

Daytime and Nighttime Visual Analog Scales May Be Useful in Assessing Asthma Control Levels Before and After Treatment

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Purpose: Few questionnaires evaluate daytime and nighttime symptoms separately, although these assessments could contribute to the improvement of disease control levels and prevention of future risks in asthma. The purpose of this retrospective study was to investigate whether daytime and nighttime visual analog scales (VAS) are useful in measuring the perception of symptoms, assessing disease control levels, and evaluating the treatment effects in asthma.

Patients and Methods: Self-reporting asthma control tests (ACT) before and after treatment are standardized tests used to determine disease control levels. A multiple regression analysis was performed to determine the correlation between daytime and nighttime VAS and the characteristics of patients before treatment, as well as the changes in VAS and lung functions and fractional exhaled nitrogen oxide after treatment in 55 treatment-naïve symptomatic adult patients with asthma.

Results: Both daytime ($r = -0.57, P < 0.0001$) and nighttime ($r = -0.46, P < 0.0001$) VAS correlated well with ACT scores, and there was a correlation between daytime and nighttime VAS ($r = 0.33, P = 0.0148$) before treatment. In addition, the changes in daytime ($r = -0.65, P < 0.0001$) and nighttime ($r = -0.44, P < 0.0001$) VAS were significantly associated with changes in the ACT scores. The multiple regression analysis (β [95% confidence interval]) revealed that improvements in the daytime (-2.33 [-4.55 to -0.11], $P = 0.0405$) and nighttime (-3.09 [-6.25 to 0.07], $P = 0.0505$) VAS were associated with an increased forced vital capacity after treatment, although there was no correlation between the VAS and characteristics before treatment.

Conclusion: Our study demonstrated that daytime and nighttime VAS were useful in assessing disease control levels and evaluating the treatment effects in asthma.

Keywords: asthma, symptoms, visual analog scale, asthma control test, adult

Plain Language Summary

We demonstrated that the daytime and nighttime visual analog scale (VAS) were associated with the asthma control test (ACT) scores before and after treatment in treatment-naïve and symptomatic patients with asthma. The nighttime VAS was higher than the daytime VAS, and the nighttime VAS also improved faster than the daytime VAS and the ACT score after treatment. We believe that both daytime and nighttime VAS are useful in assessing asthma control levels and evaluating the treatment effects in symptomatic patients with asthma.

Introduction

Uncontrolled and/or severe asthma is a social problem worldwide,¹⁻³ as well as in Japan.⁴ In 2021, a survey conducted in Middle East and North Africa, which used the Global Initiative for Asthma (GINA) criteria, reported that the percentage of patients with partly controlled and uncontrolled asthma was 29.1% and 41.5%, respectively.¹ In 2009, a US survey demonstrated that although 71% of patients self-reported “completely controlled” or “well-controlled” statuses, the

percentages of patients with asthma who needed urgent care visits twice and emergency department visits once per year were 67% and 60%, respectively.² A 2016 global cross-sectional study demonstrated that among 8111 patients, 18.0% and 38.5% of patients had partly controlled and uncontrolled asthma, respectively.³ Japanese internet surveys reported that considering the GINA criteria, 49.8% and 15.1% of patients had partly controlled and uncontrolled asthma, respectively. Daytime and nighttime asthma symptoms were experienced by 51.5% and 44.9% of patients, respectively.⁴ A global study found that undertreatments are still observed for the management of asthma worldwide.⁵

The goal of asthma management is to achieve a well-controlled asthma level.⁶ Understanding the perception of asthma symptoms is necessary for the assessment of asthma control levels. An asthma control test (ACT) has been evaluated for understanding asthma control levels and is used worldwide.^{7,8} In critical practice, the ACT has 5 items and the total ACT score, but not each item, is expressed as the disease control level.^{7,8} Similarly, the visual analog scale (VAS) has been evaluated as a useful tool for assessing the perception of respiratory symptoms.^{9–13}

Nocturnal symptoms are accompanied by circadian variations in small airway inflammation, hyperresponsiveness, and dysfunction in asthma.^{14–16} Nocturnal asthma is associated with emergency visits, increased morbidity, and worsening disease control levels. Moreover, it has an important negative impact on the quality of life of patients with asthma.^{17,18} Early detection of nocturnal symptoms is important because these symptoms are treatable.¹⁹

Therefore, not only the daytime but also the nighttime perception of asthma symptoms should be assessed in each patient. Among the items of the ACT, the questionnaire for daytime and nighttime symptoms includes only one item in each, namely item 1 and item 3, respectively. To assess both daytime and nighttime perception of asthma symptoms, we have modified and used the two types of VAS, daytime and nighttime VAS, in a primary care setting. We conducted a retrospective study for the evaluation of modified daytime and nighttime VAS. Therefore, this study investigated whether the daytime and nighttime VAS were useful in the measurement of perception of asthma symptoms, the assessment of asthma control levels, and the evaluation of treatment effects in symptomatic adult patients with asthma.

