate of biologic use.

In our cohort, LTRA and theophylline were used considerably less than in other cohorts [13, 14, 16, 39, 40]. In our cohort, long-acting anticholinergics were frequently used (43.7%). However, this is less than Germany (56.2%), the UK (53.2%) but more than Italy (35.7%), ISAR (16.7%), and Japan (14.3%) [14, 16, 38–40]. Single LABA inhalation was not very common in our cohort (6.1%) and all but 1 of those patients had additional single ICS inhaler. Germany reported higher rates of single LABA inhaler (11.4%) [40].

In summary, the Swiss cohort of severe asthma patients has a lower percentage of fixed ICS/LABA combination and lower ICS equivalent daily doses, higher rates of biologic use and lower OCS use as well as lower percentage of additional LTRA and theophylline than most other countries. This might be due to the desired and expected effect of the biologic therapies to reduce the need for OCS use [43]. Lower ICS/LABA and ICS doses could be explained by a fast dose reduction after achieving good asthma control with biologics. Further analysis of follow-up visits is required to evaluate this trend in the long-term, as well as the effect of combination of different types of treatments, which was not analysed in the current study.

However, it must be considered, that due to a possible selection bias favouring patients on biologics in our cohort, the reality of severe asthmatics in Switzerland might look different. A recent study from Germany has shown a large treatment gap with only a minority of patients with severe asthma being treated with biologics despite a much greater number having uncontrolled asthma [44].

Healthcare Utilisation

In our cohort, the exacerbation rate per year is lower than in other registries (Italy, the UK, Denmark, and the ISAR) [14, 16, 36, 38]. The rate of emergency department visits in our registry is similar to the ISAR and lower in our population than in the German and Japanese cohort [38–40]. The hospitalization rate is lower in our population than in Germany, the ISAR, and Japan [38–40]. Surprisingly, the ISAR and the Latin American registry have more patients without any exacerbations despite worse asthma control, which is expected to increase the risk of exacerbations [1]. Differences in healthcare availability and utilisation in other European countries, Latin America, and other countries outside of Europe could explain this observation. Emergency department visits and hospitalisation rates due to asthma exacerbations were significantly higher in patients with poorly controlled asthma compared to patients with well-controlled asthma. These observations are in line with recent findings from Australia that poorly controlled asthma is associated with higher direct healthcare costs [45].

Predictors of Asthma Control

Biologic treatment was associated with good asthma control, whereas higher BMI, OCS use, exacerbations, and COPD were associated with poor asthma control. Throughout our model, biologics suggested a positive effect on asthma control. This model seems to support previous findings that monoclonal antibodies improve asthma control in a real-world population, as they are known to reduce the need for oral steroids and therefore reduce side effects of short- and long-term OCS use [41, 42, 46, 47]. Only a minority of patients is currently not treated with a monoclonal antibody; therefore only limited conclusions can be made about changes in asthma control or exacerbation frequency after initiating treatment with a monoclonal antibody. Further analysis of follow-up data could investigate the development of asthma control as well as the trajectory of OCS use on biologic treatment.

BMI showed an inverse linear relationship with asthma control which is in line with our result [24, 26, 37, 48]. Overweight and obesity remain a modifiable factor in patients with severe asthma, appropriate treatment, and weight loss have shown a positive effect on asthma control and should be considered in the management of severe asthma patients [49, 50].

The association of OCS use and poor asthma control has previously been reported [26, 37, 51, 52]. However, OCS dependency should be regarded as a sign of poor symptom control, as OCS is used as a last resort when patients remain uncontrolled despite appropriate treatment according to GINA step 5 [1]. Our analyses showed, as expected, an inverse association between exacerbations and asthma control. Recurrent exacerbations in the last 3 months are risk factors for further exacerbations which have a negative impact on asthma control [53]. Additionally, studies have shown that ACT can predict the risk of asthma exacerbations and that there is a negative correlation between the ACT score and the number of exacerbations [54, 55].

