EMBER: Response to biologics along a gradient of T2 involvement in patients with severe asthma: a data-driven biomarker clustering approach

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Wang E et al. on behalf of the ISAR EMBER Working Group. Response to biologics along a gradient of T2 involvement in patients with severe asthma: a data-driven biomarker clustering approach, *JACI: In Practice* 2025; in press

Summary of the EMBER study

Objective

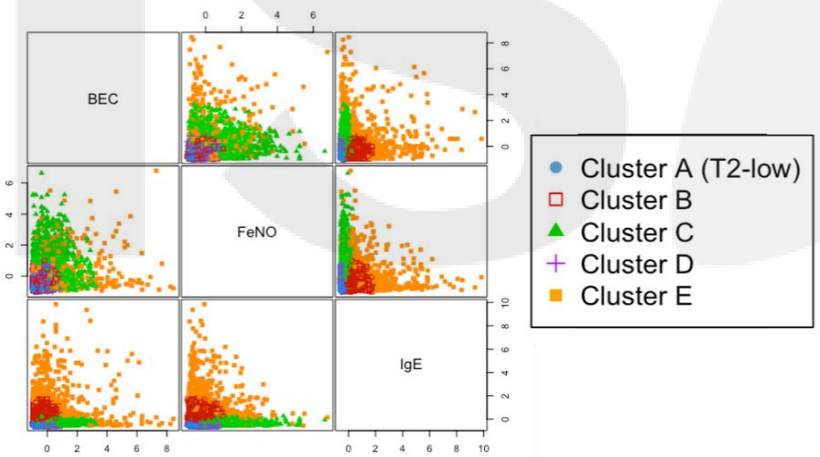
To characterize severe asthma phenotypes and compare pre- to post-biologic change in outcomes along a gradient of **T2-involvement**.

Methods

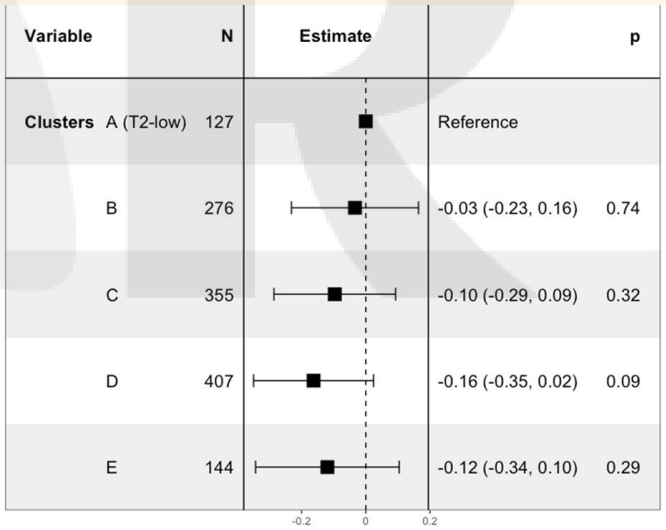
3,675 patients (23 countries) in **ISAR** were included; of these, 2,276 received biologics (Anti-IgE, Anti-IL5/5R, Anti-IL4Rα). **Clusters** were identified using a five-component Gaussian finite mixture model. **Change in outcomes** between 1 year pre- and post-biologic initiation were compared between clusters and by biologic class.

Results

Biomarker clusters identified using Gaussian finite mixture model (n=3675)



Change in annualized exacerbation rate pre- to post-biologic relative to Cluster A (T2-low)



Conclusions

Five biomarker clusters along a gradient of T2 involvement were identified using a **data-driven approach.** Biologic use was associated with **improved outcomes** in all clusters but tended to be better at the higher end of the T2 spectrum.

BEC: Blood eosinophil count; IgE: Immunoglobulin E; IL4Rα: Interleukin 4-receptor-alpha; IL5/5R: Interleukin 5/5-receptor; FeNO: Fractional exhaled nitric oxide; T2: Type 2

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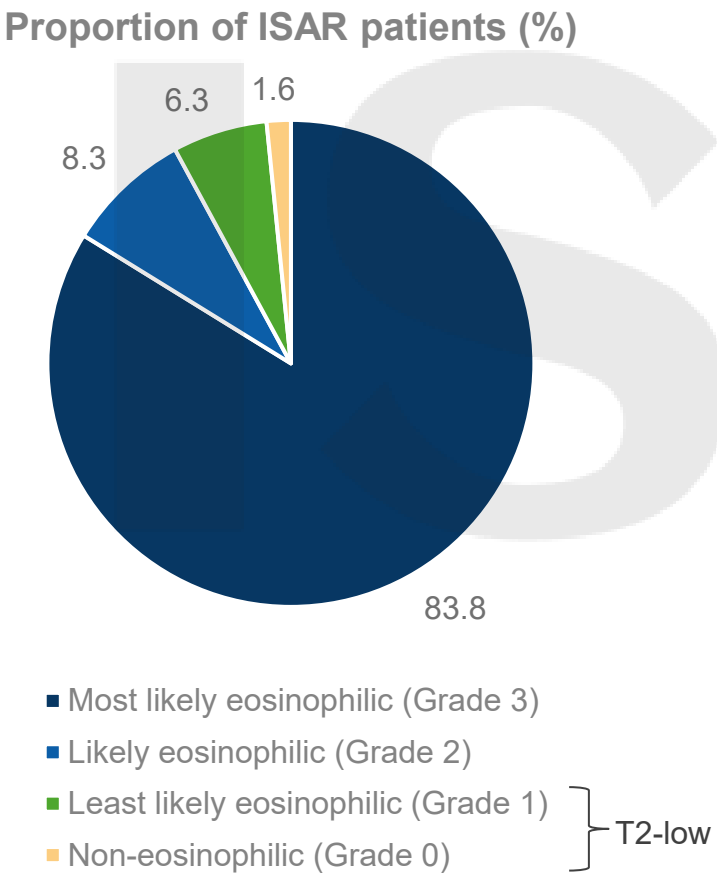
Background and Rationale