Materials and Methods

Study Protocol

A retrospective study was conducted in a single institute and primary care setting to critically evaluate daytime and nighttime VAS for the perceptions of asthma symptoms. Data on self-reported daytime and nighttime VAS, ACT scores, prescriptions, physique (body mass index, BMI), smoking habits, comorbidities, blood eosinophil counts and serum total IgE levels, lung functions by spirometry, and fractional exhaled nitrogen oxide ($F_{E}NO$) were retrospectively collected from the medical records of the patients with asthma who visited Fujiki Medical and Surgical Clinic. Data on daytime and nighttime VAS and ACT scores were collected as patient-reported outcomes (PROs) before treatment as a baseline and 4 weeks and 8 weeks after treatment. Data on $F_{E}NO$ and lung functions before treatment as the baseline and 8 weeks after treatment were collected, because the clinic usually required data on each PRO every 4 weeks and spirometry and measurement of $F_{E}NO$ every 8 weeks when new or alternative treatment was initiated (Figure 1). However, measurement of airway reversibility was not available using inhaled short-acting bronchodilators in the clinic.

Patients

Among 302 adult patients with asthma who visited the clinic between December 1, 2020, and May 31, 2021, 188 adults (age ≥ 20 years old) underwent daytime and nighttime VAS assessments before treatment and 4 weeks and 8 weeks after treatment with inhaled corticosteroids (ICS)/long-acting β_2 agonists (LABA) combination therapy. Asthma was defined by a physician's diagnosis based on the GINA report.⁶ The non-smoking, prescriptive controller-naïve (no prescriptions for controllers for asthma treatment) and symptomatic (ACT scores < 20 points)^{7,8} patients were selected for this study. The patients who smoked ($n = 31$) were prescribed with other controllers ($n = 45$) and had ≥ 20 points in the ACT scores ($n = 54$) before treatment were excluded. Three patients who had no data on lung functions before and 8 weeks after treatment were also excluded. Fifty-five patients were finally analyzed (Figure 2).



Figure 1 Study protocol.

Notes: The delta was expressed as different values from before treatment to 4 weeks or from before treatment 8 weeks after treatment.

Abbreviations: F_ENO, fractional exhaled nitrogen oxide; PROs, patient-reported outcomes.

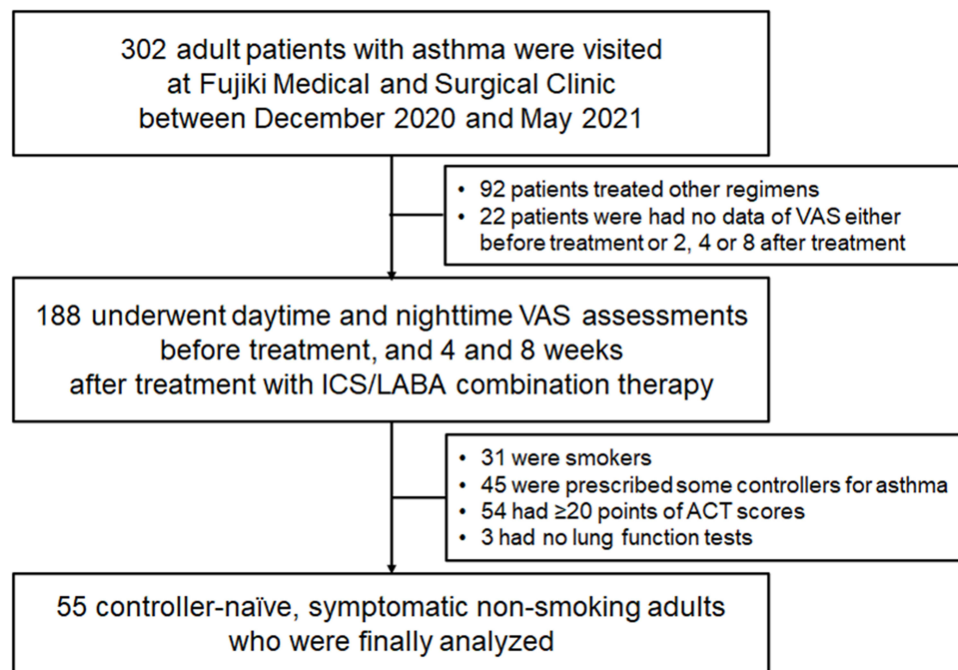


Figure 2 Flowchart of patient enrollment.

