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Original Research

The burden of mild asthma: Clinical burden and healthcare resource utilisation in the NOVELTY study

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ABSTRACT

Background: Patients with mild asthma represent a substantial proportion of the population with asthma, yet there are limited data on their true burden of disease. We aimed to describe the clinical and healthcare resource utilisation (HCRU) burden of physician-assessed mild asthma.

Methods: Patients with mild asthma were included from the NOVEL observational longiTudinal studY (NOVELTY; NCT02760329), a global, 3-year, real-world prospective study of patients with asthma and/or chronic obstructive pulmonary disease from community practice (specialised and primary care). Diagnosis and severity were based on physician discretion. Clinical burden included physician-reported exacerbations and patient-reported measures. HCRU included inpatient and outpatient visits.

Results: Overall, 2004 patients with mild asthma were included; 22.8% experienced ≥1 exacerbation in the previous 12 months, of whom 72.3% experienced ≥1 severe exacerbation. Of 625 exacerbations reported, 48.0% lasted >1 week, 27.7% were preceded by symptomatic worsening lasting >3 days, and 50.1% required oral corticosteroid treatment. Health status was moderately impacted (St George's Respiratory Questionnaire score: 23.5 [standard deviation ± 17.9]). At baseline, 29.7% of patients had asthma symptoms that were not well controlled or very poorly controlled (Asthma Control Test score <20), increasing to 55.6% for those with ≥2 exacerbations in the previous year. In terms of HCRU, at least one unscheduled ambulatory visit for exacerbations was required by 9.5% of patients, including 9.2% requiring ≥1 emergency department visit and 1.1% requiring ≥1 hospital admission.

Conclusions: In this global sample representing community practice, a significant proportion of patients with physician-assessed mild asthma had considerable clinical burden and HCRU.

1. Introduction

Asthma is a common respiratory disease with a substantial burden for patients and healthcare systems [1,2]. In 2019, it was estimated that more than 262 million people globally had asthma, with approximately 461,000 deaths in that year [3]. Patients with mild asthma represent the largest proportion of the asthma population, with estimates ranging from 50 to 75% [4,5]. Despite this, only limited data are available on the disease burden and real-world management of mild asthma [6].

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Abbreviations

ACT	Asthma Control Test
COPD	chronic obstructive pulmonary disease
eCRF	electronic case report form
FEV_1	forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
HCRU	healthcare resource utilisation
ICS	inhaled corticosteroid
LABA	long-acting β_2 agonist
LAMA	long-acting muscarinic antagonist
mMRC	modified Medical Research Council
OCS	oral corticosteroids
RSQ	Respiratory Symptoms Questionnaire
SABA	short-acting β_2 agonist
SD	standard deviation
SGRQ	St George's Respiratory Questionnaire
WPAI	Work Productivity and Activity Impairment

Although patients with mild asthma may have a low burden of symptoms that respond quickly to an inhaled reliever (as-needed short-acting β_2 agonist [SABA] or as-needed low-dose inhaled corticosteroid [ICS]/formoterol, a rapid-onset long-acting β_2 agonist [LABA] [1]), they remain at risk of exacerbations. Small studies have found that up to half of exacerbations requiring emergency care occur in patients who report asthma symptoms less than once a week [7,8]; thus, exacerbations are an important contributor to disease burden in mild asthma. Indeed, patients with reported mild asthma use considerable healthcare resources [9,10] and commonly have an impaired quality of life [9]. Furthermore, the 2012/2013 UK National Review of Asthma Deaths found that of 155 patients who died of asthma where prior treatment was known, 14 (9%) were receiving treatment for mild asthma (i.e., rescue medication alone) prior to death [11], suggesting a potential gap in treatment for patients who are considered to have mild asthma.

Definitions and prevalence of mild asthma vary across studies and guidelines [6]. The American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force on asthma control, severity, and exacerbations suggests classifying patients by the level of treatment required to maintain good asthma control [6,12], which is also the approach adopted by the Global Initiative for Asthma (GINA) [1]. In contrast, the 2007 US National Asthma Education and Prevention Program summary report provides two classifications of asthma severity, one for patients not taking controller therapy (based on symptom frequency, night-waking, SABA use, airflow limitation, lung function and impact on activity) and one for those taking controller therapy (based on the lowest treatment level required to maintain control) [13]. Without consensus, the classification of patients into the mild asthma category in clinical practice is largely at the discretion of the physician [12].

The NOVEL observational longiTudinal studY (NOVELTY; NCT02760329) is a multinational (19 countries across the Americas, Asia, Australia and Europe), prospective, observational study of 11,243 patients with a physician-assigned diagnosis or suspected diagnosis of asthma and/or chronic obstructive pulmonary disease (COPD). Using baseline data from NOVELTY, this analysis aimed to describe the clinical and healthcare resource utilisation burden of physician-assessed mild asthma, using both physician-reported and patient-reported measures.

2. Methods

2.1. NOVELTY study design

Details of the NOVELTY study design [14] have been published previously. Enrolment was stratified by physician-assigned diagnosis (asthma, COPD or both asthma and COPD [asthma+COPD]) and physician-assessed severity (mild, moderate, or severe), to ensure sufficient patient numbers for sub-group analyses.

No criteria were provided for the diagnosis of asthma or COPD, nor for the assessment of severity; instead, both diagnostic and severity criteria were left at the discretion of the managing physician to capture standards of care at the community level. Physicians were not aware of data from patient-reported questionnaires when assessing disease severity. A minimum period of 6 weeks was required between any exacerbation and the baseline visit. Data for patients from China were not included in the analysis due to a change in regulations about data transfer in May 2019, as were data from sites violating eligibility criteria.

