A retrospective cohort study in severe asthma describing commonly measured biomarkers: eosinophil count and IgE levels

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ABSTRACT

Background: Identifying asthma patients suitable for biologic therapy includes the assessment of blood biomarkers (IgE and eosinophils (EOS)). How they relate to each other is unclear.

Methods: This retrospective, database study used routinely collected clinical data to identify and evaluate an asthma cohort (classification code for asthma; ≥ 18 years; ≥1 prescription for asthma; ≥1 estimation of serum IgE, in 2 years prior to index date). Distribution into high and low IgE and EOS groups (IgE cut-point: > or ≤75 kU/L; EOS cut point: >or ≤400 µ/L), and characteristics by group are described.

Findings: In patients with severe asthma (British Thoracic Society Step (BTS) ≥4; N=884), using maximum recorded IgE/EOS, 33% had high IgE/high EOS, 28% low IgE/low EOS and approximately a fifth each had high IgE/low EOS or low IgE/high EOS. Proportions were similar when EOS values measured 2 or 4 weeks before an exacerbation were excluded. Using EOS/IgE 'same day' measurements (N=578) only identified half of the high EOS group. Patients in high IgE groups were more likely to be younger males without comorbid COPD; those in high EOS groups were more likely to be on BTS treatment Step 5 vs 4. The low IgE/low EOS group had the lowest incidence of asthma-related hospital attendances, the highest incidence was observed in the high EOS groups.

Conclusion: Maximum available EOS measurement irrespective of exacerbations may be relevant when considering therapy. These data showed low IgE/Low EOS to be more benign and high EOS groups at increased risk of frequent, severe exacerbations.

Keywords: Severe asthma; eosinophils; IgE; biologic therapy

INTRODUCTION

Whilst most patients with asthma can be effectively treated with traditional pharmacological therapy (inhaled corticosteroids (ICS), short or long acting bronchodilators and / or leukotriene receptor antagonists), a subset (<10%) with severe asthma are difficult to treat and account for a disproportionately large proportion of asthma morbidity and associated healthcare costs [1-3]. Severe asthma is defined as asthma that requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming ‘‘uncontrolled’’ or that remains ‘‘uncontrolled’’ despite this therapy [3]. It is increasingly recognized as a heterogeneous disease comprising multiple phenotypes, both at the clinical and molecular level [3], and further progress in identifying and understanding severe asthma phenotypes will enable targeted and personalized treatment, particularly in the field of biologic therapies.

Predicting responders to biologic therapy requires assessment of blood biomarkers that may not be routinely collected or considered in clinical practice. Such therapies are restricted in use by both an assessment of need after optimised care and a biomarker profile consistent with product licenses. Two established phenotype-targeted biologic therapies in severe asthma are those based on humanized monoclonal antibodies against immunoglobulin E (IgE), in severe allergic asthma, and interleukin-5 (IL-5), in eosinophilic asthma [4-6]. Eosinophilic asthma, associated with raised blood and sputum eosinophils and recurrent exacerbations, occurs in both allergic and non-allergic asthma patients, the pathophysiological mechanisms of the latter yet to be fully understood [7]. How these two biomarkers relate to each other is unclear. Sub-phenotypes of asthma that will respond differently to IgE or

Th2 cytokine targeting have been proposed, summarised in a 2x2 matrix diagram, outlining four groups by their blood eosinophil and IgE status (high and low) [8]. As part of the current analysis, we aimed to 'populate' this matrix with real-world patient data.

The measurement of blood eosinophils and serum IgE is available in routine clinical practice. By defining the biomarker status of a cohort of people with severe asthma, the potential impact of precision medicine through appropriate biologic therapies for these patients may be estimated. This analysis used a large, geographically defined, electronic database to describe the distribution and characteristics of patients with severe asthma according to their IgE and eosinophil biomarker levels.

METHODS

Study design and population

This was a retrospective, cohort, database study which used routinely collected clinical data from the whole population of National Health Service Greater Glasgow and Clyde (NHSGGC), in the 2 years prior to a pre-defined index date of 1st Jan 2016. Included patients met the following criteria: 1) Presence of a Read code [9] or International Classification of Diseases (ICD) code [10] for asthma (ever recorded), 2) Aged ≥ 18 years, 3) ≥ one prescription for any of: short-acting beta$_2$-agonist (SABA), inhaled corticosteroid (ICS), ICS/long-acting beta$_2$-agonist (LABA) combination, 4) ≥ one estimation of serum IgE.

Patients with a read or ICD code for hyper IgE(Job) syndrome, parasitic infection, allergic bronchopulmonary aspergillosis (ABPA), Churg Strauss / vasculitides, multiple myeloma, or autoimmune disease, were excluded. Patients with a read or

ICD code for bronchiectasis or interstitial lung disease, were excluded from analyses of exacerbations data.

