



Severe and non-severe asthma in the community: A large electronic database analysis



Shabtai Varsano^{a, b, c, *}, David Segev^d, David Shitrit^{a, b}

^a Department of Pulmonary Medicine, Meir Medical Center, Kfar Saba, Israel

^b Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

^c Asthma Care & Education Unit, Meir Medical Center, Kfar Saba, Israel

^d Clalit Health Services, Sharon-Shomron Medical District Headquarters, Tel Aviv, Israel

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ABSTRACT

Background: A large electronic database analysis was conducted in a community of 351,799 people, ages 20–70 years to determine the prevalence and clinical characteristics of severe asthma, according to 2014 international guidelines and healthcare utilization.

Methods: Severe asthmatics were grouped into controlled severe-asthma and uncontrolled severe-asthma and additional subgroups of uncontrolled severe asthma on the basis of medications dispensed. Non-asthmatic population at the same ages served as controls.

Results: A total of 19,991 (5.68%) were diagnosed as asthmatic, of which 4.65% had severe asthma. Of these, one-third was uncontrolled severe-asthma. Controlled severe-asthma group was similar to non-severe asthma and non-asthmatics in the rate of emergency room visits (21.5%, 22%, and 20%, respectively) and to all cause hospitalizations (7.4%, 7.4%, and 6.4%, respectively). Uncontrolled severe-asthmatics had significantly more hospitalizations (RR = 2.9) than controlled severe-asthmatics. Only 19.2% of uncontrolled-severe asthmatics had IgE testing and 3.6% were dispensed omalizumab.

Conclusions: The prevalence of severe asthma is slightly less than 5% of all asthmatics. Controlling severe asthma is crucial to reducing healthcare utilization. A simple electronic database analysis, based on dispensed medications, can help healthcare providers identify subgroups of uncontrolled severe asthmatics that require focused efforts.

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1. Introduction

Asthma is common worldwide. It is estimated that 50–80% of the total cost of asthma management and related expenses can be attributed to severe asthmatics [1,2]. The prevalence of severe asthmatics among the western asthmatic population is cited as 5–10% [3], although the basis for this estimation is not clear. The definition of severe asthma has changed over time and among medical authorities, and until recently there was no wide

consensus. In addition, assessment of severe asthma was often based on patients recruited from specialized centers with the most severely ill patients, and seldom on those from the community [3,4], while patients with concomitant cardiorespiratory comorbidities and smokers were often excluded from many studies.

ERS/ATS guidelines on severe asthma define the level of high-dose inhaled corticosteroids (ICS), combined with long acting beta-agonist (LABA), required to control severe asthma, and criteria for severe asthma that is not controlled despite treatment [5]. GINA redefined severe asthma as needing step 4 or 5 drug therapy to achieve control or as asthma that remained uncontrolled. However, according to GINA, medium/high-dose of ICS qualifies for severe asthma [6] compared to the ERS/ATS high-dose definition. In addition, ERS/ATS and GINA group controlled and uncontrolled severe asthma together.

This large database study was conducted to provide an updated

Abbreviations: ICS, Inhaled corticosteroids; LABA, Long acting beta-agonist; SABA, Short-acting beta-agonist; GC, gluco-corticosteroids; SDB, Sleep disordered breathing.

* Corresponding author. Asthma Care and Education Unit, Dept. of Pulmonary Medicine, Meir Medical Center, 59 Tshernichovsky, Kfar Saba 44281, Israel.

E-mail address: varsanos@bezeqint.net (S. Varsano).

prevalence and clinical profile according to severity. Its first endpoint was to evaluate the severity of the community asthmatic population, where severe asthma was defined based on 2014 ERS/ATS and GINA 2014 adjusted criteria, and to assess the prevalence and clinical characteristics of patients with severe asthma based on “real-world” data. The second primary endpoint was to evaluate whether physicians had considered anti-IgE therapy. The secondary endpoint was to assess healthcare utilization rates according to asthma severity.

Israel is a good model to investigate these endpoints because it has a western-style health system; all modern asthma medications are available, including anti-IgE therapy. Also, the entire population has national health insurance. Patient access to medical resources is easy due to widespread services in a small country of approximately 8 million people. Electronic medical records, including dispensed medications, have been maintained in a central database for many years.

2. Methods

This was a retrospective, cross-sectional, electronic database analysis of the population in a central district of Israel insured by Clalit Health Services (CHS) HMO, the largest healthcare provider in Israel (55% of the population). Inclusion criteria were ICD-9 physician diagnosis of bronchial asthma, (a diagnosis that does not require mandatory spirometry), in patients 20–70 years-old of all ethnicities, treated by CHS in 2012, which included 351,799 people. The local Ethics Committee approved the study.