Comorbid COPD was negatively associated with asthma control in our analysis. A negative effect of COPD on asthma control has previously been shown [48]. Patients suffering comorbid COPD have more symptoms and exacerbations, as well as higher mortality rates compared to patients with asthma or COPD alone [56]. This makes the asthma population with comorbid COPD particularly vulnerable. Comorbid COPD in patients with severe asthma may also be a fixed airflow obstruction instead of COPD, as the differential diagnosis can be difficult as the diseases can mimic each other [57–59].

Depression, female sex, and current smoking, among other factors, have been shown to predict asthma control in other cohorts [33, 37, 48, 60–62], but the association was not statistically significant in our cohort. As described above, other cohorts have had a higher proportion of female participants included than our cohort, which might have influenced that female sex is no significant predictor due to the similar sex distribution. Major depression is more often diagnosed in women than in men, which might have mediated the effect of depression in other studies and was not statistically significant in our cohort due to the similar sex distribution [63].

Another factor associated with poor asthma control is low FEV_1, which showed a statistically significant difference in the univariable comparison of the two groups [26]. Due to missing data on FEV_1 in 10% of patients, it could not be used in the multivariable analysis. As lung function values are crucial for the assessment of asthma, it is important to improve the rate of lung function values reported in the registry.

Strengths and Limitations

To our knowledge, the present study is the first systematic characterisation of patients with severe asthma in Switzerland. An important strength is the inclusion of all language regions in Switzerland, reflecting possible cultural and demographic heterogeneity of the country. Furthermore, participating centres consist of a wide range of primary, secondary, and tertiary pulmonary care facilities, which increases the number of eligible patients and allows a comprehensive overview of severe asthma patients.

Most of the patients were included from spring 2020 on, which is parallel to the beginning of the COVID-19 pandemic. During the course of the pandemic, it was observed that exacerbation frequency and severity of exacerbations were decreasing in patients with severe asthma [17, 64, 65]. Therefore, the low exacerbation rate must be interpreted with caution, as it might have been positively influenced by health policy measures during the COVID-19 pandemic (e.g., face masks or physical distancing), changes in health behaviour, reduction of air pollution, or changes in patient care [17].

One limitation of the current study is the missing data on socioeconomic status, non-compliance with the prescribed therapy and incorrect inhaler technique, which also are associated with asthma control [25, 26, 37, 52, 60]. Most patients in our cohort received inhaler technique education; hence, inhalation technique could be presumed good. However, not all inhalation mistakes could be avoided even by repetitive instruction.

Another limitation is the missing data for blood eosinophil count and serum IgE in over 50% at baseline, therefore type 2 biomarkers could not be included in the multivariable regression model despite their important role in the evaluation of biologic treatments. Furthermore, most patients were included in the registry after starting a biologic therapy that has a direct influence of type 2 biomarker levels.

Further limitations are the relatively small sample size and a possible selection bias. Additionally, study design does not allow a systematic evaluation of comorbidities and their treatment [20, 66].

Comparing registries is challenging because they do not always collect the same variables. Therefore, many differences between our registry and cohorts from other countries cannot be properly explained yet. Furthermore, the reimbursement policies for biologic treatment and healthcare systems differ across countries, which could have an impact on asthma severity and control. An international uniform registry is under development by the Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) [67].

Conclusion

The current study has allowed a demographic characterisation of severe asthma patients in Switzerland and an indirect comparison with other European cohorts. Severe asthma patients in Switzerland are more often male, have better asthma control according to GINA/ACT and lower OCS use. Biologics seem to play an important role in asthma control in our population. Still, there is a significant proportion of patients with poor asthma control, highlighting the necessity to further improve treatment and therapeutic patient education and thus lower the socioeconomic burden of severe asthma. The longitudinal cohort design of our registry will elucidate the clinical course of severe asthma and the effect of treatment and comorbidities on asthma control and other health-related outcomes. The registry will provide real-life data on the medical course of patients receiving biologic therapy, facilitating the identification of responder phenotypes that could guide physicians in choosing the right biologic for their severe asthma patients.

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Statement of Ethics

The study was conducted in accordance with the World Medical Association (WMA) Declaration of Helsinki. This study protocol was reviewed and approved by the Ethical Committee of Northwestern and Central Switzerland, BASEC ID 2018-01553. It was also approved by the local Ethical Committees (EC) EC Bern, EC Geneva, Ethical Committee of Eastern Switzerland (EKOS), EC Ticino, EC Vaud, and EC Zurich. Written informed consent was obtained from all adult patients to participate in this study. In case of patients under the age of 18, written informed consent was obtained from parents/guardians or next of kin for participation in this study.

