



# Factors associated with asthma control in patients with aspirin-exacerbated respiratory disease<sup>☆</sup>

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Received 25 November 2014; accepted 27 February 2015  
Available online 10 March 2015

## KEYWORDS

Aspirin-exacerbated  
respiratory disease;  
Asthma control;  
Asthma control test;  
Asthma phenotype;  
Nonsteroidal anti-  
inflammatory drugs

## Summary

**Background:** Effective control of asthma is the primary goal of its treatment. Despite an improved understanding of asthma pathogenesis and accessibility of novel therapies, the rate of uncontrolled asthma remains high.

**Objective:** To find potential factors associated with asthma control in patients with aspirin-exacerbated respiratory disease (AERD).

**Methods:** Clinical data were collected from a specifically structured questionnaire. Demographics, a history of upper airway symptoms, asthma course, exacerbations expressed as emergency department (ED) visits/hospitalizations, and asthma treatment were considered. Spirometry, skin prick tests, total IgE concentration, and blood eosinophil count were evaluated. Asthma control was assessed through the Asthma Control Test (ACT).

**Results:** Out of 201 AERD patients, 41 (20.4%), 69 (34.3%), and 91 (45.3%) had controlled, partially controlled, and uncontrolled asthma, respectively. A multivariate ordered logistic regression analysis revealed that hospitalizations for asthma in the previous 12 months (OR 2.88; 95%CI, 1.11–7.46), ED visits for asthma throughout its duration (OR 1.05; 95%CI, 1.004–1.10), and total IgE concentration (OR 1.28; 95%CI, 1.02–1.60) were positively associated with poor asthma control, whereas FEV<sub>1</sub> values (OR 0.98; 95%CI, 0.96–0.99) and medical care at a referential specialty clinic (OR 0.50; 95%CI, 0.27–0.95) were positively associated with good asthma control.

<sup>☆</sup> Supported by the grant from Polish Ministry of Science and Higher Education and Jagiellonian University (K/ZDS/001022).

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**Conclusions:** The prevalence of uncontrolled asthma in AERD patients is high and similar to that observed in different asthmatic populations. Owing both to the specificity and complexity of the disease, AERD patients should stay under regular care of well experienced referential medical centers to ensure that this asthma phenotype is dealt with effectively.

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## Introduction

In line with the international guidelines, achievement and maintenance of asthma control are deemed to be primary goals of current management strategies [1,2]. Despite the widespread dissemination of these guidelines and improved understanding of asthma pathogenesis, asthma control remains suboptimal for many patients. Recent community-based asthma surveys revealed that approximately half of asthmatics had an inadequately controlled disease [3–8]. In the case of asthma, unlike diabetes or hypertension, a single, easily measurable marker that effectively facilitates the assessment of disease control is unavailable. Several composite assessment instruments have been developed for this task [9], with the Asthma Control Test (ACT) being only one of them [10].

Aspirin-exacerbated respiratory disease (AERD) is a distinct asthma phenotype, which is characterized by asthma, rhinosinusitis (frequently severe), recurrent nasal polyposis and precipitation of asthma attacks by ingestion of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) [11,12]. The European Network on Aspirin-induced Asthma (AIANE) study revealed that half of AERD patients had severe asthma that required chronic treatment with oral together with inhaled corticosteroids, to effectively control their symptoms [13]. In an AERD patient cohort from the United States, asthma severity was expressed by a high consumption of inhaled and systemic corticosteroids that were required to control the disease [14]. In the Epidemiology and Natural History on Asthma: Outcomes and Treatment Regimens (TENOR) study, hypersensitivity to aspirin was associated with more severe airway obstruction, more intensive health care utilization and the need for higher corticosteroid dosages compared with aspirin-tolerant asthmatics [15]. None of the above referenced studies, however, set out to examine asthma control among AERD patients.

The Cohort for Reality and Evolution of Adult Asthma in Korea (COREA) study revealed that overall asthma control, expressed as ACT scores, was comparable between AERD patients and those with good aspirin tolerance [16]. Nevertheless, the former group was characterized by significantly more frequent asthma related health care utilization. An epidemiological study, in which AERD was diagnosed based on exclusively one question, estimated that the uncontrolled asthma prevalence in this group was 26.7% [17].

