Received: 20 November 2021 | Revised: 5 May 2022 | Accepted: 19 May 2022

DOI: 10.1111/all.15466

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

ORIGINAL ARTICLE

Different aspects of severe asthma in real life: Role of *Staphylococcus aureus* enterotoxins and correlation to comorbidities and disease severity

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Abstract

Background: Asthma, with several phenotypes and endotypes, is considered particularly suited for precision medicine. The identification of different non-invasive biomarkers may facilitate diagnosis and treatment. Recently, Staphylococcus aureus and its enterotoxins (SE) have been found to have a role in inducing persistent type 2 airway inflammation in severe asthma, but also in such comorbidities as chronic rhinosinusitis with nasal polyposis (CRSwNP).

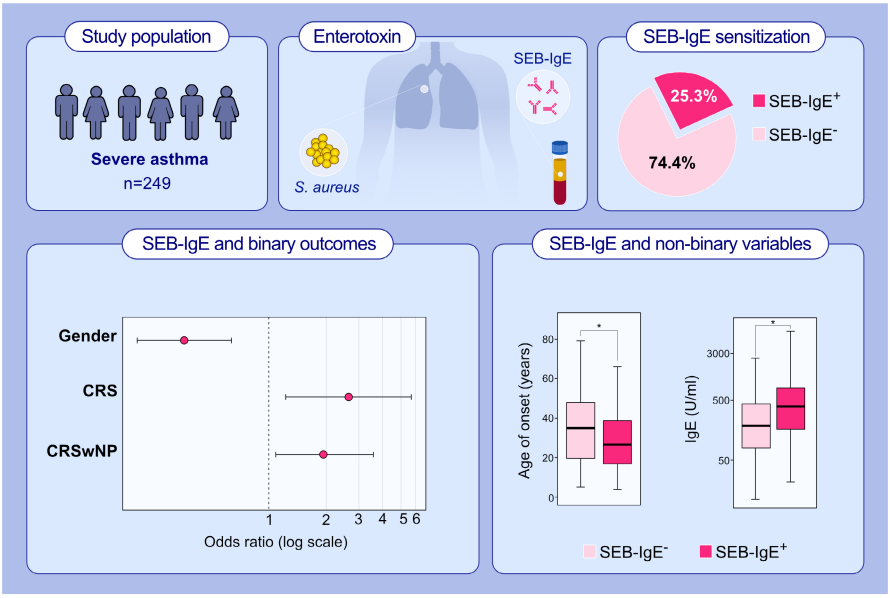
Methods: The aim of this retrospective study was to evaluate the prevalence of SE-IgE sensitization in a multicentric Italian cohort of severe asthmatic patients and correlate it with demographic and clinical characteristics.

Results: A total of 249 patients were included in the analysis, out of which 25.3% were staphylococcal enterotoxin B (SEB)-IgE positive. We found a meaningful association

between SEB-IgE and female gender, a positive association was also measured between CRS and CRSwNP. No significant association was found between SEB-IgE sensitization and atopy, the occurrence of exacerbations and corticosteroid dosages. In the SEB-IgE-positive patient, blood eosinophil count does not appear to be correlated with the severity of the disease. Patients with SEB-IgE sensitization are, on average, younger and with an earlier disease onset, thus confirming the possibility to consider SEB-IgE sensitization as an independent risk factor for developing asthma.

Conclusions: Our data confirm that the search for SE in the initial screening phase of these patients is helpful to better phenotype them, may predict the evolution of comorbidities and lead to a targeted therapeutic choice; in this point of view this represents a goal of precision medicine.

KEYWORDS
biologicals, nasal polyposis, severe eosinophilic asthma, *Staphylococcus aureus* enterotoxins, type 2 inflammation



GRAPHICAL ABSTRACT
In patients diagnosed with severe asthma in Italy, the presence of enterotoxin sensitization for Staphylococcus appears to be an independent variable related to the development of comorbidities.

1 | INTRODUCTION

The heterogeneity of asthma with several phenotypes and endotypes is considered particularly suited for precision medicine. It is important to underline that sensitization to allergens should be assessed individually, and that the presence of atopic status should always be taken into consideration.[1] The identification of different non-invasive biomarkers may facilitate diagnosis and treatment. Type 2-high and type 2-low inflammation distinguishes the main subtypes of immune responses driving asthma.[2]

Patients with severe eosinophilic asthma can experience recurrent asthma exacerbations, even when treated with high doses of inhaled corticosteroids (ICS) and controllers such as long-acting bronchodilators, leukotriene receptor antagonists, and oral corticosteroids (OCS) (SANI population 2020).[3] It is still unclear if the expression of type2 biomarkers is different in severe early-onset asthma (SEA) and severe adult-onset asthma (SAA).[4] Recent observations and associations increasingly point to *Staphylococcus aureus* and its proteins as inducers of persistent type 2 airway inflammation. The association between severe asthma and the presence of serum IgE to staphylococcal enterotoxins (SEs) has been proved by several studies.[5] IgE to SEs could be a result of a polyclonal activation without a concrete clinical relevance. However, many recent studies suggest that *S. aureus* could actively induce

type 2 immune responses and profit from them, allowing for persistence. Bachert et al. demonstrated that sensitization to SEs occurred in 21% of severe asthmatic patients previously considered non-atopic.[6] Moreover, the relationship between nasal *S. aureus* colonization and asthma prevalence in adult patients has been shown by a recent meta-analysis.[7]

