The impact of aging on outpatients with asthma in a real-world setting

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Abstract

Background Asthma is characterized by airway inflammation and bronchial hyperreactivity. It is conceived that aging may affect asthma characteristics, but this issue is still not completely clarified in clinical practice.
Objective The present study investigated whether aging may affect some clinical and functional factors in outpatients with asthma visited in a real-world setting, such as clinical practice.
Methods Globally, 391 outpatients (163 males, median age 47 years) with asthma were consecutively evaluated. The following parameters were assessed: history, including, smoking, comorbidity, and inhaled corticosteroids (ICS) use, physical examination, body mass index (BMI), lung function, level of asthma control, asthma control test (ACT), and fractional exhaled NO (FeNO).
Results The elderly with asthma had: more frequently not controlled asthma, higher BMI, higher ICS dosages, more impaired lung function, including plethysmographic parameters, than adult asthmatics ($p<0.001$ for all, but $p=0.002$ for RV and $p=0.008$ for FRC). Elderly asthmatics were also less frequently allergic ($p<0.001$) and had less rhinitis comorbidity ($p<0.001$) and less nasal symptoms ($p<0.05$) than younger asthmatics.
Conclusions The present study conducted in a real-world setting shows that aging significantly affects asthma, mainly concerning asthma control, lung function, and steroid-sensitivity.

Key words: age, asthma, asthma control, lung function, comorbidity.

Introduction

Asthma is characterized by three main pathophysiological characteristics: airways inflammation, reversible bronchial obstruction, and bronchial hyper-reactivity (BHR) to different stimuli (1). It has been reported that rhinitis and obesity may be frequent comorbidities and can worsen asthma (2,3). Clinical and economic consequences of asthma can be significant in terms of: disability, significant costs, and death which is not rare (1,4). In particular, the elderly with asthma had the second highest rate of asthma-related hospitalizations and the highest number of asthma-related mortality (5). As the aging of the general population is a worldwide characteristic, asthma in old subjects represents an important challenge for the healthcare system.

Generally speaking, lung function aging is a process that progresses throughout the entire life since the maturity (5,6). Decline of lung function is a para-physiologic event that may be further worsted by smoking, air pollution, inflammatory disorders, and other dysfunctions (5,7). In particular, raised stiffness of the chest wall, reduced lung elastic recoil, and respiratory muscles weakening characterize the lung aging (8). The aging-dependent decline in expiratory air flow is associated with progressive reduction of small airways calibre (9). Another aspect of aging lung is the risk of small airways collapsing during tidal breathing (10). Therefore, a more severe asthma in elderly patients has been advanced (11). Indeed, it has been identified a phenotype for older asthmatics having severe symptoms and impaired lung function (12,13,14). However, the above-mentioned studies did not investigate the different role of asthma duration and aging *per se* as specific pathogenic factors. A recent study addressed this issue showing that age has a greater impact than asthma duration on risk of severe asthma, but the cut-off point was by 45 years (15). However, this study has already been conducted on a selected population of patients with severe asthma enrolled in the National Hearth Lung and Blood Institute severe asthma research program (SARP). On the basis of this background, we postulated the hypothesis that older asthmatics may show a worsening in clinical and functional outcomes than younger asthma patients. Therefore, the present study has the purpose of evaluating whether aging may have an impact on clinical and functional parameters in clinical practice, such as in outpatients with asthma observed in a real-life setting.

Materials and Methods

Patients

This observational and cross-sectional study has included 391 consecutive Italian adult patients suffering from asthma. All these outpatients, included in the study, went to an asthma clinic (Asthma Clinic, San Luigi Hospital, Orbassano, Turin, Italy) for a specialist visit between January and December 2016. The visit included history, clinical examination, body mass index (BMI) measurement, spirometry, fractional exhaled nitric oxide (FeNO) measurement, asthma control test (ACT) questionnaire, and asthma control assessment according to the Global Initiative for Asthma (GINA) document (1). All these measurements were performed as routine follow-up.

The study conformed to the local ethic criteria concerning the management of clinical data and written informed consent was obtained from each subject.

