Original Article

Asthma Control Test and Correlation with Spirometry and Inflammatory Markers in Asthma Patients at a Tertiary Care Centre in India

Mohammed Noufal Poongadan[1], Nitesh Gupta[2] and Raj Kumar[1]

Department of Respiratory Allergy and Applied Immunology, Vallabhbhai Patel Chest Institute[1], University of Delhi and Department of Pulmonary Medicine, Lady Hardinge Medical College and SSK Hospital[2], Delhi, India

Abstract

Background. Asthma control test (ACT) is a simple, quick and accurate tool to assess asthma control. The present study was designed to investigate the correlation between, ACT, spirometry variables and markers of airway inflammation.

Methods. Seventy-five patients with bronchial asthma underwent baseline spirometry, fractional exhaled nitric oxide (FeNO), serum total immunoglobulin E (TIgE), high-sensitivity C-reactive protein (hs-CRP) and interleukin (IL)-6, IL-10 and IL-13 measurements. After four weeks, patients were followed up with the same set of investigations. ACT questionnaire was completed without any directions.

Results. Of 75 patients, bronchial asthma was controlled poorly in 18, well in 35 and totally controlled in 22. The forced expiratory volume in one second (FEV_1) (%) at the second visit was lowest in the poorly control group (76.94±14.20 *versus* 84.06±11.95 *versus* 91.50±10.66; $p<0.002$). The ratio of FEV_1 to forced vital capacity (FVC) at the second visit showed lowest values (71.99±10.59 *versus* 77.70±9.05 *versus* 85.77±8.37; $p<0.001$) in patients with poorly control asthma. Notably, the change in FeNO, TIgE and IL-6 levels in two visits reached significant levels ($p<0.05$). Using the step-wise method for regression analysis, ΔFeNO, FEV_1/FVC and ΔTIgE level explain a substantial amount of the variance in the ACT score ($F[1, 71] = 33.70$, $p<0.001$, $R^2 = 0.58$, $R^2_{Adjusted} = 0.57$). The negative correlation of ΔFeNO and ΔTIgE and positive correlation of FEV_1/FVC at the second visit with statistical significance at $p<0.001$.

Conclusion. The present study emphasises on combined approach including clinical features (ACT), spirometry variable (FEV_1/FVC) and airway inflammatory markers (FeNO) for documenting the precise control of asthma at the follow-up visit. **[Indian J Chest Dis Allied Sci 2018;60:239-244]**

Key words: Asthma, FeNO, Lung function, Allergic sensitisation.

Introduction

Bronchial asthma is a heterogeneous disease, characterised by chronic airway inflammation and chronic respiratory illness affecting 1%–18% of the population in different countries.[1] The prevalence of asthma in Indian adults has varied from 1%–11% while in children it ranged from 2.3%–11.9%.[2] Current guidelines suggest that the primary goal of asthma treatment should to achieve good symptom control, and to minimise future risk of exacerbations, fixed airflow limitation and side effects of the treatment.[1]

Asthma is a chronic inflammatory disease and association of uncontrolled asthma with increased airway inflammation is reflected by increased exhaled NO levels.[3] Also, higher prevalence of uncontrolled asthma has been observed in patients with increased immunoglobulin E (IgE) than in those with decreased or unchanged IgE.[4] Interleukin (IL)-10, an anti-inflammatory cytokine, is deficient in asthma patients.[5] On the contrary, IL-13, a pleiotropic TH2 cytokine, that has been shown to be central to the pathogenesis of asthma.[6] Asthmatic patients have increased levels of IL-6, a pro-inflammatory cytokine.[7] There exist a strong association between high-sensitivity C-reactive protein (hs-CRP) values and respiratory symptoms, such as wheeze, breathlessness after exertion, and nocturnal cough.[8]

[Received: October 25, 2017; accepted after revision: March 26, 2018]

Correspondence and reprint requests: Dr Raj Kumar, Professor and Head, Department, Respiratory Allergy and Applied Immunology, and Head, National Centre of Respiratory Allergy, Asthma and Immunology, V.P. Chest Institute, University of Delhi, Delhi–110 007, India; E-mail: rajkumarvpci@gmail.com

