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Eosinophilic and non-eosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort

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Summary conflict of interest statements

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225 Characterization of eosinophilic and non-eosinophilic severe asthma phenotypes and proportion of
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Abstract

Background: Phenotypic characteristics of eosinophilic and non-eosinophilic asthma patients are not well-characterized in global, real life severe asthma cohorts.

Research Question: What is the prevalence of eosinophilic and non-eosinophilic phenotypes in the severe asthma population, and can they be differentiated by clinical and biomarker variables?

Study Design and Methods: This was an historical, registry study. Adult severe asthma patients with available blood eosinophil count (BEC) from 11 countries enrolled into the International Severe Asthma Registry (01/01/2015 to 09/30/2019) were categorized according to likelihood of eosinophilic phenotype using a pre-defined gradient eosinophilic algorithm based on highest BEC, long-term oral corticosteroid use, elevated fractional exhaled nitric oxide, nasal polyps, and adult-onset asthma. Demographic/clinical characteristics were defined at baseline (i.e. 1-year prior or closest to date of BEC).

Results: 1,716 patients with prospective data were included; 83.8% were identified as “most likely” (Grade 3), 8.3% were “likely” (Grade 2), and 6.3% “least likely” (Grade 1) to have an eosinophilic phenotype. 1.6% of patients had a non-eosinophilic phenotype (Grade 0). Eosinophilic phenotype patients (i.e. Grade 2 or 3) had later asthma onset (29.1 vs 6.7 yrs; $p<0.001$), and worse lung function (post-bronchodilator % predicted FEV₁: 76.1% vs 89.3%; $p=0.027$) than those with a non-eosinophilic phenotype. Non-eosinophilic-phenotype patients were more likely to be female (81.5% vs 62.9%; $p=0.047$), have eczema (20.8% vs 8.5%; $p=0.003$) and use anti-IgE (32.1% vs 13.4%; $p=0.004$) and leukotriene receptor antagonists (50.0% vs 28.0%; $p=0.011$) add-on therapy.

Interpretation: According to this multi-component, consensus-driven, and evidence-based eosinophil gradient algorithm (using variables readily accessible in real life), the severe asthma eosinophilic phenotype was more prevalent than previously identified, and phenotypically distinct. This pragmatic gradient algorithm utilizes variables readily accessible in primary and specialist care,

addressing inherent issues of phenotype heterogeneity and phenotype instability. Identification of treatable traits across phenotypes should improve therapeutic precision.

Clinical Trial Registration: None

Key words: International Severe Asthma Registry, Europe, North America, Asia, Middle East

Abbreviations:

ADEPT: Airways Disease Endotyping for Personalized Therapeutics

BEC: blood eosinophil count

EMR: electronic medical record

FeNO: fractional exhaled nitric oxide

FEV₁: forced expiratory volume in 1 second

FVC: forced vital capacity

GINA: Global Initiative for Asthma

ICS: inhaled corticosteroids

IgE: immunoglobulin E

IL: interleukin

ISAR: International Severe Asthma Registry

ISC: ISAR Steering Committee

LABA: long-acting beta-agonists

LTRA: leukotriene receptor antagonists

mOCS: maintenance OCS

OCS: oral corticosteroid

OPC: Optimum Patient Care

ppb: parts per billion

REG: Respiratory Effectiveness Group

SARP: Severe Asthma Research Program

278 **U-BIOPRED:** Unbiased BIOmarkers for Prediction of Respiratory Disease

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Journal Pre-proof

The knowledge that asthma represents a spectrum of diverse types is nothing new. In line with the Lancet Asthma Commission recommendations, asthma should be de-constructed into its various and heterogeneous types to answer the questions, ‘what sort of asthma does the patient have?’, ‘what are the components of the airway disease?’, and ‘what are the treatable traits?’^{1,2} In particular, the term severe asthma includes many different phenotypes and endotypes, which differ in their clinical presentation, underlying pathways, and their response to treatment.³

Eosinophilic airways inflammation has emerged as the hallmark of one type of severe asthma, so much so that asthma is routinely classified as eosinophilic or non-eosinophilic.⁴ Harry Morrow Brown was the first to identify the corticosteroid-responsive eosinophilic asthma phenotype in 1958.⁵ This eosinophilic inflammation is predominantly driven by Type 2 inflammation including T-helper cells Type 2 (Th2) and group 2 innate lymphoid cells (ILC2). It is mediated by interleukin (IL)-4, IL-5, IL-13 and granulocyte macrophage-colony stimulating factor (GM-CSF), and can be predicted (to some extent) from elevated fractional exhaled nitric oxide (FeNO) concentration and sputum/blood eosinophilia.⁶ Non-eosinophilic asthma has traditionally been more arbitrarily defined as asthma without features of Th2 asthma and is generally based on the presence of neutrophils in sputum, or the absence (or normal levels) of eosinophils or other T2 markers in sputum, biopsies or blood.⁷

Knowledge of the presenting phenotype can help predict asthma attack risk and healthcare resource utilisation,^{8,9} inform targeted treatment, and predict treatment response.^{10,11} This eosinophil-targeted approach also has the advantage of reducing oral corticosteroid (OCS) use, which decreases risk of serious adverse events¹² and attenuates rates of severe exacerbations.¹³ Non-eosinophilic severe asthma needs to be better characterized if there is to be a similar advancement in its treatment.

