



The epidemiology of asthma and its comorbidities in Poland – Health problems of patients with severe asthma as evidenced in the Province of Lodz



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ABSTRACT

Introduction: Population studies supply interesting data regarding the epidemiology, comorbidity and risk factors of asthma, which have direct clinical implications for patients.

Objectives: The aim of the work was to evaluate the degree of severity of asthma in the studied group, the levels of anti-asthma treatment, the prevalence of asthma comorbidities and their influence on the clinical course of the illness.

Patients and methods: The study encompassed 451 participants: 52.11% were asthma patients (study group) and 47.89% were healthy subjects (controls). Respiratory function tests, ACT™ test and skin prick tests were performed.

Results: Asthma severity was mild in 14.89%, moderate in 49.36% and severe in 35.74%. Oral GCS were used by 29%, inhalers 44%, LABA 68%, SABA 67%, LAMA 6%, SAMA 14% and MX 16%. Rhinitis and allergy were significantly more common in patients. GERD and neurological diseases were risk factors for asthma, and GERD significantly intensified the risk of severe asthma. GERD, atherosclerosis, hypertension, ischaemic heart disease and other cardiac diseases, lipid disorders, COPD, and the presence of any neoplastic disease significantly worsened the degree of asthma control.

Discussion: Severe asthma was a significant clinical issue in over 35% of cases. The most commonly-used group of drugs were LABAs, while inhaled GCS and LAMA were uncommon, especially among severe cases. A significant problem was the high percentage of systemic GCS used by severe cases. The most important risk factor for asthma, including its severe form, is GERD. Numerous comorbid conditions significantly worsen the degree of asthma control.

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1. Introduction

Asthma is a serious health, social and economic problem both in Poland and worldwide. According to the World Health Organization (WHO), asthma affects approximately 300 million people worldwide, with morbidity ranging from 1 to 18%; Around 5% suffer from the severe form, and around 1% the very severe form [1,2].

Poland alone includes around 4 million asthma patients. Morbidity in the adult population is known to be 5.4% [3,4], with the majority of sufferers being female. A dynamic increase has been observed in the number of cases for more than 30 years [2–4] and despite the implementation of modern inhaled drugs, systemic glucocorticosteroids and biological medicines, around 250,000 people die annually; One person dies every hour in Europe, and around 600 die annually in Poland alone [1,4]. In the majority of patients (50–60%), asthma is insufficiently controlled, and the patients experience a number of clinical problems: frequent exacerbations, frequent use of fast and short-acting rescue medication, frequent visits to doctors and hospitalizations, reduced life activity and decreased quality of life. These problems are accompanied by

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increased direct and indirect treatment costs. The cost of treating patients with severe asthma alone constitutes more than 50% of all costs allocated to the care of patients with asthma [5,6].

A number of publications have provided a considerable body of data concerning the prevalence of asthma, its epidemiology, risk factors and comorbidities in various populations [6–9]. Recently published works have highlighted the problem of undiagnosed risk factors, insufficient levels of compliance and adherence with treatment, as well as incorrect diagnosis and improper treatment of asthma. It has been found that less than half of asthma patients have received a diagnosis, and less than 50% receive anti-asthma medication, of which less than 30% are anti-inflammatory drugs [6,9–13]. In addition, 60% of asthma patients aged 8–29 years have at least one co-occurring chronic disease [14]. These studies clearly indicate that the epidemiology of asthma and its comorbidities represents an important clinical issue which needs to be tackled as part of a wider public health problem which affects Poland and the rest of the world.

The aim of the work was to evaluate the degree of severity of asthma in the studied group and the level of anti-asthma treatment, as well as the frequency of comorbidities co-occurring with asthma and their influence on the clinical course of the illness.

2. Materials and methods

2.1. Ethical approval

The study was approved by the local Ethics Committee (Consent of the Research Review Board of the Medical University of Lodz, Lodz, Poland; no. RNN/133/09/KE). The participants were invited to enrol of their own free will at the beginning of the study, and written informed consent was obtained from every patient prior to enrolment.

2.2. Test group

The asthma patients were recruited at random from the group of patients under the care of the Department of Internal Medicine, Asthma and Allergy, the Department of Pneumology and Allergology, the Department of General and Oncological Pulmonology, and the Specialist Outpatient Clinic of Pulmonary Diseases and Allergology of the Norbert Barlicki University Clinical Hospital No.1, Medical University of Lodz. According to the data for the year 2013 from the Department for Medical Statistics and Monitoring of Health Services, 13,541 patients from the Norbert Barlicki University Clinical Hospital No. 1 were graded as code J45 (bronchial asthma) with a classification of ICD10. Medical data for the survey was gathered using questionnaires administered by specialist physicians from Internal Medicine, Allergology and lung disease. Other data was obtained from individual inpatient and outpatient information cards. The control group included volunteers selected randomly from the general population. The study was performed in the years 2010–2013.

