Biomarker-defined clusters by level of Type 2 inflammatory involvement in severe asthma

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Introduction

- The majority of therapies currently available for asthma are targeted towards patients displaying evidence of Type 2 (T2) inflammation, characterized by aeroallergen sensitization and eosinophilia.
- However, asthma is a heterogenous condition, and can present on a spectrum of inflammation, from high to low T2 involvement.
- There is no consensus on the definition of T2-low asthma, and there is a need for better understanding of underlying clinical attributes and patient phenotypes
- Biomarker-defined clusters of severe asthma patients have previously been identified via hierarchical cluster analysis; a cluster of older females with low-to-medium T2 biomarkers was characterized in the BRISAR study[1] but the robustness of these clusters has not been established.
- Finite mixture models provide a principled statistical approach to clustering that can assist a data-driven strategy for identifying biomarker-defined clusters in severe asthma.

Aim(s)

- To describe biomarker-defined clusters (blood eosinophil counts [BEC], FeNO, and serum IgE [IgE]) in severe asthma patients, and characterize T2-low asthma using a model-based approach to clustering.
- To compare the reductions in exacerbation rates after biologic initiation for model-defined T2-low cluster(s) and clusters with higher levels of T2 inflammation.

Methods

- Patients in the International Severe Asthma Registry (ISAR) with baseline biomarker data (BEC, FeNO and IgE) were included, regardless of biologic use.
- The baseline biomarker measure was the highest biomarker measurement in the 1 year preceding biologic initiation for biologic initiators, and the highest biomarker measurement at the first ISAR visit for non-biologic initiators.
- A Gaussian finite mixture model was used to perform cluster analyses using baseline BEC, FeNO and IgE standardized by z score.
- Among patients who initiated a biologic therapy, Poisson regression analysis was used to compare exacerbation rates across clusters following initiation of biologic therapy (Anti-IgE, Anti-IL5/IL-5R or Anti-IL4R therapy); a multivariable model was fitted with adjustment for baseline exacerbation rate.
- An alternative strategy for identifying T2-low patients was explored using prespecified clinical thresholds. Patients were defined as T2-low if BEC <300cells/µL & FeNO <25ppb & IgE <75 IU/mL.
- Comparisons were made between exacerbation rates in the T2-low sub-groups defined using cluster analysis and clinical thresholds.

Figure 1: Five component Gaussian finite mixture model

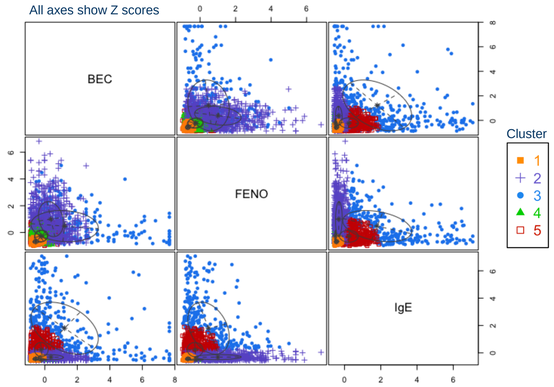

Table 1: Median (IQR) biomarker levels and characteristics of clusters

	Cluster				
	1	2	3	4	5
N	819	672	354	636	773
BEC (cells/µL)	200 (120)	744 (562)	800 (1296)	400 (320)	300 (300)
FeNO (ppb)	14 (9)	89 (70)	52 (77)	34 (24)	31 (29)
IgE (IU/mL)	61 (116)	146 (158)	1418 (1676)	39 (49)	480 (409)
Females	68%	59%	54%	66%	56%
Age	53 (21)	54 (19)	54 (24)	56 (18)	54 (21)

Low Type 2 biomarkers (consistent with BRISAR and Gaussian finite mixture 5-cluster findings)

High BEC and FeNO

Triple biomarker high

High BEC

High IgE

Varied biomarker elevations highlight the complexity of Type 2 inflammatory involvement in severe asthma

Results

- 3,254 patients from 20 countries contributed biomarker data on BEC, FeNO and IgE.
- Five clusters were identified. Cluster 1 had low T2 biomarkers. Cluster 2 had high BEC and FeNO; Cluster 3, triple T2 biomarker high; Cluster 4, high BEC; Cluster 5, high IgE. (Figure 1, Table 1)
- After adjustment for baseline exacerbation levels, the T2-low sub-group (Cluster 1) experienced the highest rate of exacerbations following biologic initiation, suggesting a lack of response to biologic treatment. (Figure 2)
- The T2-low sub-group defined using pre-specified clinical thresholds (Cluster 1*; N=463) was smaller than Cluster 1 (N=819) with similar median BEC and FeNO but lower median IgE. (Table 2)
- T2-low sub-groups had higher adjusted rates of exacerbations following biologic initiation compared to the other clusters when identified using cluster analysis (IRR 1.11, 95% CI 0.99-1.26) or clinical thresholds (IRR 1.11, 95% CI 0.93-1.31)

Figure 2: Incident rate ratios for exacerbations following biologic initiation by cluster

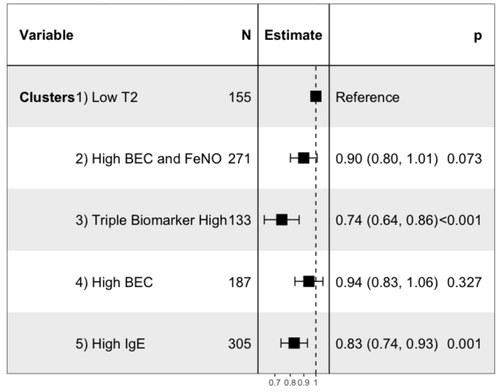

Table 2: Median biomarker levels and exacerbation rates in low T2 sub-groups defined by cluster analysis and/or use of clinical thresholds

	Clusters based on cluster analysis	
Clusters based on clinical thresholds	T2-high	T2-low
T2-high	N=2,411 BEC: 500 FeNO: 42 IgE: 215 Base exac: 3.3 △ exac: -0.7	N: 380 BEC: 200 FeNO: 15 IgE: 144 Base exac: 2.5 △ exac: -0.1
T2-low	N=24 BEC: 207 FeNO: 25 IgE: 23 Base exac: 5.3 △ exac: -0.8	N=439 BEC: 150 FeNO: 13 IgE: 22 Base exac: 3.3 △ exac: -0.2

Conclusions

- In line with BRISAR, we found a predominantly female cluster with low biomarker levels, suggesting low T2 involvement.
- The other 4 clusters varied in biomarker elevations, highlighting the complexity of T2 inflammatory involvement in severe asthma and supporting use of cluster analysis to define groups compared with using simple clinical thresholds.
- Preliminary evidence suggests that response to biologic initiation may be limited in the T2-low cluster.
- Further work is needed to characterise temporal stability and longer term outcomes for the T2-low phenotype.

References

1. Denton, E. et al. J Allergy Clin Immunol Pract 2021;9:2680-8.e7

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Audio Summary