

Supplementary Table S1: Descriptive statistics of clinical, bio-humoral and functional parameters among patients stratified by single biomarker cut-offs

Characteristic	<i>IgE</i> ≥100KU/L (N=278)	<i>IgE</i> <100KU/L (N=269)	<i>FENO</i> ≥30ppb (N=232)	<i>FENO</i> <30ppb (N=266)	<i>B-EOS</i> ≥300cells/μL (N=227)	<i>B-EOS</i> <300cells/μL (N=314)
Age (years)	56±16	61±14***	57±15	60±15*	59±15	59±16
Gender (Male)	124 (44.6%)	80 (29.7%)*	92 (39.7%)	99 (37.2%)	89 (39.2%)	114 (36.3%)
BMI	26.4±5.6	28.0±5.5***	26.1±5.5	27.9±5.7***	26.9±5.8	27.4±5.5
Age at asthma onset	33±19	37±20*	34±19	35±20	36±18	34±21
Early onset	73 (26.3%)	56 (20.8%)	50 (21.6%)	66 (24.8%)	40 (17.6%)	87 (27.7%)*
Asthma duration (years)	23±15	24±17	23±16	24±16	22±16	25±17
Vitamin D (ng/mL)	27.2±14.9	26.5±11.9	26.2±9.9	27.6±16.0	26.0±10.4	27.5±15.4
AE/y	1.40±2.37	0.83±1.50***	1.33±2.35	0.89±1.56*	1.26±1.29	1.02±1.77
FE phenotype	69 (27.7%)	49 (19.8%)*	57 (26.6%)	49 (20.4%)	53 (24.9%)	65 (23.1%)
Serious AE	93 (36.2%)	82 (32.0%)	79 (35.6%)	82 (50.9%)	76 (35.7%)	99 (33.6%)
Fibrinogen (mg/dL)	340.0±81.9	343.0±83.2	340.1±81.5	344.6±82.8	347.1±84.0	336.6±81.2
Current smokers (≥10PY)	12 (4.3%)	18 (6.7%)	11 (4.7%)	18 (6.8%)	12 (5.3%)	18 (5.7%)
Past smokers (≥10PY)	66 (23.7%)	59 (21.9%)	43 (18.5%)	70 (26.3%)*	50 (22.0%)	75 (23.9%)
Leukocytes (cells/μL)	7476±2339	7102±1914*	7340±2252	7213±2045	7779±2259	6944±1999***
Lymphocytes (cells/μL)	2374±855	2261±723	2350±781	2315±808	2483±889	2200±697***
Monocytes (cells/μL)	594±231	553±192*	576±199	560±191	629±234	538±189***
Neutrophils (cells/μL)	4133±1581	3941±1479	3968±1458	4043±1533	4068±1474	4016±1578
Basophils (cells/μL)	44±43	49±33	46±34	49±42	56±45	40±31***
Eosinophils (cells/μL)	414±569	272±264***	456±622	253±213***	-	-

FeNO (ppb)	41.8±39.2	34.4±30.3*	-	-	48.1±39.1	31.1±30.3****
Total serum IgE (kU/L)	-	-	344.6±709.3	207.2±324.4**	364.9±700.1	203.6±369.3***
Allergic sensitization	190 (63.8%)	108 (40.1%)****	144 (62.1%)	132 (49.6%)**	125 (55.1%)	170 (54.1%)
FVC(%pred.)	99.2±18.7	101.1±19.6	100.7±19.8	100.1±18.3	99.6±18.6	100.3±19.5
FEV₁(%pred.)	82.8±21.9	85.5±20.8	84.4±21.6	84.0±20.9	82.7±20.5	84.6±21.8
FEV₁/FVC (%)	67.9±14.3	68.8±10.1	68.7±13.5	68.0±11.7	67.4±13.8	68.8±11.2
RV (%pred.)	130.4±41.9	124.4±32.0	128.3±39.8	126.4±35.1	128.1±38.5	127.5±35.6
ACT	20.1±4.4	20.2±4.2	20.3±4.1	20.3±4.2	20.4±4.1	19.9±4.4
BCM HFA dose (µg)	383.7±272.2	343.8±244.2	382.2±263.9	331.9±242.0*	394.7±261.2	345.2±254.9**
Chronic OCS use	24 (8.6%)	13 (4.8%)	15 (6.5%)	16 (6.0%)	17 (7.5%)	20 (6.4%)
LABA use	229 (82.4%)	218 (81.0%)	187 (80.6%)	216 (81.2%)	195 (85.9%)	249 (79.3%)
LAMA use	44 (15.8%)	50 (18.6%)	34 (14.7%)	52 (19.5%)	36 (15.9%)	58 (18.5%)
Biologics ongoing	30 (10.8%)	9 (3.3%)	20 (8.6%)	17 (6.4%)	23 (10.1%)	16 (5.1%)
Pre Biologics	32 (11.5%)	16 (5.9%)	29 (12.5%)	16 (6.0%)	36 (15.9%)	12 (3.8%)

