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Longitudinal observation of severe asthma comorbidities and oral corticosteroids use from SANI and ISAR registries

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ABSTRACT

Background: The International Severe Asthma Registry (ISAR) reported a high rate of comorbidities differentially associated with clinical characteristics, biomarkers, and outcomes.

Methods: We aimed to compare the prevalences of comorbidities between global (ISARWORLD) and ITALY-derived ISAR cohorts and to explore characteristics of severe asthma (SA) patients progressively enrolled into the Severe Asthma Network Italy (SANI) registry over 5 years.

Results: T2-related SA comorbidities, including allergic rhinitis (AR), chronic rhinosinusitis (CRS) and nasal polyps (NPs) were more frequent ($p < 0.001$) in the ITALY cohort in addition to some oral corticosteroids (OCS)-related comorbidities, likely relating to the higher burden of OCS use. A comorbidity-dependent pattern of association for biomarkers and clinical outcomes with AR, CRS and NPs was identified in both ITALY-derived and ISARWORLD cohorts. In addition, a progressive decrease in the frequency of atopy, total IgE, number of exacerbations (AEs), chronic OCS treatment ($p < 0.001$) and a progressive increase in lung function and eosinophils count was reported longitudinally in the SANI registry. When stratifying by the presence of NPs, sex and smoking status, similar enrolment changes were identified with the additional findings of increased FeNO in NPs and Female cohorts and atopic eczema in smokers.

Conclusion: Longitudinal observation of enrolment characteristics from the Italian SANI registry and comparison with ISAR highlight changes influenced not only by regional population traits but also by the attitude of clinicians, biologics availability and eligibility and the OCS stewardship campaign.

Trial registration: The International Severe Asthma Registry (ISAR): EU PAS number EUPAS23651; Study ID 47596; registered April 16, 2018. Severe Asthma Network Italy (SANI): NCT number: NCT06625216. Retrospectively registered 2024-07-05.

Keywords: Severe asthma, Comorbidities, Oral corticosteroids, Registry, Longitudinal observation

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INTRODUCTION

The International Severe Asthma Registry (ISAR) is a worldwide adult severe asthma (SA) registry including over 30,000 patients from 29 countries and collecting information on comorbidities, clinical characteristics and outcomes.[1] ISAR has been developed in order to collect a standardized list of harmonized variables[2] to explore the characteristics of SA, biomarker profiles, the appropriate care of patients and the use, availability, and effectiveness of biologics.

Among the prioritized research of ISAR, analysis of comorbidities and multimorbidity in SA has been described in the PRISM I study,[3] revealing a high burden of comorbidity in SA patients. At least 1 potentially type 2–related, potentially OCS-related, and/or mimicking/aggravating comorbidity was reported in 69%, 67%, and 55% of patients, respectively, with 57% of patients having ≥3 comorbidities.

ISAR prevalence of comorbidities reflects the global prevalence of asthma comorbidities but retains the statistical power to compare across countries and regions and provide valuable country-specific information.[1] In the PRISM I study, data coming from the SANI Italian registry encompassed more than 1500 patients and some differences compared to the global ISAR population may exist.

Severe asthma is a heterogeneous disease, in which genetic and environmental aspects may determine and modify the natural history at a single patient level,[4] influencing and modifying the phenotype by endotype changing or overlap.[5] At the population level, this phenomenon is reflected by clinical, functional and biomarker trajectories[6] that may help in understanding unmet needs for disease management.[7]

The SANI Italian Registry was first set up in 2017 as a web-based prospective observatory collecting demographic, clinical, functional, and inflammatory data of patients with SA, recruited in Italian referral centres for SA.[8] The first report of demographic and clinical baseline characteristics of patients with SA was published after 2 years,[9] reporting comorbidity prevalences. Some other studies coming from the SANI network reported associations of comorbidities with demographic characteristics, biomarkers and asthma outcomes. Specifically, a focus on Chronic rhinosinusitis with nasal Polyps (CRSwNP), sex and smoking status were explored within the SANI population.[10–12]

The aim of this study is to report comorbidity prevalences and associations with SA characteristics over a long-term 5 year observation of patients included in the SANI registry. Data were compared to global ISAR PRISM I findings, in order to identify specific traits of SA SANI patients and suggest clinical and biomarker trajectories.

MATERIALS AND METHODS

Data sources and study design

General demographic and clinical characteristics of the severe asthma population and prevalence of comorbidities were retrieved from SANI and ISAR at registry enrolment from different cohorts of patients and compared. The date of the first enrolment (index date) was May 01, 2017 in all the cohorts analysed, while the last eligible enrolment date was different according to the study patient flow. The steps involved in data acquisition, including data collection, transfer and storage, quality control and management by ISAR is described in the ISAR methodology papers[1–3,13]

Prevalence of SA comorbidities was obtained from eligible patients of PRISM I study (ISAR-WORLD2023, N = 11821)[3] as well as from data drawn from the Italian ISAR cohort (ISARITALY2023, N = 1287) that were reported within the ISAR Country sub-analysis (Supplement, eAppendix 1)[3] and from additional unpublished data (PRISM – Results from the Italy-specific dataset), derived from SANI to ISAR data transfer (enrolment date at data transfer: January 2022); 18 comorbidities within available data out of 30 that were considered for the overall ISAR analysis were collected and compared. General demographic and clinical characteristics were retrieved from results published in the PRISM I study in patients eligible for assessment of

association with comorbidities (ISARWORLD2023, N = 8499 and ISARITALY2023 N = 1287). Specifically, age, gender (F/M), BMI, atopy (Positive test for allergens, Skin prik test or serum test), sensitization to perennial allergens, smoking status, age at asthma onset, early (<12 years) and late asthma onset (≥12 years), age at registry enrolment, exacerbations in the last year (AEs), asthma control, oral corticosteroid (OCS) chronic intake, treatment with biologics, lung function (FEV1% of predicted value, FEV1/FVC ratio), exhaled nitric oxide (FeNO), blood eosinophils count (B-eos), and serum total IgE were reported. According to the SANI Case Report Form (CRF), information on biologics treatment was obtained at the time of registry enrolment by collecting details of the current clinical management plan. The date of registration of the start of therapy may match the date of the visit or be earlier. If the patient has already completed a cycle of biological therapy, the end date of the cycle is also reported. Therefore, biologics initiators are individuals who started, continued or completed biologics treatment at the time of registry enrolment.

In order to evaluate the prevalence of comorbidities and associations to SA characteristics during a long follow-up period, data were retrieved from data of SANI Italian Registry published in 2019 (SANIITALY2019, N = 437, enrolment date at data transfer: March 2018) and in 2020 (SANIITALY2020NP, N = 695, enrolment date at data transfer: April 2019) (PART A). Among the SA comorbidities reported in the PRISM I study,[3] we selected those that could be retrieved from the published SANI observational studies to be compared. Data were available for 3 potentially T2-related conditions, namely allergic rhinitis (AR), atopic eczema, and chronic rhinosinusitis with nasal polyps (CRSwNP), and for bronchiectasis, the 1 available aggravating asthma comorbidity. Data on chronic rhinosinusitis (CRS), with and without nasal polyps, in the SANIITALY2019 and SANIITALY2020NP populations were retrieved from the original database as they were not included in the initial study design.