Notes: The controller-naïve, symptomatic, non-smoking, adult patients who underwent daytime and nighttime VAS assessments before treatment, and 4 and 8 weeks after treatment with ICS/LABA combination therapy, were enrolled at Fujiki Medical and Surgical Clinic between December 2020 and May 2021.

Abbreviations: ACT, asthma control test; ICS, inhaled corticosteroids; LABA, long-acting β_2 agonists; VAS, visual analog scale.

Data Collection

The PROs

The self-reporting ACT^{7,8} and VAS^{9–13} assessments were required before the measurement of F_ENO and lung functions. The modified ACT and VAS assessed the average perception of asthma symptoms in the last one week of the evaluation period. Two types of modified VAS, namely daytime (from 6 am to 6 pm) and nighttime (from 6 pm to 6 am), were used based on the Japanese version of the VAS utilized in a previous study.¹⁰ In VAS, the scales ranged from not at all bothersome (0 cm as a good condition) to extremely bothersome (10 cm as a bad condition). After reporting daytime and nighttime VAS, each patient continuously underwent the Japanese version of the ACT for adult asthmatics.²⁰

Measurement of F_ENO

Morning F_ENO was measured twice a day at every visit before spirometry by an online electrochemical NO analyzer (NIOX VERO[®], Circassia AB, Sweden), and the mean value obtained was used for the analysis.²¹

Lung Function Tests

Spirometry (Chestgraph Jr HI-101, CHEST, Tokyo, Japan) was repeated twice. We adopted the best values of forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC), in accordance with a Taskforce recommendation.²² The percent predicted values of FEV₁ (%FEV₁ predicted) and FVC (%FVC predicted) were calculated using a formula for Japanese individuals.²³

Ethical Approval

The study was conducted following the Good Clinical Practice guidelines and was approved by the local ethics board of Kurume University, Japan (No. 21–155, September 30, 2021). The study protocol was registered in the University Hospital Medical Information Network (UMIN) Center (UMIN No. 000045636) on October 2, 2021. Patients who visited Fujiki Medical and Surgical Clinic (Miyazaki, Japan) were allowed an opt-out option between September 30, 2021 and March 31, 2022.

Statistical Analysis

All variables were summarized by the number (% of total) of patients by category for qualitative variables and mean \pm standard deviation (SD) for quantitative variables. Changes in PROs, lung functions, and F_ENO before and after treatment were expressed as delta (Δ) (Figure 1). Means were compared from before to after treatment by the Student's *t*-test and one-way analysis of variance test. A multiple regression analysis was used to estimate an adjusted coefficient (standardized β [95% confidential interval (CI)]) affected by PROs with adjustment for potential confounders; age,²⁴ gender differences,^{25,26} BMI,^{26,27} blood eosinophils and neutrophils,^{27,28} serum total IgE levels,^{27,28} FVC and FEV₁,²⁷ F_ENO,^{27,28} and the presence of other allergic comorbidities.^{9–13,24,26,27} [Supplementary Table 1A](#) and [1B](#) were selected as adjustment variables based on a previous study,²⁹ whereas an unadjusted coefficient of correlation (*r*) between the characteristics (variances) was analyzed by Spearman tests. The changes in absolute values (L) of lung functions were used after treatment, although both absolute and predicted values (%) were used for analyses as such absolute values are affected by age, gender, and physique. In addition, the blood percentage eosinophils and neutrophils were used because the absolute numbers of these cells are affected by the white blood cell count ([Supplementary Table 2](#)). To define the minimum clinically important difference (MCID) for daytime and nighttime VAS, the receiver operating characteristic (ROC) curve analysis was used with the reference MCID > 3 points, which showed improvement of ACT scores from before to after treatment. Statistical significance was set at *P* < 0.05. JMP version 15 for Windows (SAS Institute, Cary, NC, USA) was used for data analyses.

Results

Profiles of Patients

[Table 1](#) summarizes that in the patients' demographic data. The mean (SD) age was 49.7 (16.1) years, the number (%) of women was 42 (76.4%), the mean (SD) BMI was 22.9 (3.6) kg/m² and the number (%) of patients who were obese was 12 (21.8). In terms of biomarkers, the mean % and absolute number (SD) of blood eosinophils were 3.8% (2.3%) and 239 (157) cells/ μ L, respectively, and the mean (SD) serum IgE concentration and F_ENO were 140 (230) U/mL and 49.2 (49.1) ppb, respectively. In terms of PROs, the mean (SD) ACT and daytime and nighttime VAS were 13.9 (3.9) points, 7.3 (1.9) cm, and 7.7 (1.9) cm, respectively. In terms of spirometry measurements, the mean (SD) %FVC and %FEV₁ predicted were 96.6% (18.6%) and 91.3% (22.1%), respectively, and the numbers (%) of patients with obstructive and restrictive patterns were 10 (18.2%) and 3 (5.4%), respectively. In terms of the regimens of ICS/LABA therapy, the numbers (%) of patients receiving high-dose ICS and those receiving ICS once a day were 22 (40.0%) and 26 (47.3%), respectively. All patients received new treatment with ICS/LABA combinations for asthma control, although the prescription of leukotriene receptor antagonists and anti-allergic agents was used before new treatment for asthma and the doses were not changed 8 weeks after treatment for asthma for other allergic comorbidities such as allergic rhinitis and dermatitis ([Supplementary Table 1A](#) and [1B](#)). The number (%) of patients with high and medium doses of ICS was 22 (40.0) and 33 (60.0), respectively. The doses were continued for at least 8 weeks.

