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Bronchodilator response as a marker of poor asthma control

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ABSTRACT

Background: Asthma guidelines emphasise the importance of monitoring disease control in managing asthma.
Objective: The aim of this study was to evaluate the relationship between lung function, including bronchodilator response in terms of improving in FEV_1 after administration of salbutamol, and asthma control.
Methods: 246 patients with known asthma and in regular chronic treatment according to international guidelines were consecutively enrolled in a 12 month-period. All patients were evaluated by asthma control test (ACT), spirometry and bronchodilator test with salbutamol 400 mcg.
Results: Mean ACT value was 18.8. Patients with significant bronchial reversibility had lower ACT mean values. This finding was confirmed in both patients with airway obstruction and in those with normal spirometry. There was a significant correlation between ACT values and bronchodilator response.
Conclusions: The persistence of a significant degree of bronchodilator response despite regular treatment according to guidelines was a marker of worse asthma control.
Clinical implications: Bronchodilator response, correlating with worse asthma control even in patients with normal spirometry, should be test at every visit as it may add information on asthma control.

1. Introduction

Asthma guidelines recommend to modulate the therapy according to asthma control, defined as patient's current and recent level of symptoms and functional status. Many data support the recommendation that having a high level of current control improves stability and reduces the future risk of exacerbations [1].

There are various tools for evaluating asthma control: one is to use validated questionnaires (e.g. Asthma Control Test (ACT) [2] or Asthma Control Questionnaire (ACQ) [3]), another is to evaluate symptoms and lung function as suggested by the Global Initiative for Asthma (GINA) [1].

All these tools emphasize optimal asthma control as no symptoms, undisturbed sleep, no severe exacerbations, no need of rescue medication or emergency visits, normal lung function and no limitations in daily activities. According to score obtained by each specific asthma control tool, a patient's asthma can be classified as controlled, partially controlled or uncontrolled [1–3].

Nevertheless, even among patients treated according to guidelines, control of asthma is still not reached by a great proportion of patients, ranging from 20% to 70% [4].

Abnormal lung function, both in terms of reduced FEV_1 or altered airway obstruction reversibility and/or airway hyperresponsiveness, may have an impact on asthma symptoms and it classically improves during regular treatment with inhaled corticosteroids (ICS) [5].

However, the precise relationship between symptoms and lung function is unclear and not always correlated, particularly in subjects with difficult to control asthma [6]. Therefore, also the

Abbreviations: ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; GINA, Global Initiative for Asthma; ICS, Inhaled CorticoSteroids; LLN, Lower Limit of Normal; AMP, adenosine 5′-monophosphate.

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relationship between lung function and asthma control is still not completely clear.

Moreover, it is a common finding to see patients complaining subjective poor control of asthma despite normal lung function; these patients put the clinician in front of the problem of a correct evaluation of asthma control.

The aim of this study was to evaluate the relationship between asthma control, defined according ACT, and bronchodilator response in patients with established diagnosis of bronchial asthma and in regular inhaled treatment according to international guidelines.

2. Materials and methods

2.1. Study subjects

Two-hundred and forty-six consecutive patients (145 women) older than 12 y.o., with previously diagnosed asthma according to GINA international guidelines [1] and in regular follow-up Outpatient Allergy & Asthma Clinic of AOU "Policlinico-Vittorio Emanuele" Hospital of Catania (Italy) were included into the study. Patients with airway infection in the previous 4 weeks and those with any other concomitant lung diseases were excluded from the study.

2.2. Assessment of asthma control

Asthma control was assessed in all patients by means of Asthma Control Test (ACT), which is a questionnaire consisting of five questions, each with a 5 point scale from 1 (reporting all the time or very frequent the respective symptom) to 5 (never reporting the respective symptom). Therefore, the total ACT score is between 5 and 25, with a lower score standing for poorer controlled asthma. An ACT score $\leq$19 reflects uncontrolled asthma, values between 20 and 24 partially controlled asthma, while a score of 25 means complete asthma control [2].