Comorbidity associations with demographic characteristics, biomarkers and asthma outcomes were further stratified according to different subcohorts of SA patients. Age, gender (F/M), atopy, age at asthma onset, oral corticosteroid (OCS) chronic intake, biologics treatment, lung function (FEV1% of predicted value, FEV1/FVC ratio), FeNO, highest B-eos, and serum total IgE were analysed according to the presence or absence of CRSwNP (SANIITALY2020NP, N = 695), sex (SANIITALY2021SEX, N = 1123, enrolment date at data transfer: October 2019) and smoking status (SANIITALY2022SMO, N = 1248, enrolment date at data transfer: May 2020) and compared to data coming from the Italian ISAR cohort (ISARITALY2023, N = 1287) and the whole ISAR population (ISARWORLD2023, N = 11821) (PART B).

Ethics

ISAR registry: the study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (EMA 2014; EUPAS44024) and with all applicable local and international laws and regulation. Registration of the ISAR database with the European Union Electronic Register of Post-Authorization studies was also undertaken (ENCEPP/DSPP/23720). ISAR has ethical approval from the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218). Governance was provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (registration number: ADEPT1121). All data collection sites in the International Severe Asthma Registry (ISAR) have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards and organizations.

SANI registry: The study was carried out according to the Helsinki and Oviedo Declaration. The SANI registry was set up according to the third edition recommendation on registries for evaluating patient outcomes published by the Effective Health Care Program of the Agency for Healthcare Research and Quality (https://effectivehealthcare.ahrq.gov/topics/registries-guide-3rd-edition/research/). The protocol was

designed following the principles and procedures of the Good Clinical Practice (ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996; Directive 91/507. EEC, The Rules Governing Medical Products in the European Community) and according to Italian law (D.L.vo n.211 June 24, 2003; D.L.n.200 November 6, 2007; MD, December 21, 2007). The study protocol was approved by local Ethics Committee of Area Vasta NORD-OVEST Toscana, Italy (Number of Protocol: 73714, December 2016). Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Statistics

In order to be comparable, all the presented results were reported as frequencies for categorical variables and as mean and standard deviation (SD) for continuous variables. For categorical variables comparison, Fisher's exact test or chi square test was used, depending on the sample size. One sample chi-square tests were applied in case of groups overlap. Results were considered statistically significant for $p < 0.05$. Analysis was performed using Graph Pad Prism software (version 9.0; GraphPad Software Inc, San 155 Diego, Calif). The association between clinical characteristics and asthma-outcomes with comorbidities was evaluated through multivariable models. Linear regression was applied for continuous variables and results expressed as estimates of differences. For binary variables, logistic regressions were used and the results expressed as odds ratios (ORs).

This Observational study follows STROBE protocols.

RESULTS

PART A

General demographic and clinical characteristics of severe asthma population at registry enrolment

A comparison of data about demographic and clinical characteristics in ISARITALY2023 and ISARWORLD2023 is reported in Table 1. In addition, data from SANIITALY2019 and SANIITALY2020NP cohorts are reported. Comparing patients enrolled in SANIITALY2019 and SANIITALY2020NP with those of ISARITALY2023, a progressive decrease in

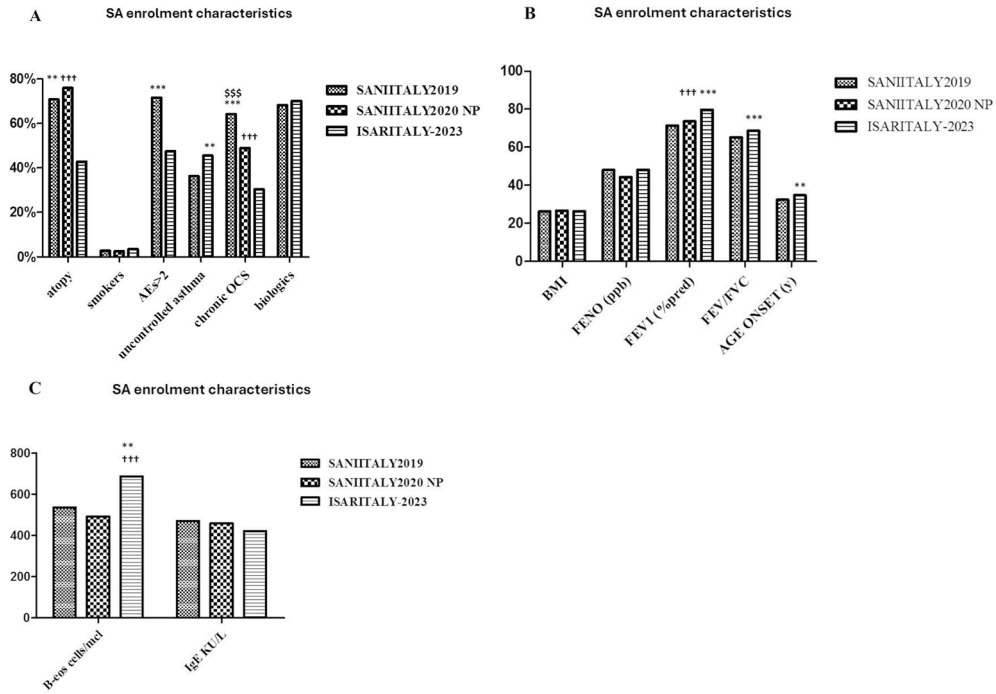

Fig. 1 **SA demographic and clinical characteristics assessment at enrollment in SANI registry over time; (A) categorical variables (B–C) continuous variables**. *$p < 0.05$ **$p < 0.01$ ***$p < 0.001$ ISARITALY2023 VS SANIITALY2019; $^{\dagger\dagger\dagger}p < 0.001$ ISARITALY2023 VS SANIITALY2020NP; $^{\$\$\$}$ $p < 0.001$ ISARITALY2020NP VS SANIITALY2019

frequency of atopy ($p < 0.001$), number of AEs in the last year ($p < 0.001$), long-term OCS treatment ($p < 0.001$) was observed as well as a progressive increase in ex-smokers ($p < 0.01$), age at asthma onset ($p < 0.01$), lung function ($p < 0.001$), and eosinophil count ($p < 0.01$). A graphical representation of parameter trajectories is shown in Fig. 1 (A-B-C). On the other hand, compared to ITALY datasets, the main differences concerning ISARWORLD2023 were higher ($p < 0.001$) frequency of atopy, active smokers, uncontrolled asthma, early onset asthma and lower ($p < 0.001$) age at asthma onset, long-term OCS use, biologics initiators as well as lower AEs numbers, eosinophils and IgE levels.