The prevalence of specific SE-IgE (≥0.10 kU/L) is approximately 40%–75% in patients with asthma, and SE-IgE levels are associated with high IgE in eosinophilic asthma.[6,8]

Due to the increasing number of biologic therapies available for the treatment of severe asthma, accurate phenotyping is becoming more and more relevant. The response to anti IL-5 biologics does not seem to be equal in every patient. Some patients show complete asthma control ("super responders"), whereas others experience residual disease manifestations ("partial responders") or show no improvement or even clinical worsening ("nonresponders").[9]

Nonetheless, the atopic status of the subject may complicate the scenario. The role of allergy in severe asthma is still under debate. There is increasing evidence for the important, but not exclusive, role of allergy in severe asthma, but if atopic sensitization is critical in determining the severity of disease in childhood disease, other interacting factors, such as virus infections, pollution, smoking, and work-related exposures, could contribute to severity in older patients. The differential diagnosis is typically performed on the basis of the presence or absence of sensitization to allergens, as the eligibility for an anti-immunoglobulin E (IgE) therapy is partially based on sensitization to perennial aeroallergens.[10]

Recently, a cluster analysis of patients with chronic rhinosinusitis with nasal polyps (CRSwNP) reported that both IL-5-positive clustering and SE-IgE-positive clustering were important factors for eosinophilic inflammation when asthma was included in the analysis as a comorbidity.[11] The occurrence of CRSwNP may be driven by superantigens. They have a bypass process of antigen-presenting cells (APCs), which directly connect with major histocompatibility II (MHC II). This helps colonization and alters the host immune response. Once activated, T cells will produce interleukins, such as IL-4, IL-5, IL-13, and eotaxin, which may lead to severe eosinophilic inflammation and local IgE production.[12] CRSwNP is commonly associated with adult early-onset asthma (onset 18–39 years of age) or adult late-onset asthma (onset after 40 years of age) and is not usually linked with childhood asthma. On the contrary, CRSsNP has been associated with childhood-onset asthma (onset before 16 years of age) and with adult early-onset asthma (onset before 40 years of age).[13–15] Staphylococcal enterotoxins A and B and toxic shock syndrome toxin-1 (TSST-1) may modify the severity of airway inflammation, and their specific role leads to more severe clinical symptoms also in patients with aspirin-exacerbated respiratory disease (AERD).[16]

The clinical differences presented by patients sensitized to SEA and by those sensitized to SEB are probably given to the fact that the homology of their amino acid sequences is only 31% and their mechanisms of binding to MHC class II molecules are different; SEA is Zn++- dependent and SEB is metal-independent.[17] Therefore, the immune behavior of each of the SEs must be studied and assessed individually.

The aim of the current real-life study was to gain data on sensitization in patients with SA who had tested negative to aeroallergens in previous tests—that is, patients being managed in clinical practice, in order to evaluate the prevalence of SE-IgE and the association with such comorbidities.

2 | METHODS

The inclusion criteria applied for the study were as follows: adult age, a former diagnosis of asthma (according to Global Initiative for Asthma [GINA] guidelines), negative tests for perennial aeroallergens by skin prick tests, RAST, or both.

Atopy was determined based on the results obtained with skin prick testing and/or sIgE to common aeroallergens, as follows: pollens (Cupressus arizonica, Platanus acerifolia, Olea europaea, Lolium perenne, Artemisia vulgaris, Salsola kali, Parietaria judaica) house dust mites (Dermatophagoides pteronyssinus, Dermatophagoides farinae), animal dander (dog, cat), and molds (Aspergillus fumigatus, Alternaria alternata, Cladosporium herbarum, Candida albicans). Skin prick test results were considered positive when a wheal diameter ≥3 mm was obtained in comparison with the negative control (normal saline) in the presence of a positive control (10 mg/ml histamine) An sIgE value ≥0.35 kU/L was considered positive.[18] According to guidelines, all patients have been initially tested for reversibility with bronchodilator and or methacholine.

As for comorbidities, patients who had nasal and/or sinusal symptoms have been evaluated by an ENT specialist, to confirm or exclude the presence of CRS and nasal polyps. Second level assessments (nasal endoscopy and TC scan) have been performed as per clinical practice, upon ENT request, according to EPOS guidelines.[19]

According to previous real-life experience in Europe, it was calculated that 300 patients could be an appropriate sample for the aim of this survey in Italy. Participants were part of the Severe Asthma Network in Italy (SANI) population from nationwide distributed centers (Genoa, Milan, Catania, Cagliari, Verona, Rome). Fondazione Policlinico A. Gemelli Ethic Committee approved the study. Informed consent has been obtained by patients.

We retrospectively analyzed the following patient characteristics and parameters at baseline and at the last available follow-up: gender, age, underlying eosinophilic diseases, smoking status, body mass index, peripheral blood eosinophil count, serum IgE, serum SE-IgE level, fractional exhaled nitric oxide (FeNO), Asthma Control Test (ACT) score, pulmonary function test results [forced volume capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC, and FEV1%], GINA step, history of previous or ongoing biological treatment, daily systemic corticosteroid maintenance therapy, number of asthma exacerbations requiring systemic corticosteroids, hospitalization and/or ER access, duration of asthma disease. In patients with CRSwNP and CRSsNP, SNOT-22 questionnaire was also performed. The FeNO level was measured using a

NIOX VERO® analyzer (Aerocrine AB) according to the American Thoracic Society/European Respiratory Society recommendations at a 50 ml/s flow rate.