The total asthmatic population was categorized according to medications dispensed and on ERS/ATS guideline criteria for defining uncontrolled asthma [5]. The ICS daily dose cutoff that we chose for severe asthma in this study needs explanation. The ERS/ATS and GINA definitions for the minimum ICS daily dose requirements for defining severe asthma are very different. A minimum ICS daily dose of 1000 mcg fluticasone propionate or 1600 mcg budesonide (high-dose) qualify according to ERS/ATS [5], while medium/high daily dose ICS qualify for GINA (asthma that needs at least step 4 drug therapy), where medium dose is >400–800 mcg and high dose is >800 mcg for budesonide and >250–500 mcg, and >500 mcg, respectively, for fluticasone propionate. In Israel, the maximum daily dose commonly used in asthma is 1000 mcg fluticasone propionate or 800 mcg budesonide. Therefore, the criteria for ICS daily use in severe asthma for this study fall between the GINA and ERS/ATS requirements, although more toward the high GINA dose. In addition, ERS/ATS defines asthma that required systemic gluco-corticosteroids (systemic GC) at least half of the previous year as severe asthma, but at the same time defines uncontrolled severe asthma as needing at least two bursts of systemic GC during the previous year. In this study, we categorized controlled severe asthma and uncontrolled severe asthma as different groups. Therefore, the need for at least two bursts of systemic GC was used as one criterion for defining uncontrolled severe asthma.

1. Essential inhaler-therapy of medium/high-dose ICS and LABA; at least 12 turbo-inhalers of budesonide/formoterol 160/4.5 (160 mcg delivered, equivalent to 200 mcg contained budesonide, 120 doses/inhaler), an equivalent of 800 mcg/daily, or at least 10 diskus inhalers of fluticasone-propionate/salmeterol 500/50 mcg per dose (60 doses/diskus), equivalent to 822 mcg/daily, dispensed in the past year. Any patient that met at least this criterion of medium/high-dose ICS/LABA was included in the umbrella group of severe asthma [6].
2. Within this group, 4 subgroups were defined according to whether additional medications identifying uncontrolled

severe-asthma despite medium/high-dose ICS/LABA, were dispensed.

Severe-controlled asthma: severe asthmatics requiring medium/high-dose ICS/LABA, without excessive short-acting beta-agonist inhalers (SABA, defined below) and without systemic GC (defined below) at least twice during the past year.

Uncontrolled severe-asthma with excessive SABA: severe asthmatics with poor symptom control, defined by excessive dispensing of SABA, salbutamol, or terbutaline (defined as at least one canister, MDI or dry powder, per 3 months and/or at least one nebulizer solution of salbutamol or terbutaline/month).

Uncontrolled severe-asthma with excessive systemic GC: severe asthmatics with frequent, severe exacerbations, expressed by any type of systemic GC dispensed at least twice in the study year.

Uncontrolled severe-asthma with excessive systemic GC+SABA: severe asthmatics dispensed excessive systemic GC and excessive SABA. We considered this subgroup as the most uncontrolled. Additional groups of asthmatics were defined:

Non-severe asthma: asthmatics not requiring medium/high-dose ICS/LABA at doses defined for severe asthmatics and/or excessive use of SABA, systemic GC, systemic GC+SABA, were considered non-severe and served as a control group for severe asthma.

Asthma-other: asthmatics that were not dispensed proper medium/high-dose ICS/LABA treatment, as defined for severe asthmatics, but were dispensed excessive SABA, systemic GC, or systemic GC+SABA. This group was entitled Asthma-other, because they did not meet definitions for severe or non-severe asthma.

Control group: Non-asthmatic patients (20,000) 20 to 70 years-old, randomized from the insured population, including patients with the same cardiorespiratory comorbidities, as those in the asthmatic population, as mentioned below.

Clinical characteristics of asthmatic patients

Sixteen clinical characteristics were assessed. The 12 basic characteristics were age, gender, ethnicity, BMI, smoking status, sleep apnea or obstructive sleep apnea (sleep disordered breathing, SDB), cardiopulmonary comorbidities, beta-blockers dispensed, corticosteroid nasal inhalers and/or nasal antihistamines dispensed, IgE testing, blood eosinophil counts, and dispensed omalizumab. The 4 healthcare utilization characteristics are described below.

Cardiopulmonary comorbidities: Patients were analyzed for comorbidities that might interfere with optimal asthma control, including concomitant ICD-9 physician diagnosis of COPD, interstitial lung disease, bronchiectasis, and heart failure.

Current or past smoking was considered a cardiopulmonary comorbidity and a separate characteristic, due to its known deleterious effects on asthma control and its natural history.

Beta-blockers: Assessed as use of beta-blocker pills or eye drops.

Eosinophil counts: Total peripheral blood eosinophils/ml, in those who had a CBC in the previous 12 months.

IgE testing and inhaled nasal corticosteroids/antihistamines:

To estimate physician attempts to evaluate patients for atopy or to address suspected atopy, we assessed the groups for rate of total IgE testing, which is required for evaluating anti-IgE eligibility, and for the rate of corticosteroid/antihistamine nasal inhalers dispensed, respectively. Since we did not have electronic data regarding skin prick testing for aeroallergens, we used these variables as clues that the physicians assessed

eligibility for anti-IgE therapy and compared the rate of these variables with that of omalizumab dispensed.

Health care utilization: number of visits per year to GP, pulmonologist, and ER were assessed, as well as hospitalizations/year in general or pulmonary wards. These were not analyzed by cause.

Statistical analysis

Data were analyzed with SPSS 22.0 (SPSS, Inc., Chicago, IL, USA). Significance was set at 0.05 and all tests were two-tailed. Baseline characteristics for total population and for subgroups are presented as means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Chi-square and independent t-tests were performed for categorical and for continuous variables, respectively. One-way ANOVA tests were used to evaluate differences between more than two groups of continuous variables followed by Bonferroni multiple comparison tests. Multivariate analysis for relationships between baseline characteristics and asthma in general, severe asthma and uncontrolled severe asthma was performed using logistic regression models. Odds Ratios (OR) with 95% confidence intervals (CI) were calculated. The goodness-of-fit of the model to the observed event rates was evaluated using the Hosmer-Lemeshow statistic.