~8% of patients in ISAR are T2-low



Much remains unknown about T2-low asthma

- **No agreed definition** or clinical biomarker profile, other than the absence of T2 inflammation
- ICS and OCS suppress T2 biomarkers, **confounding** T2-low categorization
- T2-low asthma is **less responsive to biologics**, which target T2-related pathways
- **Limited effective treatment options** for T2-low asthma

ICS: Inhaled corticosteroids; OCS: Oral corticosteroids; T2: Type 2

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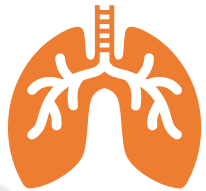
Aim

Describe **distributions of biomarkers** in patients with severe asthma along a gradient of T2 involvement

Phenotypically **characterize** patients along this gradient



Compare the **pre- to post-biologic initiation change in asthma outcomes** and HCRU across the gradient

Using a data-driven approach instead of pre-defined clinical biomarker cut-offs

HCRU: Healthcare resource utilization; T2: Type 2

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Data source: ISAR

23 countries

Total patients: **3,675**

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Methods

Patients

Inclusion criteria

- ISAR patients ≥18 years old, severe asthma*

Assessment of biomarker distributions

- Pre-biologic data for BEC, FeNO and IgE

Assessment of change in outcomes

- Received a biologic
- Data for ≥1 asthma outcomes with ≥24 weeks follow-up

Exclusion criteria

- Missing outcome data
- Outlier biomarker values†

Variables

Pre-biologic demographic and clinical characteristics

Pre-biologic biomarkers

- BEC, FeNO, IgE

Asthma outcomes:

- Annual exacerbation rate
- Highest post-bronchodilator FEV_1
- Asthma control
- HCRU

Statistical analyses

Biomarker clusters were identified using Gaussian finite mixture models.

Multivariable analysis was conducted with cluster A (T2-low) as reference.

- All models were adjusted for pre-biologic outcome, age, sex, pre-biologic long-term OCS use and country.

*Receiving treatment at Global Initiative for Asthma (GINA) 2018 Step 5 or with uncontrolled asthma at GINA Step 4; †BEC >5000 cells/μL; FeNO >500 ppb; IgE >10,000 IU/mL

BEC: Blood eosinophil count; FeNO: Fractional exhaled nitric oxide; FEV_1: Forced expiratory volume in 1 second; HCRU: Healthcare resource utilization; IgE: Immunoglobulin E; OCS: Oral corticosteroids

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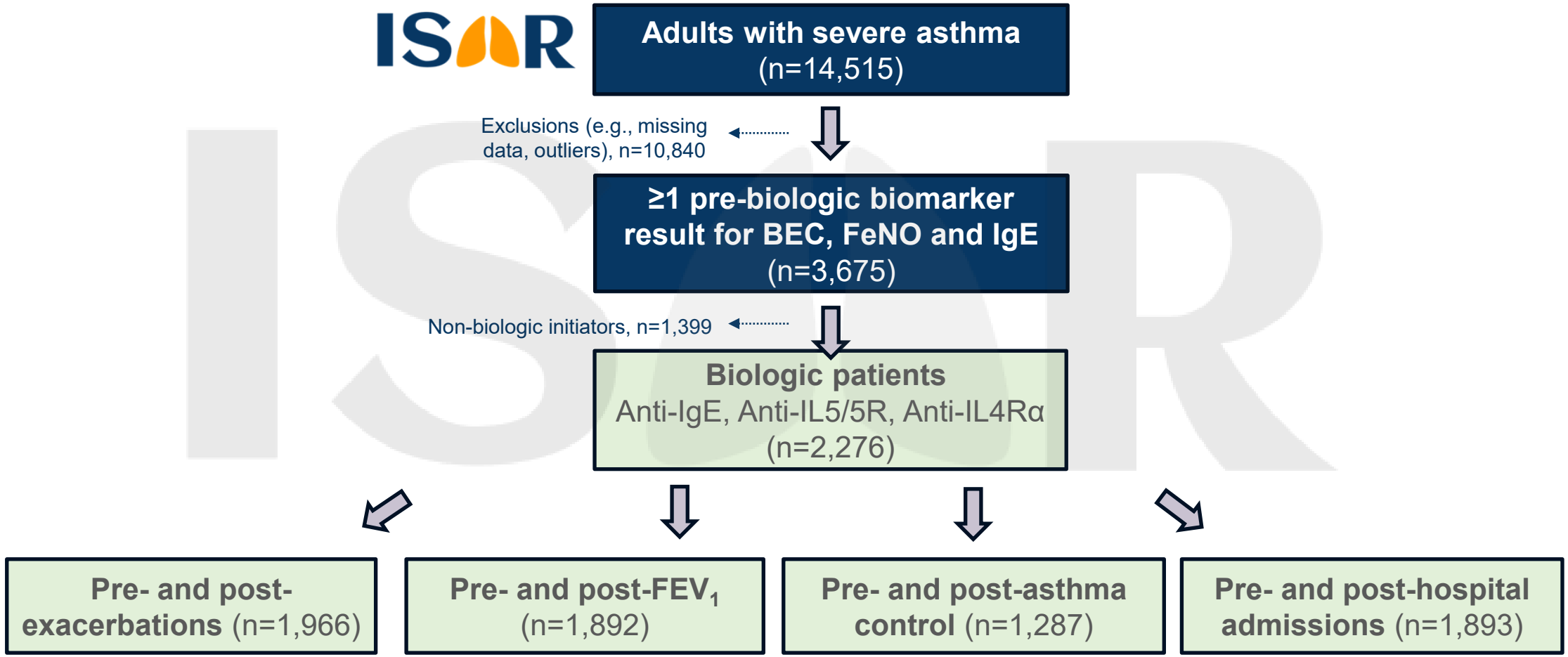
Patient Flow



