Independent risk factors of asthma exacerbations: 3-year follow-up in a single-center prospective cohort study

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Background: Because minimizing future risk is the goal of asthma chronic asthma management, it is particularly important to identify risk factors. We conducted this 3-year single-center prospective cohort study to determine the independent risk factors of asthma exacerbations (AEs).

Methods: We performed this prospective, longitudinal, observational study with a 3-year follow-up on 257 patients aged 18–81 years with at least a 1-year history of asthma. Follow-up visits are conducted through regular annual phone calls, and the primary endpoints were AE.

Results: The uncontrolled group was more likely to develop AE than the well-controlled group [odds ratio (OR): 6.34, 95% confidence interval (CI): 1.14–35.21, P<0.05]. Patients with low Asthma Quality of Life Questionnaire (AQLQ) scores were more likely to develop AE than these with high AQLQ scores (OR: 0.59, 95% CI: 0.35–0.99, P<0.05). AQLQ and Asthma Control Questionnaires (ACQ) were both strong independent risk factors within 3 years of enrollment; the cut-off values (COV) of the AQLQ and the ACQ (uncontrolled) that better evaluated the risk with the AE were ≤5.4 and >1, respectively. The AQLQ scores had a sensitivity of 79.07% and a specificity of 59.09% [area under curve (AUC): 0.70, P<0.0001], and the ACQ (uncontrolled) had a sensitivity of 81.4% and a specificity of 52.29% (AUC 0.68, P<0.0001).

Conclusions: The findings of this study suggest that patients with uncontrolled asthma and a diminished health-related quality of life had an increased risk of exacerbations in the future. Defining these risk factors associated with AE is important as it will identify these at the highest risk to patients and may guide future interventions.

Keywords: Asthma; exacerbation; independent risk factors

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Introduction

Asthma currently affects more than 300 million people worldwide and is associated with lung function decline, clinical deterioration, and worsening health-related quality of life (1,2). Frequent exacerbation results in significant morbidity and economic costs due to asthma. Thus, the prevention and management of exacerbations are crucial for asthma patients (1). According to the Global Initiative for Asthma (GINA), identifying individuals at the highest risk

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of exacerbations and designing personalized care is essential for overall asthma management (1).

Although several studies indicated that bronchodilator reversibility, spirometry, methacholine challenge testing (MCT) (3,4), peak expiratory flow rate (PEFR) (5), forced expiratory volume in one second (FEV_1) (6), and specific questionnaires (7), had been proposed as risk factors for asthma exacerbation (AE), most of them are regarded as late indicators of the loss of asthma control (8), reflecting the occurrence of symptoms rather than their imminent arrival and are not included in GINA. Findings on several established asthma risk factors, such as asthma exacerbations, low lung function, an elevated concentration of exhaled nitric oxide, poor adherence to asthma medication, adverse effects from asthma medications, incorrect inhaler technique, smoking, and blood eosinophilia were updated in the GINA (1). Because minimizing future risk is the goal of asthma chronic asthma management, it is particularly important to identify risk factors.

Asthma Control Questionnaires (ACQ) and Asthma Quality of Life Questionnaires (AQLQ) have been conveniently used as the most common measure to track change in asthma outcomes. And according to GINA (1), major psychosocial problems, including depression, are risk factors for a fatal asthma attack. Therefore, in this study, we used the ACQ, AQLQ, Hospital Anxiety and Depression Scale (HADS), together with lung function parameters, and sought to evaluate patients' individual risk in an easy way.

Most studies have conducted only short-term observations (6–12 months), and may not be adequate for evaluating long-term exacerbation risk. To address this, we conducted a 3-year prospective observational investigation to determine the ability of AQLQ, ACQ, HADS, and lung function parameters to evaluate patients' individual risk by controlling for the possible confounding effect of sociodemographic, clinical, and functional variables. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5918/rc).

Highlight box

Key findings

- Patients with uncontrolled asthma and a diminished health-related quality of life had an increased risk of exacerbations in the future. However, this relationship did not exist for hospitalization.

What is known and what is new?

- A history of ≥1 exacerbation(s) in the past year, low lung function, an elevated concentration of exhaled nitric oxide, and blood eosinophilia are independent risk factors for future asthma exacerbations.
- As the first 3-year prospective observational investigation, we found that the uncontrolled ACQ group was more likely to develop AE than the well-controlled ACQ group, and patients with low AQLQ scores were more likely to develop AE than these with high AQLQ scores.

What is the implication, and what should change now?

- As simple screening tools, AQLQ and ACQ (uncontrolled) can be used in primary care to quickly identify patients needing more detailed assessment, alerting healthcare professionals to remedial action.

Methods

Study design

This prospective, longitudinal, observational study with a 3-year follow-up was conducted at Ningbo First Hospital and was approved by the Institutional Review Board of Ningbo First Hospital (No. 2016-R017). The study was performed in accordance with the Declaration of Helsinki (as revised in 2013). All asthma patients provided written informed consent for participation.

The patients underwent lung function tests and were asked to complete AQLQ, ACQ, and HADs, and their sociodemographic characteristics, including age, gender, and education were followed up for 3 years after enrollment. None of the subjects was aware of the scoring criteria of the questionnaires before this study. The lung function parameters for each patient were reviewed by a fellowship-trained respiratory doctor who was blinded to all patient information.

In this study, a total of 11 aspects of patient data were collected from four domains. Eight baseline data included gender, age, and BMI. Two scales, the AQLQ and ACQ were used to assess asthma control, various lung function measures were used, and the HADs were used to assess psychological status. According to the rule of five to ten events per variable in logistic, about 250 patients should be included in this study to establish a multivariate logistic regression with an asthma exacerbation rate of 22% (9,10).

The primary endpoint was AE: the requirement for oral corticosteroids, an urgent health care visit for asthma symptoms, and one or more asthma episodes that lasted longer than 2 hours or resulted in shortened regular activity. The patients were managed according to the GINA

guidelines, and the number of days of bronchodilator requirement, requirement and days of oral corticosteroids, days of emergency visits, days of exacerbations, and days of hospitalization were recorded from the patients' telephone interviews and computerized hospital records. Follow-up visits are conducted through regular annual phone calls.

