



High ACT score is not sufficient to reduce the risk of asthma exacerbations in asthma with low lung function

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ABSTRACT

Background: Low forced expiratory volume in 1 s (FEV₁) is a risk factor for asthma exacerbations (AEs). We aimed to determine if asthma control could reduce the future risk of AEs in patients with low FEV₁. This study was conducted to evaluate the future risks of AEs within six months according to Asthma Control Test™ (ACT) score and FEV₁.

Methods: A total of 565 patients with asthma were enrolled from the COREA cohort. The ACT score, lung function test, and number of AEs were assessed at baseline, three-month follow-up, and six-month follow-up with conventional asthma treatments by asthma specialists in real clinical settings.

Results: Female sex, low ACT score, low FEV₁, low FVC, and AE history in the previous three months were related with increased AEs within six months. AEs during six-month follow-up occurred in 24% of patients with ACT < 20 and FEV₁ < 60% at baseline. Among patients with an ACT score ≥ 20, 3.4% of patients with an FEV₁ < 2.16 L and 9.8% of patients with FEV₁ ≥ 2.16 L had experienced AEs (P = 0.01), although no differences were observed in the presence of AEs within six months according to the predicted FEV₁ (FEV₁ ≥ 60% vs. FEV₁ < 60%, 5.66% vs. 8.51%, P = 0.65).

Conclusion: Patient with low FEV₁ seemed to show higher risk of AEs than those with near-normal FEV₁ despite ACT score ≥ 20 and asthma treatments. Therefore, treatment strategies that prevent AEs are needed in high-risk asthmatic patients.

1. Introduction

Asthma exacerbations (AEs) are related to decreased lung function, increased mortality, and increased cost burden of healthcare [1]. Among the risk factors for AEs, the predicted forced expiratory volume in 1 s (FEV₁% pred.) remained an independent predictor of subsequent asthma attacks [2]. The respiratory impairments determined at baseline by spirometry are associated with increased risks of hospitalization in

the succeeding year [3]. Several studies have reported that low FEV₁ (% pred.), particularly FEV₁ < 60%, increases the risk of AEs [4,5]. Despite the known association between low FEV₁ and AEs, it remains difficult to predict the future risk of AEs in an individual asthmatic patient [6], and there has been little research on treatment goals or strategy for reducing the future risks of AEs for patients with low FEV₁.

In addition to low FEV₁, the presence of uncontrolled symptoms is an important risk factor for exacerbations [7]. Among the tools to

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access asthma symptom control, the Asthma Control Test™ (ACT) is a symptom- and patient-based questionnaire that is widely used to evaluate asthma control status in clinical practice. Previous work has shown that an ACT score ≥ 20 is usually regarded as well-controlled asthma, whereas an ACT score < 19 (not well-controlled asthma) correctly predicted GINA-defined partly controlled/uncontrolled asthma 94% of the time [8]. Considering that asthma symptom control could be a potentially modifiable risk factor for AEs, maintaining asthma control for patients with low FEV₁ may also reduce their future risk of AEs. However, there are few data on whether the same standard, namely, ACT score ≥ 20 , could be applied to high-risk asthmatic patients and on the level of asthma control that could reduce future risks in patients with low FEV₁.

This study was conducted to evaluate the future risks of AEs within 6 months according to the ACT score and FEV₁ and whether achieving an ACT score ≥ 20 is enough for patients with low FEV₁ to prevent or reduce the future risk of AEs.

2. Methods

2.1. Study subjects

The asthmatic patients who had been followed up over 9 months were enrolled from an adult asthma cohort (≥ 18 years old), namely, the Cohort for Reality and Evolution of Adult Asthma in Korea (COREA), which was launched in 2005 and included 11 university hospitals [9]. The inclusion criteria were as follows: diagnosis of asthma based on the presence of asthma symptoms and airway reversibility [10], conventional asthma treatments by asthma specialists for more than three months, and follow-up visits over six months (Fig. 1). Patients who missed any visit during the study period or had no data on demographic characteristics, smoking status, ACT score, or lung function tests were excluded from the study. In the COREA cohort, patients were followed up every three months after their initial enrollments. There were both newly diagnosed patients and chronically treated patients at the initial enrollment for the cohort; however, after enrollment, every patient was treated conventionally by asthma specialists. At the time of enrollment, the demographic characteristics, smoking status, asthma severity, history of asthma medication, and number of AEs in the previous year were collected. At the follow-up visit every three months, data on ACT scores, lung function test, number of AEs, frequency of daytime and nighttime symptoms in the previous three months, and medication status were collected. Considering that there were no data regarding ACT score at the initial enrollment of the COREA cohort, we regarded the data at the three-month visit as the baseline data in this study (Fig. 1). The data at baseline, three-month follow-up, and six-month follow-up from baseline were then reviewed. The number of AEs was defined by the total number of unscheduled outpatient clinic visits, emergency room visits, and admissions due to

