The Predictors of Poorly Controlled Asthma in Elderly

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Purpose: To evaluate asthma control in elderly individuals and identify the factors that predict poor control. Methods: A retrospective, observational study evaluating 108 elderly individuals with asthma (59 females: ≥60 years, mean age: 70.5 years) was conducted at Ajou University Hospital from October 2010 to March 2011. Subjects were classified into two groups according to scores on the asthma control test (ACT). Group I consisted of 38 patients with ACT scores ≤19 (poor controllers) and group II included 70 patients with ACT scores >19 (controllers). Clinical data was analyzed. Spirometry was performed, and the ACT and asthma quality-of-life survey were completed. Medication possession ratios were calculated to evaluate compliance. Results: Of the 108 enrolled subjects, 54.6% were female, 7.5% were obese, and 49.0% were atopic. The mean age of the patients was 70.5, and the average of time patients had suffered from asthma was 15.5 years. Comorbid conditions were found in more than 80% of the patients. Allergic rhinitis was most common comorbid condition; this was followed by cardiovascular disease and degenerative arthritis (76.9%, 65.7%, and 51.9%, respectively). Many patients (35.2%) were in poorly controlled states characterized by significantly lower asthma quality of life scores (P<0.001) and higher admission rates (P=0.034). Multivariate logistic regression analysis showed that a history of pulmonary tuberculosis was a predictor of poorly controlled asthma in elderly individuals even after adjusting for age, sex, smoking, lung function and other comorbidities (OR=4.70, CI=1.06-20.81, P=0.042). Conclusions: The asthma of more than one-third of elderly individuals with this condition was poorly controlled, and a history of pulmonary tuberculosis may have contributed to this outcome. Proper evaluation and management of comorbid conditions in elderly patients with asthma is essential for the achievement of better control of the disease and a higher quality of life for those who suffer from it.

Key Words: Aged; asthma; asthma control; quality of life; predictor; pulmonary tuberculosis

INTRODUCTION

The incidence of bronchial asthma in the elderly population is increasing. By the year 2030, the number of such patients will more than double, to almost 5 million in the USA alone. Asthma affects 5.3% of those >65 years of age in the USA, and the rates are higher in Australia, reaching 10.1% of those >64 and 11% of those >75. In Korea, asthma was found to affect 12.7% of people >65 years of age. Although the mortality rates associated with asthma have, in general, decreased, they have increased among elderly individuals. Moreover, almost half of the asthma-related deaths per 100,000 people (5.8/100,000) occurred among those >65.

Elderly individuals with asthma have several characteristics that differ from their younger counterparts. First, they have decreased lung functioning, with stiffened chest walls, weaker respiratory muscle strength, and an increased residual volume; these impairments exist in addition to the loss of elastic recoil that occurs as part of the aging process. Second, they respond less well to asthma medications such as bronchodilators and glucocorticoids. These traits can contribute to severe symptoms in elderly patients, including impaired abilities, decreased quality of life, and frequent near-fatal episodes. Third, the coexistence of asthma and chronic obstructive pulmonary disorder (COPD) is frequent in elderly patients due to smoking habits and exposure to endotoxins, organic dust-like grains, cotton, barn environments, and drying tobacco dust as well as latent
adenovirus infections. Fourth, comorbid conditions such as
depression and obesity increase the rate of hospitalizations,
emergency-room (ER) visits, and ambulatory-care visits. To-
gether, these findings indicate that elderly individuals with asth-
ma generally experience more severe symptoms and higher rates of
poor control over the disease than do younger individuals
with this condition.

Severe asthma in elderly individuals has been associated with
frequent (>4 puffs per day) use of salbutamol, >10 years of
symptoms, and >500 mL reversibility in the forced expiratory
volume during 1 second (FEV1). A study in the USA reported
that predictors of uncontrolled asthma despite the use of stan-
dard asthma medications included younger age, Hispanic an-
cesty, male sex, lower income, less education, chronic sinus-
itis, high blood pressure, and gastroesophageal reflux disorder
(GERD). A European study suggested that suboptimal anti-
asthma drug use was the main predictor of poorly controlled
states of asthma. Both studies emphasized the need to moni-
tor asthma control through proper health care, medication use,
and coordinated care of comorbid conditions. To our knowledge,
the published study focused on the predictors of asthma control
in the elderly is rare. Therefore, we investigated the characteris-
tics of poorly controlled asthma in the elderly and identified the
factors that contributed to poor control.

