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Fixed airway obstruction and bronchodilator responsiveness phenotypes in severe asthma population from SANI registry

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ABSTRACT

Background Data on asthma with fixed airway obstruction (FAO) are heterogeneous due to different and misleading definitions. Describing the FAO phenotype has significant implications for severe asthma (SA) comprehension.

Objective To characterise SA patients with FAO in the Severe Asthma Network in Italy (SANI) registry at baseline, and to compare with those with reversible airway obstruction (bronchodilator responsiveness, BDR). The potential for re-evaluating FAO or BDR in the follow-up was explored.

Methods FAO was defined as a forced expiratory volume in the first second (FEV_1)/forced vital capacity ratio < Lower Limit of Normal (LNN) after a bronchodilator test with an increase in FEV_1 of <12% or 200 mL, compared with BDR and no airway obstruction (no-AO). Clinical reported outcomes, including asthma control (ACT), quality of life (AQLQ) and exacerbations (AEs) were collected. The effect of demographic, clinical and biohumoral variables on FAO, BDR and no-AO groups at baseline and during the follow-up was estimated.

Results Among 354 patients, 190 (53.7%) reported AO with 116 (60.1%) resulting in FAO. The overall FAO rate at enrolment was 32.8%. Compared with BDR, FAO patients had better asthma control (34.5% vs 20.3%, p=0.004), a higher ACT (17.4 vs 15.2, p=0.005) and AQLQ (4.6 vs 3.8, p=0.001) score. FAO patients were less likely to visit the emergency room or be hospitalised than BDR (p=0.050), with no difference in AEs. The effect of airway calibre on fractional exhaled nitric oxide is more likely to cause its lower level within FAO compared with BDR (29.5 vs 46.0 ppb, p=0.04) than a lower T2 burden. A variation from FAO to BDR or no-AO was associated with the Global Initiative for Asthma classification (step 4 vs 5: HR 3.58 (95% CI 1.16 to 11.03)) and the age of asthma onset (30–39 vs <20 years: HR 3.94 (95% CI 1.09 to 14.30))

Conclusion Stratifying SA patients from the SANI registry reveals an FAO phenotype that expresses different clinical outcomes and biological markers compared to BDR. Over time, FAO may be reversible in late-onset SA with less inhaled corticosteroid treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The prevalence of fixed airway obstruction (FAO) in severe asthma populations and its phenotypic characterisation is not well recognised.

WHAT THIS STUDY ADD

⇒ In the Severe Asthma Network in Italy registry, FAO is highly reported and different from reversible airway obstruction (bronchodilator responsiveness; BDR) in terms of clinical control and fractional exhaled nitric oxide expression. Transition from FAO towards BDR or normal lung function is described.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Stratification of severe asthma patients by FAO phenotype may improve patient personalised management.

INTRODUCTION

Data on the prevalence of severe asthma (SA) consistently report a frequency of less than 5% among patients with persistent asthma.[1–3] However, this is not the case when looking at the prevalence of irreversible or fixed airway obstruction (FAO) as its definition is quite different between studies as summarised in online supplemental table 1, leading to misleading interpretations. Vonk *et al*[4] reported that 16% of patients with a history of asthma developed irreversible airway obstruction, defined as a prebronchodilator forced expiratory volume in the first second (FEV_1) <80% of predicted, with improvement of less than 9% after administration of 800 µg of salbutamol. Brown *et al*[5] report that 66% of patients with SA enrolled in the 'Wessex Severe Asthma Cohort' demonstrate persistent airflow limitation (PAL) as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Severe Asthma Consensus 2014.[6] However, the ATS/ERS criteria reported 'airflow limitation' defined by 'FEV_1<80% of predicted after appropriate

bronchodilator withhold (in the face of reduced FEV_1/forced vital capacity (FVC) <lower limit of normal (LLN)). Therefore, in this study, patients were severe asthmatics with airway obstruction and not PAL. In the study of Wang *et al*,[7] the percentage of severe asthmatic subjects from the International Severe Asthma Registry with FAO, by applying a selection criterion of postbronchodilator $FEV_1/FVC<0.7$, was 43% and 47% for Global Initiative for Asthma (GINA) step 4 and step 5, respectively, lower than above reported.

A positive bronchodilator responsiveness (BDR) test has been defined by ERS/ATS International Joint Task Force in 2005,[8] as an increase of 200 mL or more and 12% or more in FEV_1 and/or FVC from baseline and recommended for the diagnosis of asthma. ERS/ATS in 2022[9] updated the criteria requested for a positive BRD (an increase ≥10% of FEV_1 and FVC of predicted). However, a recent analysis[10] on about 3100 asthmatic subjects undergoing BDR testing did not find any significant difference in FAO versus 2005 criteria (81% vs 79%).