3. Results

3.1. Distribution of asthma patients

Asthma distribution by severity within the total population of 351,799 people, 20–70 years-old insured by CHS in 2012 is depicted in Fig. 1. Of these, 19,991 (5.68%) had a diagnosis of bronchial asthma. Asthmatics that fit the umbrella definition of severe-asthma comprised 4.65% of this population, of which two-thirds had controlled severe-asthma and one-third, uncontrolled severe-asthma. Within the group of uncontrolled severe-asthma, subgroups of increasing severity, based on additional medication dispensed as a percentage of all severe asthma patients were

18.94% excessive SABA, 8.93% excessive systemic GC, and 5.16% excessive systemic GC+SABA. The asthma-other group comprised 9.76% of the asthmatic population, twice that of severe-asthma.

The 16 clinical characteristics, according to asthma severity are displayed in Tables 1–4 and Fig. 2.

3.2. Asthmatics versus non-asthmatic control group

Asthmatics were slightly younger, fewer smokers, more likely to be female, of Jewish ethnicity, have SDB and more comorbidities, dispensed corticosteroid/antihistamine nasal inhalers (3 times more), have IgE testing and higher eosinophil counts than the control group. They had more GP and pulmonologist visits, hospital admissions, and ER visits (Table 1).

In multivariate analysis, factors related to having asthma were age, gender, Jewish ethnicity smoking, SDB, cardiopulmonary comorbidities, and nasal inhalers (data not shown). Generally, within the entire asthmatic population, as severity of asthma increased and became less well-controlled (defined by medications dispensed), patients were older, had higher BMI, females, cardiopulmonary comorbidities, more nasal inhalers dispensed, and increased healthcare utilization (Tables 2–4 and Fig. 2).

3.3. Severe versus non-severe asthma

Patients with severe-asthma were older, smokers, and higher BMI and Jewish ethnicity. More had SDB and cardiopulmonary comorbidities, beta-blockers and corticosteroid/antihistamine nasal inhalers (with higher mean nasal inhalers/year) dispensed, and IgE testing and omalizumab therapy. Eosinophil counts were higher, with more GP visits, pulmonologist visits, and hospital admissions (Table 2a). In multivariate analysis, factors related to severe-asthma were age, ethnicity, nasal inhalers, and cardiopulmonary comorbidities (Table 2b).

3.4. Uncontrolled severe versus controlled severe-asthma

Table 3a and b summarize the differences between the groups of uncontrolled and controlled severe-asthma. Patients with

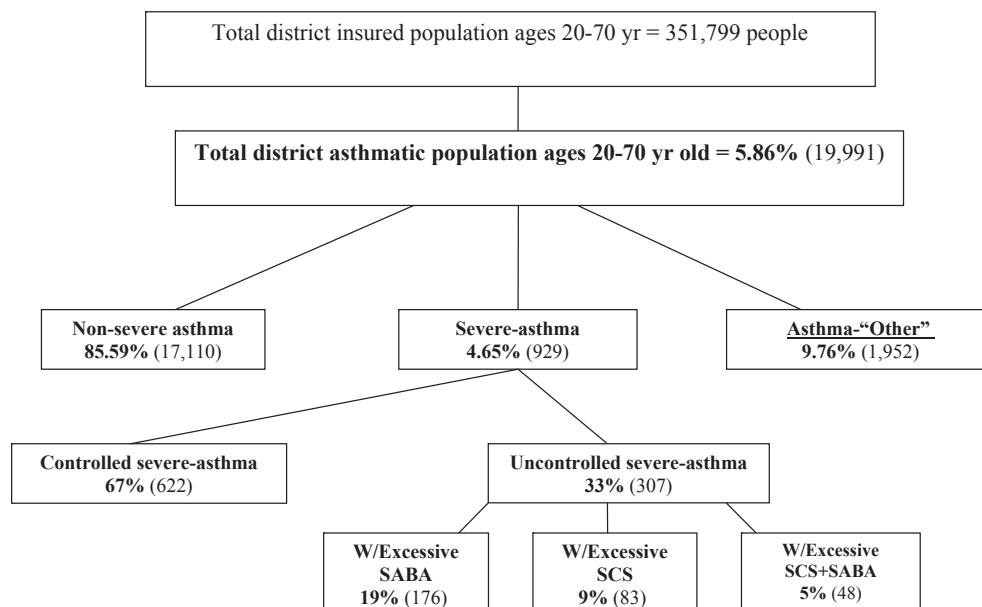


Fig. 1. Asthma distribution by severity within the total population of 351,799 people, 20–70 years-old insured by Clalit Health Services in 2012.

Table 1
Patient characteristics of Asthma and Control groups.