Conflict of Interest Statement

F.J. received advisory fees from GSK, AG Switzerland. J.D.L. received advisory fees from AstraZeneca AG, Switzerland; Boehringer Ingelheim GmbH, Switzerland; GSK AG, Switzerland; Novartis AG, Switzerland; Mepha Pharma AG, Switzerland; Mundipharma AG, Switzerland; MSD AG, Switzerland; and Sanofi AG, Switzerland. C.C. received advisory fees from Roche AG, Switzerland; Novartis AG, Switzerland; Boehringer Ingelheim GmbH, Switzerland; GSK AG, Switzerland; and AstraZeneca AG, Switzerland; Sanofi, AG, Switzerland; Vifor AG, Switzerland; OM Pharma AG, Switzerland; CSL Behring AG, Switzerland; Grifols AG, Switzerland; Daiichi Sankyo AG, Switzerland; and Mundipharma AG, Switzerland within the last 36 months. N.P. received advisory fees from AstraZeneca AG, Switzerland; GSK AG, Switzerland; Novartis AG, Switzerland; OM Pharma AG, Switzerland; and Sanofi AG, Switzerland within the last 36 months. C.V.G. received advisory fees from AstraZeneca AG, Switzerland; Boehringer Ingelheim GmbH, Switzerland; GSK AG, Switzerland; Mundipharma AG, Switzerland; Novartis AG, Switzerland; OM Pharma AG, Switzerland; Pfizer AG, Switzerland; PneumRx AG, Switzerland, Pulmonx AG, Switzerland; and Sanofi AG, Switzerland. The other authors did not declare any conflict of interest.

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Author Contributions

F.J. and L.M.T. evaluated the data and wrote the manuscript. Fabienne Jaun is the national study coordinator. S.G. performed statistical analysis and contributed to the manuscript with methodological inputs. P.-O.B., F.C., C.C., P.G., A.J., L.K., N.P., T.R., and C.v.G. are co-investigators in this study, they were involved in the planning and set up of the registry and revised and approved the manuscript. C.S.-S. and D.M. are advisors of the registry and revised the manuscript. J.D.L. is the sponsor-investigator of this study, planned and set up this registry and revised and approved the manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

References

1 Global Initiative for Asthma. Global strategy for asthma management and prevention; 2021. Available from: www.ginasthma.org.

2 Bousquet J, Akdis CA, Grattan C, Eigenmann PA, Hoffmann-Sommergruber K, Hellings PW, et al. Highlights and recent developments in airway diseases in EAACI journals (2017). Clin Transl Allergy. 2018 Nov;8(1):49.

3 von Bülow A, Kriegbaum M, Backer V, Porsbjerg C. The prevalence of severe asthma and low asthma control among Danish adults. J Allergy Clin Immunol Pract. 2014 Nov;2(6):759–67.