FAO in SA subgroups has been associated with delayed asthma diagnosis from respiratory symptoms onset, older age and longer duration of asthma[11] while not consistently related to more exacerbations.[12] The overlap of asthma and chronic obstructive pulmonary disease (COPD) diagnosis has often been suggested in the presence of FAO, although features of airway inflammation, such as increased eosinophils and CD4+T cell number, are distinctive for asthmatics with FAO.[13] Actually, the structural signature of FAO is airway remodelling, but the exact underlying mechanisms are yet to be elucidated.[14]

The aim of the present study was to describe the features of severe asthmatic subjects from the Severe Asthma Network Italy (SANI) registry with FAO defined by $FEV_1/FVC<LLN$ after 400 mcg of salbutamol and an increase of $FEV_1<12\%$ or <200 mL,[8] defining the FAO phenotype compared with SA group with BDR.

METHODS

Study population

The SANI is a web-based observatory collecting demographic, clinical, functional and inflammatory data from patients aged ≥18 years affected by SA, according to the ATS/ERS definition.[6] Patients were recruited in reference centres homogeneously distributed on the national territory. They were selected according to the recommendations of the GINA guidelines, and a final diagnosis of SA was made only after a long follow-up period during which all major factors potentially responsible for uncontrolled asthma (ie, adherence, inhaler technique, comorbidities, etc) had been appropriately managed. Moreover, considering the real-life nature of the SANI registry, no exclusion criteria (including the possibility of having received a diagnosis of asthma-COPD overlap) were present in the protocol.[15]

In December 2022, the following data were collected for each patient at baseline and during the follow-up at scheduled visits every 6 months: (1) demographic data including age, sex, height, weight and body mass index (BMI); (2) clinical data including onset age of asthma, asthma duration, smoking habit (pack years), presence of allergies and other comorbidities, asthma exacerbations (AEs) (including those requiring steroid treatment, emergency room, hospital admission, intensive care unit (ICU)), asthma control in the previous month according to standardised questionnaires (Asthma Control Test (ACT); Asthma Quality of Life Questionnaire (AQLQ); (3) asthma treatments (inhaled, oral corticosteroid, including cumulative dose, biologics); (4) lung functional measurement; (5) inflammatory markers (fractional exhaled nitric oxide (FeNO) and peripheral blood eosinophils (B-EOS)). All measurements were taken in a stable phase of the disease, out of any AE for at least 4 weeks, and without any withdrawal of the current pharmacological treatment. FeNO and B-EOS reported are measured before biologics initiation.

Spirometry was performed following the ATS/ERS statements.[16] Abnormal data were that with a Z-score >1.96 SD by applying the Global Lung Function Initiative (GLI) Network reference values.[17] Race was included in the equation to generate GLI-predicted values, ranges of normal and the Z-scores. Airway obstruction was diagnosed when a FEV_1/FVC ratio was below the LLN.[8] Patients with an FEV_1/FVC ratio below the LLN after salbutamol responsiveness test with an increase of FEV_1 or FVC <12% or <200 mL were considered affected by FAO as they did not demonstrate any significant bronchodilatation after salbutamol.[8] On the contrary, patients with BDR (ie, FEV_1 or FVC values ≥12% and ≥200 mL compared with baseline) were considered with reversible airway obstruction.

For the present analysis, we included patients with available salbutamol responsiveness test at baseline and divided them into three groups, as follows: (1) subjects with FAO, (2) subjects with BDR and (3) subjects with no airway obstruction (no-AO). Asthma control was defined as ACT ≥20; partially controlled as ACT 16–19 and uncontrolled as ACT <15.[18] The definition of a frequent exacerbator was at least two bursts of systemic corticosteroids (>3 days course each) in the previous year.[6]

The SANI initiative is supported by several pharmaceutical companies listed in the funding statement, which provided unrestricted grants and played no role in study design and planned analysis.

Patient and public involvement statement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Statistical analysis

Sociodemographic and clinical characteristics were analysed using descriptive statistics. Categorical variables were reported with absolute and relative frequencies,

continuous variables with median and IQR or mean±SD. Differences in the distributions of demographic and clinical characteristics among subjects with FAO, BDR or no-AO were evaluated using the Wilcoxon rank sum test for continuous variables and the Fisher's exact test for categorical variables. Furthermore, we performed a prospective analysis including patients diagnosed with FAO at baseline or at a follow-up visit who had at least another measurement of bronchodilator reversibility test during a subsequent follow-up visit. The time interval between the diagnosis of FAO and the date of the subsequent bronchodilator reversibility test when the subject's asthma functional condition improved (ie, switching from FAO to BDR or no-AO) was defined as the variation of asthma condition (ie, the event of interest). Subjects for whom no improvement in asthma condition was observed were censored on the date of the last bronchodilator test performed.