The Asthma Control Test (ACT) has been shown to have reliable internal consistency, validity and responsiveness. It is a simple, quick and accurate tool for assessing asthma control and can easily be incorporated into the routine assessment of patients with asthma. Thus, enabling health-care professionals to more quickly identify patients, whose asthma control can be improved, enabling changes to their management to be made, and thereby, improve outcomes.[9] Several studies have put on view a significant correlation between ACT score and clinical, functional, and biological markers of asthma.[10-12] On the contrary, studies[13-15] have shown a weak correlation of ACT to pulmonary function and biomarkers of airway inflammation. There is a paucity of data regarding the correlation of ACT scores with functional and biological parameters from India. Hence, the present study was undertaken to investigate the relationship if any, between the ACT score, spirometry, and inflammatory variables.

Material and Methods

All patients gave a written informed consent to take part in the study. The Institutional Ethics Committee approved the study protocol. Patients (n=75) newly diagnosed to have bronchial asthma between 2014-15 were prospectively studied; all received treatment was as per Global Initiative for Asthma (GINA) guidelines.[1] All patients underwent baseline spirometry, fractional exhaled nitric oxide (FeNO) test, and serum samples were obtained for measuring serum total IgE (TIgE), hs-CRP and interleukin (IL)-6, IL-10 and IL-13. After four weeks, patients were followed up for spirometry and FeNO level measurements. The blood samples were redrawn for the assessment of TIgE, hs-CRP and IL-6, IL-10 and IL-13. Furthermore, patients received a short explanation of ACT, and they were requested to fill the ACT questionnaire without any directions.

Pulmonary function testing

Pulmonary function testing (PFT) was performed on a dry, rolling-seal spirometer of the Benchmark model lung function machine (P.K. Morgan, Kent, UK). Maximal expiratory flow volume curves were obtained as per the American Thoracic Society (ATS) recommendations.[16] Dynamic lung volumes, like forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured as per guidelines.[16] The bronchodilator testing was done 20 minutes after 400mg inhaled salbutamol, according to ATS recommendations.[16]

Measurement of exhaled nitric oxide

The measurements of FeNO and nasal nitric oxide were performed using NIOX chemiluminescence analyser (Aerocrine AB, Solna, Sweden) by the 2005 ATS/European Respiratory Society (ERS) recommendations.[17] The patient has inserted the mouth-piece, inhaled through the mouth to total lung capacity (TLC) and then immediately exhaled at a constant flow rate (50 mL/s) to residual volume without breath holding. The duration of exhalation had to be sufficient (>4 seconds in subjects <12 years and >6 seconds in subjects >12 years). Repeated and reproducible exhalations were performed to obtain at least two NO plateau values that agreed within 10% of each other. The mean level of two reproducible recordings used as the result value.

TIgE, hs-CRP, and interleukin measurement

Serum TIgE was estimated by enzyme-linked immunosorbent assay (ELISA) method using MINILYSER - TECAN, Austria, Calbiotech kit as per manufacturer's instructions. Similarly, hs-CRP levels were assessed by ELISA method using the ACCUBIND automated analyser. Serum IL-6, IL-10, IL-13 were measured using commercially available RayBio Human ELISA Kits.

Asthma Control Test

All 75 patients were evaluated after one month of treatment using the ACT, a patient-completed questionnaire of five items with five response options investigating limitations at work or school due to asthma, the presence of day-time or night-time symptoms, the use of rescue medications, and the subjective perception of the level of asthma control during the previous four weeks. Depending on ACT score, the patients were categorised into three groups, total control (ACT = 25), well controlled (ACT = 20-24), and poorly controlled (ACT ≤19).[2]

Statistical Analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS, version 22.0) for Windows (SPSS, Chicago, IL, USA). Data examined for distribution and homogeneity of variances was checked before applying parametric tests. The comparison among three ACT groups was made using analysis of variance (ANOVA) (normal distribution data) and Kruskal-Wallis test (non-normal distribution data). The relationship between ACT score and other variables performed using the model of linear regression (normal distribution) and or Spearman's rank correlation (non-normally distributed data). The multiple regression analysis executed to identify the independent variable affecting the ACT score. Statistical significance set at 5% level ($p<0.05$).

