Characterization of severe asthma worldwide: data from the International Severe Asthma Registry (ISAR)


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Characterization of severe asthma globally

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Characterization of severe asthma worldwide: data from the International Severe Asthma Registry (ISAR)

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**Summary conflict of interest statements**

**Eileen Wang** has received advisory board fees from AstraZeneca. She has been an investigator on clinical trials sponsored by AstraZeneca, GlaxoSmithKline, Novartis, Teva, and National Institute of Allergy and Infectious Diseases (NIAID) for which her institution has received funding.

**Michael E. Wechsler** reports receiving consulting honoraria from AstraZeneca, Boehringer Ingelheim, Genentech, GSK, Novartis, Regeneron, Sanofi and Teva.

**Liam G. Heaney** declares he has received grant funding, participated in advisory boards and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Circassia, Hoffmann la Roche, GlaxoSmithKline, Novartis, and Teva; he has taken part in asthma clinical trials sponsored by Boehringer Ingelheim, Hoffmann la Roche, and GlaxoSmithKline for which his institution received remuneration; he is the Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma which involves industrial partnerships with a number of pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffmann la Roche, and Janssen.

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Abbreviations list
ACO: asthma COPD overlap; AR: allergic rhinitis; BEC: blood; eosinophil count; BMI: body mass index; CRS: chronic rhinosinusitis; FeNO: fractional exhaled nitric oxide; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; GAR: Global Asthma Report; GINA: Global Initiative for Asthma; HCRU: health care resource utilization; ICS: inhaled corticosteroid; IgE: Immunoglobulin E; IL: interleukin; ISAR: International Severe Asthma Registry; LABA: long-acting β₂-agonist; LAMA: long-acting muscarinic receptor antagonist; LTRA: leukotriene receptor antagonist; NP: nasal polyps; OCS: oral corticosteroid; OPC: Optimum Patient Care; RCT: randomized controlled trial; SAWD: Severe Asthma Web-based Database; WHO: World Health Organization
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Abstract

Background: To date, clinical characteristics of the international severe asthma population are unknown. Inter-country comparisons are hindered by variable data collection within regional/national severe asthma registries. Our aim was to describe demographic and clinical characteristics of patients managed in severe asthma services in the USA, Europe, and Asia/Pacific region.

Methods: The International Severe Asthma Registry (ISAR) retrospectively and prospectively collected data on severe asthma patients (≥18 years old), receiving GINA Step 5 treatment or remaining uncontrolled on GINA Step 4. Baseline demographic and clinical data were collected from the U.S., UK, South Korea, Italy, and the SAWD registry (including Australia, Singapore and New Zealand) from December 2014-December 2017.

Results: 4,990 patients were included. Average age was 55.0 (SD: 15.9) years, and age at asthma onset 30.7 (SD: 17.7) years. Patients were predominantly female (59.3%), white (72.6%), had never smoked (60.5%) and were over-weight/obese (70.4%). 34.9% were on GINA Step 5. 57.2% had poorly controlled disease. 51.1% of patients were on regular intermittent OCS and 25.4% were on biologics (72.6% for those on GINA Step 5). Mean exacerbation rate was 1.7 (SD: 2.7) per year. Inter-country variation was observed in clinical characteristics, prescribed treatments and biomarker profiles.

Conclusions: Using a common dataset and definitions, this study is the first to describe severe asthma characteristics of a large cohort of patients included in multiple severe asthma registries, and to identify country differences. Whether these are related to underlying epidemiological, environmental factors, phenotype, asthma management systems, treatment access and/or cultural factors requires further study.

Key words: Biologics, co-morbidity, eosinophils, FeNO, IgE
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Introduction

Severe asthma is defined as, “asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled,’ or which remains ‘uncontrolled’ despite this therapy.” Other definitions include lack of control on maximal optimized therapy and treatment of contributory factors. Severe asthma is thought to affect approximately 5-10% of the total asthma population, although a large prevalence range (1.8 – 38%) has been reported. Severe asthma is associated with significant morbidity, mortality, and treatment, psychological, and socio-economic burdens, with much of the costs attributable to oral corticosteroid (OCS)-induced morbidity. The cost per patient of severe asthma can be ten-fold higher that of mild disease, accounting for over 60% of asthma-related healthcare costs. Many patients are unable to maintain full time employment, with a high degree of presenteeism and absenteeism reported.

The World Health Organization (WHO) emphasizes asthma’s contribution to the global symptom and economic burden and calls for “better surveillance to map the magnitude of chronic respiratory diseases and analyze their determinants... and to monitor future trends”. The Global Asthma Report (GAR) stresses the need for asthma monitoring to be ongoing, appealing for countries to conduct asthma surveillance, with regular investigation of trends.