**MATERIALS AND METHODS**

**Study design and subjects**

The study protocol was reviewed and approved by the Ajou
University Institutional Review Board, and informed consent
was obtained from each subject. This retrospective, observa-
tional study was conducted at Ajou University Hospital from
October 2010 to March 2011. A total of 108 subjects aged ≥60
years and diagnosed with asthma were enrolled in the study.
The study subjects enrolled in this study had recurrent episodes of
wheezing, breathlessness, chest tightness, and coughing, par-
ticularly at night or in the early morning and/or airway hyper-
responsiveness or widespread, but variable, airflow obstruction
within the lung that is often reversible either spontaneously or
with treatment and this was observed by physician for at least 1
year. We excluded the patients with cognitive dysfunction. Sub-
jects were classified into two groups according to scores on the
asthma control test (ACT), which was previously validated for
use in Korea. Group I consisted of 38 patients with ACT scores
≤19 and was defined as the group with poor control. Group II
included 70 patients with ACT scores >19 and was defined as
the group with good control.

**Clinical data and comorbid conditions**

Data on age, sex, history of smoking, duration of disease, age
at onset, weight, height, aspirin hypersensitivity, and occupa-
tional relationship with asthma were collected by reviewing pa-
tient charts. Skin-prick tests were performed for 50 common
aeroallergens (Bencard, Bretford, UK). A positive reaction was
defined as a ratio of the mean wheal diameter of the allergen to
that of the histamine of >1. Atopy was diagnosed if a positive
response to at least one common inhaled allergen was observed
by either the skin-prick test or serum-specific IgE test using the
ImmunoCAP system (≥0.35 kU/L; Pharmacia-Upjohn, Upps-
ala, Sweden). The frequency and cause of admission or ER visit
during the year prior to study enrollment and the presence of
comorbid conditions were noted. The clinical features of the
study subjects are summarized in Table 1.

Pulmonary tuberculosis (TB) lesions on chest x-rays were de-
fined by the presence of discrete linear or reticular fibrotic scars
or dense nodules with distinct margins, with or without calcifi-
cation, within the upper lobes; findings were then confirmed
by a radiologist. The cases showing tissue destruction due to TB
having impact on lung function were excluded.

**Evaluation of pulmonary function**

Methacholine bronchial-challenge tests were performed ac-
cording to previously described methods. Bronchial hyper sens-
itivity was defined by a PC_{20} value ≤25 mg/mL in a methach-
oline-challenge test. Spirometry was conducted by trained pul-
monary technicians following the 1994 American Thoracic So-
ciety (ATS) recommendations using a Jaeger spirometer (Ja-
erg Pneumoscreen II/1; Epich Jaeger GmbH, Hecchinberg, Ger-

**Table 1. Clinical characteristics of study subjects**

| Variable                        | Group I (n=38) | Group II (n=70) |
|---------------------------------|---------------|-----------------|
| Male/female                     | 27/11         | 42/28           |
| Age (yr) (mean ± SD) (range)     | 65.9 ± 10.3   | 66.1 ± 10.2     |
| Obesity (BMI ≥ 30 kg/m²)        | 20 (52.6%)    | 25 (35.7%)      |
| Smoking state (NS/ES/UK)        | 22/16/0       | 31/35/4         |
| Atey                             | 12 (31.6%)    | 21 (30%)        |
| Duration (yr) (mean ± SD) (range)| 9.3 ± 3.2    | 9.2 ± 3.3       |
| Late onset (≥40-yr-old)         | 24 (63.2%)    | 56 (80%)        |
| ACT score                       | 17.3 ± 3.7    | 20.2 ± 3.7      |
| AQOL score                      | 89.9 ± 20.9   | 97.9 ± 20.9     |
| FEV1 (%) (mean ± SD) (range)    | 78.3 ± 33.6   | 88.3 ± 26.8     |
| MMFE (%) (mean ± SD) (range)    | 15.8 ± 18.3   | 67.6 ± 9.5      |
| FVC (%) (mean ± SD) (range)     | 87.0 ± 21.3   | 85.0 ± 13.5     |
| Severity (severe/moderate/mild)*| 0/17/26%      | 0/17/26%        |
| Sputum eosinophil positive (%)   | 16/52 (100%)  | 6/52 (100%)     |
| Sputum neutrophil positive (%)   | 42/52 (100%)  | 42/52 (100%)    |
| ER visits                       | 3 (8.33%)     | 9 (12.8%)       |
| Clinic admissions               | 13 (12.0%)    | 13 (12.0%)      |
| Unscheduled outpatient clinic visits | 0 (0%)  | 17 (15.7%)      |
| Steroid-burst prescriptions     | 56 (51.9%)    | 56 (51.9%)      |