Table 1 Profiles of Patients with Asthma Before Treatment

Characteristics	n = 55
Age, years (range)	49.7 ± 16.1 (20 to 86)
Female gender, n (%)	42 (76.4)
Body mass index, kg/m ² (range)	22.9 ± 3.6 (17.7 to 38.3)
Body mass index >25 kg/m ² (obese), n (%)	12 (21.8)
Any other allergic comorbidities	21 (38.2)
Allergic rhinitis	20 (36.4)
Chronic sinusitis with nasal polyps	1 (1.8)
Atopic dermatitis	1 (1.8)
Biomarkers	
White blood cells count, ×10 ⁹ cells/L	6.2 ± 1.4
% Eosinophils, %	3.8 ± 2.3
% Neutrophils, %	54.9 ± 7.5
Eosinophil count, ×10 ³ cells/μL	239 ± 157
Neutrophil count, ×10 ³ cells/μL	2072 ± 291
Serum total IgE levels, U/mL	140 ± 230
F _E NO, ppb	45.3 ± 36.6
PROs	
ACT scores, points (range)	13.9 ± 3.0 (9 to 19)
VAS, cm (range)	
Daytime	7.3 ± 1.8 (2.0 to 10.0)
Nighttime	7.7 ± 1.9 (3.0 to 10.0)
Lung function	
FVC, L	2.76 ± 0.75
%FVC predicted, %	96.6 ± 18.6
FEV ₁ , L	2.18 ± 0.68
%FEV ₁ predicted, %	91.3 ± 22.1
FEV ₁ /FVC ratio	0.78 ± 0.10
Spirometric ventilatory pattern, n (%)	
Obstructive ventilatory pattern	10 (18.2)
Restrictive ventilatory pattern	3 (5.4)
Selected ICS/LABA combination therapy, n (%)	
Doses of ICS	
High dose	22 (40.0)
Medium dose	33 (60.0)
Administration	
Once a day	26 (47.3)
Twice a day	29 (52.7)

Notes: Data are expressed as mean ± standard deviation and number (%) of patients. Doses of ICS were classified according to the Global Initiative for Asthma criteria. In other medicines, none of the patients were administered slow-release theophylline, regular oral prednisolone, and biologics. The number (%) of patients who received leukotriene receptor antagonists and anti-allergic agents, whose administration was ongoing for other allergic comorbidities prior to the use of ICS/LABA therapy, was 25 (45.4) and 12 (21.8), respectively. However, data were missing for two patients for blood tests, one for F_ENO, and one for lung function test 8 weeks after treatment.

Abbreviations: ACT, asthma control test; F_ENO, fractional exhaled nitrogen oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; Ig, immunoglobulin; LABA, long-acting β₂ agonist; PROs, patient-reported outcomes; VAS, visual analog scale.

Correlation Between ACT Scores and Daytime and Nighttime VAS Before Treatment

Figure 3 shows that the ACT scores were significantly associated with daytime ($r = -0.57$, $P < 0.0001$) and nighttime VAS ($r = -0.46$, $P < 0.0001$), respectively. There was a weak but significant correlation between daytime and nighttime VAS ($r = 0.33$, $P = 0.0148$). In the unadjusted analyses, the ACT scores were positively associated with white blood cell count ($r = 0.44$, $P = 0.0024$), whereas the daytime VAS was negatively associated with white blood cell count ($r = -0.32$,