Regional/national severe asthma registries already exist, and collect valuable country-specific data. However, they typically contain relatively small numbers, and tend to target specific subsets of severe asthma. Combining data is delayed until individual registry data are published, and hindered by different definitions used and variables collected. The International Severe Asthma Registry (ISAR; http://isaregistries.org/), the first worldwide severe adult asthma registry, overcomes some of these limitations, and answers the WHO and GAR calls to action. In partnership with national/regional registries, ISAR collects patient-level, pseudonymized, longitudinal, real-life, standardized, high-quality data, using a set of core variables, from countries across the world for ethically-approved research purposes. It contains data on a greater breadth of patients within the severe asthma definition, and has sufficient power to answer important clinical questions.
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The aim of this article is to describe the demographic and clinical characteristics of severe asthma patients managed in secondary and tertiary asthma centers in the United States, Europe, and the Asia/Pacific region, and to study inter-country differences.
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Materials & Methods

Patients
As this is an historical, registry study patients were not ‘recruited’ but rather ‘included’ into ISAR from other existing and newly created registries. ISAR essentially acts as a data custodian. Participating countries retain ownership of their own data but have agreed to provide access to, and share anonymous patient-level data with, ISAR for approved research purposes. Patient data are transferred to the ISAR database at regular intervals. Details of how data are extracted from national registries to ISAR are provided in the online supplement. A country lead has been identified for each registry and is responsible for overseeing data collection, including combining data from any satellite sites, before making the country-wide data available to ISAR. This approach, in effect, allows for the creation of a locally hosted central registry for the country’s combined data, which can be used to enhance local- and international-level research. Full details on asthma diagnostic criteria and definition of severe asthma for each of these registries is provided in the online supplement (e-Tables 1A and 1B). Patients in ISAR are aged ≥ 18 years old, received treatment at GINA Step 5, or had uncontrolled asthma at GINA Step 4 (at inclusion),\(^1,2,8\) and provided consent for their data to be included (except in the U.S. were consent was not required as data were de-identified). Smokers and those with asthma COPD overlap (ACO) were not excluded. ISAR is currently developing a protocol to identify ACO patients within its severe asthma cohort. These eligibility criteria were chosen to reflect severe asthma patients in the real-world setting and to broaden the scope to include patients with uncontrolled moderate-to-severe asthma.

Data collected
Aggregated baseline demographic and clinical data for pre-specified analyses were transferred to ISAR from secondary and tertiary severe asthma centers in the UK, Italy, South Korea and Australia. Patient level data was contributed by the US. Patients in the US registry were identified by meeting the ISAR eligibility criteria based on their diagnostic labelling medications to assess GINA Step 4- or Step-5 treatment and asthma control test score and/or pre-bronchodilator FEV\(_1\) < 80% predicted to ascertain asthma control status from their retrospective electronic medical health records. Data were collected from the
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following registries between December 2014 to December 30\textsuperscript{th} 2017: National Jewish Health Electronic Medical Record Severe Asthma Cohort (U.S., from all regions [predominantly Colorado/Wyoming] and a small proportion from other countries); the UK Severe Asthma Network and National Registry (4 sites);\textsuperscript{19} the Korean Academy of Asthma Allergy & Clinical Immunology registry (15 sites);\textsuperscript{25} the Severe Asthma Network Italy (61 sites);\textsuperscript{24} and the Australasian Severe Asthma Network’s Registry (i.e. Severe Asthma Web-based Database [SAWD], including patient data from Australia, Singapore and New Zealand, 23 sites).\textsuperscript{20}

ISAR captures 95 core variables agreed by Delphi consensus.\textsuperscript{27} Those presented in this article are summarized in e-Tables 2 and 3. Number of exacerbations was defined as the number requiring rescue systemic corticosteroids in the past 12 months. The U.S. used duration of OCS as a proxy for exacerbation (assuming 1 OCS course lasts for ≥7 days), in line with GINA 2018 recommendations, previously published research and based on discussion with the site-investigator.\textsuperscript{28,29} A retrospective analysis of NJH scripts found that most prednisolone scripts were for at least 7 days for acute use The number of hospitalization and emergency department admissions for asthma was the number in the past 12 months. The number of invasive ventilations was the number of episodes prior to data extraction. Co-morbidity was based on a formal diagnosis or reliably inferred from relevant prescription data. For the U.S. co-morbidity data was captured using ICD-10 codes for active diagnosis of comorbidity. Prescription data were used as a supplement to identify the co-morbidity status of allergic rhinitis and eczema as their active diagnosis was under-reported in the electronic medical records data. This was confirmed by the site lead and additional practitioners at the clinic. In addition to tracking regular OCS use (defined as ≥ 90 days of OCS use in a year), to capture risk for systemic corticosteroid adverse effects, intermittent OCS use was defined as the prescription for repeated OCS use and/or ≥ 2 exacerbations in a one-year period.\textsuperscript{30} Asthma control was categorized as controlled, partly-controlled or uncontrolled according to GINA criteria,\textsuperscript{28} determined using the Asthma Control Test questionnaire,\textsuperscript{31} or by the Asthma Control Questionnaire.\textsuperscript{32}

Ethics & governance
This study was designed, implemented and reported in accordance with the “European Network Centres for Pharmacoepidemiology and Pharmacovigilance study”, (EMA 2014;
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EUPAS25489), and performed in compliance with all applicable local and international laws and regulations. Governance was provided by The Anonymous Data Ethics Protocols and Transparency committee (Protocol number: 2249). All registries participating in ISAR received ethical approval in their own countries, and obtained regulatory agreement to provide de-identified data to ISAR in compliance with country-specific international data transfer laws and legislation and its relevant ethical boards and organizations. All patient-level data extracted and transferred from the U.S. were hashed and entered into the research database as anonymized patient IDs.