Prevalence of comorbidities of severe asthma population at registry enrolment

The prevalence of comorbidities in ISAR-ITALY2023 compared to the ISAR global population (ISARWORLD2023) is reported in Table 2. Among the potentially T2-related categories, SA patients from Italy reported a higher prevalence of CRS, NPs, allergic rhinitis ($p < 0.001$, respectively) and a lower prevalence of atopic eczema ($p < 0.001$). Higher prevalences of glaucoma ($p < 0.05$), cataracts ($p < 0.001$), and osteoporosis ($p < 0.001$) were among the potentially OCS-related comorbidities reported in comparison to the ISAR global population, whereas lower prevalences of hypertension ($p < 0.05$), anxiety/depression ($p < 0.01$), and heart failure/myocardial infarction ($p < 0.001$) were observed. 73.3% of patients reported at least 1 potentially T2-related comorbidity while 57.5% had at least 1 potentially OCS-related comorbidity, compared to 69.4% and 68.4% reported in ISAR-WORLD2023,[3] respectively. In addition, 19.8% of ISARITALY2023 patients reported 3 or more T2-related comorbidities and 9.6% reported 3 or more OCS-related comorbidities, compared to 15.6% and 23.2% respectively from ISAR-WORLD2023 (Supplemental Fig. 1A and B). Allergic rhinitis ($p < 0.001$) and atopic eczema ($p < 0.01$) were reported at higher and NP ($p < 0.01$) at lower rate in atopic patients in ISARITALY2023 (Supplementary table 1S). Prevalence of T2-related comorbidities in severe asthma patients was reported in SANI cohorts at different years of enrolment (SANIITALY2019, SANIITALY2020NP, ISARITALY2023) and compared to ISAR findings. Prevalence of AR increased over time in the ITALY registry, CRS decreased and CRSwNP remained stable, while a mild decrease in atopic eczema was reported. Compared to the ITALY registry, ISAR-WORLD2023 shows enrolment of patients with significantly lower frequencies of CRSwNP and bronchiectasis, and higher prevalence of atopic eczema (Fig. 2 and Supplemental Table 2S).

Comparison of patient biomarkers and clinical characteristics by individual comorbidity status and comorbidity count

Association between comorbidities and demographic and clinical characteristics in the

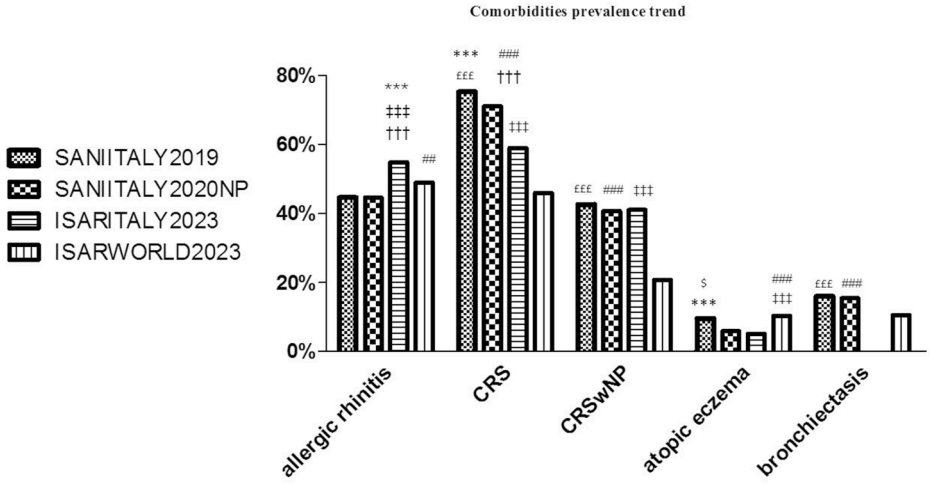

Fig. 2 Prevalence of comorbidities in severe asthma patients from SANI and ISAR registries. *$p < 0.05$ **$p < 0.01$ ***$p < 0.001$ ISARITALY2023 VS SANIITALY2019; †$p < 0.05$ ††$p < 0.01$ †††$p < 0.001$ ISARITALY2023 VS SANIITALY2020NP; ‡$p < 0.05$ ‡‡$p < 0.01$ ‡‡‡$p < 0.001$ ISARITALY2023 VS ISARWORLD2023; #$p < 0.05$ ##$p < 0.01$ ###$p < 0.001$ SANIITALY2020NP VS ISARWORLD2023; £ $p < 0.05$ ££ $p < 0.01$ £££ $p < 0.001$ SANIITALY2019 VS ISARWORLD2023; $ $p < 0.05$ $$ $p < 0.01$ $$$ $p < 0.001$ ISARITALY2020NP VS SANIITALY2019

	SANIITALY2019	SANIITALY2020 NP	ISARITALY2023	ISARWORLD2023
Enrolment May-17 (index date)	Mar-18	Apr-19	Jan-22	Jan-22
N°patients	437	695	1287	8499
Age (years)	54.1 ± 13.7	54.9 ± 16.6	55.7 ± 12.8*	54.9 ± 15.2
F/M (%)	57.2/33.8	60.6/39.4	61.2/38.8	62.4/37.6
Atopy (%)	70.7**	75.9†††	42.8	64.7$^{£\#\#\#\ddagger\ddagger\ddagger}$
Ex smokers (%)	20.1		27.0**	30.1$^{£££\ddagger}$
Active smokers (%)	2.7	2.5	3.4	5.6$^{£\#\ddagger\ddagger}$
BMI	26.2 ± 5.0	26.6 ± 16.7	26.3 ± 5.0	29.0 ± 7.0$^{\ddagger\ddagger\ddagger\#\#\#}_{£££}$
Age at asthma onset (years)	32.4 ± 17.1		34.8 ± 16.3**‡‡‡	31.9 ± 18.8
Early asthma onset (%) (<12 years)			10.2	19.1$^{\#\#\#}$
Exacerbations ≥2 (%)	71.4*** $^{£££}$		47.4‡‡‡	28.5
Asthma uncontrolled (%)	36.2		45.5**	54.7$^{£££\ddagger\ddagger\ddagger}$
FeNO (ppb)	48.0 ± 46.3	44.3 ± 48.9	48.2 ± 43.2	45.9 ± 44.8
FEV1% predicted	71.4 ± 20.2	73.6 ± 20.4	79.7 ± 21.8††† ***‡‡‡	74.7 ± 21.3$^{££}$
FEV1/FVC	0.65 ± 0.14		0.69 ± 0.12***	0.69 ± 0.12$^{£££}$
B-eos (cells/ml)	536.7 ± 650.9	492.3 ± 612.5	687.1 ± 610.7**†††‡‡‡	517 ± 514
Total IgE (kU/L)	470.3 ± 812.9	459.2 ± 850.1	422.2 ± 908.8	401 ± 828
Receiving long-term OCS (%)	64.1$^{\$\$\$}$ *** $^{£££}$	48.9$^{\dagger\dagger\dagger\#\#\#}$	30.4‡‡‡	22.9
Initiated biologics (%)	68.2$^{£££}$		70.2‡‡‡	38.2