2.3. The inclusion and exclusion criteria

For the asthma patients in the study group, the inclusion criteria were as follows: a) free consent given by the patient to join the study, b) obtaining results of spirometry with a post bronchodilator test to allow correct interpretation, c) obtaining a diagnosis of asthma according to ERS/ATS criteria, d) obtaining results of the ACTTM [2,15–18]. The exclusion criteria were as follows: a) lack of permission to take part in the study, b) inability to qualify the patient according to the severity of asthma, c) treatment with rifampicin, phenobarbital, phenytoin or ephedrine, d) infectious

exacerbation of the disease [15–18].

For the control group, the following inclusion criteria were used: a) no subjective or objective evidence of the occurrence of bronchial asthma identified from tests; b) no spirometric evidence confirming obstruction; c) lack of first degree relatives with asthma, allergy or atopy; d) lack of treatment with rifampicin, phenobarbital, phenytoin or ephedrine [15–18].

The study included 451 participants. Asthma patients constituted 52.11%, while the other 47.89% comprised the control group. The group included 289 women (64.08%) and 162 men (35.92%). The asthma patients were subdivided as follows: mild asthma – 35 people (14.89%), moderate asthma – 116 people (49.36%), severe asthma – 84 people (35.74%).

2.4. Spirometry

Respiratory function tests were performed according to ERS/ATS standards [19]. The obstructive disorders and severity of the disease were analysed by taking the best score of three spirometry readings, according to the standards of the Polish Society of Lung Diseases [20]. The analysis included the following parameters: FEV1 (forced expiratory volume in 1 s) expressed in litres, FEV1% (A/N % – percentage ratio of the measured to predicted value) expressed as per cent of the predicted value, FVC (forced vital capacity) expressed in litres, FVC% (A/N% – percentage ratio of the measured to predicted value), and the FEV1% FVC index (FEV1 to FVC ratio) expressed as absolute numbers.

2.5. ACTTM Asthma Control Test

The level of asthma control was evaluated according to the recommendations of the GINA report, designed and standardised by the Nathan Asthma Control Test (ACTTM) [2,21].

2.6. Skin prick test

The skin prick test was performed according to the guidelines of the EAACI (European Academy of Allergy and Clinical Immunology) [22]. The following criteria were used to identify positive results and evaluate the strength of reaction: a positive result required the wheal induced by an allergen and surrounded by erythema, having a diameter ≥ 3 mm greater than a wheal produced by 0.9% NaCl solution. The results were presented as diameter of the wheal and erythema in millimetres [22].

2.7. Statistical analysis

The Shapiro–Wilk test was used to determine the distribution of continuous variables. Depending on the type of variables, the hypotheses were tested with either the Pearson's Chi-squared test, Student's t-test, Multifactorial Analysis of Variance (MANOVA) with the post-hoc Tukey's test, or the Kruskal–Wallis test with multiple range comparisons. All calculations were performed using STATISTICA 12 PL software with the Medical Package.

3. Results

The obtained medical data allowed a detailed description to be made of mean age, Body Mass Index (BMI), basic spirometric values and the level of asthma control in the tested groups i.e. controls and asthma patients. The precise characteristics of the study group are given in Table 1.

All the results obtained for patients with severe asthma significantly differ from those for subjects without asthma ($p < 0.001$) and patients with mild ($p < 0.001$) and moderate asthma ($p < 0.01$)

Table 1

The selected variables in the studied groups.

Studied variable		Control group	Degree of asthma severity			p
			Mild	Moderate	Severe	
Age		45.67 ± 16.3	46 ± 15.96	47.21 ± 16.28	52.25 ± 15.06	0.02
BMI		26.08 ± 4.41	26.22 ± 4.65	27 ± 4.7	27.37 ± 5.09	0.18
FEV1	L	2.97 ± 0.79	2.74 ± 0.79	2.38 ± 0.83	1.75 ± 0.7	<0.001
	%p.v.	96.12 ± 12.57	88.46 ± 13.23	78.18 ± 16.48	58.81 ± 17.68	<0.001
FVC	L	3.76 ± 1.01	3.71 ± 1.07	3.48 ± 1.11	2.9 ± 1.02	<0.001
	%p.v.	102.7 ± 14.89	100.89 ± 13.27	95.73 ± 14.32	81.44 ± 18.52	<0.001
FEV1%FVC	%	78.97 ± 6.12	74.3 ± 8.63	68.36 ± 10.43	60.1 ± 12.29	<0.001
	%p.v.	97.73 ± 7.24	92.03 ± 10.88	84.96 ± 12.49	75.42 ± 15.39	<0.001
ACT		—	19.06 ± 3.27	18.84 ± 4.62	14.81 ± 5.3	<0.001

The table presents mean values with standard deviations for selected variables in the studied groups related to BMI values, spirometric parameters and the degree of asthma control according to ACT™. The p-value is given for the Kruskal–Wallis test. Legend: BMI – Body Mass Index; p.v. – predicted value; % – per cent; L-litre; ACT™ – Asthma Control Test; p – coefficient of statistical significance. Detailed data is presented in the text.

(Table 1). All the results for patients with moderate asthma were significantly different from findings achieved for subjects without the disease ($p < 0.001$). There was also a statistically significant difference in FEV1%FVC, both in percentage values and percentage of the predicted value ($p < 0.05$) for patients with mild asthma. No significant difference between subjects without asthma and patients with mild asthma was observed.