*Severe: FEV1 < 60%, moderate: FEV1 < 80% and ≥ 60%, mild: FEV1 ≥ 80%,
BMI, body mass index; NS, non-smoker; ES, ever-smoker; UK, unknown; ACT,
asthma control test; AQOL, asthma quality of life.
many). Reversibility was defined by an increase in FEV1 of ≥12% and ≥200 mL after a short-acting β-agonist or medical treatment. Sputum was induced using a previously described method.17 Eosinophil counts of ≥3%18 and neutrophil counts of ≥65%19 in the induced sputum samples were considered positive.

Treatment and compliance
All asthma medications prescribed to the enrolled patients were identified via their medical records; these included inhaled corticosteroids (ICSs), inhaled corticosteroids/long-acting β-agonists (ICSs/LABAs), theophylline, short acting β-agonists (SABAs), leukotriene-receptor blockers (LTRAs), and systemic corticosteroids (SCSs). The frequency and total amount of use of the asthma medications were determined for the year prior to study enrollment. Medication possession ratios (MPRs) were also calculated by dividing the number of days a medication was supplied by 365 days (the maximum ratio was 1.0 or 100%). MPR can be used as a measure of compliance.20 MPR values provide information regarding whether a patient is using the proper amount of medication within a defined time period. Medication compliance for our patients was calculated for the year following study enrollment using the median and the 75th percentile MPR, defined a priori, for ICSs with or without LABAs, LTRAs, SCSs and theophyllines. To make the control state and index about medication compliance accurate, we selected the asthmatics with previous one-year history of treatment with anti-asthmatic agents and prescribed for only the amount of medications patients asked for.

ACT and asthma quality of life (AQOL)
ACT and AQOL questionnaires were distributed to all enrolled patients.21,22 The ACT has established internal consistency reliability, known-groups validity, and responsiveness; it was previously translated into Korean.14 An ACT score of ≤19 identifies patients with poorly controlled asthma.14 AQOL is an easy and validated tool with good psychometric properties for assessing the quality of life of patients with asthma.23 Subjects were surveyed on the day of enrollment, and the time after anti-asthmatic treatment.

Statistical analysis
Clinical data were compared with Pearson chi-square tests or independent-samples t-tests. The prevalence of comorbid diseases and their medication requirements were analyzed using Pearson chi-square tests. We constructed a multivariate binary logistic regression model using poorly controlled asthma as the dependent variable and age, sex, smoking status, FEV1 value, obesity, atopy, duration of asthma, comorbid conditions, and medication compliance as independent variables. All computations were performed using SPSS software, version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS
Clinical characteristics of patients (Table 1)
Of the 108 enrolled subjects, 54.6% were female, 7.5% were obese, 32.4% had a history of smoking, and 49.0% were atopic. The mean age of the patients was 70.5, and the average amount of time patients had suffered from asthma was 15.5 years. Those with late onset (≥40 years) comprised 80.6% of patients, and this group experienced less frequent ER visits and clinical admissions than did the group with early to middle onset (5.1% vs. 26.3% for ER visits, P=0.004; 10.1% vs. 26.3% for clinical admissions, P=0.002). Aspirin-intolerance, and occupational asthma were observed in 13.0%, and 4.6% of subjects, respectively. Severe asthma with FEV1 values <60% was noted in 15.7% of patients. Pulmonary function tests resulted in mean values of FEV1, MMFE; and FVC of 88.3%, 67.6%, and 82.3%, respectively. Positive eosinophil (≥3%) and neutrophil (≥65%) counts in the sputum were observed in 36.5% and 80.8% of 52 study subjects, who did sputum exam respectively. The frequencies of unscheduled outpatient clinic visits (7.4%), ER visits (8.3%), clinic admissions (12%), and steroid-burst prescriptions (51.9%) were also examined.