The study protocol was registered and conducted according to The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) ((Ref:ENCEPP/SDPP/13134) code of conduct [11]. The database was generated by the NHSGGC Safe Haven, a large research resource which links health information datasets at the patient level. Data were then transferred to the University of Aberdeen Safe Haven for analysis. As part of this process, patient identifiable data is not released to researchers, but instead datasets are linked in-house before releasing the full research dataset in an anonymised format. Therefore, ethics approval and patient informed consent were not required for this study.

Study outcomes

Data items collected were: age at index date, sex, height, weight, body mass index (BMI), smoking status, concurrent therapies for asthma (number of prescriptions), co-morbidities (read or ICD code), and biologic marker counts and date of measurement. The current therapies of interest were: SABA, LABA, long-acting muscarinic antagonists (LAMA), ICS, ICS/LABA, leukotriene receptor antagonists (LTRA), theophylline, and prednisolone <20 mg/day (indicating chronic, not acute, usage) in the 2 years prior to the index date. Co-morbidities of interest were: chronic obstructive pulmonary disease, cardiovascular disease, cerebrovascular disease, diabetes mellitus, depression, osteoporosis, interstitial lung disease, nasal polyposis.

Total IgE measurements were done by Fluorescence Enzyme Immunoassay (FEIA) on an Immunocap250 instrument (Phadia, Sweden). Eosinophil counts were carried out as part of the full blood count. These were performed on Sysmex XN10

analysers (Sysmex UK Ltd, UK), using fluorescent laser light scatter technology. Consistent methodology was applied across NHSGGC.

The number of asthma exacerbations in the two years prior to the index date were recorded, defined as 1) prescription of oral corticosteroids ≥ 20 mg per day for asthma, 2) attendance at an emergency department due to asthma, 3) hospitalisation due to asthma. Severe exacerbations were defined as those requiring a visit to an emergency department or hospitalisation due to asthma. Every effort was made to identify attendances due to a primary diagnosis of asthma within the limits of the coding available.

Due to lack of accessible electronic recording, spirometry data cannot currently be accessed through the Safe Haven database.

Statistical analyses

For this analysis, the population of interest were those with severe asthma, defined as Step 4 and above in the British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) recommendations for asthma, version current at the time of study conduct [12]. The following IgE and eosinophil (EOS) distribution groups were determined: high EOS/high IgE, high EOS/low IgE, low EOS/high IgE, low EOS/low IgE, where IgE cut-point was defined as > or ≤75 kU/L; EOS cut point: > or ≤400 μ/L. Two analysis cohorts were considered: 1) the maximum value recorded for IgE and EOS in the two years prior to the index state, 2) the value of EOS or IgE corresponding to the same day measurement as IgE or EOS respectively, at any time in the two years prior to the index date.

Summary statistics were produced for all patient characteristics and included the mean and standard deviation (SD) or median and range (min-max) for continuous

data and number (percentage) for categorical data. Demographic and clinical factors were compared across IgE and eosinophil distribution groups. The chi squared test was used to compare categorical factors across groups, whilst the Kruskall-Wallis test was used to compare the distribution of continuous variables across IgE and eosinophil distribution groups.

All analyses were carried out using IBM SPSS Statistics version 23. Statistically significant results were defined as $p \leq 0.05$.

RESULTS

Patient population

Of the 1.36 million patients on the NHSGGC database, 1507 met the inclusion criteria for adults with a diagnosis of asthma and presence of a serum IgE measurement in the two years prior to the index date, of which 884 had severe asthma (BTS Step ≥4) (Figure 1). Within this group, 852 patients also had a recorded EOS measurement, and 578 had a same day IgE and Eos measurement.

In this severe patient population, mean (standard deviation, SD) age was 54.7 (15.9) years, a quarter were current smokers and approximately a third each had comorbid COPD and comorbid allergy (Table 1). Median (interquartile range) IgE and eosinophil counts were 86 (22-289) kU/L and 400 (200-700) µ/L respectively. Over half this group (55%) had suffered at least one asthma exacerbation in the prior two years, and 32% and 22% respectively had been hospitalized once or at least twice for asthma. Ninety-six percent of patients had been prescribed an ICS/LABA at least once in the prior two years; 66% had been prescribed a LTRA.

Distribution of patients by IgE and EOS level

The distribution of patients by their maximum measured IgE and EOS levels in the prior two years is shown in Table 2 and Figure 2a. Thirty three percent of patients had both high IgE and EOS levels, 19% had high IgE/low EOS, 20% had low IgE/high EOS, and 28% had low IgE and low EOS. This distribution pattern varied when data for same day EOS and IgE measurements were used, with the proportion of patients showing high EOS levels, on this occasion, being markedly lower (Figure 2b). The exclusion of EOS data measured 2 and 4 weeks before an exacerbation had no observable impact on the maximum IgE/EOS distribution groups (Figure 2c and 2d).

The correlation between IgE and EOS levels, measured on the same day was weak (Rank correlation coefficient: 0.276) (Figure 3).