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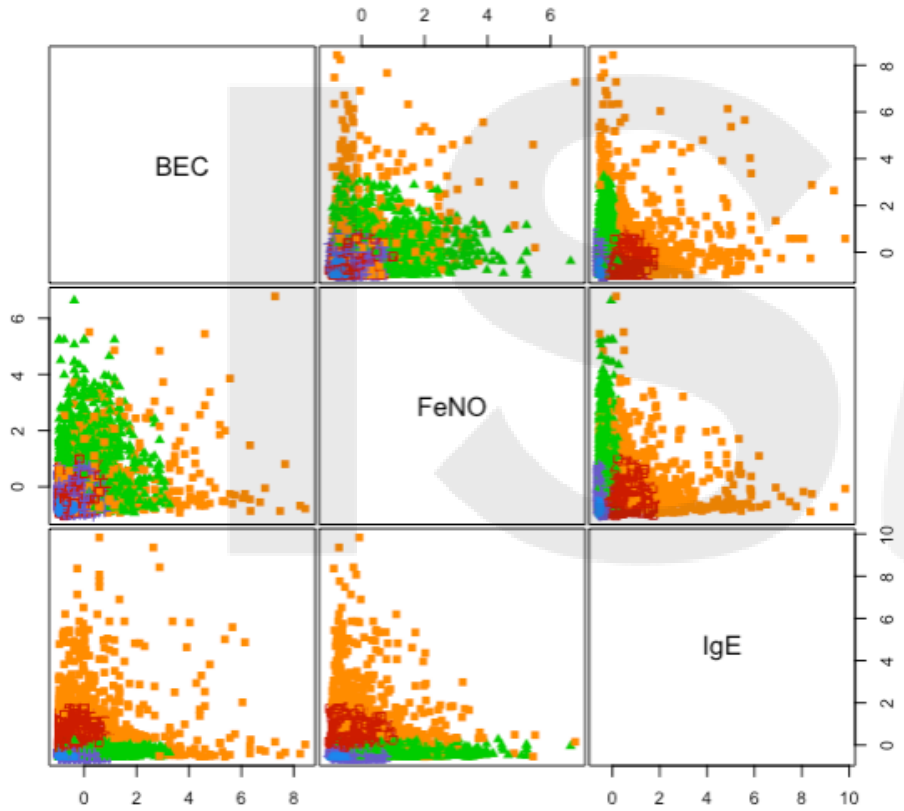
Five biomarker clusters (identified using Gaussian finite mixture models)



