Clinical & Experimental Allergy

WILEY

RESEARCH LETTER

Cluster Analysis Identifies Patients With Severe Eosinophilic Asthma Who Achieve Super-Response and Remission With Mepolizumab

Danilo Di Bona[1] | Massimo Bilancia[2] | Claudia Crimi[3] | Michelina Daddato[2] | Alida Benfante[4] | Maria Filomena Caiaffa[5] | Cecilia Calabrese[6] | Raffaele Campisi[3] | Santi Nolasco[3] | Giovanna Elisiana Carpagnano[7] | Maria D'Amato[8] | Corrado Pelaia[9] | Girolamo Pelaia[10] | Angelantonio Maglio[11] | Nicola Scichilone[4] | Giulia Scioscia[12] | Giuseppe Spadaro[13] | Massimo Triggiani[14] | Isabella Carrieri[8] | Giuseppe Valenti[15] | Alessandro Vatrella[8] | Luigi Macchia[2] | Nunzio Crimi[3]

[1]Department of Medical and Surgical Sciences (DSMC), University of Foggia, Foggia, Italy | [2]Unit of Statistics, Department of Precision and Regenerative Medicine and Jonian Area (DiMePRe-J), University of Bari Aldo Moro, Bari, Italy | [3]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy | [4]Department of Biomedicine and Internal and Specialistic Medicine, University of Palermo, Palermo, Italy | [5]Allergology and Clinical Immunology Unit, University of Foggia, Foggia, Italy | [6]Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Napoli, Italy | [7]Department of Basic Medical Sciences, Neuroscience and Sense Organs, Section of Respiratory Disease, University "Aldo Moro" of Bari, Bari, Italy | [8]Division of Pneumology, "V. Monaldi" University Hospital, Naples, Italy | [9]Department of Medical and Surgical Sciences, University "Magna Graecia" of Catanzaro, Catanzaro, Italy | [10]Department of Health Sciences, University "Magna Graecia" of Catanzaro, Catanzaro, Italy | [11]Department of Medicine, Surgery and Dentistry, University of Salerno, Salerno, Italy | [12]Department of Medical and Surgical Sciences, Institute of Respiratory Diseases, University of Foggia, Foggia, Italy | [13]Allergology and Immunology Unit, University "Federico II" of Naples, Naples, Italy | [14]Division of Allergy and Clinical Immunology, University of Salerno, Fisciano, Italy | [15]Allergology and Pulmonology Unit, Provincial Outpatient Center of Palermo, Palermo, Italy

Correspondence: Danilo Di Bona (danilo.dibona@unifg.it)

Received: 9 April 2024 | **Revised:** 27 September 2024 | **Accepted:** 30 September 2024

Funding: This work was supported by the authors' respective institutions.

Keywords: anti-IL5 | machine learning | mepolizumab | prediction of clinical response | real-life study | remission | super-response | T2-high phenotype

To the Editor,

Biological therapies have significantly improved outcomes for patients with severe eosinophilic asthma (SEA), but responses vary. Many patients who meet the criteria for monoclonal antibody treatment experience suboptimal responses, while others show exceptional improvement, referred to as 'super responders' (no exacerbations and no systemic corticosteroid use during 12 months of treatment) [1]. Recently, achieving 'clinical remission'—defined by no exacerbations, no systemic corticosteroid use, symptom control and optimised lung function—has emerged as a treatment goal [2].

Randomised and nonrandomised studies have demonstrated that mepolizumab, the first monoclonal antibody-targeting interleukin-5 (IL-5), leads to significant reductions in severe exacerbations and corticosteroid use while improving lung function and quality of life [1, 3, 4]. However, these studies report average outcomes and lack insights into the subgroups that benefit most.

Cluster analysis is a valuable tool for identifying patterns within data sets and grouping patients with similar characteristics into distinct, mutually exclusive subgroups. In this retrospective study, unsupervised cluster analysis was applied to a real-world SEA cohort to uncover sub-phenotypes within the T2-high phenotype that are particularly responsive to mepolizumab. Patients were recruited between May 2020 and June 2022 across 12 Italian asthma centres. Informed consent was obtained,

[Correction added on 24 October 2024, after first online publication: The copyright line was changed.]