Clinical Characteristics of patients by IgE/EOS groups

Patients in high IgE groups were younger, more likely to be male and less likely to have comorbid COPD than patients in low IgE groups (Table 3). The significantly higher occurrence of COPD in the low IgE groups was not accompanied by differences in smoking status. Patients in high EOS groups were significantly more likely to be on BTS Step 5 than Step 4, and had increased levels of systemic inflammation (as measured by c-reactive protein levels) compared with those in low EOS groups. Compared with other distribution groups, patients with high EOS/low IgE were more likely to have comorbid osteoporosis, and showed the greatest levels of systemic inflammation.

Asthma exacerbations and asthma therapies according to IgE/EOS groups

Across IgE/EOS groups, there were no significant differences in the number of asthma exacerbations requiring oral corticosteroids in the two years prior to the

index date (Table 4). The proportion of frequent exacerbators, defined as those with ≥2 prescriptions for oral corticosteroids or ≥ 1 hospital admission for asthma in the year prior to the index date, was significantly different across IgE/EOS groups with the highest frequency observed in the high IgE/high EOS group (76% vs. a range of 60%-68% in the other groups, $p<0.001$). The incidence of severe frequent exacerbations i.e. those requiring hospitalisation or an emergency department visit, was also significantly different across groups with the highest frequencies observed in the high EOS groups (Table 4). No significant differences were observed in the frequencies of moderate or severe exacerbations between patients with high EOS (regardless of IgE status) and those with high IgE (regardless of EOS status) (data not shown).

There were no significant differences across groups in prescriptions for maintenance therapies (Table 4).

DISCUSSION

This analysis describes the distribution and characteristics of patients according to their blood IgE and eosinophil biomarker levels, in a highly treated, severe asthma population. When using maximum-recorded IgE and EOS, a third of patients had both high IgE and EOS levels, a fifth each had high IgE/low EOS and low IgE/high EOS, and approximately a quarter had both low IgE and EOS levels. The distribution of patients was noticeably different when using same day IgE and EOS measurements (a proxy for “initiation of treatment” protocols), with the proportion of patients in the high EOS-containing distribution groups being markedly lower. Interestingly, the exclusion of EOS data measured within two or four weeks of an exacerbation appeared to have no impact on the distribution groups. The reasons for

the observed lack of extreme fluctuation in EOS around the time of an exacerbation are not clear when considering the observed inherent variability in blood eosinophils, expected in response to patient and pharmacological factors [13,14], and evidenced by the differences we observed in ‘same day’ and ‘maximum value’ results. It could be because similar fluctuations occurred with exacerbations managed at home (with use of higher doses of ICS/without the use of oral corticosteroids) or was possibly accounted for by fluctuations that occurred during sub-clinical exacerbations in which biomarker levels changed in the absence of changes in symptoms. Katz et al, in a population of severe asthmatics, whilst observing intra-patient eosinophil variability, reported that 85% of patients with a blood eosinophil count > 150 μ/L at screening, remained at or above this level in the following year [13]. They also found that blood eosinophils were a better predictor of treatment response to mepolizumab than sputum eosinophils, speculating that this may be associated with IL-5 mediated eosinophilic inflammation being the result of both local and systemic inflammation. Findings in the current study, suggest that maximum EOS in a year, regardless of exacerbation history, may be the most appropriate measure to identify patients suitable for targeted biologic therapy. Suruki et al, when describing the number of patients eligible for anti-IgE or anti-IL5 therapy in a severe population of asthmatics, used drug label criteria, potentially excluding some eligible patients from anti-IL5 therapy where EOS assessment had been based on screening (‘same day’) measurements [15].

Median EOS levels in the studied population were higher (400μ/L) than that reported by Price et al (200μ/L) in an electronic database study of primary care patients using their most recently recorded eosinophil count [16]. In comparison, we selected a severe population of asthmatics who had undergone an IgE measurement, and who

were therefore more likely to be from a secondary care population, and used maximum IgE and EOS values for describing the population. The cut-point for determining the high EOS group was 400µ/L and was primarily chosen for being the upper limit of the normal reference range in NHSGGC. Other studies evaluating the effects of anti-IL5 therapies have used cut-points of 300 µ/L [17,18] and 400µ/L [6] to determine high eosinophil status. In the context of clinical outcomes, patients with elevated blood eosinophils defined by 300µ/L [19] and 400 µ/L [16] cut-points have been reported as being at increased risk of frequent asthma exacerbations. Only a weak correlation between same day serum EOS and IgE was observed, at odds with the traditionally held view that these biomarkers are positively correlated [20], and suggests that more routine testing of IgE in severe asthma to identify patients with a treatable trait may be warranted.

In terms of patterns of demographic characteristics, the high IgE groups were more often younger, male patients, who were less likely to have comorbid COPD; whilst patients from the high EOS groups tended to be treated with oral corticosteroids (BTS step 5), be associated with a greater incidence of osteoporosis, and have higher levels of systemic inflammation. None of the patterns were suggestive of previously described phenotypes of asthma based on cluster analyses – for example, we did not observe a group of older, obese female patients with late onset asthma in the low eosinophilic groups [21-23]. Although it should be noted that age of onset of asthma was not reliably recorded in the present database.

