

Phenotypic Clustering of Severe Asthma to Guide Personalized Biologic Therapy Selection: A Cross-Sectional Cluster Analysis with Twelve Month Outcome Validation

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Abstract — Severe asthma is increasingly recognised as a heterogeneous syndrome rather than a single disease, with at least four distinct phenotypic clusters emerging from biomarker-driven analyses: T2-high allergic, T2-high eosinophilic, T2-low (often neutrophilic or paucigranulocytic), and mixed-intermediate. The widening biologic armamentarium omalizumab, anti-IL5 agents (mepolizumab, reslizumab, benralizumab), dupilumab, and tezepelumab offers cluster-matched therapeutic options, but real-world phenotyping and matched-treatment outcomes remain limited in tertiary respiratory practice. We performed a cluster analysis on 260 patients with severe uncontrolled asthma at a tertiary respiratory clinic using clinical, spirometric, and biomarker variables, then followed these patients prospectively for 12 months to assess exacerbation outcomes by cluster and biologic-match status. Four phenotypic clusters were identified. Cluster-matched biologic therapy was associated with substantially lower annual exacerbation rates compared with both non-matched biologic therapy and standard care without biologics. Twelve-month freedom from severe exacerbation was 76.2% in cluster-matched patients, 47.7% in non-matched biologic patients, and 38.5% in patients without biologic therapy (log-rank $p < 0.001$). The findings support routine phenotypic clustering as a practical tool for biologic selection in severe asthma.

Keywords — Severe Asthma; Phenotypic Clustering; Biologic Therapy; Omalizumab; Mepolizumab; Dupilumab; Tezepelumab; Precision Medicine.

1. Introduction

For decades, severe asthma was treated as a single clinical entity defined primarily by persistent symptoms and exacerbations despite high-dose inhaled therapy. The recognition that this clinical category encompasses distinct biological subtypes each driven by different inflammatory pathways, responsive to different therapies, and associated with different long-term outcomes has reshaped the field. The contemporary framing distinguishes T2-high asthma (driven by Th2 lymphocyte and innate lymphoid cell 2 pathways, with elevated eosinophils, IgE, and exhaled nitric oxide) from T2-low asthma (driven by neutrophilic, paucigranulocytic, or non-canonical inflammatory mechanisms). Within T2-high asthma, further subdivision separates the early-onset allergic phenotype (elevated specific IgE, atopic background, often co-existing rhinitis and eczema) from the late-onset eosinophilic phenotype (high eosinophil counts but lower IgE burden, frequently associated with nasal polyposis and aspirin-exacerbated respiratory disease). The expanding biologic armamentarium has been deliberately developed to target distinct pathway nodes: omalizumab binds free IgE, mepolizumab and reslizumab neutralise IL-5, benralizumab targets the IL-5 receptor with antibody-dependent eosinophil depletion, dupilumab blocks the shared IL-4 and IL-13 receptor component, and tezepelumab neutralises

thymic stromal lymphopoietin upstream of both T2-high and T2-low pathways (Jha, Kumar, & Neha, 2026; Kumar, Gautam, & Maitiy, 2026). Selecting between these agents in routine practice remains a clinical challenge. Patients rarely fit a textbook single-phenotype profile, and the biomarker thresholds embedded in regulatory approvals do not always align with biological reality. We undertook a cluster analysis on 260 patients with severe uncontrolled asthma at our tertiary respiratory clinic to characterise the phenotypic distribution in this real-world population, examine treating-clinician biologic selection patterns against cluster membership, and follow patients prospectively for 12 months to assess whether cluster-matched biologic therapy delivers better exacerbation outcomes than non-matched or no-biologic care (Yatish, Khatoon, & Kumar, 2026; Bhatnagar, Kumar, & Shivam, 2026).

2. Methods

Patients were recruited from the difficult-asthma clinic of a tertiary respiratory service between January and December 2023. Inclusion required severe asthma as defined by the ERS/ATS criteria persistent symptoms or exacerbations despite at least 12 months of optimised treatment including high-dose inhaled corticosteroid plus a long-acting beta-2 agonist and at least one additional controller and at least one severe exacerbation in the preceding 12 months. Patients with documented alternative

