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Pre-Admission Characteristics Predicting an Adverse Outcome in Asthma Exacerbation

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Abstract

Background: Pre-admission clinical parameters predicting an adverse outcome in subjects presenting to the emergency department (ED) with acute asthma exacerbation, as well as their cutoff levels, are not well defined. This study aims to identify these parameters.

In asthma patients, clinical parameters associated with adverse events are well known. However when these patients present with an acute asthma attack, the pre-admission clinical findings associated with an impending in-hospital respiratory failure, as well as their cutoff levels, are still lacking.

Our study suggests that O_2 saturation of 94 percent and lower, $PaCO_2$ levels above 51.5 mmHg and a history of previous hospitalizations due to asthma exacerbations are independent predictors of in-hospital adverse outcome of the index event.

Methods: Records of subjects with an ED diagnosis code for asthma were retrospectively reviewed for 32 clinical parameters, including: demographics, symptoms, asthma-related history, current treatment, risk factors, clinical, laboratory and radiographic findings. These parameters were analyzed for their association with an adverse outcome defined as intensive care unit admission, intubation or death.

Results: Files of 266 subjects presented to the Rambam ED with acute asthma attack between 01/01/2012 and 12/31/2015 were analyzed. Adverse outcome was recorded in 22. Parameters associated with adverse outcome in a univariate analysis included: routine use of short-acting beta agonists, recent corticosteroids prescription, and prior asthma related admissions, previous mechanical ventilation, low O_2 saturation, leukocytosis, respiratory acidosis and abnormal chest X-ray. In a multivariate analysis, the significant independent predictors for in-hospital adverse outcome were: elevated $PaCO_2$ (95% CI 1.002-1.075; p=0.038), low O_2 saturation (95% CI 0.662-0.845; p=0.034) and previous hospital admissions (95% CI 1.108-13.440; p <0.001). Cutoff values were 94% for O_2 saturation and 51.5 mmHg for $PaCO_2$ levels.

Conclusions: The current study suggests that O_2 saturation below 94 percent, $PaCO_2$ levels above 51.5 mmHg and prior asthma related admissions are independent predictors of in-hospital adverse outcome. These subjects should be managed in a more intensive manner in the ED.

Keywords: Asthma; Respiratory; Emergency department

Introduction

Asthma is the most prevalent respiratory disease. It affects about 300 million people globally and accounts for 1 in every 250 deaths worldwide [1,2]. Acute asthma exacerbations may be associated with significant morbidity and mortality [3]. According to previous studies, around 30% of asthmatic exacerbations entail hospitalization [4]; between 2% and 20% of all serious asthma exacerbations require admission to the intensive care unit (ICU) [5,6].

Features associated with an increase in asthma-related death risk include a history of near-fatal asthma requiring intubation and mechanical ventilation support, a history of exacerbation, hospitalization or emergency department (ED) visit for asthma in the past year, recent use of oral corticosteroids (OCS), overutilization of short-acting beta agonists (SABA) or underutilization of inhaled corticosteroids (ICS), poor adherence to asthma medications and food allergy [6-8].

Although these risk factors are well known, the pre-admission clinical findings associated with an impending respiratory failure are still lacking.

Fatal and near-fatal asthma outcomes are rare and can be prevented with early recognition of symptom progression and appropriate therapeutic intervention [9], such as intensification of medical therapies and monitoring. Thus, identification of these parameters may have important implications for early introduction of aggressive therapy using multimodal approaches that can lead to an improved outcome in patients with severe asthma exacerbation [10].

The aim of the current study was to identify the pre-admission clinical parameters associated with an in hospital adverse outcome, as well as their cutoff levels, among patients presenting to the ED with acute asthma exacerbation.

Materials and Methods

Study design

This retrospective non-interventional study was aimed to evaluate the pre-admission characteristics denoting an adverse outcome among subjects presenting to the ED with an acute asthma attack.

The study protocol was approved (Approval no. 0047-16-RMB) by the Institutional Review Board of the Rambam Health Care Campus, a 1500-bed tertiary care academic medical center affiliated with the Faculty of Medicine of the Technion, Israel Institute of Technology (Haifa, Israel) and providing services to a population of approximately two million people in Northern Israel.

Setting and participants

Charts of subjects with a primary diagnosis code for asthma according to the International Classification of Diseases, 9th Revision (ICD9) (ICD9 codes 49301, 49302, 49312, 49322, 49390, 49391, 49392, 49393), admitted to the Rambam ED between January 1, 2012 and December 31, 2015 were analyzed. Exclusion criteria were: age below 18, active malignancy, acute pneumonia or severe sepsis at diagnosis or an incorrect diagnosis of acute asthma attack.