Characteristics	Asthma patients N = 19,991	Control group N = 20,000	P-value
Age	41.5 ± 15	43 ± 12	<0.001
Male	9206 (46)	9860 (49)	<0.001
Jewish ethnicity	16588 (83)	13701 (68.5)	<0.001
BMI**	27.2 ± 5.9	27.2 ± 5.4	0.517
Current smokers	3587 (19)	4013 (21)	
Past smokers	2477 (13)	2216 (12)	<0.001
Sleep disordered breathing	350 (1.8)	228 (1.1)	<0.001
All cardiopulmonary comorbidities	8062 (40.3)	7440 (37.0)	<0.001
COPD comorbidity	1770 (8.8)	286 (1.4)	<0.001
Beta blockers	1386 (6.9)	1348 (6.7)	0.444
Nasal inhalers (patients dispensed)	2480 (12)	736 (4)	<0.001
Nasal inhalers (mean/yr)	2.58 ± 2.96	1.72 ± 1.86	<0.001
Total IgE blood testing	844 (4.2)	245 (1.2)	<0.001
Blood eosinophil (count/mm ³)**	280 ± 200	200 ± 140	<0.001
Mean general practitioner visits/yr	7.0 ± 6.4	5.3 ± 5.1	<0.001
General practitioner visits/yr:			
0–2	5867 (29)	8169 (41)	
3–6	6512 (33)	6560 (33)	
7–12	4803 (24)	3727 (18)	
13+	2809 (14)	1544 (8)	<0.001
Pulmonologist visits/yr:			
0	18103 (91)	19666 (98)	
1	1007 (5)	213 (1.1)	
2+	881 (4.4)	121 (0.6)	<0.001
ER visits/yr:			
0	15403 (77)	16078 (80)	
1	3251 (16)	2876 (14)	
2+	1337 (6.7)	1046 (5)	<0.001
General ward admissions/yr:			
0	18244 (91)	18725 (94)	
1	1231 (6.2)	983 (4.9)	
2+	516 (2.6)	292 (1.5)	<0.001
Pulmonary ward admissions/yr:			
0	19873 (99.4)	19981 (99.9)	
1+	118 (0.6)	19 (0.1)	<0.001

Data are for 2012. *Continuous variables are presented as mean ± SD and categorical variables are presented as frequencies and percentages. **Variables with more than 50% missing, as not all patients had this test during the preceding 12 months.

uncontrolled severe-asthma were older, had higher BMI, a more frequent history of smoking, and cardiopulmonary comorbidities. More were dispensed beta-blockers, had IgE testing and 3.6% received omalizumab. They did not differ in eosinophil counts or in percent using nasal corticosteroid/antihistamine inhalers. They had more ER visits and hospital admissions, and more GP or pulmonologist visits. However, only a fourth of severe-asthmatics and less than a third with uncontrolled severe-asthma visited a pulmonologist. Almost 43% with uncontrolled severe-asthma, 14% of all severe asthmatics were prescribed at least 2 courses of systemic GC. In multivariate analysis, age and cardiopulmonary comorbidities were related to uncontrolled severe-asthma.

3.5. Healthcare utilization in asthmatics versus controls

Increasing rates of GP and pulmonologist visits were observed in non-severe, controlled severe and uncontrolled severe-asthmatics, with respect to the control group (Fig. 2a and b). Controlled severe-asthma group was similar to non-severe asthma and even to controls in the rate of ER visits (21.5%, 22%, and 20%, respectively) and hospitalizations (7.7%, 7.7%, and 6.5%, respectively; Fig. 2c and d). Uncontrolled severe-asthma patients had the highest rates of GP, pulmonologist and ER visits, and hospital admissions of all groups. Uncontrolled severe-asthma patients had 1.4, 1.5, 1.4, and 2.9-fold more GP, pulmonologist, ER visits, and hospital admissions, respectively than did controlled severe-asthmatics (Fig. 2a–d).

3.6. Subgroups of uncontrolled severe asthma

Table 4 summarizes the differences between subgroups of uncontrolled severe-asthma. More females used excessive systemic GC ± SABA than among the excessive SABA users, and more Arabs were among the excessive systemic GC. Smoking history and cardiopulmonary comorbidities were more frequent among excessive systemic GC+SABA.

Greater frequency of nasal inhalers (39–40%) and IgE testing (25–30%) was found among uncontrolled severe-asthmatics dispensed excessive systemic GC ± SABA. Omalizumab use was up to 8.3% in the subgroup of systemic GC+SABA.

3.7. COPD as comorbidity

COPD, as an ICD-9 physician-diagnosed comorbidity, became increasingly prevalent as asthma became more severe and more uncontrolled (Tables 1, 2a, 3a), but with no difference between subgroups of severe uncontrolled asthma using system GC with or without SABA (Table 4). LAMA as tiotropium bromide Handihaler was dispensed to 1.7% of all asthmatics and to 16.2% of all asthmatics with COPD comorbidity.

4. Discussion

This is the first large study to evaluate asthma severity among adults in the community using the 2014 ERS/ATS and GINA adjusted guidelines. Whereas most previous studies assessed severe-asthma patients recruited from specialized asthma centers [3,4], this study assessed patients with controlled- and uncontrolled severe-asthma in the community and included actual comorbidities; an important difference, given that many patients with severe asthma do not see a specialist [7], as was also found here. To the best of our knowledge, this is the first analysis of clinical subgroups of uncontrolled severe-asthma. We showed that a simple, electronic database analysis using only dispensed-medication criteria could differentiate groups of asthma severity within a large population.