Statistical analysis

Data was assessed using Stata version 14 (College Station, TX, US) or SAS version 9.4/9.5 (Cary, NC, USA) according to a pre-defined data analysis plan to minimize bias. Descriptive statistics were reported as categorical variables for all variables, for the overall and country-specific patient populations. Health care resource utilization (HCRU), immunoglobulin E (IgE) count, blood eosinophil count (BEC) and co-morbidities were also stratified by severe asthma status and gender for the overall population.
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Results

Demographic characteristics

The study included 4,990 eligible patients with individual level data from the U.S. (n=3286), and aggregate data from UK (n=696), South Korea (n=439), Italy (n=310) and the SAWD registry (n=259). Patients were predominantly female, aged 55-79 years old, white, had never smoked and were overweight or obese (Table 1). South Korea had the oldest patients, the lowest prevalence of overweight/obese patients and the highest prevalence of current smokers (12.1%). Approximately 1/3 of individuals from the SAWD registry (30.0%), South Korea (33.9%) and the USA (36.8%) were ex-smokers (e-Table 4).

Clinical characteristics

Severity & lung function

Most patients had uncontrolled asthma on GINA Step 4 (Figure 1). There was a higher proportion of women in both uncontrolled GINA Step 4 (59.3%) and Step 5 patients (59.4%). Patients from the UK and Italy tended to have more severe disease and those from the U.S. and South Korea, the least severe, compared to other countries (Figure 1).

Percent predicted forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) values appeared to be independent of severity, showed some inter-country variability, and little improvement post-bronchodilator (Table 2A). The mean post-bronchodilator forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) was 0.69 (SD: 0.13) for GINA step 5 patients, and 0.71 (SD: 0.13) for those with uncontrolled asthma on GINA Step 4 (Table 2A), indicating a substantial presence of fixed airway obstruction. The % of patients with FEV₁/FVC <0.7 was 43% and 47% for GINA Step 4 and Step 5 patients, respectively. Bronchoconstriction was considered irreversible for those in both severity groups and irrespective of smoking history. Some inter-country variability was noted (Table 2B). These findings not only justify the ISAR inclusion criteria for severe asthma, but also ratify the definition of severe asthma as outlined by ERS/ATS. Incidentally, those with low or limited reversibility are routinely excluded from asthma clinical trials. The inclusive nature of ISAR, and broad definition of severe asthma means that for the first time this population can be properly studied and characterized.
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**Age of onset**
The mean age at onset was 30.7 years. 77.5% of patients developed asthma after the age of 12 years, and 34.4% developed it after the age of 40 yrs. Patients from the UK and SAWD registries developed asthma slightly earlier than this, and South Korea and Italy slightly later (Table 3 & e-Table 5).

**Asthma control, exacerbations & HCRU**
Figure 2A shows the proportion of patients with well-controlled, poorly controlled and uncontrolled asthma in the total population and also in each of the individual registries. 57.2% of patients had poorly-controlled asthma on entry to their national registry; highest in the UK and SAWD registries, and lowest in Italy and South Korea. The proportion of patients with well-controlled, partly controlled and uncontrolled asthma were similar in GINA 4 (uncontrolled at entry) and GINA 5 groups. (e-Figure 2). The mean number of exacerbations (last 12 months) was 1.7. One quarter of patients reported ≥4 exacerbations (Figure 3). This was driven by severity, with most patients uncontrolled on GINA Step 4 (at inclusion) reporting 0 exacerbations (71.1%), whereas 42.5% of GINA Step 5 patients reported ≥4 exacerbations. The mean number of exacerbations was lowest in the USA and South Korea and highest in the UK (Table 3; Figure 3). HCRU was high, highest in the UK and lowest in South Korea (Figure 4), and was slightly higher for those patients on GINA step 5 (e-Figure 3; e-Table 5).

**IgE concentration**
Half the severe asthma patient population had low IgE concentration (<150 IU/ml; Figure 5A). IgE profile varied according to severity. More patients uncontrolled on GINA Step 4 (vs GINA Step 5) had low IgE concentrations (59.4% vs 43.7%). Conversely more patients on GINA Step 5 (vs uncontrolled on GINA Step 4) had high IgE concentrations (30.6% vs 23.3%). More females had low IgE levels and more males had high IgE concentrations, irrespective of severity. Most patients from the U.S. had low IgE serum concentrations, whereas patients from the UK, South Korea and the SAWD registries showed a 50/50 split between low versus intermediate/high IgE concentrations. An even distribution of patients across the IgE concentration categories was noted in Italy (Figure 5A; e-Table 5).
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**Blood eosinophil count**
48.5% of patients had a BEC >0.3 x 10^9 cells/L. The majority of patients in the U.S., South Korea, and the SAWD registries had BEC ≤0.3, whereas the majority of patients from the UK and Italy had BEC ≥0.3 (Figure 5B).

**Fractional exhaled nitric oxide (FeNO)**
Overall, 43.1% of severe asthma patients had FeNO concentrations <25 ppb and 56.9% had a concentration ≥25 ppb. In the U.S. a similar proportion of patients had FeNO concentration <25 ppb and ≥25 ppb. Most patients from the UK, South Korea, and Italy had FeNO concentrations ≥25 ppb, whereas most SAWD patients had FeNO concentrations <25 ppb (Figure 5C).