The present study aimed to explore the potential factors associated with uncontrolled asthma, as estimated by the ACT, in a cohort of patients representing the AERD phenotype.

## Methods

### The subjects under study

The study embraced 201 patients (134 females) who were recruited from a consecutive patient group diagnosed with AERD at the Department of Internal Medicine, Jagiellonian University, Medical College, Krakow. AERD was diagnosed prior to the study. In the majority of patients, this was based on a typical history that was confirmed with a positive aspirin challenge. In 42 severe steroid-dependent asthmatics, the diagnosis was based exclusively on an unequivocal clinical picture and a history of asthma attacks after ingestion of aspirin or other NSAIDs. Owing both to low FEV<sub>1</sub> and the non-feasibility of reducing the oral corticosteroid dosage, they never qualified for aspirin challenge. All participants were clinically stable, had experienced no asthma exacerbations within the four weeks preceding the study and received asthma medications, as currently prescribed by their physicians. Ninety-three (46.3%) patients remained under medical care at our Department, 59 (29.3%) were treated by allergy or pulmonology specialists in the local outpatient departments, 32 (15.9%) were attended to by their general practitioners, and 17 (8.5%) remained without any medical attention. All patients gave an informed, written consent to participate in the study. The Jagiellonian University Ethics Review Committee endorsed the study protocol.

### Data collection

The patient data were collected from a specifically structured questionnaire. All study participants underwent a demographic and detailed medical history interview, including questions that specifically addressed their clinical asthma courses, upper airway symptoms, nasal polyps history, polypectomies and endoscopic sinus surgeries, allergy history, and any individually used asthma medications. Asthma-related emergency department (ED) visits and hospitalizations were estimated for the entire asthma duration and for the preceding 12 months. At least one exacerbation within the preceding year was assumed as a positive result. Intensive care unit (ICU) stays throughout the asthma duration were only categorized as present or non-present.

Asthma control was assessed through the Asthma Control Test (ACT) [10]. It was composed of five rating categories (1–5 scale) that reflected the asthma control level over the previous 4 weeks. Specific items addressed the actual impact of asthma on their daily activities, shortness of

breath episode frequency, nocturnal symptoms, rescue medication use, and overall asthma control self-assessment (Table 1). The maximum score was 25. Asthma was categorized as: 1) controlled (score: 25), 2) partially controlled (score: 20–24), and 3) uncontrolled (score: <20).

Asthma treatment with corticosteroids was divided into the following categories: 1) no corticosteroids; 2) inhaled corticosteroids at a daily dosage of  $\leq 500$   $\mu\text{g}$  of fluticasone equivalent; 3) inhaled corticosteroids at a daily dosage of  $> 500$   $\mu\text{g}$  of fluticasone equivalent; 4) oral corticosteroids combined with inhaled corticosteroids.

Spirometry (MasterScreen, Jaeger, Wurzburg, Germany) was carried out at baseline and after the administration of 4 salbutamol puffs (400  $\mu\text{g}$ ). The percent predicted FEV<sub>1</sub> values and FEV<sub>1</sub> reversibility after bronchodilator were calculated.

Atopy was assessed as at least one positive skin prick test response with 12 common aeroallergens (Allergopharma, Reinbek, Germany).

The total IgE concentration was measured with the nephelometric method using NLatex IgE mono assembly kits (Dade Behring, Newark, USA). Blood eosinophil counts were calculated in a Fuch's-Rosenthal chamber.

## Statistical analyses

Continuous variables were expressed as means and SDs or as medians with interquartile (25th–75th percentiles) ranges. Categorical variables were expressed as proportions. Differences in characteristics across the ACT groups were compared by the one-way analysis of variance with Tukey's *post hoc* comparison for continuous variables. In the cases of any violations of ANOVA model assumptions, the Kruskal-Wallis test was applied. For categorical variables the differences in the proportions between the respective ACT groups were examined using the chi-square test.