Additionally, attention should be drawn to the fact that patients with severe asthma were significantly older than controls ($p < 0.05$). In the Asthma Control Test (ACT™), patients with severe asthma obtained a significantly lower result than patients with moderate and mild asthma ($p < 0.001$). The authors did not find any statistically significant difference between the group of patients with mild and moderate disease.

All drugs taken by asthma patients were included in the analysis (Table 2).

Statistically significant differences in the use of all anti-asthmatic drugs were noted between the groups of different asthma severity (Table 2). However, post-hoc tests did not indicate any such statistically significant differences for short acting muscarinic antagonist (SAMA) and long acting muscarinic antagonist (LAMA) and their p-value should be considered with caution. Additionally, it was shown in post-hoc multiple comparison tests that patients with severe asthma used systemic and inhaled glucocorticosteroids (GCS), LABA, SABA, anti-leukotrienic drugs (anti-LT) ($p < 0.001$) and methylxanthines ($p < 0.05$) significantly more often than those with mild or moderate asthma. No statistically significant difference in the frequency of using particular drugs was

observed between the groups with mild and moderate asthma.

The survey data was used to evaluate the prevalence of the following complications of GCS use: diabetes, hypertension, obesity, osteoporosis, cataract, glaucoma and adrenal cortex insufficiency. A “Yes” answer to one of these complications was considered a positive result. The following results were achieved according to the groups: 1 patient with mild asthma (2.9%), 13 patients with moderate asthma (11.2%), and 49 patients with severe asthma (58.3%). Complications significantly most often concerned only patients with severe asthma ($p < 0.001$).

The collected medical data was searched to determine whether any intolerance, hypersensitivity or complications occurred after using other drugs than glucocorticosteroids, anti-asthmatics (SABA, LABA, SAMA, LAMA, MX) and antihistamines. Hypersensitivity reactions to drugs happened in 10 patients (28.6%) with mild asthma, in 28 (24.1%) with moderate asthma and in 29 (34.5%) with severe asthma. There was no evidence that hypersensitivity reactions were significantly more common in any group.

The co-occurrence of rhinitis and allergy in asthma patients is presented in Table 3.

Rhinitis, regardless of its form, significantly more often occurs in patients with asthma. However, no statistically significant differences in the prevalence of rhinitis were found between the groups with different levels of asthma severity. The occurrence of allergies are significantly more commonly associated with asthma, irrespective of their time of occurrence (seasonal or perennial). The prevalence (seasonal + perennial) was 7.5% lower in severe asthma than the moderate form. However, no statistically significant differences in the prevalence of allergy were observed between the groups of patients with different levels of asthma severity (Table 3).

The presence of the following comorbidities occurring in asthma patients was assessed: gastroesophageal reflux disease, nasal polyps, neurological diseases, thyropathies, cardiac and pulmonary diseases (other than asthma), disorders of lipid metabolism, chronic peptic ulcer disease (gastric and duodenal), neoplastic disease (any type) and immunodeficiency. This data was expanded to include the treatment or lack of treatment with allergen-specific immunotherapy, as well as the frequency of at least 2 or more asthma exacerbations per year, defined as the need for systemic glucocorticosteroids or antibiotics and systemic glucocorticosteroids (Table 4).

Analysing the data from Table 4, it is important to note that gastroesophageal reflux disease occurred significantly more often in asthma patients than in subjects without asthma. However, although the percentage values indicate that the disease was most common in patients with severe asthma, no statistically significant difference was observed between the patient groups and the control group.

Table 2

The medications used by the study participants.

Studied medications	Degree of asthma severity			p
	Mild	Moderate	Severe	
Systemic GCS	5 (14.3%)	12 (10.3%)	54 (64.3%)	<0.001
Inhaled GCS ≤ 1000 mcg	24 (68.6%)	92 (79.3%)	5 (6%)	<0.001
Inhaled GCS >1000 mcg	5 (14.3%)	12 (10.3%)	72 (85.7%)	<0.001
LABA	8 (22.9%)	102 (87.9%)	79 (94%)	<0.001
SABA	20 (57.1%)	65 (56%)	75 (89.3%)	<0.001
SAMA	2 (5.7%)	13 (11.2%)	23 (27.4%)	<0.01
LAMA	0 (0%)	1 (0.9%)	10 (11.9%)	<0.01
Anti-LT	7 (20%)	26 (22.4%)	47 (56%)	<0.001
MX	0 (0%)	5 (4.3%)	24 (28.6%)	<0.001

The table presents the number and percentage of patients in each group who took a particular drug. The p-value is given for the Pearson's Chi-squared test. Legend: GCS-glucocorticosteroids; mcg-micrograms; LABA-long acting β_2 -agonist; SABA-short acting β_2 -agonist; SAMA-short acting muscarinic antagonist; LAMA-long acting muscarinic antagonist; anti-LT- antileukotrienic drugs; MX-methylxanthines; p – coefficient of statistical significance. Detailed data is presented in the text.