With respect to asthma exacerbations, the low IgE/low EOS group was suggestive of a benign pattern despite them being highly treated i.e. consistent with a high symptom/low exacerbation profile group. On the other hand, groups with high eosinophils were more prognostic of healthcare episodes, being particularly

associated with frequent severe exacerbations. In the UK electronic medical data record, primary care study, blood eosinophils >400µ/L were associated with frequent exacerbations of all severities, possibly reflecting the differences in populations studied [16]. Patients with high IgE/high EOS had the most frequent moderate exacerbations (courses of oral steroids). In addition, the high EOS/low IgE group appeared to be associated with an excessive number (>3) of ED attendances; however, no significant differences were observed in the frequencies of moderate or severe exacerbations in patients with high EOS (regardless of IgE status) vs. those with high IgE (regardless of EOS status). Thus, EOS and IgE appear largely independent markers of asthma morbidity.

A limitation of this analysis is that a selected population that had undergone IgE testing were evaluated, and therefore the findings are not generalizable to a general population of patients with severe asthma. There are also some limitations to using electronic medical records for database evaluation, namely the reliance on complete and accurate recording of data, and items such as confirmation of diagnosis, incidence of comorbidities and patients' use of prescribed therapy, not being easily verified. In addition, whilst every effort was made to identify the primary reason for attendances to emergency departments/hospital as asthma, incorrect or incomplete coding may have resulted in some anomalies. However, the NHSGGC uses a unique patient identifier which is tagged on 99% of health events, providing an extensive number of linked datasets resulting in a comprehensive, multi-source database from both primary and secondary care.

In conclusion, this large database study identifies a considerable group of patients with severe asthma with low IgE /high EOS who are not currently suitable for anti-IgE therapy and who may benefit from an alternative. As EOS levels fluctuate over

time in response to patient and pharmacological features, we hypothesise that maximum EOS in a year, regardless of exacerbation history, may be the most appropriate measure to identify suitable patients. Interestingly, no significant correlation was observed between IgE and EOS, but our data suggest that a low IgE/low EOS sub-phenotype appears more benign and high EOS groups are at increased risk of frequent, severe exacerbations.

Author contributions

JH, AM, KGB, EM, IP: study concept and design; data interpretation; writing, editing and final approval of the manuscript. AJL: study concept and design; data acquisition, analysis and interpretation; writing, editing and final approval of the manuscript, AC: data acquisition and analysis, editing and final approval of the manuscript.

Declaration of interests

NSHI received a grant from Teva UK Ltd in support of conducting the study and writing up this analysis. JH has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline (GSK), Mundipharma/Napp, Pfizer, Teva and Zentiva for other projects. AM, KGB and IP received honoraria from NSHI for their contributions to the study design but not for their contribution in preparing the manuscript. IP has also received sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, GSK and Napp Pharmaceuticals; honoraria for attending advisory board panels from Almirall, AstraZeneca, Boehringer Ingelheim, Dey Pharma, GSK, MSD, Schering-Plough, Novartis, Napp Pharmaceuticals and RespiVert; and speaker’s honoraria from

AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis and GSK. AJL received a consulting fee from NSHI for performing the statistical analyses. AC received an educational grant from NSHI in support of this study. EM is the managing director of NSHI.

Acknowledgements

The authors acknowledge editorial support in the form of assistance in the development of manuscript drafts, collating author comments and copyediting, which was provided by Kate Hollingworth of Continuous Improvement Ltd. This support was funded by NSHI.

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Table 1: Characteristics of patients with severe asthma (BTS Step ≥4)

Characteristic	Severe asthma population (n=884)
Male gender, % (n)	31.3 (277)
Age (years), mean (SD)	54.7 (15.9)
Height (m), mean (SD)	1.62 (0.09)
Weight (kg), mean (SD)	79.1 (22.6)
BMI (kg/m^2), mean (SD)	30.0 (7.9)
Smoking status, % (n): Current Ex Never Missing n	 24.7 (87) 38.9 (137) 36.4 (128) 532
BTS step, % (n): 4 5	 70.0 (619) 30.0 (265)
Maximum IgE in 2 years prior to index date, kU/L Median (min-max) Interquartile range	 86 (2-5000) 22-289
Maximum EOS in 2 years prior to index date, µ/L Median (min-max) Interquartile range	 400 (70-4200) 200-700
Comorbidities, % (n)	
COPD	32.5 (287)
Cardiovascular disease	12.2 (108)
Cerebrovascular disease	5.2 (46)
Diabetes mellitus	13.9 (123)
Osteoporosis	4.3 (38)
Depression	5.7 (50)
Bronchiectasis	7.6 (67)
Interstitial lung disease	0
Nasal polyposis	1.0 (9)
Asthma exacerbations in 2 years prior to index date, % (n**)** ≥1 asthma exacerbation[1] Number of A&E visits due to asthma 0 1 ≥2 Number of hospitalisations due to asthma 0 1 ≥2	 55.0 (486) 85.9 (759) 8.9 (79) 5.2 (46) 46.5 (411) 31.8 (281) 21.7 (192)
≥1 prescriptions in 2 years prior to index date, % (n) SABA LABA ICS ICS/LABA LTRA	 97.3 (861) 60 (530) 24.9 (220) 96.4 (852) 66.0 (583)