Results

The study group comprised of 75 subjects (43 males, mean age 22.5±8.2 years). The description of various spirometry and inflammatory markers values at first visit is shown in table 1. Four weeks later at second visit, after initiation of treatment, patients were categorised into three sub-groups according to ACT score. Bronchial asthma was controlled poorly in 18, well in 35 and totally in 22 (Table 2). Spirometry performance by the patients in the second visit categorised according to ACT score, is outlined in table 3.

Table 1. Demographic, spirometry and inflammatory characteristics of the patients (n=75) with bronchial asthma at first visit

Age (years) (mean±SD)	22.5±8.2
Sex: Male/Female	43/32
BMI (Kg/m^2) (mean±SD)	23.0±3.6
Kuppuswamy score	3. 6±1.0
FEV_1 (L) (mean±SD)	2.48±0.68
FEV_1 (%) (mean±SD)	78.81±1.62
FVC (L) (mean±SD)	3.24±0.93
FVC (%) (mean±SD)	91.27±1.20
FEV_1/FVC (mean±SD)	76.06±1.16
FeNO	36.2±29.8
hs-CRP	12.9±1.5
Serum Total IgE	495.2±54.2
IL-10	24.2±2.4
IL-6	23.7±3.1
IL-13	18.6±2.2

Definition of abbreviations: SD=Standard deviation; BMI=Body mass index; FEV_1=Forced expiratory volume in one second; FVC=Forced vital capacity; FeNO=Fraction of exhaled nitric oxide; hs-CRP=high-sensitivity C-reactive protein; IgE=Immunoglobulin E; IL=Interleukin

Table 2. Demographic distribution of asthmatic patients (n=75) on the basis of Asthma Control Test score

Variable	Poor Control (ACT ≤19) (n=18)	Well Control (ACT 24-20) (n=35)	Total Control (ACT 25) (n=22)	p-value
ACT score (mean±SD)	17.67±1.28	22.63±1.35	25	0.0001
Age (years) (mean±SD)	26.2±7.7	22.9±8.7	18.9±6.3	0.017
Sex Male/Female	10/8	20/15	12/10	0.051
BMI (Kg/m^2) (mean±SD)	24.2±2.9	23.0±4.0	21.8±3.1	0.109
Kuppuswamy score	3.7±1.1	3.4±1.0	3.7±0.9	0.476

Definition of abbreviations: ACT=Asthma Control Test; SD=Standard deviation; BMI=Body mass index

The FEV_1% at the 2nd visit was lowest in poorly control asthma group (76.94±14.20 *versus* 84.06±11.95 *versus* 91.50±10.66; p<0.002). Also, the FEV_1/FVC ratio at second visit showed significantly lower values (71.99±10.59 *versus* 77.70±9.05 *versus* 85.77±8.37; p<0.001) in patients with poorly control of asthma in comparison to other two groups. Notably, the changes in FeNO, TIgE and IL-6 levels in two visit reached significant levels (Table 4).

Table 3. Spirometry variables documented at 2nd visit classified according to ACT score

Variable	Poor Control (ACT ≤19) (n=18)	Well Control (ACT 24-20) (n=35)	Total Control (ACT 25) (n=22)	p-value
FEV_1 (L) (mean±SD)	2.54±0.54	2.58±0.70	2.68±0.66	0.911
FEV_1 (% pred) (mean±SD)	76.94±14.20	84.06±11.95	91.50±10.66	0.002
FVC (L) (mean±SD)	3.43±1.07	3.28±0.94	3.18±0.78	0.698
FVC (% pred) (mean±SD)	90.17±14.42	92.29±11.32	95.14±8.67	0.389
FEV_1/FVC	71.99±10.59	77.70±9.05	85.77±8.37	0.001
ΔFEV_1 (L) (mean±SD)	0.17±0.55	0.10±0.32	0.17±0.26	0.802
ΔFEV_1 (%) (mean±SD)	3.89±4.26	3.29±8.25	10.77±21.01	0.173
ΔFVC (L) (mean±SD)	0.04±0.09	0.02±0.17	0.08±0.15	0.279
ΔFVC (%) (mean±SD)	1.22±2.66	0.43±6.32	3.27±6.30	0.266
ΔFEV_1/FVC	1.61±3.29	2.74±6.24	2.95±8.29	0.776