According to the Global Initiative for Asthma (GINA), the eosinophilic phenotype is found in approximately 50% of people with severe asthma.¹⁴ Cluster analyses from different asthma cohorts have identified several asthma phenotypes (mostly eosinophilic) using a range of demographic and clinical characteristics to describe them.¹⁵ However, substantial overlap was noted among phenotypes, most likely due to differences in sample population, geographic variation, variables assessed, and statistical methods used. Additionally, presence of co-morbidities, exposures, OCS use and FeNO were not included in all cluster descriptions. There is, therefore, a need to better characterize asthma phenotypes, in a large, multi-national, real-life cohort of severe asthma patients, considering the effect of steroids on type-2 biomarker concentrations and the importance of multiple blood eosinophil count (BEC) measurements when defining phenotypes. A more detailed deconstruction of asthma into its component types has the potential to make personalized treatment a reality for asthma patients, effectively jump-starting the 'stalled' asthma outcomes and asthma mortality trends that have remained unchanged for years.²

A combination of clinical characteristics and biomarkers may be a better way to characterize asthma types. GINA recommends using different combinations of factors to identify Type 2 inflammatory phenotypes, including BEC, FeNO, sputum eosinophils, need for maintenance OCS (mOCS) and presence of multiple co-morbidities.¹⁶ Only one study has previously proposed a diagnostic scheme to determine severe eosinophilic asthma, which has been agreed by severe asthma expert consensus.¹⁷ However, it has not yet been applied to a real-life clinical setting. The International Severe Asthma Registry (ISAR; <http://isaregistries.org/>), the largest adult severe asthma registry in the world, has sufficient power to investigate, characterize, quantify, and compare eosinophilic and non-eosinophilic phenotypes, and covers diverse jurisdictions, facilitating the generalizability of findings to the wider severe asthma population. ISAR captures BEC and many other variables associated with severe eosinophilic asthma (e.g. FeNO, age of onset, co-morbidities, atopic status,

330 and mOCS use),^{18,19} enabling the development of a multi-component, expert endorsed algorithm for
331 use in real life.

332 The aim of our study was to (i) describe an algorithm to better characterize severe eosinophilic and
333 non-eosinophilic asthma using both phenotype characteristics and biomarkers, (ii) quantify the
334 proportion of severe asthma patients with these phenotypes in the largest real-life severe asthma
335 cohort in the world (i.e. ISAR), and (iii) describe and compare their demographic and clinical
336 characteristics.

Journal Pre-proof

Materials & Methods

Study design and data source

This was a historical registry study to quantify and characterize eosinophilic and non-eosinophilic severe asthma for patients enrolled in ISAR from 1st January 2015 to 30th September 2019.¹⁹ Prospective, de-identified patient data incorporating standardized variables from new and pre-existing severe asthma registries were pooled from 11 countries (Bulgaria, Canada, Denmark, Greece, Italy, Japan, Kuwait, South Korea, Spain, the United Kingdom [UK], and the United States [US]). A full description of variables collected is provided in S-Table 1, including demographic variables (e.g. age, age of onset, sex, race) as well as details on asthma attack rate, asthma control status, presence of atopy and co-morbidities, biomarker concentrations (e.g. IgE and FeNO), lung function and treatment regimen. A full description of how ISAR works has previously been published.²⁰ Details on compliance with local and international codes and regulations are provided in the online supplement.

Patients

Patients were required to be aged ≥ 18 years at enrolment, have severe asthma (i.e. receiving treatment at GINA 2018 Step 5 or with uncontrolled asthma at GINA Step 4)²¹ with ≥ 1 BEC recorded. A summary how each registry diagnoses asthma and categorizes severe asthma is provided in S-Tables 2 and 3.

Development of gradient eosinophilic phenotype algorithm

A gradient eosinophilic phenotype algorithm was developed following an extensive literature review as well as discussions with, and consensus of experts of the ISAR Steering Committee (comprising scientists, clinicians, and epidemiologists) (S-Figure 1). Consensus was achieved following several face-to-face meetings and via email correspondence (online supplement). This group of experts

selected variables used to inform the algorithm and agreed cut-off values, based on published evidence, feasibility of availability in real-life clinical practice, but without knowledge of how selection of these variables (or their cut-offs) would influence eosinophil phenotype grading in our cohort. These variables and cuts-offs included highest BEC ever (≥ 300 , ≥ 150 -300, < 150 cells/ μ L), anti-IL-5/5R treatment, long-term OCS ever, elevated FeNO (≥ 25 ppb) ever, nasal polyps diagnosis ever, and adult asthma onset (≥ 18 years), and informed by the published evidence base and asthma management guidelines.^{16,22-27} Phenotypes were classified as Grade 3 (most likely eosinophilic), Grade 2 (likely eosinophilic), Grade 1 (least likely eosinophilic) and Grade 0 (non-eosinophilic) (Figure 1). Patients most likely to have an eosinophilic phenotype (Grade 3) were those with highest BEC ever of ≥ 300 cells/ μ L OR on anti-IL-5/anti-IL-5R therapy, OR with BEC ≥ 150 -300 cells/ μ L on (i) mOCS or (ii) ≥ 2 of nasal polyps, elevated FeNO, or late onset. The non-eosinophilic phenotype (Grade 0) was defined by experts as highest BEC ever of < 150 cells/ μ L in the absence of nasal polyps, elevated FeNO, late onset, or mOCS. See Figure 1 for definitions of Grade 1 and 2 eosinophilic phenotypes.

Description of eosinophilic and non-eosinophilic severe asthma phenotypes

Both demographic and clinical variables were used to describe eosinophilic and non-eosinophilic severe asthma populations. All demographic and clinical characteristic were taken within one year prior to or closest to the highest BEC recording (pre-anti-IL-5).

Statistical analysis

The statistical analysis plan was pre-defined to reduce bias. Stata version 14.1 (College Station, TX, USA) was used to conduct all statistical analyses. Descriptive statistics were computed for all demographic and clinical characteristics by phenotype (Grade 0 to 3) as continuous variables or categorical measures as appropriate. For testing differences between groups, phenotypes were collapsed into an overall eosinophilic group (i.e. Grade 2 and 3) and a definitely non-eosinophilic group (i.e. Grade 0). Grade 1 was excluded from the non-eosinophilic group as patients in this group

had at least 1 eosinophilic characteristic. Between-group differences in categorical variables were tested using the Chi-square test or Fisher's exact test (if $n < 5$). The unpaired Student's t-test and Wilcoxon Mann Whitney tests were used to compare normally and non-normally distributed data across groups, respectively. A two-sample test was used to compare proportions across groups. Statistical significance was defined as $p < 0.05$.