Study Design and setting

Asthma diagnosis was previously established and documented as well as rhinitis diagnosis and allergen-specific IgE positivity (i.e. sensitization). Inclusion criteria were adulthood (age >18 years) and documented asthma diagnosis, based on typical symptoms history consistent with reversibility to bronchodilators and/or bronchial hyper-responsiveness to methacholine (MCH) challenge. Exclusion criteria were history of lung disease other than asthma, coronary artery disease, congestive heart failure, or *cor pulmonale*, recent asthma exacerbation, presence of acute (in the last 4 weeks) or chronic upper and/or lower respiratory infections. Patients discontinued use of short acting and long acting bronchodilators, respectively for 4 and 12 hours before lung function measurement.

Age, gender, smoking (current, past, or never), presence of comorbidity, including allergy, rhinitis, referred asthma and/or rhinitis symptoms in the last month, inhaled corticosteroids (ICS) mean dosages and use based on beclomethasone equivalence, presence of asthma signs, mainly wheezing, at physical examination, forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, forced expiratory flow at 25-75% of vital capacity (FEF_{25-75}), residual volume (RV), total lung capacity (TLC,) RV/TLC ratio, functional residual capacity (FRC), FeNO, GINA asthma control level, ACT, were registered for all patients in the analysis.

Functional assessment

Forced expiratory volume in 1 second (FEV_1) and forced (FVC) and slow (VC) vital capacities were measured according to Miller et al. (16). Lung volumes were measured according to American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations (17) using a body plethysmograph (Vmax Encore 62, Carefusion®, Hoechberg, Germany).

Nitric oxide measurement

FENO was measured with a chemoluminescence analyzer (Eco Medics CLD88 sp, Duernten, Switzerland), the detection limit of the apparatus was 1–5 parts per billion (ppb), as required by ATS guidelines, with a resolution of 1 ppb. The analyzer was calibrated daily, using a certified NO mixture. Exhaled NO was recorded with the single-breath method according to published guidelines (18). Subjects inhaled to total lung capacity from NO-free air and exhaled a single breath (without nose clip) through a mouthpiece at a mouth pressure of 45 cm water and at an expiratory flow of 50 mL/s. Mouth pressure was displayed on a computer screen in order to maintain a steady flow for the patients. The measurement was rejected if a stable flow was not maintained for at least 6 s of exhalation. Nitric oxide was measured at the plateau and expressed in ppb.

Asthma control level

Asthma control level was assessed according to the GINA guidelines and patients were classified as having: controlled, partly controlled or uncontrolled asthma (1).

Asthma Control Test

ACT questionnaire consisted of 5 questions with 5 possible answers, exploring the patient's perception of his/her asthma control (19). The result could range between 0 and 25, where 25 was the optimal asthma control.

Allergy

Allergy was considered if there was a documented sensitization, assessed by skin prick test and/or measurement on serum, and the demonstration of a cause/effect relationship between exposure to sensitizing allergen and symptom occurrence.

Rhinitis

Rhinitis was considered if there was a history of typical nasal symptoms, such itching, sneezing, watery rhinorrhoea, and nasal obstruction. If the symptom occurrence was consistent with the exposure to sensitizing allergen the diagnosis of allergic rhinitis was made.

Statistical analysis

The patients were subdivided in 3 groups according to their age: 18-40 years (young adults), 41-64 years (adults), and ≥ 65 years (elderlies) as previously defined (20). The demographic and clinical features of the patients are expressed as mean ± standard deviation, median (25th – 75th percentiles, such as interquartile ranges-IQR), and frequencies (%). Chi square test was performed to determine any association between age class and clinical categorical variables. The strength of any significant relationship was indicated by the odds ratio (OR) with 95% confidence interval (CI). One way ANOVA, or the non-parametric Kruskal Wallis test when appropriate, were performed to compare the continuous data between age classes. If necessary, a Bonferroni or a Conover-Inman post hoc tests were used for pairwise comparison. Test of Spearman was used for evaluating relationships between age (evaluated as continuous variable) and clinical and functional variables. A $p < 0.05$ was considered statistically significant.

Statistical analysis was computed using Statistical Package for Social Science (SPSS version 20, IBM, USA) and MedCalc v12.

Results

Table 1 shows the clinical and functional characteristics of the whole population. All individuals were Caucasians. The median age was 47.0 years (IQR: 35-61). Elderly asthmatics, such as aging more than 65 years, were about 25% of the sample. Males were 41.7% and the mean BMI was 25.4. Most of patients were allergic (about 80%), most of them were poly-sensitized. Rhinitis comorbidity was very common: 89.8%. Referred symptoms for asthma and rhinitis were frequent: 65.5% and 75.2% respectively. The presence of asthma signs at clinical examination was 12.5%. Lung function values are reported in detail. Mean FeNO value was 30.92 ppb. ACT mean value was 20.17. About 40% of patients had good asthma control, whereas only 11.5% had uncontrolled asthma. About 90% of patients were treated with inhaled corticosteroids and the mean dosage of beclomethasone bioequivalence was 390 mcg/daily. In addition, 56.3% of patients never smoked, 35.8% were past smoker, and 8% were current smoker. Considering a possible association between smoking and the evaluated variables, there was no significant association except a trend for BMI and FeNO (p=0.053 and 0.051 respectively).