AEs. The number of severe AEs was defined as the number of AEs that require emergency room visits and admissions. Spirometry was used to determine FEV₁, forced vital capacity (FVC) and the FEV₁/FVC ratio [11,12]. Skin prick tests were performed for 13 common inhalant allergens, and a mean wheal diameter ≥ 3 mm was regarded as a positive reaction. Atopy was defined as a positive skin prick test result for one or more of the inhalant allergens. Medication history was defined as the use of any asthma-controller medications, including ICS, ICS combined with long-acting β_2 -agonists, leukotriene modifiers, oral theophylline, and oral corticosteroids, during the previous 4 weeks. The study protocol was approved by the Institutional Review Board of each participating hospital, and written informed consent was obtained from all patients.

2.2. Statistical analysis

All statistical analyses were performed using R 3.4.3 software (R Project for Statistical computing, Vienna, Austria; www.r-project.org). Baseline characteristics were presented as means and standard deviations for continuous variables and relative frequencies for categorical variables and were compared using Student's T-test, Mann-Whitney U test, or chi-squared test. Multiple logistic regression analysis was used to evaluate the effects of multiple factors on the presence of AEs during the study period. A stepwise multiple logistic regression analysis was used to establish a model that can explain future AE risk on the basis of sex, FEV₁, ACT score, and number of exacerbations in the previous three months. The cutoff of meaningful P-values in the stepwise process was $P < 0.10$. Spearman correlations were calculated for variables of interest that did not follow a normal distribution, and chi-squared test was used to compare the occurrence of AEs among patient groups according to ACT score and FEV₁. We produced receiver operating characteristic (ROC) plots for FEV₁ (L), FEV₁ (% pred.), and ACT score and calculated the area under the curve (AUC) as the performance of the classifier for each ROC curve. Statistical significance was determined at $P < 0.05$.

3. Results

3.1. Baseline characteristics

A total of 565 asthmatics were enrolled. Table 1 presents the characteristics of the study population. We observed AEs in 49 patients (8.7%), including 13 with severe AEs during the six-month follow-up. Medication history during the previous 4 weeks and the season when patients were enrolled were not different between patients with AE and without AE (supplement). They demonstrated a lower ACT score, lower FEV₁ (% pred.), lower FVC (L), and more AEs in the previous three months (Fig. 2). There were more females than males in these frequent AE patients. In a stepwise logistic regression analysis using sex, FEV₁ (%)

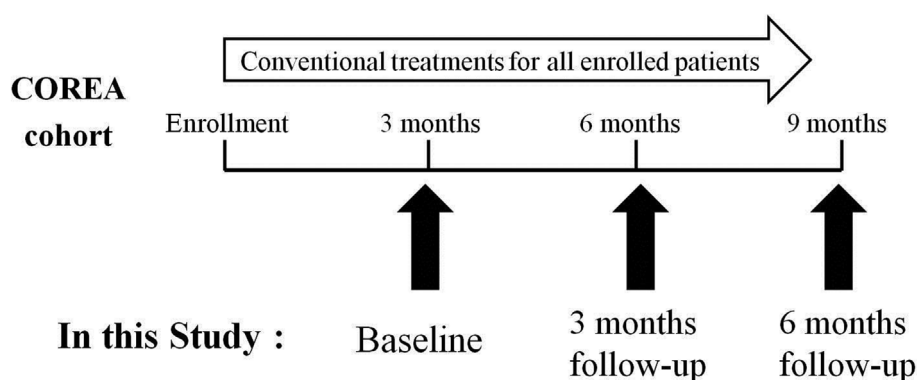


Fig. 1. Study design and FEV₁ improvement after six-month treatments.