Participants

Patients presenting in 2017/2018 attending asthma clinics in Ningbo First Hospital were screened and recruited. A total of 257 patients aged 18–81 years with at least a 1-year history of asthma and a current asthma diagnosis under the GINA 2022 were included in the study cohort. Asthma patients were eligible to participate if they complied with the following inclusion criteria: (I) age over 18 years; (II) diagnosis of asthma by a respiratory physician; (III) an increase of more than 12% in FEV_1 or more than 20% in PEFR following a dose of 200 μg salbutamol, or airway hyper-responsiveness (as assessed by the methacholine inhalation challenge test) observed on past evaluations. Asthma patients were excluded if they satisfied the following criteria: (I) experienced any AE for at least 4 weeks before participating in the study; (II) had a confounding or complicating condition; (III) could not perform acceptable spirometry or complete the questionnaires; and (IV) had an associated comorbidity. All subjects were assessed for study eligibility and screened by the corresponding author before the commencement of the study. These criteria represented a convenient sample of adults with asthma, and the subjects were enrolled when the corresponding author attended the asthma clinics.

Data collection

ACQ

The complete ACQ (also known as ACQ-7) comprises seven items: five questions about symptoms, including night-time awakening due to asthma, symptoms on waking, limitations of activities, shortness of breath, wheezing, one question about pre-bronchodilator FEV_1, and one question about the frequency of β2-agonists use (11). Patients scored how their asthma has been in the last week on a scale from 0 to 6 symptoms (0= no impairment; 6= maximum impairment). The overall score was taken as the average of the individual item scores; the lower the score, the better the asthma control. Scores of 0.75 and 1.5 on the ACQ have been identified previously as the best discriminators of asthma that is "Well-controlled," "Partial-controlled," or "Uncontrolled" (1,12).

AQLQ

The standard AQLQ comprises five items (activity limitation, symptoms, environmental stimuli, emotional function, and self-health concern) and consists of 35 questions. Activity limitation included five individualized questions that asked patients to list the five most affected activities from a list of 26 activities in the past 2 weeks using a seven-point Likert scale to rate the extent (13).

HADS

HADs consisted of questions assessing for depression (HADS-D) and anxiety (HADS-A) were used to evaluate the anxiety. Both of them consist of seven questions which are scored as 0–3 points individually. HADS-A was classified as: 0–7, no anxiety; 8–10, mild anxiety; 11–14, moderate anxiety; 15–21, severe anxiety. HADS-D was classified as: 0–7, no depression; 8–10, mild depression; 11–14, moderate depression; 15–21, severe depression (14,15).

Lung function measurement

Spirometry testing met the American Thoracic Society-European Respiratory Society ATS/ERS guidelines and was performed using a Master Screen spirometer (Jaeger, Germany) by trained healthcare professionals (16). All participants were asked to withhold short-acting beta-2-agonists for ≥6 hours and long-acting beta-agonists for ≥12 hours before the clinic visit and wear a nose clip to perform and repeat until they were comfortable with the equipment. We measured the forced expiratory volume in the first second/forced vital capacity (FEV_1/FVC), FEV_1 (%pred), the forced vital capacity (FVC) (%pred), the peak expiratory flow (PEF) (%pred), and the maximal mid-expiratory flow 75/25 (MMEF75/25) (%pred).

Statistical analysis

Quantitative data were evaluated for normality of distribution: normally distributed continuous variables [presented as the mean ± standard deviation (SD)] were analyzed by an independent *t*-test, and non-normally distributed variables (characterized by the median and 25–75 percentiles) were assessed using the Mann-Whitney U test. Categorical variables [expressed as numbers (percentages)] were evaluated by Chi-square (χ^2) tests.

Significant (P<0.1) covariates in the univariate analysis

were included in the multivariate binary logistic regression model. Odds ratio (OR), the 95% confidence interval and P value of each factor from the multivariate logistic regression models were estimated and presented. A two-tailed P value of less than 0.05 was considered to be statistically significant. Receiver operating characteristic curve (ROC) analyses were performed to obtain the area under the curves (AUC). Statistical analysis was performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Most of the missing data are related to the primary endpoint, so patients with missing data were excluded and none of their data was used.

Results

Population characteristics

In total, 197 patients who completed this study were divided into two groups based on the occurrence of AE after 3 years of surveillance. Of these, 43 (22%) patients experienced at least one exacerbation. The patients' demographic, clinical, and biological data are presented in *Table 1*. The results showed AE was significantly correlated with the patient's age and smoking index but not with gender (P=0.33), duration of asthma (P=0.83), BMI (P=0.07), or comorbidities (P=0.33) (*Table 1*). Also, more male patients developed AE compared to females, but the difference was not statistically significant (P=0.33). Patients in the AE group had a higher smoking index (P<0.01) and were older (P<0.05) than these without AE. In addition, the patients' demographic, clinical, and biological data are presented in Table S1 according to hospitalization. A higher smoking index (P<0.05) and older age (P<0.01) were observed in the hospitalization group than these in patients without hospitalization.

Univariable analysis

The AE group had lower PEF (%pred) (P=0.14), FVC (%pred) (P=0.05), FEV_1 (P=0.05), PEF (P=0.09), FVC (P=0.28), FEV_1/FVC (P=0.12), HADS-A (P=0.22), and HADS-D (P=0.84) than these without AE; however, the differences did not reach statistical significance (*Table 1*). As expected, compared with the no AE group, the FEV_1 (%pred) (P<0.05), MMEF75/25 (P<0.05), and MMEF75/25 (%pred) (P<0.01) were significantly lower in the AE group. ACQ (P<0.0001) and AQLQ (P<0.0001) were significant univariable factors of AE. The AE group also had a significantly higher ACQ score (P<0.0001) and a substantially lower AQLQ score than the no AE group (P<0.0001). The pairwise comparison also showed that the enrollment AQLQ subscale scores, including emotional function (P<0.01), self-health concern (P<0.0001), and activity limitation (P<0.01) were statistically different in terms of AE within 3 years of enrollment; however, symptoms (P=0.08), environmental stimuli (P=0.08), and the overall AQLQ score (P<0.0001) were not.