To evaluate the effect of demographic and clinical variables on the variation of asthma condition, HRs estimated from univariable Cox proportional models, along with their 95% CIs, were reported. Analyses were conducted using the SAS software V.9.4 (SAS Institute, Cary, North Carolina). A checklist for cohort study based on the Strengthening the Reporting of Observational Studies in Epidemiology cohort guidelines has been applied.

RESULTS

Characteristics of SA patients at registry enrolment

Overall, of 1653 patients with SA enrolled in the SANI registry, 371 (22.4%) with available salbutamol responsiveness test at baseline were selected. Those with an estimable LLN FEV_1/FVC (354 out of 371) were included in the study. A flowchart for the selection of subjects with fixed obstruction, reversible obstruction or no obstruction is reported in online supplemental figure S1. Spirometric values for the three groups (FAO, BDR, no-AO) are reported in table 1.

At baseline, airway obstruction (FEV_1/FVC<LLN) was reported in 190 (53.7%) of the selected patients, 116 (61.1%) of which with FAO and the other 74 (38.9%) with BDR after salbutamol responsiveness test. The overall rate of FAO and BDR in the SANI cohort at registry enrolment is 32.8% and 20.9%, respectively. A further third group of SA patients (no-AO) without obstruction (FEV_1/FVC ≥LLN) and exposed to an unnecessary salbutamol responsiveness test accounted for the remaining 164 patients (46.3%). Table 2 summarises the demographic, clinical and bio-humoral characteristics of patients divided into three groups: FAO, BDR and no-AO. A statistically significant lower proportion of males was observed in the BDR and no-AO group with respect to the FAO group (p value equals to 0.024 and 0.004, respectively). No differences were observed in BMI or smoking habits among the groups. FAO had lower age onset than no-AO (p=0.019), while asthma duration was higher in BDR than no-AO (p=0.041).

Table 1 Spirometric values at baseline in the subjects with FAO, BDR and no-AO

	1 FAO (N=116)	2 BDR (N=74)	3 No-AO (N=164)
FEV_1/FVC pre-BD ratio*			
Mean (SD)	54.7 (10.0)	60.5 (7.8)	75.9 (6.8)
FEV_1/FVC post-BD ratio*			
Mean (SD)	56.6 (10.0)	66.1 (10.3)	77.3 (7.8)
FVC pre-BD (L)			
Mean (SD)	3.1 (0.9)	2.7 (0.9)	2.9 (0.9)
FVC pre-BD (%)			
Mean (SD)	87.1 (18.6)	82.3 (20.4)	88.6 (19.7)
FVC post-BD (L)			
Mean (SD)	3.3 (1.0)	3.0 (0.9)	3.0 (0.9)
FVC post-BD (%)			
Mean (SD)	91.6 (19.4)	93.9 (22.0)	92.7 (19.5)
FEV_1 pre-BD (L)			
Mean (SD)	1.7 (0.7)	1.7 (0.6)	2.2 (0.7)
FEV_1 pre-BD (%)			
Mean (SD)	59.5 (16.5)	61.9 (17.5)	81.3 (18.9)
FEV1 post-BD (L)			
Mean (SD)	1.9 (0.7)	2.0 (0.7)	2.4 (0.7)
FEV_1 post-BD (%)			
Mean (SD)	66.0 (19.6)	78.6 (22.4)	86.7 (20.5)

*FEV_1/FVC is the ratio of FEV_1 (L) and FVC (L) expressed × 100.
BD, bronchodilator; BDR, bronchodilator responsiveness; FAO, fixed airway obstruction; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; no-AO, no-airway obstruction.

FAO group had more patients with controlled asthma compared with BDR (34.5% vs 20.3%, p value=0.004), as confirmed by a higher ACT score (17.4 vs 15.2, p value=0.005) as well as a better AQLQ value (4.6 vs 3.8, p value=0.001). There was no significant difference between no-AO and FAO patients in terms of asthma control. On the other hand, BDR patients were more prone to ICU or emergency room access or hospital admissions compared with FAO (p value=0.050); FAO and BDR had similar rates of frequent severe exacerbations, requiring more oral corticosteroids than no-AO.

Regarding expression of biomarkers, FeNO was significantly lower in the FAO than in the BDR group (29.5 ppb vs 46.0 ppb, p value=0.04), while blood eosinophils, only when expressed in percentage but not in absolute number, were higher in FAO and BDR compared with no-AO patients (p value equals to 0.047 and 0.064, respectively).

