Carpagnano et al. World Allergy Organization Journal (2025) 18:101082
http://doi.org/10.1016/j.waojou.2025.101082

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Profile of mild/moderate asthma patients: Baseline data from the MANI cohort

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ABSTRACT

Although 90% of asthmatic patients suffer from mild and moderate disease, little is known about the burden on health status and quality of life, the long-term trajectory of disease severity, and the socio-economic impact. The Mild Moderated Asthma Network of Italy (MANI) is a real-world, cross-sectional, prospective, observational cohort study designed to explore these issues. Here we aimed to provide an identikit of asthmatic patients receiving treatment according to GINA steps 1–4, and enrolled in the centers of excellence participating in the MANI. Among 679 analyzed patients, 63% were female, and the mean age was 50 $\pm$ 16 years. Asthma was mild in 15.8% of patients (GINA steps 1–2) and moderate in 84.2% (GINA steps 3–4). The mean age of asthma diagnosis was 34.3 $\pm$ 17.7 years, 50% of patients were suffering from allergic rhinitis, and 13% from nasal polyposis. Mean FEV1% was 91.4 $\pm$ 19.4%, predicted with a FEV1/FVC ratio of 74.7 $\pm$ 11.9. The mean asthma control test value was 21.2 $\pm$ 3.73, and AQLQ score was 5.74 $\pm$ 1.07. Among the included patients, 17.2% had at least one asthma exacerbation in the previous year, with 14.2% requiring systemic steroids; 6.2% were referred to an emergency room in the year prior to enrollment; 2.2% required an asthma-related hospitalization; and 0.6% had been admitted to an Intensive Care Unit (ICU). Unscheduled visits were necessary for 3.8% of patients, 6.5% reported $\geq$5 lost work days due to asthma, and 11.5% declared $\geq$10 lost days of spare time. About 70% of patients were receiving treatment according to GINA Track 1. Uncontrolled cases constituted 16.7% of patients treated according to GINA steps 1–2, and 26.3% of patients treated according to GINA steps 3-4 were uncontrolled. Compared to patients with mild asthma, those with moderate asthma had more impaired lung function (FEV1% 88.5 $\pm$ 18.4 vs 94.4 $\pm$ 17.9, $p = 0.05$; FEV1/FVC 73.0 $\pm$ 9.76 vs 79.6 $\pm$ 9.56, $p > 0.001$), exhibited greater need for systemic corticosteroids for treating exacerbations (13.8% vs 2.3%, $p = 0.032$), and showed greater adherence to therapy (TAI score 50.0 $\pm$ 5.66 vs 45.7 $\pm$ 8.42, $p < 0.001$). Overall, mild/moderate asthma exhibited a substantial clinical and care impact. Patients treated with GINA steps

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http://doi.org/10.1016/j.waojou.2025.101082

Received 29 January 2025; Received in revised from 30 May 2025; Accepted 11 June 2025
Online publication date xxx

3–4 constituted the vast majority of patients attending specialist centers. A quarter of these patients were uncontrolled, and therefore need re-evaluation or treatment upgrade. Expanding recruitment of the MANI study will allow further phenotyping of these patients.

Keywords: Asthma, Mild, Moderate, Control, Rea life

INTRODUCTION

Asthma is an heterogeneous chronic disease,[1] with an increasing global prevalence,[2] and a variable impact on health status and quality of life, according to its severity.[3] During the last decade, particular attention has been focused on severe asthma, for which new precision medicine therapies have become available in addition to inhaled drugs.[4] However, only a minority of the asthmatic population suffers severe asthma.[5] Epidemiological studies indicate that 50–75% of asthmatic patients are affected by mild asthma, and 15–75% by moderate asthma.[6] Notably, asthma classification is a subject of scientific debate, as severe exacerbations are possible even among patients with infrequent symptoms or whose symptoms are controlled with low-dose treatment.[7] Despite the clear epidemiological relevance of mild/moderate asthma, and its obvious burden on health status and quality of life, little is known about the long-term trajectory of mild/moderate asthma in term of disease severity and socio-economic impact.[8–13]

To update the available knowledge, the Italian Respiratory Society (IRS) and the Italian Society of Allergology, Asthma, and Clinical Immunology (SIAAIC) endorsed the Mild Moderated Asthma Network of Italy, whose activities include the MANI study, which is a real-world, observational study. Its primary objective is to study the long-term evolution of mild/moderate asthma to severe disease. Secondary objectives include the assessment of a broad panel of clinical, behavioral, pharmacoeconomical, and patient-reported outcomes.[14]

Here we describe mild/moderate asthmatic patients enrolled in the centers of excellence participating in the MANI network.