Sensitivity post-hoc analyses

The original gradient eosinophilic phenotype algorithm was re-formulated without adult onset asthma and without FeNO as criteria. The number of patients (prospective ISAR data) in each eosinophilic/non-eosinophilic phenotype was re-calculated and demographic and clinical characteristics for each group re-assessed. The number (%) of patients in each phenotype and a summary of their demographic/clinical characteristics were also assessed for retrospective electronic medical record (EMR) data captured for patients with severe asthma actively managed in routine care in the US (i.e. have at least 2 visits).

Results

Patients

The ISAR prospective population comprised 1,716 patients (US: n=70; UK: n=712; Spain: n=217; Italy: n=163; Kuwait: n=158; Denmark: n=127; Bulgaria: n=87; Canada: n=85; Greece: n=35; Japan: n=34; South Korea: n=28). The ISAR retrospective population (utilizing EMR data) included a further 1,891 patients with severe asthma actively managed in routine care in the US.

Gradient eosinophilic phenotype algorithm

For the ISAR prospective population (n=1716) 83.8% of patients were identified as “most likely” (Grade 3) to have an eosinophilic phenotype, 8.3% were “likely” (Grade 2), and 6.3% were “least likely” (Grade 1) to have an eosinophilic phenotype. 1.6% of patients had non-eosinophilic asthma (Grade 0) (Table 1). These phenotype classifications were re-checked for robustness by cross-examining their defining characteristics, showing an increase of age of onset, incidence of nasal polyps, and high FeNO from Grade 0 (non-eosinophilic) to Grade 3 (eosinophilic) phenotypes (Table 4). Grade 3 (most likely) eosinophilic phenotype predominated for severe asthma patients in all countries, ranging from 64% of patients in South Korea to 93% of patients in Denmark (Figure 2). The eosinophilic phenotype distribution was similar when age of asthma onset and FeNO were excluded from the gradient algorithm (Table 1; S-Figure 2; S-Figure 3). For the ISAR retrospective population actively assessed in the US (n=1891). 74.3%, 4.1% and 11.5% “most likely,” “likely,” and “least likely” had an eosinophilic severe asthma phenotype, respectively; 10.1% of patients had a non-eosinophilic phenotype.

Demographic and clinical characteristics

Original algorithm (ISAR prospective population, n=1716)

Patients in our severe asthma cohort, irrespective of phenotype (i.e. eosinophilic or non-eosinophilic severe asthma) tended to be White (68.7% vs 74.1%), and overweight/obese (70.5% vs 74.0%), atopic (i.e. specific IgE testing or skin prick test; 88.3% vs 90.9%), had elevated (>150 IU/ml) IgE concentrations (61.8% vs 70.0%) and high AR prevalence (65.5% vs 60.0%), with the majority exhibiting poor asthma control (59.9% vs 59.3%) and multiple exacerbations (≥ 2 in last year; 62.0% vs 59.1%) (Table 2). The prevalence of ex-smokers (28.4% vs 34.6%), emergency department visits (≥ 1 in last year: 33.9% vs 32.0%), and hospitalizations (≥ 1 in last year: 28.6% vs 24.0%) was high in both groups (Table 2). Although an adherence variable was not included in the current dataset, all patients were on background asthma therapy with evidence of persistence and good adherence (in the opinion of the clinician or based on other evidence, such as prescription refills).

Some differences were noted. Patients with an eosinophilic phenotype (i.e. Grade 2 or 3) tended to be older (52.4 vs 38.8 yrs; $p < 0.001$), have later asthma onset (29.1 vs 6.7 yrs; $p < 0.001$), and worse lung function (i.e. % patients with $FEV_1/FVC < 0.7$: 46.6% vs 16.7%; $p = 0.039$ and post-bronchodilator % predicted 76.1% vs 89.3%; $p = 0.027$) than those with a non-eosinophilic phenotype (Table 2; Figure 3). Those with non-eosinophilic severe asthma (i.e. Grade 0) were more likely to be female (81.5% vs 62.9%; $p = 0.047$), have eczema (20.8% vs 8.5%; $p = 0.033$), and use anti-IgE (32.1% vs 13.4%; $p = 0.004$) and LTRA (50.0% vs 28%; $p = 0.011$) add-on to ICS/LABA therapy than those patients with an eosinophilic phenotype (i.e. Grade 2 + 3; Table 2; Figure 3).

Demographic and clinical characteristics along the eosinophil phenotype gradient (i.e. Grades 0, 1, 2 and 3) are provided in the online supplement (S-Table 5).

Original algorithm without age of onset and FeNO as phenotype-defining criteria (ISAR prospective population, n=1716) and for those actively managed in the US (n=1891; EMR data)

A similar distribution of demographic and clinical characteristics was observed when age of onset and FeNO were removed as defining criteria from the eosinophil gradient algorithm (S-Table 6 and S-Table 7). When age of onset was excluded from the algorithm, those with non-eosinophilic severe asthma still tended to be younger (49.6 vs 52.3 years; $p=0.145$), have earlier asthma onset (27.4 vs 28.9 years; $p=0.637$) and eczema (12.5% vs 8.4%; $p=0.291$), although the difference between non-eosinophilic and eosinophilic phenotypes was less marked (S-Table 6). When FeNO was removed from the gradient algorithm, those with non-eosinophilic severe asthma still tended to be female (75.0 vs 62.7 years; $p=0.096$), have eczema (13.9 vs 8.3; $p=0.229$) and add-on LTRA to ICS/LABA therapy (40.0% vs 28.0%; $p=0.078$), but the difference was no longer significant compared to those with eosinophilic severe asthma (S-Table 7). The demographic and clinical characteristics for those patients with severe asthma assessed actively in the US were slightly different to the ISAR prospective data (S-Table 8).

Discussion

We demonstrated that the eosinophilic severe asthma phenotype is larger than previously estimated (i.e. >80% vs ~50%),¹⁴ and identified distinct eosinophilic and non-eosinophilic severe asthma patterns based on a combination of clinical and biomarker variables. Our proposed multi-component, eosinophil phenotype classification algorithm is based on extensive literature review and expert consensus, uses variables readily accessible both in primary and specialist care, and is linked to morbidity and treatment response. Furthermore, the algorithm takes variability in BEC (using the highest ever value) and impact of OCS into account, both of which can confound phenotype classification. We have proposed a gradient approach (i.e. likelihood of eosinophilic asthma) rather than a dichotomous approach to severe asthma phenotype classification in recognition of inherent heterogeneity within phenotypes, and the fact that they can occur in isolation or combination in any given patient and may change over time, either due to natural history of the disease or as a consequence of treatment.¹ Finally, we have pooled diverse data from large severe asthma registries to provide a real-life phenotype snapshot at the global and country levels, quantifying and characterizing both the severe eosinophilic phenotype and also the often ignored non-eosinophilic severe asthma phenotype, which has historically been a diagnosis of exclusion.