Table 2 Demographic, clinical and bio-humoral characteristics of subjects with FAO, BDR and no-AO

		FAO (N=116)	BDR (N=74)	No-AO (N=164)	P value 1 vs 2	P value 1 vs 3	P value 2 vs 3
Sex					**0.024**	**0.004**	1.000
Female	N (%)	58 (50.0)	50 (67.6)	111 (67.7)			
Male	N (%)	58 (50.0)	24 (32.4)	5 (32.3)			
BMI					0.727	0.200	0.138
	Mean (SD)	26.4 (6.2)	25.8 (4.7)	26.6 (4.7)			
Smoking habit					0.301	0.527	0.306
No	N (%)	76 (66.1)	5 (73.2)	11 (72.0)			
Yes	N (%)	7 (6.1)	6 (8.5)	7 (4.3)			
Ex-smoker	N (%)	32 (27.8)	13 (18.3)	39 (23.8)			
Not reported	N	1	3	0			
Pack years*					0.912	0.243	0.223
	Median (IQR)	11.8 (3.6–20.0)	8.8 (3.5–20.0)	15.0 (5.3–25.6)			
Age at study enrolment (years)					0.481	0.291	0.770
	Mean (SD)	54.5 (13.1)	55.7 (11.4)	56.1 (11.9)			
Asthma age onset					0.955	**0.019**	0.053
	Mean (SD)	31.0 (15.8)	31.1 (16.4)	35.8 (16.5)			
Asthma duration (years)					0.661	0.052	**0.041**
	Mean (SD)	23.7 (14.4)	25.0 (16.0)	20.5 (14.8)			
ACT					**0.005**	0.836	**0.010**
	Mean (SD)	17.4 (4.7)	15.2 (5.0)	17.1 (5.2)			
AQLQ score					**0.001**	0.443	**0.009**
	Mean (SD)	4.6 (1.3)	3.8 (1.2)	4.4 (1.4)			
GINA classification					0.107	0.685	0.195
Step 4	N (%)	13 (12.2)	3 (4.4)	15 (9.9)			
Step 5	N (%)	94 (87.9)	66 (95.7)	137 (90.1)			
Not reported	N	9	5	12			
Asthma control†‡					**0.004**	0.421	**0.020**
Controlled	N (%)	40 (34.5)	15 (20.3)	46 (28.0)			
Partially controlled or uncontrolled	N (%)	68 (58.6)	51 (68.9)	92 (56.1)			
Partially controlled	N (%)	35 (30.2)	21 (28.4)	53 (32.3)			
Uncontrolled	N (%)	33 (28.4)	30 (40.5)	39 (23.8)			
Not reported	N (%)	8 (6.9)	8 (10.8)	26 (15.9)			
AE treated with systemic steroids					0.183	**<0.001**	0.054
	Median (IQR)	2.0 (1.0–4.0)	2.0 (0.0–3.0)	1.0 (0.0–3.0)			
At least one corticosteroid-treated AE	N (%)	72 (62.1)	44 (59.5)	78 (47.6)	0.761	**0.021**	0.095
Frequent exacerbator§					0.610	**0.073**	**0.028**

Continued

Table 2 Continued

		FAO (N=116)	BDR (N=74)	No-AO (N=164)	P value 1 vs 2	P value 1 vs 3	P value 2 vs 3
No	N (%)	11 (14.1)	6 (10.7)	30 (25.2)			
Yes	N (%)	67 (85.9)	50 (89.3)	89 (74.8)			
Not reported	N (%)	38	18	45			
ICU admission					0.112	1.000	**0.032**
0	N (%)	114 (98.3)	69 (93.2)	162 (98.8)			
1	N (%)	2 (1.7)	5 (6.8)	2 (1.2)			
Emergency room admission					**0.023**	0.217	0.205
0	N (%)	104 (89.7)	57 (77.0)	138 (84.2)			
1	N (%)	12 (10.3)	17 (23.0)	26 (15.9)			
Hospital admission					0.380	0.687	0.125
0	N (%)	103 (88.8)	62 (83.8)	149 (90.9)			
1	N (%)	13 (11.2)	12 (16.2)	15 (9.1)			
ICU or emergency room or hospital admission					**0.050**	0.755	0.095
0	N (%)	96 (82.8)	52 (70.3)	132 (80.5)			
1	N (%)	20 (17.2)	22 (29.7)	32 (19.5)			
Blood eosinophils (absolute count cell/L)					0.890	0.113	0.152
	Median (IQR)	0.5 (0.2–0.8)	0.5 (0.2–0.8)	0.4 (0.1–0.7)			
Blood eosinophils (%)					0.872	**0.047**	0.064
	Median (IQR)	5.5 (2.1–10.0)	6.7 (2.3–10.9)	4.6 (1.8–7.5)			
FeNO (ppb)					**0.044**	0.693	0.116
	Median (IQR)	29.5 (20.1–50.0)	46.0 (25.0–76.0)	30.5 (19.0–60.0)			

Bold indicates p<0.05.
*Pack years calculated on smokers and ex-smokers.
† Asthma control was defined as ACT ≥20; partially controlled as ACT 16-19; uncontrolled as ACT <15.
‡ Asthma partially control and uncontrolled are merged (ACT < 19)
§Frequent exacerbator was defined as at least two bursts of systemic corticosteroids (>3 days course each) in the previous year.
ACT, asthma control test; AE, acute exacerbations; AQLQ, asthma quality life questionnaire; BD, bronchodilator; BDR, bronchodilator responsiveness; BMI, body mass index; FAO, fixed airway obstruction; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; ICU, intensive care unit; no-AO, no-airway obstruction.