Comorbid conditions (Table 2)
Common comorbid conditions were noted in our patient cohort; these included allergic rhinitis and/or nasal polyp (76.9%), cardiovascular disease (65.7%), degenerative arthritis and/or osteoporosis (51.9%), chronic pulmonary disease (29.6%), diabetes mellitus (22.2%), GERD (15.7%), malignancies (10.2%), gout and/or rheumatoid arthritis (8.3%), IgG subclass deficiency (8.3%), and depressive disorder (5.6%). Patients with poorly controlled asthma (group I) were significantly more likely than those whose asthma was well controlled (group II) (31.6% vs.

Table 2. Comparison of co-morbid disease prevalence according to the ACT scores

| n (%) | Group I (n=38) | Group II (n=70) | P-value |
|-------|---------------|----------------|--------|
| History of pulmonary tuberculosis | 12 (31.6) | 9 (12.9) | 0.019* |
| Chronic pulmonary disease | 14 (36.8) | 18 (25.7) | 0.226 |
| Allergic rhinitis ± nasal polyp | 28 (73.7) | 55 (76.6) | 0.565 |
| Cardiovascular disease | 26 (68.4) | 45 (64.3) | 0.665 |
| Diabetes mellitus | 5 (13.2) | 19 (27.1) | 0.085 |
| Degenerative arthritis ± osteoporosis | 22 (57.9) | 34 (48.6) | 0.354 |
| Gastroesophageal reflux disease | 5 (13.2) | 12 (17.1) | 0.587 |
| Malignancy | 2 (5.3) | 9 (12.9) | 0.213 |
| Gout ± rheumatoid arthritis | 4 (10.5) | 5 (7.1) | 0.543 |
| IgG subclass deficiency | 2 (5.3) | 7 (10.0) | 0.395 |
| Depression | 1 (2.6) | 5 (7.1) | 0.328 |

*P<0.05, Chronic pulmonary disease; bronchiectasis or COPD overlapping.
ACT, asthma control test; Group I, ACT≤19; Group II, ACT>19.
12.9%, \( P=0.019 \)) to have a history of TB. The 21 patients with a history of TB were predominantly male and had lower rates of obesity compared with those without a history of TB (61.9% vs. 41.4% male, \( P=0.090 \) and 0% vs. 9.3% obese, \( P=0.146 \)). Mean FEV1, MMEF, and FVC values were significantly lower in patients with a history of TB than in those without such a history (74.4% vs. 91.7% FEV1, \( P=0.007 \), 51.9% vs. 71.5% MMEF, \( P=0.029 \), and 75.8% vs. 87.2% FVC, \( P=0.027 \)). Moreover, these patients had significantly higher rates of chronic pulmonary diseases such as bronchiectasis and/or COPD (47.6% vs. 25.3%, \( P=0.044 \)) and were more often treated with ICSs/LABAs (76.2% vs. 42.5% took MPR50, \( P=0.006 \), and 38.1% vs. 19.5% took MPR75, \( P=0.070 \)).

**Asthma-control status**

The mean ACT score for all patients was 20.2, and the incidence of poorly controlled asthma (ACT ≤ 19, group I) was 35.2%. Group I was characterized by lower mean AQOL scores (26.6% vs. 23.6%), \( P=0.146 \), mean age (40.9 vs. 34.1 yr), \( P=0.001 \), mean MMEF (1.3 vs. 1.6 L/min), \( P=0.001 \), and lower mean FVC (71.8 vs. 75.8% predicted, \( P=0.027 \)). Moreover, these patients had significantly higher rates of chronic pulmonary diseases such as bronchiectasis and/or COPD (47.6% vs. 25.3%, \( P=0.029 \)), a greater proportion of patients with a history of TB (31.6% vs. 12.9%, \( P=0.019 \)), and higher admission rates for asthma-related issues (21.1% vs. 7.1%, \( P=0.034 \)) than was group II (Table 2 and 3). Patients with prescriptions for adjunctive therapies were more prevalent in group I than in group II (28.9% vs. 11.4%, \( P=0.022 \); Table 4).

