Original Article

Factors Associated with Frequent Exacerbations in the UK Severe Asthma Registry

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What is already known about this topic? Risk factors for frequent asthma exacerbations include high T2 biomarkers (fractional exhaled nitric oxide and blood eosinophil count) and asthma-associated conditions (obesity and rhinitis) in clinical trial patients or asthma populations with mixed disease severity.

What does this article add to our knowledge? Poor symptom control has the strongest correlation with frequent exacerbations in patients with severe asthma, good adherence, and treated comorbidities. The relationship between T2-high biomarkers and frequent exacerbations is less apparent in patients on maintenance oral corticosteroids.

How does this study impact current management guidelines? Tools to aid identification of poor symptom control in severe asthma are key to identifying patients with higher risk of frequent exacerbations.

BACKGROUND: Frequent exacerbations are an important cause of morbidity in patients with severe asthma.
OBJECTIVE: Our aim was to identify factors associated with frequent exacerbations in a large well-characterized severe asthma population and determine whether factors differed in patients treated with and without maintenance oral corticosteroids (OCS).
METHODS: Adults with severe asthma from specialized asthma centers across the United Kingdom were recruited to the UK Severe Asthma Registry. Demography, comorbidities and

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Abbreviations used
ACQ- Asthma Control Questionnaire
AUC- Area under the curve
BMI- Body mass index
FE- Frequent exacerbator
FeNO- Fractional exhaled nitric oxide
FEV_1- Forced expiratory volume in one second
FVC- Forced vital capacity
GERD- Gastroesophageal reflux disease
OCS- Oral corticosteroids
ROC- Receiver operating characteristic
UKSAR- United Kingdom Severe Asthma Registry

physiological measurements were collected. We conducted univariable and multivariable logistic regression analyses to identify factors associated with frequent exacerbations, defined as 3 or more exacerbations treated with high-dose systemic corticosteroids in the past year.
RESULTS: Of 1,592 patients with severe asthma from the UK Severe Asthma Registry, 1,137 (71%) were frequent exacerbators and 833 (52%) were on maintenance OCS. The frequent exacerbators were more likely to be ex-smokers, have gastroesophageal reflux disease, higher Asthma Control Questionnaire-6 (ACQ-6) score, and higher blood eosinophilia. Multivariable regression analyses showed ACQ-6 score greater than 1.5 (odds ratio [OR] 4.25; $P < .001$), past smoking history (OR 1.55; $P = .024$), and fractional exhaled nitric oxide greater than 50ppb (OR 1.54; $P = .044$) were independently associated with frequent exacerbations. Past smoking history correlated with frequent exacerbations only in patients on maintenance OCS (OR 2.25; $P = .004$), whereas ACQ-6 score greater than 1.5 was independently associated with frequent exacerbations in those treated with and without maintenance OCS (OR 2.74; $P = .017$ and OR 6.42; $P < .001$, respectively).
CONCLUSIONS: Several factors were associated with frequent exacerbations in a large UK severe asthma registry population. High ACQ-6 score had the strongest association with frequent exacerbations irrespective of maintenance OCS status. **(J Allergy Clin Immunol Pract 2021;■:■-■)**

Key words: *Severe asthma; Exacerbations; Frequent exacerbations; Asthma control; ACQ*

INTRODUCTION

Severe exacerbations are an important cause of morbidity and mortality in asthma. Frequent exacerbations are common in patients with severe asthma and are associated with poorer quality of life and higher health care costs.[1-3] Risk factors for exacerbations reported from studies of severe asthma include past history of severe exacerbations, high body mass index (BMI), chronic sinusitis, gastroesophageal reflux disease (GERD), psychological stress, a history of cigarette smoking, reduced lung function, blood or sputum eosinophilia, and raised fractional exhaled nitric oxide (FeNO).[2,4-10] It is uncertain whether risk factors identified from observational studies of participants recruited to clinical trials or cohorts of severe asthma, which have strict inclusion criteria, are generalizable to a population of adults with severe asthma managed in clinical practice. Second, elevated FeNO and peripheral eosinophilia are markers of local and systemic inflammation in asthma, which are partially or completely suppressed by inhaled and oral corticosteroid (OCS) treatment. The predictive value of these type 2 inflammatory markers for exacerbations in severe asthma patients, of whom a substantial proportion is taking continuous daily OCS, is unknown.