Sensitization to SE was defined as a specific IgE level greater than 0.35 kU/L, even if some reports used 0.1 KU/L as the lower limit in a particular population.[6]

2.1 | Statistical analysis

Statistical analysis was performed using the software package R (4.1.3 release).[20] Data were tested for normality using a visual inspection of the QQ-Plot, followed by a Shapiro–Wilk test (data not shown). Continuous variables were expressed as mean with standard deviation and/or median with interquartile range (IQR). Group differences were analyzed using the student's t-test or Wilcoxon rank-sum test according to the results of the normality assessment. Tests' results were superimposed on the boxplot analysis of the data. On some occasions, box plots have been presented together with the corresponding marginal plots for clear visualization of the data distribution. Categorical variables were expressed as percentages and/or counts and group differences were analyzed using chi-squared or Fisher's exact tests. Data visualization was carried out using the package ggplot2 of the software package R. Odd ratios and the corresponding confidence intervals were computed from the results of a univariate logistic regression using the function glm of the software package R. For greater clarity, odds ratios are represented in a logarithmic scale. Correlations between variables were evaluated with Spearman's correlation coefficients. The strength of correlation was judged using correlation coefficients of >0.90 as very strong correlation, 0.70–0.89 as strong correlation, 0.40–0.69 as moderate correlation, 0.10–0.39 as weak correlation, <0.1 as negligible correlation, as used in other similar immunological studies.[21] Correlations were visualized using Correlation heat maps calculated with the package corrplot implemented in the software R.[22,23] Only the significant correlations were represented on the computed correlation maps ($\alpha = 0.05$).

3 | RESULTS

3.1 | Association between asthma and SEB

Here, we investigate whether the presence of SEB-IgE sensitization can be associated with clinical and demographic features of severe asthma patients. Baseline and clinical parameters of patients are summarized in Table 1 for SEB-IgE positive (SEB-IgE+) and negative (SEB-IgE−), separately.

A total of 249 subjects were included in the analysis, out of which 25.3% [95% CI 19.9–30.6] were SEB-IgE-positive.

The association between SEB-IgE and selected binary outcomes is shown in Figure 1 in terms of odds ratios and confidence intervals. We found a significant association [OR = 0.35 95% CI 0.20–0.62] between gender (female vs. male) and SEB-IgE; a positive association was also measured between SEB-IgE sensitization and CRS [OR = 2.65 95% CI 1.22–5.71] and between

TABLE 1 Laboratory and clinical caratheristics of the recruited patients in Italy stratified according SEB sensitization

	SEB−			SEB+			*p*
	n (%)	Median	IQR	*n* (%)	Median	IQR	
Age	186 (73)	51	18	63 (25)	44	22.5	0.019
FEV1% (T0)	163 (64)	78	22	60 (23)	82	25.25	0.029
FEV1% (T6)	21 (8)	73	21	7 (3)	68	8.5	0.73
Disease duration	156 (61)	16	18.25	62 (24)	10	11.75	0.16
Onset age	131 (51)	35	28	54 (21)	27	21.25	0.021
Snot 22 (T0)	84 (33)	55.5	46.25	33 (13)	72	46	0.54
Snot 22 (T6)	55 (21)	30	22	22 (9)	36.5	35.5	0.28
ACT (T0)	62 (24)	15	9.75	22 (9)	14	11.25	0.64
ACT (T6)	25 (10)	20	4	6 (2)	20.5	3.25	0.6
ACT (T24)	4 (2)	24	0.25	0 (0)	NA	NA	NA
IgE	109 (43)	190	348	45 (18)	390	613	0.00074
BEC	170 (66)	540	527.5	59 (23)	410	486	0.23
FeNO	84 (33)	62	54.28	27 (11)	78	51.1	0.12
Vitamin D	28 (11)	26.2	17.92	11 (4)	27	14	0.61
BMI (T0)	37 (14)	26	6.2	20 (8)	22.84	4.27	0.0051
BMI (T6)	15 (6)	23.3	5.85	4 (2)	22.45	1.85	0.52

Abbreviations: BEC, blood eosinophil count; SEB−, staphylococcal enterotoxin B-negative patients; SEB+, staphylococcal enterotoxin B-positive patients; T0, baseline; T24, 24 months after starting therapy; T6, six months after starting therapy.