When analyzing multivariable logistic regression with covariates, smoking habit, atopy, obesity, FEV1, late onset of disease, medication compliance and comorbid conditions, a patient's history of TB was a significant predictor of poorly controlled asthma (sex and age adjusted OR=4.70, 95% CI=1.06-20.81, \( P=0.042 \), Table 5).

**DISCUSSION**

In this study, we described a cohort of 108 elderly individuals with asthma. At first, the characteristic findings were frequent unscheduled outpatient clinic visits (7.4%), ER visits (8.3%), clinic admissions (12%), and steroid-burst prescriptions (51.9%).

**Table 4.** Prescribed medications and compliance of patients in groups I and II

| n (%) | Group I (n=38) | Group II (n=70) | \( P \) value |
|-------|---------------|----------------|-------------|
| Full year MPR | | | |
| ≥ median cutoff point of ICS<sub>50</sub>LABA<sub>50</sub> | 21 (55.3) | 32 (45.7) | 0.343 |
| ≥ median cutoff point of ICS<sub>50</sub>LABA<sub>25</sub> | 11 (28.9) | 14 (20.0) | 0.292 |
| ≥ median cutoff point of LTRA<sub>25</sub> | 21 (55.3) | 34 (48.6) | 0.506 |
| ≤ 75% cutoff point of LTRA<sub>25</sub> | 10 (26.3) | 17 (24.3) | 0.816 |
| ≥ median cutoff point of SCS<sub>25</sub> | 12 (31.6) | 18 (25.7) | 0.516 |
| ≥ 50% cutoff point of SCS<sub>25</sub> | 11 (28.9) | 15 (21.4) | 0.383 |
| Prescription of adjunctive therapy | | | |
| Number ≥ 2 | 35 (92.1) | 55 (78.6) | 0.072 |
| Number = 3 | 11 (28.9) | 8 (11.4) | 0.022* |

\* \( P<0.05 \).

Group I, ACT ≤ 19; Group II, ACT > 19.

MPR, medication possession ratio; ICSs, inhaled corticosteroids; LABAs, long-acting β-agonists; LTRAs, leukotriene receptor antagonists; SCSs, systemic corticosteroids; adjunctive therapy, LABAs, LTRAs, or theophylline.
which were consistent with the findings of previous studies in Australia and USA.\textsuperscript{13} However, patients had even more frequent admission episodes than subjects of TENOR study with severe or difficult-to-treat asthma (12% vs. 4.6%).\textsuperscript{21} This might be because asthma was often more severe and hospitalization for asthma exacerbation was more frequent among elderly individuals.\textsuperscript{2,24} Second, no differences between groups I (poor controllers) and II (controllers) were detected in medication use or compliance. In Lee’s study\textsuperscript{2} from Singapore, even though elderly asthmatics were on significantly more anti-asthmatic medications (2.3+1.1 vs. 1.6+0.9, \textit{P}<0.001), they had clinically more severe symptoms (Step 2.2 ± 1.2 vs. 1.7 ± 1.0, \textit{P}<0.001) and more frequent near-fatal episodes (39% vs. 13%, \textit{X}^2 \textit{test P}<0.01) than younger patients. However, in a European sample of adults, suboptimal treatment were correlated with poor control of asthma.\textsuperscript{12} This difference might be from the different characteristics of study subject between these studies (university hospital vs. general clinic, high adherers vs. low adherers) and lack of data about proper usage of inhaler, small number of subjects and no direct comparison to matched younger patients. Third, no differences were noted in duration of asthma and smoking history between group I and II. Duration of asthma was proved as independent predictor for airflow limitation, hyperinflation and severity of asthma, and smoking history for steroid dependent asthma in elderly, but not for lack of control.\textsuperscript{25-28} This could be explained by that the predictors differ markedly depending on definition of outcome (based on lung function vs. steroid-dependent asthma vs. control status).\textsuperscript{29} Therefore, these findings suggest that the clinical features of asthma appear to be more severe in elderly patients and that close monitoring of these patients will be essential for the achievement of asthma control.

