



Predictors of asthma control in elderly patients

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Purpose of review

We are in the era of rapid aging of the global population. Elderly asthmatic patients have an increased frequency of hospitalization and a high mortality rate. In this review, we focus on comorbidities and treatment issues in terms of the predictors of asthma control in the elderly.

Recent findings

Some frequent comorbidities, such as chronic obstructive pulmonary disease, chronic sinusitis, obesity, and depression, are associated with uncontrolled asthma in elderly asthmatic patients. Smoking status in elderly asthmatic patients was associated with more frequent exacerbations. Management of comorbidities should be taken into account when we treat elderly asthmatic patients. Low treatment adherence, which is common in elderly asthmatic patients, predicts poor asthma control status. A poor knowledge about asthma, cognitive function impairment, and inappropriate inhaler technique result in low treatment adherence. Polypharmacy is associated with low treatment adherence, adverse drug reactions, and drug-drug interactions, and it is supposed to be a predictor of asthma control.

Summary

Multifactorial assessments, including comorbidities, treatment adherence, and polypharmacy, are important for better asthma control in elderly asthmatic patients. Further studies on the strategy for the management of elderly asthmatic patients in a real-world setting are warranted.

Keywords

adherence, asthma control, comorbidities, elderly

INTRODUCTION

The proportion of elderly people is increasing worldwide. By 2030, people over age 65 will constitute up to 20 and 36% of the populations of the United States and China, respectively [1,2]. The prevalence of asthma at all ages in the United States has been steadily increasing since 1980 [1,3], and that of elderly asthma has been reported to be 3.6–5.9% in the United States [4,5] and 7.1% in Korea [6]. However, estimating the exact prevalence of elderly asthma is challenging because of underdiagnosis arising from decreased perception of asthma symptoms by the elderly, misclassification as chronic obstructive pulmonary disease (COPD), and difficulty in distinguishing asthma from clinical conditions, such as congestive heart failure or COPD [2]. Considering the increasing elderly population/prevalence of asthma, and the underdiagnosis of elderly asthma, there could be a substantial proportion of elderly asthmatic patients.

Elderly asthmatic patients have been shown to have high rates of mortality, hospitalization, and near-fatal asthma-related events compared with younger ones [1,2,7]. After adjusting for comorbidities, older adults aged ≥ 65 years had a four-fold increase in overall mortality compared with

younger ones aged 18–64 years [8]. Many studies [7–9] have reported that asthma-related costs are higher in elderly asthmatic patients than in younger ones mainly because of costs of hospitalization and medication. Despite high rates of prevalence, morbidity, and costs in elderly asthmatic patients, the elderly asthma population has been excluded from most studies; therefore, there is a paucity of knowledge about elderly asthmatic patients.

The goals of asthma therapy in elderly asthmatic patients are the same as those in younger ones: achieving good asthma control status and minimizing the future risk of exacerbation [10]. To achieve asthma control status and to reduce the severity/morbidity of elderly asthmatic patients, identifying and regulating the predictors of asthma control are

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KEY POINTS

- Asthma–COPD overlap syndrome, CRS, obesity, depression, and smoking could predict asthma control in elderly asthmatic patients.
- Low adherence to antiasthmatic medications and polypharmacy, which are frequently observed in the elderly, are predictors of asthma control in elderly asthmatic patients.
- Multifactorial assessment of elderly asthma is important for better asthma control.

required. Comorbidities, including rhinosinusitis, obesity, smoking, and depression, are well known predictors of poor asthma control in the general asthma population [11]. In elderly asthmatic patients, comorbidities themselves, polypharmacy for comorbidities, and nonadherence to the polypharmacy affect asthma control status [11,12,13[■]]. In addition to the comorbidities, impairment of cognitive function and physical performance should be considered to achieve good asthma control status in the elderly population [13[■]].

In this review, we summarize recent data on the predictors of asthma control (Table 1) [2,6,11,12,13[■],14[■],15,16[■],17–28,29[■],30–32,33[■],34–39], primarily focusing on comorbidities. We also discuss the main issues in the management of elderly asthmatic patients.