Slightly less than 6% of individuals 20–70 years-old were diagnosed as asthmatics, of which 4.65% were defined as severe asthmatics. The prevalence of bronchial asthma in this study among this age group is in very good accordance with official Israeli CDC statistics [8]. However, the prevalence of severe asthma critically depends on its definition and several issues might affect it, in general and in our study. One is that ERS/ATS defines severe asthma as requiring GINA steps 4–5 medications [5], but uses much higher doses to define minimum daily ICS use, while GINA step 4 includes even medium/high doses of ICS [6]. It is obvious that choosing a different cut-off point for defining daily ICS dose would affect the prevalence of severe asthma. Although we chose a level of medium/high-dose ICS that meets GINA requirements, it was closer to the high dose zone. In this context it is appropriate to mention that ICS dose-effect curve regarding symptoms and lung function is flat beyond a prolonged daily dose of 800 mcg of ICS, while side-effects increase sharply beyond this dosage [9]. Another aspect is medication adherence. We used a high threshold for number of dispensed ICS/LABA inhalers during the previous year to define severe asthma. ERS/ATS and GINA guidelines for severe asthma do not specify the level of medication-adherence required to define “severe asthma”. Again, the adherence threshold cut-off would affect the prevalence of severe asthma. Another issue is that we defined an asthma-other group, as those who did not receive proper medium/high-dose ICS/LABA throughout the year, but nevertheless some were prescribed excessive systemic GC with or without excessive SABA. It is possible that some of these patients failed to respond to medium/high-dose ICS/LABA and therefore

Table 2

a: Asthma patient characteristics: severe vs. non-severe			
Characteristics	Non-severe asthma N = 17,110	Severe asthma N = 929	P-value
Age	40 ± 15	50 ± 14	<0.001
Male	7959 (47)	402 (43)	0.052
Jewish ethnicity	14283 (83.5)	804 (86.5)	0.014
BMI**	27 ± 5.8	28 ± 6.1	<0.001
Current smokers	2931 (18)	189 (20.5)	
Past smokers	1992 (12)	163 (18)	0.012
Sleep disordered breathing	263 (1.5)	26 (2.8)	0.003
All cardiopulmonary comorbidities	6541 (38)	474 (51)	<0.001
COPD comorbidity	1096 (6.4)	203 (21.8)	<0.001
Beta blockers	1098 (6.4)	95 (10.2)	<0.001
Nasal inhalers (patients dispensed)	1880 (11)	243 (26)	<0.001
Nasal inhalers (mean/yr)	2.26 ± 2.5	4.59 ± 4.8	<0.001
Total IgE blood testing	531 (3.1)	106 (11.4)	<0.001
Omalizumab	9 (0.1)	12 (1.3)	<0.001
Blood eosinophil (count/mm ³)**	280 ± 200	320 ± 240	<0.001
Mean general practitioner visits/yr	6.25 ± 5.7	10.1 ± 7.6	<0.001
General practitioner visits/yr			
0–2	5638 (33)	86 (9.3)	
3–6	5723 (33)	279 (30)	
7–12	3851 (22.5)	311 (33.5)	
13+	1898 (11.1)	253 (27.2)	<0.001
Pulmonologist visits/yr			
0	15907 (93)	702 (75.6)	
1	716 (4.2)	98 (10.5)	
2+	487 (2.8)	129 (13.9)	<0.001
ER visits/yr			
0	13319 (78)	700 (75)	
1	2694 (16)	168 (18)	
2+	1097 (6)	61 (6.6)	0.151
General ward admissions/yr			
0	15850 (93)	829 (89)	
1	954 (6)	70 (7.5)	
2+	305 (2)	30 (3.2)	<0.001
Pulmonary ward admissions/yr			
0	17058 (99.7)	913 (98.3)	
1+	52 (0.3)	16 (1.7)	<0.001
b: Multivariate logistic regression for severe asthma patient characteristics			
Variable	OR	95% CI	
Age	1.04	1.04–1.05	
Male	1.02	0.89–1.17	
Jewish ethnicity	1.23	1.01–1.50	
Current smokers	0.94	0.73–1.21	
Past smokers	1.12	0.87–1.43	
Beta blockers	0.81	0.64–1.03	
Sleep disordered breathing	1.14	0.75–1.74	
Cardiopulmonary comorbidities	1.53	1.24–1.90	
Nasal inhalers (patients dispensed)	2.57	2.19–3.01	

Data are for 2012. *Continuous variables are presented as mean ± SD and categorical variables are presented as frequency and percent. **Variables with more than 50% missing, as not all patients had this test during the preceding 12 months.

received systemic GC instead, an option that might increase the true prevalence of severe asthma.

Patients with severe asthma are not clinically uniform. We found that severe controlled-asthma is characterized by lower rates of ER visits and hospital admissions compared to uncontrolled severe-asthma; similar to the rates of non-severe asthma and even to those of the general non-asthmatic population. Uncontrolled severe-asthmatics visited the ER and were hospitalized much more often than severe-controlled were, especially subgroups who used excessive systemic GC; although they visited a GP or pulmonologist more often (Fig. 2). The ability to identify the most severe patients with a simple, database analysis might enable focused and enhanced medical, educational, and social management.