The characteristics associated with the asthma control status were determined by a multivariable ordinal logistic regression with a proportional odds model. Odds ratios (ORs) in this analysis represented the likelihood of being in the worse ACT category if a given factor was present. The regression analysis was completed in two steps. First, an unadjusted ordinal logistic regression analysis was completed to separately examine the association of the

asthma control categories within each characteristic. Second, the factors that had unadjusted ORs with an associated *p*-value  $\leq 0.20$  were chosen and included in the multivariable model. The proportional odds assumption was tested with the Brant test (parallelism of lines) as well as by performing two models of binomial logistic regression that compared each higher ACT category with its lowest counterpart. The latter model additionally confirmed the application of the ordinal logistic regression assumption.

Prior to the analysis, the IgE and blood eosinophil count data were transformed into a log<sub>2</sub> base scale for two reasons: 1) to access the values that more closely resembled the normal distribution and 2) to interpret an OR as being associated with a 2-fold increase in the predictor (doubling).

A two-sided *P* value of 0.05 was adopted as the criterion for statistical significance. All statistical analyses were completed with the aid of IBM SPSS Statistics for Windows, v. 21.0 (Armonk, NY: IBM Corp).

## Results

### The study subject characteristics

The patient characteristics, which were divided into three groups representing the respective three asthma control levels, are presented in Table 2. From among 201 patients, 41 (20.4%) had controlled asthma, 69 (34.3%) had partially controlled asthma, and 91 (45.3%) had uncontrolled asthma. In the controlled asthma group, the proportion of males was the highest, whereas the proportion of females was the lowest in comparison to the other two groups. The difference was not statistically significant at the 0.05 level, however.

The three groups did not differ with respect to age, body mass index (BMI), and blood eosinophil counts (Table 2). The groups also did not differ with respect to the proportion of patients with positive skin prick tests or the patients who reported current upper airway symptoms, a nasal polyps history, or any number of polypectomies. The uncontrolled asthma group was characterized by a longer disease duration (*p* = 0.02), the highest median total IgE concentration (*p* = 0.02) and a lower mean predicted

**Table 1** Questions and possible answers contained in the ACT.

| 1 Point                                                                                                                                                                                   | 2 Points             | 3 Points              | 4 Points             | 5 Points              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-----------------------|----------------------|-----------------------|
| In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?                                                                  |                      |                       |                      |                       |
| All of the time                                                                                                                                                                           | Most of the time     | Some of the time      | A little of the time | None of the time      |
| During the past 4 weeks, how often have you had shortness of breath?                                                                                                                      |                      |                       |                      |                       |
| More than once a day                                                                                                                                                                      | Once a day           | 3 to 6 times a week   | Once or twice a week | Not at all            |
| During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning? |                      |                       |                      |                       |
| 4 or more nights a week                                                                                                                                                                   | 2 to 3 nights a week | Once a week           | Once or twice a week | Not at all            |
| During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?                                                                         |                      |                       |                      |                       |
| 3 or more times per day                                                                                                                                                                   | 1 or 2 times per day | 2 or 3 times per week | Once a week or less  | Not at all            |
| How would you rate your asthma control during the past 4 weeks?                                                                                                                           |                      |                       |                      |                       |
| Not controlled at all                                                                                                                                                                     | Poorly controlled    | Somewhat controlled   | Well controlled      | Completely controlled |

**Table 2** The study subjects characteristics, stratified by the respective asthma control levels, and an unadjusted ordinal logistic regression analysis for the associations of the subject characteristics with the respective levels of asthma control.