Comparison between age subgroups showed that for all clinical and functional variables analysed, but not for FeNO and TLC, there were statistical significant differences concerning older patients (Table 2). In addition, all the asthmatics showed a lower frequency of allergy (Fig 1A), a higher frequency of partly controlled asthma (Fig 1B), a BMI higher than the other two groups (Fig 1C), and higher ICS dosages (Fig 1D). Lung function assessment revealed that there were significant differences concerning all parameters, but not for TLC (Table 2 and Fig 2). ICS dosages and measurements of lung function (in particular RV, RV/TLC, and FRC), progressively increased with increasing mean age of the patients, with statistically significant differences between the age groups ($p<0.001$). As regard to spirometric parameters such as FVC % of predicted, FEV_1 % of predicted, FEV_1/FVC, and FEF_{25-75} % of predicted, however, elderly asthmatics always showed significantly lower values compared to younger subjects. Statistically significant differences in FEV_1/FVC and FEF_{25-75} % of predicted were observed also between old asthmatics and the other two groups. On the contrary, FeNO values and ACT scores did not differ among subgroups (Table 2).

Adult asthmatics had three times more likely to have allergy than old asthmatics (OR: 3.14; IC 95%: 1.76 – 5.59; p<0.001); and the probability, for young adult asthmatics of having allergy was eight times greater than old asthmatics (OR: 8.28; IC 95%: 3.98 – 17.23; p<0.001) as reported in Table 3. Similarly, rhinitis comorbidity and referred nasal symptoms were more likely in young adults and adults in comparison with elderly patients (Table 3).

In addition, a statistically significant difference has been found between adult and old asthmatics who controlled asthma only partially or completely (Table 3). Finally, age was analysed as a continuous variable and relationships were calculated between age and clinical and functional variables. Findings are shown in Table 4. A strongly positive relationship was demonstrated between age and RV/TLC (r= 0.77); moderately positive relationship between age and BMI (r= 0.43); moderately negative relationship between age and FEV_1 (r= 0.43), FEV_1/FVC (r= 0.5), FEF_{25-75} (r= 0.48).

Discussion

It is well known that lung function declines over time and aging is associated with increased chest stiffness, reduced elastic lung recoil, and weaker respiratory muscles. However, there is poor knowledge of aging impact on asthma in the daily clinical practice. The present real-world study demonstrated that the elderly with asthma had less frequently controlled asthma, higher BMI, higher ICS dosages, more impaired lung function, including plethysmographic parameters, than younger adult asthmatics as well as elderly asthmatics had less frequently allergy and rhinitis comorbidity and less referred nasal symptoms.

In addition, there was a strongly positive relationship between age, as continuous variable, and RV/TLC as a consequence of aging of lung function. Moreover, there was a moderately positive relationship between age and BMI as expected: in fact, it is well known that adiposity increases over time. On the contrary, there were moderately negative relationships between age and FEV_1, FEV_1/FVC, and FEF_{25-75} so confirming the impact of age on bronchial obstruction as demonstrated by other analysis. Instead, smoking did not significantly affect the considered variables.

These findings are basically consistent with some previous reports on asthma in the elderly (11-15) which showed the more severe asthma during aging. However, our study investigated the grade of asthma control and included plethysmography in a real-life setting, i.e. outpatient clinic. So, the outcomes are more representative of the daily clinical practice as the large trials are usually based on selected patients populations that cannot fully reflect the real asthma patients characteristics.

The present study highlighted the concept that older asthmatics have more rarely well controlled asthma. This fact might depend on different factors, including impaired lung function, adiposity, non-eosinophilic bronchial inflammation, and consequently steroidal resistance.