**Co-morbidities**
Allergic rhinitis (AR) was the predominant co-morbidity (49.4%) in the total population, followed by chronic rhinosinusitis (CRS; 21.4%), eczema (9.6%) and nasal polyps (NP; 7.3%). AR was the predominant co-morbidity in all countries. The U.S. had the highest prevalence of co-morbid CRS (26.8%), SAWD had the highest eczema prevalence (20.5%), and Italy the highest NP prevalence (22.3%) (e-Table 5; e-Figure 1).

**Treatment**
51.1% of all patients (i.e. those on GINA Step 4 or Step 5) were receiving repeated intermittent OCS. Those from the UK, Italy and the SAWD registry had the highest intermittent OCS use, and the U.S. had the lowest (Table 3).

All patients with uncontrolled asthma on GINA Step 4 were taking ICS/long-acting β₂-agonist (LABA) therapy. The most common add-on to ICS/LABA was leukotriene receptor antagonist (LTRA), followed by long-acting muscarinic receptor antagonist (LAMA) and theophylline (Figure 6A). The same pattern was noted in the U.S. and UK registries. However, in South Korea theophylline is used more commonly than LAMA, and in Italy, LAMA is used more commonly than LTRA. UK had the highest proportion of patients on add-on LAMA. Add-on
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therapy was used sparingly in the U.S. for patients with uncontrolled asthma on GINA Step 4 (at baseline) (Figure 6A).

For patients on GINA step 5, add-on regular OCS was used by almost half of patients on GINA Step 5, anti-IgE and anti-interleukin (IL)-5 each used by about 1/3 of patients, and macrolides prescribed for a minority. A wide range of inter-country variability was noted for regular OCS use (Figure 6B). Overall, 72.6% of severe asthma patients on GINA Step 5 were on therapeutic monoclonal antibody therapy (i.e. biologics), with notably high rates noted in Italy and the UK, and a relatively low rate of usage in South Korea (Table 3; Figure 6B). In Italy the predominant biologic was anti-IgE, but in the UK it was anti-IL5. The U.S. differed from other countries, in having a fairly even anti-IgE/anti-IL5 split, and also the highest proportion of patients on macrolides (Figure 6B).
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Discussion

The international severe asthma population is predominantly female, overweight/obese, non-smoking and in the 55-79 year age range. These patients experience 1.7 exacerbations per year on average, have poorly- or not well-controlled asthma, a low FEV$_1$/FVC ratio, limited reversibility and high HCRU. AR is the predominant co-morbid disease. There is a fairly even proportion of patients with a low and intermediate/high serum IgE concentration and BEC. Most patients have a high FeNO concentration. Asthma treatment is severity-specific. Approximately 30% of patients are on regular OCS therapy, over 50% are taking OCS intermittently, and approximately three quarters of patients with most severe disease are on biologics.

There is substantial inter-registry heterogeneity in the clinical characteristics of patients managed within severe asthma services. More work is required to definitively explain many of these inter-country differences. We hypothesize that some of these differences may be indicative of variations in cultural and epidemiological patterns, as well as environmental pressures. Other differences could reflect country-specific system issues (e.g. differences in patient journey to severe asthma centers, selection bias, treatment landscape). Some differences may be explained by intrinsic differences in the asthma phenotype. ISAR has prioritized numerous research projects to help answer these outstanding questions such as investigating the impact of race, ethnicity and socioeconomic status on asthma outcomes, assessing variability in biologic access and use (both within and between countries), and comparing OCS use patterns around the world (http://isaregistries.org/isar-research-updates/).

South Korea had the oldest patients, the likely result of its aging population, and it has yet to experience the asthma epidemic seen in many western countries in the past decades. It has also the lowest prevalence of overweight/obese patients, perhaps due to the beneficial effect of Korean traditional diets. The high prevalence of current smokers in South Korea, is in keeping with this older population, who often have asthma chronic obstructive disease overlap, and further supported by the generally poorer lung function and less reversibility noted for these patients. The relatively late onset of asthma in South Korea may be linked to recent economic development there, and the subsequent spike in air pollution, associated
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with an increased hospital admissions for asthma. Conversely, the relatively early age of onset of asthma in the UK and SAWD registries may be a consequence of the epidemic of childhood asthma first described in the second half of the 20th century. Age of onset could have implications for response to biologic therapy; adult onset tends to do better on anti-IL-5 or anti IL-5R, and younger onset tends to respond better to anti-IgE.

Other inter-country differences noted could be the result of broad system differences. High numbers of GINA Step 5 patients in the UK and Italy may occur because patients come from tertiary asthma centers (with strict referral criteria), and so naturally have the most severe disease. The high numbers with well-controlled asthma in Italy, and the low numbers in UK and SAWD are most likely due to the fact that in Italy patients are generally follow-up patients on biologic therapy, whilst those from the UK and SAWD registries are generally pre-biologic, first visit patients. These factors also help to explain the high exacerbation rate and HCRU in the UK, coupled with the fact that at least 4 exacerbations/year is required for biologic prescription in the UK. By contrast, the high proportion of patients with well-controlled asthma in South Korea most likely reflects the rapid access to specialist care, and this, along with low cost of medications may explain the low HCRU there.