| Variable                                                 | All patients<br>(n = 201) | Controlled<br>(n = 41) | Partially<br>controlled<br>(n = 69) | Uncontrolled<br>(n = 91) | p value | Ordinal<br>OR     | 95%CI      | p value |
|----------------------------------------------------------|---------------------------|------------------------|-------------------------------------|--------------------------|---------|-------------------|------------|---------|
| Male                                                     | 67 (33.3)                 | 19 (46.3)              | 20 (29.0)                           | 28 (30.8)                | 0.14    | 1.0               | 0.85–2.53  | 0.17    |
| Female, n (%)                                            | 134 (66.7)                | 22 (53.7)              | 49 (71.0)                           | 63 (69.2)                |         | 1.46              |            |         |
| Age (y), mean (SD)                                       | 49.4 (12.4)               | 50.0 (14.5)            | 46.7 (11.7)                         | 51.1 (11.8)              | 0.08    | 1.01              | 0.99–1.03  | 0.22    |
| Asthma duration (y), mean (SD)                           | 19.5 (11.1)               | 18.3 (10.4)            | 17.2 (10.8)                         | 21.8 (11.2)              | 0.02    | 1.03              | 1.004–1.05 | 0.02    |
| BMI (kg/m <sup>2</sup> ), mean (SD)                      | 26.3 (4.5)                | 25.5 (3.8)             | 26.6 (4.6)                          | 26.5 (4.7)               | 0.39    | 1.03              | 0.97–1.09  | 0.36    |
| Current upper airway symptoms <sup>a</sup> , n (%)       | 163 (81.1)                | 30 (73.2)              | 56 (81.2)                           | 77 (84.6)                | 0.30    | 1.94              | 0.98–3.87  | 0.059   |
| Nasal polyps at any time point <sup>a</sup> , n (%)      | 163 (81.1)                | 34 (82.9)              | 58 (84.1)                           | 71 (78.0)                | 0.59    | 0.75              | 0.37–1.50  | 0.413   |
| Polypectomies <sup>a</sup> , median (IQR)                | 2 (4)                     | 3 (4)                  | 2 (4)                               | 2 (3)                    | 0.15    | 0.93              | 0.88–0.99  | 0.025   |
| FEV <sub>1</sub> % predicted, mean (SD)                  | 78.7 (19.8)               | 85.6 (14.5)            | 83.5 (18.3)                         | 72.0 (21.0)              | <0.001  | 0.97              | 0.96–0.98  | <0.001  |
| ΔFEV <sub>1</sub> ≥ 12%, n (%)                           | 71 (37.4)                 | 9 (24.3)               | 20 (30.3)                           | 42 (48.3)                | 0.014   | 2.32              | 1.31–4.11  | 0.004   |
| Positive skin prick test responses, n (%)                | 105 (52.2)                | 19 (46.3)              | 36 (52.2)                           | 50 (55.0)                | 0.66    | 1.26              | 0.75–2.11  | 0.39    |
| Total IgE concentration, median (IQR)                    | 87.6 (144.5)              | 51.5 (65.6)            | 84.4 (145.8)                        | 114 (183.0)              | 0.02    | 1.26 <sup>b</sup> | 1.05–1.51  | 0.014   |
| Blood eosinophil count, median (IQR)                     | 309 (427)                 | 317 (412)              | 321 (392)                           | 295.5 (480.5)            | 0.69    | 0.90 <sup>b</sup> | 0.78–1.05  | 0.18    |
| ED visits <sup>c</sup> , median (IQR)                    | 2 (5)                     | 2 (3)                  | 2 (4)                               | 3 (6)                    | 0.03    | 1.07              | 1.02–1.12  | <0.01   |
| ED visits within the previous<br>12 months, n (%)        | 39 (19.4)                 | 3 (7.3)                | 15 (21.7)                           | 21 (23.1)                | 0.088   | 1.80              | 0.91–3.54  | 0.09    |
| Hospitalizations <sup>c</sup> , median (IQR)             | 2 (5)                     | 1 (4)                  | 1 (4)                               | 3 (7)                    | <0.001  | 1.16              | 1.06–1.26  | 0.001   |
| Hospitalizations within the<br>previous 12 months, n (%) | 30 (14.9)                 | 2 (4.9)                | 8 (11.6)                            | 20 (22.0)                | 0.02    | 2.95              | 1.32–6.61  | 0.008   |
| Hospitalizations at ICU whenever, n (%)                  | 44 (21.9)                 | 7 (17.1)               | 10 (14.5)                           | 27 (29.7)                | 0.05    | 1.84              | 0.94–3.58  | 0.075   |
| Treatment at the referential<br>specialty clinic, n (%)  | 93 (46.3)                 | 16 (53.3)              | 34 (57.6)                           | 28 (35.0)                | 0.021   | 0.49              | 0.27–0.87  | 0.014   |

BMI, body mass index; ED, emergency department; ICU, intensive care unit.