The following data were retrieved from electronic medical records of study participants: age, sex, history of tobacco smoking, occupational hazards, co-morbidities, allergies, gastro-esophageal reflux (GER), a proper pulmonary clinic follow-up, most recent baseline documentation of pulmonary function tests, previous hospitalization or emergency visits for asthma during the preceding year, and previous asthma treatment. ED admission parameters including: time from onset of symptoms, white blood cell (WBC) count and eosinophil count, results of arterial blood gas test and chest X-ray were also collected. In hospital adverse outcome events of ICU admission, intubation and death were documented.

Patient records from the hospital computerized medical database were reviewed to reveal additional asthma events developing within a 6-month follow-up period after an index event (number of exacerbations requiring admission and mortality).

All subjects presented to the ED with a primary diagnosis code for asthma were divided into two groups. Group I comprised subjects who were admitted to the ICU due to asthma exacerbation, required ICU admission, and intubation and/or died during their hospitalization or within 30 days upon discharge. Group II included subjects who were ultimately not hospitalized at all or were admitted to an internal medicine department.

Variables

Acute asthma attack was defined according to the Global Initiative for Asthma (GINA) guidelines as progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness and progressive decrease in lung function [11].

Statistical analysis

Binary stepwise logistic regression was used to evaluate the best parsimonious model predicting the association of the following factors: age; sex; smoking status; current asthma treatment; comorbidities including GER, allergy, obesity and cardiovascular (CV) disorders; previous hospital admissions; previous mechanical ventilation; recent asthma attacks; asthma severity indices including symptoms control, baseline post-bronchodilation forced expiratory flow in the 1st second (PB-FEV1), regular respiratory clinic visits, and age at diagnosis; onset of symptoms; fever; hypoxemia; eosinophilia; leukocytosis; respiratory acidosis; chest X-ray findings with in-hospital adverse outcome.

A P value<.05 was taken as the threshold of significance for all statistical testing. All of the data analyses, including other descriptive statistics, were performed using SPSS software (version 23.0). Statistically significant variables were analyzed as part of a multivariate logistic regression model.

A receiver operating characteristics (ROC) curve was obtained to evaluate the best discriminating cutoff for some of the parameters. Youden's index was calculated (YI=sensitivity+specificity-1) for each coordinate point of the ROC curve to determine the best cutoff value, that has the maximum sensitivity and specificity pair.

Sample size estimations were based on previous trials [5,6,12] with a tendency for higher than mean average for severe exacerbation rates due to tertiary role of our institute. Accordingly, we assumed ratio of 1 primary outcome for 10 patients evaluated. Thus, for obtaining 20 patients with respiratory failure, we aimed for approximately 200 patients to be included in the study.

Results and Discussions

Medical files of 276 subjects evaluated at the ED with a primary diagnosis code for asthma during the time period between January 1, 2012 and December 31, 2015 were screened.

Application of inclusion/exclusion criteria resulted in the final sample size of 266 patients. Twenty-two subjects (8.3% of all subjects) suffered from acute asthma related adverse outcome, of them, 13 patients required ICU admission and 9 needed intubation and mechanical ventilation support (Figure 1). Characteristics of the study population are presented in Table 1.

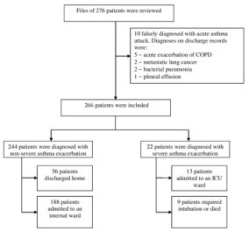

Figure 1: Study population flow chart.