2.3. Lung function

All patients underwent measurements of lung function which were done with a watersealed spirometer (Biomedin, Padua, Italy). The best of three measurements was automatically chosen by software. The parameters of interest were FEV_1 and FEV_1/FVC ratio.

Bronchodilator response to 400 mcg inhaled salbutamol was also carried out by administering inhaled salbutamol via a spacer according to a standardized protocol [1].

The patients were not asked to interrupt their therapy before perfoming spirometries (apart β2-agonists 12 h before assessments) in order to know the level of asthma control during their current treatment.

2.4. Statistics

Statistical analyses were performed using SPSS 16.0 software (SPSS, Chicago, IL, USA).

The Kolmogorov–Smirnov test was used to evaluate the normality of distribution of each continuous variable, and depending on the result of this test, the Student t-test orMann–-Whitney test were used to compare variables. Categorical variables were compared with the Fisher exact test.

Two-by-two tables of bronchodilator response (in terms of FEV_1 change after salbutamol inhalation) (high/low) versus asthma control (ACT < 20/ACT $\geq$ 20) were prepared using the percentiles of FEV_1 change distribution as cut-off points. Pre-test probability of disease, sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and accuracy were calculated for each of these tables. A receiving operating characteristic curve (ROC) was plotted in order to choose the best cut-off points.

A p-value of <0.05 was considered statistically significant.

2.5. Ethics

Informed and written consent was obtained from all participating patients and the protocol was approved by the Ethics Committee "Catania 1" (approval number: 172/PO).

3. Results

Two-hundred and forty-six asthmatic patients (mean age 42.6 years, range: 12–77; 145 females) were enrolled.

Demographic data, lung function and ACT values are summarized in Table 1.

One-hundred and seventy patients (69.1%) had a basal spirometry without any formal abnormality (FEV_1 and FVC > 80% of the predicted values, and FEV_1/VC > 70%), while the rest of patients had an obstructive spirometric pattern (FEV_1/VC < 70% and FVC > 80% of the predicted value). No restrictive (FVC < 80% predicted value and FEV1 > 80% of the predicted value) or mixed spirometric patterns were observed.

ACT mean value was 18.8 (CI 95%: 18.2–19.4) and only 31 patients (12.6%) were completely controlled according to ACT (ACT = 25); eighty-five (34.6%) and 130 (52.8%) patients had respectively partially (ACT: 20–24) and non-controlled (ACT < 20) asthma.

According to GINA classification of asthma severity, 189 patients (76.8%) were mild, 45 (18.3%) moderate and 12 (4.9%) severe asthmatics. The distribution of patients according to asthma severity and ACT classes is reported in Fig. 1.

Mean ICS dose was 322 mcg budesonide equivalents. 198 (80.5%) patients were also taking a long-acting beta2-agonist in combined formulation with ICS, and 42 (17.1%) an antileukotriene agent (Montelukast 10 mg/day). No patients were treated with other anti-asthmatic drugs (i.e.: anti-IgE monoclonal antibodies, inhaled cromons etc …).

Mean post-bronchodilator change in FEV_1 was 10.3% (CI 95%: 9.0–11.6%) compared to basal values, and 80 patients (32.5%) had a significant airway response to bronchodilator (FEV_1 change > 12% and more than 200 ml in absolute value) with mean post-bronchodilator change in FEV_1 of 21.5 ± 11.2% (compared to 5.0 ± 4.3% of those without significant bronchodilator response, p < 0.001).

Patients with significant airway response to bronchodilator had

Table 1
Demographic data, lung function and ACT values of the entire study group.