Table 1
Baseline characteristics of the study population.

Characteristics	Exacerbation (+) (n = 49)	Exacerbation (−) (n = 516)	P-value	All patients (n = 565)
Age, yr (SD)*	52.1 (± 16.7)	52 (± 14.7)	0.948	52 (± 14.9)
Sex, % female	35 (71.4%)	265 (51.4%)	0.011	300 (53.1%)
BMI (kg/m ²)	27.6 (± 25.8)	24.0 (± 3.2)	0.345	24.3 (± 8.2)
Smoking			0.361	
Never	26 (53.1%)	218 (42.8%)		237 (42.4%)
Former	18 (36.7%)	219 (42.9%)		244 (43.7%)
Current	5 (10.2%)	73 (14.3%)		78 (13.95%)
Atopy**	15/31 (48.4%)	146/322 (45.3%)	0.892	161/353 (45.6%)
Length of asthma treatment			0.902	
3 months	22 (44.9%)	215 (41.7%)		234 (41.95%)
3 months–15 months	8 (16.3%)	86 (16.7%)		94 (16.64%)
< 15 months	19 (38.8%)	215 (41.7%)		234 (41.42%)
Medication history, %	65.3	61.63	0.724	61.9
Medium to high dose ICS, %	0	2.5	NA	2.3
Low dose ICS + LABA, %	12.2	8.5	0.381	8.8
Medium to high dose ICS + LABA, %	53.1	51.1	0.799	51.3
Lung function tests (SD)*				
FEV ₁ , L	2 (± 0.7)	2.4 (± 0.8)	0.000	2.4 (± 0.8)
FEV ₁ , %	76.2 (± 22.5)	83.3 (± 19.1)	0.037	82.7 (± 19.5)
FVC, L	2.7 (± 0.7)	3.2 (± 1)	0.000	3.2 (± 1)
FVC, %	85.1 (± 14)	89 (± 16.8)	0.070	88.7 (± 16.6)
FEV ₁ /FVC, %	70.9 (± 16.2)	74.5 (± 13.6)	0.147	74.2 (± 13.9)
No. of patients with AEs (no. of AEs, median [range])				
In previous 15 months	10 (1.5 [1.0–2.75])	91 (1 [1.0–2.0])	0.413	101 (1 [1.0–2.0])
In previous 3 months	11 (0 [0–0])	24 (0 [0–0])	0.017	35 (0 [0–0])
ACT score	19.20 (± 5.05)	21.82 (± 3.31)	0.001	21.59 (± 3.57)
Everyday functioning	3.8 (± 1)	4.4 (± 0.9)	0.000	4.3 (± 0.9)
Frequency of dyspnea	4.1 (± 1.2)	4.5 (± 0.9)	0.022	4.4 (± 0.9)
Night time symptoms	3.7 (± 1.6)	4.5 (± 1)	0.000	4.5 (± 1.1)
Rescue medication usage	4.3 (± 1.1)	4.6 (± 1)	0.169	4.5 (± 1)
Sense of asthma control	3.4 (± 1)	3.8 (± 0.8)	0.002	3.8 (± 0.8)

*Mean (SD).

** Data about atopy were available for 31 and 322 patients in each group.

Exacerbation (+): patients with asthma exacerbations within six months; exacerbation (−): patients without asthma exacerbations within 6 months; SD: standard deviation; BMI: body mass index; LABA: long acting beta-agonist; ICS: inhaled corticosteroid; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; AEs: asthma exacerbations; No.: number; ACT: asthma control test.

pred.), ACT score, and number of exacerbations in the previous three months, the probability for AEs in the following six months decreased according to the unit increase at baseline in ACT score, as well as FEV₁ (% pred.) (OR: 0.90, CI 95%: 0.84–0.97, *P* = 0.01 and OR: 0.98, CI 95%: 0.97–1.00, *P* = 0.05, respectively). For FEV₁ (L) instead of FEV₁ (% pred.) in this logistic regression analysis, the probability for AEs in the following six months decreased according to the unit increase in FEV₁ (L) (OR: 0.57, CI 95%: 0.38–0.86, *P* = 0.01). There was a weak correlation between baseline ACT and FEV₁ (% pred.) (*r* = 0.196, *P* < 0.0001) and the number of AEs in the previous three months were positively correlated with the number of AEs in the following six months (*r* = 0.092, *P* = 0.002).