METHODS

The MANI study enrolled adult patients with a diagnosis of asthma according to the GINA report. As commonly done in epidemiological studies and clinical trials, patients were enrolled and classified based on the treatment they were receiving at the time of the visit, rather than on the minimum level of treatment required to achieve and maintain asthma control (https://ginasthma.org/).[15] For doing this we applied the GINA-recommended table that defines low, medium, and high daily doses of inhaled corticosteroids (ICS) for adults. Patients at steps 1–2 were classified as having mild asthma, while those at steps 3–4 were classified as having moderate asthma. All patients receiving treatment at GINA step 5 were excluded. No additional exclusion criteria were applied, except for recent or ongoing participation in interventional trials.

Patients could be enrolled either at their first visit to the recruiting center—having previously been managed by their general practitioner—or during a follow-up visit if already under specialist care.[15]

Data were collected using the web-based REDcap platform and included demographics, clinical and functional data, laboratory results, and patient-reported outcomes. The following tools were used: Asthma Control Test (ACT), Nasal Obstruction Visual Analogue Scale (VAS), Asthma Quality of Life Questionnaire standardized (AQLQ-S), Asthma Awareness Questionnaire (AAQ), Chronic Cough Impact Questionnaire (CCIQ), Patient Health Engagement (PHE), RhinAsthma Patient Perspective (RAPP), and Test of Adherence to Inhaler (TAI).

Patients were enrolled at Italian allergology and pulmonology specialist centers. The study aims to recruit a total of 20,000 patients, who will be

followed for 10 years starting from the enrollment of the last participant. Both newly referred patients—attending the center for the first time and those already under follow-up at the enrolling center—were eligible for inclusion. The follow-up schedule will be based on routine clinical practice and tailored to the individual needs of each patient. In accordance with GINA guidelines, which define asthma severity based on the treatment required to achieve disease control, we assessed asthma control by correlating the ongoing therapy with the ACT (Asthma Control Test) score.[15] This study was approved by the Ethics Committee of the Ospedale Poliniclinico IRCCS San Martino di Genova (N. Registro CER Liguria: 456/2020 - DB id 10481 d-26/10/2020 -Delib Dir. Gen, Prot. N. 2060 November 11, 2020) and performed in accordance with the Helsinki and Oviedo declaration.[16,17] All eligible participants who freely agreed to enter the study signed a written informed consent form. The MANI protocol was registered on ClinicalTrials.gov with the identification number NCT04796844.

Given the observational nature of the study, a set of essential parameters (eg, age, sex, FEV1, current therapy, and disease control level) was predefined, along with additional parameters not routinely collected in clinical practice. A sensitivity analysis was conducted to assess the robustness of the results to different thresholds of data completeness. While the main analysis included only cases with $\geq$90% of essential parameters and $\geq$70% of non-essential parameters available, alternative thresholds were tested: including cases with $\geq$70% of essential parameters (less stringent threshold), and cases with 100% of essential parameters (more stringent threshold). An additional analysis included subjects with $\geq$70% of essential parameters and $\geq$50% of non-essential parameters. Results from these analyses were compared with those of the main analysis to evaluate potential bias introduced by excluding cases with missing data. The sensitivity analyses yielded consistent results with the main analysis, suggesting that the choice of completeness thresholds did not materially affect the study conclusions.