COMORBIDITIES ASSOCIATED WITH ASTHMA CONTROL IN THE ELDERLY

Comorbidities are frequently found in asthmatic patients, especially elderly ones, affecting asthma control as predictors [40,41]. Multiple diseases may co-exist in elderly patients. A previous study [38] conducted in a Polish asthma population have revealed that the mean number of comorbid diseases is significantly larger in elderly patients than in nonelderly ones (8.4 ± 3.4 vs. 4.7 ± 2.9 , $P < 0.001$). Comorbidities are associated with increased morbidity and mortality, recurrent exacerbations, low treatment adherence, and a significantly reduced quality of life [14[■],42,43]. In addition, comorbid conditions may increase the rate of hospitalization, emergency department visit, and ambulatory care claim [44]. Frequent comorbidities

Table 1. Predictors of asthma control in the elderly

Predictor	Association with age	Effect on asthma	Effect on elderly asthma
Comorbidities			
COPD	Increase with age [14 [■]]	Associated with decline lung function, increased disease severity, and risk of exacerbations [14 [■] ,15]	COPD is associated with uncontrolled asthma [16 [■] ,17,18]
Chronic sinusitis	Frequent in elderly asthmatic patients [2]	Increase the risk to develop late-onset asthma, poor asthma control [19,20]; IgE antibodies to <i>Staphylococcus aureus</i> antigens (SE-IgE) enhanced IgE responses and eosinophilic inflammation [22]	Risk factor for recurrent exacerbation [21]; SE-IgE was associated with severe eosinophilic asthma [23]
Obesity	Frequent in older asthmatic patients [6]	Induce mechanical changes and immune responses [24,25]; associated with exacerbation [26,27]	Increase the risk of recent wheezing and corticosteroid insensitivity [20,28]
Depression	Elderly asthmatic patients are more susceptible to depression [29 [■]]	Lower asthma-related quality of life [29 [■]]; increase the risk of low adherence to therapy; poor asthma control [30,31]	Uncontrolled asthma [29 [■]]; predict future exacerbation [32]
Smoking	Frequent in old age [33 [■]]	Decline in lung function, impaired corticosteroid response, low asthma-related quality of life; hospitalization and increased mortality [6,34,35]	Associated with recurrent exacerbation [33 [■]]
Treatment issues			
Adherence	Low adherence is common in the elderly [35–37]	Low adherence is a predictor of poor asthma control [11]	As adherence increased, asthma control increased [36]
Polypharmacy	The number of medication is higher in the elderly [38,39]	Polypharmacy is associated with poor health outcome [12]	Fewer number of medication is a predictor for better asthma control [13 [■]]

COPD, chronic obstructive pulmonary disease.

in elderly asthmatic patients could be classified as: upper and lower respiratory disease (e.g. COPD and chronic sinusitis); cardiovascular diseases and hypertension; obesity and metabolic diseases (e.g. diabetes mellitus); depression; and other conditions (e.g. smoking). Herein, we summarize most relevant comorbidities predicting asthma control status in elderly patients.

Chronic obstructive pulmonary disease

Increasing attention has been drawn to the overlap of COPD with asthma because of its rising prevalence and serious effects on asthma [14[■]]. The coexistence of asthma and COPD is frequent in elderly patients, with a reported rate of 40–60%, probably resulting from smoking habits or exposure to endotoxins, environment, and latent adenovirus infections [16[■],45,46]. However, the definition of the asthma–COPD overlap syndrome is in the debate [10,14[■],16[■],17,18]. COPD is an independent predictor of the asthma control test (ACT) score (partial $R^2 = 0.05$) and associated with the increased frequency of uncontrolled asthma as defined by an ACT score of less than 20 [15]. Elderly patients with the coexistence of asthma and COPD have a higher prevalence of comorbidity, which could be related to the increased prevalence of exacerbation in these patients [14[■],16[■]]. The coexistence of asthma and COPD also worsens lung function, disease-related quality of life, decreased general health status, increased disease severity, and severe exacerbations [14[■],17,18]. Taken together, identification and appropriate management of COPD in elderly asthmatic patients are critical for better outcome.

Upper airway comorbidities

Sinus symptoms usually occur in elderly asthmatic patients, whereas younger ones often suffer from allergic rhinitis [2]. In the Severe Asthma Research Program cohort, sinus diseases showed the highest prevalence in the oldest patients (cluster 3, with late-onset asthma; cluster 5, with severe late-onset asthma) [47]. Recent papers have reported the association of chronic rhinosinusitis (CRS) with increased risk for developing late-onset asthma and poor asthma outcomes [2,24]. In the Real-world Evaluation of Asthma Control and Treatment (REACT) study [19], CRS is independently associated with uncontrolled asthma. CRS is also reported to be a significant risk factor for recurrent exacerbation in the elderly (OR, 2.24; 95% CI, 1.16–4.33) [21]. In addition, CRS with nasal polyposis has been found to increase risk for severe adult-onset asthma and asthma severity [20,23].

Although allergic rhinitis is insignificantly involved in asthma control, there is increasing evidence that *Staphylococcus aureus* superantigens may contribute to allergic airway diseases, including allergic rhinitis and asthma [48,49]. As compared with patients with allergic rhinitis only and healthy controls, elevated IgE antibody to *S. aureus* (SE-IgE) in patients with allergic asthma accompanied by allergic rhinitis suggests amplified IgE responses and eosinophilic inflammation [22]. SE-IgE is independently associated with elderly patients with severe eosinophilic asthma and comorbid CRS [23].