	Patients (n = 246)
Age (mean age; range)	42.6 years; 12–77 years
Gender (M/F)	101/145
Smokers (mean; %)	39 (15.8%)
Body Mass Index (BMI) ± SD	26.2 ± 2.1
Time from onset of asthma (mean months ± SD)	52.3 ± 4.4
FEV1% pr. (mean% ± SD)	90.1 ± 18.4%
FEV1/VC (mean% ± SD)	77.8 ± 13.5%
Patients with normal spirometry (n; %)	170; 69.1%
Post-bronchodil. change in FEV1 (mean% ± SD)	10.3 ± 10.6%
Patients with significant FEV1 reversibility (n; %)	80; 32.5%
ACT (mean values ± SD)	18.8 ± 4.8
ACT Classes:	
<20 (uncontrolled) (n; %)	130; 52.8%
20–24 (partially controlled) (n; %)	85; 34.6%
25 (completely controlled) (n; %)	31; 12.6%

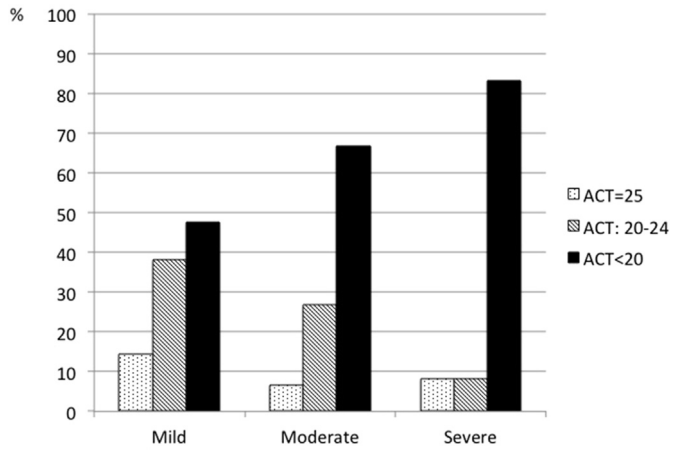

Fig. 1. Distribution of patients according to asthma severity and ACT classes.

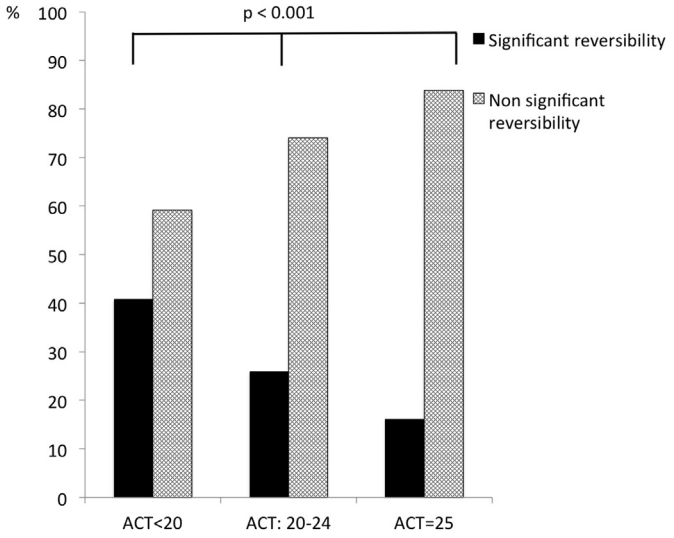

Fig. 2. Prevalence of patients with significant bronchodilator response according to ACT classes.

lower mean baseline FEV_1 percent of predicted value (78.2 ± 16.4% vs 95.7 ± 16.5%; $p < 0.001$), and lower ACT values (17.1 ± 5.0 vs 19.6 ± 4.4; $p < 0.001$) (see Table 2).

A higher prevalence of patients with significant bronchodilator response was found within patients with uncontrolled asthma (ACT < 20; 40.8%) compared to patients with partially controlled (ACT: 20–24; 25.9%) and totally controlled asthma (ACT = 25; 16,1%), $p < 0.001$ (Fig. 2).

There was a significant correlation between ACT values and post-bronchodilator FEV_1% change ($R^2 = 0.083$, $p < 0.001$) (see Fig. 3).

Patients with basal airway obstruction had lower ACT values compared with those with normal spirometry (17.3 ± 5.2 vs 19.5 ± 4.4, $p = 0.001$), but in both patients with airway obstruction and in those with normal spirometry ACT was lower in those with significant bronchial reversibility compared (16.3 ± 5.4 vs 18.7 ± 4.7, $p < 0.05$ in patients with basal airway obstruction; 18.1 ± 4.3 vs 19.8 ± 4.4, $p < 0.05$ in patients with normal basal spirometry) (see Table 3).