Abbreviations: ACT, asthma control test; BEC, blood eosinophil count; BMI, body mass index; CRwNP, chronic rhinosinusitis with nasal polyps; FEV_1, forced expiratory volume in 1 s; GINA, Global Initiative for Asthma; OCS, oral corticosteroid; SEA, severe eosinophilic asthma; SPT, skin prick test.

Summary

- Traditional clinical phenotyping in severe eosinophilic asthma does not predict biologic treatment response.
- Cluster analysis identifies patient groups with differing mepolizumab responsiveness, guiding personalised therapy.

and data were collected using a shared, anonymised database. Ethical approval was secured from each centre's ethics committee (co-ordinator centre: Catania, Italy; document number: 33/2020/PO–14/April/2020).

Eligible patients met ATS/ERS and GINA criteria for severe asthma, had eosinophil counts ≥300 cells/μL or ≥150 cells/μL if on maintenance oral corticosteroids (mOCS) and experienced at least two exacerbations in the previous year [5, 6]. Outcomes were assessed at 6 and 12 months (T6 and T12), focusing on (1) elimination of exacerbations and OCS use (super-response) and (2) elimination of exacerbations and OCS use, asthma control (ACT ≥20) and FEV1%-predicted ≥80% (remission).

Cluster analysis was performed using the Partitioning Around Medoids (PAM) algorithm, incorporating baseline variables and clinical response data. Statistical analysis included chi-square tests, Student's *t*-tests and logistic regression. Clusters were validated using bootstrap resampling, and all analyses were conducted in R 4.2.1.

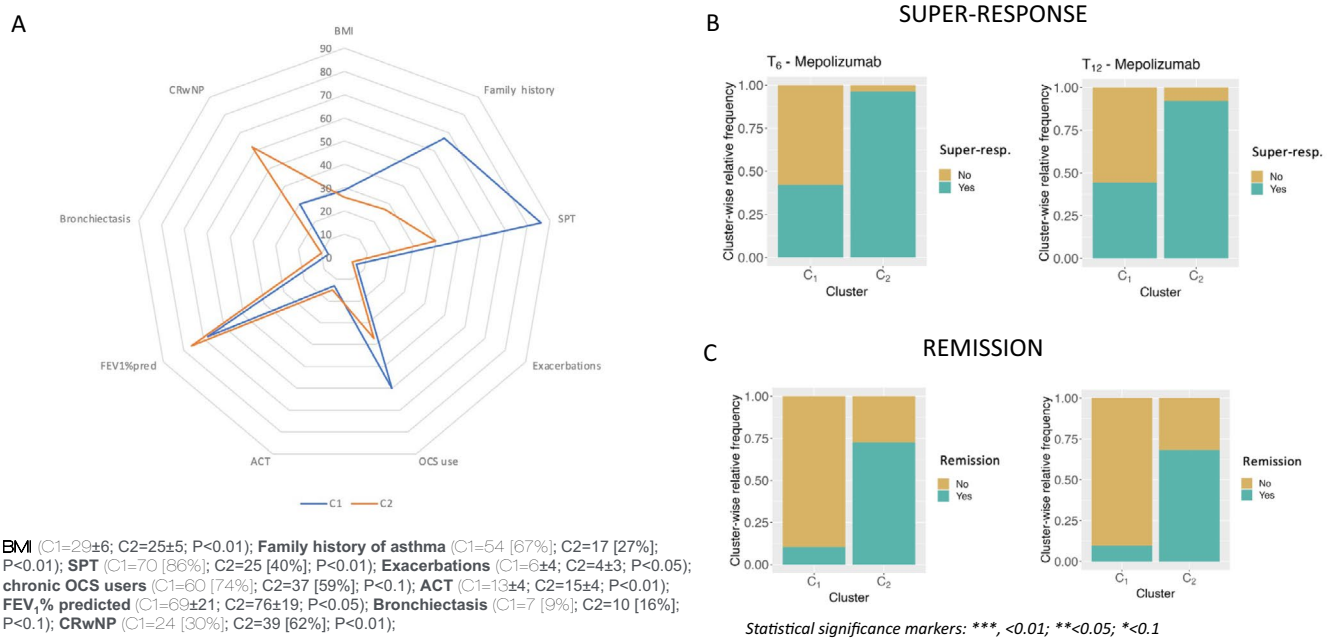
The analysis included 131 patients at T6 and 144 patients at T12. The mean age at asthma onset was 57 ± 13 years, with an average disease duration of approximately 20 years. Female patients comprised 69% of the cohort. The population was slightly overweight (mean BMI = 27 ± 6), and 67% of patients were on oral corticosteroids (OCS). A family history of asthma was reported in 50%, while 66% had a positive skin prick test (SPT) for respiratory allergens. The mean pre-bronchodilator FEV1% predicted was 72% ± 20%, 12% of patients had bronchiectasis, and 44% had chronic rhinosinusitis with nasal polyps (CRwNP). The mean blood eosinophil count (BEC) was 659 ± 476 cells/μL, and the total serum IgE was 719 ± 3321 IU/mL.