4 Hekking P-PW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. J Allergy Clin Immunol. 2015 Apr;135(4):896–902.
5 Ilmarinen P, Tuomisto LE, Niemelä O, Kankaanranta H. Prevalence of patients eligible for anti-IL-5 treatment in a cohort of adult-onset asthma. J Allergy Clin Immunol Pract. 2019 Jan;7(1):165–74.e4.
6 Accordini S, Corsico A, Cerveri I, Gislason D, Gulsvik A, Janson C, et al. The socioeconomic burden of asthma is substantial in Europe. Allergy. 2008 Jan;63(1):116–24.
7 Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014 Feb;43(2):343–73.
8 Jandus P, Duc M, Fay BC. Diagnosis and management of severe asthma in Switzerland: analysis of survey results conducted with specialists and general practitioners. Respiration. 2021;100(6):476–87.
9 Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, et al. Management of severe asthma: a European respiratory society/American thoracic society guideline. Eur Respir J. 2020 Jan;55(1):1900588.
10 Rothe T, Spagnolo P, Bridevaux P-O, Clarenbach C, Eich-Wanger C, Meyer F, et al. Diagnosis and management of asthma: the Swiss guidelines. Respiration. 2018;95(5):364–80.
11 Mauer Y, Taliercio RM. Managing adult asthma: the 2019 GINA guidelines. Cleve Clin J Med. 2020 Sep;87(9):569–75.
12 Brown T, Jones T, Gove K, Barber C, Elliott S, Chauhan A, et al. Randomised controlled trials in severe asthma: selection by phenotype or stereotype. Eur Respir J. 2018 Dec;52(6):1801444.
13 Schleich F, Brusselle G, Louis R, Vandenplas O, Michils A, Pilette C, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian severe asthma registry (BSAR). Respir Med. 2014 Dec;108(12):1723–32.
14 Heffler E, Blasi F, Latorre M, Menzella F, Paggiaro P, Pelaia G, et al. The severe asthma network in Italy: findings and perspectives. J Allergy Clin Immunol Pract. 2019 May;7(5):1462–8.
15 Milger K, Korn S, Buhl R, Hamelmann E, Herth FJF, Gappa M, et al. Age- and sex-dependent differences in patients with severe asthma included in the German Asthma Net cohort. Respir Med. 2020 Feb;162:105858.
16 Jackson DJ, Busby J, Pfeffer PE, Menzies-Gow A, Brown T, Gore R, et al. Characterisation of patients with severe asthma in the UK Severe Asthma Registry in the biologic era. Thorax. 2021 Mar;76(3):220–7.
17 Shah SA, Quint JK, Sheikh A. Impact of COVID-19 pandemic on asthma exacerbations: retrospective cohort study of over 500,000 patients in a national English primary care database. Lancet Reg Health Eur. 2022 Aug;19:100428.
18 Taegtmeyer AB, Steurer-Stey C, Price DB, Wildhaber JH, Spertini F, Leuppi JD. Predictors of asthma control in everyday clinical practice in Switzerland. Curr Med Res Opin. 2009 Oct;25(10):2549–55.
19 Leuppi JD, Steurer-Stey C, Peter M, Chhajed PN, Wildhaber JH, Spertini F. Asthma control in Switzerland: a general practitioner based survey. Curr Med Res Opin. 2006 Nov;22(11):2159–66.
20 Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M, et al. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. Thorax. 2003 Jul;58(7):561–6.
21 Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF, et al. Systematic assessment of difficult-to-treat asthma. Eur Respir J. 2003 Sep;22(3):478–83.
22 Boulet L-P, Vervloet D, Magar Y, Foster JM. Adherence: the goal to control asthma. Asthma. 2012 Sep;33(3):405–17.
23 Sanchis J, Gich I, Pedersen S; Aerosol Drug Management Improvement Team ADMIT. Systematic review of errors in inhaler use: has patient technique improved over time? Chest. 2016 Aug;150(2):394–406.