Table 4 lists different values of sensitivity, specificity, positive and negative predictive values, and accuracy for selected cut-off points of FEV_1 change (from −8% to 40%). The cut-off point of FEV_1 change of 8% was associated with the highest combination of specificity (56.9%) and sensitivity (59.2%), resulting in a negative predictive value (NPV) of 55.5% and in a positive predictive value (PPV) of 58.1%. The best PPV was reached for FEV_1 change of more than 20% of basal value (PPV = 81.3%), while the best NPV (100%) was obtained for FEV_1 change of more than − 8% compared with basal value. The ROC curve with bronchodilator response in terms

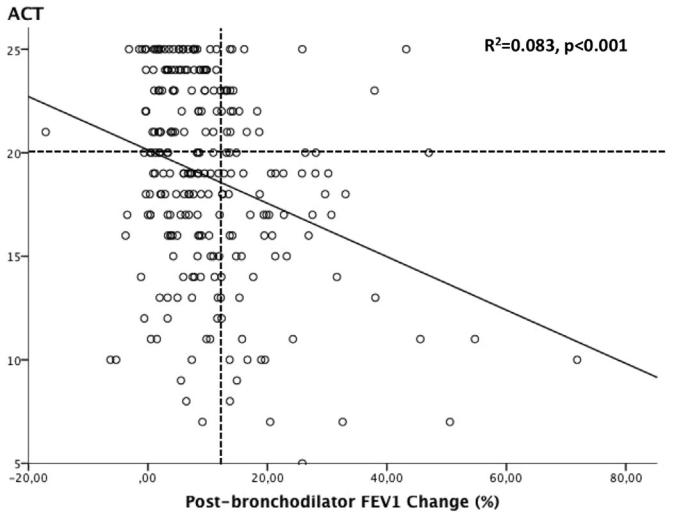

Fig. 3. Correlation between ACT values and post-bronchodilator FEV_1% change. The vertical dotted line represent the limit to distinguish significant vs non significant bronchodilator response (improvement of 12% of FEV_1), while horizontal dotted line correspond to ACT = 20, the limit to distinguish uncontrolled vs partially controlled asthma.

Table 2
Comparison between patients with significant (FEV_1 change > 12%) versus non significant airway response to bronchodilator. Significant p values are reported in bold font.

	Significant bronchodilating response (n = 80)	Non significant bronchodilating response (n = 166)	p value
Age (mean age; range)	42.2 years; 12–75 years	42.8 years; 13–77 years	0.770
Gender (M/F)	43/37	102/64	0.270
Smokers (mean; %)	16 (12.7%)	23 (13.8%)	0.216
Body Mass Index (BMI) ± SD	25.9 ± 1.8	27.5 ± 2.0	0.860
Time from onset of asthma (mean months ± SD)	51.8 ± 3.7	54.2 ± 2.9	0.770
FEV1% pr. (mean% ± SD)	78.2 ± 16.4%	95.7 ± 16.5	**<0.001**
Patients with normal spirometry. n (%)	34 (42.5%)	136 (81.9%)	**<0.001**
Post-bronchodil. change in FEV1 (mean% ± SD)	21.5 ± 11.2%	5.0 ± 4.3%	**<0.001**
ACT (mean values ± SD)	17.1 ± 5.0	19.6 ± 4.4	**<0.001**
ACT Classes:			
<20 (uncontrolled) n (%)	53 (66.2%)	77 (46.4%)	**<0.001**
20–24 (partially controlled) n (%)	22 (27.5%)	63 (37.9%)	
25 (completely controlled) n (%)	5 (6.3%)	26 (15.7%)	

Table 3
Comparison between patients with significant (FEV_1 change > 12%) versus non significant airway response to bronchodilator according to the presence of basal airway obstruction. Significant p values are reported in bold font.