The optimal number of clusters for both time points was two. Cluster 1 (C1) had a higher proportion of patients with a family history of asthma (C1 = 67% vs. C2 = 27%), positive SPT (C1 = 86% vs. C2 = 40%), higher BMI (C1 = 29 ± 6 vs. C2 = 26 ± 5), more exacerbations per year (C1 = 6 ± 4 vs. C2 = 4 ± 3), lower prevalence of CRwNP (C1 = 30% vs. C2 = 62%), worse disease control (ACT C1 = 13 ± 4 vs. C2 = 15 ± 4) and more compromised lung function (FEV1% predicted C1 = 68 ± 21% vs. C2 = 76 ± 19%) (Figure 1A).

Super-response rates in Cluster 2 (C2) were significantly higher at both T6 (96.4%) and T12 (92.1%) compared to Cluster 1 (C1: 42.1% at T6, 44.4% at T12) ($p < 0.01$) (Figure 1B). Remission rates were also higher in C2 (72.7% at T6, 68.3% at T12) vs. C1 (10.5% at T6, 9.9% at T12) ($p < 0.01$) (Figure 1C).

At T12, super-response was primarily predicted by a family history of asthma in both clusters OR_C1 = 3.15; OR_C2 = 1.35; ratio C_1/C_2 = 2.34, indicating that patients with a family history of asthma in C1 had a 134% higher chance of responding to mepolizumab compared to those in C2. Remission at T12 was similarly predicted by family history of asthma (OR_C1 = 3.89; OR_C2 = 2.96), SPT (OR_C2 = 3.09; OR_C1 = 1.19) and FEV1% predicted (OR_C2 = 2.88; OR_C1 = 1.89).

At T6, super-response was strongly predicted by positive SPT in both clusters (OR_C1 = 14.55; OR_C2 = 2.01) and ACT



BMI (C1=29±6; C2=25±5; P<0.01); **Family history of asthma** (C1=54 [67%]; C2=17 [27%]; P<0.01); **SPT** (C1=70 [86%]; C2=25 [40%]; P<0.01); **Exacerbations** (C1=6±4; C2=4±3; P<0.05); **chronic OCS users** (C1=60 [74%]; C2=37 [59%]; P<0.1); **ACT** (C1=13±4; C2=15±4; P<0.01); **FEV$_1$% predicted** (C1=69±21; C2=76±19; P<0.05); **Bronchiectasis** (C1=7 [9%]; C2=10 [16%]; P<0.1); **CRwNP** (C1=24 [30%]; C2=39 [62%]; P<0.01);

*Statistical significance markers: ***, <0.01; **<0.05; *<0.1*

FIGURE 1 | Differences in selected variables between the clusters (A). Super-response (B) and remission (C) at T6 and T12, according to different clusters.