Obesity

There are vague conclusions on obesity and its association with elderly asthma. Excessively obese patients with a high BMI of greater than 35 have been demonstrated to correlate with the prevalence of wheeze and physician-diagnosed asthma [50]. A high BMI is independently associated with the ACT score and increases the frequency of uncontrolled asthma (ACT < 20) [15]. Obesity is considered a risk factor for exacerbation in newly diagnosed and preexisting asthma [26]. From a European internet-based survey comparing well controlled (ACT ≥ 20) versus partially controlled asthmatic patients (ACT ≤ 19), the latter is older and has a higher prevalence of obesity [27].

Amelink *et al.* [20] have reported that obesity may not be related to asthma severity in asthmatic patients with adult-onset phenotypes, since there is no significant difference in BMI between severe and nonsevere asthmatic patients. However, the impact of obesity on asthma pathogenesis should be verified in terms of mechanical changes and immune responses related to the adipose tissue [25]. In adult and elderly patients, comorbid obesity has been reported to increase the risk of recent wheezing and corticosteroid insensitivity [20,28,51].

Depression

Although psychological conditions affect asthma control, there are increasing concerns about depression and its impact on asthma. Depression is found to be associated with poor asthma control because of modified behaviors and low quality of life [30,31]. High levels of depressive symptoms increase the frequency of low treatment adherence, leading to poor asthma control in elderly patients [52]. Moreover, elderly asthmatic patients are more likely to suffer from depression. Choi *et al.* [29[■]] have shown a significantly increased prevalence of depression in elderly patients with uncontrolled asthma compared with those with controlled asthma. Patients

with asthma and depression show a significant lower asthma-related quality of life as evaluated by the ACT and Asthma-Specific Quality of Life questionnaire, although there is no significant difference between elderly and nonelderly groups [29[¶]]. Depression is determined as a predictor of future exacerbation, highlighting the need for depression screening and evaluation in the elderly population [32].

Smoking

Smoking is well documented as a risk factor for many clinical conditions, such as asthma and COPD, which in turn aggravate asthma symptoms [24,34]. Many investigators have indicated that smoking increases the frequency of uncontrolled asthma [15,27,34]. In a Korean elderly asthma cohort, a history of exacerbation is frequent in smoking patients (cluster 3) (14.8%) [33[¶]]. Moreover, smoking is related to rapid lung function deterioration, impaired corticosteroid response, low asthma-related quality of life, frequent hospitalization, and increased mortality [34,35]. It is noteworthy that smoking is a modifiable factor and that in adult asthma patients who stop smoking showed amelioration in airway obstruction compared with asthmatic patients who continue to smoke [53]. In line with the beneficial effect of smoking cessation in adult asthma patients, this should be considered in the management of elderly asthma, and further studies about the effect of smoking cessation in the elderly population are needed.

Other comorbidities

In addition to identified predictors, some clinical factors, such as a history of pulmonary tuberculosis, infectious exacerbation, occupational exposure, persistent airway obstruction, and obstructive sleep apnea, are found to be associated with uncontrolled asthma in the elderly [40,54,55]. Elderly patients may suffer from corticosteroid-related diseases, such as osteoporosis and cataracts [35]. These diseases show increasing prevalence with age and are associated with asthma treatment with inhaled/oral corticosteroids [56,57]. Further studies on these corticosteroid-related diseases in elderly asthmatic patients are warranted.

EOSINOPHILIC INFLAMMATION

Airway eosinophilic inflammation has been shown to be a marker for disease activity [58], and monitoring sputum eosinophil counts has been suggested to be used for evaluation of asthma control status

[59]. It is not known whether age-related changes in immune responses, termed immunosenescence, affect the activation of eosinophils and eosinophilic inflammation in elderly asthmatic patients. In a study comparing eosinophil function between a younger group (20–40 years old) and an older group (55–80 years old), airway eosinophilia was comparable in younger and older asthmatic patients, however, eosinophil degranulation in response to IL-5 stimulation was significantly decreased in the older asthmatic group [60]. There are several studies of animal models that examined the effect of aging on airway inflammation. One of these studies demonstrated attenuated airway inflammation, especially eosinophils, in aged rats. However, there is concern that these animal models do not accurately represent human elderly asthma [61]. Further studies on the role of eosinophil inflammation with a large elderly asthma cohort, especially the proportion of eosinophilic asthma or the role of eosinophil activation in elderly asthma exacerbation/control status compared to younger population asthma, are warranted.