24 Laforest L, Van Ganse E, Devouassoux G, Bousquet J, Chretin S, Bauguil G, et al. Influence of patients' characteristics and disease management on asthma control. J Allergy Clin Immunol. 2006 Jun;117(6):1404–10.
25 Zaihra T, Ernst P, Tamblyn R, Ahmed S. Tailoring interventions: identifying predictors of poor asthma control. Ann Allergy Asthma Immunol. 2015 Jun;114(6):485–91.e1.
26 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.
27 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 Pract. 2021 Jul;9(7):2802–11.e2.
28 Interdisziplinäres zentrum klinische STudien (IZKS), SSP team, tobias E, daniel V. German asthma Net e.V. ECCT Login. [Internet]. MedReg-Schweres Asthma V480; 2023. Available from: https://ecct.izks-mainz.de/system/?hint=logout_successful&redirect_to=%252Fmedreg%252Fprojects%252Fsevere_asthma%252Findex.php%253Fframe%253Dsubjects%2526currentTab%253Dsubjects.
29 Stanojevic S, Kaminsky DA, Miller MR, Thompson B, Aliverti A, Barjaktarevic I, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. Eur Respir J. 2022 Jul;60(1):2101499.
30 World Health Organization. International statistical classification of diseases and related health problems: alphabetical index: World Health Organization; 2004.
31 Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004 Jan;113(1):59–65.
32 Thomas M, Kay S, Pike J, Williams A, Rosenzweig JRC, Hillyer EV, et al. The Asthma Control Test (ACT) as a predictor of GINA guideline-defined asthma control: analysis of a multinational cross-sectional survey. Prim Care Respir J. 2009 Mar;18(1):41–9.
33 Miedinger D, Neukomm E, Chhajed PN, Schnyder A, Naef M, Ackermann M, et al. The use of the Asthma Control Test in general practice and its correlation with asthma control according to the GINA guidelines. Curr Med Res Opin. 2011 Dec;27(12):2301–8.
34 Lovrić M, Banić I, Lacić E, Pavlović K, Kern R, Turkalj M. Predicting treatment outcomes using explainable machine learning in children with asthma. Children. 2021;8(5):376.
35 R Core Team. A language and environment for statistical computing: R Foundation for Statistical Computing; 2020.
36 Hansen S, Hilberg O, Ulrik CS, Bodtger U, M Rasmussen L, D Assing K, et al. The Danish severe asthma register: an electronic platform for severe asthma management and research. Eur Clin Respir J. 2020;8(1):1842117.
37 Neffen H, Chahuàn M, Hernández DD, Vallejo-Perez E, Bolivar F, Sánchez MH, et al. Key factors associated with uncontrolled asthma: the Asthma Control in Latin America Study. J Asthma. 2020 Feb;57(2):113–22.
38 Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN, et al. Characterization of severe asthma worldwide: data from the international severe asthma registry. Chest. 2020 Apr;157(4):790–804.
39 Tanosaki T, Kabata H, Matsusaka M, Miyata J, Masaki K, Mochimaru T, et al. Clinical characteristics of patients with not well-controlled severe asthma in Japan: analysis of the Keio Severe Asthma Research Program in Japanese population (KEIO-SARP) registry. Allergol Int. 2021 Jan;70(1):61–7.
40 Korn S, Milger K, Skowasch D, Timmermann H, Taube C, Idzko M, et al. The German severe asthma patient: baseline characteristics of patients in the German Severe Asthma Registry, and relationship with exacerbations and control. Respir Med. 2022 Apr;195:106793.
41 Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014 Sep;371(13):1189–97.
42 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 Jun;376(25):2448–58.

