



# Predictors of Asthma Control by Stepwise Treatment in Elderly Asthmatic Patients

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The geriatric population is increasing, and asthma severity increases with age. We determined the predictors of asthma control, exacerbation, and the factors that affect asthma-specific quality of life (A-QOL) in elderly asthmatic patients. This was a prospective, multicenter, real-life study for 6 months with stepwise pharmacologic treatment based on the Global Initiative for Asthma (GINA) guideline. A total of 296 asthmatic patients aged  $\geq 60$  yr were recruited from 5 university centers in Korea. The improved-asthma control group was defined as the group of patients who maintained well-controlled or improved disease and the not-improved asthma control group was defined as the remaining patients. Fewer number of medications for comorbidities ( $2.8 \pm 3.3$  in the improved vs.  $4.5 \pm 4.4$  in the control) and higher physical functioning (PF) scale ( $89.8 \pm 14.2$  in the improved vs.  $82.0 \pm 16.4$  in the control) were significant predictors in the improved-asthma control group (OR = 0.863,  $P = 0.004$  and OR = 1.028,  $P = 0.018$ , respectively). An asthma control test (ACT) score of  $\leq 19$  at baseline was a significant predictor of asthma exacerbation (OR = 3.938,  $P = 0.048$ ). Asthma duration ( $F = 5.656$ ,  $P = 0.018$ ), ACT score ( $F = 12.237$ ,  $P = 0.001$ ) at baseline, and the presence of asthma exacerbation ( $F = 5.565$ ,  $P = 0.019$ ) were significant determinants of changes in A-QOL. The number of medications for comorbidities and performance status determined by the PF scale may be important parameters for assessing asthma control in elderly asthmatic patients.

**Keywords:** Elderly; Asthma; Control; Performance; Comorbidity

## INTRODUCTION

The geriatric population is increasing worldwide. In the United States, the proportion of people over age 65 is projected to grow up to 25% of the population by 2050 (1) and in Korea, up to 40% until 2060 according to Statistics Korea (2). Although the prevalence of asthma in the elderly is similar to that in all adults (about 5% to 10%) (3), the severity and mortality of asthma are reported to increase with age (4, 5).

The greater mortality of asthma in elderly patients than in younger asthmatics is ascribed to several factors. Elderly asthmatic patients commonly have comorbidities, which make asthma treatment difficult in terms of drug-drug interactions, unintentional non-adherence resulting from complicated medication regimens, poor knowledge of the disease, and incorrect use of medications, especially inhalers (6-8). Another factor is intentional non-adherence that arises from excessive concern about medication complexity (6-8).

To reduce the severity and mortality of asthma in elderly asthmatic patients, we need to regulate the predictors of uncontrolled asthma. The predictors of uncontrolled asthma include old age, low socioeconomic status, smoking, obesity, low adherence, and comorbidities (rhinitis, sinusitis, reflux, and anxiety-depression) (9). However, little is known about predictors of asthma control in elderly patients, because most of the research excluded the elderly as subjects. In the present study, we designed a prospective, multicenter, real-life study to investigate whether comorbidities in elderly Korean asthmatic patients influence asthma control status, predictive factors for asthma control, and exacerbation during the Global Initiative for Asthma (GINA) guideline-based step-

wise treatment (10) for 6 months in an elderly asthma cohort of Korea. In addition, we analyzed factors that affect the asthma-specific quality of life (A-QOL) which is a well-known tool for assessing the overall asthma treatment efficacy (11).

## MATERIALS and METHODS

### Study design and patients

The present study is a prospective, multicenter, non-interventional study from 5 centers in Korea from July 2011. A total of 296 patients aged 60 yr or older who were diagnosed with asthma at least 1 yr before enrollment were recruited for the study. After the subjects were enrolled, they received a stepwise treatment according to the GINA guideline (10) and were followed up every 3 months for 6 months.

The diagnosis of asthma was made on the basis of the GINA guideline (10). According to the GINA guideline (10), the improved-asthma control group (group A) was defined as a group of patients who had improved status (from uncontrolled to partly or well-controlled status or from partly controlled to well-controlled status) or maintained well-controlled status during the 6-month follow up, while the not-improved asthma control group (group B) was defined as the group of patients who did not improve.