Statistical analysis

Descriptive analysis was performed for variables collected at baseline. After testing for normal distribution, continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range, and between-group comparisons were performed using the chi-square test for qualitative variables, student *t*-test for normally distributed quantitative variables, and Mann-Whitney for non-normally distributed quantitative variables. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using Jamovi® software.[18]

RESULTS

A total of 700 patients were enrolled, 21 of whom were excluded because they were treated as per GINA step 5. Sixty-three percent were female and the mean (SD) age was 50 (16.9) years. Based on inhaled treatment at enrollment, 15.8% had mild asthma (GINA steps 1–2) and 84.2% had moderate asthma (GINA steps 3–4). One-third reported a family history of asthma and/or allergies. The mean (SD) time from first asthma diagnosis was 30 (18.6) years. Among comorbidities, upper airway diseases were predominant, with 50.4% suffering from allergic rhinitis, and 13% from nasal polyposis. 3.9% of patients reported at least one episode of pneumonia, 3.6% had a previous diagnosis of bronchiectasis, and 13.7% had a positive history of pediatric bronchiolitis.

Lung function parameters were available at enrolment for 406 patients, and showed a mean (SD) FEV1% of 91.4 (19.4)% predicted, a mean (SD) FVC% of 101 (20.8)% predicted, and a mean (SD) FEV1/FVC ratio of 74.7 (11.9). Mean (SD) blood eosinophil counts was 291 (207) cells/mcL, mean (SD) ppb FeNO 30.5 (25.9), and mean (SD) total IgE 380 (810) kU/L. The mean (SD) asthma control test score was 21.2 (3.73), whereas the mean (SD) quality of life value, measured by AQLQ, was 5.74 (1.07). 6.2% had required at least one emergency room visit during the year prior to enrollment, 2.2% required an asthma-related hospitalization, and 0.6% was admitted to an ICU. 17.2% had experienced at least one asthma exacerbation during the previous year, with the need for systemic steroids in 14.2% of cases; 3.8% had required unscheduled visits; 6.5% reported $\geq$5 lost work days due to asthma; and 11.5% declared that they lost $\geq$10 days of their spare time (Table 1).

Variable	n = 679
Demographic data	
Gender, %	F: 62.7% M: 37.3%
Age, mean (SD)	50 ± 16.9
Ethnicity (%)	Caucasian: 97.6% African: 0.8% South-East Asia: 0.9% Other: 0.7%
Profession (%)	Employed 67.8% Not employed: 4.8% Housewives: 7.7% Students: 9.3% Retired: 10.4%
BMI (mean ± SD)	26.4 ± 14.6
Pet owners (%)	22.8%
Place of residence,(%)	City: 89.7% Countryside: 10.3%
Family history of asthma (%)	28.5%
Family history of allergy (%)	33.3%
Preterm birth (%)	16.2%
Milky crust (%)	5.3%
Pediatric bronchiolitis (%)	13.7%
Smoking (%)	Never: 60.4% Former: 27.5% Current: 12.1%
Asthma Features	
Age of asthma onset (mean ± SD)	30 ± 18.3
Asthma control test (mean ± SD)	21.2 ± 3.73
Asthma control test (ACT) score (mean ± SD)	21.2 ± 3.73
Uncontrolled (%)	24.6%
Partially controlled (%)	54.5%
Controlled (%)	20.9%

(continued)

Variable	n = 679
Asthma quality of life questionnaire (AQLQ) total score (mean ± SD)	5.74 ± 1.07
AQLQ symptoms	5.60 ± 1.20
AQLQ activity limitation	5.91 ± 1.04
AQLQ emotional functions	5.80 ± 1.22
AQLQ environmental stimuli	5.57 ± 1.32
Rate of spirometry data availability at baseline (%)	73.2%
FEV1/FVC (mean ± SD)	74.7 ± 11.9
FEV1% (mean ± SD)	91.4 ± 19.4
FVC% (mean ± SD)	101 ± 20.8
FeNO (mean ± SD) (n = 189)	30.5 ± 25.9
Blood eosinophils (mean ± SD) (n = 178)	291 ± 207
Total gE (mean ± SD) (n = 151)	380 ± 810)
Asthma burden in the year before enrollment	
Working days lost (%)	0: 92.4% 1: 1.1% 5: 0.8% 10: 0.8% >15: 4.9%
Spare time days lost (%)	0: 88.1% 1: 0.4% 10: 1.9% 15: 0.9% >15: 8.7%
ICU admissions (%)	0.6%
Emergency room admissions (%)	6.2%
Hospitalization for asthma (%)	2.2%
Unscheduled visits (%)	3.8%
One or more moderate exacerbations (%)	0: 82.8% 1: 8.8% 2: 3.6% ≥3: 4.8%