A gradient and multi-component eosinophil classification algorithm is useful to reflect heterogeneity not only within severe asthma, but within eosinophilic and non-eosinophilic phenotypes too. Use of elevated BEC as the sole marker for defining an eosinophilic phenotype may be misleading for several reasons. The amount of eosinophils in the blood is both time- and treatment-dependent; eosinophil counts fluctuate in a circadian pattern and are also reduced during OCS therapy.^{28,29} Additionally, a low BEC does not necessarily rule out the presence of airway eosinophilia. Its use as a single surrogate marker for airway eosinophilia in patients with asthma “will lead to a substantial

number of false positives or false negatives.”³⁰ A combination of clinical parameters and biomarkers may safeguard against phenotype mis-classification, and is one explanation for the >80% of patients with severe eosinophilic asthma observed in the present study. Both the SARP and the Leicester cohorts have used this combination approach.³¹

Using a multi-component gradient eosinophil algorithm to characterize eosinophilic and non-eosinophilic phenotypes of severe asthma within ISAR (Figure 1) permitted us to take a phenotype snapshot.¹ We found that that the vast majority of patients (>80%) in severe asthma centers globally have background eosinophilic asthma (irrespective of algorithm used), and that the proportion of patients with a completely non-eosinophilic phenotype is very rare (only 1.6% in the current study). Others have recently validated our findings, showing a similarly high prevalence of eosinophilic asthma (83.4%), defined as ≥ 300 cells/ μ L ever in the past 10 years, in a real life difficult-to-treat UK asthma population.³² However, arguably the ISAR gradient eosinophil algorithm affords a more practical means of determining eosinophilic asthma status than reliance on protracted, sequential BEC.

The low prevalence of non-eosinophilic phenotype in the present study could be due to the strict non-eosinophilic phenotype definition employed, OCS over-treatment and/or possibly due to anti-IgE treatment and LTRA treatment which may have suppressed some algorithm variables (e.g. BEC).^{33,34} This low-eosinophilic phenotype prevalence remained when age of onset and FeNO were removed as criteria from the gradient algorithm. Those with an eosinophilic severe asthma phenotype have an elevated BEC (i.e. ≥ 150 cells/ μ L), and are more likely to have nasal polyps and FeNO ≥ 25 ppb (by algorithm definition), are older, and have adult-onset asthma and worse lung function (than those with non-eosinophilic severe asthma). On the flip side, our preliminary findings, based on small numbers, found that those with a non-eosinophilic severe asthma phenotype have a

relatively low BEC (i.e. <150 cells/ μ L), no nasal polyps, low FeNO (i.e. <25 ppb), and early onset disease, and are more likely to be female, have eczema, and be treated with anti-IgE and LTRA add-on to ICS/LABA therapy (presumably due to ineligibility for anti-IL5/5R treatment by virtue of low BEC). This finding highlights the lack of other treatment options, and the need to develop treatments targeted at this often overlooked sub-set of severe asthma patients. The higher likelihood of eczema reported relative to patients with an eosinophilic phenotype may be due to the greater prevalence of OCS and biologic use in the latter group, which may reduce the severity of both conditions so they are not currently active.

In common with most severe asthma cohorts, we found a clear female predominance (irrespective of phenotype). Interestingly, the prevalence of male sex appeared to be proportionately greater in the eosinophilic group (37.1% vs 18.5%), which in conjunction with older age and later onset seen in the eosinophilic group aligns with Azim and colleagues³⁵ who recently identified a male, adult-onset, eosinophilic, difficult asthma phenotype that has so far received scant attention in the literature. Similarity of healthcare resource utilization for both eosinophilic and non-eosinophilic severe asthma suggests comparable asthma severity across phenotypes. Similarity across phenotypes for asthma control and asthma attacks may be attributable to the fact that ISAR selects patients that are more likely to experience an asthma attack. However, this finding may suggest that despite complete suppression of eosinophilic inflammation (with corticosteroids or biologic therapy) in those with definite eosinophilic asthma, symptoms and asthma attacks can persist; that other factors (besides the eosinophil) are important (e.g. co-morbidities, healthcare access, and socio-economic factors). Characterization of non-eosinophilic mechanisms that persist when eosinophilic inflammation has been suppressed warrants further characterization. The relatively lower prevalence of the severe eosinophilic phenotype in the US retrospective population (74%), is mainly attributed to lack of nasal polyps and age of asthma onset data, and speaks to the benefit of standardized, prospective data collection and coding employed in ISAR as well as the importance of longitudinal assessment of BEC.

Table 3 compares this global view of eosinophilic phenotype description with cluster analyses from 3 large, asthma cohorts (SARP, U-BIOPRED, and ADEPT).¹⁵ All clusters identified a predominance of eosinophilic clusters, but differed in the size of the eosinophilic and non-eosinophilic clusters identified, ranging from 49-56% and 16-31%, respectively,^{36,37} and markedly differed from the results of the current study (Table 3). These differences may be due in part to inclusion of mild asthma in these clusters (e.g. the percentage of patients with an eosinophilic phenotype increases to 81.2% when mild patients are discounted from the SARP cohort), due to differences in choice of variables, and complicated by the inclusion of a mixed granulocyte phenotype in the UBIOPRED and ADEPT cohorts which includes neutrophilic types. Indeed, Burgel and colleagues³⁸ argue that cluster analyses should be viewed as an exploratory analysis and the results validated using clinically-relevant endpoints in multiple cohorts of patients. Use of multiple clinical biomarkers, a well-characterized cohort, and variables that are treatable to define phenotypes (as done in our study) may have a superior biological responsiveness predictive value.^{3,39}

