Cluster analysis according to biomarker profile differentiates clinical subgroups in the International Severe Asthma Registry (ISAR)

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Abstract

Background

Inflammatory biomarkers are used to guide severe asthma therapy and may also identify activation of underlying inflammatory pathways. We examined biomarker profiles [immunoglobin E (IgE), blood eosinophils, and fractional exhaled nitric oxide (FeNO)] in a severe asthma cohort by employing both conventional cut-off values and cluster analysis.

Methods:

Our cross-sectional study included all adults with severe asthma (GINA step 5 or GINA step 4 and uncontrolled) enrolled in the International Severe Asthma Registry (ISAR) with available baseline measurement of three biomarkers. Pre-defined cut-off points for positivity were: IgE >=75kU/L, blood eosinophils >=300 cells/uL, FeNO >=25ppb. Hierarchical cluster analysis was performed using the three biomarkers, standardised by z-score, via Ward's method with an agglomerative approach.

Results:

Altogether, 1175 adult patients from 10 countries with severe asthma were included in the analysis with 64% females, mean age 53±15 (SD) years, body mass index (BMI) 30±8, post-bronchodilator FEV_1 2.2±0.8 litres, and 74±20% predicted. Overall, 59% were IgE positive, 57% eosinophil positive, and 58% FeNO positive, with considerable overlap. Cluster analysis yielded five clusters (*Table 1*, *Figure 1*). **Cluster 1** represented a large group (61% of total patients), typically comprised of highly symptomatic, older females with elevated BMI with relatively low biomarkers. **Cluster 2** (18% of patients) typically comprised older females with lower BMI than the first group with higher eosinophils and FeNO. **Cluster 3** (14%) typically comprised of older patients with lower BMI and preserved lung function and very high FeNO. **Cluster 4** (6%) comprised young patients with equal gender balance, low lung function, elevated BMI, a long duration of asthma, and very high IgE. **Cluster 5** (1%) was a small cluster of young males with low BMI, poor lung function, very high eosinophils and a high burden of sinonasal disease including nasal polyps. Maintenance oral corticosteroid use occurred in 46% overall and was similar across clusters.

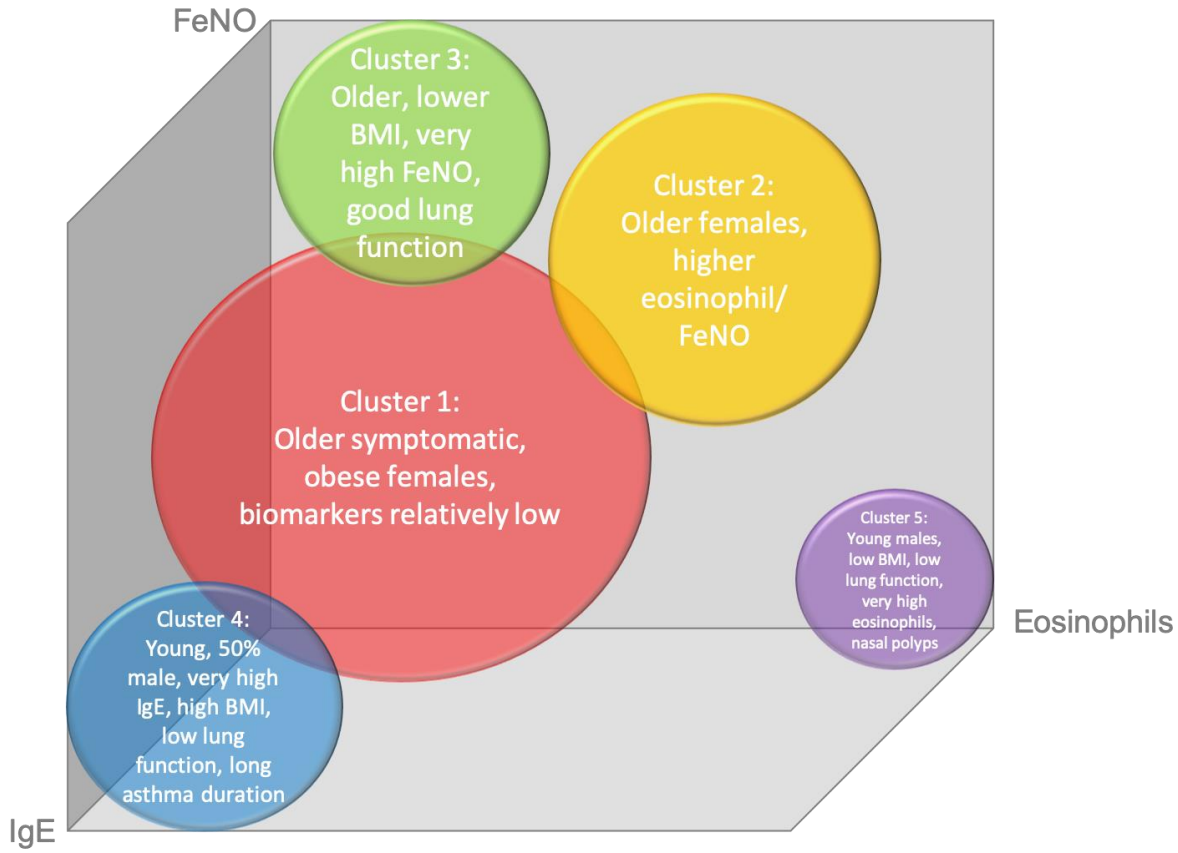
Conclusions:
In this large international severe asthma cohort, there was considerable overlap of biomarkers. Cluster analysis according to biomarker levels yielded five clusters, potentially indicating differential activation of underlying inflammatory pathways, important in the era of personalised medicine.