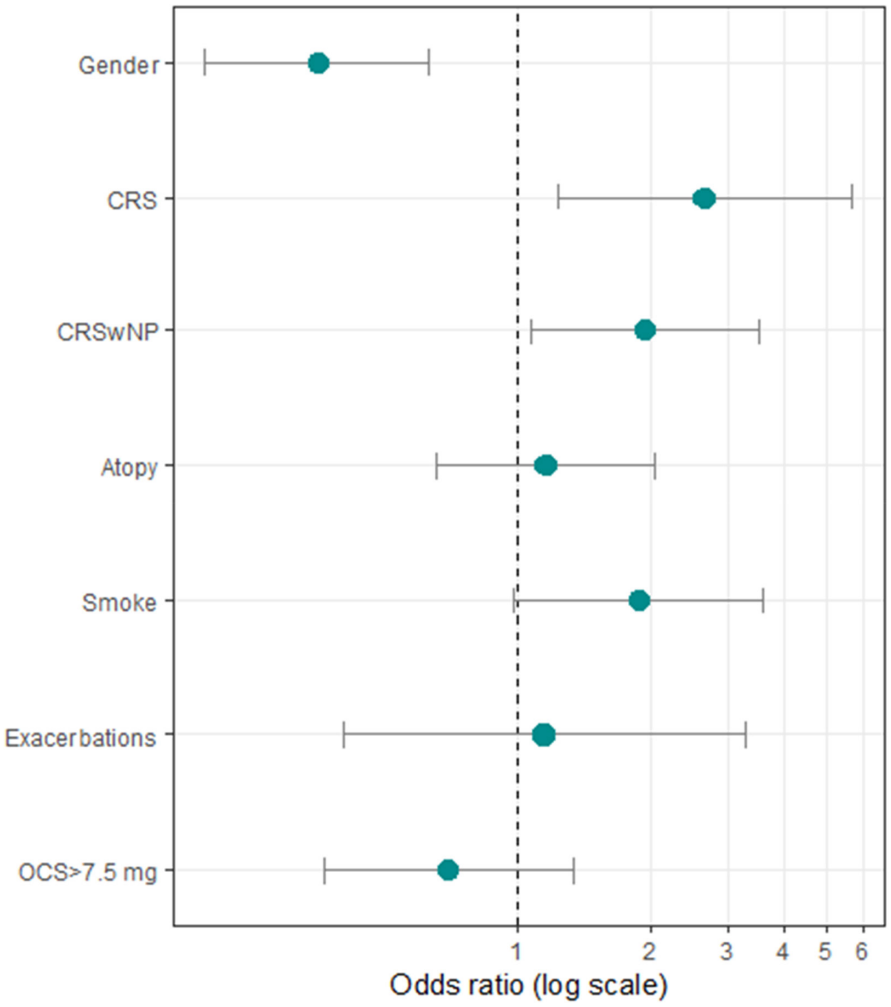


FIGURE 1 Odds ratio analysis for the presence of enterotoxin B-specific IgE (SEB-IgE) in patients with severe asthma.

SEB-IgE sensitization and CRS with Nasal Polyp [OR = 1.98 95% CI 1.08–3.52]. A suggested (but slightly not significant) increase in the odds for a smoker to be diagnosed with SEB-IgE sensitization [OR = 1.9, 95% CI 0.98–3.60] was also observed and further commented in the discussion section. No significant association was found between SEB-IgE sensitization and atopy, the occurrence of exacerbations, and a high dosage of corticosteroids (prednisone >7.5 mg/day).

Figure 2A investigates the presence of correlations among selected non-binary clinical and demographical variables in the entire recruited population. To provide a more in-depth understanding of the role of SEB-IgE sensitization, the same analysis was carried out on SEB-IgE-positive (2b) and SEB-IgE-negative (2c) patients, separately. In the entire population (2a), a moderate negative correlation is observed between FEV1 values and asthma severity (ρ = −0.53; p = 6e-14). Additional weak negative correlations were measured between Age and FEV1% (ρ = −0.21; p = 3.87e-03), FEV1% and duration of the disease (ρ = −0.28; p = 1.47e-04), and FEV1% and number of exacerbations (ρ = −0.38; p = 2.87e-07). Weak positive correlations were reported between Age and GINA Step (ρ = 0.27; p = 2.54e-04), Age and duration of the disease (ρ = 0.18; p = 1.75e-02), step and number of exacerbations (ρ = 0.30; p = 5.68e-05), and between blood eosinophil count (BEC) and number of exacerbations (ρ = 0.19; p = 1.30e-02).

For SEB-IgE patients (Figure 2B), a similar situation was observed, with some notable differences, that is, (i) the arising of a weak and negative correlation between FEV1% and BEC (ρ = −0.20; p = 2.60e-02), which was absent in the entire population (2a) and in the SEB-IgE-negative subjects (2c); (ii) a strengthening of the positive correlation between BEC and asthma severity, as evaluated by step (ρ = 0.40; p = 3.28e-06), which is also not observed in Figure 2C.

In Figure 2D–F, we report a Box plot analysis of selected demographic and clinical parameters in SEB-IgE-positive and SEB-IgE-negative patients. Significant differences were reported in Age (p = 0.019), Age of the onset (p = 0.021), and IgE levels (p = 0.00074). Data are summarized in Table 1 in terms of the number of subjects, median values, and IQRs.

3.2 | Possible predictors and risk factors for severe asthma

In order to highlight possible factors with a significant association with severe asthma, we divided recruited patients into two groups:

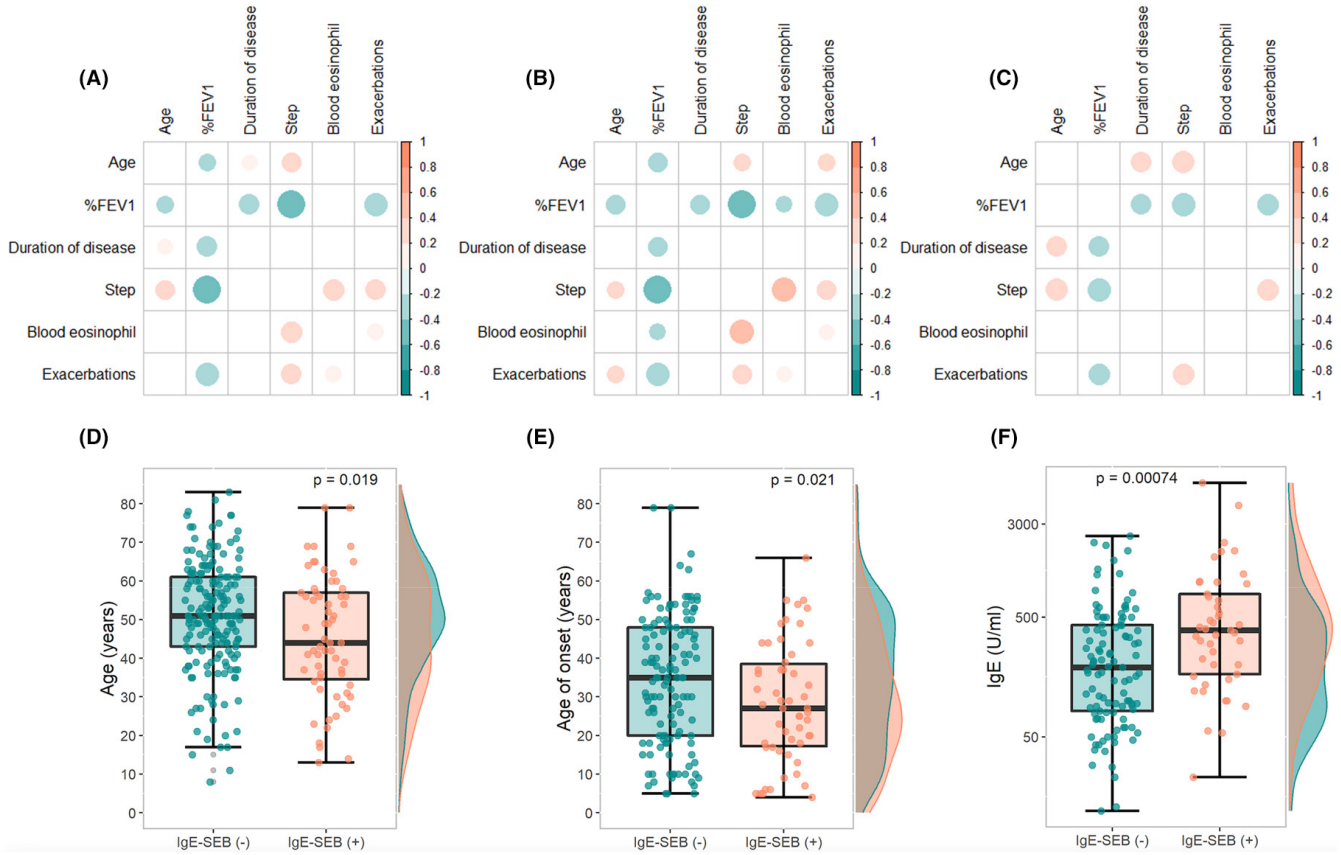


FIGURE 2 Relationship between SEB-IgE sensitization and selected non-binary variables. (A) Correlogram among parameters measured on the entire population, (B) SEB-IgE negative and (C) SEB-IgE positive patients. Boxplot data analysis of (D) patient age, (E) age of onset and (F) IgE level

those diagnosed with severe asthma (step = 5) and those found in less severe conditions (step<5).

Figure 3 shows the presence of a significant and positive association between severe asthma and the presence of CRS with Nasal Polyps [OR = 1.93; 95% CI 1.15–3.24], and an expected positive and significant association between the severity of the disease and the occurrence of at least 1 exacerbation in the last year [OR = 3.23 95% CI 1.21–8.66].

Notably, no relevant association was found between SEB-IgE sensitization and severe asthma, a result that is commented more in-depth into the discussion section. In addition, we noticed a strong and significant positive association between asthma severity and high corticosteroids dosages (>7.5 mg) necessary to control advanced disease stages [OR = 2.34; 95% CI 1.43–3.83].

Figure 4 shows that, on average, patients with severe asthma are older (p = 7.7e-6, Figure 4A) and with a longer duration of the disease (p = 0.016, Figure 4B) than those in milder conditions. It can be interesting to notice that BEC arises higher in patients with severe asthma than in their counterparts (p = 4.4e-6, Figure 4C). Consistently to Figure 3, no statistically significant differences were found between the proportion of SEB-IgE-positive patients with and without severe asthma (4d), while relevant differences in the distribution of the number of exacerbations during the last year are reported (Figure 4E). Additionally, we confirm that the presence of nasal polyps has significantly increased in the severe asthma population (Figure 4F), as well as in the population with higher blood eosinophils (Figure 4G). These data are summarized in Table 2.

Ultimately, in Figure 5, we analyze possible factors associated with a high dosage of corticosteroids. For this purpose, we stratified the population into two groups, using daily prednisone =7.5 mg as a cutoff. A remarkable difference is found with regard to the duration of the disease: the higher the dosage, the longer the duration of the disease (p = 0.0072).

4 | DISCUSSION

The prevalence of SE-IgE sensitization in our cohort of patient is consistent with the values reported by Tomassen et al. in a large-scale study based on a random sample of approximately 3000 subjects, where a prevalence of 29.3% was observed [95% CI 26.8–31.8][24] and in close agreement with Tanaka et al.[17] that presented a prevalence of 24.2%. In agreement with previous findings, we also found a significant association between female gender and SEB-IgE.