Prevention of frequent exacerbations and of persistent asthma symptoms are key goals for establishing asthma control. The Asthma Control Questionnaire (ACQ) is a validated tool for assessing asthma control based on patient self-reported symptoms; a higher score indicates poorer control.[11] *Post hoc* analysis of clinical trial data showed a positive correlation between ACQ score and exacerbation rates.[12,13] The correlation between persistent symptoms and frequent exacerbations in patients with severe asthma is not well established. Replication of these findings in a well-characterized severe asthma population not recruited into clinical trials would support the use of ACQ in clinical practice to determine the risk of frequent exacerbations. This would, in turn, offer useful guidance for management planning.

The UK Severe Asthma Registry (UKSAR) was developed in 2015 to collect standardized data on patients referred to specialist asthma services across England, Scotland, and Northern Ireland. Specialist centers identified patients with well-characterized severe refractory asthma for inclusion in the registry from subjects with difficult-to-control asthma referred by primary and secondary care centers. The registry provides observational data on the clinical characteristics, lung function, and inflammatory variables in patients with severe asthma of whom half are taking continuous daily OCS. We hypothesized, in a UK severe asthma registry population, asthma symptom control is independently associated with frequent exacerbations and maintenance OCS use will affect factors that correlate with frequent exacerbations.

METHODS

Study population

All subjects on the UKSAR who were between the age of 18 and 80 years at first assessment during 2015 or later were included in the study. No other exclusion criteria were applied. The UKSAR is a Web-based database collecting data from severe asthma patients attending specialist asthma centers across the United Kingdom.[14] Severe asthma is defined as asthma that requires high-dose inhaled corticosteroids plus at least one other preventer therapy and/or maintenance OCS.[15] Maintenance OCS is defined as daily use of OCS to maintain asthma control. All subjects provided written informed consent prior to data collection in the registry. Data from 13 specialist centers were included in the analysis. Approval from the UKSAR Steering Committee was obtained prior to data analysis.

Study design

A retrospective analysis of cross-sectional pseudoanonymized data from UKSAR was used to identify factors associated with frequent exacerbations. Variables used in the analysis were recorded at the initial systematic assessment and included demography, medical history, spirometry, and inflammatory biomarkers. Initial systematic assessments were undertaken at specialist centers and defined as baseline in this study. The number of severe exacerbations during the 12 months previous to baseline assessment was recorded and

used to stratify patients into frequent exacerbators (FEs) and non-FEs, defined as those who had three or more and fewer than three severe exacerbations, respectively.[7,9] Severe exacerbation was defined as a worsening of asthma symptoms that led to at least three consecutive days of OCS treatment or hospital admission. All OCS courses within seven days of each other were counted as one exacerbation.

Study assessments

Twenty-eight potential risk factors for frequent exacerbations were evaluated in the severe asthma cohort. Several comorbidities were assessed, including nasal polyps, GERD, eczema, cardiac disease, depression, and anxiety. Physicians diagnosed GERD based on clinical symptoms or previous eosophagogastroduodenoscopy findings. Obesity was defined as BMI of 30 kg/m^2 or greater. Continuous variables were categorized to enable detection of nonlinear effects. The ACQ, a 7-component questionnaire, was used to evaluate asthma symptoms control. The score is based on patient self-assessment of asthma symptoms, short-acting beta-agonist use over the past week and prebronchodilator forced expiratory volume in one second (FEV_1) percentage of predicted. The latter is not required in a shortened version of the questionnaire (ACQ-6). In both versions, a score of 0 to 0.75, 0.75 to 1.5, and greater than 1.5 indicates well-, intermediate-, and poorly controlled asthma symptoms, respectively. We used the ACQ-6 score as a measure of symptom control, given spirometry results were not strictly prebronchodilation. Spirometry was performed in a clinical setting; therefore, treatment restrictions were not applied prior to testing. Baseline blood eosinophil count was recorded at the initial assessment. Highest ever blood eosinophil count was collected, retrospectively. Serum total immunoglobulin E concentrations and FeNO were also measured.