In particular, the current findings clearly showed, and confirmed, worsening of lung function, mainly concerning FEV_1, FVC, and RV. Thus, aging in asthma might mean greater limitation of air flows and air trapping (RV) probably because of diminished elastic recoil. This fact might be associated with a predominant neutrophilic bronchial inflammation as recently reported (21). This hypothesis is indirectly confirmed in our patients by lower FeNO values and lower allergy prevalence. This issue

might be associated with the reported steroidal resistance. In this regard, the present study showed that older asthmatics use higher ICS dosages. This outcome could depend on different pathways. First, immune system is characterized by a diminished function as a consequence of imbalance of cellular pattern and cytokine profile (22). The elderly usually shows reduced lymphocytes and increased neutrophils (22,23). FeNO, a surrogate biomarker for type2 airway inflammation, trend to diminish in elderly asthmatics (23,24). Consistently, atopy inversely correlates with age and it could be speculated that airway neutrophilia may be sustained by a type1 and type3 immune response (25,26). In particular, Th17 polarization could identify asthmatics with a peculiar phenotype: the frequent exacerbators as recently reported (27). In addition, aging is characterized by a cytokine profile characterized by predominance of IL-1, IL-6, and TNF-α: pro-inflammatory cytokines. This pattern maintains a chronic low-grade inflammation: the so called “inflammaging” (24).

Another pathogenic factor may be adiposity. In fact, it is well known that there is a close link between asthma and obesity (28,29). Very recently, it has been reported that obese (and overweight) asthmatics have more impaired lung function than normo-weight ones (30).

On the other hand, the outcomes of the current study are partially conflicting with a previous study that reported a strong association with rhinitis in elderly asthmatics (31). However, that study was conducted only on aged subjects. Another Italian study reported inconsistent data about the rate of uncontrolled asthma in elderly patients: on 350 patients about 1/3 had uncontrolled asthma, but also this study had no control groups (32). A Polish study reported very high rate of elderly asthmatics with uncontrolled asthma, but the authors did not demonstrate an association with comorbidities, and in addition observed that concomitant medications can significantly affect asthma control (33).

Recent reviews on the evaluation and management of asthma in the elderly pointed out some relevant peculiarities: particularly functional and immunological changes associated with aging significantly affect the presentation of asthma (34-37).

Moreover, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study demonstrated that older (>65 years) asthmatics had significantly lower lung function, less nasal and ocular symptoms, lower health care use, greater use of ICSs, and fewer asthma control than younger asthmatics (38). Accordingly, the TENOR study further showed that very poorly

controlled asthma was strongly predictive of future asthma exacerbations (38). A more recent TENOR updating reinforced these concepts underlying the importance of the difference in management between allergists and pulmonologists, mainly concerning older subjects (39).

The present study has some relevant limitation: it was cross-sectional, no biomarkers were measured, asthma duration, cognitive function, frailty, recent exacerbations, and adherence to treatment were not considered, and the number of patients was relatively limited. In particular, cognitive function, other comorbidities, and general frailty may significantly affect an adequate medication consumption as well as inhaler technique that may impair compliance and adherence to treatments (40,41). These issues deserve careful attention in the management of elderly asthmatics, as it is necessary more time to explain medication use and asthma education in elderly people than younger. All these aspects may significantly and negatively influence the control of asthma in elderly asthmatics. Moreover, the current study was conducted in a specific group of subjects, i.e. outpatients visited at an Asthma Clinic, therefore the outcomes could not be generalized, so further studies should be performed to answer to these unmet questions.

On the basis of these concepts, it is conceivable that asthma in the elderly has various characteristics, including common comorbidities, cognitive impairment, reduced immune response, chronic low-grade inflammation, steroid-resistance, polypharmacy which could affect the control of asthma and lung function. Recently, it has been thereby proposed that ageing could also define a distinct asthma phenotype with impact on diagnosis and management (36). Therefore, there is the need to use a multidisciplinary approach able to consider in holistic fashion physical aspects, including assessment of lung function, airway inflammation, comorbidity, current polypharmacy, cognitive function, social-economic situation, and psychological issues. In this regard, it has been recently reported that anxiety and depression may affect asthma control, even though age minimally affects this aspect in that cohort (42). Another relevant point, raised by TENOR study, is that elderly asthmatics perceive a poor communication with physicians. So, in managing elderly patients with asthma there is the need to adequately consider a good communication between patient and doctor, provide a clear action plan, including appropriate use of ICSs, correct inhaler technique, use of objective measure of asthma

control, and adherence to prescribed medication regimens. In other words, to spend time for educating old asthmatics.