The ACT score at baseline was lower in patients with AEs during six months than in patients without AEs (AE: median [range], 21 [8–25] vs. non-AE: 23 [5–25]; *P* = 0.0008; Fig. 2). Among the five items assessed in the ACT, the effect of asthma on everyday functioning, frequency of dyspnea, frequency of nighttime symptoms, and subjective sense of asthma control were also lower in patients with AEs in the following six months. However, there were no differences in the frequency of rescue medication usage at baseline between patients with AEs during six months and those without AEs (Table 1).

3.2. Prediction of AEs using ACT and FEV₁

To predict AEs in the following six months by using ACT or FEV₁, the ROC curve showed low sensitivity and specificity (Fig. 3). By using an optimal cutoff value of ACT score = 20, the sensitivity and specificity were 46.9% and 79.5%, respectively, with an AUC of 0.656. By using the optimal cutoff value of FEV₁ (% pred.) = 95.7%, the AUC was 0.588, whereas the AUC was 0.647 using FEV₁ (L), the optimal cutoff

value 2.16 L. When the ACT score and FEV₁ (% pred.) were combined to improve sensitivity, the combined values of ACT score = 18 and FEV₁ (% pred.) = 77% increased the AUC to 0.658 and the sensitivity to 79.6%, but specificity decreased to 53.5%.

Fig. 4 shows the distribution of baseline ACT scores and FEV₁ in our study sample according to the presence of AEs after six months. There was a difference in the presence of AEs within 6 months according to ACT score (ACT ≥ 20: 6.0% vs. ACT < 20: 17.8%, *P* < 0.0001). However, no significant difference was observed for FEV₁ groups (FEV₁ ≥ 60%: 7.9% vs. FEV₁ < 60%: 13.9%, *P* = 0.078, Fig. 3A). No differences were observed in the presence of AEs within six months according to FEV₁ (FEV₁ ≥ 60% vs. FEV₁ < 60%) among patients with ACT ≥ 20 (5.66% vs. 8.51%, *P* = 0.65), and among those with ACT < 20 (16.35% vs. 24%, *P* = 0.54). Meanwhile, AEs occurred in 24% of patients with both ACT < 20 and FEV₁ < 60%. For the criteria of ACT score = 20 and FEV₁ = 2.16 L, which was the optimal cutoff value for FEV₁ (L) in the ROC curve, there were significant differences in the presence of AEs between patients with FEV₁ < 2.16 L and those with FEV₁ ≥ 2.16 L among patients with ACT ≥ 20 (3.44% vs. 9.77%, *P* = 0.01).

4. Discussion

Among asthmatic patients undergoing conventional treatment, female sex, low ACT score, low FEV₁, low FVC (L), and AEs in the previous three months were related to AEs in the following six months. The risk of AEs in the following six months seemed to be higher in asthmatic patients with low FEV₁ than in those with near-normal FEV₁ despite asthma symptom control in terms of ACT score ≥ 20.