Nasal polyposis was the most represented comorbidity with the higher percentage of more than 50% in SA with FAO. However, the proportion of FAO patients with at least a comorbidity was higher than that of no-AO (p value=0.012) (table 3).

SA with BDR was more oral corticosteroid dependent than no-AO, while long-acting muscarinic antagonists (LAMAs) were significantly more used in FAO compared with no-AO (27.6 vs 15.9%, p=0.024). No further differences were found in treatment administration among the three groups, including biologic drugs (table 4).

Change in FAO asthma condition during follow-up

Sixty-two patients were diagnosed with FAO and had at least a second measurement of bronchodilator reversibility test obtained during a subsequent follow-up visit (median follow-up: 8.7 months (IQR: 5.9–14.1)). In 27 out of 62 patients (43.5%), a variation in asthma condition (ie, switching from FAO to BDR or no-airway

Table 3 Comorbidities of subjects with FAO, BDR and no-AO

		FAO (N=116)	BDR (N=74)	No-AO (N=164)	P value 1 vs 2	P value 1 vs 3	P value 2 vs 3
CRSsNP					0.972	0.664	0.677
Never	N (%)	79 (69.9)	49 (69.0)	120 (74.5)			
Yes, former	N (%)	15 (13.3)	9 (12.7)	17 (10.6)			
Yes, ongoing	N (%)	19 (16.8)	13 (18.3)	24 (14.9)			
Not reported	N	3	3	3			
Nasal polyps					0.490	0.057	0.718
No	N (%)	54 (47.0)	39 (53.4)	93 (58.1)			
Yes, CT or endoscopic confirmation	N (%)	57 (49.6)	30 (41.1)	57 (35.6)			
Yes, suspected	N (%)	4 (3.5)	4 (5.5)	10 (6.3)			
Not reported	N	1	1	4			
Bronchiectasis					0.854	0.136	0.333
No	N (%)	76 (76.0)	52 (77.6)	116 (84.1)			
Yes	N (%)	24 (24.0)	15 (22.4)	22 (15.9)			
Not reported	N	16	7	26			
Cardiovascular disease					0.866	0.674	0.872
No	N (%)	78 (71.6)	52 (73.2)	115 (74.2)			
Yes	N (%)	31 (28.4)	19 (26.8)	40 (25.8)			
Not reported	N	7	3	9			
Number of comorbidities					0.452	**0.012**	0.241
0	N (%)	19 (16.4)	17 (23.0)	52 (31.7)			
1	N (%)	54 (46.6)	29 (39.2)	66 (40.2)			
≥ 2	N (%)	43 (37.1)	28 (37.8)	46 (28.1)			
Perennial allergen Skin Prick Test sensitisation					0.572	0.874	0.471
None	N (%)	26 (34.2)	20 (40.0)	34 (33.0)			
Yes	N (%)	50 (65.8)	30 (60.0)	69 (67.0)			
HDM	N	40	17	51			
Alternaria	N	5	4	12			
Aspergillus	N	4	4	5			
Dog dander	N	8	9	15			
Cat dander	N	14	10	19			
Other	*N*	8	9	15			
Not reported		40	24	61			

Bold indicates p<0.05.
BDR, bronchodilator responsiveness; CRSsNP, chronic rhinosinusitis without nasal polyps; CT, Computed Tomography; FAO, fixed airway obstruction; HDM, house dust mite; no-AO, no-airway obstruction.

obstruction) was observed: 12 (19.4%) patients switched from FAO to no-AO, 15 (24.2%) switched from FAO to BDR and 35 (56.5%) did not show any change in FAO condition. The association of the patient's demographic and clinical characteristics with the variation of asthma condition is shown in online supplemental table 2. GINA classification (step 4 vs step 5) and age of asthma onset (30–39 vs <20 years) were the only factors found to be associated with variation in asthma condition (HR 3.58 (95% CI 1.16 to 11.03) and HR 3.94 (95% CI 1.09 to 14.30), respectively). Figure 1 shows the cumulative incidence curve of variation in asthma condition stratified by GINA classification (n=6 step 4, n=52 step 5).