2.2. Ethics approval

The NOVELTY study was approved in each participating country by the relevant institutional review boards and all patients provided written informed consent.

2.3. Patients

Details of the NOVELTY patient population, including some data for patients with physician-assessed mild asthma, have been described previously [15]. This pre-defined, cross-sectional analysis of baseline data includes patients with physician-assessed mild asthma with available exacerbation outcome and medication data; patients with physician-assessed moderate or severe asthma, or a physician-assigned label of COPD or asthma+COPD, were excluded from this analysis.

2.4. Outcomes

The clinical burden of mild asthma was assessed using both physician- and patient-reported measures. Physician-reported measures were collected using electronic case report forms and included asthma exacerbations reported in the 12 months prior to baseline (defined as a worsening of asthma beyond the patient's usual day-to-day variation), the duration of symptom worsening prior to exacerbations, the proportion of exacerbations treated with a short course of oral corticosteroids (OCS; defined as 3 or more days) and the duration of OCS treatment. Severe exacerbations were classified based on ATS/ERS Task Force criteria [12], requiring OCS for 3 or more days, or an emergency department visit or hospitalisation that resulted in OCS treatment.

Patient-reported measures included symptom control, assessed using the Asthma Control Test (ACT) [16] and Respiratory Symptoms Questionnaire (RSQ) [17]; respiratory health status, assessed using the St George's Respiratory Questionnaire (SGRQ) [18,19]; dyspnoea, assessed using the modified Medical Research Council (mMRC) grade [20]; and work productivity, assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire [21]. Hours of work lost due to health problems in the previous week were reported as the proportion of hours worked that week. Other questions included the number and proportion of patients with one or more patient-reported episode of symptomatic worsening in the past 3 months (defined as a worsening of the patient's breathing beyond what they experienced in a typical day), and the proportion of these treated with OCS. It was not appropriate to compare physician-reported exacerbations and patient-reported episodes of symptomatic worsening, due to different definitions and recall periods used in the study.

Healthcare resource utilisation burden was described as patient medication usage and the number and proportion of patients with one or more physician-reported event related to asthma exacerbations during the 12 months prior to baseline. These included hospital visits (which refers to the aggregate of unscheduled non-emergency hospital or clinic visits, emergency department visits, and hospital admissions), emergency department visits and hospital admissions due to exacerbations. Data were also collected for hospital admissions not related to

respiratory disease. For selected analyses, patients with physician-assessed mild asthma were also categorised by treatment step using GINA 2017 recommendations [22] to compare severity classification methods. GINA 2017 treatment steps were used as these represented the recommendations that applied at the time these data were collected.

2.5. Statistical analysis

Results are reported descriptively without adjustment for confounding variables. Subgroup analyses were performed in a cohort of patients with physician-assessed mild asthma but excluding those patients on maintenance OCS or biologics. Further analyses were performed in patients with physician-assessed mild asthma limited to those on GINA treatment steps 1 and 2, and in all NOVELTY patients with physician-assigned asthma on GINA treatment steps 1 and 2, according to GINA 2017 treatment steps [22].

All analyses were performed using R version 3.5.1 or higher [23].

3. Results

3.1. Patient demographics and characteristics

Of the 5932 recruited patients with physician-assigned asthma, 2004 (33.8%) had physician-assessed mild asthma, comprising the study sample. Mean age was 50.1 years (standard deviation [SD] ± 17.6); the majority were female (63.8%) and 63.1% had never smoked (Table 1). Mean post-bronchodilator forced expiratory volume in 1 second (FEV_1) was 92.3% (SD ± 16.7) predicted; 19.7% of patients had post-bronchodilator FEV_1 <80% predicted (Table 1). Of patients with physician-assessed mild asthma, 31.7% were prescribed SABA alone or low-dose ICS, corresponding collectively to GINA 2017 steps 1 and 2 (Table 1); 29.2% were classified as GINA 2017 step 4 or step 5. Of patients with available medication data, 25.3% were receiving medium/high-dose ICS + LABA treatment (Supplementary Table 1).

3.2. Physician-reported exacerbations

In total, 1997 patients with physician-assessed mild asthma (99.7%) had data available for physician-reported exacerbations. Among these, 455 (22.8%) patients experienced one or more physician-reported exacerbation in the previous 12 months (Fig. 1A), corresponding to an annualised exacerbation rate of 0.3 (SD ± 0.8, range 0–16) (Table 1). Of patients who experienced exacerbations, 329 (72.3%) had one or more severe exacerbation, with an annualised rate of 0.2 (SD ± 0.6, range 0–5) (Table 1).

During the 12 months prior to baseline, 9.5% of patients had one or more exacerbation-related hospital or clinic visit (including non-scheduled emergency visits), 9.2% had one or more emergency department visit and 1.1% had one or more hospital admission due to exacerbations (Fig. 1B). Of a total of 625 exacerbation events reported in the previous 12 months, 27.7% were associated with more than 3 days of preceding symptom worsening (Figs. 1C) and 48.0% lasted for more than one week (Fig. 1D).

Overall, 246 (12.3%) patients had one or more exacerbation in the previous 12 months treated with a short course of OCS (Fig. 1B), corresponding to an annualised rate of 0.2 (SD ± 0.5, range 0–5) (Table 1). In terms of exacerbation events, 50.1% were treated with OCS in addition to usual medications, of which 93.9% were treated with OCS for 3 or more days.