Assessment of treatment adherence

Data on treatment adherence were collected for patients added to the UKSAR. Treatment adherence was assessed using clinical judgment in conjunction with FeNO suppression testing, prescription refill records, and serum prednisolone and cortisol measurements where appropriate. In general, the criteria for treatment adherence at the participating centers are over 70% to 80% use of preventer therapy. Testing of FeNO suppression is a novel and effective way of identifying nonadherence to inhaled corticosteroids using remote monitoring technology (Vitalograph INCA device and Aerocrine NIOX Vero). A positive FeNO suppression test suggests previous suboptimal treatment adherence; however, a small proportion of patients are recognized as having severe asthma despite positive FeNO suppression testing.[16]

Statistical analyses

Descriptive statistics were calculated using means (with SDs), medians (with interquartile ranges), and counts (with percentages) as appropriate. Initial multivariable logistic regression models were built including variables that have been previously associated with increased exacerbations and those with strong univariate associations. Variables were removed from the initial multivariable model using modified backward stepwise selection. All models included year of presentation at the clinic and hospital site as fixed effects. Variables examined for association with frequent exacerbations and included in multivariable logistic regression analysis are listed in the online repository file (Tables E1 and E2; available in this article's Online Repository at www.jaci-inpractice.org). Model discrimination was assessed using the receiver operating characteristic (ROC) curve; goodness-of-fit was quantified using the area under the curve (AUC). We assessed bias using 10-fold internal cross-validation.[17]

Our primary analysis was based on complete cases; however, we used multiple imputation with chained equations, which assumes that the data were missing at random, to assess the impact of missing data.[18] We conducted additional sensitivity analysis using a cut-off of 2 or fewer or 4 or more exacerbations to define an FE. All analyses were conducted using the STATA 16 software package (StataCorp).

RESULTS

Patient characteristics

Of 1,592 patients in the UKSAR included in the study, 1,137 (71.4%) were FEs and 455 (28.6%) were non-FEs. Over the previous year, most patients (60.0%) had four or more severe exacerbations and only 11.6% of patients had no exacerbations. There were 1,005 (63.1%) female patients and 1,214 (76.3%) were Caucasian. Fifty-two percent of patients were taking maintenance OCS. Sixty-four percent of all patients included in the study went on to receive biological therapy (Table I).

Key patient characteristics for FEs and non-FEs are shown in Table I. The two groups were similar in gender and ethnicity distribution. The FEs were more likely to be ex-smokers (29.2% vs 21.7%; $P = .028$), have GERD (21.3% vs 14.4%; $P = .006$), higher ACQ-6 score (mean [SD] 3.1 [1.3] vs 2.4 [1.4]; $P < .001$) and baseline blood eosinophil count (median 0.37×10^9 cells/L vs 0.30×10^9 cells/L; $P = .006$). Highest ever median blood eosinophil count was 0.6×10^9 cells/L for both FEs and non-FEs ($P = .434$). Non-FEs were more likely to be taking maintenance OCS or have allergic rhinitis. There were no differences between the two groups for BMI, depression or anxiety, FeNO, and total immunoglobulin E level. The difference in percentage of predicted FEV_1 between the two groups was not clinically significant (66.0% vs 68.6%; $P = .045$).

Factors associated with frequent exacerbations

An association between frequent exacerbations and several factors were identified using univariate regression analyses. Factors that correlated with frequent exacerbations included ACQ-6 score greater than 1.5 (odds ratio [OR] 3.16; $P < .001$), past smoking history (OR 1.49; $P = .003$) and GERD (OR 1.61; $P = .002$). High blood eosinophil count ($>0.45 \times 10^9$ cells/L) was associated with frequent exacerbations (OR 1.49; $P = .006$), but elevated FeNO (>50ppb) was not associated with increased exacerbations (OR 1.24; $P = .144$). Obesity, history of nasal polyps, depression or anxiety, and low FEV_1 percentage of predicted did not correlate with frequent exacerbations. Unsurprisingly, treatment with maintenance OCS was associated with reduced likelihood of frequent exacerbations (OR 0.69; $P = .001$) (Table II).