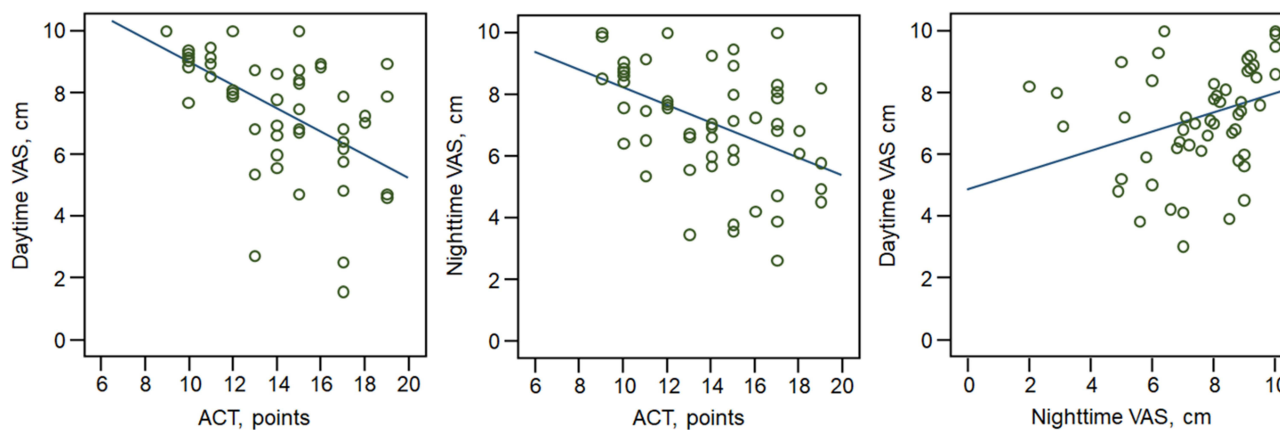


Figure 3 The correlation between ACT scores, and daytime and nighttime VAS before treatment.

Abbreviations: ACT, asthma control test; VAS, visual analog scale.

$P = 0.0222$) and $F_{E}NO$ ($r = -0.41$, $P = 0.0019$), and the nighttime VAS was negatively associated with white blood cell count ($r = -0.50$, $P = 0.0006$) and serum total IgE levels ($r = -0.33$, $P = 0.0152$) before treatment ([Supplementary Table 3A](#)). However, upon multiple regression analysis, neither the ACT scores nor the daytime and nighttime VAS were significantly associated with the PROs and characteristics before treatment ([Supplementary Table 3B](#)). In patients with but not those without other allergic comorbidities ([Supplementary Table 3C](#)), the daytime VAS was negatively associated with the percentage neutrophils in the multiple regression analysis ($\beta = -0.35$, $P = 0.0035$) ([Supplementary Table 3D](#)).

Effects of ICS/LABA Combination Therapy on PROs, Lung Functions, and $F_{E}NO$

[Figure 4](#) shows that all PROs were improved by treatment with ICS/LABA combinations. In lung functions, the $\%FEV_{1}$, but not FVC, predicted, and the FEV_{1}/FVC ratio was significantly improved, and the $F_{E}NO$ levels were significantly decreased 8 weeks after treatment ([Supplementary Table 4](#)).

Correlation Between Changes in PROs, Lung Functions, and $F_{E}NO$ from Before Treatment to 8 Weeks After Treatment

[Figure 5](#) shows that the changes in the ACT scores were significantly associated with changes in daytime ($r = -0.65$, $P < 0.0001$) and nighttime VAS ($r = -0.44$, $P < 0.0001$), respectively; however, there was a significant correlation between

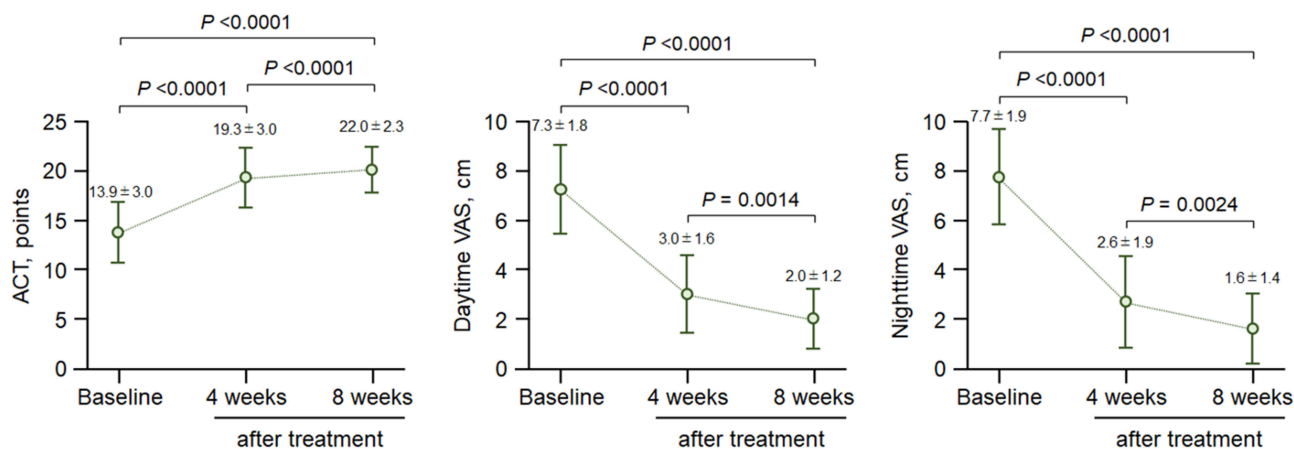


Figure 4 Changes in the mean ACT scores, and daytime and nighttime VAS after treatment.