Maintaining ACT ≥ 20 could reduce the future risk of AE in

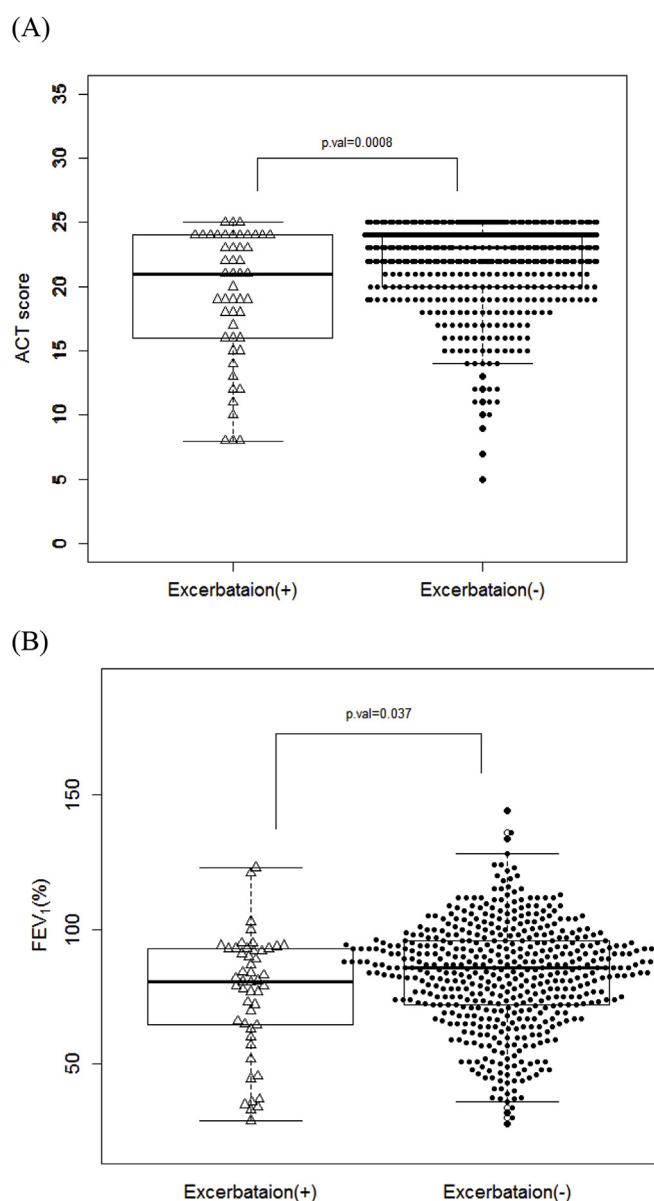


Fig. 2. (A) The ACT score and (B) FEV₁ (% pred.) at baseline were lower in patients with AEs during six months ($P = 0.0008$ and $P = 0.037$, respectively). Box and whisker plots present the median with interquartile range and full range.

asthmatic patients with low FEV₁, but it does not appear to be enough to reduce the future risk of AE among asthmatic patients with near-normal FEV₁. These data suggest that treatment strategies, including more strict asthma control or additional medications to prevent AEs, are needed. The FEV₁ is the most significant and independent predictor for AEs [2], and low FEV₁ has previously been associated with an increased risk of AEs in one to three years [2–5]. On the contrary, asthma symptom control is related to the risk of AEs in the relatively near future [13–15]. Schatz et al. [13] showed a 33% increase in the prevalence of AEs over the next 12 months for a 3 unit difference in ACT score. McCoy et al. [16] demonstrated that symptom questionnaires were predictive of subsequent asthma episodes, including an increase in rescue medication usage and a decrease in peak flow within 28 days. Our current study showed consistent results that ACT score was closely related with AEs within 6 months but also suggested that an ACT score ≥ 20 was not enough to prevent AEs in the near future for asthmatic patients with low FEV₁. More than twice the number of patients