The lung function parameters also were significant univariable factors of hospitalization (Figures S1-S3). The pairwise comparison showed that the FEV_1 (%pred) (P<0.01), FVC (%pred) (P<0.01), PEF (%pred) (P<0.05), FEV_1 (P<0.05), PEF (P<0.05), MMEF75/25 (P<0.05), MMEF75/25 (%pred) (P<0.05), and FVC (P<0.05) of the hospitalization group were markedly lower than these of the no hospitalization group. Moreover, the hospitalization group also had a significantly higher ACQ score (P<0.05) and a substantially lower AQLQ score (P<0.05), which comprised the enrollment AQLQ subscale scores [including emotional function (P<0.05), self-health concern (P<0.0001), and activity limitation (P<0.05)] than the no hospitalization group (Table S1). However, all significant univariable factors were not found to be significant multivariable factors of hospitalization (P>0.05) (Table S2).

And low AQLQ score was not significantly associated with the number of days of AE or days of hospitalization [unadjusted HR, 0.937; 95% confidence interval (CI), 0.640–1.372; P=0.74] by using Cox regression analyses. Notably, repeating these analyses using the lung function parameters, ACQ, produced similar results (Tables S3,S4).

Multivariable analysis

We used multivariate logistic regression to determine the parameters that were independently associated with AE; variables that achieved P<0.1 in the univariate analysis were included in the multivariate regression (*Figures 1-3*). Logistic regression showed that two of the 13 interrogated variables were associated with AE within the 3 years following randomization (*Table 2*). ACQ (uncontrolled) and AQLQ identified independent risk factors associated with AE by regression analysis at 3 years of follow-up. The uncontrolled ACQ group was more likely to develop AE than the well-controlled ACQ group [odds ratio (OR): 6.34, 95% CI: 1.14–35.21, P<0.05]. Also, patients with low AQLQ scores were more likely to develop AE than these with high AQLQ scores (OR: 0.59, 95% CI: 0.35–0.99, P<0.05) (*Figure 4*).

The ROC curves of subjects' AQLQ and ACQ (uncontrolled)

Table 1 Study cohort characteristics at the start were stratified by asthma exacerbation status

Characteristic	Exacerbations (N=43)		No exacerbations (N=154)		P value
	N	Value	N	Value	
Female gender^	20	25%	59	75%	0.33
Comorbidities^	15	26%	42	74%	0.33
Allergy^	19	24%	59	76%	0.53
Allergic rhinitis^	17	19%	73	81%	0.37
FEV_1 (%pred)*	43	65±20.7	154	72.4±19.4	<0.05
PEF (%pred)*	43	68.8±28.8	154	75.4±24.4	0.14
FVC (%pred)*	43	80.1±14.4	154	85.3±15.5	0.05
Smoking Index#	43	0 (0–24.4)	154	0 (0~0)	<0.01
Duration of asthma#	43	6 (1.8–15)	154	5 (1~28.8)	0.83
Age#, years	43	59 (48–63.5)	154	50 (39~60.8)	<0.05
BMI#, kg/m^2	43	24.1 (22–26.3)	154	22.7 (20.8~26)	0.07
FEV_1#	43	1.6 (1.2–2.0)	154	1.9 (1.4~2.3)	0.05
PEF#	43	4.3 (2.9–5.9)	154	5.1 (3.6~6.4)	0.09
MMEF75/25#	43	0.8 (0.4–1.5)	154	1.1 (0.7~1.7)	<0.05
MMEF75/25 (%pred)#	43	22.4 (14.3–41.6)	154	33 (21.3~49.2)	<0.01
FVC#	43	2.5 (1.9–3.1)	154	2.7 (2.2~3.1)	0.28
FEV_1/FVC#	43	69.4 (57.4–79.7)	154	73.2 (62.6~81.2)	0.12
AQLQ#	43	5.1 (4.1–5.4)	154	5.6 (5.0~6.1)	<0.0001
Symptoms#	43	5.6 (4.6–6.1)	154	5.9 (4.9~6.3)	0.08
Emotional function#	43	5.6 (4.7–6.6)	154	6.4 (5.8~6.8)	<0.01
Environmental stimuli#	43	5.4 (4.4–6.6)	154	6.2 (5~7)	0.08
Self-health concern#	43	5 (4–5.6)	154	6 (5~6.5)	<0.0001
Activity limitation*	43	4.5±1.0	154	5.00±1.1	<0.01
ACQ#	43	–	154	–	<0.0001
HADS-A#	43	7 (0.8–12.7)	154	5 (0~12.4)	0.22
HADS-D#	43	5 (0–9.9)	154	4 (0~9.4)	0.84

Data are expressed as *, mean ± SD; #, median; 25–75th percentile; ^, data are expressed as %. P values: comparisons between groups were tested using Pearson's χ^2 or Fisher's Exact test (categorical variables) or independent *t*-test (normally distributed continuous variables) and Mann–Whitney U test (no normally distributed variables or nonparametric data). FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow; FVC, forced vital capacity; BMI, body mass index; MMEF75/25, maximal mid-expiratory flow 75/25; AQLQ, Asthma Quality of Life Questionnaire; ACQ, Asthma Control Questionnaires; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression.

were also analyzed. The cut-off values (COV) were calculated for these parameters in terms of AE incidence during an average follow-up period of 3 years. The COV, AUC, sensitivity, and specificity are presented in *Figure 5*. Among the subjects, the AQLQ and ACQ were both independent risk factors within 3 years of enrollment; the COV of the AQLQ and the ACQ (uncontrolled) that better evaluated the risk with the AE were ≤5.4 and >1,

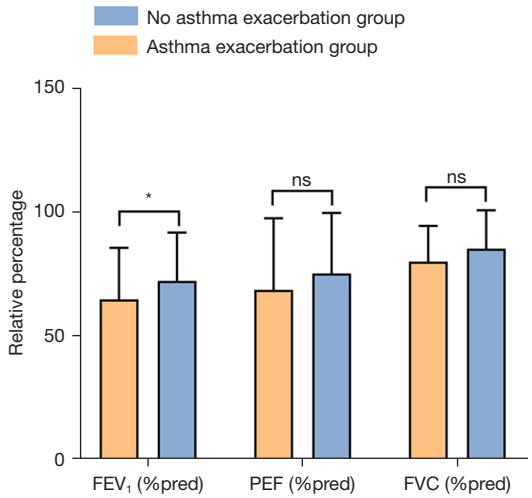

Figure 1 Histogram showing the FEV_1 (%pred), PEF (%pred), and FVC (%pred) of the AE and no AE groups. Asthma patients were divided into the AE and no AE groups. Data are expressed as the median values with interquartile ranges. *, P<0.05, ns, no significant, independent *t*-test. FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow; FVC, forced vital capacity; AE, asthma exacerbation.