The results are expressed as mean with standard deviation or as a number of subjects with percentage. *= $p<0.05$; **= $p<0.01$; ***= $p<0.001$; ****= $p<0.0001$.

Supplementary Table S2: Binomial LRM of variables for asthmatic patients stratified according to serum Total IgE and T2 inflammatory phenotype

Characteristic	<i>T2_{Low}-IgE_{Low}</i>			<i>T2_{Low}-IgE_{High}</i>			<i>T2_{High}-IgE_{Low}</i>			<i>T2_{High}-IgE_{High}</i>		
	OR	LB	UB	OR	LB	UB	OR	LB	UB	OR	LB	UB
Age	0.990	0.932	1.051	0.948	0.857	1.049	1.007	0.975	1.039	1.005	0.974	1.036
BMI	1.222*	1.047	1.427	0.987	0.798	1.222	1.008	0.930	1.092	0.920	0.843	1.004
Age at asthma onset	1.036	0.991	1.083	1.037	0.961	1.119	1.004	0.978	1.030	0.975*	0.950	1.000
FE phenotype	0.515	0.046	5.724	3.287	0.203	53.112	2.304	0.688	7.715	0.805	0.254	2.546
AE/years	0.922	0.501	1.698	1.248	0.714	2.181	0.738	0.524	1.038	1.148	0.873	1.510
FVC (L)	0.118	0.012	1.163	1.740	0.090	33.791	1.249	0.433	3.605	1.702	0.610	4.747
FEV ₁ (L)	19.528*	1.165	327.304	0.255	0.006	11.441	0.922	0.238	3.570	0.463	0.124	1.729
FRC (%pred)	1.040*	1.007	1.075	1.018	0.980	1.057	0.978*	0.962	0.994	1.010	0.994	1.026
Activity limitation	0.789	0.391	1.592	0.432	0.140	1.333	0.874	0.580	1.318	1.333	0.893	1.989
Gender (male)	0.900	0.121	6.702	4.339	0.318	59.183	0.591	0.230	1.520	1.333	0.531	3.344
Early onset	2.854	0.298	27.328	0.729	0.025	21.687	0.696	0.238	2.029	1.523	0.522	4.443
Past smokers (≥10PY)	0.226	0.043	1.185	3.403	0.571	20.303	1.569	0.703	3.501	0.783	0.354	1.733
Rhinitis	0.476	0.147	1.542	2.211	0.221	22.124	0.947	0.461	1.946	1.416	0.682	2.939
CRSwNP	0.158	0.012	2.100	1.162	0.109	12.334	1.343	0.581	3.103	0.940	0.403	2.196

GINA (step 1)	0.000	0.000	-	0.426	0.014	12.965	0.670	0.164	2.740	3.783	0.917	15.598
GINA (step 2)	0.695	0.106	4.579	0.094	0.002	4.296	1.000	0.294	3.401	1.350	0.391	4.663
GINA (step 3)	1.175	0.140	9.840	0.034	0.000	2.871	0.590	0.149	2.341	1.770	0.451	6.950
GINA (step 4)	0.048*	0.004	0.637	0.087	0.002	4.728	1.522	0.375	6.169	2.235	0.544	9.188

*=p<0.05, **=p<0.01, ***=p<0.001. Bold font highlights statistically significant results. LB: lower bound, UB: upper bound; FVC: forced vital capacity; FEV₁: forced expiratory capacity in the first second; FRC: Functional residual capacity; CRSwNP: Chronic Rhinosinusitis with nasal polyps; LAMA: long-acting muscarinic antagonist; GINA: Global Initiative for Asthma; Obesity= BMI≥30.