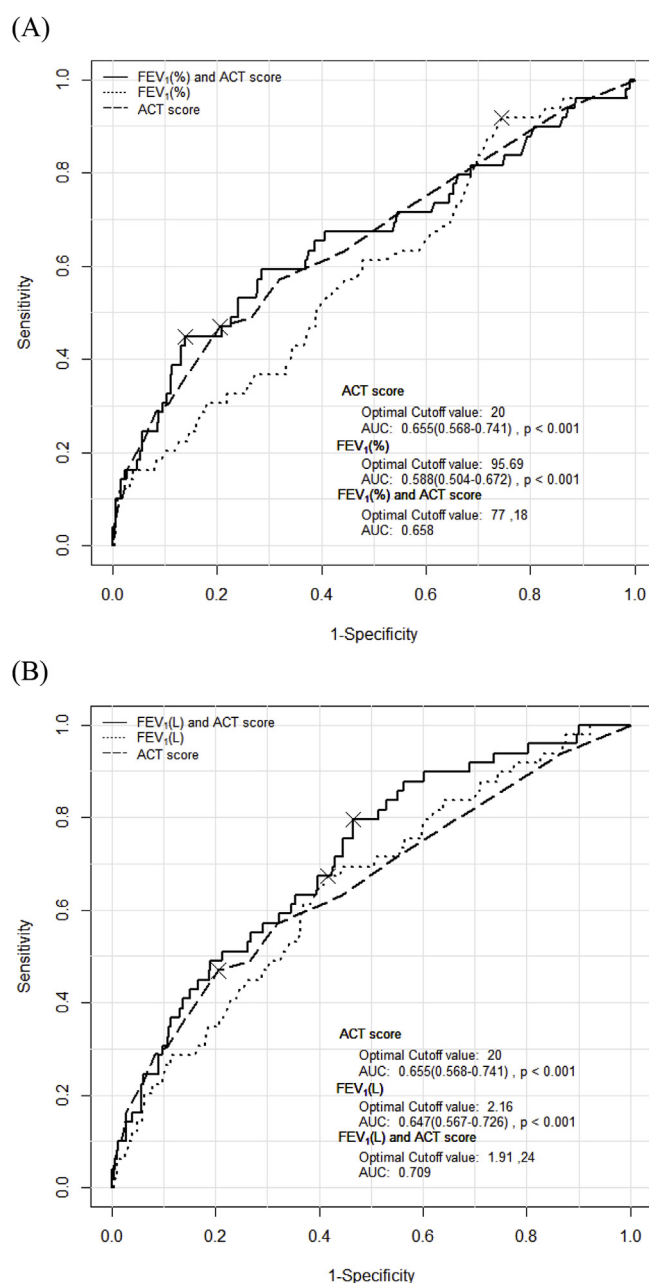


Fig. 3. ROC curve to predict AEs in the following six months. (A) ROC curve with FEV₁ (% pred.) and ACT score, (B) ROC curve with FEV₁ (L) and ACT score.

experienced AEs within six months despite the asthma treatments by asthma specialists. Although differences in AE risk was not statistically significant between patients with FEV₁ (% pred.) $\geq 60\%$ and $< 60\%$ (probably because of the small number of patients with low FEV₁), FEV₁ (L) showed differences in AE risk between asthmatic patients with FEV₁ (L) ≥ 2.16 L and < 2.16 L more clearly.

The findings in the current study suggest that management for the future risk of AEs in high-risk patients is not enough in current stepwise treatment strategies using ICS because asthmatic patients with a low FEV₁ and ACT showed significant increases in AE risk in the near future despite the asthma treatment by specialists. We observed AEs in 24% of patients with ACT < 20 and FEV₁ $< 60\%$. Current asthma guidelines focus on the day-to-day control of symptoms but there are currently no details on the management of future risks. Many studies have suggested that daily control and future risk could be separate entities in asthma