[1]Exacerbation defined by the number of courses of oral corticosteroids ≥20mg/day.BMI: body mass index; BTS: British Thoracic Society; A&E: accident & emergency;SABA: short-acting beta$_2$-agonist; LABA: long-acting beta$_2$-agonist; ICS: inhaled corticosteroid; LTRA: leukotriene receptor antagonist

Table 2: Distribution of patients with severe asthma (BTS Step ≥4) according to IgE/EOS level groups (N=852)

	High IgE	**Low IgE**	**Total**
High EOS	33.2 (283)	20.2 (172)	455
Low EOS	19.0 (162)	27.6 (235)	397
Total	445	407	852

Data presented as % (n).

Table 3: Demographic and clinical characteristics according to IgE/EOS distribution groups in patients with severe asthma (BTS Step ≥4)

Characteristic	**High EOS/ High IgE (n=283)**	**High EOS/ Low IgE (n=172)**	**Low EOS/ High IgE (n=162)**	**Low EOS/ Low IgE (n=235)**	**P-value**
Male gender, % (n)	34.6 (98)	28.5 (49)	36.4 (59)	24.7 (58)	0.031
Age (years), mean (SD)	51.6 (16.2)	59.2 (16.2)	52.1 (15.4)	57.9 (14.0)	<0.001
Height (m), mean (SD)	1.65 (0.11)	1.61 (0.08)	1.63 (0.09)	1.61 (0.10)	0.045
Weight (kg), mean (SD)	82.1 (21.6)	74.5 (22.5)	81.9 (22.0)	78.6 (24.3)	0.031
BMI (kg/m^2), mean (SD)	30.5 (8.2)	28.5 (8.0)	31.1 (7.7)	30.1 (7.8)	0.128
Smoking status, % (n): Current Ex Never Missing n	 24.5 (23) 40.4 (38) 35.1 (33) 189	 16.2 (12) 45.9 (34) 37.8 (28) 98	 33.3 (19) 36.8 (21) 29.8 (17) 105	 25.7 (29) 36.3 (41) 38.1 (43) 122	0.428
BTS step: 4 5	 64.7 (183) 35.3 (100)	 64.0 (110) 36.0 (62)	 80.2 (130) 19.8 (32)	 73.2 (172) 26.8 (63)	0.001
Comorbidtities, % (n)					
COPD	25.1 (212)	37.2 (64)	25.69 (42)	42.1 (99)	<0.001
Cardiovascular disease	9.2 (26)	18.0 (31)	11.7 (19)	12.3 (29)	0.050
Cerebrovascular disease	4.6 (13)	6.4 (11)	5.6 (9)	4.7 (11)	0.829
Diabetes mellitus	14.1 (40)	9.9 (17)	11.1 (18)	18.3 (43)	0.066
Osteoporosis	3.9 (11)	7.6 (13)	0.6 (1)	5.5 (13)	0.016
Depression	2.5 (7)	4.1 (7)	7.4 (12)	8.9 (21)	0.007
Bronchiectasis	6.4 (18)	11.6 (20)	4.3 (7)	8.9 (21)	0.057
Nasal polyposis	1.8 (5)	0.6 (1)	0	0.9 (2)	0.275
Allergy*	38.2 (108)	30.8 (53)	38.9 (63)	32.8 (77)	0.251
Biomarkers, median (interquartile range)					
C Reactive Protein (mg/l) Min, Max Missing n	24.0 (6-88) 1, 531 19	43 (8-205) 0.9, 448 13	13.5 (4-75) 1, 391 20	17.5 (6-65) 1, 498 15	<0.001

Neutrophil count (10^9/l) Min, Max Missing n	9.9 (7.0-14.1) 2, 30.7 0	10.3 (7.2-14.9) 2.9, 38.5 0	8.1 (6-11.1) 2.1, 33.3 0	8.7 (5.5-12.4) 2.1, 42.7 0	<0.001
Lymphocyte count (10^9/l) Min, Max Missing n	3 (2.3-3.9) 1.1, 8.0 0	3 (2.2-3.9) 1.3, 5.8 0	2.5 (2-3.3) 0.8, 7.8 0	2.7 (1.9-3.4) 0.6, 8.7 0	<0.001
Platelet count (10^9/l) Min, Max Missing n	344 (293-417) 139, 947 0	358 (307-440) 159, 1119 0	304 (254-381) 61, 878 0	315 (265-385) 102, 1202 0	<0.001