The low exacerbation rate noted in the U.S. is most likely artificial, since exacerbation data were not captured directly, but rather by-proxy and conservatively via OCS use. This is because exacerbations are rarely coded in the US registry, but rather added in the free-text box. Future work to capture this free text information, as well as co-morbidity information, is ongoing and will be provided in future analyses. In the interim these data represent a useful benchmark to assess whether proxy OCS is a good or bad indicator of exacerbation rate. Definition overlap may account for the high prevalence of CRS in the U.S. (vs AR), whereas routine nasal examination of patients in Italy may explain the high prevalence of NP noted there. The high prevalence of eczema in the SAWD registry may be accounted for by a selection bias towards atopy, a requirement for omalizumab therapy.

Inter-country differences in treatment strategies were also noted. The high OCS and biologic use in both UK and Italy, may be severity driven. Biologic treatment pattern also differed among these countries, with Italy being anti-IgE high, UK being anti-IL-5 high and the U.S.
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exhibiting an even anti IgE/anti IL-5 split. These different patterns probably reflect biologic availability or perhaps point to phenotypic differences. The high prevalence of LAMA and LTRA add-on therapy noted in the UK aligns with British Thoracic Society guideline-directed care for GINA Step 4, and is in keeping with treatment at primary care. In South Korea, high regular OCS use (for GINA Step 5) and add-on theophylline and LTRA use (for GINA Step 4) was also noted, but here the drivers may be different (e.g. patient preference for oral therapies, availability and reimbursement for these medications). Biologics are not reimbursed in South Korea and rarely used.

This first ISAR dataset also facilitates categorization and comparison of asthma biomarker phenotypes across countries. The UK and Italy appear to have a predominance of TH2-high, eosinophilic asthma, evidenced by consistently high FeNO and BEC. The earlier onset of asthma in the UK, combined with a tendency for higher IgE levels could indicate a predominance of allergic asthma, while the later asthma onset, lower IgE levels and high prevalence of NP in Italy suggests the predominance of non-allergic phenotype. Although baseline IgE levels may not predict likelihood of response to biologics, higher BEC noted both in UK and Italy do predict better response, both to anti-IgE, and to anti-IL-5/IL-5R. High exacerbation rates/year noted in both countries, and presence of NP in Italy are also factors which may predict good response to anti-IL-5 therapy. By contrast, the low BEC and low FeNO biomarker profile noted for the SAWD registry is more indicative of a predominant non-eosinophilic, TH2-low asthma population, whereas the profiles observed in the U.S. and South Korea registries are more ambiguous and could suggest a split of TH2 high and TH2-low asthma phenotypes (e-Table 5).

Merging data from pre-existing registries brought its own challenges, including inter-country variability in the type of patients included in registries and standardization of variable definitions, as well as use of retrospective data. Although there was a bias towards white patients in this first ISAR dataset, a much broader ethnic diversity is will be contained in future datasets as ISAR continues to expand into Asia, Africa and South America. A strength of this study is its size, and the fact that data collected in registries are more heterogeneous than that collected in RCTs, and more representative of patients in real-life. Use of patient level data also provides the opportunity to conduct biostatistical multivariate analyses, to
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track patient progress longitudinally, and to analyze response to treatment and changes in medical management. It is important to have both baseline and prospective data in order to describe the patient journey, to compare a baseline to a post-biologic timeline and even answer the question, “who ends up with severe asthma?”

Conclusion
This study provides the first description of an international managed severe asthma population, and facilitated a comparison of demographic and clinical characteristics across-country and health care systems. Initial country-specific biomarker profiles have been identified. Prospective data collection for the ISAR registry began in 2018 in Italy, USA, South Korea, and the UK. This will ensure better standardization of data fields, facilitating more accurate cross-country comparisons, and reducing any data incongruence in upcoming ISAR datasets.
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Acknowledgements

Author contributions
All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in data acquisition, analysis or interpretation of data, as well as the critical revision of the manuscript for important intellectual content. Development of study concept and design was undertaken by TT, LB and DB. EW, RM and DP were responsible for drafting the manuscript. LB, VC, IC, NE and NH provided additional administrative, technical and material support. The study was supervised by DP.

ISAR is conducted by Optimum Patient Care Global Limited, and co-funded by OPC Global and AstraZeneca. The ISAR steering committee comprises 43 experts in the field of severe asthma who contribute or have agreed to contribute data to ISAR. AstraZeneca has 4 members on the ISAR steering committee. All countries taking part in ISAR have 1 vote each when selecting the annual core global and prioritized research projects and AstraZeneca has a single vote OPC is responsible for database management, data processing and analyses and holds the casting vote in the event of ties.

The following individuals have contributed substantially to ISAR. US: Pearlanne Zelarney, Joy Zimmer, Juno Pak, Christena Kolakowski, Margo Brown, Jessica Cummings; Italy: Ms. Concetta Sirena; SAWD: Helen Reddel, Gregory Katsoulotos, Mariko Koh, John Upham, Ian Yang, Vicky Kritikos, Lata Jayaram, Belinda Cochrane, Connie Katelaris, Jeff Bowden, Heather Powell, Peter Wark, Janet Rimmer, Christine Jenkins, Elaine Yap, Jeffrey Garrett, Li Ping Chung, Peter Middleton, Philip Bardin, David Langton, Paul Reynolds.
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References


9. Foster JM, McDonald VM, Guo M, Reddel HK. “I have lost in every facet of my life”: the hidden burden of severe asthma. *Eur Respir J* 2017;50(3);pii 1700765.