	Patients with airway obstruction (n = 76)			Patients with normal spirometry (n = 170)		
	Significant bronchodilating response (n = 46)	Non significant bronchodilating response (n = 30)	p value	Significant bronchodilating response (n = 34)	Non significant bronchodilating response (n = 136)	p value
Age (mean age; range)	47.6 years; 12–75 years	53.3 years; 22–77 years	0.127	34.9 years; 12–65 years	40.5 years; 13–70 years	**<0.05**
Gender (M/F)	26/20	14/16	0.483	17/17	88/48	0.120
Smokers (mean; %)	11 (23.9%)	6 (20.0%)	0.762	5 (14.7%)	17 (12.5)	0.830
Body Mass Index (BMI) ± SD	25.0 ± 3.1	26.8 ± 3.2	0.650	26.3 ± 4.2	27.8 ± 2.1	0.760
Time from onset of asthma (mean months ± SD)	53.0 ± 2.2	54.3 ± 3.0	0.870	50.9 ± 3.5	53.8 ± 3.7	0.780
FEV1% pr. (mean% ± SD)	68.9 ± 14.2%	76.3 ± 14.6%	**<0.05**	90.6 ± 9.4%	100.8 ± 11.3%	**<0.001**
FEV1/VC (mean% ± SD)	64.4 ± 12.6%	68.2 ± 9.9%	0.156	79.5 ± 7.3%	84.6 ± 9.1%	**<0.01**
Post-bronchodil. change in FEV1 (mean% ± SD)	25.4 ± 12.9%	5.7 ± 4.5%	**<0.001**	16.5 ± 5.4%	4.8 ± 4.3%	**<0.001**
ACT (mean values ± SD)	16.3 ± 5.4	18.7 ± 4.7	**<0.05**	18.1 ± 4.3	19.8 ± 4.4	**<0.05**
ACT Classes:						
<20 (uncontrolled) n (%)	33 (71.7%)	16 (53.4%)	0.259	20 (58.8%)	60 (44.8%)	0.098
20–24 (partially controlled) n (%)	9 (19.6%)	10 (33.3%)		13 (38.2%)	53 (39.0%)	
25 (completely controlled) n (%)	4 (8.7%)	4 (13.3%)		1 (2.9%)	22 (16.2%)	

Table 4
Distribution of patients according to bronchodilator response (FEV_1 change after salbutamol inhalation compared to basal values) and its sensitivity, specificity, PPV, NPV and accuracy, according to asthma control.

Cut-off level	Controlled asthma (ACT ≥ 20)	Uncontrolled asthma (ACT < 20)	Sensitivity	Specificity	PPV	NPV	Accuracy
>−8	115	130	1.000	0.009	53.1	**100**	53.3
>−4	115	128	0.985	0.009	52.7	33.3	52.7
>0	106	122	0.938	0.086	53.5	55.6	53.7
>4	74	102	0.785	0.362	58.0	60.0	58.5
>8	50	77	**0.592**	**0.569**	60.6	55.5	**58.1**
>12	27	53	0.408	0.767	66.3	53.6	57.7
>16	10	35	0.269	0.914	77.8	52.7	57.3
>20	6	26	0.200	0.948	**81.3**	51.4	55.3
>24	6	17	0.131	0.948	73.9	49.3	51.6
>28	4	12	0.092	0.966	75.0	48.7	50.4
>32	3	7	0.054	0.974	70.0	47.9	48.8
>36	3	5	0.038	0.974	62.5	47.5	48.8
>40	2	4	0.031	0.983	66.7	47.5	48.8

of FEV_1 change compared to basal value for uncontrolled asthma (ACT < 20) is shown in Fig. 4. The area under the ROC curve was 0.63 (Fig. 4).

4. Discussion

The main finding of this study is that in asthmatic patients under regular treatment according to international guidelines, the degree of response to a short-acting β2-agonist agent (salbutamol), in terms of improvement of FEV_1, correlates with poor asthma control defined using the ACT questionnaire. This finding was confirmed not only in patients with airway obstruction at the time of evaluation, but also in those with normal spirometry. Moreover, ROC analysis results strengthen the finding of bronchodilator response as one of the determinants of asthma control.