Clinical attempts to evaluate eligibility for anti-IgE therapy, as assessed by percent of severe-asthma patients tested for total IgE,

seemed very poor. As we did not have electronic data for skin-prick testing and as total IgE evaluation is required for anti-IgE therapy, we used the rate of IgE testing as a marker for attempts to evaluate atopy and perhaps offer anti-IgE therapy. Only 11% of the severe-asthma population had this simple, inexpensive test. The rate of background atopy in these patients was likely much higher, as 25% were dispensed nasal corticosteroid/antihistamine inhalers, which increased up to 40% in subgroups of uncontrolled severe-asthma. Evaluation for IgE increased among subgroups of uncontrolled severe-asthma according to severity, demonstrating clinician awareness of anti-IgE therapy, but that was still too low. Although a normal IgE level does not rule out atopy, it can be a positive predictor among established asthmatics [10–12]. Therefore, it should be used in every uncontrolled severe-asthmatic, along with skin-prick testing for aeroallergens. It is reasonable to assume that if

Table 3

a: Severe asthma patient characteristics: controlled/uncontrolled			
Characteristics	Controlled severe asthma n = 622	Uncontrolled severe asthma n = 307	P-value
Age	49 ± 14.5	52.6 ± 12.0	<0.001
Male	276 (44)	126 (41)	0.335
Jewish ethnicity	546 (88)	254 (84)	0.284
BMI**	27.4 ± 6.1	28.8 ± 6.1	0.009
Current smokers	115 (19)	74 (24)	
Past smokers	102 (16.5)	61 (20)	0.026
Sleep disordered breathing	20 (3.2)	6 (2.0)	0.273
All cardiopulmonary comorbidities	278 (44.7)	196 (63.8)	<0.001
COPD comorbidity	109 (17.5)	94 (30.6)	<0.001
Beta blockers	55 (8.8)	10 (13.0)	0.048
Nasal inhalers (patients dispensed)	155 (25)	88 (29)	0.222
Nasal inhalers (mean/yr)	4.40 ± 4.11	4.92 ± 5.78	0.416
Total IgE blood testing	47 (7.6)	59 (19.2)	<0.001
Omalizumab	1 (0.2)	11 (3.6)	<0.001
Blood eosinophil (count per mm ³)**	320 ± 230	320 ± 250	0.955
Mean general practitioner visits/yr	8.65 ± 6.4	12.7 ± 9.0	<0.001
General practitioner visits/yr			
0–2	73 (11.7)	13 (4.2)	
3–6	213 (34)	66 (21.5)	
7–12	206 (33)	105 (34.2)	
13+	130 (21)	123 (40.1)	<0.001
Pulmonologist visits/yr			
0	494 (79)	208 (68)	
1	59 (9.5)	39 (13)	
2+	69 (11)	60 (19.5)	<0.001
ER visits/yr			
0	488 (78.5)	212 (69)	
1	102 (16.4)	66 (21.5)	
2+	32 (5.1)	29 (9.4)	0.004
General ward admissions/yr			
0	576 (93)	253 (82)	
1	37 (6)	33 (11)	
2+	9 (1)	21 (7)	<0.001
Pulmonary ward admissions/yr			
0	620 (99.7)	293 (95.4)	
1+	2 (0.3)	14 (4.6)	<0.001
b: Multivariate logistic regression for uncontrolled severe-asthma patient characteristics			
Variables	OR	95% CI	
Age	1.02	1.00–1.03	
Male	0.89	0.67–1.19	
Jewish ethnicity	0.79	0.53–1.19	
Current smokers	0.69	0.42–1.11	
Past smokers	0.79	0.49–1.27	
Beta blockers	1.20	0.76–1.91	
Sleep disordered breathing	0.45	0.17–1.19	
Cardiopulmonary comorbidities	2.59	1.70–3.96	
Nasal inhalers (dispensed patients)	1.29	0.93–1.78	

Data are for 2012. *Continuous variables are presented as mean ± SD and categorical variables are presented as frequency and percent. **More than 50% missing as not all patients had this test during the preceding 12 months.

physicians did not evaluate IgE status, they probably did not refer many patients for skin-prick tests either. In accordance with the low rate of total IgE evaluation and in contrast to the relatively higher rate of dispensed corticosteroid/antihistamine nasal inhalers, the rate of anti-IgE therapy was also very low. Only 3.6% of all uncontrolled severe-asthmatics were dispensed omalizumab.

Compared to non-severe asthmatics, severe-asthmatics were older, more likely to be female, have higher BMI, more SDB, ever smoked, had more cardiopulmonary comorbidities, were dispensed more beta-blockers and nasal inhalers and had higher eosinophil counts, with the limitation that only about half of the patients had eosinophil counts; all in agreement with other studies [13–15], which reinforces our findings. Eosinophil count was not a differential marker among severe-asthma groups or subgroups. Jewish ethnicity was more prevalent than was Arab ethnicity within asthmatics, as compared with the control group. We do not know

the reason for this difference, but in a previous survey in Israel, similarly, asthma was more prevalent in Jews than in Arabs [16].

Association of comorbidities with severe and uncontrolled asthma, as found here, reinforces similar findings from recent studies [14,15,17–19], but this study differs by including physician COPD diagnosis as a comorbidity. The rate of COPD as a comorbidity increased as asthma became severe and more uncontrolled. While asthma overlap with COPD is estimated to be 10–20% [20], the prevalence of COPD overlap with asthma is not known; but is presumed to be higher, either due to smoking or, in non-smokers, might represent different asthma phenotypes [20], resulting in irreversible structural changes. The rate of COPD comorbidity in this study increased as asthma became severe and uncontrolled.