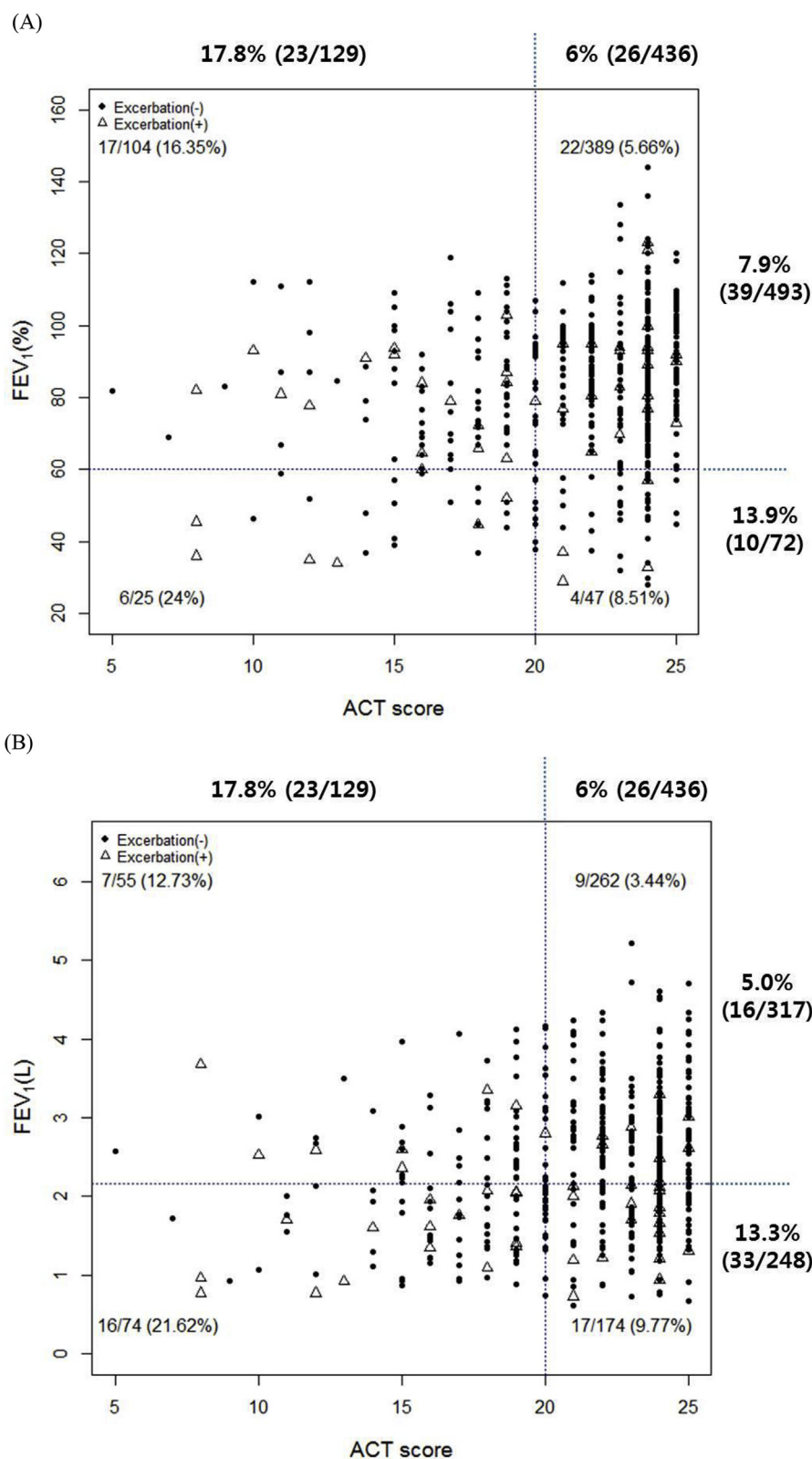


Fig. 4. Distribution of baseline ACT score and FEV₁ in the study population: (A) 24% of patients with ACT < 20 and FEV₁ < 60% (dashed line) showed AEs within 6 months despite conventional asthma treatments by asthma specialists; (B) 21.62% of patients with ACT < 20 and FEV₁ < 2.16 L (dashed line) showed AEs within 6 months.

treatments. The benefits of conventional asthma treatments were unequal in asthma control and the future risk of AEs [17,18]. Uncontrolled eosinophilic bronchitis in asthma may lead to fewer daily symptoms but a higher rate of asthma attacks [19,20]. A high dose of ICS could reduce

AEs; on the contrary, β -agonist could improve symptoms but could possibly increase the risk of fatal asthma attacks. Furthermore, Turner et al. [21] reported that AEs were not reduced despite an increase in ICS usage. Many clinicians shorten the follow-up interval for asthmatic

patients who are showing risk factors for AEs (including low FEV₁) to monitor FEV₁ and asthma control. However, there have been no new strategies for reducing the risk of AEs. Fortunately, there has been an increase in the reports of asthma treatments to reduce AEs. Biological agents, such as mepolizumab, had no effect on symptom improvements but showed a decrease in exacerbations [22,23]. Sputum-guided treatment is also associated with a reduced risk of AEs when compared with current stepwise treatment [24].

The current study showed that FEV₁ (L) may be more effective in identifying patients who are at high risk of AEs within six months than FEV₁ (% pred.). This might be explained by FEV₁ (L) reflecting other risk factors for exacerbations, such as sex and age [2,5,25], whereas FEV₁ (% pred.) is assessed as a percentage relative to the normal population of people with the same age, sex, and height. Prediction models with ACT and FEV₁ in the current study showed low sensitivity and specificity to predict AEs within six months. This suggests that there are many other factors related to the risk of future healthcare utilization. Current study showed that female sex and frequent exacerbations in the previous three months were associated with increased AE risk within the next six months; this finding is consistent with previous findings [2,5,25–28]. Among the five questions assessed in the ACT, there was no association between the frequency of reliever use and AEs within six months; although other four items on the ACT regarding symptom frequency and effect of asthma on daily living showed an association with exacerbations. Conversely, Cajigal et al. [29] reported that rescue medication usage is the most sensitive question in predicting the risk of severe AEs within six months among patients with severe asthma, 30% of whom experienced severe AEs during the six-month study period. These studies suggest that the interpretation of individual questions in ACT for predicting the risk of AEs could be different among asthmatic patients with various severities of asthma and regional background because the usage of reliever medications could be dependent not only on their symptoms but also on individual difference in thresholds or experience. The current study suggests that the frequency of reliever usage in ACT may not be a sensitive predictor for AE among patients with mild to moderate asthma in the clinical field in Korea.