Definition of abbreviations: ACT=Asthma Control Test; SD=Standard deviation; FEV_1=Forced expiratory volume in one second; FVC=Forced vital capacity

Table 4. Difference in inflammatory markers recorded at 1st and 2nd visit classified according to ACT score

Variable	Poor Control (ACT ≤19) (n=18)	Well Control (ACT 24-20) (n=35)	Total Control (ACT 25) (n=22)	p-value
ΔFeNO (ppb) (mean±SD)	44.28±37.12	7.25±28.47	-18.06±20.66	0.0001
Δhs-CRP (mean±SD)	-1.13±2.03	-0.76±1.64	1.99±1.6	0.731
ΔS.TIgE (mean±SD)	475.83± 394.93	-124.37± 561.66	-127.05± 224.60	0.0001
ΔIL-10 (mean±SD)	-14.53±2.56	-3.03±2.48	3.13±2.80	0.057
ΔIL-6 (mean±SD)	29.24±5.31	31.16±4.31	35.17±1.76	0.236
ΔIL-13 (mean±SD)	-4.23±2.96	-6.47±2.51	-8.94±1.64	0.460

Definition of abbreviations: ACT=Asthma control test; SD=Standard deviation; FeNO=Fraction of exhaled nitric oxide; ppb=Parts per billion; hs-CRP=High-sensitivity C-reactive protein; S.TIgE=Serum total immunoglobulin E; IL=Interleukin

Significant inverse correlation was observed between ACT score and age, body mass index (BMI), FEV_1%, ΔFeNO and ΔTIgE (Table 5). Furthermore, significant positive correlations of FEV_1/FVC at the second visit with ACT score was observed (Table 5).

Table 5. Correlation between different demographic, spirometry and inflammatory marker level and ACT score in asthma patients (n=35).

Variable	ACT Score	
	r	p
Age	-0.326	<0.004
BMI (Kg/m^2)	-0.244	<0.035
FEV_1(%)	-0.406	<0.004
ΔFeNO	-0.621	<0.0001
	rho	p
FEV_1/FVC	0.509	<0.0001
ΔS.TIgE	-0.467	<0.0001

r and rho represent the correlation coefficient using parametric and non-parametric analysis.

Definition of abbreviations: ACT=Asthma Control Test; BMI=Body mass index; FEV_1=Forced expiratory volume in one second; FeNO=Fraction of exhaled nitric oxide; FVC=Forced vital capacity; S.TIgE=Serum total immunoglobulin E

The multiple regression analysis using step-wise method was performed to identify the independent variables affecting ACT score (Table 6). An analysis of standard residuals was carried out, which showed that the data contained no outliers (Standard residual minimum = -2.527, standard residual maximum = 1.988). The data met the assumption of independent errors (Durbin-Watson value = 2.31).

Table 6. Results from multiple linear regression analysis using step-wise method.

Variable	Mean±SD	Correlation with ACT	Multiple Regression Weights	
			B	β
ACT score	22.13±2.93			
ΔFeNO	8.71±36.50	-0.621*	-0.010*	-0.490
FEV_1/FVC	78.70±10.47	0.486*	0.024*	0.344
ΔS.TIgE	18.89±531.68	-0.396*	0.000*	-0.295

*=p<0.001

Definition of abbreviations: ACT=Asthma Control Test; FeNO=Fraction of exhaled nitric oxide; FEV_1=Forced expiratory volume in one second; FVC=Forced vital capacity; S.TIgE=Serum total immunoglobulin E

The histogram of standardised residuals indicated that the data contained approximately normally distributed errors, as did the normal P-P plot of standardised residuals, which showed points that were not completely on the line, but close. The data also met the assumption of non-zero variances. Using the step-wise method it was observed that ΔFeNO, FEV_1/FVC and ΔTIgE level explain a significant amount of the variance in the ACT score ($F[1, 71] = 33.70$, $p < 0.001$, $R^2 = 0.58$, $R^2_{Adjusted} = 0.57$). The negative correlation of ΔFeNO and ΔTIgE and positive correlation of FEV_1/FVC at the second visit with statistical significance at p<0.001.