Notes: All data were expressed as mean (open circles) \pm SD (bars). Data of baseline were the values of PROs before treatment.

Abbreviations: ACT, asthma control test; PROs, patient-reported outcomes; VAS, visual analog scale.

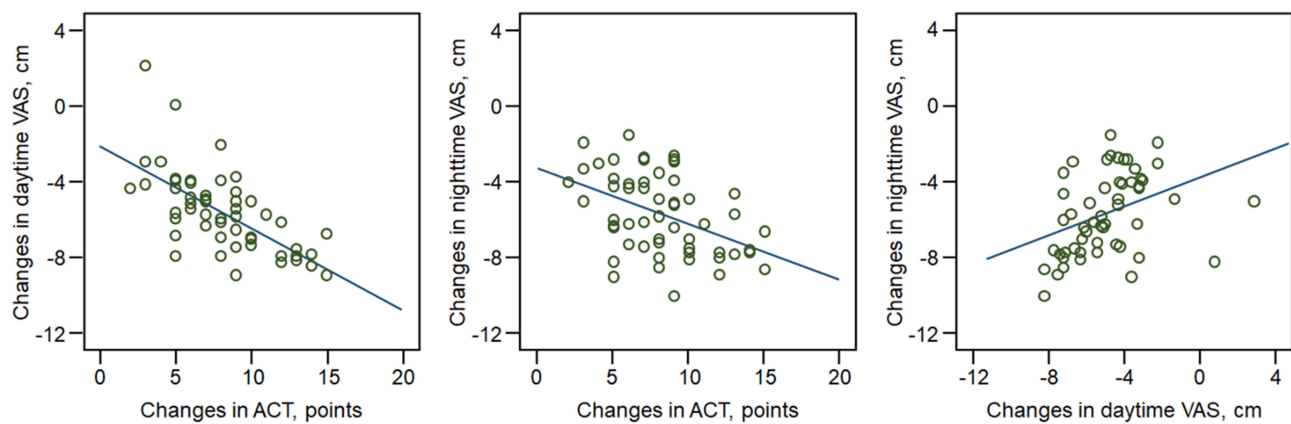


Figure 5 The correlation between changes in the ACT scores, and daytime and nighttime VAS from before to 8 weeks after treatment.

Abbreviations: ACT, asthma control test; VAS, visual analog scale.

Table 2 Multiple Regression Analysis of Changes in PROs and Changes in Lung Functions and F_ENO 8 Weeks After Treatment

Covariates	ACT Scores		Daytime VAS		Nighttime VAS	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
Changes in F _E NO, ppb	0.15 (-0.04 to 0.08)	0.5	-0.02 (-0.05 to 0.00)	0.1	-0.01 (-0.05 to 0.03)	0.6
Changes in FVC, L	3.47 (-1.46 to 8.41)	0.5	-2.33 (-4.55 to -0.11)	0.0405*	-3.09 (-6.25 to 0.07)	0.0505
Changes in FEV ₁ , L	-1.73 (-6.78 to 3.33)	0.5	1.18 (-1.09 to 3.46)	0.3	2.63 (-0.61 to 5.87)	0.1

Notes: The multiple regression analysis was adjusted for covariates, the following age, gender, body mass index, and the presence of other allergic comorbidities before treatment. * $P < 0.05$ with a significant correlation between changes in daytime VAS and FVC.

Abbreviations: ACT, asthma control test; CI, confidence interval; F_ENO, fractional exhaled nitrogen oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PRO, patient-reported outcome; VAS, visual analog scale.

changes in daytime and nighttime VAS ($r = 0.38$, $P = 0.0038$) 8 weeks after treatment. Upon multiple regression analysis, changes in the daytime VAS were significantly associated with changes in FVC (Table 2), whereas the unadjusted analysis revealed that PROs, the white blood cell count, cell differentiation, total serum IgE levels, and F_ENO before treatment affected changes in PROs (Supplementary Table 5). However, the mean \pm SD nighttime VAS (5.0 ± 2.3) improved faster than did the ACT scores (2.2 ± 1.2 , $P < 0.0001$), when assuming that the maximum total score of 25 points was converted to 10 points. The daytime VAS increased from before treatment to 4 weeks after treatment (4.3 ± 2.0 , $P = 0.0211$), although the change in the nighttime VAS (1.1 ± 1.2) was no different from those in the daytime VAS (1.1 ± 1.1 , $P > 0.05$) and ACT score (1.1 ± 0.9 , $P > 0.05$) from 4 to 8 weeks after treatment. In the different administrations of ICS/LABA therapy, there was no difference between administrations of once a day and twice a day in changes in the ACT scores and daytime and nighttime VAS 4 and 8 weeks after treatment (data not shown).