The baseline demographics for patients with and without a history of exacerbations in the 12 months prior to baseline are reported in Table 2; a higher proportion of patients with exacerbation history were female compared with those who experienced no exacerbations. The proportion of patients with one or more exacerbation varied by region, as did the proportion of these patients who were treated with OCS, which ranged from 1.2% in Germany to 25.0% in Australia (Supplementary Table 2).

3.3. Patient-reported measures

The baseline patient questionnaire regarding episodes of symptomatic worsening was completed by 1420 (70.9%) patients with physician-assessed mild asthma, of whom 805 (56.7%) reported one or more episode of symptomatic worsening in the past 3 months. Of these, 199 (24.7%) had been treated with OCS for symptomatic worsening in the previous 3 months. The proportion of patients who reported one or more episode of symptomatic worsening varied by region, from 38.9% in Korea to 75.0% in Latin America (Supplementary Table 3).

Mean ACT score at baseline was 20.8 (SD ± 3.9), with 29.7% of patients classified as having not well controlled or very poorly controlled symptoms (ACT<20) over the previous 4 weeks (Table 1; Fig. 2A); for patients who had two or more exacerbations in the previous 12 months, 55.6% were classified as having not well controlled or very poorly controlled symptoms (Fig. 3). Of those with well controlled asthma at baseline, 18.8% had one or more exacerbation in the previous 12 months. Mean RSQ total score was 3.6 (SD ± 3.4) (Table 1; Fig. 2B). Mean mMRC dyspnoea grade was 0.6 (SD ± 0.8; median 0); 199 patients (10.1%) had clinically important dyspnoea (mMRC grade ≥2) (Table 1). Mean SGRQ total score was 23.5 (SD ± 17.9). When stratifying SGRQ scores by ACT score categories, mean SGRQ total score for patients with well controlled symptoms (ACT score 20–25) was 16.0 (SD ± 11.3), 32.4 (SD ± 14.6) for patients with not well controlled symptoms (ACT score 16–19) and 52.1 (SD ± 18.1) for patients with very poorly controlled symptoms (ACT score 5–15).

Of 1356 patients with available WPAI data on employment, 54.5% were currently employed; of those employed, 11.4% reported having missed any work in the previous 7 days due to health problems. Percentage mean hours of work lost due to health problems in the past 7 days was 4.1 (SD ± 15.4) (Table 1).

3.4. Analyses of patients on GINA steps 1 and 2 treatment

Within the physician-assessed mild asthma cohort, 636 (31.7%) patients were taking GINA 2017 treatment steps 1 or 2; analyses for these patients are presented in Supplementary Table 4. Within the previous 12 months, 17.8% of these patients had one or more physician-reported exacerbation, 12.1% had one or more physician-reported severe exacerbation, and 9.0% had one or more physician-reported exacerbation treated with a short course of OCS. In terms of symptom control, 25.1% of patients were classified as having not well controlled or very poorly controlled asthma symptoms (ACT<20) over the previous 4 weeks. As reported using the WPAI, 54.9% of patients were currently employed. Of those with data available (n = 228), 8.3% reported having missed any work in the previous 7 days due to health problems.

When including all NOVELTY patients with physician-assigned asthma on GINA 2017 treatment steps 1 or 2 (including those assessed by their physicians as having moderate or severe disease) (N = 911), few differences were observed in patient demographics and clinical characteristics compared with the physician-assessed mild asthma cohort. Of these patients on GINA 2017 treatment steps 1 or 2, 20.9% had one or more physician-reported exacerbation in the previous 12 months, and 15.6% had one or more physician-reported severe exacerbation (Supplementary Table 5). This pattern was also evident when excluding patients on maintenance OCS and biologics from the physician-assessed mild asthma cohort (Supplementary Table 6).

4. Discussion

Despite the emerging evidence of a burden in mild asthma, which is greater than has been historically reported [6], asthma research largely focuses on severe disease, leaving mild asthma understudied [24–27]. Approximately one-quarter of patients with physician-assessed mild asthma in NOVELTY experienced one or more physician-reported exacerbation during the previous 12 months, with approximately 15%

Table 1
Baseline characteristics of patients with physician-assessed mild asthma.

Characteristic	Physician-assessed mild asthma (N = 2004)
Patient demographics	
Age (years), mean (SD)	50.1 (17.6)
Female, n (%)	1279 (63.8)
Smoking history, n (%)	
Patients with data, n	2001
Current smoker	174 (8.7)
Former smoker	565 (28.2)
Never smoker	1262 (63.1)
GINA 2017 treatment step[a], n (%)	
Steps 1 & 2 (SABA alone/low-dose ICS)	636 (31.7)
Step 3 (low-dose ICS + LABA)	783 (39.1)
Step 4 (medium-/high-dose ICS + LABA)	533 (26.6)
Step 5 (medium-/high-dose ICS + LABA with LAMA, biologic or maintenance OCS)	52 (2.6)
Spirometry assessments	
Pre-bronchodilator FEV_1% predicted	
Patients with data, n	1804
Mean (SD)	88.8 (17.1)
Post-bronchodilator FEV_1% predicted	
Patients with data, n	1606
Mean (SD)	92.3 (16.7)
<80% predicted, n (%)	316 (19.7)
Patient-reported measures	
ACT score	
Patients with data, n	1381
Mean (SD)	20.8 (3.9)
mMRC dyspnoea grade	
Patients with data, n	1965
Mean (SD)	0.6 (0.8)
Median	0
Grade ≥2, n (%)	199 (10.1)
RSQ total score	
Patients with data, n	1405
Mean (SD)	3.6 (3.4)
SGRQ total score	
Patients with data, n	1368
Mean (SD)	23.5 (17.9)
WPAI percent work missed due to health problems in the past 7 days	
Patients with data, n	705
Mean (SD)	4.1 (15.4)
Physician-reported exacerbations (previous 12 months)[b]	
Exacerbations	
Patients with data, n	1997
Mean (SD)	0.3 (0.8)
Patients with ≥1 exacerbation, n (%)	455 (22.8)
Severe exacerbations[c]	
Patients with data, n	1997
Mean (SD)	0.2 (0.6)
Patients with ≥1 severe exacerbation, n (%)	329 (16.5)
Exacerbations requiring OCS	
Patients with data, n	1997
Mean (SD)	0.2 (0.5)
Patients with ≥1 exacerbation requiring OCS, n (%)	246 (12.3)
Exacerbation treatment (previous 12 months)[d], n (%)	
Patients with data, n	67
Oral/injected corticosteroids	48 (71.6)
Antibiotics	30 (44.8)
Oral/injected corticosteroids and antibiotics	15 (22.4)
Comorbidities, n (%)	
Rhinosinusitis[e]	1182 (59.0)
Anxiety/depression	283 (14.1)
Cardiovascular disease	144 (7.2)
Nasal sinus polyps	67 (3.3)
≥1 non-respiratory comorbidity	1239 (61.8)

