

## **Supplementary material**

### **Relationship between blood eosinophil levels and their variability with exacerbations in patients with COPD: A population-based study**

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**Table 1S.** Baseline characteristics for patients not taking inhaled corticosteroids in the year prior to the index date and in the year of follow-up. (n=24014).

Patients variables	COPD Patients with cut point < 150 cells/ $\mu$ l N=6444	COPD Patients with cut point 150-300 cells/ $\mu$ l N=11043	COPD Patients with cut point 300-500 cells/ $\mu$ l N=5042	COPD Patients with cut point > 500 cells/ $\mu$ l N=1485	P-value
Sociodemographic characteristics					
Age (years), mean (SD)	68.7 (10.4)	68.1 (10.4)	68.0 (10.4)	67.9 (10.6)	<0.001
Sex; male	4718 (73.2)	8628 (78.1)	4192 (83.1)	1280 (86.2)	<0.001
Years of evolution, median (interquartile range)	2.61 [0.38;7.18]	2.45 [0.28;6.92]	2.32 [0.15;6.79]	2.26 [0.13;7.09]	0.152
Tobacco consumption					
Non-smoker	26 (0.40)	58 (0.53)	22 (0.44)	8 (0.54)	0.772
Ex-smoker	2371 (36.8)	3945 (35.7)	1763 (35.0)	526 (35.4)	
Smoker	1016 (15.8%)	1822 (16.5%)	887 (17.6%)	288 (19.4%)	
Unknown	3031 (47)	5218 (47.3%)	2370 (47%)	663 (44.6%)	
Body mass index (Kg/m <sup>2</sup> ) (n=), mean (SD)	28.2 (5.00)	28.6 (4.94)	28.5 (4.89)	28.2 (4.72)	<0.001
Spirometry n (%)	2600 (40.3%)	4361 (39.5%)	1915 (38.0%)	578 (38.9%)	0.025
FEV1 (%predicted), mean (SD)	69.7 (21.6)	69.6 (20.3)	68.3 (20.6)	70.2 (20.9)	0.013
GOLD stage					0.022
Gold I	808 (31.1)	1250 (28.7)	511 (26.7)	165 (28.5)	
Gold II	1449 (55.7)	2571 (59)	1123 (58.6)	341 (59)	
Gold III	233 (9)	391 (9)	219 (11.4)	57 (9.9)	
Gold IV	110 (4.2)	149 (3.4)	62 (3.2)	15 (2.6)	
Blood leukocyte cells/ $\mu$ l mean (SD)	7180 (2409)	7860 (2021)	8537 (2127)	9354 (2546)	<0.001
Blood eosinophil cells/ $\mu$ l mean (SD)	101 (36.8)	217 (42.1)	376 (55.2)	692 (331)	<0.001
Exacerbation registered in the previous year	2423 (37.63%)	4011 (36.3%)	1820 (36.1%)	588 (39.6%)	<0.001
N <sup>o</sup> of exacerbations, mean (SD)	0.57 (0.89)	0.52 (0.84)	0.52 (0.85)	0.58 (0.88)	<0.001
$\geq$ 1 admission for exacerbation	110 (1.7)	135 (1.2)	89 (1.8)	36 (2.4)	<0.001
Phenotypes					<0.001
ACO	157 (2.4)	256 (2.3)	124 (2.5)	35 (2.4)	
Exacerbator	830 (12.9)	1211 (11.0)	546 (10.8)	188 (12.7)	
Non-exacerbator	5457 (84.7)	9576 (86.7)	4372 (86.7)	1262 (85.0)	
Comorbidities					
Hypertension	3589 (55.7%)	6300 (57.0%)	2999 (59.5)	879 (59.2%)	<0.024
Dyslipidemia	3395 (52.7%)	6044 (54.7%)	2786 (55.3%)	838 (56.4%)	<0.001
Diabetes Mellitus tipe2	1580 (24.5)	2930 (26.5)	1391 (27.6)	462 (31.1)	<0.001
Osteoporosis	528 (8.19)	629 (5.70)	253 (5.02)	51 (3.43)	<0.001
Depression	1030 (16.0)	1658 (15.0)	703 (13.9)	176 (11.9)	<0.001
Gastroesophageal reflux	335 (5.20)	478 (4.33)	218 (4.30)	50 (3.37)	0.004
Ischemic heart disease	708 (11.0)	1224 (11.1)	632 (12.5)	203 (13.7)	0.003
Congestive heart failure	369 (5.73)	545 (4.94)	244 (4.84)	72 (4.85)	<0.001
Respiratory					

comorbidities					
Sleep apnoea	363 (5.63)	627 (5.68)	310 (6.15)	77 (5.19)	0.158
Bronchiectasis	224 (3.48)	403 (3.65)	177 (3.51)	57 (3.84)	0.041
Pneumonia	261 (4.05)	374 (3.39)	156 (3.09)	56 (3.77)	<0.001

The data are %, unless otherwise indicated. \*, only patients with the resource considered

Abbreviations: HRCT: High resolution computed tomography; SD: Standard deviation; PC: Primary care.