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## Table 1: Patient demographic characteristics of all patients in the ISAR database

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%) – N=4986</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2957</td>
<td>(59.3)</td>
</tr>
<tr>
<td>Male</td>
<td>2029</td>
<td>(40.7)</td>
</tr>
<tr>
<td><strong>Age (years) – N=4967</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>55.0</td>
<td>(15.9)</td>
</tr>
<tr>
<td>18-34, n (%)</td>
<td>658</td>
<td>(13.2)</td>
</tr>
<tr>
<td>35-54, n (%)</td>
<td>1510</td>
<td>(30.4)</td>
</tr>
<tr>
<td>55-79, n (%)</td>
<td>2588</td>
<td>(52.1)</td>
</tr>
<tr>
<td>≥ 80, n (%)</td>
<td>211</td>
<td>(4.2)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%) – N=4912</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3568</td>
<td>(72.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>589</td>
<td>(12.0)</td>
</tr>
<tr>
<td>African</td>
<td>263</td>
<td>(5.4)</td>
</tr>
<tr>
<td>Mixed</td>
<td>31</td>
<td>(0.6)</td>
</tr>
<tr>
<td>Other</td>
<td>130</td>
<td>(2.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>331</td>
<td>(6.7)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²), n (%) – N=4901</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>105</td>
<td>(2.1)</td>
</tr>
<tr>
<td>Normal (≥18.5 to &lt; 25)</td>
<td>1345</td>
<td>(27.4)</td>
</tr>
<tr>
<td>Overweight (≥25 to &lt; 30)</td>
<td>1531</td>
<td>(31.2)</td>
</tr>
<tr>
<td>Obese (≥ 30)</td>
<td>1920</td>
<td>(39.2)</td>
</tr>
<tr>
<td><strong>Smoking status, n (%) – N=4947</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>294</td>
<td>(5.9)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1656</td>
<td>(33.4)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>2997</td>
<td>(60.5)</td>
</tr>
</tbody>
</table>

ISAR: Internal Severe Asthma Registry; SD: standard deviation; BMI: body mass index

* N refers to total number of patients with non-missing data
Characterization of severe asthma globally

Table 2A: Lung function for patients uncontrolled on GINA Step 4 or on GINA Step 5 included in ISAR and according to country/registry

<table>
<thead>
<tr>
<th></th>
<th>Pre-bronchodilator</th>
<th>Post-bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEV₁ (%)</td>
<td>FVC (%)</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>71.9 (15.3)</td>
<td>78.7 (14.9)</td>
</tr>
<tr>
<td>n=2801^</td>
<td>n=2936</td>
<td>n=2633</td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>72.3 (13.7)</td>
<td>78.2 (14.1)</td>
</tr>
<tr>
<td>n=2244</td>
<td>n=2382</td>
<td>n=2512</td>
</tr>
<tr>
<td><strong>UK</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>72.5 (22.3)</td>
<td>85.2 (17.8)</td>
</tr>
<tr>
<td>n=117</td>
<td>n=114</td>
<td></td>
</tr>
<tr>
<td><strong>SK</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>68.1 (20.1)</td>
<td>76.7 (18.0)</td>
</tr>
<tr>
<td>n=341</td>
<td>n=341</td>
<td>n=12</td>
</tr>
<tr>
<td><strong>IT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>74.2 (20.5)</td>
<td>91.5 (18.8)</td>
</tr>
<tr>
<td>n=99</td>
<td>n=99</td>
<td>n=109</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Pre-bronchodilator</th>
<th>Post-bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEV₁ (%)</td>
<td>FVC (%)</td>
</tr>
<tr>
<td><strong>GINA Step 5</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70.4 (19.0)</td>
<td>82.5 (17.3)</td>
</tr>
<tr>
<td>(n=1437^)</td>
<td>(n=1484)</td>
<td>(n=1045)</td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>74.9 (15.8)</td>
<td>80.1 (15.3)</td>
</tr>
<tr>
<td>(n=625)</td>
<td>(n=688)</td>
<td>(n=740)</td>
</tr>
<tr>
<td><strong>UK</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>65.2 (22.0)</td>
<td>84.5 (20.4)</td>
</tr>
<tr>
<td>(n=503)</td>
<td>(n=487)</td>
<td></td>
</tr>
<tr>
<td><strong>SK</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>68.0 (20.7)</td>
<td>77.5 (19.0)</td>
</tr>
<tr>
<td>(n=98)</td>
<td>(n=98)</td>
<td>(n=8)</td>
</tr>
<tr>
<td><strong>IT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70.7 (18.8)</td>
<td>88.3 (18.4)</td>
</tr>
<tr>
<td>(n=211)</td>
<td>(n=211)</td>
<td>(n=297)</td>
</tr>
</tbody>
</table>

FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; SK: south Korea; IT: Italy
FEV₁ and FVC: data presented as mean % predicted (standard deviation)
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% predicted data are based on aggregate level data from UK, USA, SK and IT; aggregate data for % predicted lung function was not available for SAWD patients. FEV₁/FVC is derived from patient level lung function data from USA, SK and IT.