One limitation of the study includes a potential selection bias for the eosinophilic phenotype within ISAR. Although the ISAR population may be enriched for those with high BEC, frequent asthma attacks, and suitability for biologic prescription in some countries (e.g. UK), thus positively selecting for the severe eosinophilic phenotype, this is not true for all countries. Indeed, a recent study including data from 7 ISAR-participating countries (US, UK, South Korea, Italy, Australia, New Zealand, and Singapore) found that only 25.4% of severe asthma patients were receiving biologic therapy (either anti-IgE or anti-IL-5).⁴⁰ A similarly high prevalence of eosinophilic asthma and low prevalence of non-eosinophilic asthma has also been reported in a primary care cohort using the same eosinophil phenotype gradient algorithm,⁴¹ and in the actively managed US EMR population presented in the current study). Furthermore, a similarly low prevalence of non-eosinophilic asthma

has been reported in the RASP-UK asthma cohort using a different algorithm.⁴² Our algorithm is intended to aid phenotype classification and does not capture all asthma sub-types. For example, there exists a sub-type of asthmatics with low BEC and elevated FeNO and nasal polyps who do respond well to anti-IL4/13.⁴³ This phenotype can be more fully explored within ISAR when IL4/13 use becomes more widespread.' Additional limitations include a reliance on BEC rather than sputum eosinophil count, possibility of recall bias (e.g. for onset of asthma), and the large imbalance in patient numbers between the groups when describing demographic and clinical characteristics. However, it should be noted that although sputum induced by hypertonic saline is generally considered a reliable, non-invasive method to assess and monitor eosinophilia, it can be problematic in patients with severe and uncontrolled asthma inducing airway narrowing and/or failure to produce an adequate sputum sample in about a quarter of patients.⁴⁴ Blood eosinophilia is an accurate surrogate marker for sputum eosinophils, with a reported ROC AUC of 89%.⁴⁵

It is recommended to apply this gradient algorithm in a different severe asthma study population with longitudinal BEC records to assess the specificity of the eosinophil phenotype definition and to assess the generalizability of the reported results. Future work could evaluate the internal and external validity of the gradient algorithm, more fully examine the eosinophil phenotype characteristics by country, characterize the ISAR cohort according to Type 2 and non-Type 2 endotypes and examine overlap between phenotypes and biomarkers.

Interpretation

This multi-component, expert-endorsed, eosinophil gradient algorithm, using variables readily accessible in real life, has shown that the prevalence of the severe asthma eosinophilic phenotype was higher than previously thought, and phenotypically distinct. Use of this algorithm may enable physicians to ascertain what type of asthma their patients have, the components of the airway

disease, and its treatable traits, bringing us one step closer to the practice of precision medicine and selection of targeted phenotype-specific treatments.

Take-Home Points

- Study Question: What is the prevalence of eosinophilic and non-eosinophilic phenotypes in the severe asthma population, and can they be differentiated by clinical and biomarker variables?
- Results: Of 1,716 patients included, 83.8%, “most likely” had an eosinophilic phenotype. These patients were older, had later onset asthma, and worse lung function compared to those with a non-eosinophilic phenotype (1.6%).
- Interpretation: The severe asthma eosinophilic phenotype is more prevalent than previously thought and phenotypically distinct, when defined using variables readily accessible in real life.

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Guarantor Statement

David Price agrees to be accountable for all content and aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Author Contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in data acquisition or analysis and interpretation, as well as the critical revision of the manuscript for important intellectual content. LGH, LP, MA, VB, JB, GWC, GC, BC, JMF, EH, TI, DJJ, AMG, NGP, AP, PEP, TAP, CMP, CKR, MS, YT, EW, MW, MA, AA, LB, USB, AB, GGB, RB, RWC, MH, MKS, SL, LL, MP, CT, ChT, TT, JZ, and DBP were involved in the conception and design of the study and in reaching consensus on the eosinophil gradient algorithm. LGH, LB, VC, IC, NE, NH, MK, RM, CP and DBP were responsible for drafting the manuscript. IC, NE and LB provided additional administrative, technical, and material support. The study was supervised by DBP. All authors approved the final version of this manuscript and agree to be accountable for all aspects of the work.

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Journal Pre-proof

Characterization of eosinophilic and non-eosinophilic severe asthma phenotypes

914 **Table 1: Characterization of eosinophilic and non-eosinophilic phenotypes and the proportion of severe asthma patients with these phenotypes in ISAR**

Highest BEC available (cells/ μ L) ^a	Treatment or clinical characteristic	Eosinophilic phenotype	Prospective ISAR population (N=1,716) [Original algorithm]		Prospective ISAR population (N=1,716) [Original algorithm - age of onset]		Prospective ISAR population (N=1,716) [Original algorithm – FeNO]	
			N (%)	(%)	N (%)	%	N (%)	%
≥ 300		Grade 3: most likely	1196 (69.7%)	83.8%	1196 (69.7%)	82.6%	1196 (69.7%)	82.7%
Anti-IL5		Grade 3: most likely	178* (10.4%)		178* (10.4%)		178* (10.4%)	
≥ 150 to < 300	Long-term OCS	Grade 3: most likely	37 (2.2%)		37 (2.2%)		37 (2.2%)	
	Presence of ≥ 2 of the following: NP, FeNO ≥ 25 ppb or adult onset ^b (no long-term OCS)	Grade 3: most likely	27 (1.6%)		7 (0.4%)		8 (0.5%)	
	Either NP, FeNO ≥ 25 ppb or adult onset (no long-term OCS)	Grade 2: likely	67 (3.9%)		45 (2.6%)		71 (4.1%)	
	No NP, elevated FeNO, adult onset or long-term OCS	Grade 1: least likely	27 (1.6%)		69 (4.0%)		42 (2.4%)	
< 150	Long term OCS	Grade 2: likely	75 (4.4%)	4.4%	75 (4.4%)	4.4%	75 (4.4%)	4.4%
	Either NP, FeNO ≥ 25 ppb or adult onset (no long-term OCS)	Grade 1: least likely	81 (4.7%)	4.7%	40 (2.4%)	2.4%	64 (3.7%)	3.7%
	No NP, elevated FeNO, adult onset or long-term OCS	Grade 0: unlikely (non-	28 (1.6%)	1.6%	69 (4.0%)	4.0%	45 (2.6%)	2.6%