MCID of Daytime and Nighttime VAS Related to ACT Scores by ROC Curve Analysis

The number (%) of patients with improvements of >3 points (MCID) of ACT scores 4 weeks and 8 weeks after treatment was 47 (85.5%) and 54 (98.2%), respectively. The ROC curves analysis with the MCID of the ACT scores as a reference showed that the area under the curve (sensitivity and 1-specificity) and the estimated MCID were 0.86 (0.85 and 0.13, $P = 0.0054$) and -3.2 cm for daytime VAS and 0.69 (0.58 and 0.25, $P = 0.1179$) and -3.3 cm for nighttime VAS 4 weeks after treatment; similarly, the values were 0.77 (0.76 and 0.00, $P = 0.5350$) and -4.6 cm for daytime VAS and 0.75 (0.74 and 0.00, $P = 0.4468$) and -4.1 cm for nighttime VAS 8 after treatment (Supplementary Figure 1). However, the number (%) of patients who achieved total asthma control with 25 points in the ACT scores 4 weeks and 8 weeks after treatment was 0 (0) and 3 (5.5), respectively. In addition, no patients who achieved total asthma control with 0 cm in the daytime and nighttime VAS 4 weeks and 8 weeks after treatment showed.

Discussion

Our retrospective study demonstrated that the ICS/LABA combination therapy significantly improved ACT scores as well as daytime and nighttime VAS in treatment-naïve symptomatic adult patients with asthma. The therapy was also significantly positively associated with the %FEV₁ predicted and negatively associated with the F_ENO levels 8 weeks after treatment. Before treatment, both daytime and nighttime VAS were significantly associated with ACT scores. There was a correlation between daytime and nighttime VAS, although nighttime VAS was slightly higher than daytime VAS. After treatment, changes in both the daytime and nighttime VAS were significantly associated with changes in the ACT scores. However, there was a significant correlation between changes in the daytime and nighttime VAS. The MCID of +3 points in the ACT scores was equivalent to a difference of −3.2 cm in the daytime and −3.2 cm in nighttime VAS 4 weeks after treatment, and −4.6 cm in the daytime and −4.1 cm in nighttime VAS 8 weeks after treatment. However, multiple regression revealed that improvements in the daytime and nighttime VAS may be associated with an improvement in FVC after but not before treatment, although we investigated the correlation between the PROs and characteristics (including lung function and biomarker levels) before and after treatment. We also found that the PROs before treatment affect changes in the PROs after treatment ([Supplementary Table 5](#)). Poorer PROs may result in a greater improvement in PROs after optimal treatment in patients with asthma.

The GINA report recommends the use of the ACT for assessing asthma symptoms as one of the standard questionnaires in adult patients with asthma.⁶ The ACT has 5 simple items and can be easily understood by the patients.^{7,8,10} Subsequently, we adopted the ACT as a standardized questionnaire for the perception of asthma symptoms in this study. The evidence on the correlation between VAS and ACT is still limited for adult patients with asthma,^{10,30–33} although VAS has been evaluated as a useful tool for assessing the perception of respiratory symptoms.^{9–13} A large-scale previous Japanese study of adult asthma patients with rhinitis reported that the VAS was well-correlated with asthma control levels using the GINA criteria.¹⁰ The VAS was also well-expressed not only in disease control but also in severity levels.¹¹ However, the VAS was standardized as an average perception of symptoms during a full day and the previous 4 weeks of an evaluation period. Hence, the applicability of VAS may remain a problem for assessments of asthma daytime and nighttime conditions. To our knowledge, our study using the modified VAS, which assessed symptoms of averaged daytime and nighttime asthma, and during the previous one week of the evaluation period, was the first to perform such assessments in adult patients with asthma. In our primary care setting, most patients required a shorter-term evaluation period after treatment than the standardized evaluation period in previous studies.^{7,8,10} Our study successfully demonstrated that the daytime and nighttime VAS before treatment and changes in the VAS after treatment were significantly associated with the ACT scores before treatment and changes in the ACT scores after treatment in adult patients with asthma, respectively. We found that the nighttime VAS improved faster than the ACT score and the daytime VAS with optimal treatment. It may be possible to predict the treatment effect earlier using the nighttime VAS in treatment-naïve and symptomatic patients with asthma, although our study detected the efficacy of ICS/LABA therapy 4 weeks after treatment.