DISCUSSION

The main finding of our observational study of SA patients with airway obstruction is that 61% of those undergoing a salbutamol responsiveness test according to 2005 ERS/ATS criteria[8] demonstrate FAO. We applied a definition of FAO that is a FEV_1/FVC ratio below the LLN after salbutamol responsiveness test with an increase of FEV_1 or FVC <12% or <200 mL, that is to our opinion the most appropriate.[14] The overall rate of FAO in the SANI cohort

Table 4 Treatment of subjects with FAO, BDR and no-AO

		FAO (N=116)	BDR (N=74)	No-AO (N=164)	P value 1 vs 2	P value 1 vs 3	P value 2 vs 3
Oral corticosteroid treatment at baseline	N (%)* [a]	16 (13.8)	17 (23.0)	17 (10.4)	0.118	0.452	**0.015**
Chronic oral corticosteroids	N (%)†	*9 (56.3)*	*14 (82.4)*	*7 (41.2)*			
Oral corticosteroid treatment administered within 12 months before enrolment	N (%)*	21 (18.1)	19 (25.7)	25 (15.2)	0.274	0.624	0.071
Cumulative dose, median (IQR)		1488 (40–4775)	1560 (425–1825)	1828 (150–9125)			
Biologic treatment at baseline	N (%)*	38 (32.8)	23 (31.1)	60 (36.0)	0.874	0.527	0.463
Omalizumab	N (%)†	21 (55.3)	12 (52.2)	32 (53.3)			
Mepolizumab	N (%)†	13 (34.2)	9 (39.1)	25 (41.7)			
Dupilumab		0 -	1 (4.3)	1 (1.7)			
Benralizumab	N (%)†	4 (10.5)	1 (4.3)	2 (3.3)			
Treatment duration (months), median (IQR)		*12.6 (3.1–36.7)*	23.0 (3.1–68.2)	21.1 (9.1–42.4)			
Rhinitis treatment at baseline	N (%)*	18 (15.5)	12 (16.2)	39 (23.8)	1.000	0.099	0.233
Inhaled corticosteroid treatment at baseline	N (%)*	116 (100)	74 (100)	164 (100)	–	–	–
Inhaled corticosteroids alone	N (%)†	*5* (4.3)	4 (5.4)	4 (2.4)			
Inhaled corticosteroids and bronchodilator	N (%)†	111 (95.7)	70 (94.6)	160 (97.6)			
Inhaled corticosteroid treatment prescribed within 12 months before enrolment	N (%)*	55 (47.4)	39 (52.7)	74 (45.1)	0.552	0.717	0.327
Cumulative dose, median (IQR)		57 350 (36 500–73200)	65 700 (36 500–91250)	73 000 (45 688–91250)			
LAMAs at baseline‡	N (%)*	32 (27.6)	19 (25.7)	26 (15.9)	0.867	**0.024**	0.077

Bold indicates p<0.05.
*The denominators of the proportions in these lines are total group sizes (ie, 116 for FAO, 74 for BDR and 164 for No-AO).
†The denominators of the proportions in these lines are the subgroup sizes of patients under specific treatments (ie, among FAO patients, 9 out of 16 patients (56.3%) under oral corticosteroids treatment at baseline were treated with chronic oral corticosteroids).
‡LAMAs: tiotropium, Tiotropium Respimat.
BDR, bronchodilator responsiveness; FAO, fixed airway obstruction; LAMAs, long-acting muscarinic antagonists; no-AO, no-airway obstruction.

at registry enrolment is 32.8%. FAO is less prevalent in the SANI registry than it is in the ISAR worldwide population.[7] In addition, when considering patients with high steroid exposure from ISAR (long-term maintenance OCS therapy for at least 1 year, or ≥4 courses of steroid bursts in a year), post-BD FEV_1/FVC <0.7 increased up to 56.8% in those who initiated biologics.[19] On the contrary, in SANI, FAO prevalence is consistently stable both in SA with chronic OCS and biologic initiators.

It is well known that some subjects with asthma (and not with COPD) are not responsive to salbutamol,[20 21] although their magnitude varies among studies depending on the selected criteria for defining FAO (online supplemental table 1). Independent risk factors that have