Characterization of eosinophilic and non-eosinophilic severe asthma phenotypes

		eosinophilic)						
Anti-IL5/5R: anti interleukin 5/5-receptor; BEC: blood eosinophil count; eCRF: electronic clinical report form; EMR: electronic medical record; FeNO: fractional exhaled nitric oxide; ISAR: International Severe Asthma Registry; NP: nasal polyps; OCS: oral corticosteroids. ^a independent criteria specified in each row; pre-Anti-IL5/5R or long-term OCS was used wherever possible; ^b Onset of asthma: ≥ 18 years old; *Of 178 patients on Anti-IL-5, n=125 had a BEC < 150 (n=88 on mOCS; 37 never on mOCS) and 53 had a BEC ≥ 150 to <300 (n=38 on mOCS, n=15 never on mOCS). Of the 37 with BEC < 150 without OCS, n=26 did NOT have a pre-anti-IL5 BEC. N=11 (from Canada [n=1] Denmark [n=2], Spain [n=3] & USA [n=5]) had a pre-anti-IL5 BEC								

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Table 2: Demographic and clinical characteristics according to eosinophilic (Grade 2 & 3) and non-eosinophilic (Grade 0) phenotype, categorized according to the original algorithm (ISAR prospective population; N=1,716)

	Non- Eosinophilic (Grade 0; N=28)	Eosinophilic (Grade 2 &3; N=1580)	P-value
Gender			
Non-missing, n (%)	27 (96.4)	1571 (99.4)	0.047 ^{a*}
Female, n (%)	22 (81.5)	988 (62.9)	
Age			
Non-missing, n (%)	26 (92.9)	1513 (95.8)	0.000 ^{b*}
Mean (SD)	38.8 (12.1)	52.4 (13.8)	
18-34, n (%)	10 (38.5)	177 (11.7)	0.000 ^{c*}
35-54, n (%)	14 (53.8)	631 (41.7)	
55-79, n (%)	2 (7.7)	683 (45.1)	
≥80, n (%)	0 (0)	22 (1.4)	
Ethnicity			
Non-missing, n (%)	27 (96.4)	1549 (98.0)	0.650 ^c
Caucasian, n (%)	20 (74.1)	1064 (68.7)	
Asian, n (%)	3 (11.1)	140 (9.1)	
African, n (%)	0 (0)	55 (3.5)	
Mixed, n (%)	0 (0)	12 (0.8)	
Other, n (%)	4 (14.8)	272 (17.6)	
Unknown, n (%)	0 (0)	6 (0.4)	
BMI*			
Non-missing, n (%)	27 (96.4)	1546 (98.0)	0.943 ^c
Underweight (<18.5), n (%)	0 (0)	25 (1.6)	
Normal (≥18.5-<25), n (%)	7 (25.9)	431 (27.9)	
Overweight (≥25 - <30), n (%)	10 (37.0)	504 (32.6)	
Obese (≥30), n (%)	10 (37.0)	586 (37.9)	
Smoking Status			
Non-missing, n (%)	26 (92.9)	1540 (97.5)	0.570 ^c
Current smokers, n (%)	1 (3.8)	53 (3.4)	
Ex-smokers, n (%)	9 (34.6)	438 (28.4)	
Never-smoked, n (%)	16 (61.5)	1049 (68.1)	
Age of asthma onset (years)			
Non-missing, n (%)	23 (82.1)	1493 (90.9)	0.000 ^{b*}
Mean (SD)	6.7 (4.1)	29.1 (18.0)	
<18, n (%)	23 (100.0)	424 (29.5)	-
18-29, n (%)	0 (0.0)	283 (19.7)	
≥30, n (%)	0 (0.0)	729 (50.8)	
Comorbidities ever			
Non-missing, n (%)	24 (85.7)	1493 (94.5)	-
NP, n (%)	0 (0.0)	492 (32.9)	
Non-missing, n (%)	14 (50.0)	851 (53.9)	0.467 ^a
CRS	6 (42.9)	448 (52.6)	
Non-missing, n (%)	13 (46.4)	514 (32.5)	0.577 ^a
CRS without NP, n (%)	6 (46.1)	198 (38.5)	

Non-missing, n (%)	-	314 (19.9)	-
CRS with NP, n (%)	0 (0.0)	234 (74.5)	
Non-missing, n (%)	15 (53.6)	869 (55.0)	0.658 ^a
AR, n (%)	9 (60.0)	569 (65.5)	
Non-missing, n (%)	24 (85.7)	1275 (80.7)	0.033^{a*}
Eczema, n (%)	5 (20.8)	109 (8.5)	
Atopy			
Non-missing, n (%)	22 (78.6)	1362 (86.2)	P=0.701 ^e
Atopy, n (%)	20 (90.9)	1202 (88.3)	
Asthma Control			
<i>Asthma control, non-missing n (%)</i>	27 (96.4)	1296 (82.0)	
Poorly controlled, n (%)	16 (59.3)	776 (59.9)	0.828 ^a
Not well controlled, n (%)	5 (18.5)	190 (14.7)	
Well controlled, n (%)	6 (22.2)	330 (25.5)	
<i>Asthma attacks, non-missing n (%)</i>	22 (78.6)	1354 (85.7)	
Mean (SD)	3.2 (3.0)	3.4 (3.7)	0.919 ^b
0, n (%)	5 (22.7)	350 (25.9)	0.698 ^c
1, n (%)	4 (18.2)	166 (12.3)	
2, n (%)	1 (4.5)	180 (13.3)	
3, n (%)	2 (9.1)	129 (9.6)	
≥4, n (%)	10 (45.5)	529 (39.1)	
Health care resource utilization			
<i>Invasive ventilation, non-missing n (%)</i>	22 (78.6)	1395 (88.3)	
Mean (SD)	0.1 (0.5)	0.1 (0.6)	0.724 ^b
0, n (%)	20 (90.9)	1294 (92.8)	0.442 ^c
1, n (%)	1 (4.5)	75 (5.4)	
≥2, n (%)	1 (4.5)	26 (1.9)	
<i>ED visit, non-missing n (%)</i>	25 (89.3)	1461 (92.5)	
Mean (SD)	1.6 (4.2)	1.2 (3.2)	0.978 ^b
0, n (%)	17 (68.0)	965 (66.0)	0.912 ^c
1, n (%)	2 (8.0)	161 (11.0)	
≥2, n (%)	6 (24.0)	335 (22.9)	
<i>Hospitalization, non-missing n (%)</i>	25 (89.3)	1446 (91.5)	
Mean (SD)	0.6 (1.9)	0.7 (1.5)	0.676 ^b
0, n (%)	19 (76.0)	1033 (71.4)	0.808 ^c
1, n (%)	2 (8.0)	202 (14.0)	
≥2, n (%)	4 (16.0)	211 (14.6)	
Biomarkers			
<i>IgE (IU/mL), non-missing n (%)</i>	20 (71.4)	1270 (80.4)	
<150, n (%)	6 (30.0)	485 (38.2)	0.709 ^a
150-400, n (%)	7 (35.0)	357 (28.1)	
>400, n (%)	7 (35.0)	428 (33.7)	
<i>FeNO, ppb, non-missing n (%)</i>	23 (82.1)	1080 (68.4)	
<25, n (%)	23 (100.0)	299 (27.7)	-
≥25 - <50, n (%)	0 (0.0)	338 (31.3)	
≥50, n (%)	0 (0.0)	443 (41.0)	
Lung Function			
<i>Post-BD FEV₁ % predicted, non-missing n (%)</i>	14 (50.0)	823 (52.1)	0.027^{d*}