Table 3

The impact of rhinitis and allergy on asthma severity.

Analysed variable		Control group	Degree of asthma severity			p
			Mild	Moderate	Severe	
Rhinitis	Sporadic	2 (0.9%)	3 (8.6%)	4 (3.4%)	1 (1.2%)	<0.001
	Chronic	6 (2.8%)	15 (42.9%)	61 (52.6%)	44 (52.4%)	
	Seasonal	3 (1.4%)	8 (22.9%)	25 (21.6%)	8 (9.5%)	<0.001
	Perennial	5 (2.3%)	10 (28.6%)	40 (34.5%)	37 (44.0%)	
	Treated with nGCS	1 (0.5%)	7 (20.0%)	29 (25.0%)	19 (22.6%)	<0.001
Allergy	anti-H1	4 (1.9%)	13 (37.1%)	51 (44.0%)	46 (54.8%)	<0.001
	Seasonal	0 (0.0%)	3 (12.0%)	12 (48.0%)	10 (40.0%)	<0.001
	Perennial	0 (0.0%)	8 (17.0%)	24 (51.1%)	15 (31.9%)	<0.001
	Seasonal + Perennial	0 (0.0%)	12 (17.9%)	30 (44.8%)	25 (37.3%)	<0.001

The table presents the number and percentage of subjects with different types of rhinitis and who were receiving medication, taking into account the time period of occurrence. The p-value is given for the Pearson's Chi-squared test. Legend: % – per cent; nGCS – nasal glucocorticosteroids; anti-H1 – antihistamine drugs blocking H1-receptor; p – coefficient of statistical significance. Detailed data is presented in the text.

Table 4

The impact of selected disease on the severity of asthma.

Analysed variable		Control group	Degree of asthma severity			p
			Mild	Moderate	Severe	
Gastroesophageal reflux disease		22 (10.2%)	4 (11.4%)	22 (19%)	22 (26.2%)	<0.01
Used PPI		119 (8.8%)	2 (5.7%)	20 (17.2%)	30 (35.7%)	<0.001
Nasal polyps		6 (2.8%)	0 (0%)	7 (6%)	7 (8.3%)	0.08
Neurological diseases		6 (2.8%)	3 (8.6%)	10 (8.6%)	6 (7.1%)	0.10
Thyroid goitre		3 (1.4%)	1 (2.9%)	7 (6%)	3 (3.6%)	0.14
Hypothyroidism		7 (3.2%)	1 (2.9%)	2 (1.7%)	2 (2.4%)	0.87
Hyperthyroidism		12 (5.6%)	5 (14.3%)	1 (0.9%)	3 (3.6%)	<0.01
Atherosclerosis		12 (5.6%)	0 (0%)	3 (2.6%)	3 (3.6%)	0.32
Arterial hypertension		61 (28.2%)	8 (22.9%)	34 (29.3%)	30 (35.7%)	0.48
Arrhythmia		14 (6.5%)	5 (14.3%)	6 (5.2%)	8 (9.5%)	0.24
Ischaemic heart disease		16 (7.4%)	2 (5.7%)	15 (12.9%)	10 (11.9%)	0.28
Myocardial infarction		12 (5.6%)	0 (0%)	7 (6%)	4 (4.8%)	0.53
Other cardiac diseases		12 (5.6%)	2 (5.7%)	3 (2.6%)	7 (8.3%)	0.35
COPD		0 (0%)	5 (14.3%)	21 (18.1%)	29 (34.5%)	<0.001
Sarcoidosis		2 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0.53
TBC		4 (1.9%)	0 (0%)	1 (0.9%)	2 (2.4%)	0.70
Other pulmonary diseases		1 (0.5%)	0 (0%)	0 (0%)	1 (1.2%)	0.63
Lipid disorders		0 (0%)	5 (14.3%)	21 (18.1%)	29 (34.5%)	0.36
Peptic ulcer disease		2 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0.34
Neoplastic disease		4 (1.9%)	0 (0%)	1 (0.9%)	2 (2.4%)	0.89
Immunodeficiency		1 (0.5%)	0 (0%)	0 (0%)	1 (1.2%)	0.63
>=2 exacerbations			0 (0%)	8 (6.9%)	42 (50%)	<0.001
Allergen-SIT			1 (2.9%)	11 (9.5%)	1 (1.2%)	0.03

A comparison of the prevalence of selected diseases in patients with varying degrees of asthma severity and in subjects without asthma. Legend: PPI – proton-pump inhibitor; COPD – chronic obstructive pulmonary disease; TBC – tuberculosis; allergen-SIT – allergen-specific immunotherapy; p – coefficient of statistical significance. Detailed data is presented in the text.

Bold values indicates $p < 0.05$.

No statistically significant differences in the prevalence of either nasal polyps, neurological diseases (any disease) or cardiac diseases (any disease) were found between the groups of patients with asthma as regards its severity in comparison to controls (Table 4).

A statistically significant difference was noted in the prevalence of hyperthyroidism between the studied groups. However, the subgroup responsible for this correlation was not detected in the post-hoc test.