n=3,675

- Cluster A (T2-low)
- Cluster B
- Cluster C
- Cluster D
- Cluster E

Cluster A (16.4%)
- T2-low, triple-biomarker-low

Cluster B (20.4%)
- High IgE, intermediate BEC

Cluster C (22.9%)
- High BEC + FeNO

Cluster D (30.3%)
- Triple-biomarker-intermediate

Cluster E (10.0%)
- Triple-biomarker-high

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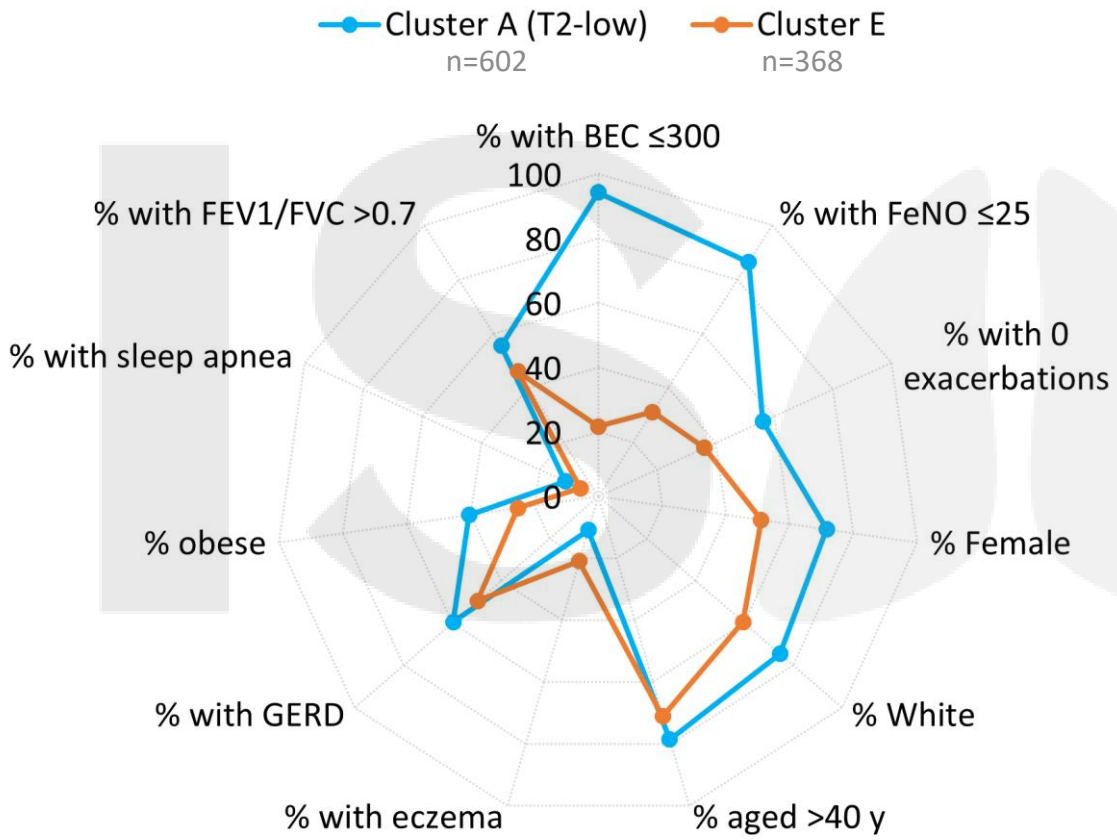
Demographic and clinical characteristics of Clusters A and E



Cluster A (vs Cluster E)

- Tended to be female, White, and have a lower exacerbation rate
- More likely to have GERD and other potentially OCS-related comorbidities

BEC: Blood eosinophil count; FeNO: Fractional exhaled nitric oxide; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; GERD: Gastroesophageal reflux disease; IgE: Immunoglobulin E; T2: Type 2

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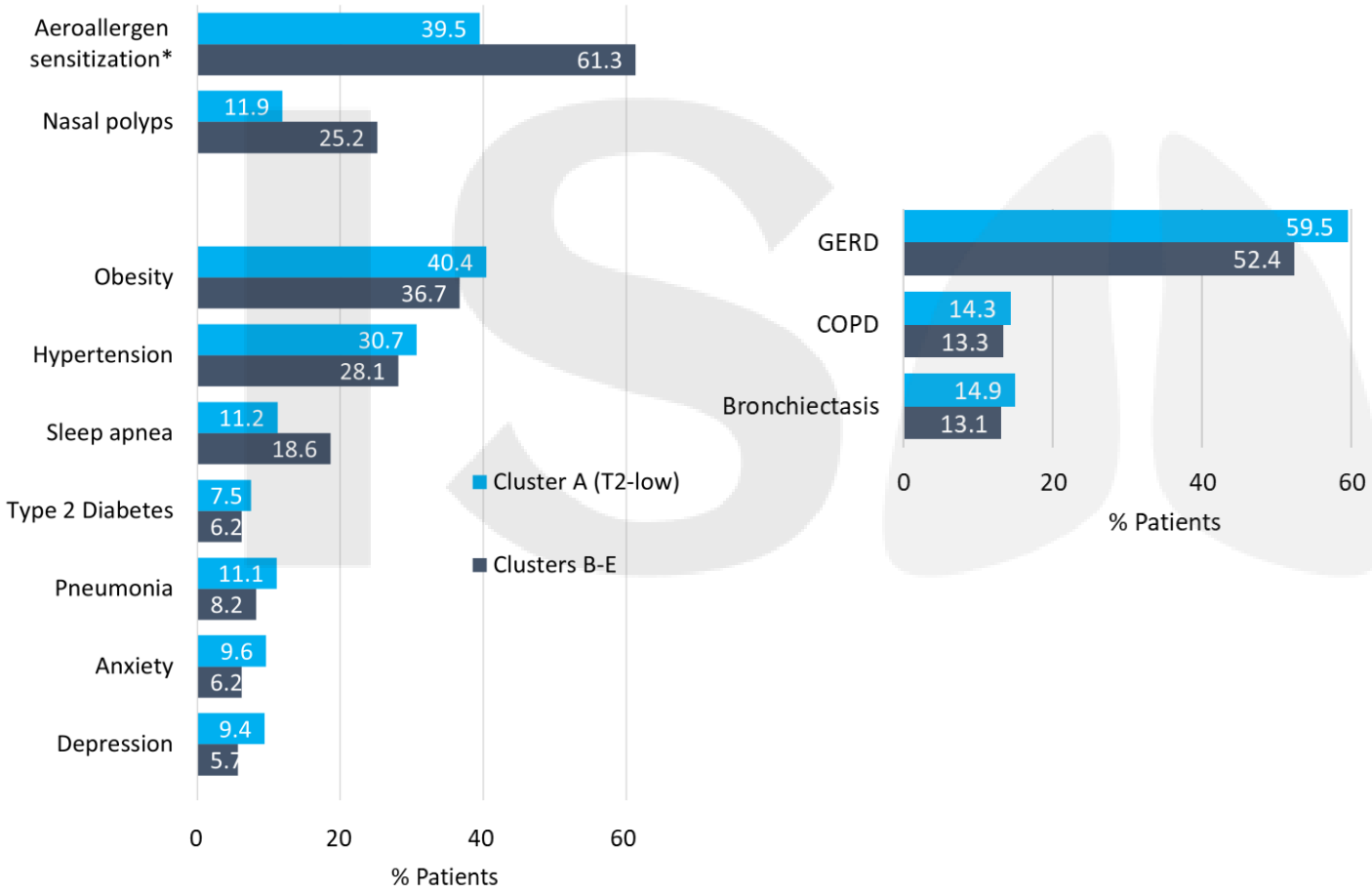
Demographic and clinical characteristics of biomarker clusters (N=3,675)