### Clinical data and comorbidities

We reviewed data on age, sex, body mass index (BMI), asthma duration, type and number of comorbidities, type and number of medications for asthma and comorbidities, smoking history, pulmonary function tests (PFTs), sputum analyses, and medication adherence for 1 yr before the enrollment. The medications for comorbid conditions and asthma that were administered for at least more than 90 days were counted, and only the asthma controllers or reliever medications defined by the GINA guideline (10) were considered asthma medications. Asthma medication before enrollment of each individual was classified as treatment step 1 to 5 according to the GINA guideline (10). After the enrollment, the asthma control test (ACT), A-QOL (12) questionnaire, the PFT, sputum analysis, and asthma control status based on the GINA guideline (10) were assessed 3 times at enrollment and every 3 months; in addition, the frequency of asthma exacerbation during the study period was monitored.

Current comorbidities and related medications were checked by reviewing patient medical records or self-reports. The comorbidities were classified by the system organ class (SOC) code. The medications for comorbidities were classified by the anatomical therapeutic chemical (ATC) classification according to the World Health Organization (13). There are 14 main groups for the first level of the ATC code: A alimentary tract, B blood and forming organs, C cardiovascular system, J anti-infectives, M musculoskeletal system, N nervous system, R respiratory sys-

tem and so on. Medication adherence was determined by the medication possession ratio (MPR) (14).

Asthma exacerbation was considered "present" if a patient had experienced hospitalization, emergency department visits, unscheduled visits, or more than 20 mg of oral corticosteroid intake for  $\geq 3$  days due to asthma symptom aggravation.

### Geriatric assessment

To assess functional performance status or depression of elderly asthmatics, we performed geriatric assessment using the physical functioning (PF) scale and the Korean version of the short-form geriatric depression score (SGDS-K) at screening visits. The PF scale (15) is composed of 2 domains, mobility and self-care, which include 5 items in each domain (PF1: walking 400 meters, PF2: walking up 10 stairs without resting, PF3: stooping, crouching, or kneeling, PF4: reaching up over your head, PF5: lifting or carrying a bag of rice (8 kg), PF6: bathing or showering, PF7: dressing, PF8: getting in and out of bed or chairs, PF9: shopping for personal items or medications, PF10: riding bus or subway). Limitations in performing specific tasks on upper and lower body mobility, activities of daily living (ADL) and instrumental ADL (IADL) are also assessed. The summated PF score ranges from 0 to 100, with higher scores denoting higher levels of functioning (15). Depression was defined when the SGDS-K was  $> 9$  (16).

### Statistical analysis

Continuous variables were compared using Student's *t*-test, and Pearson's chi-square test or Fisher's exact test was used for categorical variables. Binary logistic regression analysis was applied to assess predictors of changes in asthma control status and for asthma exacerbation. Univariate and multivariate general linear analyses were performed to assess factors for determining changes in A-QOL. Pearson correlation analysis was used to determine the factors related to A-QOL. All computations were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

### Ethics statement

This study was approved by Ajou University institutional review board (IRB No. MED-SUR-11-128), and the other 4 hospitals approved the study. Informed consent was obtained from each patient.

## RESULTS

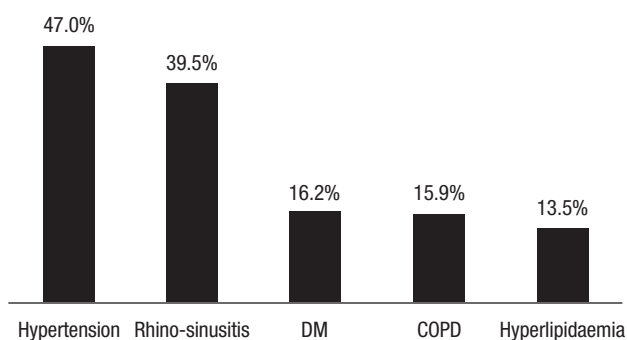
### Clinical characteristics and comorbidities of the study patients

A total of 296 subjects were enrolled in the present study. Table 1 summarizes the clinical characteristics of the total study patients and comparisons between group A and B. The mean asth-