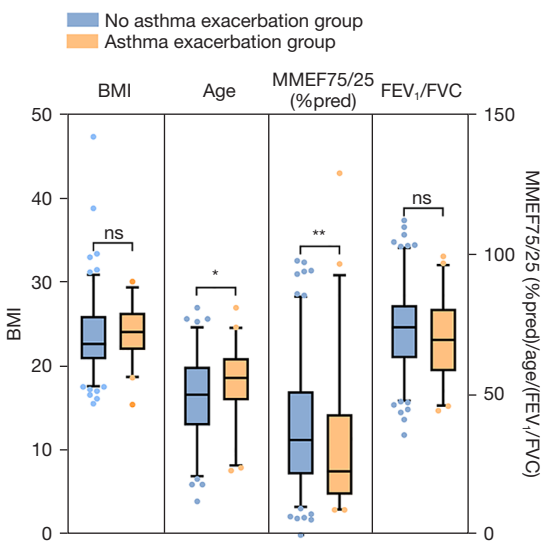

Figure 2 Box-and-whisker plots showing the median BMI, age, MMEF75/25 (%pred), and FEV_1/FVC of the AE and no AE groups. Boxes denote the upper and lower quartiles. Whiskers represent minimum and maximum values, excluding values >1.5 times the higher or lower quartile range (displayed as separate points). *, P<0.05, **, P<0.01, and ns, no significant, Mann-Whitney U test. BMI, body mass index; MMEF75/25, maximal mid-expiratory flow 75/25; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; AE, asthma exacerbation.

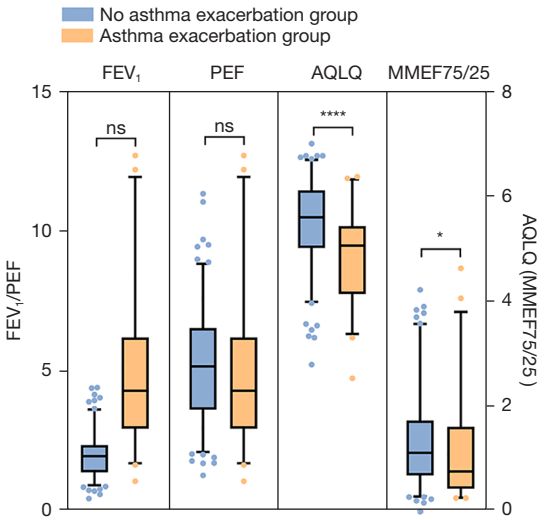

Figure 3 Box-and-whisker plots showing the median BMI, age, MMEF75/25, and FEV1/PEF of the AE and no AE groups. Boxes denote the upper and lower quartiles. Whiskers represent minimum and maximum values, excluding values >1.5 times the higher or lower quartile range (displayed as separate points). *, P<0.05, ****, P<0.0001, and ns, no significant, Mann-Whitney U test. BMI, body mass index; MMEF75/25, maximal mid-expiratory flow 75/25; FEV1, forced expiratory volume in one second; PEF, peak expiratory flow; AE, asthma exacerbation.

respectively. The AQLQ score had a sensitivity of 79.07% and a specificity of 59.09% (AUC 0.70, P<0.0001), and the ACQ (uncontrolled) had a sensitivity of 81.4% and a specificity of 52.29% (AUC 0.68, P<0.0001).

Discussion

According to GINA, AEs are episodes characterized by a progressive increase in symptoms such as shortness of breath, cough, wheezing, or chest tightness and a progressive decrease in lung function (1). AEs and hospitalization are critical problems in asthma management. In the acute setting, lung function measurements are more reliable indicators of the severity of the exacerbation than symptoms. However, the frequency of symptoms may be a more sensitive measure of the onset of an exacerbation than the lung function measurements (1). Thus, to determine the potential risk factors for exacerbations and hospitalization in asthma patients, we conducted this 3-year prospective observational study involving 257 participants.

The results showed the uncontrolled group was more likely to develop AE than the well-controlled group. Patients

Table 2 Multivariate analysis for exacerbation in asthma patients

Variables	B	P	OR	95% CI for OR	
				Min	Max
Smoking index	0.01	1.01	1.01	0.99	1.03
Age, years	0.05	1.05	1.05	0.99	1.09
BMI, kg/m^2	0.03	1.03	1.03	0.92	1.15
FEV_1	0.73	2.08	2.08	0.21	20.90
FEV_1 (%pred)	–0.01	0.99	0.99	0.89	1.09
PEF	–0.10	0.90	0.90	0.45	1.81
PEF (%pred)	0.02	1.02	1.02	0.97	1.07
MMEF75/25	0.83	2.29	2.29	0.11	46.27
MMEF75/25 (%pred)	–0.02	0.98	0.98	0.88	1.09
FVC (%pred)	–0.006	0.99	0.99	0.91	1.08
FEV_1/FVC	–0.01	0.99	0.99	0.93	1.04
ACQ	–	0.03	–	–	–
ACQ (well-controlled)	0	–	1	–	–
ACQ (partial-controlled)	0.68	0.45	1.98	0.33	11.84
ACQ (uncontrolled)	1.85	<0.05	6.34	1.14	35.21
AQLQ	–0.52	<0.05	0.59	0.35	0.99
Constant	–2.81	0.44	0.06		

Binary logistic regression was used. OR, odds ratio; CI, confidence interval; Max, maximum; Min, minimum; BMI, body mass index; FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow; FVC, forced vital capacity; MMEF75/25, maximal mid-expiratory flow 75/25; AQLQ, Asthma Quality of Life Questionnaire; ACQ, Asthma Control Questionnaires.

with low AQLQ scores were more likely to develop AE than these with high AQLQ scores. AQLQ and ACQ were both independent risk factors associated with AE within three years of enrollment; the COV of the AQLQ and the ACQ (uncontrolled) that better evaluated the risk with the AE were ≤5.4 and >1, respectively. The AQLQ scores had a sensitivity of 79.07%, a specificity of 59.09%, and an AUC of 0.70. Meanwhile, ACQ (uncontrolled) had a sensitivity of 81.4%, a specificity of 52.29%, and an AUC of 0.68.