ACT, Asthma Control Test; FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; N, total number of patients; n, number of patients in the specified category; OCS, oral corticosteroid; RSQ, Respiratory Symptoms Questionnaire; SABA, short-acting β_2 agonist; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; WPAI, Work Productivity and Impairment.

[a] Based on GINA 2017 step classifications [22].

[b] Results from question in electronic case report form: "During the past 12 months, on how many occasions has your patient experienced an exacerbation of their asthma beyond the patient's usual day to day variance?"

[c] Defined according to American Thoracic Society/European Respiratory Society Task Force criteria [12].

[d] Patients for whom data on exacerbation medications were available (oral/injected corticosteroids, antibiotics or other treatment).

[e] Defined as allergic or non-allergic rhinitis/sinusitis, or perennial or seasonal rhinitis/sinusitis or eye allergy.

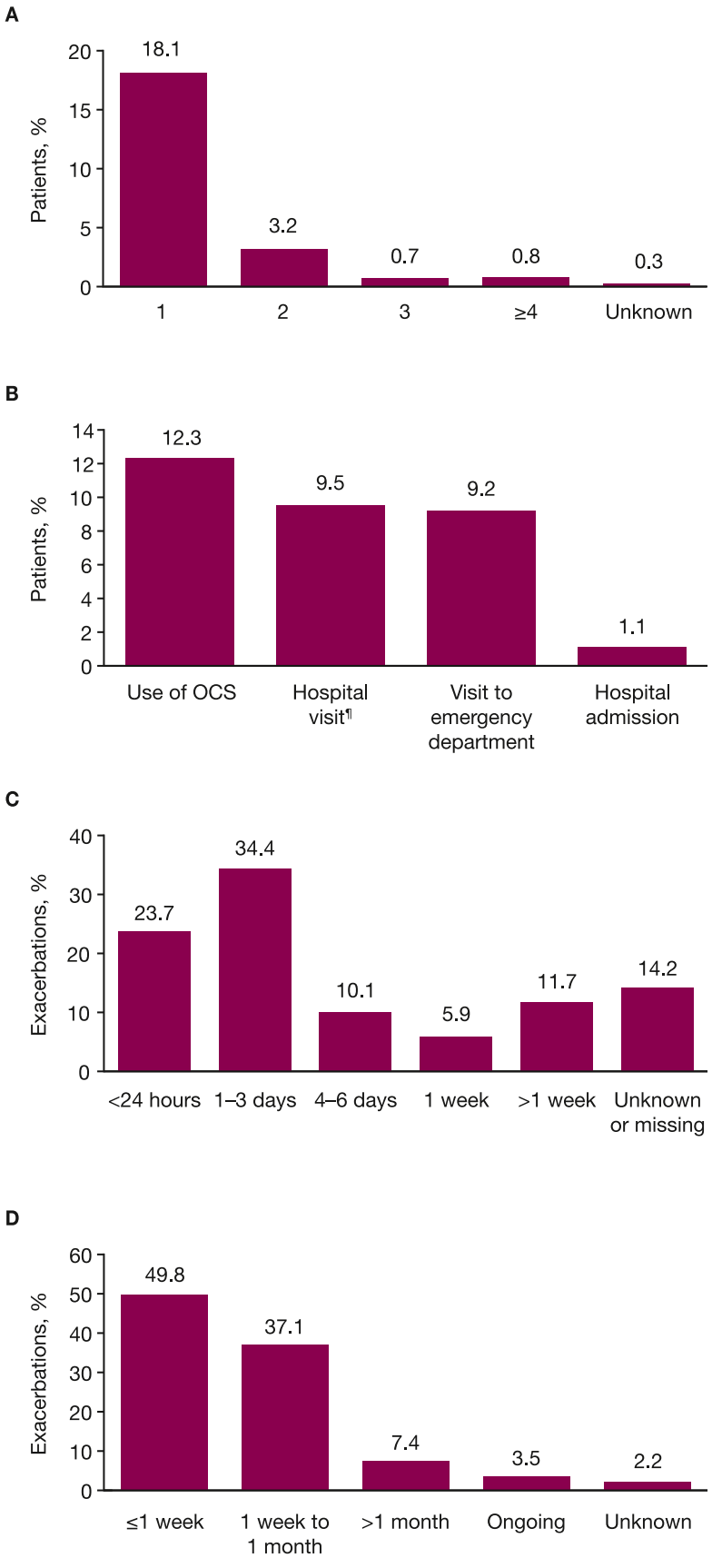

Fig. 1. (A) Proportion of patients with mild asthma who experienced one or more physician-reported exacerbations in the last year*†. (B) Proportion of patients with mild asthma who experienced one or more physician-reported exacerbation which required OCS or healthcare resource utilisation*. (C) Duration of symptom worsening prior to a physician-reported exacerbation‡§. (D) Duration of physician-reported exacerbations‡. Reporting of exacerbation data is restricted to those exacerbations where details were recorded in the eCRF. n, number of patients in the specified category; eCRF, electronic case report form. *n = 1997. †Results from question in eCRF: "During the past 12 months, on how many occasions has your patient experienced an exacerbation of their asthma beyond the patient's usual day to day variance?" ‡n = 625. §Results from patient question: "During the past 3 months, how many times has your breathing worsened beyond what you usually experience in a typical day (e.g. increased shortness of breath, wheezing, cough or chest tightness)?" ¶Hospital visit refers to the aggregate of unscheduled visits to a clinic or hospital, including emergency department visits and hospital admissions.

Table 2
Baseline demographics for patients with mild asthma with and without a history of exacerbations in the previous 12 months.

Characteristic	Patients with ≥1 exacerbation (N = 455)	Patients with no exacerbations (N = 1542)
Age (years), mean (SD)	48.8 (17.3)	50.5 (17.7)
Female, n (%)	321 (70.5)	953 (61.8)
Smoking history, n (%)		
Current smoker	37 (8.1)	137 (8.9)
Former smoker	125 (27.5)	437 (28.3)