Discussion

Bronchial asthma is a chronic inflammatory disorder of the airways, manifesting as recurrent episodes of wheezing, breathlessness, chest tightness, and cough; delineated by bronchial hyperresponsiveness and variable airflow obstruction that is often reversible either spontaneously or with treatment. Control of asthma is a condition in which none of the manifestations of the active disease are present. However, manifestations are at clinical, physiological, pathological, immunological and even molecular level. Whereas relief from symptoms along with freedom from acute exacerbations points to an excellent response to treatment, assessment of activity limitation is a critical component of control.[18]

The literature suggests that asthma control in the general population is inadequate. Laforest *et al*[19] in their evaluation of the impact of patient characteristics on asthma control, reported smoking, female sex and BMI as independent determinants of asthma control. In the present study, patients with a high BMI were more likely to have their asthma inadequately controlled. The above findings attributed to the effect of obesity on lung mechanisms, like reduced functional residual capacity (FRC) and tidal volume, which promotes further airway narrowing and exacerbation in patients with asthma.[20]

Fractional exhaled nitric oxide measurement is a non-invasive, simple and well-accepted method as a clinical biomarker for the assessment of airway inflammation.[21] Sipple *et al*[22] reported a significant correlation of FeNO with measures of asthma control, such as daily use of β2-agonists, symptom scores of the prior two weeks, and reversibility of airway obstruction. Jones *et al*[23] reported a single measure of exhaled nitric oxide, along with a change in exhaled nitric oxide, were predictive of loss of asthma control following steroid withdrawal. Senna *et al*[24] evaluated 27 newly diagnosed asthmatics in Italy and reported an excellent correlation between ACT score and FeNO (r=0.7, p=0.001). Ricciardolo *et al*[25] surveyed FeNO levels and asthma control in 363 subjects and reported that FeNO values >25 ppb (parts per billion) were associated with poorly controlled asthma [odds ratio (OR) 3.71], asthma signs (OR 3.5) and symptoms (OR 1.79). A FeNO cut-off value of 29.9 ppb was

reasonably predictive of (area under curve [AUC] 0.7) poorly controlled asthma. However, the study failed to establish a significant correlation between ACT and FeNO.[25] Similarly, other studies reported no relationship between ACT and FeNO.[15,26] The present study displayed significantly higher FeNO values in poorly controlled compared to both good and totally controlled asthmatics. The study also established the significant correlation of change in FeNO values from baseline and ACT ($p<0.001$). Thus FeNO, especially change in FeNO levels could be a practice in routine for the objective assessment and documentation of the airway inflammation in patients with poorly controlled asthma.

Lung function and symptoms assessment denote the core measure of asthma control. FEV_1 has a critical role, as it is a strong independent predictor of future risk and exacerbations.[1] Leblanc *et al*[26], reported dependency with statistical significance between FEV_1 or $FEF_{25\%-75\%}$ and ACT scores, according to the GINA classification ($p=0.001$ and 0.034, respectively). Nathan *et al*[9] too documented a good correlation between ACT and FEV_1. On the contrary, literature also reports the poor correlation of ACT with pulmonary function.[15] Statistical analysis of the present study documented the significantly lower values of FEV_1% and FEV_1/FVC ($p=0.002$ and $p=0.001$, respectively) performed at the second visit in patients with no control of asthma in comparison to good and total control asthma groups. The FEV_1% showed a negative correlation with ACT score while multiple regression models documented positive correlation of FEV_1/FVC with ACT score. Thus, signifying the importance of lesser airway obstruction with better individual control of asthma. The present finding strengthens the need for the assessment of pulmonary functions at follow-up visits to objectively document the asthma control.