<sup>a</sup> Adjusted for upper airway symptom duration.

<sup>b</sup> For the logistic regression, which was included as logarithmically transformed log<sub>2</sub> base scale values.

<sup>c</sup> Adjusted for asthma duration.

FEV<sub>1</sub>% value ( $p < 0.001$ ). Reversible airway obstruction was also the most common in this group ( $p < 0.014$ ).

## Exacerbations

Asthma-related ED visits and hospitalizations, as recorded throughout the asthma duration, were more frequent in the uncontrolled asthma group (Table 2). As estimated by an ordinal logistic regression, any additional ED visits significantly increased the odds of worse asthma control by 7%. When a short-term assessment was considered (at least one ED visit within 12 months preceding the study), no significant differences, neither with respect to the proportion of patients across the groups, nor with regard to the impact on asthma control, were encountered. The results regarding the asthma-related hospitalizations were more consistent. Any additional hospitalization increased the proportional odds of worse asthma control by 16%; likewise, recent hospitalizations led to 3-fold worse asthma control odds. Similar results were observed for ICU hospitalizations, although this relationship was of borderline statistical significance ( $p = 0.05$ ).

## Treatment

In the controlled asthma group, the lowest percentage of patients without any corticosteroid treatment and the

highest percentage of patients treated with inhaled corticosteroids in combination with oral corticosteroids was noted (Table 3). In the uncontrolled asthma group, the patient distribution was exactly the opposite. The intensification of corticosteroid treatment had a beneficial impact on asthma control. It was particularly apparent with regard to the combined inhaled and oral corticosteroid treatment.

Overall, 46.3% of patients stayed under medical care at our Department (the referential specialty clinic). The lowest proportion of these patients was encountered in the uncontrolled asthma group ( $p = 0.021$ ) (Table 2). Treatment in the referential specialty clinic consequently diminished the likelihood of being in a worse ACT group by half.

## Factors associated with asthma control

In the unadjusted ordinal logistic regression models, nearly all of the characteristics referenced above were associated with the asthma control groups (Table 2). Uncontrolled asthma was therefore more likely to occur in patients with longer disease duration (3% per year increase), with reversible airway obstruction (by 2.3-fold) and with an increasing number of asthma-related ED visits and hospitalizations. A statistically significant effect was also reported for total IgE, as a 2-fold increase in its concentration increased the likelihood of being in the worse asthma control category by 26%. When the whole group was

**Table 3** Therapeutic asthma management with consideration of the respective asthma control levels.

| Asthma treatment, n (%) | Patient number (n = 201) | Controlled (n = 41) | Partially controlled (n = 69) | Uncontrolled (n = 91) | p value | Ordinal OR <sup>a</sup> | 95%CI     | p value |
|-------------------------|--------------------------|---------------------|-------------------------------|-----------------------|---------|-------------------------|-----------|---------|
| Without CS              | 60 (29.9)                | 3 (7.3)             | 20 (29.0)                     | 37 (40.7)             | <0.001  | 1.0                     |           |         |
| ICS ≤ 500 µg/d          | 66 (32.8)                | 16 (39.0)           | 22 (31.9)                     | 28 (30.8)             |         | 0.35                    | 0.17–0.74 | 0.006   |
| ICS > 500 µg/d          | 46 (22.9)                | 7 (17.1)            | 19 (27.5)                     | 20 (22.0)             |         | 0.40                    | 0.18–0.92 | 0.031   |
| ICS + OCS               | 29 (14.4)                | 15 (36.6)           | 8 (11.6)                      | 6 (6.6)               |         | 0.13                    | 0.04–0.41 | <0.001  |

CS, corticosteroids; ICS, inhaled corticosteroid; OCS, oral corticosteroids.

<sup>a</sup> Adjusted for sex, asthma duration, and medical treatment received at the referential specialty clinic.

stratified into patients with positive (n = 105) and negative (n = 96) skin prick test responses the odds of being in the worse asthma control category related to the increase of total IgE concentration was insignificant, irrespective of the presence (OR 1.28; 95%CI, 0.997–1.649) or absence (OR 1.23; 95%CI, 0.942–1.607) of a concomitant allergic sensitization.