P-values adjusted for multiple testing using Bonferroni correction.

**Table 2S.** Baseline respiratory treatment of COPD for patients not taking inhaled corticosteroids in the year prior to the index date and in the year of follow-up. Within the groups defined

Respiratory treatment	COPD Patients with cut point < 150 cells/ $\mu$ l N=6444	COPD Patients with cut point 150-300 cells/ $\mu$ l N=11043	COPD Patients with cut point 300-500 cells/ $\mu$ l N=5042	COPD Patients with cut point > 500 cells/ $\mu$ l N=1485	P-value
SABA	1189 (18.5%)	1956 (17.7%)	958 (19.0%)	318 (21.4%)	<0.001
SAMA	1080 (16.8%)	1878 (17.0%)	940 (18.6%)	264 (17.8%)	0.006
LABA	938 (14.6%)	1642 (14.9%)	773 (15.3%)	222 (14.9%)	0.114
LAMA	1260 (19.6%)	2346 (21.2%)	993 (19.7%)	296 (19.9%)	0.034
SABA_SAMA	0 (0.00%)	1 (0.01%)	1 (0.02%)	0 (0.00%)	0.118
LABA_LAMA	54 (0.84%)	67 (0.61%)	38 (0.75%)	15 (1.01%)	0.004
IPD4	5 (0.08%)	14 (0.13%)	3 (0.06%)	3 (0.20%)	0.013
Theophylline	10 (0.16%)	24 (0.22%)	8 (0.16%)	2 (0.13%)	0.720
Without treatment	3399 (52.7%)	5738 (52.0%)	2567 (50.9%)	763 (51.4%)	<0.001

P-values adjusted for multiple comparisons using Bonferroni correction.

Abbreviations: COPD: Chronic obstructive pulmonary disease; SABA: Short-acting bronchodilators; LABA: long-acting beta-2 agonists; LAMA: long-acting antimuscarinic agents; ICS: Inhaled corticosteroids.