Characteristics	Non-adverse outcome group (n=244)	Adverse outcome group (n=22)	Total No. of study patients (n=266)	P
Females (%)	145 (59.4)	13 (59.1)	158 (59.4)	-
Age, mean, years ± SD	35.9 ± 12.1	39.8 ± 12.8	36.5 ± 12.3	0.164
Never smoked	147 (60.2)	14 (63.6)	161 (60.5)	-
Past smokers	30 (12.3)	3 (13.6)	33 (12.4)	-
Active smokers	63 (25.8)	5 (22.7)	68 (26.7%)	0.184
Unknown smoking status	4 (1.6)	(0)0	4 (1.6)	-
Routine SABA use	96 (39.3)	16 (72.7)	112 (42.1)	0.017
Routine ICS use	131 (53.7)	10 (45.4)	141 (53.0)	0.46
Routine LABA use	108 (44.3)	9 (41.0)	117 (44.0)	0.758
Other asthma medications: (Montelukast, Omalizumab, Theophylline)	31(12.7)	5 (22.7)	36 (13.5)	-
OCS (Prev. 1 month)	59 (24.2)	10 (45.4)	69 (26.0)	0.01
Known GER	30 (12.3)	3 (13.6)	33 (12.4)	0.592
Known allergy	51 (21.0)	4 (18.2)	55 (20.6)	0.919
Obesity	49 (20.1)	6 (27.2)	55 (20.6)	0.434
Cardiovascular comorbidities	49 (20.1)	8 (36.4)	57 (21.4)	0.058
Occupational hazards	10 (4.1)	1 (4.5)	11 (4.1)	0.901
Asthma exacerbation in the previous 6 months	89 (36.5)	9 (41.0)	98 (36.8)	0.448
Admission in the previous year	54 (22.1)	9 (41.0)	63 (23.7)	0.037
History of previous mechanical ventilation	(2.4)6	2(9.1)	8 (3.0)	0.01
Partially controlled or uncontrolled symptoms	(27.0)66	9 (41.0)	75 (28.2)	0.149
Baseline FEV1 <50% of predicted	33 (13.5)	3 (13.6)	36 (13.5)	0.835
No regular respiratory clinic surveillance	121 (49.6)	13 (59.1)	134 (50.4)	0.724
Asthma diagnosis in adulthood	54 (22.1)	3 (13.6)	57 (21.4)	0.583
Symptom onset >24 hours prior to admission	138 (56.6)	10 (45.4)	148 (56.6)	0.393
Fever	23 (9.4)	3 (13.6)	26 (9.7)	0.448
O_2 saturation (%)	95.5 ± 3.7	87.8 ± 7.1	94.6 ± 4.5	0.04
Absolute eosinophil count, mean	352.7	309.2	345.3	0.605
Eosinophil percentage, mean	2.51%	3.51%	2.62%	0.535
WBC (± SD) count	10.9 ± 4.1	14.8 ± 4.9	11.2 ± 4.3	<0.001
pH (± SD)	7.39 ± 0.12	7.26 ± 0.19	7.38 ± 0.13	0.005
$PaCO_2$ (± SD)	41.5 ± 10.2	58.6 ± 29.2	43.0 ± 13.2	0.015

Abnormal CXR	20 (0.8)	5 (22.7)	25 (9.4)	0.37

Table 1: SABA: short-acting β2-agonists; ICS: inhaled corticosteroids; LABA: long-acting beta agonists; OCS: oral corticosteroids; GER: gastro-esophageal reflux; FEV1: forced expiratory flow in the 1st second; WBC: white blood cells; $PaCO_2$: partial pressure of carbon dioxide; CXR: chest X-ray.

Approximately 76% of study participants had long-standing asthma (diagnosed more than 5 years earlier).

With regard to the asthma profile, 28.2% of subjects reported on partially controlled or uncontrolled asthma symptoms, and 50.4% were not regularly followed-up by a . Forty four percent of subjects were treated with long acting beta agonists (LABA) and 53% received ICS. Other drugs (montelukast, omalizumab or Theophylline) were prescribed to 13.5% of patients. In the study cohort, only one subject received omalizumab. Forty two percent of study participants were using SABA treatment on a daily basis.

Thirty six percent of patients had an asthma exacerbation requiring an ED visit within 6 months prior to the index event. Twenty three percent of patients were hospitalized because of their asthma within the 12 months preceding the index event, and 3% of subjects had mechanical ventilation support for acute asthma exacerbation in the past.

Demographic variables and asthma severity

Data comparison between asthma patients with an adverse outcome (group I) and non-adverse outcome (group II) is presented in Table 1.

The overall mean age (± SD) was 39.8 ± 12.8; females composed 59.2% of the study population. Age and gender did not significantly differ between the groups.

Although obesity and cardiovascular (CV) disorders were more prevalent among the adverse outcome group, statistical significance was not reached (P=0.434 for obesity and P=0.057 for CV disorders).

Airflow limitation, defined as the most recent baseline post bronchodilation FEV1 measurement documented at the clinic, was found to be similar in both groups (P=0.149 and 0.835, respectively). However, the number of subjects reporting daily use of SABA was almost double in the adverse outcome group (p=0.017). Similarly, a significantly higher rate of oral corticosteroid prescriptions within the 4 weeks prior to an admission event was observed in group I than in group II (45.5% versus 24.2%, respectively; P=0.019).