It is important to stress that many severe asthmatics do not see a pulmonologist, although they could have been referred by their GP, in accordance with findings of another large study [7]. Only 25% of

Table 4

Severe asthma characteristics: uncontrolled by sub-groups.

Characteristics	Excessive SABA (1) N = 176	Excessive Systemic GC (2) N = 83	Excessive (Systemic GC+SABA) (3) N = 48	P 1-2-3	P 1-2	P 1-3	P 2-3
Age	51 ± 12.2	54 ± 11.2	55 ± 11.8	0.057	0.201	0.148	0.999
Male	82 (47)	27 (32.5)	17 (35)	0.069	0.032	0.167	0.736
Jewish ethnicity	157 (89)	60 (72)	41 (85)	0.008	0.001	0.468	0.085
BMI**	29 ± 5.4	28 ± 6.8	29 ± 6.1	0.587	0.999	0.999	0.999
Current smoker	48 (27)	17 (20.5)	9 (19)				
Past smoker	36 (21)	10 (20.5)	15 (32)	0.032	0.239	0.229	0.811
Sleep disordered breathing	4 (2.3)	1 (1.2)	1 (2.1)	0.843	0.560	0.937	0.693
All cardiopulm. comorbid.	101 (57.4)	56 (67.5)	39 (81)	0.007	0.121	0.002	0.089
COPD comorbidity	40 (22.7)	33 (39.8)	21 (43.8)	0.002	0.007	0.007	0.714
Beta blockers	24 (13.6)	11 (13.3)	5 (10.4)	0.839	0.933	0.556	0.633
Nasal inhalers (patients dispensed)	37 (21)	32 (39)	19 (40)	0.003	0.003	0.008	0.907
Nasal inhalers (mean/yr)	5.03 ± 4.7	5.94 ± 7.7	3.00 ± 2.7	0.213	0.999	0.642	0.242
Total IgE blood testing	23 (13)	21 (25)	15 (31)	0.005	0.014	0.003	0.462
Omalizumab	4 (2.3)	3 (3.6)	4 (8.3)	0.135	0.534	0.045	0.247
Eosinophil (count/mm ³)**	310 ± 182	320 ± 290	350 ± 340	0.691	0.999	0.988	0.999
Mean general practitioner visits/yr	10.6 ± 8.1	15 ± 9.0	16.4 ± 9.6	<0.001	<0.001	<0.001	0.999
General practitioner visits/yr							
0–2	11 (6.3)	1 (1.2)	1 (2.1)				
3–6	51 (29)	10 (12)	5 (10)				
7–12	64 (36)	26 (31)	15 (31)				
13+	50 (28)	46 (55)	27 (56)	<0.001	<0.001	0.002	0.973
Pulmonologist visits/yr							
0	143 (81)	40 (48)	25 (52)				
1	17 (10)	14 (17)	8 (17)				
2+	16 (9)	29 (35)	15 (31)	<0.001	<0.001	<0.001	0.897
ER visits/yr							
0	132 (75)	56 (67.5)	24 (50)				
1	33 (19)	18 (22)	15 (31)				
2+	11 (6)	9 (11)	9 (19)	0.013	0.328	0.002	0.135
General ward admissions/yr							
0	156 (89)	64 (77)	33 (69)				
1	14 (8)	10 (12)	9 (19)				
2+	6 (3.4)	9 (11)	6 (12.5)	0.008	0.026	0.003	0.522
Pulmonary ward admissions/yr							
0	174 (98.9)	77 (92.8)	42 (87.5)				
1+	2 (1.1)	6 (7.2)	6 (12.5)	0.001	0.008	<0.001	0.314

Data are for 2012. SABA Short-acting beta-agonist inhalers; SYSTEMIC GC Systemic gluco-corticosteroids *Continuous variables are presented as mean ± SD and categorical variables are presented as frequency and percent. **Variables with more than 50% missing as not all patients had this test during the preceding 12 months.

severe asthmatics visited a pulmonologist and less than one-third of those with uncontrolled severe-asthma, some of them most probably, as a prescheduled follow-up.

Another very intriguing finding was the relatively large number of patients in the asthma-other group. These patients were not dispensed proper medium/high-dose ICS/LABA treatment, as required by GINA guidelines, but received excessive SABA, systemic GC, or systemic GC+SABA. This important group, which is twice as large as the severe-asthma group, deserves further detailed analysis to investigate their characteristics and the reasons for their status. However, this was out of the scope of this study.

Our findings show that uncontrolled severe-asthmatics can be easily screened by a simple database analysis and strongly suggest that these patients should be referred to an asthma specialist for evaluation, including eligibility for anti-IgE therapy and should have optimal management of cardiopulmonary comorbidities and smoking habits in coordination with their GP. Given the low rates of total IgE evaluation and anti-IgE therapy, we suggest that many more severe-asthmatics and every uncontrolled severe-asthmatic should be tested for total IgE, along with skin-prick testing, and given the recently approved new biologic therapies, an eosinophil blood count.