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

Characteristics	Total (n = 296)	Group A (n = 115)	Group B (n = 107)	P value
Gender (Male/Female)	149/147 (50.3/49.7)	71/44 (61.7/38.3)	54/53 (50.5/49.5)	0.091
Age (yr)	69.9 ± 6.2 (60-93)	69.7 ± 6.5	70.3 ± 6.3	0.499
Medication adherence (%)	99.1 ± 6.5 (50-164.1)	98.3 ± 5.3	99.7 ± 2.1	0.010
Treatment step				
Step 1	0	0	0	-
Step 2	40 (13.5%)	10 (8.7%)	14 (13.1%)	0.293
Step 3	151 (51.0%)	57 (49.6%)	51 (47.7%)	0.777
Step 4	104 (35.1%)	48 (41.7%)	41 (38.3%)	0.603
Step 5	1 (0.3%)	0 (0%)	1 (0.9%)	0.299
Number of co-morbidities	2.7 ± 2.0 (0-11)	2.8 ± 2.0	3.0 ± 2.1	0.361
Number of medication for comorbidities	3.4 ± 3.8 (0-21)	2.8 ± 3.3	4.5 ± 4.4	0.010
PF scale	85.7 ± 15.6 (13.3-100)	89.8 ± 14.2	82.0 ± 16.4	< 0.001
Depression (GDS > 9)	49 (16.6%)	17 (14.8%)	18 (16.8%)	0.715
%FEV <sub>1</sub> at baseline	81.1 ± 26.3 (22.8-166.7)	80.4 ± 27.9	76.7 ± 26.9	0.354
ACT score at baseline	19.7 ± 4.2 (5-25)	20.2 ± 3.8	18.8 ± 4.8	0.015
A-QOL at baseline	93.1 ± 22.3 (20-120)	96.4 ± 20.4	89.1 ± 23.9	0.016
Asthma control status at baseline				
Uncontrolled	37 (12.5)	18 (15.7%)	15 (14.0%)	1.000
Partly controlled	96 (32.4)	22 (19.1%)	46 (43.0%)	0.035
Well controlled	163 (55.1)	75 (65.2%)	46 (43.0%)	0.440
The number of subjects who experienced asthma exacerbation for 6 months	18 (6.1)	4 (3.7%)	13 (12.9%)	0.021

Group A, the improved-asthma control group; Group B, the not-improved asthma control group; PF scale, physical functioning scale; GDS, geriatric depression score; ACT, asthma control test; A-QOL, asthma-specific quality of life. Values are presented as n (%) or mean ± standard deviation (range). P value is calculated by Pearson's Chi-square test and the independent samples *t*-test.



**Fig. 1.** Prevalence of comorbid conditions of study subjects. DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.

ma duration of the total study patients was 10 ± 10.4 yr. The number of current smokers was 19 (6.4%), and there were no significant differences in the proportion of smokers according to changes in asthma control status. The mean BMI was 23.9 ± 3.1 kg/m<sup>2</sup> in the total study population and it was not significantly different between group A and B. The mean sputum eosinophil and neutrophil counts at baseline were 12.7% ± 24.3% and 69.2% ± 31.5%, respectively. The mean sputum eosinophil count showed no significant difference between the two groups, while the mean sputum neutrophil count was significantly lower in group A than in group B (55.8% vs. 77.8%, *P* = 0.020).

Fig. 1 shows the major comorbidities of the total study patients. According to the SOC code, 41 (13.9%) and 17 (5.7%) of the 296 patients suffered from gastrointestinal and psychiatric

disorders, respectively. The mean numbers of medications for comorbidities and asthma were 3.4 and 3.1, respectively. The most frequent class of medications for comorbidities was ATC code R (n = 111, 49.8%), followed by C, A, B, M, N, and J (n = 89 [39.7%], 73 [32.6%], 46 [20.5%], 36 [16.1%], 32 [14.3%], and 16 [7.1%], respectively). The type and number of comorbidities and their SOC code did not show any differences in changes in asthma control status; however, the number of medications for comorbidities did. The numbers of patients administered ATC code A, C, and M were significantly lower in group A than in group B (26 [36.1%] vs. 46 [63.9%], *P* = 0.002; 36 [40.9%] vs. 52 [59.1%], *P* = 0.009; and 12 [34.3%] vs. 23 [65.7%], *P* = 0.027). Treatment step before enrollment showed no significant difference between group A and B (Table 1).

### The predictors of changes in asthma control status

We analyzed predictors of asthma control status. By a univariate binary regression model using improved-asthma-control status as a dependent variable, we found the number of medications for comorbidities and total disease, PF scale score, and ACT score, and A-QOL at baseline were significant predictors (OR = 0.885, *P* = 0.002; OR = 0.904, *P* = 0.002; OR = 1.035, *P* < 0.001; OR = 1.081, *P* = 0.015; OR = 1.015, *P* = 0.017, respectively). Based on these findings, we tested a multivariate binary regression model. A small number of medications for comorbidities and a high PF scale score were predictors of changes in asthma control status (OR = 0.863, *P* = 0.004 and OR = 1.028,