Chronic obstructive pulmonary disease (COPD) was recorded significantly more often among patients with asthma: superimposed COPD syndrome was stated in the group of patients with severe asthma. Bronchiectasis was not diagnosed in any patient from the study group.

No significant relationship was identified between the level of asthma severity and lipid disorders, peptic ulcer disease, neoplastic disease, or immunodeficiency as compared to the control group (Table 4).

A statistically significant difference was found between the groups of asthma patients with regard to the causal treatment of allergy in asthma using immunotherapy ($p = 0.03$). However, due

to the fact that in the group of patients with mild and severe asthma only 1 patient was treated in each of the above groups, the obtained result should be approached with caution.

Two or more heavy exacerbations of the disease per year were significantly more often reported among the patients with severe than with mild ($p < 0.001$) and moderate ($p < 0.001$) asthma as compared to the control group. The authors did not observe significant differences in the frequency of asthma exacerbations between the patients with mild and moderate asthma.

Interestingly, a statistically significant difference in the prevalence of hyperthyroidism was revealed between the groups of asthma patients according to asthma severity. Unfortunately, no subgroup of patients responsible for this relationship was identified in the post-hoc test.

Correlations between the impact of selected diseases and the groups of diseases on the likelihood of asthma development and the level of its course were evaluated (Table 5).

Gastroesophageal reflux disease and neurological diseases increase the likelihood of asthma development. An inverse correlation was found between the prevalence of reflux disease and the

Table 5

The impact of selected disease in comparison to controls and cases.

Analysed entity	Asthma vs control group			Severe asthma vs control group/non-severe asthma		
	OR	95%CI	p	OR	95%CI	p
Nasal polyps	2.19	(0.82–5.86)	0.12	2.44	(0.92–6.43)	0.07
Gastroesophageal reflux disease	2.01	(1.15–3.52)	0.01	2.01	(1.11–3.66)	0.02
Neurological diseases	2.89	(1.12–7.44)	0.03	1.23	(0.47–3.23)	0.67
Thyroid goitre	3.55	(0.96–13.15)	0.06	1.16	(0.31–4.36)	0.83
Hypothyroidism	0.57	(0.17–1.86)	0.35	0.76	(0.16–3.6)	0.72
Hyperthyroidism	0.51	(0.2–1.29)	0.15	0.51	(0.14–1.86)	0.31
Atherosclerosis	0.33	(0.12–0.95)	0.04	0.58	(0.16–2.14)	0.41
AH	0.79	(0.48–1.3)	0.35	0.95	(0.52–1.73)	0.86
Arrhythmia	1.04	(0.49–2.23)	0.92	1.1	(0.45–2.66)	0.84
IHD	1.25	(0.61–2.58)	0.54	0.9	(0.39–2.09)	0.8
MI	0.63	(0.26–1.54)	0.31	0.6	(0.19–1.9)	0.38
Other cardiac diseases	0.69	(0.28–1.71)	0.43	1.27	(0.47–3.45)	0.64
TBC	0.64	(0.14–2.92)	0.56	1.45	(0.27–7.84)	0.67
Other pulmonary diseases	0.79	(0.05–13)	0.87	3.35	(0.2–55.99)	0.4
Lipid disorders	1.04	(0.49–2.22)	0.91	1.49	(0.65–3.4)	0.34
Peptic ulcer disease	0.67	(0.34–1.34)	0.26	1.06	(0.46–2.45)	0.89
Neoplastic diseases	0.85	(0.38–1.92)	0.70	0.55	(0.18–1.7)	0.3
Immunodeficiency	0.47	(0.02–9.07)	0.61	2.58	(0.14–48.8)	0.53

A comparison of the effects of selected disease groups and entities on asthma severity. The results were corrected according to patient age, BMI and sex. Legend: OR – odds ratio; CI – confidence interval; p – coefficient of statistical significance; BMI – body mass index; HA – hypertension; IHD – ischaemic heart disease, MI – myocardial infarction; TBC – tuberculosis; Detailed data is presented in the text.

risk of hyperthyroidism. It is particularly important to note that the reflux disease increases the degree of asthma severity at a significance level of $p = 0.02$. Gastroesophageal reflux disease increases the likelihood of developing severe asthma more than twofold ($OR = 2.01$) compared with non-severe asthma or a lack of asthma (control group). Similarly, it is worth noting that asthma significantly reduces the risk of atherosclerosis ($OR = 0.33$) in the group of asthmatic patients compared to controls (Table 5).

The following part of the study examines whether the co-occurrence of additional diseases worsens the degree of asthma control measured by using the ACT™. The obtained data is presented in Table 6.

It has been found that comorbidity of reflux disease, atherosclerosis, lipid disorders, arterial hypertension, ischaemic heart disease or other cardiac diseases decreases the level of asthma control. Moreover, the co-occurrence of COPD or any neoplastic disease reduces the scores obtained by asthma patients in ACT™ (Table 6).

It should be emphasized that no nasal polyps, atherosclerosis and myocardial infarction were reported among the patients with mild asthma.

Finally, the influence of the development of asthma as a primary disease on the co-occurrence of subsequent nosological entities was determined. Detailed data is presented in Table 7.