The number of hospital admissions due to asthma exacerbation within the preceding year and the proportion of events requiring mechanical ventilation support in the past were also significantly higher among subjects from the adverse outcome group (P=0.037 and 0.01, respectively).

Clinical features of an asthma exacerbation event

Clinical parameters of the index event are presented in Table 1. The symptom onset period preceding presentation to the ED was shorter in the adverse outcome group (P=0.393). Likewise, abnormal chest X-ray findings, mostly consolidation or diffuse interstitial thickening, were detected far more frequently in the adverse outcome group than in the non- adverse outcome group (22.7% versus 0.8%; P=0.037).

Laboratory features of an asthma exacerbation event

The plasma mean absolute eosinophil count and their percentage were similar in both study groups (non-adverse outcome group: 352.7/μl and 2.51%; adverse outcome group: 309.2/μl and 3.51%).

The mean WBC count (± SD) was found to be significantly higher in the adverse outcome group (14800/μl ± 4900 versus 10900/μl ± 4100; P<0.001). In ROC analysis, the WBC value of 12060/μl appeared to be the best discriminating cutoff between the groups (Figure 2). The AUC was 0.748 (95% CI: 0.648-0.847) (P value<0.001).

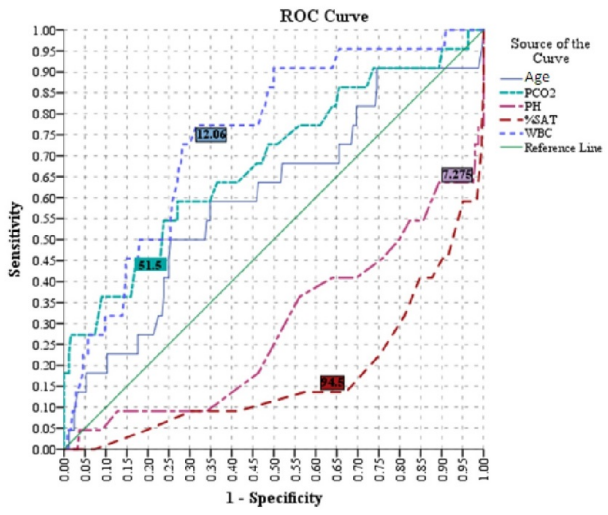

Figure 2: Receiver operating characteristics (ROC) evaluating pre-specified variables as predictors of adverse outcome.

As expected, O_2 saturation, measured on admission, significantly differed between the groups (87.8 ± 7.1% versus 95.5 ± 3.7%; P=0.004). ROC analysis identified the room air O_2 saturation value of 94.5% as the best cutoff for discrimination between the groups (Figure 2). The AUC was 0.174 (95% CI: 0.072-0.276) (P value<0.001).

Statistically significant differences were also evident in the mean pH value (± SD) (7.26 ± 0.19 versus 7.39 ± 0.12 in adverse outcome group versus non-adverse outcome group, respectively; P=0.005) and mean levels of arterial partial pressure of carbon dioxide ($PaCO_2$), (58.6 ± 29.2 versus 41.5 ± 10.2, respectively; P=0.015). The best discriminating cutoff between the groups according to ROC analysis for pH was 7.275, AUC=0.291 (95% CI: 0.165-0.416) (P value=0.001) and for $PaCO_2$ value was 51.5 mmHg, AUC= 0.685 (95% CI: 0.556-0.813).

Univariate regression analysis found routine use of SABA (P=0.017), recent prescription of OCS (P=0.01), hospital admission due to asthma in the previous year (p=0.037), history of mechanical ventilation (p=0.01), decreased O_2 saturation (p=0.04), leukocytosis (P<0.001), elevated $PaCO_2$ levels (P=0.015), decreased pH (P=0.005) and

abnormal chest X-ray findings (P=0.037) to be the factors, associated with a high risk of adverse outcome during asthmatic attack.

Multivariate analysis confirmed that elevated $PaCO_2$ levels (95% CI, 1.002-1.075; p=0.038), low O_2 saturation (95% CI, 0.662-0.845; p=0.034), and previous hospital admissions due to an asthma event (95% CI, 1.108-13.440; p <0.001) were associated with a higher likelihood of adverse outcome.