Patients with significant bronchodilator response (FEV_1 change > 12% and more than 200 ml in absolute value) were those with lower ACT values and a worse distribution into the defined ACT classes (ACT < 20 for uncontrolled asthma; 20–24 for partially controlled asthma; 25 for completely controlled asthma) (see Table 2). This peculiar distribution of patients into ACT classes was lost when dividing patients into two subgroups (patients with and without bronchial obstruction) despite the persistence of a significant inverse correlation between ACT absolute values and bronchodilator response (see Table 3); that was probably due to the reduced number of subjects in each subgroup.

The latest international documents on asthma [1] emphasise that the main objective in managing asthma is to gain current control of the disease defined as absence of symptoms, normal lung function, no exacerbations and no limitation in daily life activities. According to this definition, one of the determinant of complete asthma control is the absence of airway obstruction, defined as FEV_1 < 80% of predicted or PEF < 80% of personal best value.

Interpretation of lung function tests is usually based on comparisons of data measured in an individual subject with reference (predicted) values based on healthy subjects with the same anthropometric (gender, age and height) and ethnic characteristics of the patient being tested. Ideally, reference values are calculated with equations derived from measurements observed in a representative sample of healthy subjects in a general population [7]. However, using percent predicted values may lead to misdiagnosis of airway function in more than 20% of patients, giving false positive results for airway obstruction or restrictive defects particularly in older men, while in younger patients this method gives a higher proportion of normal spirometry if compared to the “lower limit of normal” (LLN) method which defines abnormal any parameter which is below the 5th percentile of reference values [8,9]. Our studied population was quite young (about 42 years of mean age)

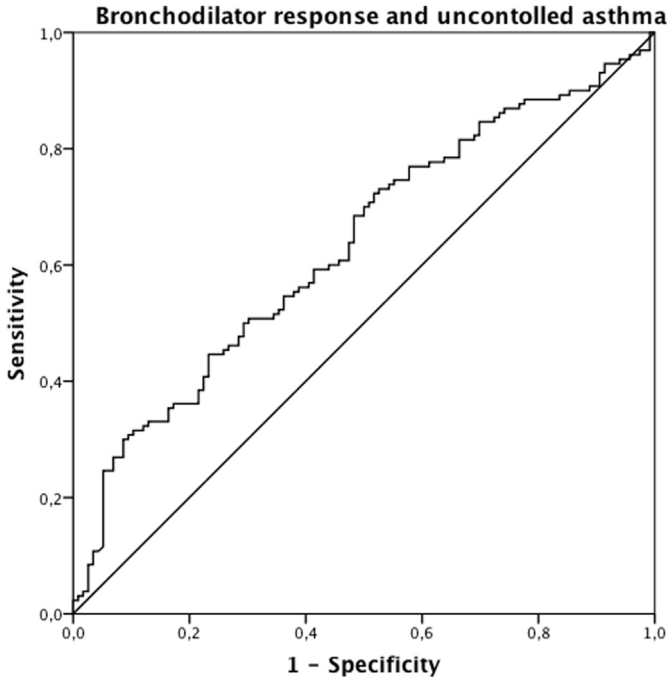

Fig. 4. Receiving operating characteristic (ROC) curve for bronchodilator response (FEV_1 percent change after salbutamol inhalation compared with basal values) and non controlled asthma (ACT < 20).

and this may explain why even patients with formally normal spirometry had a substantial bronchodilation after administration of inhaled salbutamol.

The concept of "personal best" value has been developed and used for PEF monitoring, as it has been suggested that it represents the reference value for evaluating significance changes in peak expiratory flow suggestive of airway obstruction [10]. Asthma is by definition a disease characterized by variable expiratory airflow limitation, and the concept of "personal best" as the reference value for each single patient should be applied also to spirometric parameters as FEV_1 and FEV_1/VC, at least for monitoring the patients with a confirmed diagnosis of asthma.