Immunoglobulin E is a crucial factor for the development of bronchial hyperresponsiveness in asthmatics.[27] Epidemiological studies documented higher total IgE level in asthma patients, particularly in children than in non-asthmatics.[28,29] de Marco *et al*[30] reported a high level of IgE as a strong predictor of moderate-to-severe asthma. Tanaka *et al* in their longitudinal evaluation of 154 asthma patients reported that 34.1% of the patients with increased IgE had uncontrolled asthma, compared with 12.7% and 10.0% of patients with decreased and unchanged IgE, respectively ($p<0.01$).[31] These results suggest that a longitudinal increase in IgE is associated with poor asthma control. Similarly, Maneechotesuwan *et al*[32] reported the logarithm of total serum IgE was significantly higher in patients with uncontrolled allergic asthma than in those with well-controlled disease ($p < 0.0001$). The present study too documented change in serum TIgE levels significantly correlated with ACT score, with the highest change, recorded in no control asthmatics. Thus, serial follow-up measurements of TIgE may predict the asthma control.

The serum inflammatory markers including hs-CRP, IL-6, IL-10, and IL-13 recorded in the present study, and no significant correlation documented either of them with ACT score. Sigari *et al*[34] too reported no association between hs-CRP and ACT among 100 asthmatics in Iran. However, there is a paucity of data regarding the importance of change in the levels of other serum inflammatory markers and asthma control.

Conclusions

The present study by statistical analysis proposes documentation of ΔFeNO, FEV_1/FVC and ΔTIgE levels in follow-up visits to explain a significant amount of the variance in the ACT score. Furthermore, the findings of the present study highlight the importance of a combined approach including clinical features (ACT), spirometry variable (FEV_1/FVC) and airway inflammatory markers (FeNO) for documenting the precise control of asthma at follow-up visits and preventing future exacerbations. The small sample size is a potential limitation of the study, and hence, a larger population-based study would highlight the strength of the present study.

References

1. GINA Report, Global Strategy for Asthma Management and Prevention [Internet]. The Global Initiative for Asthma (GINA); 2009 May [updated 2010 Jan 12, cited 2010 Aug 23]. pdf 1.0Mb. *Available at URL*: http://www.ginasthma.com/Guidelineitem.asp??l1=2&l2=1&intId=1561. Accessed on 23 August, 2017.
2. Agarwal R, Dhooria S, Aggarwal AN, Maturu VN, Sehgal IS, Muthu V, *et al*. Guidelines for the diagnosis and management of bronchial asthma: Joint ICS/NCCP (I) recommendations. *Lung India* 2015;32:3–42.
3. Alvarez-Gutiérrez FJ, Medina-Gallardo JF, Pérez-Navarro P, Martín-Villasclaras JJ, Martin Etchegoren B, Romero-Romero B, *et al*. Comparison of the Asthma Control Test (ACT) with lung function, levels of exhaled nitric oxide and control according to the Global Initiative for Asthma (GINA). *Arch Bronconeumol* 2010;46:370–7.
4. Wu LC, Zarrin AA. The production and regulation of IgE by the immune system. *Nat Rev Immunol* 2014;14:247–59.
5. Xystrakis E, Kusumakar S, Boswell S, Peek E, Urry Z, Richards DF, *et al*. Reversing the defective induction of IL-10 secreting regulatory T cells in glucocorticoids resistant asthma patients. *J Clin Invest* 2006;116:146–55.
6. Corren J. Role of interleukin-13 in asthma. *Curr Allergy Asthma Rep* 2013;13:415–20.
7. Hirano T. Interleukin 6 and its receptor: ten years later. *Int Rev Immunol* 1998;16:249–84.
8. Takemura M, Matsumoto H, Niimi A, Ueda T, Matsuoka H, Yamaguchi M, *et al*. High sensitivity C-reactive protein in asthma. *Eur Respir J* 2006;27:908–12.