Never smoker	293 (64.4)	967 (62.7)
Ethnicity, n (%)		
Caucasian	380 (83.5)	1084 (70.3)
Other	74 (16.3)	456 (29.6)
Unknown	1 (0.2)	2 (0.1)
Region, n (%)		
Australia and Canada	110 (24.2)	318 (20.6)
Europe	184 (40.4)	539 (35.0)
Japan & Korea	32 (7.0)	283 (18.4)
Latin America	30 (6.6)	66 (4.3)
Nordic/The Netherlands	16 (3.5)	99 (6.4)
USA	83 (18.2)	237 (15.4)

N, total number of patients; n, number of patients in the specified category; SD, standard deviation.

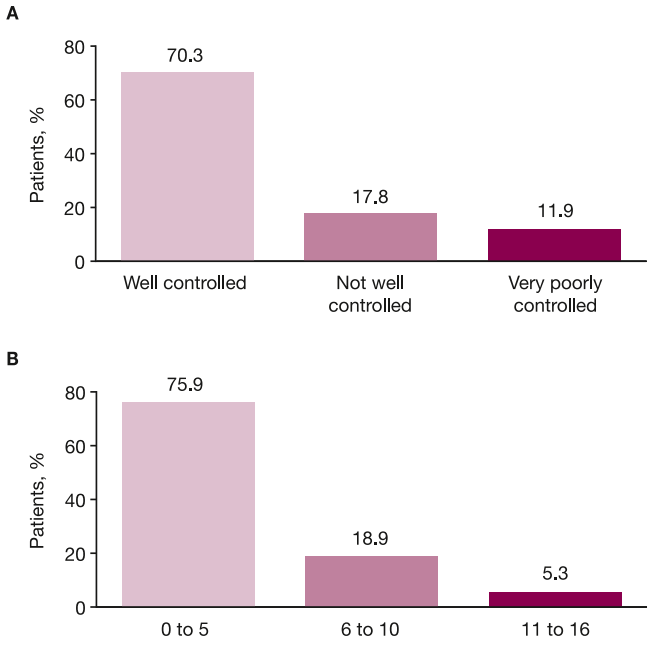

Fig. 2. (A) Symptom control over the past 4 weeks by ACT* and (B) Respiratory Symptoms Questionnaire score†, in patients with physician-assessed mild asthma. ACT, Asthma Control Test; n, number of patients in the specified category. *n = 1381; Responses to five questions (scored 1–5). Lower scores indicate worse symptoms. ACT score ≥20 = well controlled, ACT score 16–19 = not well controlled, ACT score ≤15 = very poorly controlled. †n = 1405; Responses to four questions (items 1–4) are scored 0–4, with higher scores indicative of worse symptoms. Total score range: 0–16.

of patients experiencing severe exacerbations. Of all exacerbation events, almost half lasted for more than 1 week and half necessitated treatment with OCS. Approximately 10% of patients visited an emergency department due to physician-reported exacerbations, some of whom required hospital admission for their exacerbations. These findings indicate that physician-assessed 'mild' asthma can have a significant clinical burden on patient lives.

Consistent with the findings of the current NOVELTY analysis, a previous real-world cross-sectional study of patients with mild asthma reported that 19% of patients had one or more exacerbation of any severity within the previous 12 months, and 13% had at least one severe exacerbation (defined as those treated with OCS and/or antibiotics, required emergency department visit or hospital admission) [25]. This contrasts a randomised, open-label controlled trial of patients with mild asthma conducted primarily in primary care, which reported that 7% of patients had experienced one or more severe exacerbation in the previous 12 months [28]. With regard to symptom control, the cross-sectional study found that 25% of patients with mild asthma had an ACT score <20 [25], similar to the 30% of patients reported in the current analysis. However, the cross-sectional study defined mild asthma using GINA treatment steps [25] (which is only recommended for epidemiologic studies, where other patient data are not available), reflecting patients' current prescriptions, rather than physician assessment of severity.