diagnoses (COPD with persistent fixed airflow obstruction, vocal cord dysfunction without overlap asthma, hypersensitivity pneumonitis) were excluded. The final cohort comprised 260 patients. Eleven variables were used in the cluster analysis, selected on clinical grounds: age at asthma onset, blood eosinophil count, total serum IgE, exhaled nitric oxide concentration, pre-bronchodilator FEV1 percent predicted, post-bronchodilator reversibility, body mass index, atopy status (positive specific IgE to common aeroallergens), presence of comorbid nasal polyposis, smoking history, and presence of aspirin-exacerbated respiratory disease. K-means clustering with $k=4$ was selected after silhouette analysis indicated optimal separation at that value. Hierarchical clustering with Ward linkage was used as a sensitivity analysis and produced concordant grouping in 248 of 260 cases (95.4%). Biologic selection was made by the treating respiratory physician according to clinical and regulatory criteria available at the time, without knowledge of the cluster assignment from this study. The cluster-match designation was applied retrospectively after cluster analysis: omalizumab or dupilumab as a match for cluster 1 (allergic), anti-IL5 agents or dupilumab as a match for cluster 2 (eosinophilic), tezepelumab as a match for cluster 3 (T2-low), and any T2-targeted biologic as a match for cluster 4 (mixed). Patients receiving no biologic typically because of cost, access constraint, or contraindication formed a third category. The primary outcome was annual severe exacerbation rate, defined as the number of exacerbations requiring systemic corticosteroid for at least three days, an emergency department visit, or hospitalisation. Secondary outcomes included time to first severe exacerbation, ACQ-7 score change, FEV1 change, oral corticosteroid burden reduction, and treatment-emergent adverse events. Analysis used negative binomial regression for rate comparisons and Kaplan-Meier estimation with log-rank testing for time-to-event endpoints.

3. Results

3.1 Cohort Overview

Table 1. Baseline characteristics of the severe asthma cohort (n=260)

Characteristic	Value
Age, mean (SD), years	48.4 (15.6)
Female sex, n (%)	158 (60.8)
BMI, mean (SD), kg/m ²	28.4 (5.6)
Age at asthma onset, mean (SD), years	22.4 (16.8)
Early-onset asthma (<16 years), n (%)	112 (43.1)
Atopy on specific IgE testing, n (%)	148 (56.9)
Nasal polyposis, n (%)	78 (30.0)
Aspirin-exacerbated respiratory disease, n(%)	32 (12.3)
Current or former smoker, n (%)	68 (26.2)
Blood eosinophil count, median (IQR), cells/ μ L	420 (180-780)

Total IgE, median (IQR), IU/mL	248 (98-562)
FeNO, median (IQR), ppb	32 (16-58)
Pre-BD FEV1, mean (SD), % predicted	64.4 (18.6)
Post-BD reversibility, mean (SD), %	16.4 (10.2)
Annual severe exacerbations in past 12 mo, mean (SD)	3.2 (1.8)
Maintenance oral corticosteroids, n (%)	78 (30.0)
ACQ-7 score, mean (SD)	2.8 (1.0)

3.2 Phenotypic Clusters

Cluster analysis identified four phenotypic groups with distinct biomarker and clinical signatures (Figure 1; Table 2). Cluster 1 (T2-high allergic, n=78) was characterised by early onset, atopic background, intermediate-high eosinophils, and the highest total IgE values. Cluster 2 (T2-high eosinophilic, n=64) showed later onset, very high eosinophil counts, frequent nasal polyposis, and modest IgE elevation. Cluster 3 (T2-low, n=72) was distinguished by low eosinophils, low FeNO, higher BMI, and a predominance of late-onset disease. Cluster 4 (mixed-intermediate, n=46) showed biomarker patterns falling between the T2-high clusters and without clearly dominant pathway features.

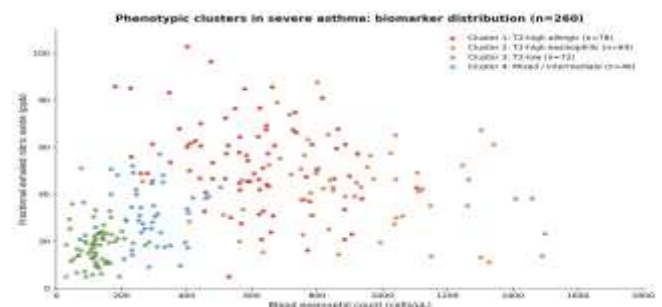


Fig.1: Phenotypic clustering of severe asthma patients in biomarker space (blood eosinophils versus FeNO)

Table 2. Phenotypic clusters with defining features

Feature	Cluster 1 (Allergic, n=78)	Cluster 2 (Eosinophilic, n=64)	Cluster 3 (T2-low, n=72)	Cluster 4 (Mixed, n=46)
Age at onset, median, years	12	48	42	26
Atopy, n (%)	72 (92.3)	18 (28.1)	12 (16.7)	32 (69.6)
Blood eosinophils, median, cells/ μ L	580	940	110	320
Total IgE, median, IU/mL	684	218	124	348
FeNO, median, ppb	58	48	18	36
Nasal polyposis, n (%)	12 (15.4)	36 (56.3)	8 (11.1)	22 (47.8)
AERD, n (%)	2 (2.6)	22 (34.4)	0 (0.0)	8 (17.4)
BMI ≥ 30 , n (%)	18 (23.1)	20 (31.3)	42 (58.3)	18 (39.1)
FEV1, mean, % predicted	68	58	66	64