In multivariable regression analyses, the correlation between ACQ-6 score and frequent exacerbations remained significant ($P < .001$). In comparison with patients who had well-controlled symptoms, an ACQ-6 score greater than 1.5 increased the odds for frequent exacerbations by over fourfold. The association between frequent exacerbations and past smoking history also remained significant (OR 1.55; $P = .024$). Interestingly, when adjusted for other factors, peripheral eosinophilia was no longer associated with frequent exacerbations (OR 1.0; $P = .683$), whereas the relationship between elevated FeNO (>50 ppb) and frequent exacerbations became stronger (OR 1.54; $P = .044$).

TABLE I. Baseline characteristics for all severe asthma patients and comparison of baseline characteristics in FEs and non-FEs

Characteristic*	n	All severe asthma patients (n = 1,592)	Non-FE (n = 455)	FE‡ (n = 1,137)	*P* value§
Age at first assessment, y [mean (SD)]	1,592	49.4 (14.4)	51.0 (14.2)	48.8 (14.5)	**.008**
Age at onset of symptoms, y [mean (SD)]	1,393	23.9 (19.0)	25.5 (19.6)	23.3 (18.7)	.059
Female, n (%)	1,005	1,005 (63.1)	279 (61.3)	726 (63.9)	.344
Ethnicity, n (%)	1,579				.685
Caucasian		1,214 (76.9)	343 (76.1)	871 (77.2)	
Southeast Asian		92 (5.8)	24 (5.3)	68 (6.0)	
Northeast Asian		61 (3.9)	18 (4.0)	43 (3.8)	
African		79 (5.0)	22 (4.9)	57 (5.1)	
Mixed		14 (0.9)	7 (1.6)	7 (0.6)	
Other		119 (7.5)	37 (8.2)	82 (7.3)	
BMI, kg/m^2 [mean (SD)]	1,559	30.6 (7.0)	30.1 (6.6)	30.8 (7.1)	.065
Smoking status, n (%)	1,564				**.028**
Never smoked		1,084 (69.3)	333 (74.5)	751 (67.2)	
Ex-smoker		423 (27.0)	97 (21.7)	326 (29.2)	
Current smoker		57 (3.6)	17 (3.8)	40 (3.6)	
Pack-years smoked†, y	391	0 (0-1)	0 (0-0)	0 (0-3)	**.007**
Atopic disease, n (%)	1,581	976 (61.7)	282 (62.4)	694 (61.5)	.940
Eczema, n (%)	1,559	59 (3.8)	21 (4.7)	38 (3.4)	.315
Rhinitis, n (%)	1,563	136 (8.7)	46 (10.3)	90 (8.1)	.345
Allergic rhinitis, n (%)	1,558	97 (6.2)	41 (9.2)	56 (5.0)	**.009**
Chronic rhinitis, n (%)	1,555	3 (0-2)	1 (0-2)	2 (0-2)	.962
Nasal polyps, n (%)	1,560	291 (18.7)	94 (21.1)	197 (17.7)	.298
GERD, n (%)	1,563	302 (19.3)	64 (14.4)	238 (21.3)	**.006**
Depression or anxiety, n (%)	1,562	125 (8.0)	33 (7.4)	92 (8.2)	.730
Hospital admissions for asthma in last 12 mo†	1,572	0 (0-1)	0 (0-1)	0 (0-2)	**<.001**
Number of invasive ventilation events ever†	1,398	0 (0-0)	0 (0-0)	0 (0-0)	.267
Blood eosinophil count† ($\times 10^9$ cells/L)	1,571	0.34 (0.17-0.60)	0.30 (0.11-0.55)	0.37 (0.20-0.60)	**.006**
Highest ever blood eosinophil count† ($\times 10^9$ cells/L)	1,530	0.60 (0.37-0.94)	0.60 (0.37-1.00)	0.60 (0.37-0.90)	.434
FeNO† (ppb)	1,302	39.0 (20.0-74.0)	39.0 (20.0-70.0)	40.0 (21.0-77.0)	.230
Total IgE† (IU/mL)	1,515	166 (56-475)	180 (64-528)	158 (53-456)	.192
FEV_1 L [mean (SD)]	1,409	1.98 (0.80)	2.06 (0.82)	1.95 (0.79)	**.015**
FEV_1 % predicted (%) [mean (SD)]	1,308	66.8 (21.3)	68.6 (21.4)	66.0 (21.2)	**.045**
ACQ-6 score [mean (SD)]	1,380	2.9 (1.4)	2.4 (1.4)	3.1 (1.3)	**<.001**
ACQ-7 score [mean (SD)]	1,387	3.0 (1.3)	2.6 (1.3)	3.2 (1.2)	**<.001**
Inhaled corticosteroid dose† beclometasone equivalent (μg)	1,431	2,000 (1,600-2,000)	2,000 (1,600-2,000)	2,000 (1,600-2,000)	.865
Home nebulizer, n (%)	1,560	310 (19.9)	56 (12.6)	254 (22.8)	**<.001**
Maintenance OCS use, n (%)	1,581	833 (52.7)	267 (59.2)	566 (50.1)	**.004**
Maintenance OCS dose† (mg)	823	10.0 (7.5-17.5)	10.0 (7.0-15.0)	10.0 (10.0-20.0)	**<.001**
Number of rescue OCS courses in the last 12 mo, n (%)	1,590				**<.001**
0		185 (11.6)	185 (40.7)	0 (0.0)	
1		140 (8.8)	140 (30.8)	0 (0.0)	
2		130 (8.2)	130 (28.6)	0 (0.0)	
3		179 (11.3)	0 (0.0)	179 (15.8)	
≥4		956 (60.1)	0 (0.0)	956 (84.2)	
Met ERS/ATS criteria for severe asthma	1,592	1,202 (88.7)	355 (88.8)	847 (88.7)	>.999