Supplementary Table S3: Multinomial LRM of variables comparing each group of patients stratified according to serum Total IgE and T2 inflammatory phenotype

Characteristic	<i>T2_{Low}-IgE_{Low}</i>			<i>T2_{High}-IgE_{High}</i>			<i>T2_{Low}-IgE_{Low}</i>			<i>T2_{low}-IgE_{high}</i>			<i>T2_{low}-IgE_{low}</i>			<i>T2_{High}-IgE_{low}</i>		
	<i>vs. T2_{High}-IgE_{high}</i>			<i>vs. T2_{Low}-IgE_{Low}</i>			<i>vs. T2_{low}-IgE_{high}</i>			<i>vs. T2_{Low}-IgE_{Low}</i>			<i>vs. T2_{High}-IgE_{low}</i>			<i>vs. T2_{low}-IgE_{low}</i>		
	OR	LB	UB	OR	LB	UB	OR	LB	UB	OR	LB	UB	OR	LB	UB	OR	LB	UB
Gender (male)	0.274	0.072	1.046	3.651	0.956	13.94	0.150	0.021	1.057	6.676	0.946	47.09	0.464	0.120	1.792	2.155	0.558	8.321

BMI	1.153	1.016	1.309	0.867	0.764	0.984	1.120	0.903	1.388	0.893	0.720	1.107	1.086	0.963	1.225	0.921	0.817	1.039
	*			*														
Age at asthma onset	1.044	1.015	1.074	0.958	0.931	0.985	1.023	0.977	1.072	0.977	0.933	1.023	1.035	1.006	1.065	0.966	0.939	0.994
	**			**									*			*		
FE phenotype	0.430	0.104	1.785	2.324	0.560	9.640	0.127	0.016	0.996	7.866	1.004	61.63	0.488	0.118	2.012	2.051	0.497	8.465
							*			*		5						
Past smoker	0.565	0.140	2.275	1.770	0.440	7.125	0.212	0.030	1.519	4.723	0.658	33.88	0.400	0.100	1.599	2.498	0.625	9.978
												3						
Rhinitis	0.317	0.106	0.948	3.151	1.055	9.410	0.117	0.017	0.821	8.529	1.218	59.72	0.349	0.117	1.038	2.866	0.963	8.530
	*			*			*			*		3						
emphysema	3.984	0.995	15.94	0.251	0.063	1.005	1.238	0.145	10.55	0.808	0.095	6.893	3.964	0.958	16.40	0.252	0.061	1.044
	*		8	*					6						8			
OSAS	0.601	0.020	18.30	1.665	0.055	50.76	0.131	0.003	5.796	7.634	0.173	337.8	0.501	0.022	11.54	1.996	0.087	46.01
			9			8						10			8			9
GERD	0.735	0.228	2.368	1.360	0.422	4.379	0.510	0.081	3.217	1.962	0.311	12.38	0.757	0.240	2.390	1.321	0.418	4.169

Obesity	0.409	0.084	1.986	2.445	0.504	11.86	0.216	0.020	2.342	4.629	0.427	50.19	0.516	0.114	2.330	1.938	0.429	8.755
						8						4						
Arterial hypertension	0.940	0.314	2.816	1.063	0.355	3.185	0.931	0.149	5.807	1.074	0.172	6.694	0.841	0.279	2.534	1.189	0.395	3.585
Heart failure	7.988	1.062	6.010	1.252	1.252	2.891	0.1	5.78 ^E	1.273	1.273	1.273	2.052	0.273	15.43	0.487	0.065	3.666	
	E8***	E8	E9	E-9	E-9	E-9	E8	-8	E-9	E-9	E-9				8			