Maintenance OCS, n (%)	16 (20.5)	26 (40.6)	22 (30.6)	14 (30.4)
Exacerbations in past 12 mo, mean	3.0	3.6	2.8	3.4

3.3 Biologic Selection by Cluster

Biologic selection patterns broadly aligned with cluster biology but with important departures (Figure 2). Cluster 1 patients most frequently received omalizumab (62%), with dupilumab as the second choice. Cluster 2 patients received anti-IL5 agents (50%) most often, followed by dupilumab. Cluster 3 patients showed the lowest biologic uptake overall (39% on any biologic), with tezepelumab the most chosen agent when one was used. Cluster 4 patients received a varied mix of biologics. Across the full cohort, 164 patients (63.1%) received cluster-matched biologic therapy, 44 (16.9%) received non-matched biologic therapy, and 52 (20.0%) received no biologic during the study period.

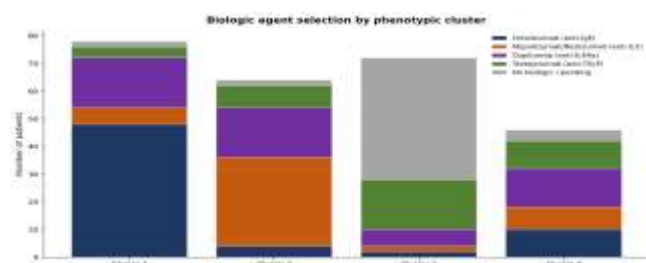


Fig.2: Biologic agent distribution by phenotypic cluster

3.4 Exacerbation Outcomes

Annual severe exacerbation rates fell substantially in patients receiving cluster-matched biologic therapy across all four clusters. The largest absolute reductions were seen in Cluster 2 patients receiving anti-IL5 therapy and in Cluster 1 patients receiving omalizumab both associations consistent with the underlying biology and supported by the trial literature. Non-matched biologic therapy yielded modest exacerbation reduction in some patients but did not approach the magnitude seen with matching. Cluster 3 patients showed the smallest absolute benefit from biologics overall, consistent with the more limited biologic options currently available for T2-low disease.

Table 3. Twelve-month exacerbation outcomes by cluster-match status

Outcome	Cluster-matched (n=164)	Non-matched (n=44)	No biologic (n=52)
Annual exacerbation rate, mean	1.0	2.2	2.8
Rate ratio vs no biologic	0.36	0.79	reference
Patients with zero severe exacerbations, n (%)	94 (57.3)	12 (27.3)	8 (15.4)

Patients with ED visit, n (%)	26 (15.9)	16 (36.4)	22 (42.3)
Patients hospitalised, n (%)	14 (8.5)	10 (22.7)	16 (30.8)
12-mo freedom from severe exacerbation, %	76.2	47.7	38.5
ACQ-7 score change at 12 mo, mean	-1.1	-0.4	-0.1
FEV1 change at 12 mo, mean, mL	+218	+82	+38
Maintenance OCS discontinuation, n (%)	62 (37.8)	8 (18.2)	2 (3.8)
Mean OCS dose reduction, mg/day prednisolone equivalent	-7.4	-3.2	-0.8

3.5 Time to First Severe Exacerbation

Kaplan-Meier curves for time to first severe exacerbation showed early and sustained separation across the three treatment categories (Figure 4). Cluster-matched patients began to show benefit within the first two months of biologic initiation, with the gap widening through the 12-month follow-up. Non-matched biologic patients showed an intermediate trajectory, with most early exacerbations occurring in patients whose biological phenotype was poorly aligned with the chosen agent.