Many studies have tried to predict AEs, but there are limited studies to guide clinicians on methods to discriminate patients who are at higher risk for AEs in the near future and develop risk management strategies for those patients. Gelb [30] studied 13 stable asthmatics with a combined baseline fractional concentration of exhaled nitric oxide > 28 ppb and an FEV₁ (% pred.) < 76% and found that 85% of patients had increased probability for future exacerbation within 18 months. Sato et al. [15] suggested that the standard to discriminate the exacerbations was ACT ≤ 23 and FEV₁ (% pred.) ≤ 91.8% for stratifying the risk of future exacerbations within 1 year by classification and regression tree analysis. Most of these studies were small sample studies or on a relatively long-term basis. Urs Frey [26] proposed a complex dynamic model by using the fluctuation analysis of a long time series of lung function to assess the risk of future asthma episodes, but it uses long-term prognosis in individuals instead of a clinical method to discern the patients with the highest risk in real clinical practice. The current study could reconfirm the importance of FEV₁ and asthma control as risk factors for AEs in the near future and could demonstrate that controlling asthma with conventional treatments is the most practical way to reduce AE incidence in the future. Furthermore, additional treatment strategies for reducing AE risk are needed in high-risk asthmatics with low FEV₁.

This study has several limitations. First, there were a small number of patients in this study and even fewer patients with AEs during our study period. In particular, the number of asthmatic patients with low FEV₁ was small, thus possibly explaining the lack of significant differences in the future risk of AEs between patients with low FEV₁ and with near-normal FEV₁. However, the current study had enough statistical power to demonstrate the importance of asthma control for patients

with low FEV₁ because the study was designed to define AEs and evaluate ACT score and lung function in real clinical practice settings as a cohort study. Second, there are many other factors that affect asthmatic symptoms in addition to lung function. For example, there were many cases with discrepancies between changes in asthma symptoms and changes in FEV₁ in patients under asthma treatment. Larger studies with more clinical data are needed to discriminate high-risk patients and determine the best course of risk management. Third, there are some data which were not evaluated in COREA cohort. Systemic use of corticosteroids and usage of SABA have been widely used to assess the asthma exacerbation [31]. Unfortunately systemic use of corticosteroids is not included in follow-up information of COREA cohort although usage of SABA was collected as one of asthma control test item. The causes of AEs were not evaluated in most cases in COREA cohort. However, unscheduled outpatient clinic visits, emergency department visits and hospitalization are also widely-used definitions of AEs, especially in observational studies including cohort study regardless of etiologies for AEs [31]. Finally, this study could not suggest which treatment strategies would reduce the risk for AEs caused by low FEV₁. This study just showed the unmet needs for additional treatments strategies for high risk asthmatic patients. Large prospective studies are needed to find treatments to reduce risk of AEs in asthmatic patients with low FEV₁.

In conclusion, asthmatic patients with low FEV₁ showed a higher risk of AEs within six months than those with near-normal FEV₁ despite asthma symptom control in terms of ACT score ≥ 20. Asthma treatments based on asthma control do not go far enough to reduce the future risk of AEs in patients with low FEV₁. Treatment strategies such as stricter asthma control or additional medications to reduce the risk of AEs may be needed to treat asthmatic patients with low FEV₁.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2019.02.010>.

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Supplement

Table S1. The season when the patients were enrolled

	Exacerbation (+) (n = 49)	Exacerbation (-) (n = 516)	P-value
Spring	12 (24.5%)	88 (17.1%)	<i>P</i> = 0.515*
Summer	15 (30.6%)	146 (28.3%)	
Fall	12 (24.5%)	158 (30.6%)	
Winter	10 (20.4%)	124 (24.0%)	

* Chi-squared test