Values highlighted in bold are *P* values <.05.
ATS, American Thoracic Society; *ERS*, European Respiratory Society; *IgE*, immunoglobulin E.
*Results are shown as count (%), mean (SD).
†Median [interquartile range].
‡FE: ≥3 exacerbations treated with high-dose systemic corticosteroids in the past year.
§*P* values are shown for comparison between FEs and non-FEs.

The odds for having three or more exacerbations in a year reduced by 42% in patients treated with maintenance OCS compared with those without maintenance OCS (Table II and Figure 1).

Factors associated with frequent exacerbations in patients treated with and without maintenance OCS

Factors associated with frequent exacerbations differed in patients treated with and without maintenance OCS. In patients

TABLE II. Factors associated with frequent exacerbations in severe asthma—univariable and multivariable logistic regression

	Univariable model (n = 1,592)			Multivariable model* (n = 877)	
	n	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male	587	0.90 (0.72-1.12)	.344	1.01 (0.71-1.43)	.950
Age at first assessment, y					
18-34	278	1		1	
35-54	683	0.83 (0.60-1.15)	.257	0.61 (0.37-0.99)	**.047**
55-79	631	0.69 (0.50-0.95)	**.024**	0.55 (0.33-0.91)	**.020**
Ethnicity					
Caucasian	1,214	1		1	
Southeast Asian	92	1.12 (0.69-1.81)	.656	0.45 (0.22-0.94)	**.033**
Northeast Asian	61	0.94 (0.54-1.65)	.832	0.84 (0.37-1.93)	.689
African	79	1.02 (0.61-1.69)	.938	0.79 (0.41-1.54)	.493
Mixed	14	0.39 (0.14-1.13)	.083	0.29 (0.06-1.34)	.114
Other	119	0.87 (0.58-1.31)	.513	1.26 (0.71-2.23)	.436
BMI, kg/m^2					
<24.9	329	1		1	
25-29.9	475	0.93 (0.68-1.26)	.633	1.04 (0.66-1.64)	.859
≥30	758	1.19 (0.89-1.59)	.230	1.10 (0.72-1.69)	.655
Smoking status					
Never smoked	1,084	1		1	
Ex-smoker	423	1.49 (1.15-1.93)	**.003**	1.55 (1.06-2.26)	**.024**
Current smoker	57	1.04 (0.58-1.87)	.886	1.12 (0.51-2.43)	.783
Nasal polyps	291	0.80 (0.61-1.06)	.121	0.72 (0.48-1.09)	.119
GERD	302	1.61 (1.19-2.18)	**.002**	1.02 (0.67-1.56)	.911
Depression or anxiety	125	1.12 (0.74-1.69)	.590	0.63 (0.33-1.19)	.156
ACQ-6 score					
Well-controlled (score 0.0-0.75)	122	1		1	
Gray zone (score 0.75-1.5)	145	1.40 (0.86-2.26)	.176	2.02 (1.04-3.94)	**.038**