Uncontrolled asthma was less likely to occur with an increasing number of polypectomies, predicted FEV<sub>1</sub>%, and treatment at the referential specialty clinic (Table 2). For instance, a 1% increase in FEV<sub>1</sub> diminished the likelihood of being in the worse asthma control group by 3%, whereas the reversible airway obstruction doubled the proportional odds of worse asthma control. The comparison between patients with airflow obstruction (FEV<sub>1</sub> ≤ 80% predicted) and without airflow obstruction (FEV<sub>1</sub> > 80% predicted) revealed that uncontrolled asthma occurred 1.9 times more frequent in the former group (59.6% vs. 31.4%, p < 0.001). The subsequent division of patients with airflow obstruction into those with and without reversible airway obstruction demonstrated that the proportion of patients with uncontrolled asthma in the former group was by 16% higher than in the latter group but the difference was not statistically significant (66.0% vs. 50.0%, p = 0.31). The mean value of FEV<sub>1</sub>% predicted in the subgroup with reversible airflow obstruction was significantly lower than in the subgroup without reversible airway obstruction (67.3 ± 15.8 vs. 84.5 ± 19.6; p < 0.001). Furthermore, in patients with airway obstruction the presence of reversibility

(ΔFEV<sub>1</sub> ≥ 12%) was observed 2.5 times more frequently than in patients with normal airflow. Additionally, negative correlation between FEV<sub>1</sub>% predicted and ΔFEV<sub>1</sub> was found for the total group (r = −0.43, p < 0.001) as well as for the subgroup with airflow obstruction (r = −0.22, p < 0.027) and with normal airflow (r = −0.35, p < 0.001).

A multivariate ordered logistic regression model, to determine the predictors, gave the estimates of the association, which is illustrated in Table 4. Following a sex and BMI adjustment, the asthma-related ED visits throughout the asthma duration, hospitalizations within the previous 12 months, total IgE concentration, FEV<sub>1</sub> values, and a stay-over in a referential specialty clinic remained independently associated with the ordered asthma control levels. The actual magnitude of these estimates was similar to the crude effects. Only the asthma duration effect lost its statistical significance.

The goodness of fit statistic values for the final model (Pearson's Chi2 = 322.88, df = 328, p = 0.57 and a similar result for the deviance chi square) indicated that both the data under study and the values estimated by the fitted model were consistent. Likewise, the assumption for the proportional odds (parallel lines test) for the full model was effectively satisfied (Chi2 = 14.25, df = 8, p = 0.08).

## Discussion

The results yielded by the present study revealed that the prevalence of uncontrolled asthma in AERD patients was high and similar to that observed in different asthmatic populations. Only 20.4% of them had the disease under control, whereas 34.3% and 45.3% had partially controlled and uncontrolled asthma, respectively. The multivariate analysis, which was based on a broad spectrum of clinical data, revealed that asthma-related ED visits throughout the asthma duration and hospitalizations within the previous 12 months, total IgE concentration, FEV<sub>1</sub> values, and medical care in a referential specialty clinic were the strongest independent determinants that were predictive of asthma control in this particular group of asthmatics.

An ACT, a brief, patient-administered questionnaire composed of five items addressing different aspects of asthma control over the past four weeks as well as providing numerical values to distinguish different levels of asthma control, was used for asthma control evaluations [9,10]. It was successfully applied in some population-based studies that were focused on this issue [3–6].

**Table 4** Factors in the multivariate ordered logistic regression analysis for the respective asthma control categories.

| Variable                                       | OR <sup>a</sup> | 95% CI     | p value |
|------------------------------------------------|-----------------|------------|---------|
| Asthma duration (y)                            | 1.01            | 0.97–1.04  | 0.77    |
| Hospitalizations within the previous 12 months | 2.88            | 1.11–7.46  | 0.029   |
| ED visits <sup>b</sup>                         | 1.05            | 1.004–1.10 | 0.03    |
| Total IgE concentration <sup>c</sup>           | 1.28            | 1.02–1.60  | 0.032   |
| FEV <sub>1</sub> (% predicted)                 | 0.98            | 0.96–0.99  | 0.004   |
| Treatment at the referential specialty clinic  | 0.50            | 0.27–0.95  | 0.034   |

<sup>a</sup> Adjusted for sex and BMI.<sup>b</sup> Number of visits throughout the asthma duration.<sup>c</sup> Logarithmically transformed into the log<sub>2</sub> base scale.