Cluster A (vs other clusters)

- More likely to have potentially OCS-related comorbidities
- Less likely to have any diagnosed allergy* and nasal polyps

*Aeroallergen sensitization by skin prick testing or serum allergen testing

BEC: Blood eosinophil count; FeNO: Fractional exhaled nitric oxide; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; GERD: Gastroesophageal reflux disease; IgE: Immunoglobulin E; T2: Type 2

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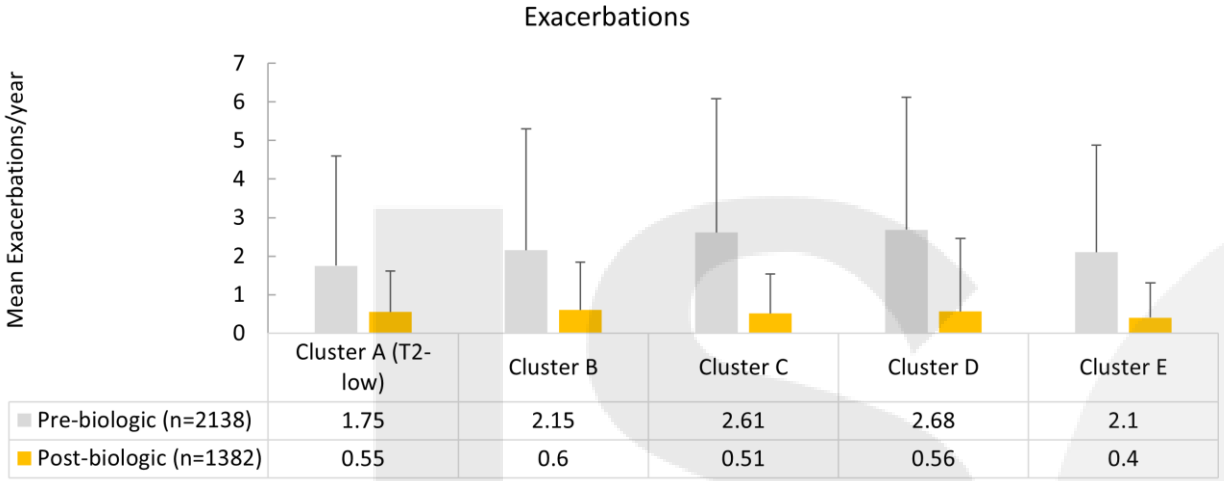
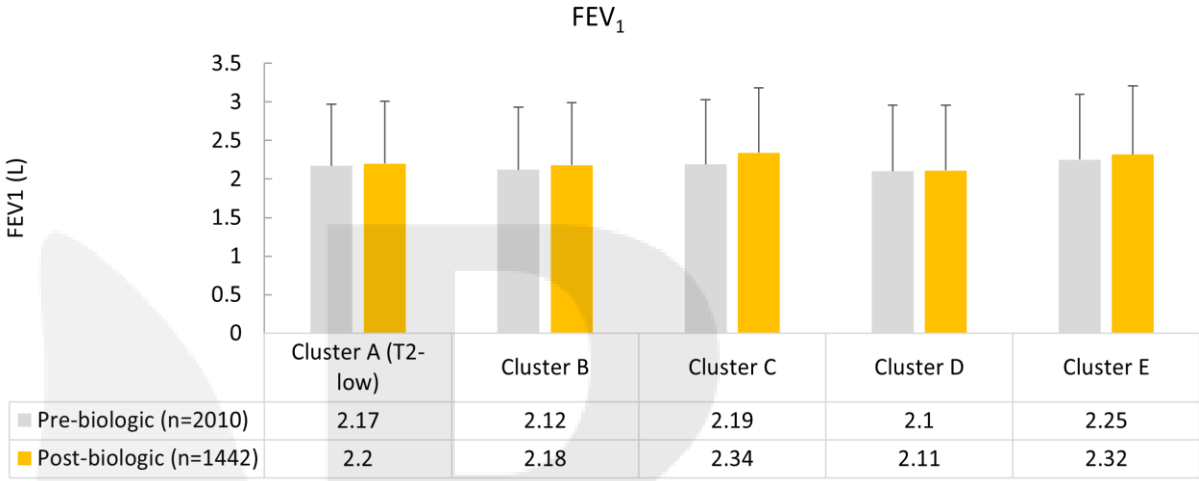
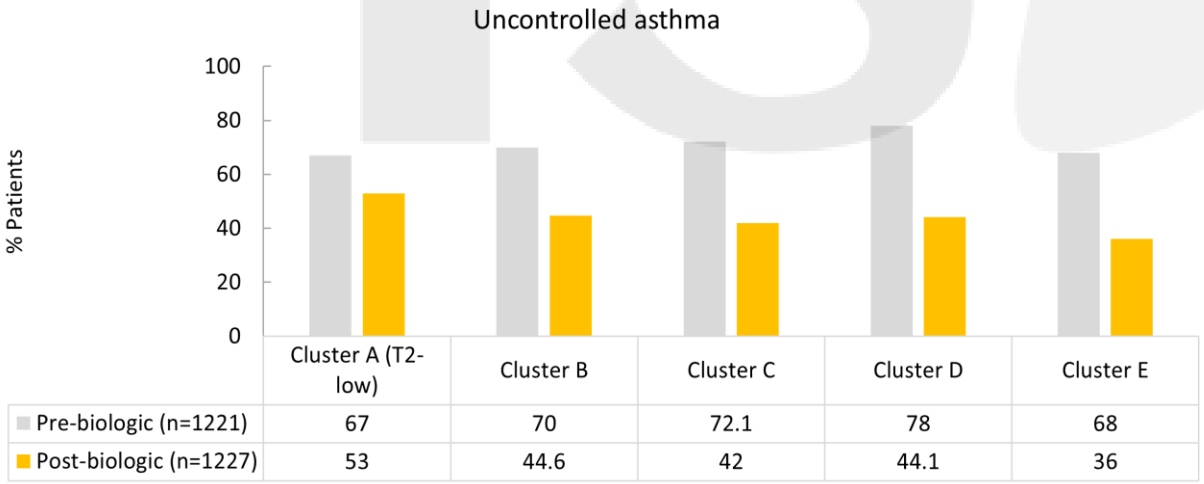
Pre- to post-biologic change in asthma outcomes for each cluster (univariate analysis)