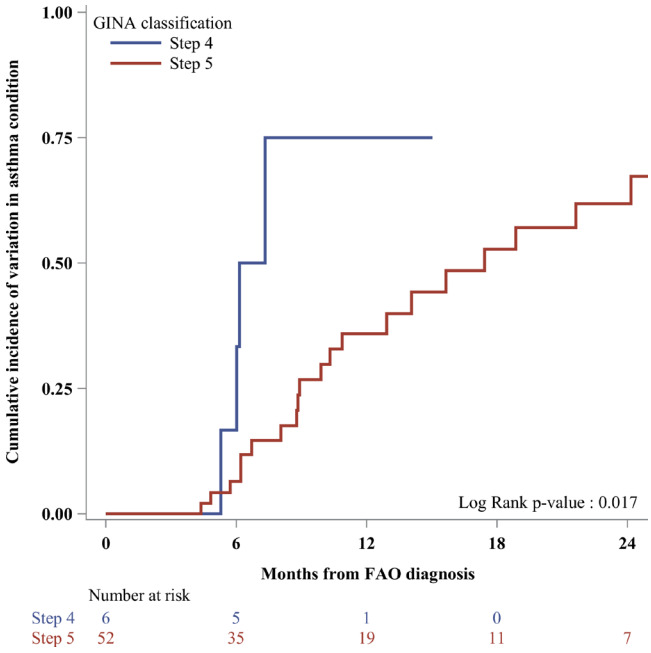

Figure 1 Cumulative incidence curve of variation in asthma condition (switching from FAO to BDR or no-AO) from baseline through follow-up visits stratified by GINA classification. BDR, bronchodilator responsiveness; FAO, fixed airway obstruction; GINA, Global Initiative for Asthma; no-AO, no-airway obstruction.

been identified for PAL include exposure to cigarette smoke or noxious agents, chronic mucus hypersecretion and AEs in patients not taking inhaled corticosteroids (ICS).[22] In people with asthma, this trait has previously been reported to be associated with a longer duration of asthma,[23 24] more hyperinflation and elevated sputum eosinophil counts.[25] Furthermore, evidence suggests that patients with difficult-to-treat asthma who currently smoke or have a history of smoking have a higher risk of developing FAO.[26] Recently, Kole *et al*[27] reported older age at baseline, longer duration of asthma (24 years vs 12 years), male sex (51% *vs* 38%), higher blood eosinophil counts (median 0.27×10^9 cells/L vs 0.20×10^9 cells/L), and more exacerbations during 1 year of follow-up, to be independently associated with a postbronchodilator FEV_1/FVC <LLN regardless the degree of GINA classification asthma severity. However, in this study, associations of FAO with sex, duration of asthma and risk of exacerbations were not validated when using data from the BIOPRED cohort.

In our study, the FAO group, by definition BDR, seems consistently more controlled and less prone to severe exacerbations leading to emergency department access compared with those with BDR at entry of the registry. The result is consistent with a more stable airway tone, protective in terms of severe exacerbations as reversible airway obstruction also reflects instability of the bronchomotor tone.[28] High airway reversibility is considered a risk factor for future exacerbations,[8 29] and recently, Hanania *et al*[30] identified in SA a high BDR as a risk for exacerbation, irrespective of FAO. However, Omalizumab, an anti-IgE biologic drug, reduced exacerbations compared with placebo much more in patients with high BDR, compared with FAO+low BDR, suggesting the impact of type-2 inflammatory target treatment on this phenotype. In addition, the better asthma control we observed in FAO may be explained by a different control of respiratory drive: poor dyspnoea perception in asthmatic subjects may depend on the level of airway narrowing.[31]

BDR phenotype, that is, patients with an FEV_1/FVC ratio below the LLN with reversible airway obstruction (BDR, ie, FEV_1 or FVC values ≥12% and ≥200 mL compared with baseline), has not been so much explored in SA cohorts. The mean FEV_1/FVC ratio is 0.66, which implies that many of these patients have still airway limitations although significantly reversible. Crisafulli and coauthors[32] observed that a high proportion of patients with asthma and PAL had bronchodilator reversibility (46%). In the reanalysed post-hoc data in the ATLANTIS study patients with PAL had bronchodilator reversibility in 60% of cases, however without resulting independently associated with exacerbations when combined in the model with PAL.[33]

While LAMAs were significantly more used in FAO compared with no-AO, as expected by the consistent data about improvements in lung function in asthmatics with varying degrees of severities across different age groups,[34] the SA patients with BDR were more oral corticosteroid dependent. These results may be in line with the high exacerbation rate above reported.

We found lower levels of airway inflammation as measured by exhaled nitric oxide in FAO compared with BDR. These data are not sustainable by a lower burden of T2-high phenotype, as smoking habit, atopy, type-2 comorbidities such as nasal polyps and use of T2 target biologics do not differ among the groups. Lower FeNO levels within FAO may be explained by the effect of airway calibre on FeNO values. Many studies performed by airway challenges showed that a reduction of airway calibre reduces FeNO levels in the absence of any inflammatory changes.[35] A recent real-world study showed airway calibre to be an independent and significant determinant of FeNO when measured in patients with asthma.[36]