The lung function parameters, ACQ, and AQLQ were found to be significant univariable factors of hospitalization. However, none of them were independent risk factors associated with AE. So, we focused more on the AE and no AE groups. A total of 43 exacerbations were observed among the 197 patients over the 3 years. The exacerbation rate was comparable to that in other study with similar patient populations (17). The pairwise comparison also showed that FEV_1 (%pred), MMEF75/25, and MMEF75/25 (%pred) in the AE group were considerably lower than these in the no AE group. As mentioned in GINA, low FEV_1 is a strong independent factor of the risk of exacerbations, even after adjustment for symptom frequency. Some patients have impaired bronchoconstriction perception, with few symptoms despite low lung function. Thus, we decided to validate the lung function parameters as strong independent risk factors of AE. However, although FEV_1 (%pred), MMEF75/25, and MMEF75/25 (%pred) were found to be significant univariable factors, they were not significant multivariable factors of AE. Asthma is characterized by variable expiratory airflow limitation, and multiple comparisons of the variability in lung function per patient over a prolonged time may validate lung function parameters as strong risk factors of AE.

In this prospective, longitudinal, observational study, ACQ (uncontrolled) and AQLQ were found to be significantly associated with AE. This finding demonstrated

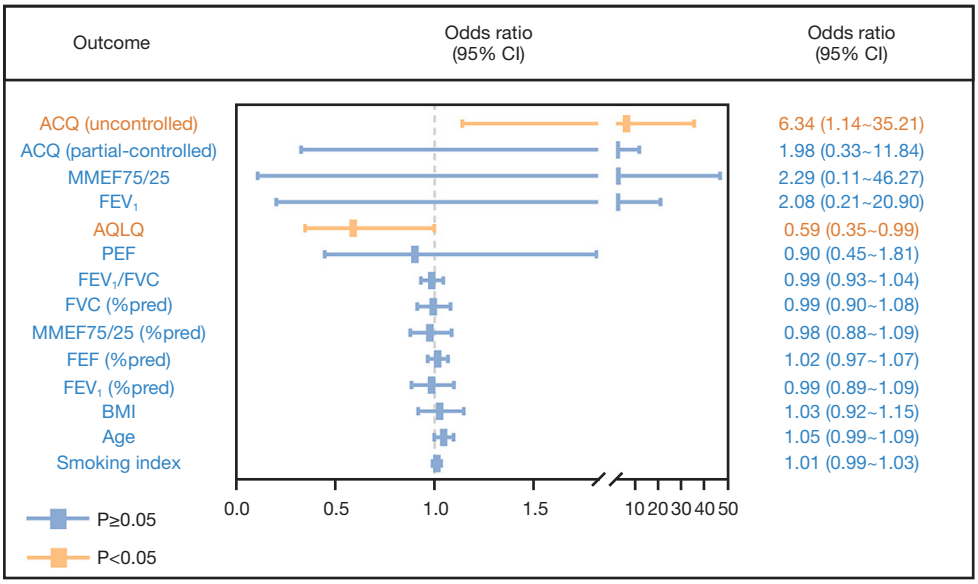

Figure 4 Odds ratios of the independent variables to predict asthma exacerbation. Binary logistic regression data showing the OR with 95% CI for ACQ (uncontrolled), ACQ (well-controlled), MMEF75/25, FEV_1, AQLQ, PEF, FEV_1/FVC, FVC (%pred), MMEF75/25 (%pred), FEF (%pred), FEV_1 (%pred), BMI, age, and smoking index to predict asthma exacerbation. OR, odds ratio; CI, confidence interval; ACQ, Asthma Control Questionnaires; MMEF75/25, maximal mid-expiratory flow 75/25; FEV_1, forced expiratory volume in one second; AQLQ, Asthma Quality of Life Questionnaire; PEF, peak expiratory flow; FVC, forced vital capacity; BMI, body mass index.

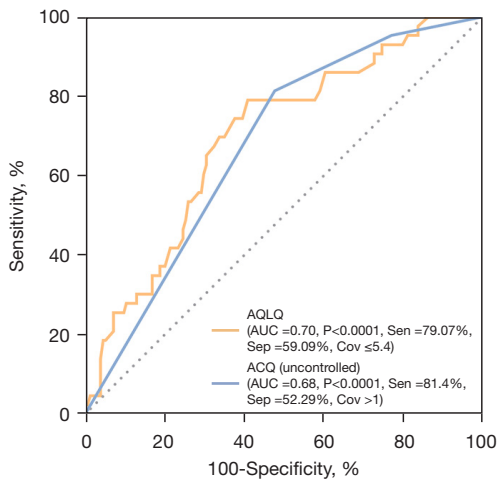

Figure 5 ROC curve analysis of AQLQ and ACQ (uncontrolled) for predicting the asthma exacerbation phenotypes. AQLQ, Asthma Quality of Life Questionnaire; AUC, area under the curve; Sen, sensitivity; Spe, specificity; Cov, cut-off value; ACQ, Asthma Control Questionnaires; ROC, receiver operating characteristic.

higher odds of AE with an increase in the proximate AQLQ score. Higher odds of AE were also observed with an increase in the ACQ (uncontrolled) group than in ACQ (well-controlled) group. A direct correlation between ACQ (uncontrolled), AQLQ, and the risk of future exacerbation was demonstrated in this study. The present study also showed that AQLQ and ACQ (uncontrolled) may be able to assess the risk of AE within 3 years. Specifically, AQLQ had a sensitivity of 79.07%, a specificity of 59.09%, and an AUC of 0.70; ACQ (uncontrolled) had a sensitivity of 81.4%, a specificity of 52.29%, and an AUC of 0.68. This means the role of AQLQ and ACQ (uncontrolled) is to help identify patients at greater risk of AE, not as criteria for the diagnosis of AE.