When we restricted patients in the physician-assessed mild asthma subgroup to those who were on GINA 2017 treatment steps 1 and 2, the resulting sample had broadly similar clinical characteristics to the overall physician-assessed mild asthma cohort. Likewise, few differences were observed between the overall physician-assessed mild asthma cohort and all NOVELTY patients with physician-assigned asthma on GINA 2017 treatment steps 1 and 2, with the proportion of patients who had an exacerbation in the previous 12 months being similar between the two patient groups. This was also evident for patients with physician-assessed mild asthma but excluding patients on maintenance OCS and biologics from the cohort. The use of physician assessment to categorise disease severity in the main analysis provides an important insight into how asthma severity is defined in routine clinical practice, which may provide greater clinical relevance.

Patients with mild asthma are reported to have less frequent exacerbations than patients with severe asthma, as demonstrated for physician-assessed severity in NOVELTY [15] and elsewhere by British Thoracic Society steps [24]. Despite this, exacerbations in patients with mild asthma may still be life threatening [6,11]. It has been reported that patients with 'mild persistent' asthma, as defined by the 1997 US National Asthma Education and Prevention Program guidelines [29], may seek emergency care almost as frequently as patients with 'moderate to severe persistent' asthma [10], indicating that disease burden may not be aligned with conventional severity classification. The present data also support findings from previous studies that have reported significantly worse health status in patients whose asthma symptoms are not well controlled [30], with impacts noted across domains, including sports/recreation, normal physical activity, social activity and sleep [31].

In this analysis, half of exacerbations were treated with OCS, while a quarter of patients who reported symptom worsening in the past 3 months had at least one episode treated with OCS. The extent of OCS use among patients in this real-world study is a concern, since GINA guidelines currently only recommend short courses of OCS for patients with severe uncontrolled asthma [1]. Previous studies have demonstrated that, over median follow-up times of 5.3–7.4 years, patients with asthma receiving one or more prescription for OCS had a significantly increased risk of adverse events [32,33] and mortality [33] versus patients without a prescription for OCS, with an evident dose–response relationship [32]. OCS use is also associated with increased healthcare resource utilisation, with the recent PACEHR observational cohort study of patients with asthma finding that the yearly healthcare resource utilisation cost of patients receiving regular OCS (≥5 mg/day) was three times greater than that for non-OCS users [34]. It is therefore important to address the cumulative risk of long-term adverse events associated with OCS use [32]. To reduce the necessity for courses of OCS, GINA recommends the use of as-needed ICS/formoterol as a reliever in mild asthma [1], as it has been shown to be more effective in preventing severe exacerbations than as-needed SABA, and similarly preventative to maintenance ICS with as-needed SABA [35].

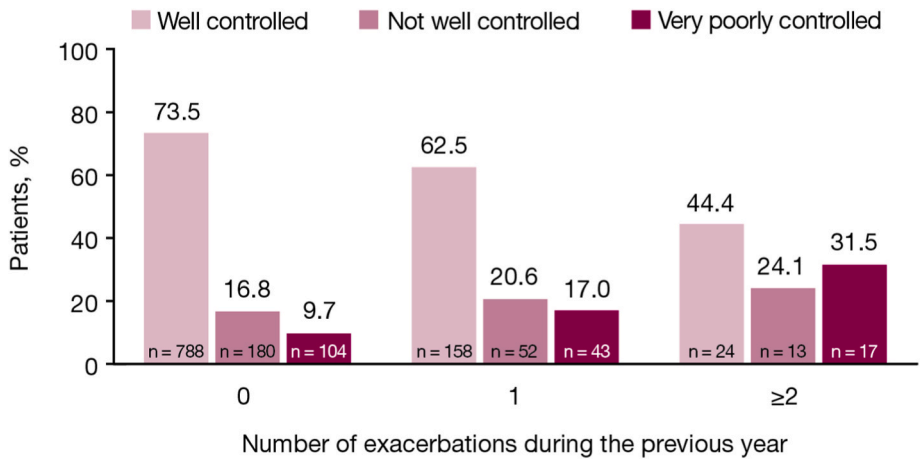

Fig. 3. Asthma symptom control (ACT) in the previous 4 weeks in patients with mild asthma by number of physician-reported exacerbations in the last year. Two patients with unknown ACT score were not included. ACT, Asthma Control Test; n, number of patients in the specified category.

Although exacerbations are a prominent feature of poorly controlled asthma and severe asthma, they can still be experienced by patients with any level of disease severity or symptom control [36]. Indeed, up to half of exacerbations requiring emergency care occur in patients who report symptoms only on exertion [7,8]. This is supported by the findings in the current analysis that patients with physician-assessed mild asthma can have severe exacerbations, and even exacerbations among those with well controlled asthma symptoms in the previous 4 weeks. Consequently, it would be interesting to assess the recently developed Asthma Impairment and Risk Questionnaire [37], which includes both asthma symptom control and exacerbation risk together, in patients with mild asthma.

There is considerable variation in the definitions of disease severity across national and international guidelines [1,12,13] and previous literature [6], although the general concept is agreed that once patients are on treatment, mild asthma is asthma that can be well controlled with reliever alone or with low-dose controller ICS [1,6,12,13]. However, in the present cohort of patients with physician-assessed mild asthma, over a quarter were treated with medium- or high-dose ICS + LABA, and some with biologic therapy, suggesting that different criteria were used by their physicians. Likewise, there may be discordance between patient perception and guidelines for severity. Thus, standardised definitions of mild asthma are needed from both a clinical perspective and for progressing further research [6,15].