An additional interesting result comes from univariate analysis of predictors of change from FAO to BDR or no-AO. The strongest association was reported for GINA (step 4 vs step 5, HR 3.58 (95% CI 1.16 to 11.03)) and age of asthma onset (30–39 vs <20 years, HR 3.94 (95% CI 1.09 to 14.30)). GINA step 4 seems more susceptible to interventions able to modify airflow limitation, which can suggest a less prominent irreversible airway remodelling in this FAO group.[37] We did not observe such a high effect of treatments on the change in functional asthma condition. It is to be noted that our results point out that a significant proportion of FAO patients started ICS in the last 12 months. Some studies, although mainly

in the setting of mild asthma, postulated that early intervention with ICS may prevent the development of irreversible airway obstruction.[38] The fact that medium ICS dose reflects more the possibility of reverting from FAO suggests that patients in GINA step 5 (high dose) are becoming steroid resistant. On the other hand, how ICS can modulate the mechanisms of airway remodelling is still unclear, although some studies showed improvement of improved airflow limitation in ICS-treated patients with increased periostin.[39] An additional issue, that we were not able to detect, is whether during follow-up a drop-down in adherence to inhaled treatment was observed. This is an innovative topic that deserves additional studies by objective measures.[40]

Airway remodelling and chronic inflammation may be determinants of FAO development in asthma. The U-BIOPRED Study Group explored the transcriptomic gene signatures in nasal, sputum and endobronchial samples, associated with PAL in SA, recognising eosinophilic airway inflammation, IL-13 pathway and specific CD4+T cells as the main involved.[41] Although genes involved in bronchial structural alterations seem crucial in inducing remodelling, reticular basement membrane thickness was not different in moderate to severe persistent compared with intermittent airflow limitation asthmatics.[42] Further studies are needed for a clear comprehension of the mechanism underlying FAO and its association with BDR. Actually, long-term trajectories of FAO are still to be elucidated, although persistent FAO has been associated with higher baseline sputum neutrophil content and airway smooth muscle quantification.[43]

One limitation of our study is the heterogeneity in terms of treated patients and clinical settings. However, this is consistent with a real-life approach. This observational study was conducted in highly selected asthma centres and this guarantees that, at enrolment, treatment was optimised at the step 4 level for defining asthma as severe, in a stable phase of the disease not recently diagnosed. Actually, the mean duration of asthma from diagnosis was over 20 years, implying that many patients had undergone diagnostic BDR testing long before registry enrolment. This is the reason for not requiring BDR testing for enrolment as per protocol. Therefore, we are aware that only some of the patients with airway obstruction included in this study underwent the BDR testing, which represents a major limitation. However, the mean disease duration reported in this study overlaps with that reported in a recent update from the entire SANI population (median 19 years, n=1922)[44] as well as in a high-steroid-exposed ISAR cohort (mean 23 years, n=1412),[19] favouring the generalisation of our results. In addition, our aim was not to detect how many patients were non-responders to salbutamol but rather to characterise those with FAO versus those with BDR. We believe that the characterisation of FAO in a cohort of patients with long-lasting SA, many years after diagnosis, provides valuable insights into the natural history of the disease, additionally identifying a subgroup of patients who still preserve BDR.

Finally, we are aware that a document published in July 2022 by ERS/ATS entitled 'Interpretative strategies for routine lung function test'[9] suggests the increase of FEV1 or FVC >10% of the predicted value to define a significant response to salbutamol. However, a new analysis of our data applying this criterion yields baseline FAO to be reduced from 116 to 97, with unchanged results. When analysing BDR as a treatable trait in asthma and COPD, Beasley *et al*[10] found a modest difference in response between the 2005 and 2022 criteria (20% vs 18%). Moreover, their results are similar to that found in our severe asthmatic subjects, reporting less control in those with BDR.

In conclusion, in our cohort of SA patients from the SANI registry, the FAO phenotype, defined by a postbronchodilator FEV_1/FVC <LLN and an increase of FEV_1 <12% or <200 mL, is characterised by better control, quality of life and lower FeNO values and less disease exacerbations compared with patients with reversible airway obstruction (BDR). Factors associated with FAO transition towards reversible obstruction or normal lung function were the age of asthma onset and GINA classification, rather than pharmacological treatment.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was carried out according to the Helsinki and Oviedo Declaration. The SANI registry was set up according to the third edition recommendation on registries for evaluating patient outcomes published by the Effective Health Care Program of the Agency for Healthcare Research and Quality (https://effectivehealthcare.ahrq.gov/topics/registries-guide-3rd-edition/research/). The protocol was designed following the principles and procedures of the Good Clinical Practice (ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996; Directive 91/507. EEC, The Rules Governing Medical Products in the European Community) and according to Italian law (D.L.vo n.211 24 June 2003; D.L.n.200 6 November 2007; MD, 21 December 2007). The study protocol was approved by the local Ethics Committee of Area Vasta NORD-OVEST Toscana, Italy. Approval number: number of protocol: 73 714, December 2016. Participants gave informed consent to participate in the study before taking part.

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