Poorly controlled (score > 1.5)	1,113	3.16 (2.16-4.62)	**<.001**	4.25 (2.50-7.22)	**<.001**
FEV_1 % predicted (%)					
<50	298	1		1	
50-70	438	1.20 (0.86-1.68)	.292	1.53 (0.97-2.40)	.065
70-90	384	0.80 (0.57-1.12)	.194	0.96 (0.61-1.51)	.848
>90	188	0.71 (0.48-1.05)	.084	0.80 (0.47-1.38)	.421
FeNO (ppb)					
Low (<25)	390	1		1	
Intermediate (25-50)	383	0.99 (0.73-1.33)	.923	1.25 (0.83-1.90)	.290
High (>50)	529	1.24 (0.93-1.65)	.144	1.54 (1.01-2.34)	**.044**
Blood eosinophil count ($\times 10^9$ cells/L)					
≤0.15	366	1		1	
0.15-0.30	221	0.94 (0.66-1.34)	.723	0.85 (0.52-1.38)	.499
0.30-0.45	369	1.24 (0.91-1.71)	.175	1.16 (0.72-1.88)	.542
>0.45	615	1.49 (1.12-1.99)	**.006**	1.09 (0.71-1.69)	.683
Maintenance OCS	833	0.69 (0.55-0.86)	**.001**	0.58 (0.41-0.82)	**.002**

Values highlighted in bold are *P* values <.05.
95% CI, 95% confidence interval.
*Hospital and assessment year also achieved statistical significance in our univariable analysis and were included as independent variables in our multivariable regression model.

not on maintenance OCS, univariate regression analyses showed ACQ-6 score of greater than 1.5 (OR 4.70; $P < .001$), GERD (OR 1.64; $P = .028$), FeNO greater than 50 ppb (OR 1.63; $P = .022$), and blood eosinophil count greater than 0.45×10^9 cells/L (OR 1.66; $P = .035$) correlated with increased exacerbations. Multivariable regression analyses showed ACQ-6 score greater than 0.75 was the only independent factor associated with frequent exacerbations in patients not on maintenance OCS (Table III and Figure 2, *A*). In patients treated with maintenance OCS, ACQ-6 score greater than 1.5 (OR 2.74; $P = .017$), and past smoking history (OR 2.25; $P = .004$) correlated with frequent exacerbations after adjustment for other factors (Table IV and Figure 2, *B*). High FeNO and blood eosinophil count did not correlate with frequent exacerbations in patients on maintenance OCS. An ACQ-6 score greater than 1.5 was independently associated with increased exacerbations

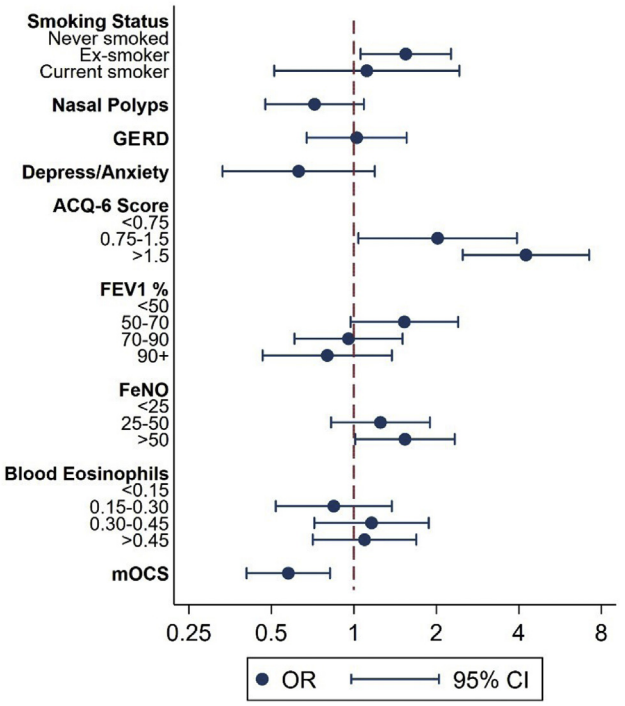

FIGURE 1. Factors associated with frequent exacerbations in severe asthma—multivariable logistic regression. GERD, gastroesophageal disease; mOCS, maintenance oral corticosteroids.