Mean (SD)	89.3 (18.2)	76.1 (22.1)	
Pre-BD FEV ₁ % Predicted	N=21	N=1174	0.427d
Mean (SD)	77.1 (23.2)	72.9 (24.1)	
Post-BD FEV ₁ /FVC, non-missing n (%)	12 (42.9)	641 (40.6)	0.429 ^d
Mean (SD)	0.7 (0.1)	0.7 (0.2)	
<0.7, n (%)	2 (16.7)	299 (46.6)	0.039^{e*}
Reversibility, non-missing n (%)	11 (39.3)	616 (39.0)	0.933 ^b
Mean (SD)	7.5 (8.0)	7.9 (8.6)	
<9%, n (%)	7 (63.6)	616 (64.1)	0.973 ^e
Therapy ever			
Non-missing, n (%)	28 (100.0)	1580 (100.0)	-
Anti-IL-5/5R	0 (0.0)	790 (50.0)	
Mepolizumab	0 (0.0)	638 (80.7)	
Benralizumab	0 (0.0)	129 (16.3)	
Reslizumab	0 (0.0)	23 (2.9)	
Long-term OCS	0 (0.0)	697 (44.1)	
Baseline Therapies			
Non-missing, n (%)	28 (100.0)	1580 (100.0)	
Anti-IgE	9 (32.1)	212 (13.4)	0.004^{a*}
Anti-IL4	0 (0)	2 (0.1)	0.576 ^a
Long-term OCS	0 (0.0)	581 (36.7)	-
Macrolide	1 (3.6)	78 (4.9)	0.596 ^c
Add on to ICS/LABA			
LAMA	11 (39.3)	503 (31.8)	0.402a
LTRA	14 (50.0)	443 (28.0)	0.011^{a*}
LAMA + LTRA	7 (25.0)	237 (15.0)	0.144 ^a
Theophylline	2 (7.1)	188 (11.9)	0.765 ^c
CRS: chronic rhinosinusitis; FeNO: fractional exhaled nitric oxide; FEV ₁ : forced expiratory volume in one second; FVC: forced vital capacity; ICS: inhaled corticosteroid; IgE: Immunoglobulin E; ISAR: International Severe Asthma Registry; LAMA: long-acting muscarinic receptor antagonist; LABA: long-acting β ₂ -agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid; SD: standard deviation ^a chi-square test, ^b Wilcoxon-Mann-Whitney Test, ^c Fisher's exact, ^d t-test, ^e two-sample test-of-proportions * p-value <0.05			

Characterization of eosinophilic and non-eosinophilic severe asthma phenotypes

Table 3. Comparison of ISAR eosinophilic phenotypes versus clinical cluster analyses from 3 large, well-phenotyped asthma cohorts

ISAR cohort characteristics N=1716	%	SARP cluster ³⁷ N=726	%	U-BIOPRED cluster ³⁶ N=82	%	ADEPT clusters ³⁶ N=156	%
-		1. Early onset, mild , atopic, eosinophilic (n=110)		1. Mild asthma, good lung function, early onset, low inflammation (n=25)		1. Mild , normal lung function, early onset, low inflammation (n=28)	
1. Eosinophilic (BEC ≥150), adult onset, high FeNO (>25 ppb), nasal polyps, older, worse lung function	83.8%	1. Early onset, moderate, atopic, eosinophilic (n=321) 3. Late onset, non-atopic, eosinophilic , female, obese (n=59) 4. Early onset, severe atopic reversible, obstruction, eosinophilic (n=120)	68.9%	2. Moderate, hyperresponsive, eosinophilic (n=32) 3. Severe uncontrolled, severe reversible obstruction, mixed granulocytic (n=8)	48.8%	2. Moderate, atopic, mild reversible obstruction, hyperresponsive, eosinophilic (n=44) 3. Severe uncontrolled, severe reversible obstruction, mixed granulocytic (n=35)	50.6%
2. Non-eosinophilic (low BEC <150), early onset, low FeNO (<25 ppb), no nasal polyps, female, eczema, better lung function	1.6%	5. late onset, long duration, severe, fixed airflow obstruction (n=116)	16.0%	4. Mixed severity, mild reversible obstruction, non-eosinophilic, neutrophilic (n=17)	20.7%	4. Mixed severity, mild reversible obstruction, non-eosinophilic, neutrophilic (n=49)	31.4%

Table adapted from Carr et al, 2018.¹⁵

Characterization of eosinophilic and non-eosinophilic severe asthma phenotypes

927 ADEPT: Airways Disease Endotyping for Personalized Therapeutics; BEC: blood eosinophilic count; FeNO: fractional exhaled nitric oxide; ISAR: International
928 Severe Asthma Registry; ppb: parts per billion; SARP: Severe Asthma Research Program; U-BIOPRED: Unbiased Biomarkers for the Prediction of Respiratory
929 Disease
930

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Legends to Figures

Figure 1: Original eosinophilic and non-eosinophilic severe asthma phenotype algorithm flow chart.