Numerous population-based studies demonstrated the uncontrolled asthma rate was high, effectively concerning 41–57% of patients [3–8]. Any comparisons between respective studies are hard to attempt, as they addressed different populations and applied different methods for the actual asthma control evaluations. On the other hand, the controlled studies demonstrated that asthma control could be achieved in a large proportion of patients taking only inhaled corticosteroids or in combination with the long-acting  $\beta_2$ -agonists [18,19].

The results of the present study are fully consistent with the above-cited population-based studies that were carried out in real-life conditions. Our study was not a population-based one because it would be very difficult to gain large enough group of AERD patients from the general population for the purposes of the study. AERD patients were picked-up from a large group of asthmatics referred to our centre and they represented an unequivocally diagnosed coherent asthma phenotype. However, the study involved a real-life setting. Patients were recruited under the condition that they had experienced no asthma exacerbations within the four weeks preceding the study; nevertheless, they continued to receive asthma medications, as prescribed by their attending physicians. Thus, they might well have been either over-treated or under-treated. Consequently, the study proved that the poor asthma control is a general problem in different asthma populations.

One of the factors that was most effectively predictive of uncontrolled asthma in the present study was any prior asthma exacerbation. The uncontrolled asthma group comprised the highest proportion of patients with the highest number of ED visits, hospitalizations, and ICU stays throughout their asthma duration. Furthermore, hospitalizations within the previous 12 months increased the risk of worse asthma control by almost 3-fold. In another study, the patients with multiple exacerbations had an increased subsequent severe exacerbation risk despite intensive chronic anti-inflammatory treatment and were characterized by longer asthma duration, persistent irreversible airflow limitation, chronic rhinosinusitis and NSAIDs hypersensitivity, compared with the stable asthmatics [20]. Kupczyk et al. [21] demonstrated that frequent exacerbators used higher corticosteroid doses, had worse asthma control, lower quality of life, more rapid decline in their FEV<sub>1</sub>/FVC ratio, and higher sputum eosinophils than the non-frequent exacerbators. In contrast to the present study, the authors of the above referenced studies assumed at least two asthma exacerbations within a previous year as the cut-off point, which set apart the frequent and non-frequent exacerbations. Similar to our study, Corrado et al. [22] revealed that the proportion of patients with at least one exacerbation within a previous year was the highest in the uncontrolled asthma group.

Rhinosinusitis, as a co-morbid condition, exerts a significant impact on asthma outcomes, irrespective of its phenotype. Vandenplas et al. [23] reported that the co-existence of rhinitis resulted in a significantly higher uncontrolled asthma risk. Ponte et al. [24] revealed that moderate to severe rhinitis was a strong predictor of any ED visits and uncontrolled asthma in the severe asthmatic group. In the present study, no differences with respect to the prevalence of current upper airway symptoms and a

nasal polyps history were encountered across the three asthma control groups. This was probably due to the fact that chronic rhinosinusitis was very common in AERD patients and that it was encountered in a majority of the study participants. Nevertheless, the current upper airway symptom incidence tended to increase the worse asthma control risk, whereas an increasing number of polypectomies and endoscopic sinus surgeries yielded quite an opposite effect. This corroborates the beneficial effects of sinus surgeries and overall pharmacological treatment of upper airways on asthma control improvement in AERD patients.