A history of ≥1 exacerbation in the previous year, poor adherence, incorrect inhaler technique, chronic sinusitis, and smoking have been identified as independent risk factors, even if there are few symptoms (18). Poor asthma symptom control itself substantially increases the risk of exacerbations (4,17,19). However, most studies used ACQ and AQLQ as clinical endpoints for interventional phase II, III, and IV trials (20-23). Therefore, we used the ACQ, AQLQ, HADS, and lung function parameters, and sought to evaluate whether they could be strong risk factors for AE and hospitalization. The result showed that ACQ (uncontrolled) and AQLQ were associated with AE within the three years following randomization. The uncontrolled

ACQ group was more likely to develop AE than the well-controlled ACQ group, and patients with low AQLQ scores were more likely to develop AE than these with high AQLQ scores.

Several limitations of this study should be acknowledged. Firstly, this study only includes a single comparison per patient and a small sample size. Secondly, every recruited patient filled out the AQLQ, ACQ, and HADs, and underwent lung function tests only once due to restrictions in the study protocol. Thirdly, the number of days of AE and days of hospitalization, were time-to-event data, we analyzed the data by using Cox regression analyses. However, the independent variables were not significantly associated with the number of days of AE or days of hospitalization. Further research on this issue is warranted. Thus, larger studies with more advanced statistical methods are needed to seek the strong risk factors for AE.

Conclusions

In conclusion, ACQ (uncontrolled) and AQLQ are strong risk factors for AE. As simple screening tools, AQLQ and ACQ (uncontrolled) can be used in primary care to quickly identify patients needing more detailed assessment, alerting healthcare professionals to remedial action. They can also guide treatment decisions. The findings of this study suggest that patients with uncontrolled asthma and a diminished health-related quality of life had an increased risk of exacerbations in the future. However, this relationship did not exist for hospitalization.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5918/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5918/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5918/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethical approvals for this study were obtained from the Institutional Review Board of Ningbo First Hospital (No. 2016-R017). The study was performed in accordance with the Declaration of Helsinki (as revised in 2013). All participants included in this study provided informed consent.

References

1. 2022 GINA report, global strategy for asthma management and prevention (2022 update). Available online: https://ginasthma.org/gina-reports
2. Ivanova JI, Bergman R, Birnbaum HG, et al. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. J Allergy Clin Immunol 2012;129:1229-35.
3. Eisner MD, Ackerson LM, Chi F, et al. Health-related quality of life and future health care utilization for asthma. Ann Allergy Asthma Immunol 2002;89:46-55.
4. Wu AC, Tantisira K, Li L, et al. Predictors of symptoms are different from predictors of severe exacerbations from asthma in children. Chest 2011;140:100-7.
5. Osborne ML, Pedula KL, O'Hollaren M, et al. Assessing future need for acute care in adult asthmatics: the Profile of Asthma Risk Study: a prospective health maintenance organization-based study. Chest 2007;132:1151-61.
6. Denlinger LC, Phillips BR, Ramratnam S, et al. Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations. Am J Respir Crit Care Med 2017;195:302-13.
7. Blanco-Aparicio M, Vázquez I, Pita-Fernández S, et al. Utility of brief questionnaires of health-related quality of life (Airways Questionnaire 20 and Clinical COPD

Questionnaire) to predict exacerbations in patients with asthma and COPD. Health Qual Life Outcomes 2013;11:85.
8. Magnan A. Tools to assess (and achieve?) long-term asthma control. Respir Med 2004;98 Suppl B:S16-21.
9. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 2007;165:710-8.
10. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. BMJ 2020;368:m441.
11. Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.
12. Juniper EF, Bousquet J, Abetz L, et al. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med 2006;100:616-21.
13. Juniper EF, Guyatt GH, Ferrie PJ, et al. Measuring quality of life in asthma. Am Rev Respir Dis 1993;147:832-8.
14. Yue T, Li Q, Wang R, et al. Comparison of Hospital Anxiety and Depression Scale (HADS) and Zung Self-Rating Anxiety/Depression Scale (SAS/SDS) in Evaluating Anxiety and Depression in Patients with Psoriatic Arthritis. Dermatology 2020;236:170-8.
15. Mitchell AJ, Meader N, Symonds P. Diagnostic validity of the Hospital Anxiety and Depression Scale (HADS) in cancer and palliative settings: a meta-analysis. J Affect Disord 2010;126:335-48.
16. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948-68.
17. Meltzer EO, Busse WW, Wenzel SE, et al. Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. J Allergy Clin Immunol 2011;127:167-72.
18. Loymans RJ, Honkoop PJ, Termeer EH, et al. Identifying patients at risk for severe exacerbations of asthma: development and external validation of a multivariable prediction model. Thorax 2016;71:838-46.
19. Schatz M, Zeiger RS, Yang SJ, et al. The relationship of asthma impairment determined by psychometric tools to future asthma exacerbations. Chest 2012;141:66-72.
20. Hatter L, Houghton C, Bruce P, et al. Asthma control with ICS-formoterol reliever versus maintenance ICS and SABA reliever therapy: a post hoc analysis of two randomised controlled trials. BMJ Open Respir Res 2022;9:e001271.
21. Bourdin A, Virchow JC, Papi A, et al. Dupilumab efficacy in subgroups of type 2 asthma with high-dose inhaled corticosteroids at baseline. Respir Med 2022;202:106938.
22. Menzies-Gow A, Gurnell M, Heaney LG, et al. Adrenal function recovery after durable OCS-sparing with benralizumab in the PONENTE study. Eur Respir J 2022;60:2103226.
23. Menzies-Gow A, Gurnell M, Heaney LG, et al. Oral corticosteroid elimination via a personalised reduction algorithm in adults with severe, eosinophilic asthma treated with benralizumab (PONENTE): a multicentre, open-label, single-arm study. Lancet Respir Med 2022;10:47-58.