Table 1: Baseline characteristics of clusters

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Total	P-value
Number	669	200	149	66	13	1097	
Female sex	66%	67%	58%	53%	39%	64%	0.01
Age	53 ± 15	54 ± 14	56 ± 15*	49 ± 18*	51 ± 15	53 ± 15	0.03
BMI	31 ± 8*#	28 ± 6#	28 ± 6*	31 ± 8	27 ± 6	30 ± 8	<0.001
FEV_1 %predicted	71 ± 21	73 ± 23	75 ± 23	69 ± 18	68 ± 18	72 ± 22	NS
Blood eosinophils	240 ± 174	911 ± 372	509 ± 310	333 ± 225	4475 ± 1755	452 ± 581	<0.001
IgE	167 ± 202	187 ± 234	358 ± 402	1932 ± 1181	698 ± 824	318 ± 584	<0.001
FeNO	23 ± 17	51 ± 23	166 ± 140	38 ± 29	54 ± 44	46 ± 48	<0.001
Allergic sensitisation	78%	84%	72%	81%	60%	78%	NS
Asthma duration	26 ± 17	25 ± 17	26 ± 18	33 ± 17	28 ± 17	26 ± 17	NS
Asthma exacerbations	4.1 ± 3.9	4.5 ± 4.7	3.6 ± 3.2	3.7 ± 3.3	3.4 ± 2	4.1 ± 3.9	NS
Asthma control (poor)	84%	72%	80%	68%	71%	79%	0.003
Allergic rhinitis (current)	58%	63%	62%	65%	82%	60%	NS
Chronic rhinosinusitis (current)	66%	70%	62%	64%	75%	67%	NS
Nasal polyps (current)	30%	44%	34%	44%	71%	36%	0.01
Baseline oral corticosteroids	47%	48%	45%	38%	39%	46%	NS

* Denote significant between group values

Figure 1:


FeNO
Cluster 3: Older, lower BMI, very high FeNO, good lung function
Cluster 2: Older females, higher eosinophil/ FeNO
Cluster 1: Older symptomatic, obese females, biomarkers relatively low
Cluster 5: Young males, low BMI, low lung function, very high eosinophils, nasal polyps
Cluster 4: Young, 50% male, very high IgE, high BMI, low lung function, long asthma duration
Eosinophils
IgE