More than half of the elderly asthma patients in our study reported chronic comorbid conditions such as allergic rhinitis, cardiovascular disease, and degenerative arthritis. In the Real-world Evaluation of Asthma Control and Treatment (REACT) Study, hay fever and allergic rhinitis were experienced by >50% of the 1,812 enrolled adult patients with asthma; arthritis, high blood pressure, obesity, and GERD were present in >25% of these patients.\textsuperscript{30} Cazzola et al.\textsuperscript{31} reported that hypertension (23.8%), allergic rhinitis (19.7%), and GERD (18.7%) were the most frequent comorbid conditions suffered by Italian adults with asthma, with cardiovascular disease and osteoporosis also common. The prevalence of allergic rhinitis in adults with asthma was reported to be 60%-80% in Korea,\textsuperscript{32} and this condition was also closely associated with more frequent asthma attacks, ER visits, and poor asthma control.\textsuperscript{33,34} Elderly women with asthma were particularly likely to have weakened bone structures after a 6-month treatment regimen with ICS, this was replicated in our data (degenerative arthritis and/or osteoporosis, 71.2% in female vs. 28.6% in male, \textit{P}<0.001).\textsuperscript{35} These findings suggest that comorbid conditions are common among elderly patients with asthma and that evaluation and proper control of these conditions will improve asthma control in this population.

In this study, 35.2% of the subjects suffered from asthma that was poorly controlled like 36.5% in UK GP practice.\textsuperscript{36} Patients with poorly controlled asthma were more likely to have a history of pulmonary TB and hospital admission despite the high rates with which this group used adjunctive therapies. Additionally, the quality of life of patients with poorly controlled asthma tended to be worse than those of patients whose asthma was well controlled, a result reported by this and other studies.\textsuperscript{13,37} The history of the previous TB was an independent risk factor for obstructive lung disease in a recent Korean study.\textsuperscript{38} Our data also demonstrated an association between pulmonary TB and uncontrolled asthma with odd ratio, 4.61, even after adjusting for sex, age, smoking history and lung function. It is likely that prior TB infection may contribute to an irreversible change in the airways that results in poorly controlled asthma in elderly individuals.\textsuperscript{35}

Our study has several limitations. This was a cross-sectional, retrospective study involving a sample that was not sufficiently large to permit statistically significant conclusions about the factors that predict asthma control. Moreover, the clinical characteristics of the study cohort were similar, and all patient records were obtained from a single university hospital. Future prospective, multicenter studies with large cohorts are needed to thoroughly examine the factors that contribute to asthma control in elderly individuals with asthma.

### Table 5. Adjusted odd ratios for poorly controlled asthma in elderly

| Co-morbid conditions | Odd ratio | 95% confidential interval | \(P\text{-value}\) |
|----------------------|-----------|---------------------------|-----------------|
| History of pulmonary tuberculosis | 4.70 | 1.06-20.81 | 0.042* |
| Chronic pulmonary disease | 2.26 | 0.57-9.02 | 0.246 |
| Allergic rhinitis ± nasal polyp | 0.67 | 0.17-2.64 | 0.569 |
| Cardiovascular disease | 1.90 | 0.55-6.57 | 0.309 |
| Diabetes mellitus | 0.31 | 0.07-1.28 | 0.104 |
| Degenerative arthritis ± osteoporosis | 1.42 | 0.45-4.51 | 0.556 |
| Gastroesophageal reflux disease | 0.46 | 0.09-2.42 | 0.360 |
| Malignancy | 0.23 | 0.03-1.69 | 0.149 |
| Gout ± rheumatoid arthritis | 3.43 | 0.22-52.9 | 0.376 |
| IgG subclass deficiency | 0.39 | 0.07-5.24 | 0.638 |

\(P\text{-values were applied by multivariate binary logistic regression, }{^*P}<0.05\). MPR, medication possession ratios.
In conclusion, asthma in elderly patients presents with more severe and higher rates of comorbid conditions. One-third of these patients had poor control over their disease, leading to frequent clinical admissions. Given that a history of pulmonary TB was a predictor of poor control over asthma, careful evaluation and proper management of comorbid conditions should improve the control wielded by elderly individuals over their asthmatic conditions.