(continued)

Variable	n = 679
Treatment with OCS during exacerbations (%)	0: 85.8% 1: 9.4%) 2: 2.5% ≥3: 2.3%
OCS days during exacerbation (mean ± SD)	8.73 ± 4.32
Comorbidities	
Rhinitis (%)	50.4%
Rhinitis classification (%)	Mild intermittent: 36.5% Mild persistent: 33.2% Moderate intermittent: 7.7% Moderate persistent: 22.6%
Allergic rhinitis (%)	87.6%
Rhinitis duration (%)	Perennial: 55.2% Seasonal: 44.8%
Chronic rhinosinusitis without nasal polyposis (%)	11.7%
Nasal polyposis (%)	13%
Polypectomies (N)	62
Patients with NP who underwent one or more polypectomies (N, %)	0: 11.3% 1: 48.4% 2: 17.7% ≥3: 22.6%
Atopic dermatitis (%)	11.3%
Urticaria (%)	7.6%
Psoriasis (%)	2.7%
NSAIDs hypersensitivity (%)	9.1%
Gastroesophageal reflux (%)	24%
Autoimmune diseases (%)	7.1%
Rheumatoid arthritis	15.6%
Systemic lupus erythematosus	9.4%
Thyroiditis	75%
Chronic cough (%)	6.6%

(continued)

Variable	n = 679
Cardiovascular diseases (%)	16.6%
Ocular pathology (%)	5.9%
Depression (%)	4.6%
Anxiety (%)	6.8%
Diabetes (%)	3.3%
Pneumonia (%)	3.9%
Bronchiectasis (%)	3.6%
Osteoporosis (%)	4.2%

Table 1. (Continued) Baseline demographic and clinical characteristics. *Values are the proportion (%) of the cohort unless otherwise noted. Abbreviations: ACT, asthma control test; ACQ: asthma control questionnaire; AQLQ, asthma quality of life questionnaire; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ICU, intensive care unit; IgE, immunoglobulin E; NSAID, nonsteroidal anti-inflammatory drug; OCS, oral corticosteroid; SD, standard deviation*

At enrollment, 325 patients were treated with a fixed-dose combination (FDC) of ICS/LABA (48.25% beclomethasone/formoterol, 28.5% budesonide/formoterol, 19.8% fluticasone/vilanterol, 2.0% fluticasone/formoterol, and 1.2% fluticasone/salmeterol). Additionally, 85 patients were receiving treatment with oral antileukotriene in addition to a medium/high dose of ICS, and 27 patients with a medium/high dose of ICS. Moreover, 114 patients were receiving treatment with ICS/formoterol as needed, and 29 with SABA on demand.

There were 16.7% of patients treated according to GINA steps 1–2, and 26.3% of patients treated according to GINA steps 3–4, had uncontrolled asthma (Fig. 1). Patients with moderate asthma had more impaired lung function than those with mild asthma