	Cluster A (T2-low)	Cluster B	Cluster C	Cluster D	Cluster E
Pre-biologic (n=2138)	1.75	2.15	2.61	2.68	2.1
Post-biologic (n=1382)	0.55	0.6	0.51	0.56	0.4



	Cluster A (T2-low)	Cluster B	Cluster C	Cluster D	Cluster E
Pre-biologic (n=2010)	2.17	2.12	2.19	2.1	2.25
Post-biologic (n=1442)	2.2	2.18	2.34	2.11	2.32



	Cluster A (T2-low)	Cluster B	Cluster C	Cluster D	Cluster E
Pre-biologic (n=1221)	67	70	72.1	78	68
Post-biologic (n=1227)	53	44.6	42	44.1	36

Pre- to post-biologic improvements *were shown for exacerbations, lung function and asthma control,* ***irrespective of the degree of T2 involvement***

FEV_1: Forced expiratory volume in 1 second; T2: Type 2

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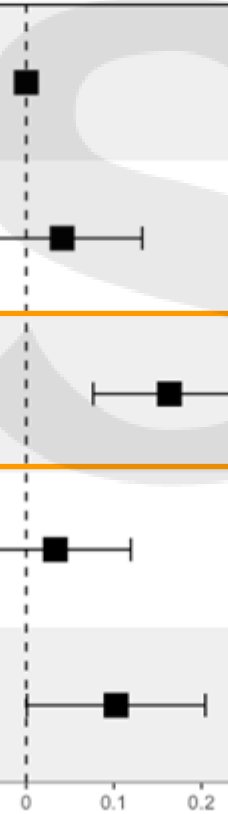
Pre- to post-biologic change in lung function relative to Cluster A (T2-low)

Variable		N	Estimate	p
Clusters	A (T2-low)	131		Reference
	B	279		0.04 (-0.05, 0.13) 0.38
	C	367		0.16 (0.08, 0.25) <0.001
	D	414		0.03 (-0.05, 0.12) 0.45
	E	154		0.10 (0.00, 0.20) 0.05



*Patients in **Cluster C (high BEC + FeNO)** had a **significantly greater increase in FEV_1** vs Cluster A*

BEC: Blood eosinophil count; FeNO: Fractional exhaled nitric oxide; FEV_1: Forced expiratory volume in 1 second; T2: Type 2

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Pre- to post-biologic change in asthma outcomes relative to Cluster A (T2-low) for patients who received Anti-IL5/5R

Exacerbations

Variable	N	Estimate	p
Clusters A (T2-low)	67	Reference	
B	126	-0.08 (-0.38, 0.22)	0.59
C	254	-0.30 (-0.56, -0.03)	0.03
D	280	-0.31 (-0.58, -0.05)	0.02
E	93	-0.15 (-0.46, 0.16)	0.35