**Table 3S.** Baseline characteristics of COPD patients according peripheral blood eosinophils variability level.

Patients variables	Total N=15769	Unvariable N=9784	Little variable N=5310	Very variable <sup>1</sup> N=675	Overall p-value
Sociodemographic characteristics					
Age (years), mean (SD)	71.1 (10.2)	71.0 (10.1)	71.1 (10.3)	71.6 (10.5)	0.389
Gender; male	11731 (74.4%)	7190 (73.5%)	3998 (75.3%)	543 (80.4%) *	<0.001
Years of evolution, median (interquartile range)	4.41 [1.16;9.08]	4.39 [1.16;8.98]	4.41 [1.13;9.27]	4.64 [1.34;9.70]	0.226
Tobacco consumption					
Non-smoker	75 (0.48%)	52 (0.53%)	21 (0.40%)	2 (0.30%)	0.131
Ex-smoker	6161 (39.1%)	1485 (15.2%)	846 (15.9%)	121 (17.9%)	
Smoker	2452 (15.5%)	3811 (39.0%)	2080 (39.2%)	270 (40.0%)	
Unknown	7081 (44.9%)	4436 (45.3%)	2363 (44.5%)	282 (41.8%)	
Body mass index (Kg/m <sup>2</sup> ) (n=), mean (SD)	29.1 (5.16)	29.1 (5.11)	28.7 (5.08)	29.1 (5.25)	0.109
Spirometry					
FEV1 (%predicted),mean (SD)	64.3 (22.0)	64.5 (22.0)	64.3 (21.7)	61.8 (23.2)	0.116
Gold stage					
Gold I	1729 (11.0%)	1088 (22.7%)	578 (22.3%)	63 (19.6%)	0.067
Gold II	4244 (26.9%)	2628 (54.9%)	1447 (55.9%)	169 (52.6%)	
Gold III	1297 (8.22%)	807 (16.9%)	424 (16.4%)	66 (20.6%)	
Gold IV	422 (2.68%)	260 (5.44%)	139 (5.37%)	23 (7.17%)	
Blood leukocyte cells/μl mean (SD)	8011 (2592)	7850 (2511)	8163 (2542)	9153 (3596) **	<0.001
Blood eosinophil cells/μl mean (SD); median (interquartile range)	252 (199); 210 [137;315]	236 (187); 206 [117;275]	263 (143); 253 [153;316]	375 (264); 339 [230;424] **	<0.001
Exacerbations registered in the previous year	8429 (53.5%)	5085 (52.0%)	2922 (55.0%)	422 (62.5%) **	<0.001
Nº of exacerbations, mean (SD)	0.97 (1.21)	0.93 (1.18)	1.01 (1.24)	1.25 (1.42) **	<0.001
≥ 1 admission for exacerbation	822 (5.21%)	445 (4.55%)	306 (5.76%)	71 (10.5%) **	<0.001
Phenotypes					
ACOS	1379 (8.75%)	845 (8.64%)	473 (8.91%)	61 (9.04%)	<0.001
Exacerbator	3557 (22.6%)	2111 (21.6%)	1244 (23.4%)	202 (29.9%)	
Non-exacerbator	10833 (68.7%)	6828 (69.8%)	3593 (67.7%)	412 (61.0%)	
Comorbidities					
Hypertension	10300 (65.3%)	6304 (64.4%)	3549 (66.8%)	447 (66.2%)	0.011
Dyslipidemia	9046 (57.4%)	5635 (57.6%)	3043 (57.3%)	368 (54.5%)	0.293
Diabetes Mellitus tipe2	5797 (36.8%)	3578 (36.6%)	1960 (36.9%)	259 (38.4%)	0.620
Osteoporosis	1408 (8.93%)	920 (9.40%)	431 (8.12%)	57 (8.44%)	0.027
Depression	2744 (17.4%)	1755 (17.9%)	892 (16.8%)	97 (14.4%)	0.022
Gastroesophageal reflux	859 (5.45%)	534 (5.46%)	289 (5.44%)	36 (5.33%)	0.990
Ischemic heart disease	2461 (15.6%)	1483 (15.2%)	852 (16.0%)	126 (18.7%)	0.029
Congestive heart failure	1649 (10.5%)	985 (10.1%)	594 (11.2%)	70 (10.4%)	0.100
Respiratory comorbidities					
Sleep apnoea	1219 (7.73%)	755 (7.72%)	412 (7.76%)	52 (7.70%)	0.995
Bronchiectasis	977 (6.20%)	593 (6.06%)	346 (6.52%)	38 (5.63%)	0.446
Pneumonia	849 (5.38%)	500 (5.11%)	307 (5.78%)	42 (6.22%)	0.134

\*\*=p value<0.001, \*=p value<0.05; Very variable<sup>1</sup> is compared with little variable group.

**Table 4S.** Baseline respiratory treatment of COPD patients according peripheral blood eosinophils variability.

<b>Respiratory treatment</b>	<b>Total N=15769</b>	<b>Unvariable N=9784</b>	<b>Little variable N=5310</b>	<b>Very variable<sup>1</sup> N=675</b>	<b>Overall p-value</b>
SABA	5701 (36.2%)	3461 (35.4%)	1952 (36.8%)	288 (42.7%) *	<0.001
SAMA	4600 (29.2%)	2761 (28.2%)	1611 (30.3%)	228 (33.8%)	0.001
LABA	2814 (17.8%)	1758 (18.0%)	928 (17.5%)	128 (19.0%)	0.558
LAMA	5618 (35.6%)	3416 (34.9%)	1934 (36.4%)	268 (39.7%)	0.014
SABA_SAMA	36 (0.23%)	24 (0.25%)	10 (0.19%)	2 (0.30%)	0.728
LABA_LAMA	264 (1.67%)	165 (1.69%)	85 (1.60%)	14 (2.07%)	0.658
LABA_ICS	6037 (38.3%)	3634 (37.1%)	2101 (39.6%)	302 (44.7%) *	<0.001
ICS	2899 (18.4%)	1739 (17.8%)	1016 (19.1%)	144 (21.3%)	0.016
IPD4	156 (0.99%)	99 (1.01%)	48 (0.90%)	9 (1.33%)	0.532
Theophylline	164 (1.04%)	96 (0.98%)	58 (1.09%)	10 (1.48%)	0.417
Without treatment	4273 (27.1%)	2748 (28.1%)	1382 (26.0%)	143 (21.2%) *	<0.001

\*\*=p value<0.001, \*=p value<0.05; Very unstable<sup>1</sup> is compared with unstable group.