There was not enough statistical data to point out the presence of a significant association between smoking status and SEB-IgE sensitization. The latter finding also agrees with previous data,[24] where statistical significance is reached only after thresholding the

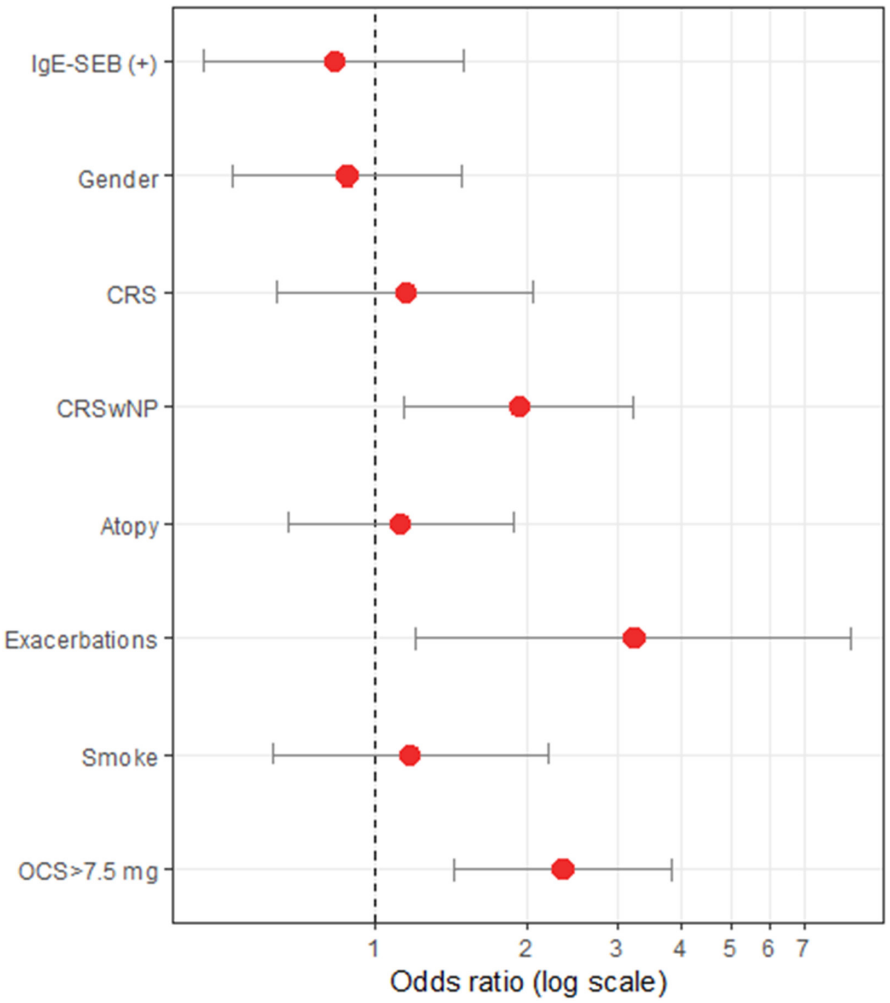


FIGURE 3 Odds ratio analysis for the severity of asthma (Step = 5) in patients with severe asthma

population according to the number of cigarette packs/year (>15 for statistical significance), highlighting a dose-dependent relationship between the two variables.

A qualitative analysis of Figures 1B,C shows very similar outcomes, with some remarkable differences. Before discussing in greater detail the remaining correlation matrices, a caveat is necessary. The significance of a correlation coefficient depends on the strength of the correlation and the sample size. Therefore, the appearance of a significant correlation in the two subpopulations that was absent in the entire population is likely to be more meaningful than its disappearance, as the latter could arise solely because of the reduction of data points. Interestingly, in the SEB-IgE-positive population, BEC does not appear to be correlated with the severity of the disease, suggesting that SEB-IgE may be a possible independent factor in the clinical outcome of asthmatic patients.

Moreover, patients with SEB-IgE sensitization are on average younger and with an earlier disease onset, thus confirming the possibility to consider SE-IgE sensitization as an independent risk factor for developing asthma. Additionally, according to several previous studies, SEB-IgE-positive patients have, on average, higher total IgE blood levels.

Despite the retrospective design of the study did not allow consistent outcome speculation, some interesting suggestions could come from shown data.

The response rate to biological therapy was not an outcome of the study; however, not all the patients evaluated in this retrospective study reported the same response rate to various biologics. For example, some of them did not show a brilliant response after omalizumab or after benralizumab or mepolizumab, especially those who had nasal polyposis. It could be hypothesized that such asthma patients are not *IL-5 positive* with CRSwNP but are *SE-IgE-positive*, and this is the reason why their response to anti IL-5 treatments was not complete. In this way, patients sensitized to SEs could be potential candidates to anti-IgE monoclonal antibodies or others. Indeed, several studies have shown the efficacy of anti-IgE treatment also in patients with non-allergic asthma, who responded to add-on omalizumab therapy, with significant improvements in symptom control, quality of life, lung function, and asthma exacerbation rate.[25] Furthermore, a recent study has shown the efficacy of omalizumab in non-atopic patients with nasal polyps and asthma comorbidity, most of whom were positive for SE-IgE.[26]