BMI: body mass index; BTS: British Thoracic Society

Table 4: Summary of asthma exacerbations and asthma therapies in 2 years prior to index date according to IgE/EOS distribution groups in patients with severe asthma (BTS Step ≥4)

Characteristic	High EOS/ High IgE (n=283)	High EOS/ Low IgE (n=172)	Low EOS/ High IgE (n=162)	Low EOS/ Low IgE (n=235)	P-value
Number of exacerbations* of asthma, median (IQR)	1 (0-5)	0 (0-4)	1 (0-4)	1 (0-4)	0.695
1 or more (% (n))	53.0 (150)	49.4 (85)	61.1 (99)	57.9 (136)	
Min, Max	0, 13	0, 12	0, 12	0, 11	
Frequent exacerbator**	76.0 (215)	60.5 (104)	67.9 (110)	60.4 (142)	<0.001
Number of hospital admissions for asthma, % (n)					
0	35.3 (100)	46.5 (80)	47.5 (77)	54.5 (128)	0.009
1	33.9 (96)	32.6 (56)	32.7 (53)	30.2 (71)	
2	13.1 (37)	6.4 (11)	12.3 (20)	6.8 (16)	
3	7.1 (20)	4.1 (7)	2.5 (4)	3.4 (8)	
4	5.3 (15)	4.1 (8)	1.2 (2)	2.1 (5)	
5 or more	5.3 (15)	5.8 (10)	3.7 (6)	2.9 (7)	
Med (IQR)	1 (0-2)	1 (0, 1)	1 (0, 1)	0 (0, 1)	
Min, Max	0, 14	0, 17	0, 13	0, 13	
Number of A&E attendances for asthma, % (n):					
0	80.6 (228)	86.0 (148)	85.2 (138)	91.1 (214)	0.044
1	12.7 (36)	7.0 (12)	11.1 (18)	5.1 (12)	
2	4.2 (12)	2.3 (4)	1.2 (2)	1.7 (4)	
3 or more	2.5 (7)	4.7 (8)	2.5 (4)	2.1 (5)	
Med (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	
Min, Max	0, 6	0, 9	0, 9	0, 4	
≥1 prescriptions in 2 years prior to index date, % (n)					
SABA	99.3 (281)	97.1 (167)	98.1 (159)	94.9 (223)	0.025
LABA	58.7 (166)	59.3 (102)	63.0 (102)	60.9 (143)	0.662
ICS	26.9 (76)	29.7 (51)	29.6 (48)	25.1 (59)	0.648
ICS/LABA	97.5 (276)	92.4 (159)	96.9 (157)	97.0 (228)	0.219
LTRA	72.8 (206)	63.4 (109)	67.3 (109)	58.7 (13.8)	0.480

*Exacerbation defined by the number of courses of oral corticosteroids ≥20mg/day;**Frequent exacerbator defined as those with ≥2 Rx for prednisolone ≥20mg DDD in the year prior to index date OR ≥ 1 hospital admission for asthma in the year prior to the index date. IQR: interquartile range; A&E: accident & emergency; SABA: short-acting beta$_2$-agonist; LABA: long-acting beta$_2$-agonist; ICS: inhaled corticosteroid; LTRA:

Figures legend

Figure 1: Flow of patients

ABPA: allergic bronchopulmonary aspergillosis

[§]Read code or ICD code for asthma, and in the 2 years prior to index date: aged ≥ 18 years, ≥ one prescription for any of: SABA, ICS, ICS/LABA, ≥ 1 estimation of IgE

[¥]Three patients appeared in both categories

Figure 2: Comparison of IgE/EOS distribution groups in patients with severe asthma, using different measurement criteria

Figure 3: Scatterplot and correlation coefficient of same day EOS versus same day IgE for BTS step 4 and above