In conclusion, the present study conducted in a clinical practice scenario shows that the elderly with asthma have rarely controlled asthma, more frequently impaired lung function, higher BMI, higher ICS dosages, and less frequently nasal problems than adult asthmatics.

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Figures legends

Figure 1: A=frequency of presence or absence of allergy; B= frequency of well controlled, partly controlled, and uncontrolled asthma; C= median, IQR, and SD of BMI; D= median, IQR, SD of ICS-dosages. All parameters are evaluated in the 3 sub-groups of age.

Figure 2: A= median, IQR, and SD of FVC expressed as % of predicted; B= median, IQR, and SD of FEV_1 expressed as % of predicted; C= median, IQR, and SD of FEV_1/FVC; D= median, IQR, and SD of FEF_{25-75} expressed as % of predicted. All parameters are evaluated in the 3 sub-groups of age.

Age (yrs)		47.32±16.31 47.00 [35.00 – 61.00]
Age classes	**18-40**	142 (36.3)
	41-64	149 (38.1)
	65-85	100 (25.6)
Males, n (%)		163 (41.7)
BMI		25.43±4.98 25.00 [22.00 -28.00]
Allergy, n (%)		312 (79.8)
Polysensitization, n (%)		228/312 (73.1)
Rhinitis comorbidity, n (%)		351 (89.8)
Asthma symptoms, n (%)		256 (65.5)
Rhinitis symptoms, n (%)		294 (75.2)
Asthma signs, n (%)		49 (12.5)
FVC % of predicted		100.06±18.19 100 [89.00 – 110.00]
FEV_1 % of predicted		88.56±20.91 90.50 [77.35 – 102.50]
FEV_1/FVC		74.79±13.13 83.00 [77.00 – 90.00]
FEF_{25-75} % of predicted		63.75±30.73 63.00 [40.60 – 87.00]
RV % of predicted		133.16±42.76 126.00 [101.00 – 155.50]
TLC % of predicted		110.82±18.49 109.00 [102.00 -120.00]
RV/TLC		43.11±13.01 42.00 [34.00 – 53.00]
FRC % of predicted		117.53±31.16 110.00 [96.75 – 137.00]
FeNO (ppb)		30.92±25.13 22.00 [13.50 – 40.00]
Asthma Control Test (ACT)		20.17±4.34 21.00 [17.00 – 24.00]
Control of the asthma, n (%)	**Not controlled**	11.5%
	Partly controlled	45.5%
	Controlled	41.2%
ICS dosages (mcg) (N=186)		390.32±311.50 250.00 [200.00 – 500.00]
ICS use	**None**	10.2%
	Low dose	62.9%
	High dose	26.9%

Table 1. Demographic and clinical characteristics (N = 391). Values are expressed as mean ± standard deviation, median (25th – 75th), frequency (%). BMI (Body Mass Index); ICS (Inhaled CoricoSteroids); for lung function variables see the text.

	Age: 18-40 yrs	Age: 41-64 yrs	Age: 65-85 yrs	p value	Post hoc analysis
BMI	22.10 (20.00 – 25.00)	24.86 (22.13 – 27.91)	27.00 (25.00 – 30.00)	<0.001*	<0.001 (18-40 vs 41-60) <0.001 (18-40vs 65-85) <0.001 (41-64vs 65-85)
FVC % of predicted	100.88±14.69	103.75±17.40	93.32±21.81	<0.001*	0.004 (18-40 vs 65-85) <0.001 (41-64vs 65-85)
FEV_1 % of predicted	95.00 (86.00 - 105.00)	92.50 (80.00 - 103.00)	78.00 (54.00 - 99.00)	<0.001*	<0.001 (18-40vs 65-85) <0.001 (41-64vs 65-85)
FEV_1/FVC	80.91±11.36	74.32±10.85	66.84±14.23	<0.001*	<0.001 (18-40 vs 41-60) <0.001 (18-40vs 65-85) <0.001 (41-64vs 65-85)
FEF_{25-75} % of predicted	77.50 (57.00 - 96.00)	63.00 (44.00 - 87.00)	36.70 (19.00 - 57.00)	<0.001*	<0.001 (18-40 vs 41-60) <0.001 (18-40vs 65-85) <0.001 (41-64vs 65-85)
FeNO	26.00 (15.40 - 45.00)	21.75 (13.50 - 40.00)	19.75 (12.80 - 34.00)	0.146	
Asthma Control Test (ACT)	21.00 (18.00 - 24.00)	22.00 (17.00 - 24.50)	20.00 (16.00 - 22.50)	0.051	
ICS dosages (mcg)	200.00 (0.00 - 250.00)	250.00 (200.00 - 400.00)	400.00 (250.00 - 600.00)	<0.001*	<0.001 (18-40vs 65-85) <0.001 (41-64vs 65-85)
RV	100.50 (87.50 - 138.00)	125.00 (102.50 - 148.50)	141.00 (116.00 - 165.00)	0.002*	<0.001 (18-40vs 65-85)
RV/TLC	30.12±8.62	38.75±10.28	53.57±8.51	<0.001*	<0.001 (18-40 vs 41-60) <0.001 (18-40vs 65-85) <0.001 (41-64vs 65-85)
FRC	107.50 (92.00 - 117.00)	105.00 (92.00 - 133.00)	124.50 (104.50 -145.00)	0.008*	0.009 (18-40vs 65-85) 0.009 (41-64vs 65-85)
TLC	107.00 (101.00 -115.50)	110.00 (104.00 - 117.00)	112.00 (102.00 - 125.00)	0.437	