FEV_1

Variable	N	Estimate	p
Clusters A (T2-low)	71	Reference	
B	125	0.10 (-0.02, 0.23)	0.1
C	265	0.22 (0.11, 0.33)	<0.001
D	272	0.09 (-0.02, 0.20)	0.1
E	101	0.06 (-0.07, 0.20)	0.4

Uncontrolled asthma

Variable	N	Odds ratio	p
Clusters A (T2-low)	56	Reference	
B	106	0.55 (0.26, 1.16)	0.1
C	182	0.60 (0.30, 1.19)	0.1
D	223	0.67 (0.34, 1.30)	0.2
E	57	0.48 (0.20, 1.14)	0.1

Lower exacerbation rates *and* ***greater improvements in lung function and asthma control*** *were noted for Anti–IL5/5R (but not Anti-IgE or Anti-IL4Rα) for all clusters relative to cluster A*

FEV_1: Forced expiratory volume in 1 second; IgE: Immunoglobulin E; IL4Rα: Interleukin 4-receptor-alpha; IL5/5R: Interleukin 5/5-receptor; T2: Type 2

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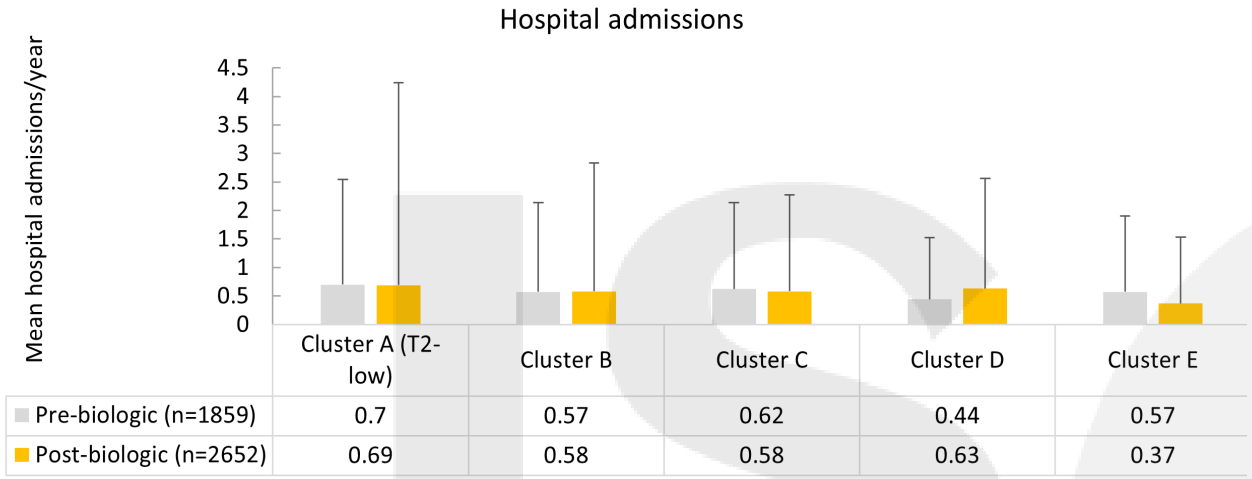
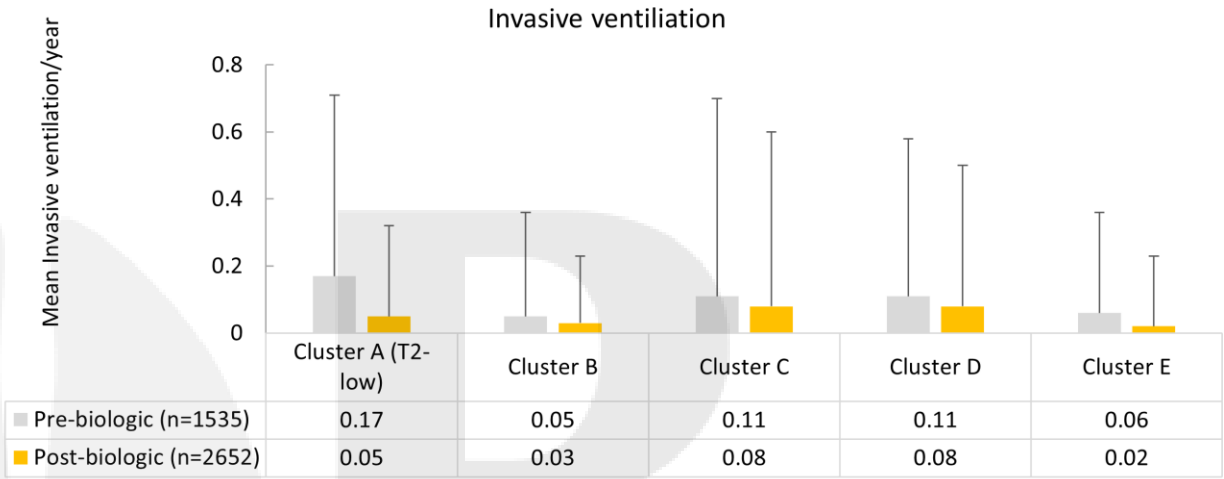
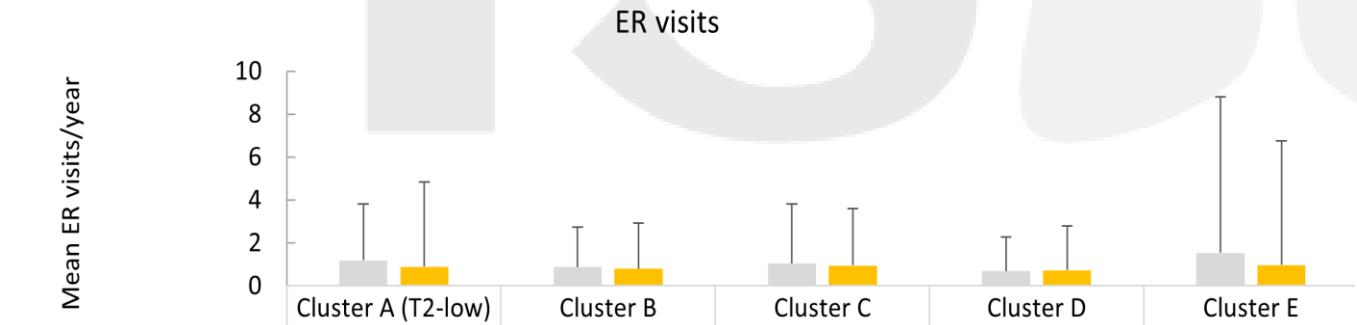
Pre- to post-biologic change in HCRU for each cluster (univariate analysis)