**Table 2.** Predictors of changes in asthma control status for the following 6 months

Predictors	Group A (n = 115)	Group B (n = 107)	OR	95% CIs		P value
				Lower	Upper	
Number of medication for co-morbidities	2.8 ± 3.3	4.5 ± 4.4	0.863	0.782	0.953	0.004
PF scale	89.8 ± 14.2	82.0 ± 16.4	1.028	1.005	1.051	0.018
ACT score at baseline	20.2 ± 3.8	18.8 ± 4.8	1.048	0.961	1.143	0.292
Number of co-morbidities	2.8 ± 2.0	3.0 ± 2.1	1.155	0.969	1.377	0.107
A-QOL at baseline	96.4 ± 20.4	89.1 ± 23.9	0.997	0.979	1.015	0.737

Group A, the improved-asthma control group; Group B, the not-improved asthma control group; PF scale, physical functioning scale; ACT, asthma control test; A-QOL, asthma-specific quality of life. Binary logistic regression was used for analysis.

**Table 3.** Predictors of asthma exacerbation

Predictors	Exacerbation		OR	95% CIs		P value
	Absence (n = 192)	Presence (n = 18)		Lower	Upper	
A-QOL at baseline	94.1 ± 22.7	83.8 ± 20.6	1.004	0.976	1.032	0.782
ACT (< = 19) at baseline	70 (36.6%)	11 (61.1%)	3.938	1.014	15.292	0.048
PF scale	87.3 ± 14.4	78.3 ± 20.4	0.977	0.941	1.015	0.231
%FEV <sub>1</sub> at baseline	79.8 ± 27.4	74.5 ± 25	0.997	0.978	1.016	0.748

A-QOL, asthma-specific quality of life; ACT, asthma control test; PF scale, physical functioning scale. Binary logistic regression was used for analysis.

**Table 4.** Factors that affect asthma-specific quality of life

Parameters	F	P value
Asthma duration (yr)	5.656	0.018
Total number of medications for all disease	0.158	0.692
PF scale	1.770	0.185
GDS	0.339	0.561
ACT score at baseline	12.237	0.001
Asthma exacerbation during 6 months	5.565	0.019

PF scale, physical functioning scale; GDS, geriatric depression score; ACT, asthma control test. A general linear model was used for analysis.

$P = 0.018$ , respectively) as summarized in Table 2.

### The predictors of asthma exacerbation

The PF scale and ACT scores at baseline were the predictors of asthma exacerbation (OR = 0.969,  $P = 0.021$  and OR = 0.900,  $P = 0.045$ , respectively). When we conducted a multivariate binary regression test with the PF scale score, ACT score, A-QOL, and FEV<sub>1</sub> at baseline as variables, the ACT score at baseline was found to be a significant predictor of asthma exacerbation for the following 6 months (OR = 3.938,  $P = 0.048$ ) (Table 3).

### Factors affecting A-QOL

Table 4 presents factors that affect changes in A-QOL. Asthma duration ( $F = 5.656$ ,  $P = 0.018$ ), the ACT score ( $F = 12.237$ ,  $P = 0.001$ ) at baseline, and the presence of asthma exacerbation ( $F = 5.565$ ,  $P = 0.019$ ) during the study period were significant determinants of changes in A-QOL for the following 6 months. Each A-QOL at 0, 3, and 6 months was significantly correlated with the ACT score at 0, 3, and 6 months ( $r = 0.636$ ,  $P < 0.001$ ;  $r = 0.708$ ,  $P < 0.001$ ; and  $r = 0.725$ ,  $P < 0.001$ , respectively). A positive correlation was found between changes in A-QOL and ACT scores during the study period ( $r = 0.549$ ,  $P < 0.001$ ). A-

QOL at 0, 3, and 6 months showed negative correlations with the GDS ( $r = -0.453$ ,  $P < 0.001$ ) at screening and the number of medications for all diseases ( $r = -0.152$ ,  $P = 0.023$ ).

## DISCUSSION

This is the first study to report predictors of changes in asthma control and exacerbation, and factors that affect A-QOL, with pharmacological treatment for 6 months in Korean elderly asthmatic patients. Our results indicate that less number of medications for comorbidities and higher PF scale can predict improved-asthma control in elderly asthmatic patients. Moreover, the uncontrolled asthma status by the ACT score at baseline predicted asthma exacerbation for the following 6 months. Asthma duration, the ACT score at baseline, and the presence of asthma exacerbation were significant determinants of changes in A-QOL.