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REFERENCES

1. Jones SC, Iverson D, Burns P, Evers U, Caputi P, Morgan S. Asthma and ageing: an end user’s perspective—the perception and problems with the management of asthma in the elderly. Clin Exp Allergy 2011;41:471-81.
2. Stupka E, deShazo R. Asthma in seniors: Part 1. Evidence for underdiagnosis, undertreatment, and increasing morbidity and mortality. Am J Med 2009;12:6-11.
3. Kim YK, Kim SH, Tak YJ, Lee YK, Lea BJ, Park HW, Jung JW, Bahn JW, Chang YS, Choi DC, Chang SI, Min KU, Kim YY, Cho SH. High prevalence of current asthma and active smoking effect among the elderly. Clin Exp Allergy 2002;32:1766-72.
4. Bellia V, Pedone C, Catalano E, Zito A, Davi E, Palange P, Forastiere F, Incalzi RA. Asthma in the elderly: mortality rate and associated risk factors for mortality. Chest 2007;132:1175-82.
5. Krcmarik JP, Kain KP. Diagnosis and treatment of asthma in elderly patients. AARC Times 2007;31:38-40.
6. Reed CE. Asthma in the elderly: diagnosis and management. J Allergy Clin Immunol 2010;126:681-7; quiz 8-9.
7. Lee KH, Chin NK, Lim TK. Asthma in the elderly--a more severe disease. Singapore Med J 2000;41:579-81.
8. Quadrelli SA, Roncoroni A. Features of asthma in the elderly. J Asthma 2001;38:377-89.
9. Gershon AS, Wang C, Guan J, To T. Burden of comorbidity in individuals with asthma. Thorax 2010;65:651-62.
10. Parameswaran K, Hildreth AJ, Taylor IK, Keaney NP, Bansal SK. Predictors of asthma severity in the elderly: results of a community survey in Northeast England. J Asthma 1999;36:613-8.
11. Peters SP, Jones CA, Haselkorn T, Mink DR, Valacer DJ, Weiss ST. Real-world Evaluation of Asthma Control and Treatment (REACT): findings from a national Web-based survey. J Allergy Clin Immunol 2007;119:1454-61.
12. Cazzozetti L, Marcon A, Janson C, Corsico A, Jarvis D, Pin I, Accordini S, Almar E, Bugiani M, Carolei I, Duran-Tauleria E, Gislonadon D, Gulsvik A, Jögi R, Marimon Á, Martínez-Moratalla J, Vermeire P de Marco R; Therapy and Health Economics Group of the European Community Respiratory Health Survey. Asthma control in Europe: a real-world evaluation based on an international population-based study. J Allergy Clin Immunol 2007;120:1360-7.
13. Kwon HS, Lee SH, Yang MS, Lee SM, Kim SH, Kim DI, Sohn SW, Park CH, Park HW, Kim SS, Cho SH, Min KU, Kim YY, Chang YS. Correlation between the Korean version of Asthma Control Test and health-related quality of life in adult asthmatics. J Korean Med Sci 2008;23:621-7.
14. Thomas M, Kay S, Pike J, Williams A, Rosenberg J, Hillyer EV, Price D. The Asthma Control Test (ACT) as a predictor of GINA guideline-defined asthma control: analysis of a multinational cross-sectional survey. Prim Care Respir J 2009;18:41-9.
15. Park HS, Kim HY, Nahm DH, Son JW, Kim YG. Specific IgG, but not specific IgE, antibodies to toluene diisocyanate-human serum albumin conjugate are associated with toluene diisocyanate bronchoconstriction test results. J Allergy Clin Immunol 1999;104:847-51.
16. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med 1995;152:1107-36.
17. Park H, Jung K, Kim H, Nahm D, Kang K. Neutrophil activation following TDI bronchial challenges to the airway secretion from subjects with TDI-induced asthma. Clin Exp Allergy 1999;29:1395-401.
18. Nair P, Pizzichini MM, Kjaersgaard M, Inman MD, Ethimiadis A, Pizzichini E, Hargreave FE, O’Byrne PM. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med 2009;360:985-93.
19. Sukkar MB, Wood LG, Tooke M, Simpson JL, McDonald VM, Gibson PG, Wark PA. Soluble RAGE is deficient in neutrophilic asthma and COPD. Eur Respir J 2012;39:721-9.
20. Stern L, Berman J, Lunwry W, Katz L, Wang L, Rosenblatt L, Doyle JJ. Medication compliance and disease exacerbation in patients with asthma: a retrospective study of managed care data. Ann Allergy Asthma Immunol 2006;97:402-8.
21. Nathan RA, Sorkness CA, Kosinski M, Sachtz M, Li JT, Marcus P, Murray JJ, Pendergraft TB. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol 2004;113:59-65.
22. Lee EH, Kim SH, Choi JH, Lee YK, Nahm DH, Park HS. Development and evaluation of an Asthma-Specific Quality of Life (A-QOL) questionnaire. J Asthma 2009;46:716-21.
23. Sullivan SD, Wenzel SE, Bresnahan BW, Zheng B, Lee JH, Pritchard M, Kamath TV, Weiss ST; TENOR Study Group. Association of control and risk of severe asthma-related events in severe or difficult-to-treat asthma patients. Allergy 2007;62:655-60.
24. Huss K, Naumann PL, Mason PJ, Nanda JP, Huss RW, Smith CM, Hamilton RG. Asthma severity, atopic status, allergen exposure and quality of life in elderly persons. Ann Allergy Asthma Immunol 2001;86:524-30.
25. Cassino C, Berger KJ, Goldring RM, Norman RG, Kamerman S, Ciotoli C, Reibman J. Duration of asthma and physiologic outcomes in elderly non-smokers. Am J Respir Crit Care Med 2000;162:1423-8.
26. Zureik M, Orehek J. Diagnosis and severity of asthma in the elderly: results of a large survey in 1,485 asthmatics recruited by lung specialists. Respirion 2002;69:223-8.
27. Ishioka S, Terada M, Haruta Y, Hiyama K, Hozawa S, Yamakido M. Smoking as a predictor for loosing control of treated bronchial asthma. Pneumologia 2009;58:186-9.
28. Miha...
30. Haselkorn T, Chen H, Miller DP, Fish JE, Peters SP, Weiss ST, Jones CA. Asthma control and activity limitations: insights from the Real-world Evaluation of Asthma Control and Treatment (REACT) study. Ann Allergy Asthma Immunol 2010;104:471-7.