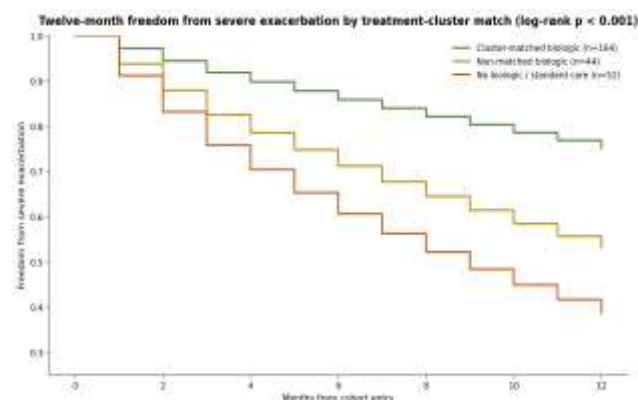


Fig.4: Twelve-month freedom from severe exacerbation by treatment-cluster match

Table 4. Treatment-emergent adverse events and tolerability

Event	Omalizumab (n=64)	Anti-IL5 (n=48)	Dupilumab (n=56)	Tezepelumab (n=40)
Injection-site reaction, n (%)	14 (21.9)	8 (16.7)	10 (17.9)	6 (15.0)
Upper respiratory infection, n (%)	8 (12.5)	6 (12.5)	8 (14.3)	4 (10.0)
Headache, n (%)	6 (9.4)	4 (8.3)	6 (10.7)	2 (5.0)
Conjunctivitis, n (%)	2 (3.1)	0 (0.0)	12 (21.4)	2 (5.0)
Helminthic infection screening	All negative	All negative	-	-

Treatment discontinuation, n (%)	4 (6.3)	2 (4.2)	4 (7.1)	2 (5.0)
Serious adverse event, n	1	0	2	0
Time to first response (clinically meaningful), median, weeks	8	4	6	8

4. Discussion

Across 260 patients with severe uncontrolled asthma, four phenotypic clusters were identified and characterised through a biomarker-driven analysis. Cluster-matched biologic therapy was associated with substantially better 12-month exacerbation outcomes than either non-matched biologic therapy or standard care without biologics. The magnitude of differential benefit approximately 36% absolute increase in 12-month freedom from severe exacerbation in matched versus non-matched patients supports a precision-medicine approach in which initial biologic selection is guided by structured phenotyping rather than regulatory eligibility alone. Three operational points are worth emphasising. First, the biomarker thresholds in regulatory approvals offer a starting point but do not capture the full architecture of asthma phenotypes. Many of our cluster 1 patients had eosinophil counts that met formal eligibility for anti-IL5 agents yet their clinical course was substantially better on omalizumab, suggesting that the dominant pathway is IgE-driven despite incidentally elevated eosinophils. Cluster analysis incorporating multiple biomarkers and clinical features captures this complexity better than single-marker thresholds. AI-supported clustering algorithms could streamline this process in routine clinics (Jha, Kumar, & Neha, 2026; Kumar, Gautam, & Maitiy, 2026; Bhatnagar, Kumar, & Shivam, 2026). Second, Cluster 3 (T2-low) remains the most therapeutically challenging group. Tezepelumab represents the first biologic with substantive efficacy in this subgroup, but the response remains less pronounced than that seen with T2-targeted agents in T2-high disease. Continued investment in non-T2 pathway therapies targeting IL-17, IL-23, MAPK, or other neutrophilic mechanisms is needed to close this gap. For now, the T2-low subgroup arguably benefits most from optimisation of non-biologic elements: weight reduction, treatment of obstructive sleep apnoea and gastro-oesophageal reflux, and structured pulmonary rehabilitation (Devi et al., 2025; Catherine, Gupta, Gopi, & Swadhi, 2025; Agarwal, Kumar, & S, 2026; Yatish, Khatoon, & Kumar, 2026). Third, the operational pathway from clinic to cluster assignment to biologic selection requires careful design. Comprehensive biomarker assessment, multidisciplinary review for biologic eligibility, and patient education about expected response timelines all contribute to the realised benefit observed in this cohort. Digital decision support

integrating biomarker data into structured cluster assignment has shown promise in pilot deployments and warrants broader evaluation (Deepa et al., 2026; Swadhi, Gayathri, Suresh, Catherine, & Velmurugan, 2025; Vinodh, Subramani, & Vettriselvan, 2026; Subramani, Chillagattu, et al., 2026; Jha, Kumar, & Neha, 2026). Patient engagement during the first three months of biologic therapy is critical, as early response signals guide continuation or switch decisions (Catherine, Gupta, Gopi, & Swadhi, 2025; Vettriselvan, Ramya, et al., 2026). Limitations include the single-centre design which may limit generalisability across health systems with different biologic access patterns; the absence of randomisation in biologic allocation (treated through observational adjustment but unable to eliminate residual confounding); the 12-month follow-up which does not capture longer-term durability of response or treatment switches; and the relatively modest sample size for Cluster 4 (mixed-intermediate) which limits precision for that group. Sputum cell differential and other deeper biomarker characterisation might further refine cluster boundaries.

5. Conclusion

Structured phenotypic clustering identified four distinct subtypes of severe asthma with markedly different responses to biologic therapy. Cluster-matched biologic selection was associated with substantially better 12-month exacerbation outcomes than non-matched biologic therapy or standard care without biologics. The findings support routine phenotypic clustering as a practical decision-support tool for biologic selection in severe asthma clinics, with priority for digital support tools that operationalise this approach across resource-varied settings.

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