Regarding the clinical characteristics of the study population, there is no consistent definition for the elderly and researchers are using either 60 (17) or 65 yr old (18, 19) as a criteria. The present study used 60 yr to define the elderly because we considered that this group of patients has the characteristics of the elderly population and enabled us to enroll a large number of patients. A previous study reported 75.7% of the study subjects adhere to asthma medication, which is lower than that of our result (19). Good adherence is a predictor of asthma control (17), while in the present study low medication adherence was noted in group A. This result attributed to use MPR for assessing medication adherence which lacks information about the proper use of inhalers. In addition, the present study investigated the changes in asthma control status which was different from the previous study (17), indicating that the patients who



were well controlled or improved in their asthma control status did not tend to adhere to asthma medications. Taken together, we can speculate that it is crucial to evaluate the administration technique of inhalers for elderly asthmatic patients in addition to the prescription rate, and to inform and educate patients about maintaining medications, even when their control status is well controlled or improved.

Comorbidities are essential factors for predicting asthma control (9, 20). The prevalence of comorbid conditions varies depending on study populations (17-19, 21). One study revealed rhinitis is the most prevalent comorbid condition (19), while the others reported hypertension was the most prevalent one, in concordance with the present study (17, 18). In addition, consistent with previous studies (17, 19), the present study found that the GDS score is negatively correlated with the ACT score and A-QOL. Similar to comorbidities, medications for comorbidities, including beta-blockers (22), and their numbers are crucial in asthma control (23, 24). A large number of medications are associated with unfavorable outcomes (6, 25, 26), therefore, it is recommended that treatment regimens should be as simple as possible for elderly asthmatic patients (27). A large number of medications for comorbidities may be ascribed to many comorbidities in the elderly and administration of more medications than clinically indicated (25). In the present study, there was no significant difference in the prevalence of comorbidities themselves, but significant difference in the number of administered medications between the 2 groups. Taken together, we can speculate that the number of medications can be a crucial predictor of asthma control in elderly patients rather than the sorts and number of comorbidities. Therefore, for better asthma control, it is essential to recognize the risks and poor outcomes of a greater number of medications and to clearly investigate all medications of each patient.

The low functional performance status of elderly asthmatics is associated with poor asthma outcome (19). In concordance with the prior study (19), the present study found that a high PF scale is a good predictor of improved asthma control. Among the items of the PF scale, the item instrumental activities of daily living is known to represent cognitive function of routine activities in the elderly, and these questionnaires are used to evaluate cognitive impairment in the field of neurology (28). Cognitive function of elderly patients affects disease control in terms of performance of action plans, correct use of medications and so on. Taken together, the functional performance status of elderly patients is a crucial factor for predicting asthma control status; therefore, we need to evaluate the functional performance status and to use the PF scale as appropriate tools for assessing asthma control status.

Current asthma control status and previous history of asthma exacerbation are known to predict the future risk of asthma exacerbation (9, 29). In addition, quality of life is reported to be

positively associated with current asthma control status (25) and negatively with asthma exacerbation and asthma duration (26, 27). The present study found that current asthma control status predicted asthma exacerbation; however, the presence of asthma exacerbation at 3 months did not predict asthma exacerbation at 6 months (data was not shown), different from the results of previous studies (9, 29). A relatively short follow-up duration is suggested to contribute to this disparity of results. Moreover, in concordance with previous studies (25-27, 30), asthma control status, asthma duration, and asthma exacerbation were significant determinants of changes in A-QOL. Therefore, it is essential to control current asthma control status for less asthma exacerbation and better A-QOL.

A limitation of the present study is a relatively short study duration; therefore, further studies with a longer duration are warranted. The strong point of the present study is the study subjects' characteristics. The subjects enrolled in our study are a real world asthma population, unlike most of the clinical trials or well-organized studies involving nonsmokers and younger patients that represent only a small percentage of the real asthma population. Thus, our study showed more reliable results that can be used in clinical practice. In addition, the present study focused on changes in asthma control status as a main outcome, and the prospective study design make it possible that the findings may be more useful in practice.

In conclusion, the number of medications for comorbidities and functional status determined by the PF scale are considered important parameters for assessing and predicting asthma control status in elderly asthmatic patients. In addition, multifactorial assessment of medications is essential in the treatment of elderly asthmatic patients.

## DISCLOSURE

All of the authors have no potential conflicts of interest to disclose.

## AUTHOR CONTRIBUTION

Research conception and study design: Ye YM, Park HS. Enrollment of subjects: Ban GY, Ye YM, Lee Y, Kim JE, Nam YH, Lee SK, Kim JH, Jung KS, Kim SH, Park HS. Data analysis and drafting: Ban GY, Ye YM, Park HS. Approval of manuscript: all authors

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