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Supplementary

Table S1 Study cohort characteristics at the start were stratified by hospitalization status

Characteristic	Hospitalizations (N=23)		No Hospitalizations (N=174)		P value
	N	Value	N	Value	
Female gender^	10	87.3%	69	12.7%	0.82
Comorbidities^	10	17.5%	47	82.5%	0.14
Allergy^	11	14.1%	67	85.9%	0.37
Allergic rhinitis^	17	19%	73	81%	0.37
FEV_1 (%pred) *	23	60.7±16.5	174	72.1±19.9	<0.01
FVC (%pred) *	23	76.3±9.9	174	85.3±15.7	<0.01
Smoking Index#	23	26.3 (0~77)	174	0 (0~45)	<0.05
Duration of asthma#	23	23 (3~56.6)	174	21 (1~55)	0.10
Age#, years	23	60 (50~65)	174	50 (39~60)	<0.01
BMI#, kg/m^2	23	23.7 (21.6~26.4)	174	22.9 (21~26)	0.52
PEF (%pred) #	23	62.3 (47.1~80)	174	77.1 (54.7~92)	<0.05
FEV_1#	23	1.98 (1.04~3.1)	174	2.35 (1.4~3.7)	<0.05
PEF#	23	4 (2.6~5.4)	174	5.1 (3.6~6.5)	<0.05
MMEF75/25#	23	0.6 (0.4~1.6)	174	1.1 (0.7~1.7)	<0.05
MMEF75/25 (%pred) #	23	18.5 (14.7~40.4)	174	32.9 (21.2~49.5)	<0.05
FVC#	23	2.3 (1.7~3.1)	174	2.7 (2.2~3.2)	<0.05
FEV_1/FVC#	23	66.4 (55.6~76.2)	174	73.5 (63.1~81.8)	0.06
AQLQ#	23	5.0 (4.3~5.3)	174	5.5 (4.9~6)	<0.05
Symptoms#	23	5.7 (4.1~6.1)	174	5.9 (4.9~6.4)	0.06
Emotional function#	23	5.6 (4.4~6.6)	174	6.4 (5.6~6.8)	<0.05
Environmental stimuli#	23	5.8 (4.4~7)	174	6 (4.8~7)	0.49
Self-health concern#	23	4.8 (4~5.5)	174	6 (5~6.5)	<0.0001
Activity limitation*	23	4.3±1.1	174	4.9±1.1	<0.05
ACQ#	23	-	174	-	<0.05
HADS-A#	23	3 (1~7)	174	2 (0~5)	0.17
HADS-D#	23	3 (0~7)	174	1 (0~4)	0.08

Data are expressed as the *mean ± SD; #median; 25–75th percentile; ^ Data are expressed as %. P values: comparisons between groups were tested using Pearson´s X^2 or Fisher´s Exact test (categorical variables) or independent *t*-test (normally distributed continuous variables) and Mann-Whitney U test (non-normally distributed variables or non-parametric data).

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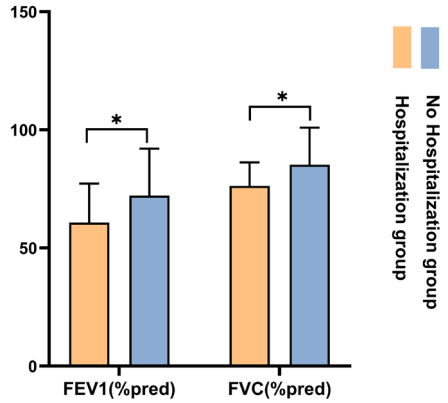

Figure S1 Histogram showing the FEV_1 (%pred) and FVC (%pred) of the hospitalization and no hospitalization groups Asthma patients were separated into the hospitalization and no hospitalization groups. Data are expressed as the median values with interquartile ranges. *, P<0.05, independent *t*-test.

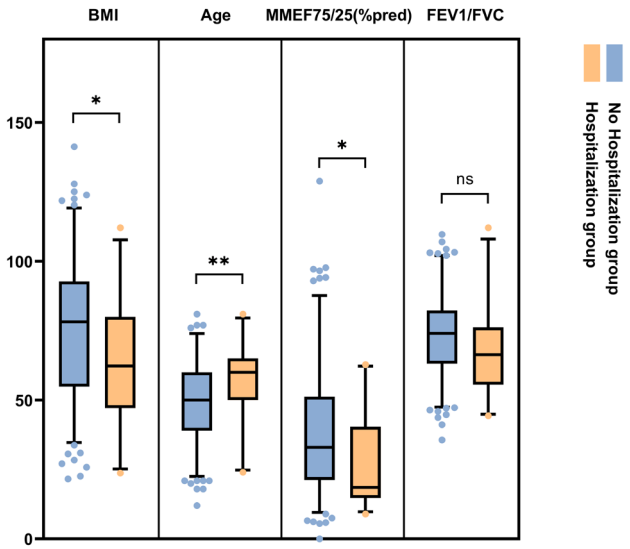

Figure S2 Box-and-whisker plots showing the BMI, age, MMEF75/25 (%pred), and FEV_1/FVC of the hospitalization and no hospitalization groups. Boxes denote the upper and lower quartiles. Whiskers represent minimum and maximum values, excluding values >1.5 times the higher or lower quartile range (displayed as separate points). *, P<0.05, **, P<0.01, and ns, no significant, Mann-Whitney U test.

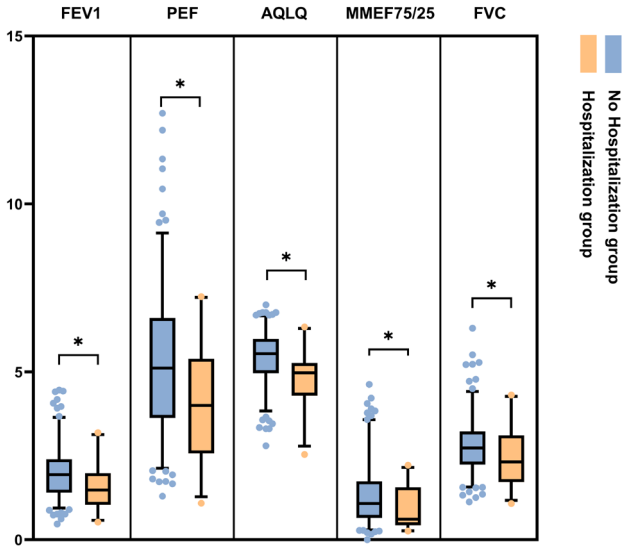

Figure S3 Box-and-whisker plots showing the median FEV, PEF, AQLQ, MMEF75/25, and FVC of the hospitalization and no hospitalization groups. Boxes denote the upper and lower quartiles. Whiskers represent minimum and maximum values, excluding values >1.5 times the higher or lower quartile range (displayed as separate points). *, P<0.05, Mann–Whitney U test.