31. Cazzola M, Calzetta L, Bettoncelli G, Novelli L, Cricelli C, Rogliani P. Asthma and comorbid medical illness. Eur Respir J 2011;38:42-9.

32. Park HS, Choi GS, Cho JS, Kim YY. Epidemiology and current status of allergic rhinitis, asthma, and associated allergic diseases in Korea: ARIA Asia-Pacific workshop report. Asian Pac J Allergy Immunol 2009;27:167-71.

33. Bousquet J, Gaugris S, Kocevar VS, Zhang Q, Yin DD, Polos PG, Bjermer L. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the investigation of montelukast as a partner agent for complementary therapy [corrected]. Clin Exp Allergy 2005;35:723-7.

34. Clatworthy J, Price D, Ryan D, Haughney J, Horne R. The value of self-report assessment of adherence, rhinitis and smoking in relation to asthma control. Prim Care Respir J 2009;18:300-5.

35. Sasagawa M, Hasegawa T, Kazama JJ, Koya T, Sakagami T, Suzuki K, Hara K, Satoh H, Fujimori K, Yoshimine F, Satoh K, Narita I, Arakawa M, Geyo F, Suzuki E. Assessment of bone status in inhaled corticosteroid user asthmatic patients with an ultrasound measurement method. Allergol Int 2011;60:459-65.

36. Sims EJ, Price D, Haughney J, Ryan D, Thomas M. Current control and future risk in asthma management. Allergy Asthma Immunol Res 2011;3:217-25.

37. Juniper EF, Wisniewski ME, Cox FM, Emmett AH, Nielsen KE, O’Byrne PM. Relationship between quality of life and clinical status in asthma: a factor analysis. Eur Respir J 2004;23:287-91.

38. Lee SW, Kim YS, Kim DS, Oh YM, Lee SD. The risk of obstructive lung disease by previous pulmonary tuberculosis in a country with intermediate burden of tuberculosis. J Korean Med Sci 2011;26:268-73.