^ N refers to total number of patients with non-missing data

*Patient-level data was used to compute FEV₁/FVC ratio; it was not available for UK; was available for 12 and 8 patients (GINA Step 4 and 5, respectively) from SK.

~Data not available for post-BD % predicted FVC for IT.
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Table 2B: Bronchodilator reversibility (%) as a function of asthma severity and smoking status for all patients included in ISAR and according to country/registry

<table>
<thead>
<tr>
<th>Country</th>
<th>GINA Step 4</th>
<th>GINA Step 5</th>
<th>GINA Step 4</th>
<th>GINA Step 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smokers</td>
<td>Non-smokers</td>
<td>Smokers</td>
<td>Non-smokers</td>
</tr>
<tr>
<td>ERS definition (change from % predicted FEV$_1$; threshold &gt;9%)$^{33}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n*=2120)</td>
<td>6.9% (6.9)</td>
<td>6.7% (7.8)</td>
<td>7.6% (8.1)</td>
<td>7.0% (8.6)</td>
</tr>
<tr>
<td>USA (n=1849)</td>
<td>7.0% (6.9)</td>
<td>6.6% (6.9)</td>
<td>7.0% (7.9)</td>
<td>6.5% (7.8)</td>
</tr>
<tr>
<td>SK (n=20)</td>
<td>6.2% (6.9)</td>
<td>5.0% (4.9)</td>
<td>4.1% (3.1)</td>
<td>9.0% (5.1)</td>
</tr>
<tr>
<td>IT (n=251)</td>
<td>7.5% (7.0)</td>
<td>9.0% (17.5)</td>
<td>9.9% (9.0)</td>
<td>7.6% (9.8)</td>
</tr>
<tr>
<td>ATS definition (change from initial FEV$_1$ (%); threshold &gt;12%)$^{53}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=2238)</td>
<td>12.0% (16.3)</td>
<td>8.2% (8.0)</td>
<td>13.2% (14.8)</td>
<td>12.0% (17.7)</td>
</tr>
<tr>
<td>USA (n=1967)</td>
<td>12.0% (16.4)</td>
<td>11.9% (17.9)</td>
<td>13.0% (15.4)</td>
<td>11.9% (17.4)</td>
</tr>
<tr>
<td>SK (n=20)</td>
<td>10.1% (11.4)</td>
<td>13.1% (22.6)</td>
<td>6.9% (5.7)</td>
<td>11.4% (7.0)</td>
</tr>
<tr>
<td>IT (n=251)</td>
<td>10.7% (9.2)</td>
<td>13.1% (22.6)</td>
<td>14.8% (13.2)</td>
<td>12.1% (18.3)</td>
</tr>
</tbody>
</table>

GINA: Global Initiative for Asthma; SK: South Korea; IT: Italy; FEV$_1$: forced expiratory volume in one second; FVC: forced vital capacity; ERS: European Respiratory Society; ATS: American Thoracic Society

Bronchodilator Reversibility (% change in lung function) are presented as mean (standard deviation) bronchodilator reversibility according to ERS/ATS definition.

* N represents total number of patients with non-missing data; includes both GINA Step-4 and Step-5 patients

*Patient-level data from USA and IT was used to compute bronchodilator reversibility (% change in lung function); it was not available for UK; was available for 20 patients from SK.
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Table 3: Demographic and clinical characteristics for all patients included in ISAR and according to country/registry