Anxiety-depression	1.869	0.391	8.939	0.535	0.112	2.560	4.329	9.050	2.071	8.497	0.000	-	0.497	0.119	2.080	2.011	0.481	8.411
							E7***	E7	E8	E-9								

Poor control	3.454	1.162	10.26	0.290	0.097	0.861	0.328	0.051	2.118	3.046	0.472	19.64	0.398	0.138	1.150	2.513	0.870	7.262
	*		8	*								4						
FEV ₁ (L)	1.567	0.588	4.176	0.638	0.239	1.701	1.696	0.322	8.928	0.590	0.112	3.105	1.401	0.524	3.747	0.714	0.267	1.909
FRC (%pred)	1.008	0.984	1.032	0.992	0.969	1.016	1.001	0.964	1.039	0.999	0.962	1.037	1.028	1.004	1.054	0.972	0.949	0.996
													*			*		
GINA	0.605	0.357	1.023	1.654	0.977	2.799	0.762	0.325	1.787	1.313	0.560	3.078	0.623	0.368	1.054	1.606	0.949	2.716
Chronic OCS use	0.813	0.134	4.937	1.229	0.203	7.461	0.398	0.023	6.766	2.514	0.148	42.76	1.569	0.226	10.90	0.637	0.092	4,42
												0			5			8

LAMA use	9.873	2.411	40.43	0.101	0,025	0.415	5.710	0.604	53.94	0.175	0.019	1.654	3.358	0.885	12.74	0.298	0.078	1.130	
	**		5	**					9						1				
Nasal CS use	0.280	0.101	0.777	3.567	1.287	9.890	0.557	0.103	3.006	1.796	0.333	9.701	0.278	0.100	0.770	3.598	1.299	9.965	
	*			*									*			*			
antileukotrienes	1.853	0.328	10.45	0.540	0.096	3.045	1.786	0.1	3.57	2.060	0.000	-		1.213	0.223	6.582	0.825	0.152	4.476
			7				E7		E-7	E-8									

	<i>T2_{low}-IgE_{high}</i>			<i>T2_{High}-IgE_{Low}</i>			<i>T2_{low}-IgE_{high}</i>			<i>T2_{High}-IgE_{High}</i>			<i>T2_{High}-IgE_{low}</i>			<i>T2_{High}-IgE_{High}</i>		
Characteristic	<i>vs. T2_{High}-IgE_{Low}</i>			<i>vs. T2_{low}-IgE_{high}</i>			<i>vs. T2_{High}-IgE_{High}</i>			<i>vs. T2_{Low}-IgE_{High}</i>			<i>vs. T2_{High}-IgE_{High}</i>			<i>vs. T2_{High}-IgE_{low}</i>		
	OR	LB	UB	OR	LB	UB	OR	LB	UB	OR	LB	UB	OR	LB	UB	OR	LB	UB
Gender (male)	3.098	0.568	16.89	0.323	0.059	1.761	1.829	0.350	9.541	0.547	0.105	2.853	0.590	0.265	1.314	1.694	0.761	3.773
			8															
BMI	0.970	0.799	1.177	1.031	0.850	1.252	1.030	0.849	1.249	0.971	0.801	1.178	1.062	0.968	1.165	0.942	0.859	1.033
Age at asthma onset	1.011	0.970	1.054	0.989	0.948	1.031	1.020	0.980	1.063	0.980	0.941	1.021	1.009	0.991	1.027	0.991	0.974	1.009
FE phenotype	3.835	0.662	22.22	0.261	0.045	1.512	3.385	0.622	18.43	0.295	0.054	1.609	0.883	0.354	2.199	1.133	0.455	2.822
			7									2						