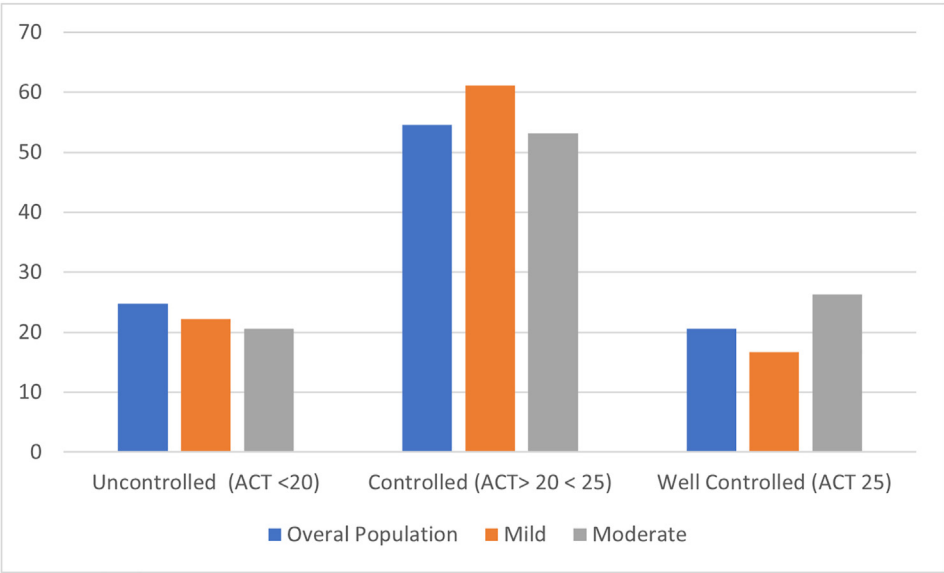

Fig. 1 Percentage of asthma control levels in overall, mild (GINA 1–2), and moderate (GINA 3–4) populations.

Variable N = 679*	Steps 1-2 (15.8%)	Steps 3-4 (84.2%)	p value
Demographic data			
Gender (%)	F: 52.6% M: 47.4%	F: 58.2% M: 41.8%	0.433
Age (mean ± SD)	47 ± 15.3	50.2 ± 16.7	0.184
Ethnicity (%)	Caucasian: 96.4% African: 1.8% South-East Asia: 0% Others: 1.8%	Caucasian: 98.3% African: 1.1% South East Asia: 0% Others: 0.3%	0.530
Profession (%)	Employed: 62.5% Unemployed:12.5% Housewives: 8.3% Student: 6.3% Retired: 10.4%	Employed: 65.4% Unemployed: 4.1% Housewives: 11.1% Student: 10.3% Retired 9.1%	0.183
BMI (mean ± SD)	25.6 ± 4.86	26.3 ± 5.41	0.377
Pet owner (%)	16.7%	28.3%	0.178
Place of residence (%)	15.8%	11.5%	0.457
Family history of asthma (%)	44.1%	30.7%	0.116
Family history of allergies (%)	37.5%	37.7%	0.986
Preterm birth (%)	0%	11%	0.162
Milky crust (%)	16.7%	6.7% (n = 6)	0.232
Pediatric bronchiolitis (%)	6.3% (n = 1)	18.4% (n = 19)	0.225
Smoking (%)	Never: 57.4% Former: 29.6% Current: 13%	Never: 61.9% Former: 29.7% Current: 8.4%	0.551
Packs/year (mean, range)	6.55 (1.60-180)	7.20 (1-94)	0.143
Asthma features			
Years since asthma onset (mean ± SD)	34.3 ± 17.7	31.7 ± 18.3	0.375
ACT score(mean ± SD) Uncontrolled (%) Partially controlled (%) Controlled (%)	21.8 ± 3.09 (n = 54) 16.7 61.1 22.2	21.1 ± 4.01 (n = 243) 26.3 53.1 20.6	0.247
AQLQ score (mean ± SD)	5.90 ± 1.06 (n = 37)	5.60 ± 1.16 (n = 197)	0.145
FEV1/FVC (mean ± SD)	79.6 ± 9.57	73.0 ± 9.76	<0.001
FEV1% predicted (mean ± SD)	94.4 ± 17.9	88.5 ± 18.4	0.05
FVC % predicted (mean ± SD)	102 ± 20.8	102 ± 16.5	0.969
FeNO (mean ± SD)	31.7 ± 24.3	36.9 ± 41.1	0.593

(continued)