irrespective of maintenance OCS status. However, the odds of having frequent exacerbations were much higher in patients not treated with maintenance OCS versus those who were (OR 4.70 vs OR 2.74).

Asthma Control Questionnaire

The majority of UKSAR patients completed an ACQ-6 at initial assessment (n = 1,381; 87%), 1,341 (97%) of whom performed baseline spirometry on the same day while on usual asthma treatments. The ACQ-7 was calculated using FEV_1 percentage of predicted from baseline spirometry and ACQ-6 score. The majority of FEs (85.6%) and non-FEs (69.2%) had an ACQ-6 score greater than 1.5 (Table E3; available in this article's Online Repository at www.jaci-inpractice.org). Therefore, exploratory analysis was performed using a higher ACQ-6 score cut-off point of 2.5. This showed the odds of having frequent exacerbations are much greater in those with very high ACQ-6 scores (ACQ-6 score > 2.5, OR 5.10; $P < .001$) than in those with scores just above the validated threshold for poorly controlled symptoms (ACQ-6 score 1.51-2.50, OR 3.10; $P < .001$) (Table E4; available in this article's Online Repository at www.jaci-inpractice.org). We also compared the predictive properties of ACQ-6 and ACQ-7 for frequent exacerbations using AUC ROC analysis. The ACQ-6 was as good a predictor for frequent exacerbation as ACQ-7 (AUC 0.710 vs 0.715) (Figures E1 and E2; available in this article's Online Repository at www.jaci-inpractice.org).

Sensitivity analysis and specialist centers

The internally cross-validated AUC was 0.70 suggesting little test error. Our conclusions were broadly unchanged when using multiple imputation to account for missing, or when using a threshold of greater than 2 or greater than 4 exacerbations as the threshold to define an FE (Table E5; available in this article's Online Repository at www.jaci-inpractice.org). The distribution of FEs and non-FEs across all specialist centers is shown in Table E6 (available in this article's Online Repository at www.jaci-inpractice.org).

Treatment adherence

Ten percent of the UKSAR population was deemed to have severe asthma with suboptimal treatment adherence. To confirm the correlation between frequent exacerbations and high ACQ-6 score for patients with severe asthma, we repeated our analyses in a more selective cohort within the UKSAR who had severe asthma and no adherence issues or missing data on treatment adherence. Of 1,592 patients included in our total study population, 1,202 patients (75.5%) fulfilled the European Respiratory Society/American Thoracic Society criteria for severe asthma. Results from univariable and multivariable regression analyses are shown in Tables E7 to E10 (available in this article's Online Repository at www.jaci-inpractice.org). Compared with the whole study population, the relationship between past smoking history and FEs was weaker (OR 1.52; $P = .058$) in patients with European Respiratory Society/American Thoracic Society defined severe asthma. However, the correlation between ACQ-6 score greater than 1.5 and frequent exacerbations remained significant (ACQ-6 score 1.5-2.5, OR 2.88; $P = .002$; ACQ-6 score >2.5, OR 5.54; $P < .001$).

DISCUSSION

We showed, in a large well-characterized severe asthma population, poor symptom control correlated significantly with frequent exacerbations. The odds of having three or more exacerbations over a 12-month period increased by fourfold in patients with an ACQ-6 score greater than 1.5 compared with those who had a score less than 0.75. The association between high ACQ-6 score and frequent exacerbations remained significant after adjustment for other factors. In particular, high ACQ-6 score correlated with frequent exacerbations regardless of maintenance OCS status. Our findings support the predictive value of symptom control for frequent exacerbations previously demonstrated in clinical trial patients.[13,19,20] Type 2 inflammatory markers such as FeNO and blood eosinophil count were associated with frequent exacerbations, but this association was most prominent in severe asthma patients not taking maintenance OCS and in isolation prior to adjustment for other factors. Past smoking history correlated with frequent exacerbations, particularly in patients receiving maintenance OCS. The presence of GERD is an important comorbidity that contributes to frequent exacerbations but was not independent of other variables. To our knowledge, this is the largest study of factors associated with frequent exacerbations in a well-characterized severe adult asthma population not recruited into clinical trials.