43 McGregor MC, Krings JG, Nair P, Castro M. Role of biologics in asthma. Am J Respir Crit Care Med. 2019 Feb;199(4):433–45.
44 Bergmann K-C, Skowasch D, Timmermann H, Lindner R, Virchow JC, Schmidt O, et al. Prevalence of patients with uncontrolled asthma despite NVL/GINA step 4/5 treatment in Germany. J Asthma Allergy. 2022;15:897–906.
45 Lartey ST, Lung T, Serhal S, Bereznicki L, Bereznicki B, Emmerton L, et al. Healthcare expenditure and its socio-demographic and clinical predictors in Australians with poorly controlled asthma. PLoS One. 2023 Jan;18(1):e0279748.
46 Kirchnerová OR, Valena T, Novosad J, Teřl M; Czech eXpeRience Study Group. Real-world effectiveness and safety of omalizumab in patients with uncontrolled severe allergic asthma from the Czech Republic. Postepy Dermatol Alergol. 2019;36(1):34–43.
47 Zhang M, Jin M, Zhou X, Lin J, Liu X, Liu C, et al. Effectiveness of omalizumab in patients with severe allergic asthma: a retrospective study in China. Respir Med. 2021 Sep;186:106522.
48 Tomisa G, Horváth A, Sánta B, Keglevich A, Tamási L. Epidemiology of comorbidities and their association with asthma control. Allergy Asthma Clin Immunol. 2021 Sep;17(1):95.
49 Juel CT-B, Ali Z, Nilas L, Ulrik CS. Asthma and obesity: does weight loss improve asthma control? a systematic review. J Asthma Allergy. 2012;5:21–6.
50 Özbey Ü, Balaban S, Sözener ZÇ, Uçar A, Mungan D, Mısırlıgil Z. The effects of diet-induced weight loss on asthma control and quality of life in obese adults with asthma: a randomized controlled trial. J Asthma. 2020 Jun;57(6):618–26.
51 González Barcala FJ, de la Fuente-Cid R, Álvarez-Gil R, Tafalla M, Nuevo J, Caamaño-Isorna F. Factores asociados con el control del asma en pacientes de atención primaria en España: el estudio CHAS. Arch Bronconeumol. 2010;46(7):358–63.
52 Mulugeta T, Ayele T, Zeleke G, Tesfay G. Asthma control and its predictors in Ethiopia: systematic review and meta-analysis. PLoS One. 2022 Jan;17(1):e0262566.
53 Miller MK, Lee JH, Miller DP, Wenzel SE; TENOR Study Group. Recent asthma exacerbations: a key predictor of future exacerbations. Respir Med. 2007 Mar;101(3):481–9.
54 Vega JM, Badia X, Badiola C, López-Viña A, Olaguíbel JM, Picado C, et al. Validation of the Spanish version of the asthma control test (ACT). J Asthma. 2007 Jan;44(10):867–72.
55 Kwon J-W, Kim S-H, Kim T-B, Park H-W, Chang Y-S, Jang A-S, et al. Relationship between asthma control test and the improvement of FEV_1 in treated patients with asthma. D39. Evaluation and monitoring of asthma and COPD. Am Thor Soc. 2012:A5751.
56 Barrecheguren M, Pinto L, Mostafavi-Pour-Manshadi S-M-Y, Tan WC, Li PZ, Aaron SD, et al. Identification and definition of asthma: COPD overlap: the CanCOLD study. Respirology. 2020 Aug;25(8):836–49.
57 Rogliani P, Ora J, Puxeddu E, Cazzola M. Airflow obstruction: is it asthma or is it COPD? Int J Chron Obstruct Pulmon Dis. 2016;11:3007–13.
58 Marcon A, Locatelli F, Dharmage SC, Svanes C, Heinrich J, Leynaert B, et al. The coexistence of asthma and COPD: risk factors, clinical history and lung function trajectories. Eur Respir J. 2021 Nov;58(5):2004656.
59 Godbout K, Gibson PG. Defining asthma-chronic obstructive pulmonary disease overlap. Immunol Allergy Clin North Am. 2022 Aug;42(3):507–19.
60 De Vries MP, van Den Bemt L, Lince S, Muris JWM, Thoonen BPA, van Schayck CP. Factors associated with asthma control. J Asthma. 2005 Jan;42(8):659–65.
61 Grosso A, Pesce G, Marcon A, Piloni D, Albicini F, Gini E, et al. Depression is associated with poor control of symptoms in asthma and rhinitis: a population-based study. Respir Med. 2019 Aug;155:6–12.
62 Gaffin JM, Castro M, Bacharier LB, Fuhlbrigge AL. The role of comorbidities in difficult-to-control asthma in adults and children. J Allergy Clin Immunol Pract. 2022 Feb;10(2):397–408.
63 Otten D, Tibubos AN, Schomerus G, Brähler E, Binder H, Kruse J, et al. Similarities and differences of mental health in women and men: a systematic review of findings in three large German cohorts. Front Public Health. 2021;9:553071.
64 Davies GA, Alsallakh MA, Sivakumaran S, Vasileiou E, Lyons RA, Robertson C, et al. Impact of COVID-19 lockdown on emergency asthma admissions and deaths: national interrupted time series analyses for Scotland and Wales. Thorax. 2021 Sep;76(9):867–73.
65 Cvietusa PJ, Goodrich GK, Steiner JF, Shoup JA, King DK, Ritzwoller DP, et al. Transition to virtual asthma care during the COVID-19 pandemic: an observational study. J Allergy Clin Immunol Pract. 2022 Jun;10(6):1569–76.
66 von Bülow A, Backer V, Bodtger U, Søes-Petersen NU, Vest S, Steffensen I, et al. Differentiation of adult severe asthma from difficult-to-treat asthma: outcomes of a systematic assessment protocol. Respir Med. 2018 Dec;145:41–7.
67 Djukanovic R, Adcock IM, Anderson G, Bel EH, Canonica GW, Cao H, et al. The severe heterogeneous asthma research collaboration, patient-centred (SHARP) ERS clinical research collaboration: a new dawn in asthma research. Eur Respir J. 2018 Nov;52(5):1801671.