Variable N = 679*	Steps 1-2 (15.8%)	Steps 3-4 (84.2%)	p value
Blood eosinophils, absolute value	253 ± 224	355 ± 211	0.865
IgE total (mean ± SD)	172 ± 154	336 ± 529	0.254
Asthma burden in the year before the enrolment			
Working days lost (N, %)	0: 92.4% 1: 1.1% 5: 0.8% 10: 0.8% >15: 2.1% Other: 2.8%	0: 92.4% 1: 1.1% 5: 0.8% 10: 0.8% >15: 2.1% Other: 2%	-
Lost spare time days (N, %)	0: 100% 1: 0% 10: 0% 15: 0% >20: 0%	0: 80.2% 1: 1.1% 10: 2.7% 15: 1.6% >20: 5.2% Other: 8.9% (n=23)	-
ICU admissions	0%	0.5%	0.633
Emergency room admissions (%)	7%	5.5%	0.644
Hospitalization for asthma (%)	0%	2.5%	0.223
Unscheduled visits (%)	2.3% (n = 1)	4.5% (n = 9)	0.497
One or more moderate exacerbations (%)	6.5%	17.3% (n = 34)	0.068
Treated with OCS during exacerbations (%)	2.3%	13.8%	0.032
Mean number of OCS days during exacerbation	3.00	8.43 ± 4.91	0.29
OCS daily dose during exacerbations (mean ± SD)	42 (4-80)	25 ± 3.500	0.751
Comorbidities			
Rhinitis (%)	47.4% (n = 27)	55.5% (n = 167)	0.260
VAS rhinitis symptoms (mean ± SD)	2.84 ± 2.20	3.67 ± 2.86	0.248
Rhinitis classification (%) Mild intermittent Mild persistent Moderate intermittent Moderate persistent	 57.1% 28.6% 4.8% 9.5%	 35.9% 34.4% 7.8% 21.9%	0.277
Allergic rhinitis (%)	73.1%	86.1%	0.091
Rhinitis duration (%)	Perennial: 40.9% Seasonal: 59.1%	Perennial: 62.1% Seasonal: 37.9	0.06
Rhinosinusitis without polyposis (%)	112.3%	15%	0.600

(continued)

Variable N = 679*	Steps 1–2 (15.8%)	Steps 3–4 (84.2%)	p value
Nasal polyposis (%)	10.7% (n = 6)	19.3% (n = 58)	0.123
Polypectomies (N/N pts) n = 49	1 = 4 2 = 2 ≥3 = 0	1 = 22 2 = 9 >3 = 12	
Atopic dermatitis (%)	7% (n = 4)	14.8% (n = 45)	0.115
Urticaria (%)	11.1%	8.2%	0.485
Psoriasis (%)	1.9%	2.7%	0.721
NSAIDs hypersensitivity (%)	3.7%	14%	0.036
Gastroesophageal reflux (%)	25%	28.8%	0.567
Bronchiectasis (%)	3.8%	3.2%	0.814
Autoimmune diseases (%)	3.7%	11.1%	0.098
Chronic cough (%)	3.7%	8.6%	0.222
Cardiovascular diseases (%)	17.9%	21.2%	0.575
Ocular pathology (%)	7.4%	8.5%	0.798
Depression (%)	1.9%	4.0%	0.435
Anxiety (%)	7.4%	8.1%	0.860
Diabetes (%)	0%	3.6%	0.154
Pneumonia (%)	13.3%	5.8%	0.519
Bronchiectasis (%)	3.7%	5%	0.677

Table 2. (Continued) Demographic and clinical characteristics at baseline steps 1–2 (mild asthma) vs 3–4 (moderate asthma). *Steps 1–2, mild asthma; steps 3–4, moderate asthma. Values are percent of subpopulation unless otherwise noted. Abbreviations: ACT, asthma control test; ACQ: asthma control questionnaire; AQLQ, asthma quality of life questionnaire; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ICU, intensive care unit; IgE, immunoglobulin E; NSAID, nonsteroidal anti-inflammatory drug; OCS, oral corticosteroid; SD, standard deviation; VAS, visual analogue scale*

(mean (SD) FEV1% 88.5 (18.4) VS. 94.4 (17.9), p-value: 0.05; mean (SD) FEV1/FVC 73.0 (9.76) vs. 79.6 (9.57), p-value >0.001), had a greater need for systemic corticosteroids to treat exacerbations (13.8% vs. 2.3%, p-value: 0.032), and showed greater adherence to therapy (mean (SD) TAI score 50.0 (5.66) vs. 45.7 (8.42), p-value <0.001) (Table 2).