Table 1. General demographic and clinical characteristics of severe asthma population at registry enrolment. *Continuous variables are expressed as mean ± SD; FeNO: Exhaled nitric oxide; B-eos: Highest blood eosinophils in baseline period. *p < 0.05 **p < 0.01 ***p < 0.001 ISARITALY2023 VS SANIITALY2019; †p < 0.05 ††, p < 0.01, p < 0.001 ISARITALY2023 VS SANIITALY2020NP; ‡p < 0.05, ‡‡p < 0.01, ‡‡‡p < 0.001 ISARITALY2023 VS ISARWORLD2023; $^{\#}$p < 0.05, $^{\#\#}$p < 0.01 $^{\#\#\#}$p < 0.001 SANIITALY2020NP VS ISARWORLD2023; $^{£}$p < 0.05 $^{££}$ p < 0.01; $^{£££}$ p < 0.001 SANIITALY2019 VS ISARWORLD2023; $^{\$}$ p < 0.05; $^{\$\$}$ p < 0.01; $^{\$\$\$}$ p < 0.001 ISARITALY2020NP VS SANIITALY2019*

ISARITALY2023 cohort as compared to ISARWORLD2023 are reported in Table 3. We confirmed a comorbidity-dependent pattern of association for biomarkers and clinical outcomes with T2-related comorbidities.[3] The ISARITALY2023 cohort confirmed that AR and CRS were significantly and directly related to an increase in FeNO and B-eos, and were associated with exacerbation rates. Age at asthma onset was found to be significantly inversely related to AR, and directly related to CRS, though no correlation was found with

Comorbidities	ISARITALY2023		ISARWORLD2023	
	Sample size	Prevalence	Sample size	Prevalence
Potentially T2-related comorbidities				
Allergic rhinitis	913	55%***	11281	49%
Chronic rhinosinusitis[a]	1228	59%***	11223	46%
Nasal polyposis	1261	41%***	11613	21%
Eczema/atopic dermatitis	1265	5.1%***	11600	10%
Potentially OCS-related comorbidities				
Obesity	1258	20%***	11583	42%
Hypertension	1015	20%**	9252	23%
Osteoporosis	1003	17%***	10742	13%
Anxiety/depression	1100	10%***	11019	14%
Pneumonia	1083	9.2%	10300	8.5%
Other significant infections	1176	8.1%	6918	8.1%
Diabetes	1111	5.9%***	11422	12%
Cataract	1054	5.4%***	10923	2.4%
Heart failure/myocardial infarction	865	4.7%***	11039	8.9%
Glaucoma	1021	2.1%*	10888	1.3%
Peptic ulcer	1100	1.6%*	10323	2.6%
Pulmonary embolism/venous thromboembolism	837	0.60%***	9972	2.5%
Chronic kidney disease	1107	0.54%**	11032	1.5%
Cerebrovascular accident	834	0.36%	9968	0.63%

Table 2. Prevalence of 18 comorbidities in severe asthma patients from ISAR PRISM I study. *Variations in sample size are due to missing values for individual patients.*** p-value is < 0.001; **p-value is < 0.01 *p-value is < 0.05. [a]With or without nasal polyposis*

potentially OCS-related comorbidities. In terms of estimates of differences, ISARITALY2023 differed from ISARWORLD2023 in the lack of association between eczema and higher IgE and between NP and higher FEV1, and an association between eczema and higher FEV1 was detected.

Table 4 shows the rate of comorbidities according to age at registry enrolment in the ISARITALY2023 and ISARWORLD2023 cohorts. A progressive decrease in AR and atopic eczema ($p < 0.001$) prevalence and a progressive increase in CRS, NP and OCS-related comorbidities ($p < 0.001$) were observed with increasing age at enrolment. We confirmed the association of CRS, NP and hypertension with late onset asthma (>12 years) and of eczema with early onset, nor was this the case for AR (see Supplementary Table 2S), which accounted for 56% of late-onset asthma. In

Comorbidities	Age at asthma onset (years) Difference[a] (95% CI) *p-value*		B-eos (cells/μL) Difference[a] (95% CI) *p-value*		IgE (IU/mL) Difference[a] (95% CI) *p-value*		FeNO (ppb) Difference[a] (95% CI) *p-value*	
Potentially T2-related comorbidities								
	ISARITALY2023	**ISARWORLD2023**	**ISARITALY2023**	**ISARWORLD2023**	**ISARITALY2023**	**ISARWORLD2023**	**ISARITALY2023**	**ISARWORLD2023**
Allergic rhinitis	−2.62 (−4.62; −0.61) **0.011**	−2.95 (−3.98; −1.92) **<0.001**	+136.5 (+42.7; +230.2) **0.004**	+29.5 (+1.2; +57.9) **<0.001**	+147.3 (+9.4; +285.1) **0.037**	+100.3 (+50.3; +150.2) **<0.001**	+11.7 (+1.8; +21.6) **0.021**	+5.4 (+2.1; +8.7) **0.001**
Chronic rhinosinusitis	+1.85 (+0.17; +3.54) **0.031**	+1.70 (+0.75; +2.64) **<0.001**	+275.2 (+186.9; +363.6) **<0.001**	+158.9 (+131.8; +186.1) **<0.001**	+57.6 (−77.8; +193.0) 0.405	−5.6 (−53.3; +42.1) 0.812	+22.1 (+13.7; +30.4) **<0.001**	+12.6 (+9.5; +15.7) **<0.001**
Nasal polyposis	+1.04 (−0.62; +2.70) 0.221	+1.10 (+0.12; +2.08) **0.028**	+203.5 (+113.1; +293.9) **<0.001**	+200.9 (+166.7; +235.2) **<0.001**	−117.5 (−263.0; +28.0) 0.114	−20.7 (−79.7; +38.3) 0.492	+25.5 (+17.6; +33.4) **<0.001**	+17.7 (+14.0; +21.5) **<0.001**
Eczema/atopic dermatitis	−3.32 (−7.00; +0.35) 0.077	*−3.54 (-4.97; -2.11)* **<0.001**	+101.3 (−96.6; +299.2) 0.316	+37.3 (-9.1; +83.6) 0.115	−71.4 (−382.9; +240.0) 0.653	+271.2 (+191.9; +350.4) **<0.001**	−12.4 (−31.6; +6.8) 0.205	−1.5 (−6.7; +3.7) 0.573
Potentially OCS-related comorbidities								
Obesity	+0.36 (−1.73; +2.44) 0.737	−0.66 (−1.66; +0.34) 0.193	−89.8 (−201.2; +21.6) 0.114	−63.4 (−91.2; −35.5) **<0.001**	−86.8 (−266.5; +93.0) 0.344	−47.9 (−96.8; +1.0) **0.055**	−6.3 (−16.3; +3.6) 0.211	−9.3 (−12.4; −6.2) **<0.001**
Hypertension	+0.64 (−1.73; +3.01) 0.597	+0.17 (−1.56; +1.90) 0.849	−30.2 (−156.4; +96.0) 0.640	−41.7 (−76.7; −6.7) **0.019**	−65.3 (−283.8; +153.1) 0.558	−14.7 (−82.2; 52.8) 0.669	+3.6 (−9.0; +16.2) 0.578	−7.6 (−11.7; −3.5) **<0.001**
Osteoporosis	+0.41 (−2.14; +2.96) 0.753	−0.49 (−2.09; +1.11) 0.552	+104.1 (−26.8; 234.9) 0.120	+43.2 (+1.8; +84.6) **0.041**	+103.7 (−110.9; +318.3) 0.344	+36.7 (−38.0; +111.3) 0.336	+0.1 (−13.5; +13.6) 0.992	−3.9 (−8.8; +0.9) 0.114
Anxiety/depression	−1.56 (−4.49; +1.37) 0.297	−0.87 (−2.39; +0.65) 0.261	+19.2 (−130.3; +168.7) 0.801	−43.7 (−80.4; −7.0) **0.020**	−52.4 (−289.5; +184.7) 0.665	−51.4 (−118.7; +15.8) 0.134	−11.4 (−26.1; +3.4) 0.131	−5.8 (−10.0; −1.5) **0.008**