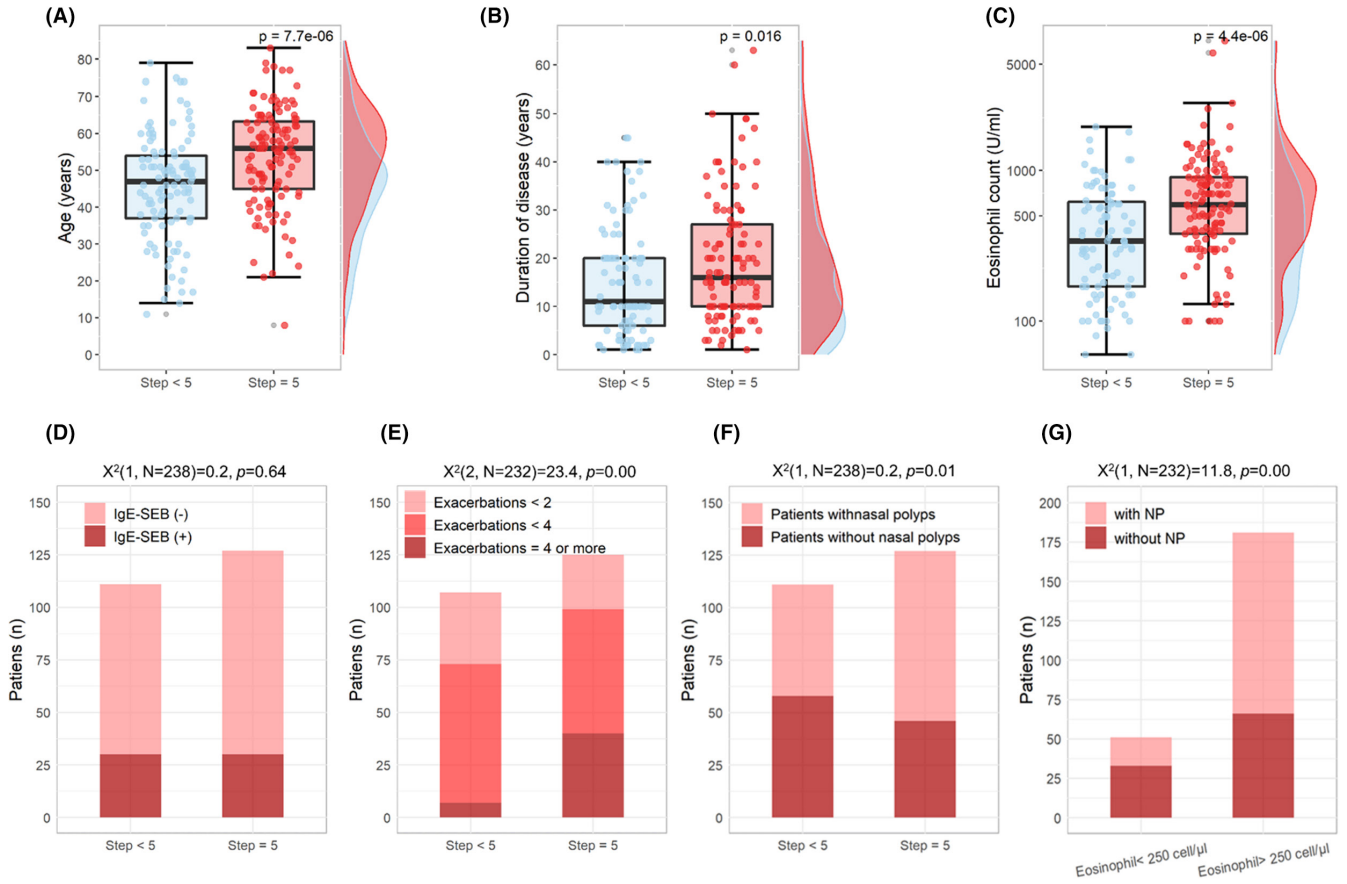


FIGURE 4 Relationship between severity of asthma and selected variables. Boxplot data analysis of (A) patient age, (B) duration of disease and (C) peripheral blood eosinophil count in patients with severe (Step = 5) and less severe (Step < 5) asthma. Stacked barplot revealing the number of patients, grouped by the severity of asthma, which show the presence of (D) SEB- IgE (E) exacerbations and (F) nasal polyps. (G) Number of patients, grouped by the eosinophil count, which show the presence of nasal polyps

TABLE 2 Laboratory and clinical caratheristics of the recruited patients in Italy stratified according to disease severity

	Step < 5			Step = 5			
	n (%)	Median	IQR	*n* (%)	Median	IQR	*p*
Age	109 (46)	47	17	124 (52)	56	18.25	7.70E-06
FEV1%	98 (41)	85.5	16	115 (48)	70	23	5.00E-11
Disease duration	94 (39)	11	14	112 (47)	16	17	0.016
Onset age	94 (39)	29	26.5	79 (33)	37	29.5	0.15
Snot 22 (T0)	37 (16)	52	33	79 (33)	60	51	0.48
Snot 22 (T6)	4 (2)	20	8	73 (31)	31	24	0.32
ACT (T0)	21 (9)	13	5	62 (26)	16	10	0.064
ACT (T6)	8 (3)	20	2.5	23 (10)	21	5.5	0.15
IgE	68 (29)	232	447.75	84 (35)	242.5	336.75	0.86
BEC	96 (40)	340	448.75	122 (51)	595	520	4.40E-06
Exacerbations	107 (45)	2	1	125 (53)	2	2	0.00011
FeNO	35 (15)	73.2	52.15	75 (32)	62	58.05	0.16
Vitamin D	20 (8)	31.5	16.5	18 (8)	24.95	11.25	0.15
BMI (T0)	27 (11)	25.26	5.82	28 (12)	24.1	6.63	0.79
BMI (T6)	4 (2)	21.22	8.99	15 (6)	23.3	5.4	0.23

Abbreviations: BEC, blood eosinophil count; T0, baseline; T6, six months after starting therapy.