The development of asthma increases the likelihood of comorbidities accompanying the primary entity twofold, and this possibility increases by up to three times in severe asthma. Interestingly, while the presence of asthma, or severe asthma, doubles the possibility of developing three subsequent additional diseases, it should be emphasized that the logistic regression model did not indicate any effect of asthma on the occurrence of one, two, or at least four additional nosological conditions.

4. Discussion

Asthma represents a serious public health problem. It is one of

Table 6

The effect of selected diseases on the degree of asthma control.

Analysed variable	Results of ACT™ Asthma Control Test in the group of asthma patients	Results of ACT™ Asthma Control Test in the group of subjects without asthma	p
Nasal polyps	16.22 ± 5.71	17.50 ± 5.05	0.36
Gastroesophageal reflux disease	15.56 ± 4.87	17.90 ± 5.05	<0.01
Neurological diseases	16.22 ± 5.51	17.52 ± 5.05	0.28
Thyroid goitre	16.54 ± 6.28	17.46 ± 5.04	0.56
Hypothyroidism	13.60 ± 4.28	17.50 ± 5.08	0.09
Hyperthyroidism	19.00 ± 3.00	17.34 ± 5.15	0.34
Atherosclerosis	11.84 ± 3.43	17.56 ± 5.05	<0.01
AH	15.74 ± 4.96	18.14 ± 4.99	<0.001
Arrhythmia	16.42 ± 4.75	17.50 ± 5.12	0.38
IHD	14.88 ± 5.07	17.74 ± 5.01	<0.01
MI	15.36 ± 4.86	17.52 ± 5.09	0.17
Other cardiac diseases	13.34 ± 4.16	17.64 ± 5.05	<0.01
COPD	15.54 ± 5.71	17.98 ± 4.76	<0.01
TBC	18.66 ± 6.81	17.40 ± 5.08	0.67
Lipid disorders	15.16 ± 5.82	17.62 ± 5.00	0.04
Peptic ulcer disease	16.24 ± 4.62	17.5 ± 5.12	0.32
Neoplastic diseases	14.36 ± 5.61	17.62 ± 5.01	0.02

The table describes the median values with interquartile ranges in brackets, which were achieved by the study participants in the ACT™ test with the division into subgroups (patients with asthma and study participants without asthma). The results in this table were corrected according to patient age, BMI and sex. Legend: OR – odds ratio; CI – confidence interval; p – coefficient of statistical significance; BMI – body mass index; AH – arterial hypertension; IHD – ischaemic heart disease, MI – myocardial infarction; COPD – chronic obstructive pulmonary disease; TBC – tuberculosis; Detailed data is presented in the text.

Table 7

The influence of asthma on the risk of occurrence of additional comorbidities.

Analysed variable	Asthma vs control group			Severe asthma vs control group/non-severe asthma		
	OR	95%CI	p	OR	95%CI	p
Number of comorbidities						
0	0.57	(0.39–0.83)	<0.01	0.34	(0.19–0.58)	<0.001
1	1.08	(0.71–1.64)	0.73	1.43	(0.85–2.4)	0.17
2	1.31	(0.75–2.3)	0.34	1.34	(0.69–2.62)	0.39
3	2.35	(1.1–5.05)	0.03	2.25	(1.05–4.81)	0.04
4 and more	1.42	(0.79–2.55)	0.24	1.73	(0.89–3.36)	0.11

An analysis of the impact of asthma as a primary entity on the risk of occurrence of additional diseases presented as odds ratios with a 95% confidence interval. The results in this table were corrected according to patient age, BMI and sex. Legend: OR – odds ratio; CI – confidence interval; p – coefficient of statistical significance.

the most common chronic illnesses with constantly increasing morbidity rates, and one of the most common in people aged under 30 years. Despite widespread interest in allergy and asthma, these diseases still represent an underestimated clinical problem, as demonstrated by numerous studies confirming that more than half of asthma patients are clinically uncontrolled.

Our findings indicate that only 35% of patients with severe asthma are under the care of outpatient and inpatient specialist care centres, despite this being a key challenge faced by modern Pulmonology and Allergology. The prevalence of severe asthma ranges from 2.4 to 10%, depending on country: a very large percentage, which involves a number of complications and poor prognosis [23]. It is important to note that patients with severe asthma tend to demonstrate higher BMI values and lower spirometric parameters than those with the mild or moderate forms (Table 1). The comorbidities that accompany asthma, particularly severe obesity and bronchial obstruction, contribute to a loss of control of clinical disease (classified as uncontrolled asthma by the ACT™ test), the occurrence of persistent symptoms during day and night, and the limitation of everyday life activities. The presence of obesity correlates with severe symptoms, and is a known risk factor for the development of asthma. Our analysis confirmed this relationship with BMI, as well as with a number of other factors (Tables 5–7).