Figure 1: Flow of patients

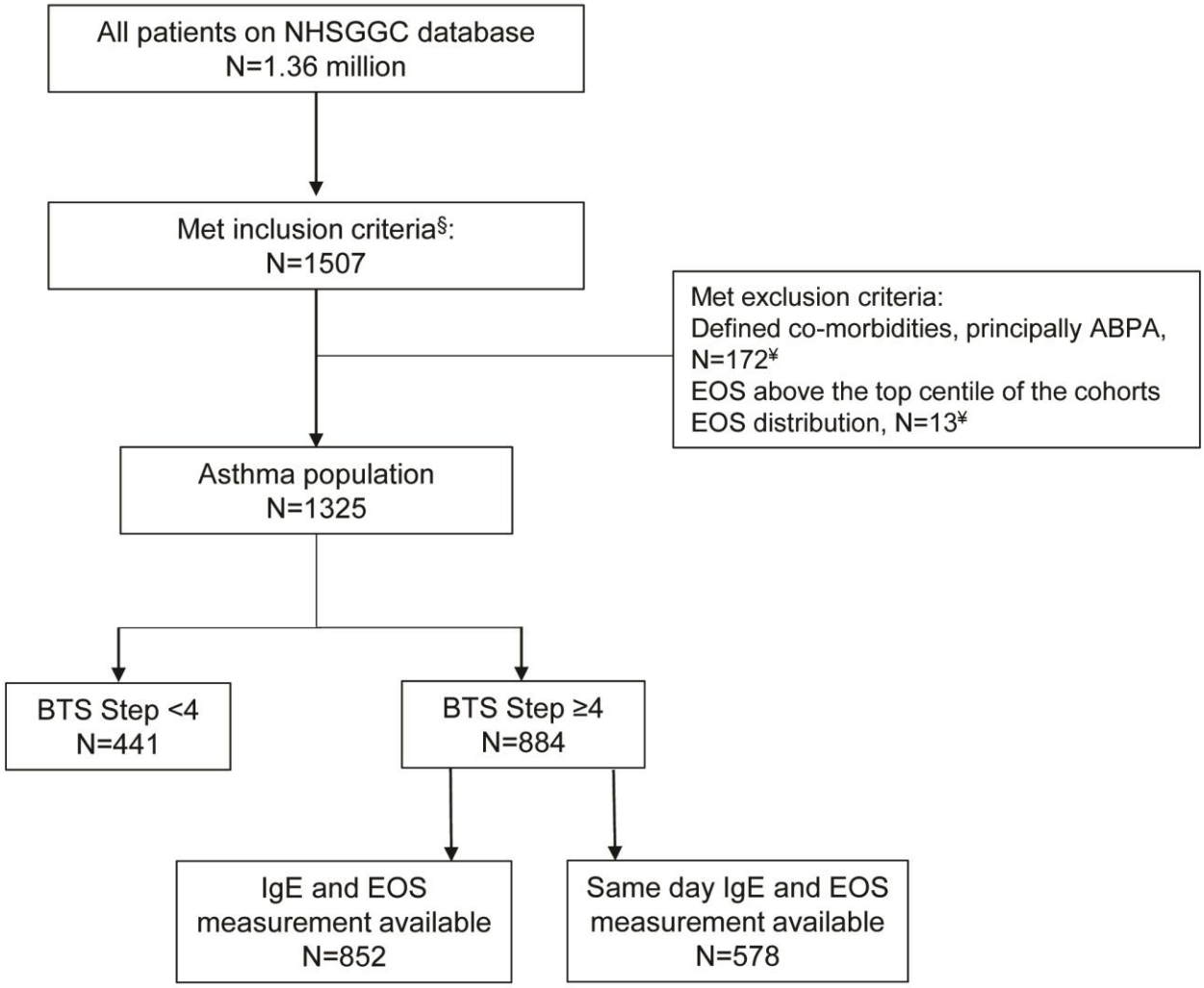


Figure 2: Comparison of IgE/EOS distribution groups in patients with severe asthma, using different measurement criteria