(OR_C2 = 1.62; OR_C1 = 0.57). Remission was associated not only with SPT (OR_C2 = 2.70; OR_C1 = 1.51) but also with CRwNP (OR_C2 = 2.76; OR_C1 = 1.21), FEV1% predicted (OR_C2 = 1.91; OR_C1 = 1.61), OCS use (OR_C2 = 2.43; OR_C1 = 1.32) and smoking (OR_C2 = 5.12; OR_C1 = 0.81).

This study's findings align with previous research in some areas but diverge in others [7–9]. Higher FEV1 remains a strong predictor of remission with mepolizumab, consistent with earlier studies. However, traditional biomarkers like BEC and total serum IgE, often linked to treatment outcomes, showed limited predictive value in this analysis.

Notably, clinical phenotypes like chronic rhinosinusitis with nasal polyps (CRwNP) and allergy sensitisation (SPT) did not fully explain the different responses to mepolizumab. While SPT and family history of asthma were more prevalent in Cluster 1, they were linked to better outcomes within each group, indicating complex interactions between these factors and treatment responses, depending on the broader patient profile.

The strength of this study lies in its novel clustering approach, using bootstrapping to identify two distinct and clinically meaningful subgroups of SEA patients. This method, unlike traditional geometric clustering, better reflects the biological variability of SEA and simplifies treatment decision-making. By focusing on only two clusters, the study avoids the complexity of multiple subgroup comparisons and offers more actionable insights for personalised treatment strategies. The multicentre nature of the research enhances its generalisability, with several predictors validated by previous studies.

These findings underscore the importance of subgroup identification in personalised treatment strategies. Prospective validation studies are needed to confirm whether this clustering approach can guide biologic selection.

Author Contributions

D.D.B. and M.B. developed the concept of this study. M.B. did the statistical analysis. D.D.B. wrote the first manuscript draft. G.P. and N.C. revised the first manuscript draft. All Authors contributed to collect patients' data and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. J. E. Kavanagh, G. d'Ancona, M. Elstad, et al., "Real-World Effectiveness and the Characteristics of a "Super-Responder" to Mepolizumab in Severe Eosinophilic Asthma," *Chest* 158, no. 2 (2020): 491–500.

2. I. Pavord, F. Gardiner, L. G. Heaney, et al., "Remission Outcomes in Severe Eosinophilic Asthma With Mepolizumab Therapy: Analysis of the REDES Study," *Frontiers in Immunology* 12, no. 14 (2023): 1150162.

3. E. H. Bel, S. E. Wenzel, P. J. Thompson, et al., "Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma," *New England Journal of Medicine* 371, no. 13 (2014): 1189–1197.

4. I. D. Pavord, S. Korn, P. Howarth, et al., "Mepolizumab for Severe Eosinophilic Asthma (DREAM): A Multicentre, Double-Blind, Placebo-Controlled Trial," *Lancet* 380 (2012): 651–659.

5. F. Holguin, J. C. Cardet, K. F. Chung, et al., "Management of Severe Asthma: A European Respiratory Society/American Thoracic Society Guideline," *European Respiratory Journal* 55, no. 1 (2020): 1900588.

6. Global Initiative for Asthma, "Global Strategy for Asthma Management and Prevention," (2024) Updated May 2024.

7. C. Bal, W. Pohl, K. Milger, et al., "Characterization of Obesity in Severe Asthma in the German Asthma Net," *Journal of Allergy and Clinical Immunology: In Practice* 11, no. 11 (2023): 3417–3424.e3.

8. D. Thomas, V. M. McDonald, S. Stevens, et al., "Biologics (Mepolizumab and Omalizumab) Induced Remission in Severe Asthma Patients," *Allergy* 79, no. 13 (2024): 384–392.

9. S. Hansen, M. Søndergaard, A. von Bülow, et al., "Clinical Response and Remission in Patients With Severe Asthma Treated With Biologic Therapies," *Chest* S0012–3692, no. 23 (2023): 5695–5697.