An elevated IgE concentration was established as one of the risk factors for an ICU admission in asthmatic children [25]. In the present study, the uncontrolled asthma group was discernible by the highest IgE concentration, and its increase consequently increased the likelihood of being in the worse asthma control group. It did not correspond with positive skin prick tests, which were equally distributed across the three groups. It seems quite likely that the oral corticosteroid treatment may have resulted in negative responses, at least in a certain proportion of the studied subjects. We did not measure allergen-specific IgE, which might otherwise have facilitated much deeper insight into this issue. However, when the whole group was stratified into patients with positive and negative skin prick test responses the likelihood of being in the worse asthma control category related to the increase of total IgE concentration was insignificant, irrespective of the allergic status. It may suggest that in the AERD patients the role of IgE may be independent of allergy and confirms the recent observation of six AERD patients in whom total serum IgE was elevated in the absence of any clear atopy [26]. It was hypothesized that superantigens generated by *Staphylococcus aureus* promoted a polyclonal IgE response that was reflected by an increased total IgE concentration [27]. Staphylococcal enterotoxin IgE antibodies were found to be the risk factors for asthma severity [28]. The AERD patients with higher levels of staphylococcal superantigens had higher total IgE levels, airway hyperresponsiveness, and eosinophil activation, which contributed to more severe clinical symptoms [29]. The same phenomenon may have been responsible for poor asthma control in the present study population.

In the present study, the uncontrolled asthma patients had a lower predicted FEV<sub>1</sub>% than the patients from the two other groups, and an increase of this parameter increased the odds of better asthma control. Moreover, uncontrolled asthma occurred significantly more frequent in patients with airflow obstruction than in patients with normal lung function. Treatment intensification may have improved FEV<sub>1</sub> values and asthma control as a result. Corrado et al. [22] also found that the mean predicted FEV<sub>1</sub>% values were lower in their uncontrolled asthma patients group. In an asthma patient group that was treated in a primary care facility, poor asthma control was associated with reduced FEV<sub>1</sub> values, female gender, concomitant co-morbidities and increased asthma severity [30]. The uncontrolled asthma group in the present study comprised concomitantly the highest proportion of patients with reversible airway obstruction. Such relation could be simply explained by the lowest mean value of FEV<sub>1</sub>% predicted in the uncontrolled asthma group and a wider scope of improvement after

bronchodilator than in patients with a predicted FEV<sub>1</sub>% above 80%. Actually, in patients with airflow obstruction uncontrolled asthma occurred almost two times more frequent than in patients with normal airflow and reversible airway obstruction was 2.5 more frequent. In the subgroup with airflow obstruction only, uncontrolled asthma was still more likely to occur in patients who had reversible airway obstruction than in those who had not, though the difference lost its statistical significance possibly due to the smaller sample size. Furthermore, FEV<sub>1</sub> and ΔFEV<sub>1</sub> were inversely related including similar relation in both airway obstruction strata. Taken together, the influence of reversible airway obstruction on worse asthma control cannot be ruled out. We did not assess a postbronchodilator FEV<sub>1</sub>/FVC ratio as an irreversible airway obstruction criterion. In the TENOR study, aspirin sensitivity was found to be one of the risk factors for persistent airflow limitation [31].

It seems that a potential obstacle for effectively securing asthma control in the present study may have consisted of poor adherence to the actual therapy, as the highest proportion of patients receiving no corticosteroid treatment and the lowest proportion of patients taking the inhaled corticosteroids in combination with the oral treatments was encountered in the uncontrolled asthma group. Most likely, the attending physicians undervalued asthma control in their patients, so more intensive corticosteroid treatment might well have improved this condition. The most important reasons for the non-adherence to treatment are related to limited access to health care professionals, poor patient-physician communication, low expectations, and poor access to asthma education [32]. In the present study, only half of the participants regularly visited an outpatient clinic at our Department (i.e., medical referential specialty clinic) and stayed under the medical care of physicians who were experienced in the management of AERD patients. The results proved that this type of medical care undoubtedly contributed to better asthma control as it diminished the likelihood of being in a worse asthma control group by half. It follows that AERD patients should be treated in medical centers that actually specialize in this specific asthma phenotype, as they need education and comprehensive medical care with regard to both asthma and upper airways disease.

## Conclusions

This is the first report that focused on estimating asthma control predictors in a well-defined cohort of AERD patients. The results indicate that the uncontrolled asthma prevalence in this asthma phenotype was relatively high and comparable with the results yielded by large studies that evaluated different asthmatic populations. Our findings highlight that attention should more specifically be focused on the therapeutic management of AERD patients so that they are treated in well experienced medical centers to ensure this specific asthma phenotype is dealt with effectively.

## Conflict of interest

None declared.

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