Comorbidities	Receiving long-term OCS OR[b] (95% CI) *p-value*		Exacerbation rates Ratio of means[c] (95% CI) *p-value*		Post-bronchodilator FEV1%pred. Difference[a] (95% CI) *p-value*		Uncontrolled asthma OR[b] (95% CI) *p-value*	
Potentially T2-related comorbidities								
	ISARITALY2023	**ISARWORLD2023**	**ISARITALY2023**	**ISARWORLD2023**	**ISARITALY2023**	**ISARWORLD2023**	**ISARITALY2023**	**ISARWORLD2023**
Allergic rhinitis	1.56 (1.15; 2.10) **0.004**	0.97 (0.86–1.10) 0.653	1.54 (1.24; 1.91) **<0.001**	1.12 (1.04–1.21) **0.003**	+4.47 (+0.65; +8.28) **0.022**	+3.16 (+2.02; +4.30) **<0.001**	0.95 (0.69; 1.30) 0.755	0.95 (0.83–1.09) 0.436
Chronic rhinosinusitis	1.61 (1.24; 2.09) **<0.001**	1.46 (1.30–1.64) **<0.001**	1.34 (1.11; 1.62) **0.002**	1.29 (1.21–1.38) **<0.001**	+1.29 (−2.08; +4.67) 0.453	+2.22 (+1.14; +3.30) **<0.001**	1.28 (0.97; 1.69) 0.082	0.91 (0.79–1.03) 0.140
Nasal polyposis	1.42 (1.11; 1.81) **0.006**	1.40 (1.22–1.60) <**0.001**	1.13 (0.94; 1.36) 0.179	1.16 (1.07–1.25) **<0.001**	−0.24 (−3.55; +3.08) 0.889	+1.86 (+0.45; +3.27) **0.010**	0.97 (0.74; 1.28) 0.835	0.91 (0.78–1.06) 0.222
Eczema/atopic dermatitis	0.70 (0.39; 1.28) 0.247	0.87 (0.71–1.06) 0.172	1.08 (0.73; 1.59) 0.699	1.11 (0.99–1.23) 0.072	+7.34 (+0.26; +14.42) **0.042**	+1.80 (−0.09; +3.68) 0.062	1.50 (0.83; 2.73) 0.179	1.22 (0.99–1.51) 0.063
Potentially OCS-related comorbidities								
Obesity	0.72 (0.52; 0.99) **0.044**	1.12 (1.00–1.27) 0.057	0.92 (0.74; 1.15) 0.463	1.04 (0.97–1.11) 0.254	−2.44 (−6.41; +1.54) 0.230	−0.52 (−1.61; +0.57) 0.347	1.16 (0.83; 1.60) 0.383	1.47 (1.29–1.69) **<0.001**
Hypertension	0.97 (0.68; 1.39) 0.886	1.33 (1.13–1.56) <**0.001**	1.51 (1.14; 1.98) **0.004**	1.15 (1.03–1.28) **0.015**	−5.09 (−10.12; −0.06) **0.048**	−2.64 (−4.08;-1.20) **<0.001**	1.76 (1.17; 2.65) **0.007**	1.38 (1.15–1.65) **<0.001**
Osteoporosis	2.87 (2.00; 4.11) **<0.001**	2.77 (2.35–3.27) **<0.001**	1.69 (1.28; 2.23) **<0.001**	*1.61 (1.45–1.79)* <**0.001**	−1.29 (−6.14; +3.56) 0.601	−3.42 (−5.06;-1.77) **<0.001**	0.95 (0.63; 1.43) 0.793	1.29 (1.05–1.57) **0.015**
Anxiety/depression	2.46 (1.64; 3.70) **<0.001**	1.42 (1.21–1.66) **<0.001**	1.98 (1.45; 2.71) **<0.001**	*1.40 (1.28–1.54)* <**0.001**	−0.60 (−6.33; +5.14) 0.838	−0.74 (−2.21; +0.73) 0.326	1.42 (0.87; 2.31) 0.157	1.68 (1.40–2.02) **<0.001**

Table 3. Association between comorbidities and asthma clinical characteristics and biomarkers in patients with severe asthma. *p values statistically significant are reported in bold.* [a]*Difference Estimates and 95% confidence intervals comparing patients with the respective comorbidity to those without it, adjusted for country, age at registry enrolment, and sex. Estimates were derived from linear regressions using absence of the considered individual comorbidity as the reference and adjusting for country, age at registry enrolment and sex.* [b]*Ods ratios and 95% confidence intervals comparing patients with the respective comorbidity to those without it, adjusted for country, age at registry enrolment, and sex (logistic regressions).* [c]*Comparing patients with the respective comorbidity to those without it, adjusted for country, age at registry enrolment, and sex (negative binomial regressions)*