This study had some limitations. It was based on electronic data of physician-diagnosed asthma. As in other countries, spirometry is not a prerequisite in Israel for ICD-9 diagnosis asthma [21,22] and pulmonary function test results could not be analyzed. Therefore, it is possible that asthmatic patients with COPD comorbidity had

asthma/COPD overlap or were even diagnosed as asthmatic instead of with COPD. Patients were included in this study even if they had additional cardiopulmonary comorbidities, physician diagnosis of COPD along with asthma, use of beta-blockers, left heart failure or smoked; comorbidities and co-factors that frequently coexist with asthma. We could not know whether these comorbidities were optimally treated and we did not analyze whether GP visits, ER visits, and general hospital admissions were asthma-related. However, we compared visit rates with those of the control group and among asthmatics. In spite of these limitations, we believe that this cross-sectional study, presents real-world conditions that reflect the characteristics of asthma severity in the community.

The findings indicate that severe-asthmatics must be differentiated as controlled or uncontrolled. We found that referrals of severe-asthmatics to specialists and evaluation for anti-IgE therapy need improvement. In addition, a large group of asthma-other patients in the community needs further investigation. A simple, electronic database analysis, based on dispensed medications, might help providers recognize subgroups of severe asthmatics that require focused efforts and attention.

Author contributions

Shabtai Varsano contributed to developing the protocol, assessing the data, and preparing the manuscript. David Shitrit contributed to manuscript preparation and David Segev contributed to data collection and manuscript review.

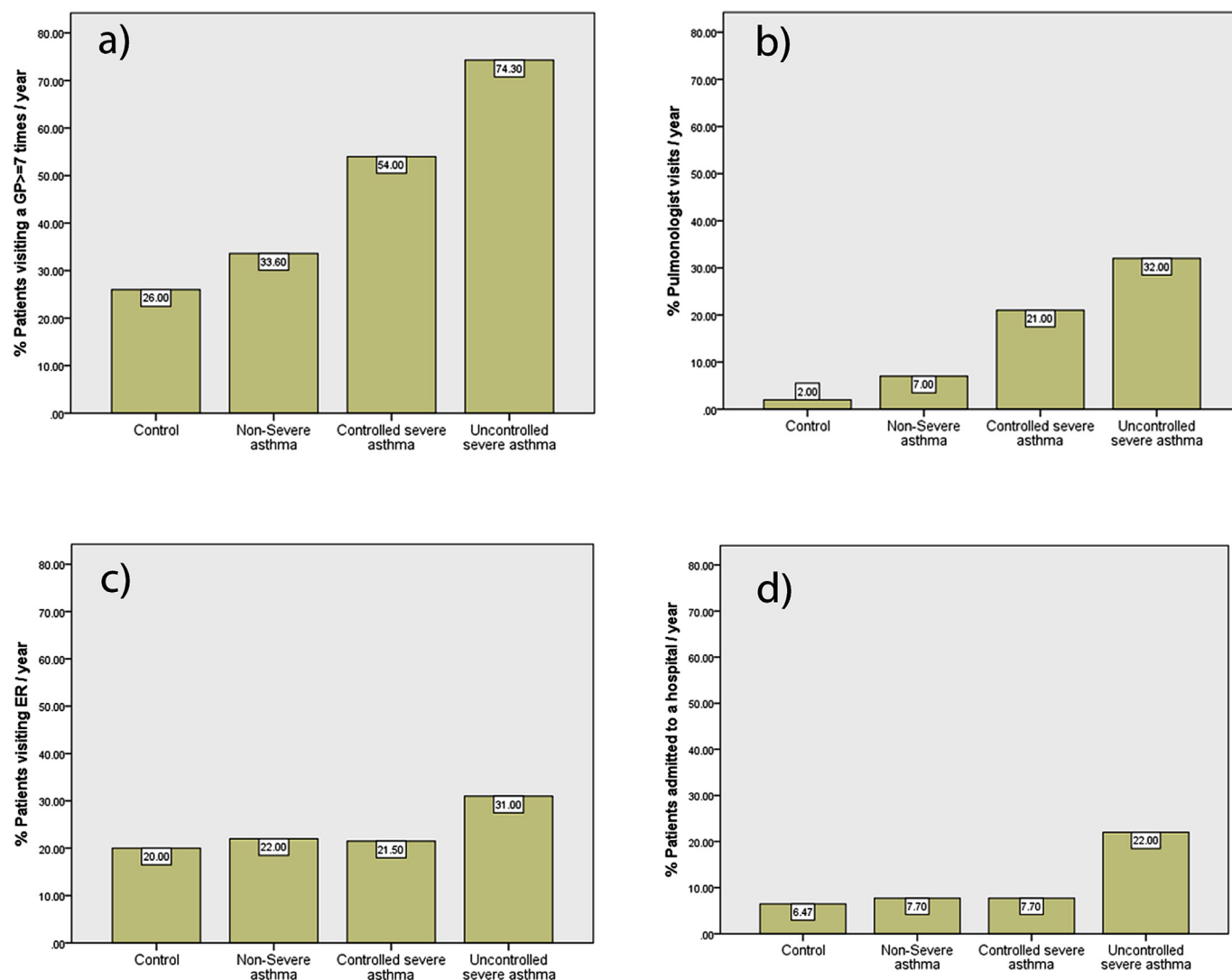


Fig. 2. Healthcare utilization: a) % patients visiting a GP ≥ 7 times a year; b-d) % patients visiting a pulmonologist, ER or admitted to hospital at least once during the study year.

Guarantor statement

S. Varsano had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects, as well as full responsibility for the integrity of the submission as a whole, from inception to published article.

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Conflict of interest

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