Among these parameters, the highest correlation for the primary outcome was found with the history of previous admissions within the past year. Each previous hospitalization tripled the risk for adverse outcome.

Discussion

Risk factors for more severe long-term course of asthma patients are well validated [11,13,14], while the pre-admission parameters and their cutoff levels for in hospital adverse outcome acute asthma exacerbation have not been fully elucidated.

In the present study, a univariate analysis identified the following nine parameters as prognostic features for adverse outcome in an acute asthma exacerbation event: routine use of SABA, recent prescription of OCS, hospital admission due to asthma in the past year, a history of mechanical ventilation, low O_2 saturation, leukocytosis, elevated $PaCO_2$ levels and abnormal chest X-ray findings. However, in a multivariate analysis, only elevated $PaCO_2$, low O_2 saturation and asthma-related hospital admissions in the past year have been demonstrated to independently predict in-hospital adverse outcome.

While reduced PaO_2 or elevated $PaCO_2$ are usually used as part of the definition of respiratory failure, the data regarding their correlation with worse clinical outcomes and their cutoff levels remain scarce. The current study demonstrates a direct relationship between these laboratory parameters and acute respiratory failure in the ED among subjects with asthma. The ROC curve analysis has identified O_2 saturation of 94%, pH <7.275 and $PaCO_2$>51.5 mmHg as the most accurate predictors of respiratory failure. These data emphasize the necessity of treatment intensification in patients with such findings.

Furthermore, the level of asthma control is a good predictor of future exacerbations, and the absence of exacerbation events for 12 months is a part of the GINA definition of controlled asthma [12]. In our study, poor symptom control and a history of asthma exacerbation events in the previous 6 months were more prevalent in the adverse outcome group, albeit without reaching statistical significance. This finding could be related in part to non-uniform documentation of asthma symptoms in patients who were not on routine follow-up care by a pulmonologist or to light symptoms of previous asthma events, which did not require hospitalization. The current study clearly demonstrated that either hospital admissions due to asthma in the last year or mechanical ventilation in the past were significantly more prevalent in the adverse outcome group, being thus associated with impending respiratory failure. These data are in conformity with the results of previous studies [6,15].

The rate of in hospital adverse outcome observed in the current study was 0.083. These data are comparable to the results of previous studies, estimating that about 10% of individuals admitted to hospital for asthma exacerbation require ICU hospitalization, with 2% of the admitted patients being intubated [6,16].

In contrast to our expectations based on earlier studies [6,17-20], classic risk factors, like active smoking, recent asthma exacerbation events, frequent use of beta agonists, recent systemic corticosteroid use, higher clinical asthma severity, lack of regular pulmonologist follow-up and longer time to ED presentation appeared to be poor discriminators of patients who required intensive care, mechanical ventilation and died of respiratory failure. These findings could be explained by the heterogeneity of asthma phenotypes among the study population or by the underpowered nature of the study, as only 22 of subjects experienced an adverse outcome event.

The issue of connection between elevated plasma eosinophil counts and an increased exacerbation risk in asthma remains debatable. While previous studies confirmed the existence of such correlation [21-23], the present study provided no evidence on the association of these parameters with an adverse outcome. We assume that pre-hospital administration of systemic corticosteroids at referral clinics or by ambulance teams could mask the true incidence of elevated eosinophil counts in a large portion of our patients.

The current study has a number of considerable strengths. Its relatively large sample size originating from a single center, which limits the heterogeneity in measurements of subject parameters and lab results, makes the findings trustworthy. Furthermore, a wide range of factors, including patient medical history, current treatment, comorbidities and ED presentation parameters has been examined. All the evaluated parameters have been crossed in a multivariate analysis for best predictors of the primary outcome.

This study has several noteworthy limitations. First, the decision to admit a patient to an ICU is based on physician's assessment only. However, this is an accepted patient management strategy in the ED. Second, this is an observational study, with all the data retrospectively collected, which implies that some information regarding risk factors and medical history may be missing. Third, this study was conducted in a single center with its specific patient demographics, which could potentially limit the applicability of its results.

Conclusion

In conclusion, the current study suggests that O_2 saturation of 94 percent and lower, $PaCO_2$ levels above 51.5 mmHg and a history of previous hospitalizations due to asthma exacerbations are independent predictors of in-hospital adverse outcome of the index event. Subjects with acute asthma exacerbation displaying these parameters should be monitored and treated intensively as severe asthma exacerbation according to GINA guidelines [11] when presenting to the ED. Further confirmation of these findings in a large prospective clinical trial is warranted.