9. Nathan NA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, *et al*. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59–65.
10. Khalili B, Boggs PB, Shi R, Bahana SL. Discrepancy between asthma control assessment tools and fractional exhaled nitric oxide. *Ann Allergy Asthma Immunol* 2008;101:124–9.
11. Shirai T, Furuhashi K, Suda T, Chida K. Relationship of the asthma control test with pulmonary function and exhaled nitric oxide. *Ann Allergy Asthma Immunol* 2008;101:608–13.
12. Ko FW, Leung TF, Hui DS, Chu HY, Wong GW, Wong E, *et al*. Asthma Control Test correlates well with the treatment decisions made by asthma specialists. *Respirology* 2009;14:559–66.
13. Jatakanon A, Lim S, Kharitonov SA, Chung KF, Barnes PJ. Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma. *Thorax* 1998;53:91–95.
14. Louis R, Lau LC, Bron AO, Roldaan AC, Radermecker M, Djukanovic R. The relationship between airways inflammation and asthma severity. *Am J Respir Crit Care Med* 2000;161:9–16.
15. Melosini L, Dente FL, Bacci E, Bartoli ML, Cianchetti S, Costa F, *et al*. Asthma control test (ACT): comparison with clinical, functional, and biological markers of asthma control. *J Asthma* 2012;49:317–23.
16. American Thoracic Society. Standardisation of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152:1107–36.
17. American Thoracic Society; European Respiratory Society. ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171:912–30.
18. Chhabra SK. Assessment of control in asthma: the new focus in management. *Indian J Chest Dis Allied Sci* 2008;50:109–16.
19. Laforest L, Van Ganse E, Devouassoux G, Bousquet J, Chretin S, Bauguil G, *et al*. Influence of patients' characteristics and disease management on asthma control. *J Allergy Clin Immunol* 2006;117:1404–10.
20. Ramasamy AK, Gupta N, Kumar R. Impact of obesity on bronchial asthma in Indian population. *Lung India* 2014;31:121–6.
21. Gupta N, Goel N, Kumar R. Correlation of exhaled nitric oxide, nasal nitric oxide, and atopic status: a cross-sectional study in bronchial asthma and allergic rhinitis. *Lung India* 2014;31:342–7.
22. Sippel JM, Holden WE, Tilles SA, O' Hollaren M, Cook J, Thukkani N, *et al*. Exhaled nitric oxide levels correlate with measures of disease control in asthma. *J Allergy Clin Immunol* 2000;106:645–50.
23. Jones SL, Kittleson J, Cowan J, Flannery EM, Hancox RJ, McLachlan CR, *et al*. The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. *Am J Respir Crit Care Med* 2001;164:738–43.
24. Senna G, Passalacqua G, Schiappoli M, Lombardi C, Wilcock L. Correlation among FEV_1, nitric oxide and asthma control test in newly diagnosed asthma. *Allergy* 2007;62:207–8.
25. Ricciardolo FL, Sorbello V, Bellezza Fontana R, Schiavetti I, Ciprandi G. Exhaled nitric oxide in relation to asthma control: a real-life survey. *Allergol Immunopathol* (Madr) 2016;44:197–205.
26. Leblanc A, Botelho C, Coimbra A, da Silva JP, de Castro ED, Cernadas JR. Assessment of asthma control: clinical, functional and inflammatory aspects. *Eur Ann Allergy Clin Immunol* 2013;45:90–96.
27. Wu LC, Zarrin AA. The production and regulation of IgE by the immune system. *Nat Rev Immunol* 2014;14:247–59.
28. Criqui MH, Seibles JA, Hamburger RN, Coughlin SS, Gabriel S. Epidemiology of immunoglobulin E levels in a defined population. *Ann Allergy* 1990;64:308–13.
29. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med* 1989;320:271–7.
30. de Marco R, Marcon A, Jarvis D, Accordini S, Almar E, Bugiani M, *et al*. European Community Respiratory Health Survey Therapy Group: Prognostic factors of asthma severity: a 9-year international prospective cohort study. *J Allergy Clin Immunol* 2006;117:1249–56.
31. Tanaka A, Jinno M, Hirai K, Miyata Y Mizuma H, Yamaguchi M, *et al*. Longitudinal increase in total IgE levels in patients with adult asthma: an association with poor asthma control. *Respir Res* 2014;15:144.
32. Maneechotesuwan K, Sujaritwongsanon P, Suthamsmai T. IgEproduction in allergic asthmatic patients with different asthma control status. *J Med Assoc Thai* 2010;93:S71–78.
33. Sigari N, Ghasri H. Correlation between hs-CRP and asthma control indices. *Tanaffos* 2013;12:44–48.