DISCUSSION

Seven hundred patients recruited in the MANI study were described in the present study. The majority were treated according to GINA steps 3–4. The severity was defined on the treatment needed for optimal disease control. Patient reclassification showed that, at the time of the visit, about 20% considered to have mild asthma and 25% of those considered to have moderate asthma actually had more severe disease. This can be associated with poor adherence (which was indirectly assessed using the TAI questionnaire and found to be satisfactory) or with the need of different medication doses or types. Interestingly, with regards to the asthma burden in the year prior to enrollment, over 14% suffered at least one exacerbation treated with oral corticosteroids. Relevant impact in terms of lost work and leisure time, emergency room admissions, hospitalization, and unscheduled visits was found. Upper airway pathology was one of the most prevalent comorbidities, with 50% suffering rhinitis and 12% chronic rhinosinusitis, and 13% with nasal

polyposis (three times the rate expected in the general population),[19,20] necessitating 62 polypectomies. No substantial differences between patients with mild versus moderate asthma were found, except that moderate asthma was associated with a worse functional pattern, a higher rate of exacerbations treated with oral steroids, and a higher rate of adverse reactions to nonsteroidal anti-inflammatory drugs (NSAIDs). Mean fractional exhaled nitric oxide (FeNO) levels above the normal value were found. This can be attributed to several factors. Firstly, type 2 (T2) inflammation is not limited to severe asthma; it also plays a substantial role in mild and moderate disease. Elevated FeNO levels in these patients may reflect underlying eosinophilic airway inflammation, a hallmark of the T2-high asthma phenotype. Secondly, increased FeNO levels may indicate under-treatment with inhaled corticosteroids (ICS) or poor adherence to prescribed therapy. As a non-invasive biomarker, FeNO is valuable in identifying patients who are not adequately managed with ICS and who may benefit from treatment adjustment. Furthermore, in a subset of patients with persistent symptoms despite therapy, elevated FeNO levels may be associated with specific endotypic characteristics, such as steroid-resistant T2 inflammation. These patients might require alternative therapeutic strategies, including biologic agents targeting key inflammatory pathways. The increasing recognition of the role of biomarkers in asthma management has led to their inclusion in the 2025 Global Initiative for Asthma (GINA) recommendations, which now suggest FeNO assessment not only in severe asthma but also in milder forms. This underscores the envisaged clinical utility of FeNO in guiding treatment decisions and monitoring disease control across the full spectrum of asthma severity. The mean duration of oral corticosteroid (OCS) therapy in our cohort appears to be longer than what is typically reported in international clinical practice. In the Italian clinical setting, it is common for physicians to adopt a tapering regimen even for short-term OCS courses. This practice stems from a precautionary approach aimed at reducing the risk of adrenal suppression, particularly in patients with a history of frequent exacerbations or repeated OCS exposure. Consequently, OCS therapy may extend beyond the standard 5–7 day duration, thereby increasing the recorded length of treatment without necessarily affecting the cumulative dose. This observation reflects a real-world pattern of care and emphasizes the importance of considering regional clinical habits when interpreting observational data. It also points to a broader need for alignment and education regarding evidence-based tapering strategies to optimize patient outcomes while avoiding unnecessary prolongation of systemic corticosteroid use.

Patients with mild and moderate asthma account for 90% of asthmatics. However, many issues related to mild/moderate asthma remain controversial. Notably, the definitions of mild and moderate do not fully reflect the long-term impact on patients' lives, and the disease trajectory is not yet fully understood. Moreover, follow-up and treatment plan must account for the heterogeneity of presentations, and responses to triggers and medications. Therefore, more evidence is needed to clearly define the long-term progression, stability, and its outcomes. Real-world evidence, acquired using scientific methodology and checked for data quality, will substantially contribute to addressing the abovementioned issues.

Acknowledgments

The authors would like to thank the SIP/IRS secretariat, the Italian Respiratory Society (SIP/IRS), the Italian Society of Allergology, Asthma and Clinical Immunology (SIAAIC) for their valuable research support.

Funding

The Mild Moderated Asthma Network of Italy (MANI) was supported by through unrestricted from AstraZeneca, A. Menarini, Chiesi Farmaceutici S.p.A, and GlaxoSmithKline.