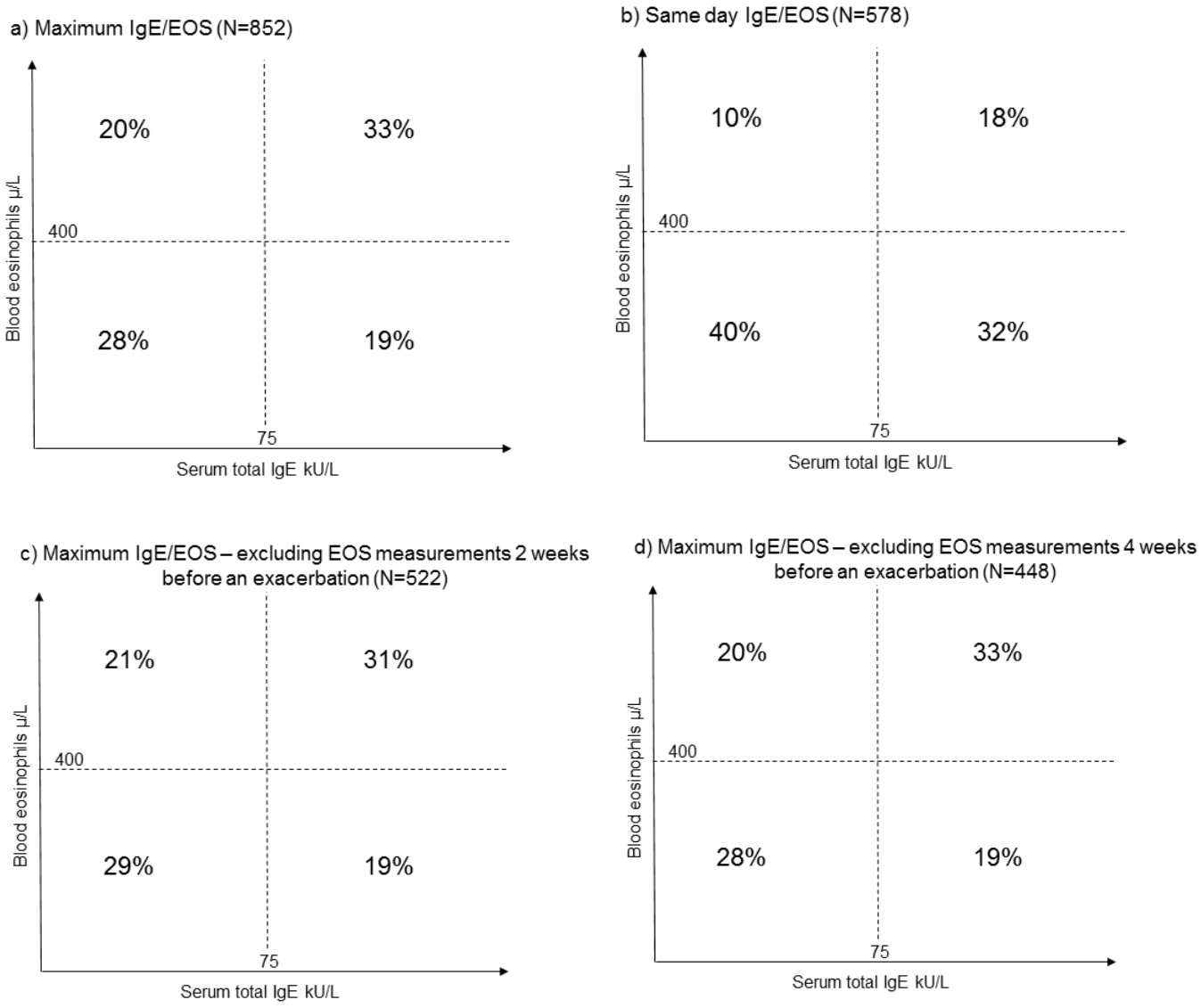
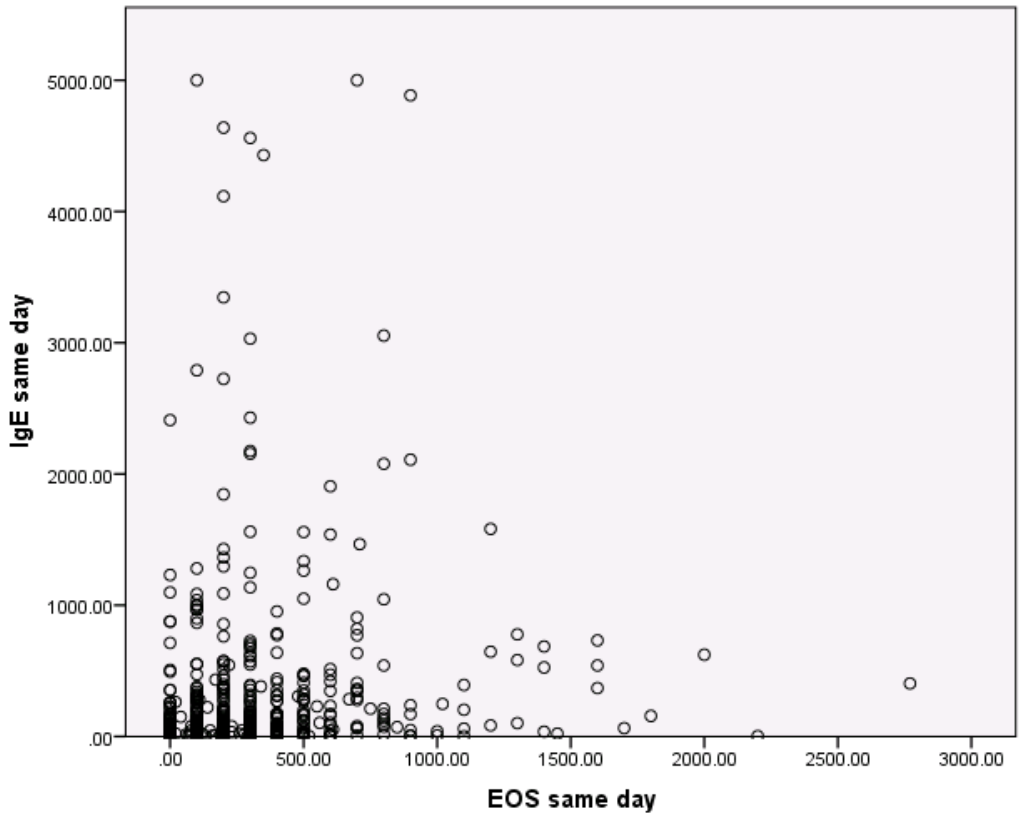


Figure 3: Scatterplot and rank correlation coefficient of same day EOS (µ/L) versus same day IgE (kU/L) for BTS step 4 and above



Rank correlation coefficient = 0.276, p<0.001 (N=578)