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References

1. Fergeson JE, Patel SS, Lockey RF (2017) Acute asthma, prognosis, and treatment. J Allergy Clin Immunol 139: 438-447.
2. Braman SS (2006) The global burden of asthma. Chest 130: 4S-12S.
3. Weiss KB, Sullivan SD (2001) The health economics of asthma and rhinitis. I. Assessing the economic impact. J Allergy Clin Immunol 107: 3-8.

4. Graham LM, Eid N (2015) The impact of asthma exacerbations and preventive strategies. Curr Med Res Opin 31: 825-835.
5. McFadden ER Jr (2003) Acute severe asthma. Am J Respir Crit Care Med 168: 740-759.
6. Pendergraft TB, Stanford RH, Beasley R, Stempel DA, Roberts C, et al. (2004) Rates and characteristics of intensive care unit admissions and intubations among asthma-related hospitalizations. Ann Allergy Asthma Immunol 93: 29-35.
7. Alvarez GG, Schulzer M, Jung D, Fitzgerald JM (2005) A systematic review of risk factors associated with near-fatal and fatal asthma. Can Respir J 12: 265-270.
8. Pumphrey RS, Gowland MH (2007) Further fatal allergic reactions to food in the United Kingdom, 1999-2006. J Allergy Clin Immunol 119: 1018-1019.
9. Rubin BK, Pohanka V (2012) Beyond the guidelines: Fatal and near-fatal asthma. Paediatr Respir Rev 13: 106-111.
10. Rowe BH, Sevcik W, Villa-Roel C (2011) Management of severe acute asthma in the emergency department. Curr Opin Crit Care 17: 335-341.
11. GINA Report (2017) Global strategy for asthma management and prevention. Global Initiative for Asthma (GIA).
12. Holgate S, Bisgaard H, Bjermer L, Haahtela T, Haughney J, et al. (2008) The Brussels Declaration: The need for change in asthma management. Eur Respir J 32: 1433-1442.
13. Turner MO, Noertjojo K, Vedal S, Bai T, Crump S, et al. (1998) Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. Am J Respir Crit Care Med 157: 1804-1809.
14. Patel M, Pilcher J, Reddel HK, Qi V, Mackey B, et al. (2014) Predictors of severe exacerbations, poor asthma control, and beta-agonist overuse for patients with asthma. J Allergy Clin Immunol Pract 2: 751-758.
15. Miller MK, Lee JH, Miller DP, Wenzel SE, TENOR Study Group (2007) Recent asthma exacerbations: A key predictor of future exacerbations. Respir Med 101: 481-489.
16. Rodrigo GJ, Rodrigo C, Hall JB (2004) Acute asthma in adults: A review. Chest 125: 1081-1102.
17. Haselkorn T, Zeiger RS, Chipps BE, Mink DR, Szefler SJ, et al. (2009) Recent asthma exacerbations predict future exacerbations in children with severe or difficult-to-treat asthma. J Allergy Clin Immunol 124: 921-927.
18. Patel M, Pilcher J, Reddel HK, Pritchard A, Corin A, et al. (2013) Metrics of salbutamol use as predictors of future adverse outcomes in asthma. Clin Exp Allergy 43: 1144-1151.
19. Osborne ML, Pedula KL, O'Hollaren M, Ettinger KM, Stibolt T, et al. (2007) Assessing future need for acute care in adult asthmatics: The Profile of Asthma Risk Study: A prospective health maintenance organization-based study. Chest 132: 1151-1161.
20. Diette GB, Wu AW, Skinner EA, Markson L, Clark RD, et al. (1999) Treatment patterns among adult patients with asthma: Factors associated with overuse of inhaled beta-agonists and underuse of inhaled corticosteroids. Arch Intern Med 159: 2697-2704.
21. Tran TN, Khatry DB, Ke X, Ward CK, Gossage D (2014) High blood eosinophil count is associated with more frequent asthma attacks in asthma patients. Ann Allergy Asthma Immunol 113: 19-24.
22. Schleich FN, Chevremont A, Paulus V, Henket M, Manise M, et al. (2014) Importance of concomitant local and systemic eosinophilia in uncontrolled asthma. Eur Respir J 44: 97-108.
23. Belda J, Giner J, Casan P, Sanchis J (2001) Mild exacerbations and eosinophilic inflammation in patients with stable, well-controlled asthma after 1 year of follow-up. Chest 119: 1011-1017.