	Cluster A (T2-low)	Cluster B	Cluster C	Cluster D	Cluster E
Pre-biologic (n=1859)	0.7	0.57	0.62	0.44	0.57
Post-biologic (n=2652)	0.69	0.58	0.58	0.63	0.37



	Cluster A (T2-low)	Cluster B	Cluster C	Cluster D	Cluster E
Pre-biologic (n=1535)	0.17	0.05	0.11	0.11	0.06
Post-biologic (n=2652)	0.05	0.03	0.08	0.08	0.02



	Cluster A (T2-low)	Cluster B	Cluster C	Cluster D	Cluster E
Pre-biologic (n=1850)	1.19	0.87	1.04	0.69	1.53
Post-biologic (n=2652)	0.89	0.79	0.94	0.73	0.97

Pre- to post-biologic reductions *were shown for hospitalizations, ER visits and invasive ventilation,* ***irrespective of the degree of T2 involvement***

ER: Emergency room; HCRU: Healthcare resource utilization; T2: Type 2

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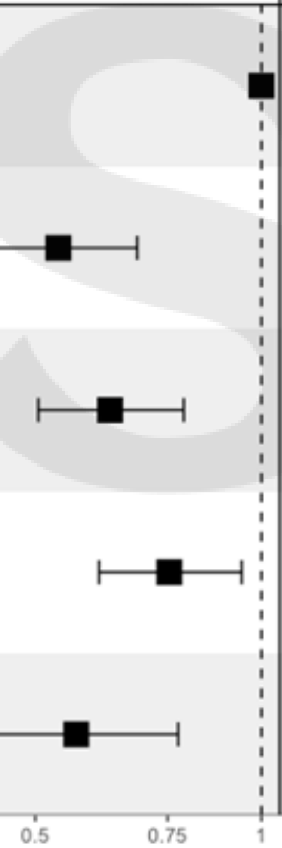
Pre- to post-biologic change in hospital admissions relative to Cluster A (T2-low)

Variable		N	Estimate	p
Clusters	A (T2-low)	68	Reference	
	B	197	0.54 (0.42, 0.68)	<0.001
	C	222	0.63 (0.50, 0.79)	<0.001
	D	315	0.75 (0.61, 0.94)	0.01
	E	77	0.57 (0.41, 0.77)	<0.001



*Patients in clusters B, C, D and E had **significantly greater reductions in hospital admissions for asthma** vs Cluster A*

T2: Type 2

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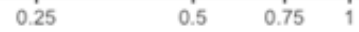
Pre- to post-biologic change in ER visits relative to Cluster A (T2-low)

Variable		N	Estimate	p
Clusters	A (T2-low)	68	Reference	
	B	196	0.53 (0.43, 0.65)	<0.001
	C	224	0.68 (0.57, 0.83)	<0.001
	D	313	0.60 (0.50, 0.73)	<0.001
	E	76	0.37 (0.27, 0.49)	<0.001



*Patients in clusters B, C, D and E had **significantly greater reductions in ER visits** vs Cluster A*

ER: Emergency room; T2: Type 2

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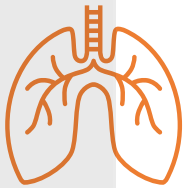
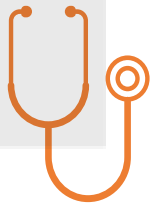
Conclusions

Five biomarker clusters along a gradient of T2 involvement were identified using a data-driven approach.



Biologic use was associated with improved outcomes in all clusters but tended to be better at the higher end of the T2 spectrum.



T2-targeted biologics have utility in the management of triple-biomarker-low asthma, but more effective therapies are needed.

Further research is needed to identify pathways specific to T2-low asthma that can be targeted by treatment.

T2: Type 2

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