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Table S2 Multivariate analysis for hospitalization in asthma patients

Variables	B	P	OR	95% C.I. for OR	
				Min	Max
Smoking Index	0.004	0.79	1.004	0.98	1.03
Age	0.08	0.02	1.08	1.01	1.15
FEV_1	6.66	0.23	776.6	0.02	36021562
FEV_1 (%pred)	–0.08	0.51	0.92	0.71	1.18
PEF	–0.56	0.26	0.57	0.22	1.51
PEF (%pred)	0.02	0.60	1.02	0.95	1.096
MMEF75/25	–0.91	0.77	0.41	0.001	162.5
MMEF75/25 (%pred)	0.004	0.97	1.01	0.83	1.21
FVC	–2.51	0.42	0.08	0	38.1
FVC (%pred)	0.01	0.89	1.01	0.84	1.22
FEV_1/FVC	–0.02	0.59	0.98	0.91	1.06
ACQ	–	0.19	–	–	–
ACQ (Well controlled)	0	–	1	–	–
ACQ (Partly controlled)	–1.17	0.33	0.31	0.03	3.23
ACQ (Uncontrolled)	–1.39	0.09	0.25	0.04	1.28
AQLQ	–0.51	0.13	0.61	0.32	1.15
HADS–D[#]	0.03	0.65	1.03	0.89	1.19
Constant	–0.31	0.94	0.73		

CI, confidence interval; Max, maximum; Min, minimum; OR, odds ratio. Binary logistic regression was used.

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Table S3 Univariable Predictors of asthma exacerbation

Variables	Asthma Exacerbation	Unadjusted HR(95%CI)	P Value
Female gender	20(25)	1.051(0.576,1.920)	0.87
Comorbidities	15(26)	0.934(0.492,1.771)	0.83
Allergy	19(24)	0.892(0.483,1.648)	0.72
Allergic rhinitis	17(19)	1.211(0.638,2.298)	0.56
FEV_1 (%pred)	43(21.8)	1.002(0.987,1.017)	0.78
PEF (%pred)	43(21.8)	1.002(0.991,1.012)	0.77
FVC (%pred)	43(21.8)	1.002(0.983,1.022)	0.83
Smoking Index	43(21.8)	1.000(0.988,1.013)	0.97
Duration of asthma	43(21.8)	0.995(0.976,1.015)	0.64
Age	43(21.8)	0.985(0.963,1.008)	0.19
BMI	43(21.8)	1.039(0.944,1.143)	0.44
FEV_1	43(21.8)	1.250(0.840,1.861)	0.27
PEF	43(21.8)	1.056(0.929,1.202)	0.40
MMEF75/25	43(21.8)	1.166(0.838,1.624)	0.36
MMEF75/25 (%pred)	43(21.8)	1.004(0.991,1.017)	0.58
FVC	43(21.8)	1.252(0.860,1.823)	0.24
FEV_1/FVC	43(21.8)	1.004(0.982,1.027)	0.73
AQLQ	43(21.8)	0.937(0.640,1.372)	0.74
Symptoms	43(21.8)	0.974(0.790,1.201)	0.80
Emotional function	43(21.8)	1.020(0.798,1.303)	0.88
Environmental stimuli	43(21.8)	0.974(0.831,1.140)	0.74
Self-health concern	43(21.8)	0.926(0.736,1.165)	0.51
Activity limitation	43(21.8)	0.952(0.686,1.320)	0.77
ACQ(partial-controlled)	6(14.0)	0.591(0.116,2.998)	0.53
ACQ (uncontrolled)	35(81.4)	0.499(0.116,2.143)	0.35
HADS-A	43(21.8)	0.992(0.914,1.077)	0.86
HADS-D	43(21.8)	0.985(0.894,1.086)	0.76

Values are n (%) unless otherwise indicated, CI ¼ confifidence interval.

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Table S4 Univariable Predictors of hospitalization

Variables	Asthma Exacerbation	Unadjusted HR(95%CI)	P Value
Female gender	10(87.3)	1.300(0.488,3.464)	0.60
Comorbidities	10(17.5)	1.011(0.377,2.715)	0.98
Allergy	11(14.1)	0.667(0.237,1.873)	0.44
Allergic rhinitis	17(19)	0.800(0.285,2.248)	0.67
FEV_1 (%pred)	23(11.7)	0.996(0.966,1.027)	0.79
PEF (%pred)	23(11.7)	1.000(0.978,1.023)	0.98
FVC (%pred)	23(11.7)	0.990(0.941,1.041)	0.70
Smoking Index	23(11.7)	1.004(0.983,1.025)	0.72
Duration of asthma	23(11.7)	1.003(0.978,1.028)	0.84
Age	23(11.7)	0.984(0.951,1.019)	0.38
BMI	23(11.7)	1.083(0.922,1.272)	0.33
FEV_1	23(11.7)	1.051(0.516,2.139)	0.89
PEF	23(11.7)	1.089(0.818,1.450)	0.56
MMEF75/25	23(11.7)	1.061(0.480,2.347)	0.88
MMEF75/25 (%pred)	23(11.7)	0.999(0.969,1.030)	0.96
FVC	23(11.7)	1.086(0.601,1.965)	0.78
FEV_1/FVC	23(11.7)	0.994(0.963,1.026)	0.72
AQLQ	23(11.7)	0.826(0.472,1.448)	0.51
Symptoms	23(11.7)	0.896(0.588,1.363)	0.61
Emotional function	23(11.7)	0.851(0.600,1.208)	0.37
Environmental stimuli	23(11.7)	0.917(0.694,1.210)	0.54
Self-health concern	23(11.7)	0.925(0.674,1.270)	0.63
Activity limitation	23(11.7)	0.999(0.631,1.581)	0.99
ACQ(partial-controlled)	2(8.7)	0.500(0.031,7.994)	0.62
ACQ (uncontrolled)	20(87)	0.700(0.092,5.323)	0.73
HADS-A	23(11.7)	1.017(0.895,1.157)	0.79
HADS-D	23(11.7)	1.055(0.912,1.220)	0.47

Values are n (%) unless otherwise indicated, CI ¼ confifidence interval.

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