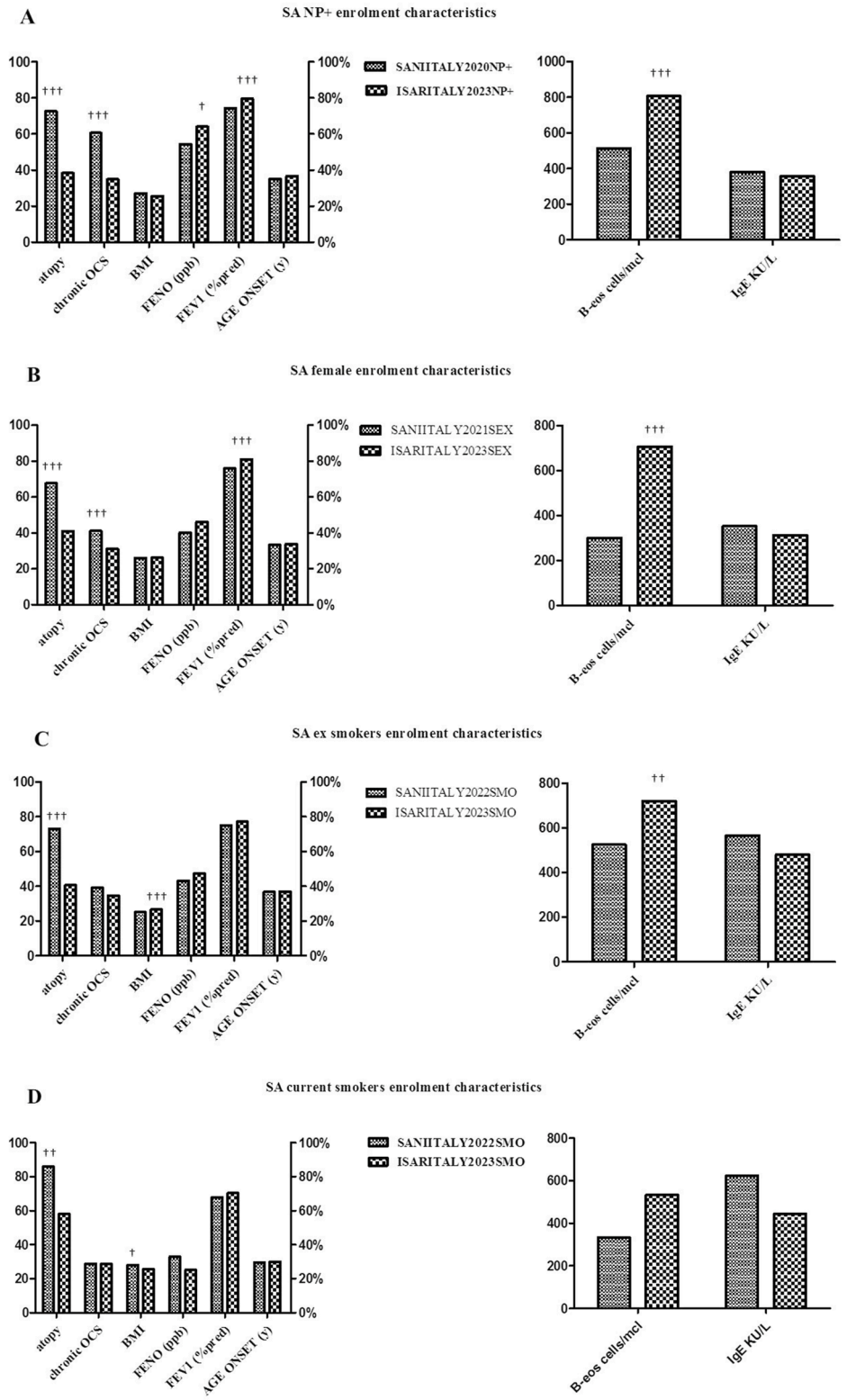

Fig. 3 **SA demographic and clinical characteristics assessment at enrollment in SANI registry over time by Chronic rhinosinusitis with nasal polyps (A) female SEX (B) and smoking habit: ex (C) and current smokers (D)**. $^{\dagger}p < 0.05$ $^{\dagger\dagger}p < 0.01$ $^{\dagger\dagger\dagger}p < 0.001$.

ISARWORLD2023 Comorbidities	Age (years) <40	40-49	50-59	60-69	70+	p value[c]
Potentially T2-related categories						
Allergic rhinitis	56%	55%	48%	46%	40%	**<0.001**
Chronic rhinosinusitis[a]	39%	44%	48%	50%	40%	**0.082**
Nasal polyposis	20%	22%	26%	21%	15%	**<0.001**
Eczema/atopic dermatitis	16%	11%	7.8%	8.4%	7.6%	**<0.001**
Potentially OCS-related comorbidities						
Obesity	35%	41%	43%	43%	38%	**0.007**
Hypertension	5.0%	13%	20%	29%	40%	**<0.001**
Anxiety/depression[b]	12%	11%	15%	16%	16%	**<0.001**
Osteoporosis	3.4%	4.5%	11%	17%	21%	**<0.001**
ISARITALY2023	Age (years)					
Comorbidities	**<40**	**40-49**	**50-59**	**60-69**	**70+**	**P value[c]**
Potentially T2-related categories						
Allergic rhinitis	64%	56%	56%	54%	44%	0.049
Chronic rhinosinusitis[a]	47%	55%	64%	60%	57%	0.010
Nasal polyposis	34%	40%	46%	41%	35%	0.029
Eczema/atopic dermatitis	13%	2.5%	5.3%	4.0%	3.7%	<0.001
Potentially OCS-related comorbidities						
Obesity	12%	16%	22%	24%	21%	0.022
Hypertension	3.9%	5.0%	18%	31%	36%	<0.001
Osteoporosis	3.2%	8.8%	15%	27%	28%	<0.001
Anxiety/depression[b]	3.1%	7.7%	10%	14%	13%	0.008

Table 4. Prevalence of the most common comorbidities by age at registry enrollment. *Abbreviations: OCS: oral corticosteroids.*p *values statistically significant are reported in bold.* [a]*With or without nasal polyposis.* [b]*Can also mimic/aggravate asthma.* [c]*Kruskal-Wallis rank sum test comparing age distributions in patients with versus without comorbidity*

the multivariable model (see Supplementary Table 3S), atopy was negatively associated with worse asthma control and a higher age at asthma onset, both as continuous and categorical variables ($p < 0.001$). Atopy was also positively associated with biologic use, but not with worse lung function, more exacerbations, or OCS use (see Supplementary Table 4S).

PART B

Characteristics of severe asthma population stratified by CRSwNP, sex and smoking status

CRSwNP

Data of patients with SA and comorbid CRSwNP (NP+) was obtained from 3 cohorts: SANIITALY2020NP, ISARITALY2023 and ISARWORLD2023. When comparing SANIITALY2020NP with ISARITALY2023, patients with comorbid NP did not differ in terms of age, sex, BMI, or age of onset over time. A significant disparity in enrolment was observed in the decrease of atopy, numbers of AEs, chronic OCS intake, and atopic eczema ($p < 0.001$), as well as in an increase of FeNO ($p < 0.05$), lung function and B-eos ($p < 0.001$). (Supplemental Table 5S). A graphical representation of major parameter trajectories is reported in Fig. 3 (A)**.** Compared to ITALY registries, ISARWORLD2023NP + reported more allergies, uncontrolled asthma and atopic eczema ($p < 0.001$), less biologics initiation ($p < 0.001$) and lower age at asthma onset, FEV1 and B-eos ($p < 0.01$), and exacerbations ($p < 0.05$) while not differing in the other characteristics.

Sex

Data on patients with SA and sex was obtained from 3 cohorts: SANIITALYSEX2021, ISARITALY2023 and ISARWORLD2023 (Supplemental table 6S). When looking at the enrolment of female patients over time (SANIITALYSEX2021 vs ISARITALY2023), the most appreciable change was observed in a decrease in AEs number ($p < 0.01$), atopy and OCS intake ($p < 0.001$), as well as in an increase of FeNO ($p < 0.01$), lung function and B-eos ($p < 0.001$). No change was observed for age at asthma onset and total IgE levels. A graphical representation of parameter trajectories is shown in Fig. 3 (B). Compared to ITALY registries, ISARWORLD2023 female patients differed in terms of increased atopy, smoking habit, BMI, uncontrolled asthma, and atopic eczema, and lower age at asthma onset, exacerbation rate, OCS intake, and comorbid NPs. The ratio of biologics initiation in females was comparable to that of the general SA population.