Patients with severe asthma were recipients of greater amounts of anti-asthma medication of all types than other patients (Table 2). It is important to note two key points in our results: not all patients with severe asthma were using inhaled GCS at doses higher than 1000 µg (85.7%), 64.3% were using systemic GCS, 94% were using long-acting β-adrenoceptor agonists (LABA), and only 11.9% were using long-acting muscarinic antagonists (LAMA). Therefore, patients with severe asthma were not receiving the levels of treatment intensity recommended by The Global Initiative for Asthma (GINA) or The American Thoracic Society (ATS). Inappropriate treatment of asthma, particularly severe asthma, is a serious problem which is not restricted to Poland [6]. Patients with severe asthma experience severe and frequent exacerbations, are hospitalized more frequently than other patients and are subject to a higher risk of death. They also used significantly more rescue medication (Tables 2 and 4), with more patients with severe asthma demonstrating complications after using anti-asthma medication in the form of GCS (58.3%) than patients with moderate asthma (11.2%) or mild asthma (2.9%). Although they are often life-saving drugs, they are burdened with significant percentage of adverse effects, and patients should receive regular examinations regarding the complications arising from GCS use and prophylactic activities.

In this regard, it is important to note the very small percentage of patients with severe asthma who undergo biological therapy. In the period 2010–2013, during the course of the study, only 16 severe asthma patients underwent omalizumab therapy (19%). Bearing in mind that biological therapy of severe asthma avoids the use of steroids, i.e. reduces the need for them, modern

immunological medicines, according to current standards, should be combined with the optimised treatment in these patients to a much greater extent than to date. Another contributory factor was the fact that in November 2012, the Polish Minister for Health announced a programme for the treatment of severe, allergic, IgE-dependent bronchial asthma using omalizumab, resulting in a lower number of patients treated with this drug in the centre in which the present study was carried out. Even so, this is a significant number as it demonstrates that at least 20% of patients with severe asthma turned to biological therapy within one year of the start of the programme. Such a large number of participants for the anti-IgE programme gives patients hope for a better future, i.e. a reduction of symptoms, reduced frequency of exacerbations and hospitalisation, fewer GCS doses without deterioration of disease control, improved ventilation parameters, improved asthma control and improved quality of life.

The frequency of use of systemic GCS by asthma patients was found to be 29.63%, whereas 55.10% used inhaled GCS doses lower than 1000 mcg and 36.76% higher than 1000 mcg. The frequency of use of oral (16.9%) and inhaled GCS (36.4%) was found to be much higher than in other Polish studies, as was LABA, which was reported by 68.26% of respondents in the present study and 46.8% elsewhere. In contrast, anticholinergic drug use was reported by 11.42%, which is lower than the mean value for the country as a whole (13.0%), and although no patients reported using cromones in the study, their frequency of use in Poland is around 11.7% [6].

A further problem encountered by asthma sufferers, especially the severe form, is represented by comorbidities. These may result from the presence of the shared genetic bases of many diseases and exposure to environmental factors [24]. On its own, asthma may increase the occurrence of certain disorders, such as depressive disorders, anxiety disorders and obesity, and initiate the progression of existing conditions [15,24–27]. However, our findings indicate that although rhinitis was found significantly more often in patients with asthma, regardless of the form, no difference was observed in its frequency of occurrence with regard to the severity of asthma. Epidemiological data indicates that the frequency of occurrence of allergic and non-allergic rhinitis ranges from 51 to 95% in groups of severe asthma patients [23]. In the present study, chronic rhinitis was found to occur in 52.4% of asthma patients and was predominantly treated with oral antihistamines (54.8%). In addition, although the asthma patients were also significantly more likely to suffer allergies, their symptoms did not correlate significantly with the severity of the primary disease. The prevalence of asthma was therefore higher in patients with rhinitis, irrespective of whether it was allergic or not. Rhinitis is thus an independent risk factor of asthma; however, not all patients with asthma demonstrated symptoms of rhinitis. It is important to note how few patients with severe asthma were treated by allergen immunotherapy (mild 2.9%, moderate 9.5%, severe 1.2%). Bearing in mind that asthma is mainly caused by allergies, our work highlights the problem of how rarely the examined patients were assigned therapies intended for those diagnosed with allergies.

The clinical consequences of co-occurring allergies, rhinitis and asthma include poorer disease control, impaired quality of life and a reduction in daily activities. In addition, asthma patients were found to be significantly more likely to demonstrate particularly severe gastroesophageal reflux disease (26.2%), which was treated by proton pump inhibitors in only 35.7% of cases (Table 4). This is one example of the widespread use of completely ineffective treatment for one of the most common asthma comorbidities which results in worsened disease control [28–30]. Gastroesophageal reflux disease was significantly more common in the study group than the control group, and its prevalence was slightly lower than given in literature data (40–80%) [30]. This may indicate a failure to diagnose gastroesophageal reflux disease in previous studies, especially in patients with severe asthma. Clinical studies have shown that treatment of concomitant coughing in the course of asthma and gastroesophageal reflux disease using proton pump inhibitors reduces the symptoms of regurgitation, improves ventilation parameters and reduces the need for rescue medication. No treatment can contribute to a lack of asthma control and to diagnose the “difficult to treat asthma” phenotype in this group of asthma patients [30].