<table>
<thead>
<tr>
<th>Country</th>
<th>Mean Age, yrs (SD)</th>
<th>% Overweight/obese (95% CI)</th>
<th>Mean age of onset, yrs (SD)*</th>
<th>Mean Exacerbations/yr (SD)</th>
<th>% on repeated Intermittent OCS (95% CI)</th>
<th>% on Regular OCS (95% CI)</th>
<th>% on Biologics (Anti IgE/Anti IL-5) (95% CI)</th>
<th>% on Regular OCS (95% CI)</th>
<th>% on Biologics (Anti IgE/Anti IL-5) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (4990)</td>
<td>55.0 (15.9)</td>
<td>70.4% (69.1-71.7%)</td>
<td>30.7 (17.7)</td>
<td>1.7 (2.7)</td>
<td>51.1% (49.8-52.5%)</td>
<td>30.1% (24.5-35.7%)</td>
<td>25.4% (24.2-26.6%)</td>
<td>48.8% (38.8-58.7%)</td>
<td>72.6% (63.8-81.5%)</td>
</tr>
<tr>
<td>USA (n=3286)</td>
<td>55.5 (16.7)</td>
<td>74.2% (70.0-78.3%)</td>
<td>N/A</td>
<td>0.8 (1.6)‡</td>
<td>26.8%‡ (25.3-28.4%)</td>
<td>23.3% (21.8-24.7%)</td>
<td>16.2% (15.0-17.5%)</td>
<td>20.4% (17.5-23.2%)</td>
<td>69.8% (60.7-78.9%)</td>
</tr>
<tr>
<td>UK (n=696)</td>
<td>48.3 (14.1)</td>
<td>78.2% (74.3-82.1%)</td>
<td>25.4 (18.7)</td>
<td>5.0 (4.0)</td>
<td>100.0% (0-0%)</td>
<td>59.6% (56.0-63.3%)</td>
<td>67.3% (63.8-70.8%)</td>
<td>72.9% (69.3-76.6%)</td>
<td>82.4% (74.8-89.9%)</td>
</tr>
<tr>
<td>South Korea (n=439)</td>
<td>62.4 (14.1)</td>
<td>35.1% (30.6-39.6%)</td>
<td>41.0 (17.1)</td>
<td>1.1 (1.5)</td>
<td>48.3% (43.6-53.0%)</td>
<td>20.7% (16.9-24.5%)</td>
<td>1.4% (0.3-2.4%)</td>
<td>92.9% (87.8-98.0%)</td>
<td>6.1% (1.4-10.9%)</td>
</tr>
<tr>
<td>Italy (n=310)</td>
<td>54.5 (13.8)</td>
<td>54.6% (49.9-59.3%)</td>
<td>34.4 (17.1)</td>
<td>3.7 (7.2)</td>
<td>92.3% (89.3-95.2%)</td>
<td>63.1 (56.5, 69.1%)</td>
<td>69.3% (64.2-74.5%)</td>
<td>61.4% (54.9-68.0%)</td>
<td>100.0% (0-0%)</td>
</tr>
<tr>
<td>SAWD§ (n=259)</td>
<td>55.1 (15.3)</td>
<td>80.6% (76.9-84.3%)</td>
<td>22.7 (17.1)</td>
<td>3.3 (2.9)</td>
<td>85.3% (81.0-89.6%)</td>
<td>24.7% (19.5-30.0%)</td>
<td>17.0% (12.4-21.6%)</td>
<td>66% (56.6-75.4%)</td>
<td>45.4% (35.5-55.2%)</td>
</tr>
</tbody>
</table>
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Footnotes: * US data not available for age of asthma onset; † defined by ACT or ACQ; ‡ duration of OCS exposure used as a proxy for asthma exacerbation assuming 1 course lasts for ≥ 7 days; § Australia: n=225; Singapore: n=16; New Zealand: n=18; # GINA Step 5 (N): All (n=1740), USA (n=765), UK (n=569), South Korea (n=98), IT (n=211), SAWD (n=97).

Definitions – exacerbations: requiring rescue steroids in the past year OR defined according to duration of OCS (assume 1 course last for ≥ 7 days); Regular OCS: prescription for ≥90 days of OCS exposure in the observation year; Intermittent OCS use: prescription for repeated OCS use and/or ≥ 2 exacerbations (treated with OCS). Abbreviations: SD: standard deviation; OCS: oral corticosteroid; IgE: Immunoglobulin E; IL-5: interleukin-5; SAWD: Severe Asthma Web-based Database
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4 **Figure Legends**

5 **Figure 1:** Asthma severity distribution in the total International Severe Asthma Registry population and by country. GINA: Global Initiative for Asthma; IT: Italy; SAWD: Severe Asthma Web-based Database; SK: South Korea.

6 **Figure 2:** Proportion of patients with poorly-, not well- and well-controlled asthma in the total International Severe Asthma Registry population and by country. Control defined according to Asthma Control Test or Asthma Control Questionnaire categorizations. ACT: well-controlled: 20-25; not well controlled: 16-20; and very poorly controlled: 5-15.\(^{33}\) Asthma Control Questionnaire - well controlled: 0-0.75; grey zone: 0.75-1.5; and poorly controlled: >1.5.\(^{34}\) IT: Italy; SAWD: Severe Asthma Web-based Database; SK: South Korea.

7 **Figure 3:** Proportion of patients with 0, 1, 2, 3 and ≥4 asthma exacerbations in the last 12 months in the total International Severe Asthma Registry population and by country. An exacerbation was defined as a symptom episode requiring rescue steroids in the past year. *In the USA duration of oral corticosteroid (OCS) was used as a proxy for exacerbation (assuming 1 OCS course lasts for 7 days). IT: Italy; SAWD: Severe Asthma Web-based Database; SK: South Korea.

8 **Figure 4:** Healthcare resource utilization in the total International Severe Asthma Registry population and by country. IT: Italy; SAWD: Severe Asthma Web-based Database; SK: South Korea. HCRU data not available for U.S.

9 **Figure 5:** Biomarker distribution in the total International Severe Asthma Registry population and across countries. IT: Italy; SAWD: Severe Asthma Web-based Database; SK: South Korea. Units for blood eosinophil counts: x 10^9 cells/L.

10 **Figure 6:** Medication regimen for (A) those with uncontrolled asthma on GINA Step 4 on ICS+LABA add-on therapies and (B) those on GINA Step 5, in the total International Severe Asthma Registry population and by country. GINA: Global Initiative for Asthma; IgE: Immunoglobulin E; IL-5: Interleukin-5; IT: Italy; LAMA: long-acting muscarinic receptor antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid; SAWD: Severe Asthma Web-based Database; SK: South Korea. SAWD data not available for LAMA, LTRA (GINA step 4) or Anti-IL-5, macrolides or other steroid sparing agents (GINA Step 5).