Smoking status

Data on patients with SA and smoking status was obtained from 3 cohorts: SANIITALYSMO2022, ISARITALY2023 and ISARWORLD2023 (Supplemental Table 7S). When comparing SANIITALYSMO2022 with ISARI TALY2023, a general overlapping aspect of clinical and bio-humoral characteristics was observable, apart from a lower frequency of atopy ($p < 0.001$) and allergic rhinitis ($p < 0.05$) in ISARITALY2023 and higher prevalence of atopic eczema among current smokers ($p < 0.001$). A graphical representation of parameter trajectories is shown in Fig. 3 (C-D). The characteristics of ISARWORLD2023 smokers compared to the ITALY cohorts encompassed those observed in the whole population (PART A, Table 2): namely, increased BMI and uncontrolled asthma and lower rates of AEs, B-eos, OCS and biologics were reported. Finally, the differences among ex and current smokers, as reported in paper by Caminati et al,[12] were confirmed in ISARITALY2023 and ISARWORD2023, including a lower age of onset in current smokers.

DISCUSSION

This longitudinal retrospective study demonstrates the differences in comorbidity frequency and clinical phenotype between patients in the International Severe Asthma Register (ISAR) and the Italian Severe Asthma Register (SANI). The trajectories of comorbidities reflect changes in the phenotypes and therapeutic opportunities of patients in the registries. Severe asthma registries have been set up in order to collect standardized variables about clinical characteristics, comorbidities, biomarkers and patient outcomes through prospective observational studies, therefore enrolling consecutive new patients that fulfil the inclusion criteria and updating data collected during regular follow-up visits. ISAR is a multicountry registry project collecting shared standardised anonymous patient-level, longitudinal, real-life data from 29 participating worldwide registries.[13] Up to 24 studies have been published since ISAR's inception, leading to a better understanding of severe asthma epidemiology across countries and regions[14] and facilitating phenotyping and endotyping by the burden of

illness and comorbidities,[3] biomarker expression[15] and lung function trajectories.[16]

PRISM I study[3] reported a high prevalence of comorbidities and multimorbidity among the adult SA patients clustered in potentially type 2–related, potentially OCS-related, and or mimicking or aggravating asthma. In addition, the presence of specific comorbidities was significantly associated with asthma clinical characteristics and outcomes. A significantly different comorbidity pattern resulted from the ITALY cohort and the whole ISAR2023 population, with a predominance of some T2-related (AR, CRS and NP) and a lower prevalence of some T2 low associated comorbidities (obesity, hypertension, cardiac disease). These results may reflect particular regional genetic and clinical traits of the Italian population.[17] On the other hand, the high prevalence in the ITALY cohort of some OCS-related comorbidities, such as osteoporosis and glaucoma, may reflect the higher OCS burden.[18] T2 comorbidities are generally associated with higher biomarkers, but differentially to SA age onset. We reported that age at asthma onset was significantly inversely related to allergic rhinitis and atopic eczema and directly to CRS and NPs. Moreover, a progressive decrease in AR and atopic eczema prevalence and a progressive increase in CRS, NP and OCS related comorbidities was observed with increase of age enrolment. Although AR is typically a feature of early-onset asthma, we found it in more than 50% of cases of late-onset asthma. This finding may be partly explained by the existence of a mixed phenotype characterised by an initial period of long-standing mild-to-moderate allergic asthma, followed by a severe intrinsic (eosinophilic) phenotype in which sensitization to aeroallergens can be clinically irrelevant.[19] On the other hand, it is possible co-existence of T2-high clusters with T2 low clinical traits.[15,20] It is likewise confirmed that both T2- and OCS-related comorbidities are related to worse clinical and functional outcomes, consistent between World and ITALY cohorts.

SA Patients are progressively enrolled into the registry[8,13] according to eligibility criteria defined by SA international guidelines.[21] We here reported a progressive increase in the number of patients in the SANI registry from the first enrolment (May-2017) to 437 (2018), 695 (2019) and 1287 (2023) that follows a parallel change in clinical characteristics of enrolment. First, we observed a decrease in the proportion of patients who had atopy with lower total IgE levels, better lung function and fewer exacerbations. These aspects reflect the inclusion in SANI of «milder » patients, who can access biologics without being allergic. At the beginning of the biologic era, anti-IgE treatment drew attention towards the allergic severe asthma phenotype[22] that often included early-onset patients, with a long history of the disease, use of OCS and obstructive function. In the following years, criteria to offer biologics expanded to include non-atopic, late-onset, less severely functionally compromised patients including those characterized by the refractory eosinophilic phenotype.[23] Accordingly, the proportion of patients with raised basal B-eos (>300 cells/μl) has grown over time alongside sustained numbers with SA and concomitant NPs. CRSwNP is significantly more prevalent in the Italian SA population[10] than the ISAR cohort, impacting significantly on phenotype, outcomes and costs.[24] An intense focus has been placed by clinicians, through a multidisciplinary approach, on the SA and NPs association, leading to great attention in diagnosis and management.[25] The increase of late-onset eosinophilic patients in the registry, often with NPs, follows the availability of anti-IL5/IL5R therapeutic strategies.[26] A decrease in atopy, number of AEs, and an increase of FeNO, lung function and B-eos was observed within the SA population with comorbid NPs, reflecting the general criteria of enrolment mentioned above. The decrease in the proportion of patients with atopy may reflect the inclusion of patients who can access biologics regardless of allergy status in the SANI registry. These data are consistent with an increase in the number of patients with a late-onset, less severe, non-atopic, refractory eosinophilic phenotype. Atopy plays a key role in determining comorbidities in severe asthma. Interestingly, clinical signs of rhinitis are often observed in patients who are not atopic. It is possible that non-allergic rhinitis (NAR) could be misclassified as AR due to nasal hyperresponsiveness, which is a clinical feature of patients with both conditions.[27] In addition, allergy tests could not cover enough potential allergens to detect allergen sensitization.

SA Patients enrolled in SANI are progressively less OCS dependent, leading to a halving of the use of OCS. A great effort has been established to alert clinicians to the short and long-term side effects of chronic systemic corticosteroid treatment in asthma.[28] This may reflect the efficacy of the OCS stewardship campaign,[18,24,29] although disproportionate OCS use, even in mild asthma, remains significant in practice.[30] Moreover, our study found that 1 year of observation could influence the use of OCS (from 64.1% to 48.9%). This suggests that referring patients for a specialist assessment as part of a personalized asthma action plan can help with OCS stewardship.[31,32] Disseminating knowledge about patients, clinical and system barriers to reducing the use of oral corticosteroids (OCS) in patients with severe asthma, and raising awareness of OCS tapering strategies and the dose-sparing effects of add-on biologics represents a multidimensional approach to OCS stewardship from the perspectives of patients and healthcare professionals.[33] Due to a lack of available data, we were unable to capture changes in corticosteroid-related manifestations over time in this report. An interesting point to consider is whether reducing OCS use over time reflects a lower prevalence of OCS-related comorbidities. We observed a similar proportion of long-term OCS use, but a higher prevalence of OCS-related comorbidities, in ISARWORLD2023 compared to SARSANI2023. As the prevalence of uncontrolled asthma and atopy are higher and the use of biologics in ISARWORLD2023 is lower, we hypothesise a more frequent use of OCS bursts in this population, leading to long-term comorbidities.[34] Actually more than 2 out of 3 SA patients have access to biologics in SANI cohorts, in line with an appropriate phenotyping. This proportion is maintained on for SA with NP+ in ISARWORLD2023, indicating a recognized comorbid trait responsive to biologics.[35]

The global SA population from ISAR looks different to the Italian population. In terms of comorbidities, a high global prevalence of atopic eczema is reported, reflecting a very high prevalence in some countries. On the other hand, the ITALY cohort's low prevalence is in line with that of other Mediterranean countries ([3], eSupplement). Interestingly, eczema appears to be positively associated with smoking in ITALY cohorts, confirming some other epidemiologic studies,[36] as well as with female gender. Some other studies concerning comorbidity data from Regional SA registries, focusing on some relevant aspects such as obesity,[37] never specifically compare regional data with those from an International Registry.