Asthma is a cause of severe and irreversible disturbances in ventilation associated with permanent remodelling of the airway wall (remodelling bronchitis). Our results show that the presence of severe asthma is associated with the problem of reinforcement of the bronchial obstruction and overlaps with COPD (Table 4). This problem was found to affect up to 34.5% of patients with severe asthma. It should be noted that the frequent exacerbations experienced by patients with severe asthma contribute to impaired ventilation and accelerate the remodelling of the bronchus, which quickly leads to a respiratory disability. Lung function is hence, an important predictor and prognostic agent in this regard. Our results also reveal a statistically significant correlation between the incidence of hyperthyroidism and the incidence of asthma compared to the control group. This is a phenomenon not previously reported in scientific studies, which we believe requires further epidemiological, genetic and immunological evaluation [31–34].

The group of asthma patients demonstrated a greater likelihood of experiencing gastroesophageal reflux disease [OR = 2.01; 95% CI(1.15–3.52)] and neurological diseases [OR = 2.89; 95% CI(1.12–7.44)], as well as a lower risk of atherosclerosis [OR = 0.33; 95% CI(0.12–0.95)]. Of these, only reflux disease was found to be a significant risk factor for severe asthma [OR = 2.01; 95% CI (1.11–3.66)] in our study group (see Table 5). Although the Multi-Ethnic Study of Atherosclerosis (MESA) found that asthma was associated with increased risk of cardiovascular disease (CVD), including coronary death, myocardial infarction, angina, stroke, and death due to CVD, our results indicate a significantly lower prevalence of atherosclerosis in asthma patients compared with non-asthmatics. This may explain why systemic GCS treatment (e.g. with prednisone) reduces neointimal formation and modifies/remodels vascular inflammation. This observation has been confirmed in experimental animal models such as a rabbit model of established atherosclerosis.

As also noted in previous works, the present epidemiological study revealed no increased prevalence of comorbidity (OR) between cardiovascular diseases or immune disorders and asthma. It did however identify relationships between the occurrence of asthma and the presence of diseases of the vascular, endocrinal and neurological systems, as well as of the gastrointestinal tract. Similarly to previous studies, our results reveal no comorbid relationships between asthma and neoplastic diseases [31–39].

However, if gastroesophageal reflux disease, atherosclerosis, hypertension, ischaemic heart disease or other cardiac diseases, lipid disorders, COPD or any form of neoplastic disease does coexist

with asthma, it will significantly deteriorate the degree of asthma control. In this sense, these diseases represent important factors deteriorating the clinical course of asthma (Table 6).

The presented complex epidemiological analysis found asthma to be accompanied by extensive clinical comorbidity in the collected material. The presence of primary disease doubles the chance of the occurrence of up to three additional diseases. It contributes to manifestation of expression of various symptoms in the entire clinical picture of patients. Additional diseases accompany the multivariate and complex heterogeneous pathogenesis of asthma. Our observations are in line with international epidemiological studies which show the risk of coexisting additional diseases in asthma patients to be nearly 50% higher than in patients without asthma: this risk was 47% higher in the 18–44-year age group, and 49% higher in the 45–64-year age group [31]. Nevertheless, our findings reveal this risk on a much higher level, four times greater in fact, than reported in the above study, which was based on health administrative data on all individuals living in Ontario, Canada (population 12 million). This may be attributed to the fact that in the present study, the patients were recruited from a multidisciplinary referral centre, which collects the most seriously ill patients with multiple complications from the macro-region of Lodz, central Poland (Lodz Province, population 2.5 million).

It is worth noting that the co-occurrence of other diseases with asthma affects not only the control of respiratory diseases, but is important in planning asthma treatment, and acts as a marker of the risk of poor response to them, i.e. to treatment [30]. The co-occurrence of other diseases with asthma indicated by the present study demands the adoption of a more holistic approach of treating patients in order to improve compliance and adherence to medication and increase the degree of control of the primary disease.

Our study does have some limitations. The clinical material tested was not a random sample of patients from the general Polish population but were recruited from a centre for patients who are more seriously ill than those found in the general population. It is also difficult to compare the population of Lodz to a non-European population when considering the many other agents present in different geographical regions which may influence the course of asthma. While the presented study is associative, it does not have a clinical character. Most importantly, the study was performed in a highly-specialised referral centre, and asthma was diagnosed and treated only by specialists from the areas of Allergology and Pulmonology. Therefore, it is difficult to compare these results with those of other questionnaire-based studies performed by family doctors/basic health care providers (sensitivity of asthma diagnosis 59%) and those of non-medical personnel, or only administered as telephone surveys [6,38,39].

To summarise, other chronic states which co-occur with asthma and have considerable clinical significance, influence the effectiveness of treatment and control of asthma, as well as the quality of life of the patient, and therefore a holistic approach to treatment involving specialisations from many areas of Medicine is needed to provide therapy which is more intensive than is currently available to patients.

Conflict of interest statement

I (we) certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Contribution statement

M. Panek – study design, data interpretation, final revision of

the manuscript

Ł. Mokros – statistical analysis
T. Pietras – manuscript revision
P. Kuna – manuscript revision

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