The main strengths of this analysis are the characteristics of the NOVELTY study itself as a large, global, longitudinal observational study of patients recruited from clinical practice [14]. No criteria were provided to physicians for severity assessment and this, together with the fact that almost half of the patients were from primary care, makes these findings relevant to clinical practice. Asthma severity was physician-assessed in order to understand the characteristics and burden of patients judged by clinicians as having mild asthma. While the NOVELTY population as a whole is not representative of asthma prevalence (due to recruitment being stratified by severity), this limitation does not apply within the mild asthma population studied here.

Limitations of this analysis include delay of the baseline assessment if the patient had experienced a recent exacerbation until at least 6 weeks after resolution, and the recruitment of patients from clinical practice potentially leading to biased selection of patients making frequent healthcare visits [14]. Data were missing for some measures, notably for details of individual events of physician-reported exacerbations and related treatments. Furthermore, several measures could be subject to recall bias; physician-reported exacerbations and healthcare resource utilisation were reported for the previous 12 months, patient-reported measures were completed at the baseline visit and symptom worsening was reported for the past 3 months. It should also be noted that due to different definitions and recall periods, physician-reported exacerbations and patient-reported episodes of symptomatic worsening cannot be directly compared. Rather, they separately provide information on the burden of disease for patients with mild asthma.

5. Conclusions

While many patients with physician-assessed mild asthma had few symptoms and experienced minimal impact on their health status, this patient group had an appreciable burden of disease, in terms of exacerbations and related healthcare resource utilisation, poor asthma symptom control and at least partial impairment of respiratory-related health status. In this 'real-world' global study, many patients were classified by their physicians as having mild asthma, despite being prescribed medication consistent with more severe disease. This may result in these patients not receiving appropriate care commensurate with their degree of asthma severity and highlights a potential opportunity for improving outcomes in this large patient population.

Contributors

Authors who were AstraZeneca employees contributed to the study design, analysis, and/or interpretation of data and critical review of the manuscript. All authors had full access to, and contributed to the interpretation of, all data reported herein. The corresponding author had final responsibility for the decision to submit for publication.

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CRediT authorship contribution statement

Sarowar Muhammad Golam: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Christer Janson:** Investigation, Writing – original draft, Writing – review & editing. **Richard Beasley:** Writing – original draft, Writing – review & editing. **J Mark FitzGerald:** Writing – original draft, Writing – review & editing. **Tim Harrison:** Investigation, Writing – original draft, Writing – review & editing. **Bradley Chipps:** Writing – original draft, Writing – review & editing. **Rod Hughes:** Conceptualization, Writing – original draft, Writing – review & editing. **Hana Müllerová:** Conceptualization, Writing – original draft, Writing – review & editing. **José María Olaguibel:** Investigation, Writing – original draft, Writing – review & editing. **Eleni Rapsomaniki:** Data curation, Formal analysis, Methodology,

Writing – original draft, Writing – review & editing. **Helen K. Reddel:** Investigation, Writing – original draft, Writing – review & editing. **Mohsen Sadatsafavi:** Writing – original draft, Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.rmed.2022.106863.