Past smoker	1.891	0.369	9.686	0.529	0.103	2.709	2.669	0.535	13.31	0.375	0.075	1.870	1.411	0.616	3.236	0.709	0.309	1.625
	8																	
Rhinitis	2.976	0.497	17.79	0.336	0.056	2.010	2.707	0.469	15.62	0.369	0.064	2.132	0.910	0.428	1.933	1.099	0.517	2.336
	8																	
enphisema	3.203	0.414	24.76	0.312	0.040	2.413	3.219	0.449	23.07	0.311	0.043	2.227	1.005	0.293	3.449	0.995	0.290	3.415
	2																	
OSAS	3.824	0.337	43.45	0.261	0.023	2.971	4.585	0.399	52.65	0,218	0,019	2,505	1,199	0.202	7.124	0.834	0.140	4.957
	6																	
GERD	1.486	0.287	7.695	0.673	0.130	3.487	1.443	0.285	7.294	0.693	0.137	3.504	0.971	0.423	2.232	1.030	0.448	2.367
Obesity	2.388	0.287	19.88	0.419	0.050	3.486	1.893	0.235	15.28	0.528	0.065	4.262	0.793	0.258	2.433	1.261	0.411	3.870
	0																	
Arterial hypertension	0.903	0.171	4.776	1.108	0.209	5.862	1.010	0.195	5.233	0.991	0.191	5.134	1.118	0.519	2.412	0.894	0.415	1.928
Heart failure	2.611	2.611	2.611	1.409	0.000	-	1.017	1.017	1.017	0.984	0.000	-	8.93	3.893	3.893	2.569	2.569	2.569
	E-9	E-9	E-9	E8									E7	E8	E8	E-9	E-9	E-9
Anxiety-depression	4.225	4.225	4.225	8.706	2.975	2.548	1.588	1.588	1.588	2.317	2.317	2.317	3.758	1.284	10.99	0.266	0.091	0.779
	E-9	E-09	E-09	E7	E7	E8	E-8	E-08	E-08	E7	E7	E7	*		5	*		
Poor control	1.212	0.223	6.598	0.825	0.152	4.492	0.882	0.167	4.647	1.134	0.215	5.975	0.728	0.338	1.567	1.374	0.638	2.960

FEV₁ (L)	0.826	0.185	3.683	1.210	0.272	5.393	0.924	0.212	4.034	1.082	0.248	4.725	1.118	0.606	2.063	0.894	0.485	1.650
FRC (%pred)	1.027	0.994	1.062	0.974	0.942	1.006	1.006	0.975	1.039	0.994	0.962	1.026	0.980	0.965	0.995	1.020	1.005	1.036
													*			*		
GINA	0.818	0.379	1.764	1.223	0.567	2.640	0.794	0.371	1.697	1.260	0.589	2.694	0.971	0.689	1.368	1.030	0.731	1.452
Chronic OCS use	3.945	0.262	59.44	0.253	0.017	3.819	2.045	0.157	26.66	0.489	0.038	6.376	0.518	0.117	2.303	1.929	0.434	8.573
			9						7									
LAMA use	0.588	0.075	4.629	1.700	0.216	13.38	1.729	0.229	13.03	0.578	0.077	4.360	2.940	1.072	8.060	0.340	0.124	0.933
						4			4				*			*		
Nasal CS use	0.499	0.107	2.321	2.003	0.431	9.310	0.504	0.112	2.258	1.986	0.443	8.902	1.009	0.495	2.054	0.991	0.487	2.019
antileukotrienes	2.50	2.50	2.50	1.473	0.000	-	3.82	3.82	3.82	9.636	0.000	-	1.528	0.556	4.198	0.654	0.238	1.797
	E-08	E-08	E-08	E7			E-08	E-08	E-08	E6								

*=p<0.05, **=p<0.01, ***=p<0.001. Bold font highlights statistically significant results. LB: lower bound, UB: upper bound. FE: frequent exacerbator (≥ 2 exacerbation/year); OSAS: obstructive sleep apnoea syndrome; GERD: gastroesophageal reflux disease; FEV₁: forced expiratory capacity in the first second; FRC: Functional residual capacity; GINA: Global Initiative for Asthma; LAMA: long-acting muscarinic antagonist; Obesity= BMI ≥ 30 .