Our multiple regression analyses did not reveal any promising correlations between the PROs and lung function and biomarker levels before and after treatment. Some previous studies reported that the ACT scores negatively correlated with type-2 inflammation in patients with asthma,^{34–38} whereas other previous studies demonstrated that the ACT scores were not related to any inflammatory biomarkers, such as airway and systemic eosinophilic inflammation and F_ENO.^{39–41} Hence, the interaction between ACT scores and type-2 inflammation is still controversial in asthma. The unadjusted analyses revealed that all PROs were negatively associated with white blood cell counts in our study ([Supplementary Table 3](#)). Previous studies demonstrated that the white blood cell count may contribute to cigarette smoking and other atopic comorbidities or allergic sensitization, although the correlation between white blood cell count and asthma control levels is controversial.^{42–44} The presence of not only asthma but also of other allergic comorbidities may affect the white blood cell count and the differentiation of eosinophils and neutrophils ([Supplementary Tables 1 and 2](#)). Furthermore, the presence of other allergic comorbidities may also have affected the F_ENO in our study ([Supplementary Tables 1 and 2](#)). Our multiple regression analyses, in which we adjusted for the presence of other allergic comorbidities, did not reveal any correlation between the PROs and type-2 inflammation markers, such as eosinophils, IgE, and F_ENO before and after treatment. In addition, some previous studies also reported weak-to-moderate correlations between ACT scores and either

FEV₁ or %FEV₁ predicted,^{37,38,45–48} although some studies demonstrated that there was no correlation between ACT scores and lung function in patients with asthma.^{39,49} The correlation between ACT scores and lung function thus lacks corroboration in studies on asthma. Our multiple regression analyses revealed no association of daytime and nighttime VAS with lung function before treatment. However, the increase in the FVC may contribute to the improvement of daytime and nighttime VAS after treatment (Table 2). The reason why the FEV₁ was not related to the treatment effects as represented by PROs may be that 18.2% of patients have obstructive ventilation patterns⁵⁰ or poorly controlled asthma with air-trapping in the lungs.⁵¹

Our study has several limitations. First, our study was retrospective and conducted in a single primary care setting. Second, the sample size could have been small for the evaluation of PROs when compared with previous studies (mean sample size was 207 [range 68–471]).^{7,8,20,34–40,48,49} Third, we modified the methods of assessing PROs for a short evaluation period during treatment. The average perception of asthma symptoms in the last one week before treatment may have affected our results. Fourth, our study did not assess airway eosinophilic inflammation, such as sputum eosinophilia, although a previous study demonstrated that nocturnal symptoms were associated with sputum eosinophilia.³⁶ Fifth, patient adherence to medicines was not assessed. However, good adherence to medicines was assumed, because all patients were reconfirmed to receive medicines every 4 weeks based on the refill methods in the study.⁵² Sixth, our selection of treatment regimens may have had issues. We selected the first-line ICS/LABA combination therapy as a companion medicine for evaluating the changes in PROs. The high-credible MCID for VAS could not be obtained, because the chosen combination therapy might have led to over-treatment, which made most of the patients reach MCID in the ACT scores immediately. However, most patients did not achieve complete asthma control in 8 weeks after treatment, although early improvement may have been achieved by the chosen combination therapy in the primary setting. Nevertheless, the discrepancy between changes in the daytime and nighttime VAS after treatment is still unclear. The mechanism of the discrepancy could be clearer if we selected different regimens such as high-dose ICS alone for anti-type-2 inflammations or low-dose ICS/LABA plus LAMA for maximal bronchodilations. A multi-institution, long-term period, and prospective study will be therefore needed in the future.

Conclusion

In conclusion, our study demonstrated that nighttime VAS was higher than daytime VAS, whereas there was a significant positive correlation between daytime and nighttime VAS before and after treatment in symptomatic patients with asthma, as preliminary findings. The nighttime VAS may be able to detect an improvement of condition faster than the ACT scores and the daytime VAS following optimal treatment. We believe that daytime and nighttime VAS assessments for perceived asthma symptoms, together with the ACT, are useful for the assessment of asthma control levels before and after treatment in symptomatic patients with asthma.

Abbreviations

ACT, asthma control test; ANOVA, analysis of variance; AUC, area under the curve; BMI, body mass index; CI, confidence interval; F_ENO, fractional exhaled nitrogen oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting β_2 agonists; MCID, minimum clinically important difference, PROs, patient-reported outcomes; ROC, receiver operating characteristic; SD, standard deviation; UMIN, University Hospital Medical Information Network; US, United States; VAS, visual analog scale.

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