References

[1] Global Initiative for Asthma, Global Strategy for Asthma Management and Prevention: 2021 Report, 2021. https://ginasthma.org/gina-reports/. (Accessed 15 October 2021).
[2] D.J. Jackson, A. Sykes, P. Mallia, S.L. Johnston, Asthma exacerbations: origin, effect, and prevention, J. Allergy Clin. Immunol. 128 (2011) 1165–1174.
[3] Global Burden of Disease Collaborative Network, Global Burden of Disease Study 2019 (GBD 2019) Results, Institute for Health Metrics and Evaluation (IHME), Seattle, WA, USA, 2021. http://ghdx.healthdata.org/gbd-results-tool. (Accessed 23 September 2021).
[4] D. Dusser, D. Montani, P. Chanez, et al., Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations, Allergy 62 (2007) 591–604.
[5] F. Firoozi, C. Lemière, M.F. Beauchesne, A. Forget, L. Blais, Development and validation of database indexes of asthma severity and control, Thorax 62 (2007) 581–587.
[6] J.M. FitzGerald, P.J. Barnes, B.E. Chipps, et al., The burden of exacerbations in mild asthma: a systematic review, ERJ Open Res 6 (2020).
[7] I. Mitchell, S.C. Tough, L.K. Semple, F.H. Green, P.A. Hessel, Near-fatal asthma: a population-based study of risk factors, Chest 121 (2002) 1407–1413.
[8] S. Salmeron, R. Liard, D. Elkharrat, et al., Asthma severity and adequacy of management in accident and emergency departments in France: a prospective study, Lancet 358 (2001) 629–635.
[9] K.R. Chapman, Impact of 'mild' asthma on health outcomes: findings of a systematic search of the literature, Respir. Med. 99 (2005) 1350–1362.
[10] A.L. Fuhlbrigge, R.J. Adams, T.W. Guilbert, et al., The burden of asthma in the United States: level and distribution are dependent on interpretation of the national asthma education and prevention program guidelines, Am. J. Respir. Crit. Care Med. 166 (2002) 1044–1049.
[11] Royal College of Physicians, Why asthma still kills: the National Review of Asthma Deaths (NRAD) confidential enquiry report, 2014. https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills. (Accessed 1 September 2021).
[12] H.K. Reddel, D.R. Taylor, E.D. Bateman, et al., An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations. Standardizing endpoints for clinical asthma trials and clinical practice, Am. J. Respir. Crit. Care Med. 180 (2009) 59–99, https://doi.org/10.1164/rccm.200801-060ST.
[13] National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma, Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma–summary report 2007, J. Allergy Clin. Immunol. 120 (2007) S94–S138.
[14] H.K. Reddel, M. Gerhardsson de Verdier, A. Agustí, et al., Prospective observational study in patients with obstructive lung disease: NOVELTY design, ERJ Open Res 5 (2019).
[15] H.K. Reddel, J. Vestbo, A. Agustí, et al., Heterogeneity within and between physician-diagnosed asthma and/or COPD: NOVELTY cohort, Eur. Respir. J. 58 (2021), 2003927.
[16] R.A. Nathan, C.A. Sorkness, M. Kosinski, et al., Development of the asthma control test: a survey for assessing asthma control, J. Allergy Clin. Immunol. 113 (2004) 59–65.
[17] N. Karlsson, M.J. Atkinson, H. Müllerová, et al., Validation of a diagnosis-agnostic symptom questionnaire for asthma and/or COPD, ERJ Open Res 7 (2021).
[18] P.W. Jones, Y. Forde, St George's Respiratory Questionnaire Manual, 2009. Version 2.3, https://meetinstrumentenzorg.nl/wp-content/uploads/instrumenten/SGRQ-handl-Eng.pdf. (Accessed 1 September 2021).
[19] P.W. Jones, F.H. Quirk, C.M. Baveystock, P. Littlejohns, A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire, Am. Rev. Respir. Dis. 145 (1992) 1321–1327.
[20] C.M. Fletcher, Standardized questionaries on respiratory symptoms: a statement prepared for, and approved by, the medical research council's committee on the Aetiology of chronic bronchitis, BMJ 2 (1960) 1665.
[21] M.C. Reilly, A.S. Zbrozek, E.M. Dukes, The validity and reproducibility of a work productivity and activity impairment instrument, Pharmacoeconomics 4 (1993) 353–365.
[22] Global Initiative for Asthma, Global Strategy for Asthma Management and Prevention, 2017. https://ginasthma.org/archived-reports/. (Accessed 1 September 2021).
[23] R Core Team, R: a Language and Environment for Statistical Computing, 2018. https://www.r-project.org/. (Accessed 1 September 2021).
[24] C.I. Bloom, F. Nissen, I.J. Douglas, et al., Exacerbation risk and characterisation of the UK's asthma population from infants to old age, Thorax 73 (2018) 313–320.
[25] B. Ding, M. Small, Disease burden of mild asthma: findings from a cross-sectional real-world survey, Adv. Ther. 34 (2017) 1109–1127.
[26] W. Chen, J.M. FitzGerald, L.D. Lynd, D.D. Sin, M. Sadatsafavi, Long-term trajectories of mild asthma in adulthood and risk factors of progression, J. Allergy Clin. Immunol. Pract. 6 (2018) 2024–2032.E5.
[27] O. Kalayci, H. Abdelateef, C.F. Pozo Beltrán, et al., Challenges and choices in the pharmacological treatment of non-severe pediatric asthma: a commentary for the practicing physician, World Allergy Organ J. 12 (2019), 100054.
[28] R. Beasley, M. Holliday, H.K. Reddel, et al., Controlled trial of budesonide-formoterol as needed for mild asthma, N. Engl. J. Med. 380 (2019) 2020–2030.
[29] National Asthma Education and Prevention Program, Second Expert Panel on the Management of Asthma, Expert panel report 2: guidelines for the diagnosis and management of asthma, National Heart, Lung and Blood Institute (US), Bethesda, MD, 1997. https://www.nhlbi.nih.gov/files/docs/guidelines/asthgdln_archive.pdf?msclkid=d717725cd06b11ecaee2c097fbe664c9. (Accessed 15 July 2022).
[30] T.W. Guilbert, C. Garris, P. Jhingran, et al., Asthma that is not well-controlled is associated with increased healthcare utilization and decreased quality of life, J. Asthma 48 (2011) 126–132.
[31] M.R. Gazzotti, O.A. Nascimento, F. Montealegre, J. Fish, J.R. Jardim, Level of asthma control and its impact on activities of daily living in asthma patients in Brazil, J. Bras. Pneumol. 39 (2013) 532–538.
[32] D.B. Price, F. Trudo, J. Voorham, et al., Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study, J. Asthma Allergy 11 (2018) 193–204.
[33] M. Ekstrom, B.I. Nwaru, P. Hasvold, et al., Oral corticosteroid use, morbidity and mortality in asthma: a nationwide prospective cohort study in Sweden, Allergy 74 (2019) 2181–2190.
[34] C. Janson, K. Lisspers, B. Stallberg, et al., Health care resource utilization and cost for asthma patients regularly treated with oral corticosteroids - a Swedish observational cohort study (PACEHR), Respir. Res. 19 (2018) 168.

[35] I. Crossingham, S. Turner, S. Ramakrishnan, et al., Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma, Cochrane Database Syst. Rev. 5 (2021) CD013518.
[36] D.R. Taylor, E.D. Bateman, L.P. Boulet, et al., A new perspective on concepts of asthma severity and control, Eur. Respir. J. 32 (2008) 545–554.
[37] K.R. Murphy, B. Chipps, D.A. Beuther, et al., Development of the Asthma Impairment and Risk Questionnaire (AIRQ): a composite control measure, J. Allergy Clin. Immunol. Pract. 8 (2020) 2263–2274.e5.