The post-bronchodilator spirometric values may reflect the "personal best" results for each patient. Obtaining the personal best FEV_1, and therefore a reduced airway variability, should be one of the aim of regular asthma treatment, probably being more accurate than the FEV_1 normality defined only as % predicted values.

Bronchodilator response has been reported to inversely correlate with the degree of hyperresonsiveness to adenosine 5′-monophosphate (AMP) during bronchial challenge [11], which is known to reflect the persistence of underlying bronchial inflammation in asthma [12]. Moreover, there is evidence of correlation between bronchodilator response and other markers of airway inflammation such as exhaled nitric oxide [13,14], eosinophils in bronchial biopsy specimens [15] or a combination of serum IgE, blood eosinophils and exhaled nitric oxide [16].

Under these perspectives, the correlation between degree of FEV_1 response to salbutamol and worse asthma control is not surprising, as it probably indicates that patients with a residual response to bronchodilator are undertreated and may benefit from a step-up in their treatment. A cluster analysis approach to patients with asthma demonstrated that the more severe clusters of patients were the ones with higher degree of bronchodilator response despite regular treatment [17], strengthening the validity of our results.

In large population studies, some Authors have identified higher bronchodilator reversibility as an independent risk factor for mortality [18,19]. Bronchodilator reversibility despite regular asthma treatment may therefore be considered as a determinant of increased future risk of loosing asthma control, increasing the need to step up the treatment.

Particularly interesting is that the relationship between poor control of asthma and FEV_1 response to bronchodilator is conserved also in patients with normal spirometric values according to percent of predicted values. This finding reinforce the concept that, at least in monitoring patients with an already established diagnosis of asthma, percent of predicted values method to assess normality may be not enough informative, while the post-bronchodilator FEV_1 value can give additional information about the need to increase the level of treatment.

In a previous study [20], the degree of FEV_1 response to bronchodilator was not correlated to asthma control evaluated by ACT, but anyway the Authors in their conclusions suggests that pulmonary function assessment, including airway reversibility after bronchodilator test, may represent additional measurements potentially useful in asthma management. The over-mentioned study had some limitations, first of all it was conducted in a small group of mild-to-moderate asthmatics (68 patients, 30 of which were on regular treatment while the remaining 38 were at their first evaluation and were not taking any anti-asthmatic drugs) and this may had led to underestimate the significance of the relationship between airway reversibility and asthma control.

A bigger study from Spanish Authors [21] comparing asthma control level as defined by GINA document with lung function and airway inflammatory markers, found similar results to ours, with higher airway reversibility in patients with uncontrolled compared to controlled asthma.

Moreover, there was a significant correlation between ACT values and post-bronchodilator FEV_1% change. This is not surprisingly as asthma control may depend on several parameters (i.e.: asthma phenotype, the presence of comorbidities, the level of adherence to treatment, etc …), and bronchodilator response may be one of its determinant. The relevance of this correlation is supported by the finding that only 16% of patients with complete asthma control, compared to 26% and 41% with partial and non controlled asthma respectively, had a significant response to bronchodilator (see Fig. 2).

Finally, in our study, accordingly to what reported in previous epidemiological studies [4], a high prevalence of uncontrolled asthma was observed (about 53% of patients) despite having followed international guidelines suggestions for treatment of patients with asthma. This finding should increase our attention to this big proportion of patients in order to better understand the components of worse control.

In conclusion, our study highlights that lung airway reversibility is an important component of poor asthma control both in patients with airway obstruction than in those with normal spirometry according to percent of predicted method of evaluation.

We suggest that, contrary to what reported by some international documents [22,23], bronchodilation test should be done in all patients with asthma at each visit as it may give additional information on asthma control level and it may indicate the need to achieve the personal best FEV_1 value for each single patient as reference value for normality. ACT is a good tool for assessing asthma control, but in our opinion should be evaluated together with lung function, including bronchodilation test.

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Conflict of interest

None.

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