Other distinctive characteristics of the global SA population are the lower AEs rate and use of OCS, but also the greater proportion of uncontrolled SA patients. This is not surprising, and it reflects the tendency of progressively treating patients that do not reach control despite optimization of co-factors, even if the rate of AEs is not so high.

In conclusion, the longitudinal observation of enrolment characteristics in the registry of severe asthma patients over 5 years highlights the changes in clinicians' comprehension of the disease. The impact of SA comorbidities may be influenced by regional population traits, the attitude of clinicians to investigate, availability and required prescription criteria of biologics and the OCS stewardship campaign. This knowledge may be useful in implementing the search for personalized medicine in SA guided by treatable traits, and in identifying the way to overcome the barriers to achieving remission.[38]

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Author contributions

GG, GS, DF, VC, EH, DP, GWC, FB, PP, MC, FLMR, GIS: conception and design.
GG, GS, DF, software, data analyses and drafting the manuscript.
GG, GS, DF, VC, EH, DP, GWC, FB, PP, MC, FLMR, GIS: drafting and data curation.
GG, GS, DF, EH, DP, GWC critical revision and editing.
GG, GS, DF have directly accessed and verified the underlying data reported in the manuscript.
All authors have read and agreed to the published the final version of the manuscript.

Ethics statement

ISAR registry: the study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (EMA 2014; EUPAS44024) and with all applicable local and international laws and regulation. Registration of the ISAR database with the European Union Electronic Register of Post-Authorization studies was also undertaken (ENCEPP/DSPP/23720). ISAR has ethical approval from the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218). Governance was provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (registration number: ADEPT1121). All data collection sites in the International Severe Asthma Registry (ISAR) have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards and organizations.
SANI registry: The study was carried out according to the Helsinki and Oviedo Declaration. The SANI registry was set up according to the third edition recommendation on registries for evaluating patient outcomes published by the Effective Health Care Program of the Agency for Healthcare Research and Quality (https://effectivehealthcare.ahrq.gov/topics/registries-guide-3rd-edition/research/). The protocol was designed following the principles and procedures of the Good Clinical Practice (ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996; Directive 91/507. EEC, The Rules Governing Medical Products in the European Community) and according to Italian law (D.L.vo n.211 24 June 2003; D.L.n.200 6 November 2007; MD, 21 December 2007). The study protocol was approved by local Ethics Committee of Area Vasta NORD-OVEST Toscana, Italy (Number of Protocol: 73714, December 2016). Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Declaration of competing interest

GG reports a fee as a speaker for AstraZeneca, Menarini, all outside of the submitted work; GS is a consultant for Observational and Pragmatic Research Institute (OPRI). OPRI conducted this study in collaboration with Optimum Patient Care, a co-funder of the International Severe Asthma Registry. DF is an employee of Optimum Patient Care (OPC). OPC is a co-funder of the International Severe Asthma Registry. FB reports financial grants from AstraZeneca, Chiesi Farmaceutici S.p.A and Insmed Inc.; consulting fees from Menarini and Zambon; speaker fees from AstraZeneca, Chiesi Farmaceutici S.p.A, Glaxo Smith Kline, Guidotti, Grifols, Insmed Inc., Menarini, Novartis AG, Sanofi-Genzyme, Viatris Inc., Vertex Pharmaceuticals, and Zambon outside the submitted work. EH declares grants paid to his Institution from Chiesi; consulting fees from Apogee Therapeutics, Bosch Healthcare, Celltrion Healtcare, GSK, Regeneron, Chiesi, Almirall, Sanofi; payment for lectures, presentations, speakers bureaus, manuscript writing or educational events from Astrazeneca, GSK, Chiesi, Sanofi, Lofarma, Orion Pharma, Gentili; support for attending meetings and/or travel from Astrazeneca and GSK; personal fees for participation on a Data Safety Monitoring Board or Advisory Board from Astrazeneca, Sanofi, Regeneron, GSK, Novartis, Allergy Therapeutics, Celltrion Healthcare, Blueprint Medicines. PP reports grants for educational events from AstraZeneca, Chiesi Farmaceutici, Glaxo Smith Kline, Guidotti and Sanofi; grants for participation to Advisory Board from Chiesi Farmaceutici, Glaxo Smith Kline, and Sanofi outside the submitted work. VC is an employee of Optimum Patient Care (OPC). OPC is a co-funder of the International Severe Asthma Registry. MC declares financial grants from AstraZeneca, GSK, and Sanofi; consulting fees from AstraZeneca; honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, and GSK. FLMR reports grants, personal fees, and other compensation from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, and Novartis, and personal fees and grants to support scientific research from Sanofi; GS declares financial grants from AstraZeneca, GSK, Novartis, and Sanofi; and fees for Advisory Board from AstraZeneca, GSK, Novartis, and Sanofi. DP has advisory board membership with AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Viatris, Teva Pharmaceuticals; consultancy agreements with AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Viatris, Teva Pharmaceuticals; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Chiesi, Viatris, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, and UK National Health Service; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Inside Practice, GlaxoSmithKline, Medscape, Viatris, Novartis, Regeneron Pharmaceuticals and Sanofi Genzyme, Teva Pharmaceuticals; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Novartis, Medscape, Teva Pharmaceuticals.; owns 74% of the social enterprise Optimum Patient Care

Ltd (Australia and UK) and 92.61% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); is peer reviewer for grant committees of the UK Efficacy and Mechanism Evaluation Programme, and Health Technology Assessment; and he was an expert witness for GlaxoSmithKline. GWC reports research grants, honoraria for lectures, and advisory board fees from from A. Menarini, Allergy Therapeutics, AstraZeneca, Chiesi Farmaceutici, Faes, Firma, Glaxo Smith Kline, Guidotti-Malesci, Hal Allergy, Innovacaremd, Novartis, OmPharma, RedMaple, Sanofi-Aventis, Sanofi-Genzyme, Stallergenes-Greer, Uriach Pharma, ThermoFisher, Valeas outside the submitted work.

Submission declaration

The manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

Use of generative artificial intelligence (AI) and AI-assisted technologies

Nothing to disclose

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2026.101345.

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