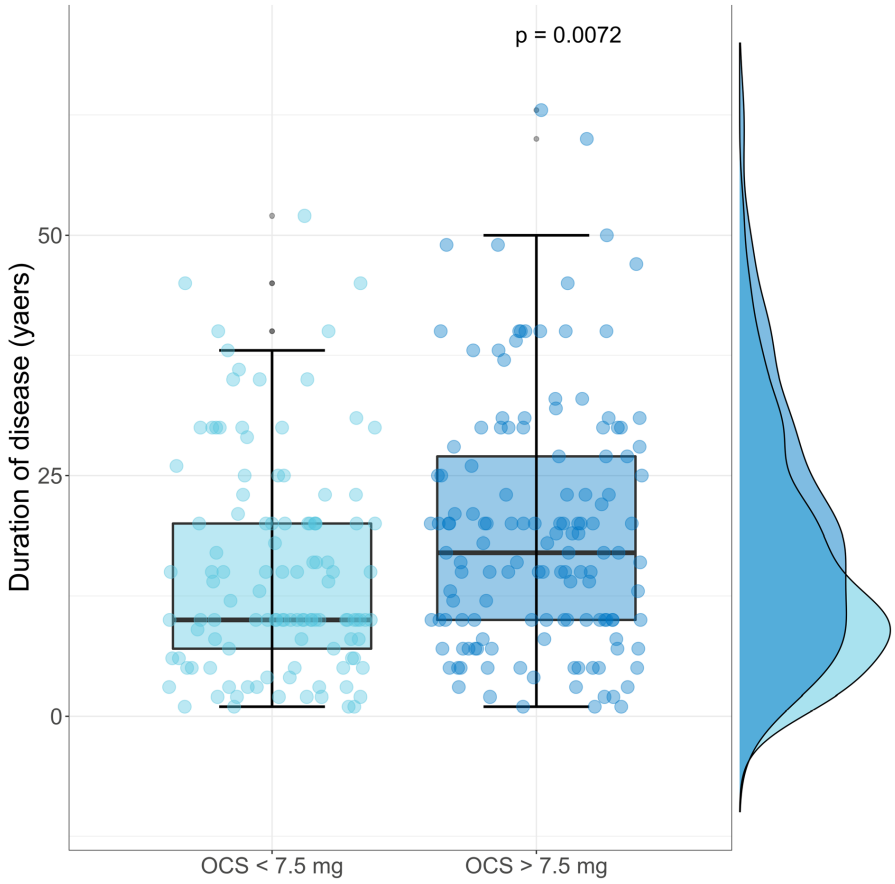


FIGURE 5 Relationship between oral corticosteroids (OCS) and duration of disease in patients treated with more (>7.5 mg) and less (<7.5 mg) than 7.5 mg of prednisone.

5 | CONCLUSIONS

Our data confirm that the search for SEBs in the initial screening phase of severe asthmatic patients could be not only helpful to better phenotype patients but may predict the evolution of comorbidities, leading to a better therapeutic choice, thus increasing precision medicine.

Perspectively, these data could be interesting for new biological therapies indication and patient selection. In fact, recent approaches have demonstrated that Staphylococcus aureus, regardless of enterotoxins production, may damage the airway epithelial cells, thus inducing the release of the alarmins IL-25, IL-33 and thymic stromal lymphopoietin (TSLP), which in turn can activate the type-2 innate lymphoid cells (ILC2) involved in IL-5 mediated eosinophilic inflammation. On the contrary, it is not surprising that the interest toward epithelial barrier damage has been already evaluated in other settings, beyond respiratory diseases. In fact, other evidence pointed out the role of staphylococcal colonization in skin diseases such as atopic dermatitis, but also in non T2 diseases.[27,28]

These findings showcase the value of severe asthma networks to gather real-world experience (RWE) data and to extrapolate the results of randomized controlled trials (RCTs) to multifaceted patient populations, confirming or refuting the effectiveness of RWE in populations treated in standard clinical care.[29]

AUTHOR CONTRIBUTIONS

C.C. and S.C. conceptualized and supervised the study. M.S., D.B., and E.H. performed the experiments. S.D.G., G.W.C., A.G., R.I., and D.F. provided patient care, collected samples, and clinical data. C.C., S.C., and S.D.G. wrote the paper. C.C. edited the manuscript. All authors reviewed and approved the final version of the manuscript.

ACKNOWLEDGMENTS

Thank you to Fondazione Roma (Via del Corso 239, 00187, Rome) for the relevant and continuous support to CEMAD in clinical research and its applications.

CONFLICT OF INTEREST

The authors declare no conflict of interest in relation to this paper.

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How to cite this article: Caruso C, Stefania C, Ciasca G, et al. Different aspects of severe asthma in real life: Role of *Staphylococcus aureus* enterotoxins and correlation to comorbidities and disease severity. *Allergy*. 2022;00:1-10. doi: 10.1111/all.15466