Data availability statement

Data and materials that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contribution

GEC: investigator, writer, reviewer; MB: investigator, writer, reviewer; ML: investigator; EN: investigator; IP: investigator; FP: investigator; GS: investigator; PS: investigator, reviewer; GS: statistical analysis consultant, reviewer; FB: writer, reviewer; GWC: writer, reviewer; PP: writer, reviewer; AA: investigator; IB: writer, reviewer; DB: investigator; BB: investigator, writer, statistical analysis consultant; GC: investigator; FC: investigator; GF: investigator; LM: investigator; MM: investigator; GP: investigator; DR: investigator; VP: investigator; PT:

investigator; VNQ: investigator; RV: investigator; FB: investigator, writer, reviewer.

Ethics approval

The MANI study was approved by the Ethics Committee of the Ospedale Policlinico IRCCS San Martino di Genova (N. Registro CER Liguria: 456/2020 - DB id 10481 d-26/10/2020 -Delib Dir. Gen, Prot. N. 2060 November 11, 2020) and performed in accordance with the Helsinki and Oviedo declarations. All eligible participants who freely agreed to enter the study provided written informed consent. The MANI protocol was registered at ClinicalTrials.gov under the identification number NCT04796844.

Authors' consent for publication

All authors have approved the submission of this manuscript. The results have not been previously published and are not being considered for publication in another journal.

Declaration of competing interest

MB received financial grants and consulting fees from AstraZeneca, Chiesi, Glaxo Smith Kline, Lallemand, Omron, Sanofi; he declares speaker fees from AstraZeneca, Chiesi, Glaxo Smith Kline, Lusofarmaco, Menarini, Omron, Sanofi; as well as financial support for attending meetings and/or travel from AstraZeneca, Lusofarmaco, Sanofi. FP received consulting fees, payment for lectures and for participation on a Data Safety Monitoring Board or Advisory Board from: Sanofi, Regeneron, AstraZeneca, Glaxo Smith Kline, Mundipharma, Alk Abello, Stallergenes Greer, Menarini, and Chiesi. PS received financial grants from Insmed Inc., AstraZeneca, GSK, Novartis, and Roche. GS received consulting fees from Pfizer, AstraZeneca, Insmed, and Quiagen. FB received financial grants from AstraZeneca, Chiesi Farmaceutici S.p.A and Insmed Inc.; he worked as a paid consultant for A. Menarini and Zambon; he received speaker fees from AstraZeneca, Chiesi Farmaceutici S.p.A., Glaxo Smith Kline, Guidotti, Grifols, Insmed Inc., A. Menarini, Novartis AG, Sanofi-Genzyme, Viatris Inc., Vertex Pharmaceuticals and Zambon. GWC reports having received research grants as well as being lecturer or having received advisory board fees from: A. Menarini, Allergy Therapeutics, AstraZeneca, Chiesi Farmaceutici, Faes, Firma, Guidotti-Malesci, Glaxo Smith Kline, Hal Allergy, Innovacaremd, Novartis, OmPharma, RedMaple, Sanofi-Aventis, Sanofi-Genzyme, Stallergenes-Greer, Uriach Pharma, ThermoFisher, Valeas. PP received grants for educational activities from AstraZeneca, Chiesi Farmaceutici, Glaxo Smith Kline, Guidotti, and Sanofi; he declares grants for participation to advisory board from Chiesi Farmaceutici, Glaxo Smith Kline, and Sanofi. IB received consulting fees from Sanofi; payment for lectures from AstraZeneca, Glaxo Smith Kline, and Sanofi; grants for participation to Participation on a Data Safety Monitoring Board or Advisory Board from Sanofi and Menarini. FC declares SIP/IRS 2024 Research Fellowship; she received payment for lectures from Chiesi Farmaceutici S.p.A., Doxa Pharma, GSK, Sanofi, as well as financial support for attending meetings and/or travel from AstraZeneca, GSK, Guidotti-Malesci, and Sanofi. MM received speaker fees from AstraZeneca. GP reports payment or honoraria for lectures from Glaxo Smith Kline, LoFarma, and Astrazeneca. DR received consulting fees from AstraZeneca and honoraria for lectures and presentations as a speaker from: Berlin Chemie, Menarini, Glaxo Smith Kline, AstraZeneca, Roche. FB received consulting fees from Sanofi, AstraZeneca, Menarini International and GSK; he reports payment for lectures presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, GSK, Chiesi Farmaceutici S.p.A, Menarini group, and Sanofi. The other authors declare that they have no relevant conflicts of interest.

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