Anti-IL-5: anti-interleukin 5; BEC: blood eosinophil count; FeNO: fractional exhaled nitric oxide; OCS: oral corticosteroid

Figure 2: Eosinophilic severe asthma phenotype distribution by country for prospective ISAR population (defined according to the original algorithm)

Figure 3: Spider plot showing the clinical and biomarker variable distribution pattern for the eosinophilic (n=1580) and non-eosinophilic (n=28) severe asthma phenotype for the ISAR prospective population. BEC: blood eosinophil count; FeNO: fractional exhaled nitric oxide; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; IgE: immunoglobulin E; LTRA: leukotriene receptor antagonist add-on to ICS/LABA therapy.

Figure 1

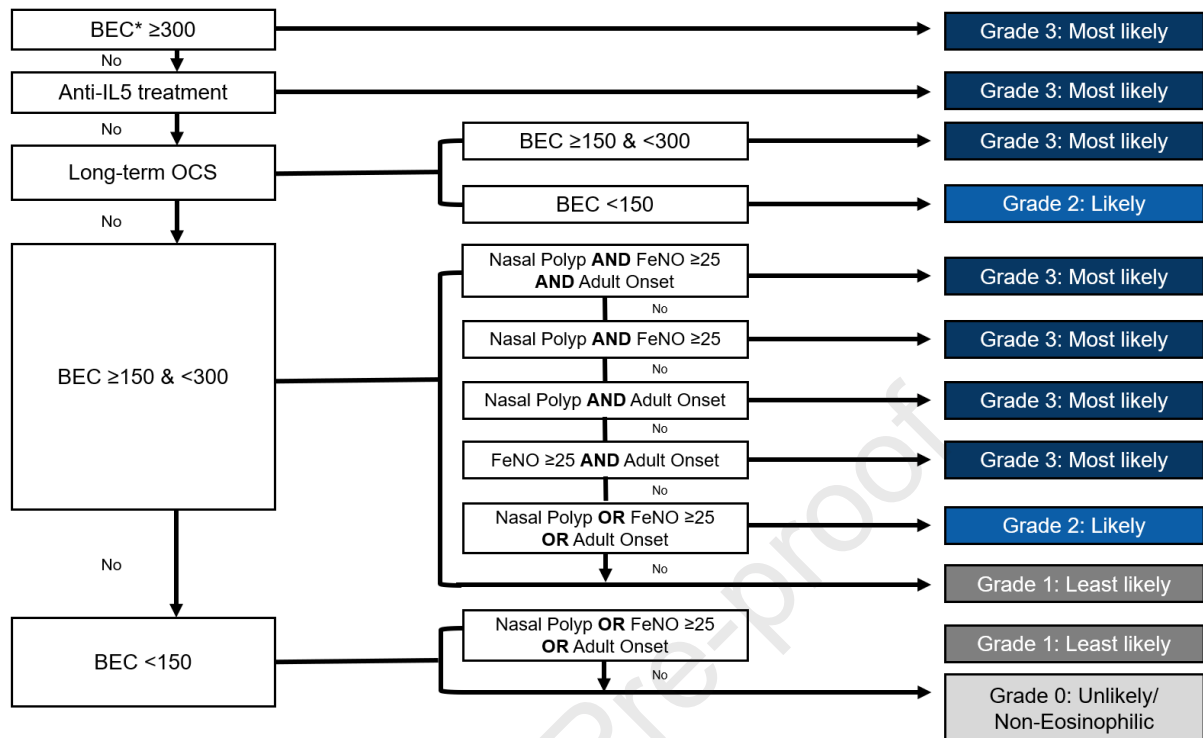


Figure 2

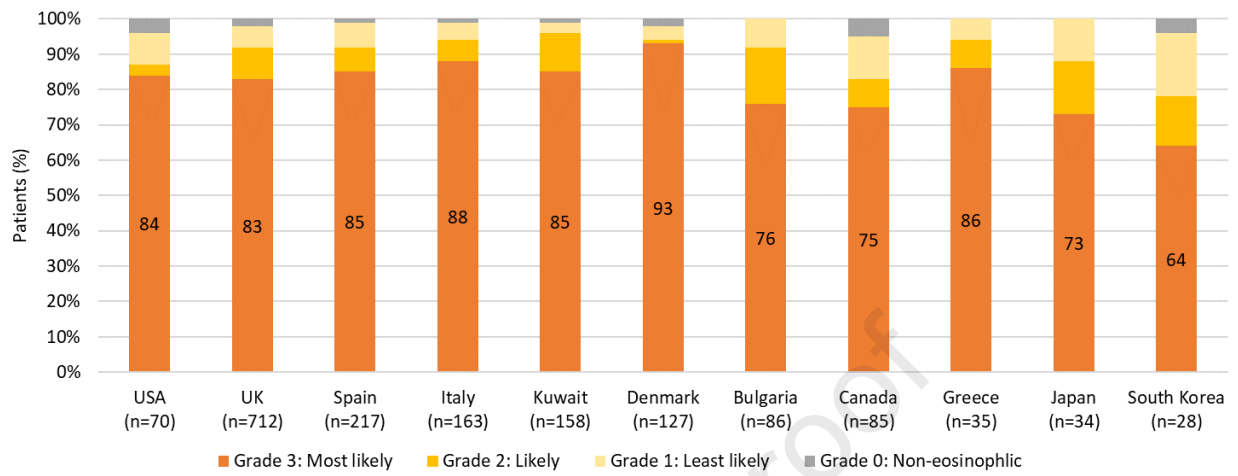


Figure 3