TREATMENT ISSUES ASSOCIATED WITH ASTHMA CONTROL IN THE ELDERLY

Treatment adherence

Low treatment adherence is a predictor of poor asthma control and asthma exacerbation in both the general and elderly asthma populations [11,32,62]. In a randomized, placebo-controlled trial, long-term use of antiasthmatic medications, even in case of mild asthma with low-dose inhaled corticosteroids (ICSs), reduces asthma symptoms, improve asthma control and quality of life, improves lung function, diminishes airway hyperresponsiveness, and reduces the frequency and severity of exacerbation [63]. Low treatment adherence has been reported to be common in an elderly asthma population [2]. Only 9–21% of the total study patients had high treatment adherence in a retrospective study [36]. As treatment adherence increased by proper monitoring based on an electronic diary and drug usage, asthma control assessed by the ACT and the peak expiratory flow rate increased in a 1-year follow-up study of elderly asthmatic patients [36]. Therefore, proper monitoring and improvement of adherence to anti-asthmatic medications are essential for achieving asthma control in elderly asthmatic patients.

Several factors intentionally or unintentionally lead to low treatment adherence in an elderly asthma population [35]. Excessive concerns about side-effects of medication, cost considerations, a poor knowledge about asthma, and asthma treatment or

its consequences can cause elderly asthmatic patients not to adhere to regular treatment [35,37]. Complicated medication regimens, decreased cognitive function, impaired vision, and musculoskeletal abnormalities, which affect the ability to use inhaler devices, are factors that make elderly asthmatic patients fail to adhere to treatment [64].

Cognitive function, as assessed by Mini-Mental State Examination, correlates with treatment adherence regardless of tools for evaluating the treatment adherence [36]. A significant positive correlation between cognitive function and asthma control status has been studied [Hur and Ye, unpublished work]. A recent study has revealed that cognitive function explains the impact of health literacy on health behaviors and suggested the needs to decrease cognitive burden and to simplify the tasks for better asthma control in elderly asthmatic patients [65²²]. A low physical functioning score, which can be influenced by cognitive function, is associated with poor asthma control [13²,66].

Appropriate techniques for inhaler device use are challenging in elderly asthmatic patients. A majority of elderly asthmatic patients are unable to properly use inhalers, especially metered-dose ones, even after proper instructions [2,65²²,67]. Inadequate timing of actuation and inhalation is the most frequent error. Although dry-powder inhalers are easier to use than metered-dose ones, inadequate handling of turbuhalers are associated with older age [2,67,68].

A randomized, open-labelled, prospective study provides evidence for treatment strategy in elderly asthmatic patients [69²²]. This study revealed that the efficacy of the addition of montelukast to low-dose ICS (MON-400BUD group) was comparable to that of medium-dose ICS (800BUD group) on asthma control and that the MON-400BUD group had reduced frequencies of asthma exacerbations and adverse reactions, including sore throat, compared with the 800BUD group. Given that challenges of appropriate use of inhaler devices and high adherence to oral medications compared with ICSs [70], prescription of oral anti-inflammatory agents, including leukotriene receptor antagonists, as a maintenance medication can be a good strategy for asthma control in elderly asthmatic patients. Therefore, we should consider multiple factors that affect treatment adherence in elderly asthma and provide adequate patient education about asthma treatment on a regular basis [2].

Polypharmacy

The number of ingested medications was larger in elderly patients than in younger ones [38].

Polypharmacy is a known risk factor for mortality and mobility in older adults [12,39]. It has been documented that polypharmacy is a predictor of hospitalization, emergency department visit, and mortality in the elderly [62]. In a recent prospective study, fewer medications used by elderly patients is a significant predictor of good asthma control (OR, 0.863; [0.782, 0.953], $P = 0.004$) [13²]. Although large number of medications is supposed to result from primarily higher number of comorbidities in the elderly, there is no direct association of the number of comorbidities and asthma control, but there is close relation between the number of medication/the sort of medication with asthma control [13²,38]. Many studies have suggested that a large number of medications are associated with adverse health outcomes caused by low treatment adherence, adverse drug reactions, drug–drug interactions, side-effects of medications, and inappropriate prescriptions [12,37]. Considering low cognitive function in elderly asthmatic patients, polypharmacy may result in low treatment adherence. Apart from the higher prevalence of comorbidities in elderly asthmatic patients, polypharmacy can affect asthma control status. There have been a few intervention studies showing the reduction in number of medications in the elderly [12]. For better asthma control, it is essential to investigate all medications that each patient is taking and to reduce the number of medications.

CONCLUSION

We are in the era of rapid aging of the global population. Considering the increasing prevalence of asthma and high morbidity/mortality of elderly asthmatic patients, identifying and regulating the predictors of asthma control are critical. Compared with younger asthmatic patients, elderly asthmatic patients are affected by various factors, including comorbidities, low treatment adherence, and polypharmacy, which make the management of elderly asthmatic patients difficult. Multifactorial assessment of elderly asthma is important for better asthma control. Further studies on the strategy for elderly asthma management are warranted.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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