Table 2. Differences in clinical variables between age class of patients. *Values are expressed as mean ± standard deviation or median (25^{th} – 75^{th}).* ***BMI (Body Mass Index); ICS (Inhaled CoricoSteroids); for lung function variables see the text.***

		Age: 18-40 yrs	Age: 41-64 yrs	Age: 65-85 yrs	p value
Allergy	**No**	11 (7.7)	27 (18.1)	41 (41.0)	<0.001*
	Yes	131 (92.3)	122 (81.9)	59 (59.0)	
	OR [95%IC], p value	*8.28 [3.98 – 17.23], <0.001**	*3.14 [1.76 – 5.59], <0.001**	*Ref.*	
Rhinitis comorbidity	**No**	6 (4.2)	11 (7.4)	23 (23.0)	<0.001*
	Yes	136 (95.8)	138 (92.6)	77 (77.0)	
	OR [95%IC], p value	*6.77 [2.64 – 17.35], 0.001**	*3.75 [1.73 – 8.10], 0.001**	*Ref.*	
Rhinitis symptoms	**No**	27 (19.0)	36 (24.3)	33 (33.0)	0.045*
	Yes	115 (81.0)	112 (75.7)	67 (67.0)	
	OR [95%IC], p value	*2.10 [1.16 – 3.79], 0.014**	*1.53 [0.87 – 2.69], 0.136*	*Ref.*	
Asthma signs	**No**	121 (86.4)	133 (89.9)	85 (85.0)	0.48
	Yes	19 (13.6)	15 (10.1)	15 (15.0)	
Asthma symptoms	**No**	40 (28.2)	54 (36.5)	40 (40.0)	0.13
	Yes	102 (71.8)	94 (63.5)	60 (60.0)	
Control of the asthma, n (%)	**Not controlled**	15 (10.9)	21 (14.2)	9 (9.1)	0.001*
	Partly controlled	56 (40.9)	58 (39.2)	64 (64.6)	
	OR [95%IC], p value	*0.53 [0.21 – 1.29], 0.16*	*0.39 [0.17 – 0.92], 0.031**	*Ref.*	
	Controlled	66 (48.2)	69 (46.6)	26 (26.3)	
	OR [95%IC], p value	*1.52 [0.59 – 3.91], 0.38*	*1.14 [0.46 – 2.80], 0.78*		

Table 3. Relationship between age class of patients and clinical variables. Values are expressed as frequencies (percentage)

		Age (years)	Correlation grade
FVC	Rho of Spearman	-0.136**	*Very weakly negative*
	p value	0.008	
	N	385	
FEV_1	Rho of Spearman	-0.285**	*Weakly negative*
	p value	0.000	
	N	385	
FEV_1/FVC	Rho of Spearman	-0.499**	*Moderaelye negative*
	p value	0.000	
	N	385	
FEF_{25-75}	Rho of Spearman	-0.477**	*Moderately negative*
	p value	0.000	
	N	349	
FeNO	Rho of Spearman	-0.095	*No correlation*
	p value	0.075	
	N	351	
BMI	Rho of Spearman	0.428**	*Moderately positive*
	p value	0.000	
	N	279	
RV/TLC	Rho of Spearman	0.766**	*Strongly positive*
	p value	0.000	
	N	139	

Table 4. Relationship between age (evaluated as continuous variable) and clinical variables.