Previous literature reported risk factors in populations that included patients with severe asthma.[4-10] Severe asthma is often included within a wider group known as difficult-to-control asthma. Distinguishing severe asthma from difficult-to-control or mild/moderate asthma is important because management options differ between these groups. In a difficult-to-control asthma population, ten Brinke and colleagues[9] reported psychological dysfunction and nasal sinus disease as independent risk factors for frequent exacerbations. This is unsurprising given

TABLE III. Factors associated with frequent exacerbations in patients not on maintenance OCS—univariable and multivariable logistic regression

	Univariable model (n = 740)			Multivariable model* (n = 465)	
	n	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male	255	0.99 (0.70-1.41)	.961	0.97 (0.57-1.64)	.910
Age at first assessment, y					
18-34	156	1		1	
35-54	327	1.05 (0.67-1.63)	.841	0.62 (0.32- 1.20)	.154
55-79	265	1.01 (0.64-1.59)	.983	0.59 (0.29-1.18)	.135
Ethnicity					
Caucasian	532	1		1	
Southeast Asian	60	0.97 (0.52-1.80)	.923	0.24 (0.10-0.61)	**.003**
Northeast Asian	37	1.01 (0.46-2.19)	.988	1.06 (0.33-3.39)	.925
African	51	1.05 (0.53-2.07)	.885	0.78 (0.31-1.97)	.605
Mixed	6	1.62 (0.19-13.97)	.662	0.57 (0.03-10.55)	.705
Other	54	0.77 (0.41-1.42)	.402	0.86 (0.35-2.09)	.733
BMI, kg/m^2					
<24.9	163	1		1	
25-29.9	227	1.12 (0.71-1.76)	.624	1.64 (0.84-3.21)	.147
≥30	339	1.41 (0.92-2.16)	.117	1.41 (0.75-2.68)	.289
Smoking status					
Never smoked	501	1		1	
Ex-smoker	208	1.33 (0.90-1.97)	.152	1.12 (0.63-1.98)	.710
Current smoker	31	0.63 (0.29-1.35)	.236	0.55 (0.18-1.67)	.293
Nasal polyps	121	0.86 (0.55-1.33)	.496	0.53 (0.27-1.04)	.065
GERD	161	1.64 (1.06-2.56)	**.028**	1.01 (0.54-1.88)	.980
Depression or anxiety	67	1.05 (0.58-0.89)	.871	0.62 (0.22-1.74)	.366
ACQ-6 score					
Well-controlled (score 0.0-0.75)	59	1		1	
Gray zone (score 0.75-1.5)	61	1.71 (0.83-3.52)	.146	2.97 (1.08-8.12)	**.034**
Poorly controlled (score > 1.5)	522	4.70 (2.70-8.19)	**<.001**	6.42 (2.99-13.80)	**<.001**
FEV_1 % predicted (%)					
<50	135	1		1	
50-70	188	1.21 (0.70-2.08)	.500	1.43 (0.69-2.93)	.333
70-90	195	0.69 (0.42-1.15)	.156	0.82 (0.41-1.62)	.561
>90	98	0.56 (0.31-1.01)	.053	0.85 (0.38-1.92)	.694
FeNO (ppb)					
Low (<25)	208	1		1	
Intermediate (25-50)	208	1.30 (0.85-2.00)	.231	1.36 (0.74-2.49)	.321
High (>50)	261	1.63 (1.07-2.47)	**.022**	1.41 (0.75-2.64)	.286
Blood eosinophil count ($\times 10^9$ cells/L)					
≤0.15	132	1		1	
0.15-0.30	121	0.76 (0.45-1.30)	.314	0.64 (0.30-1.36)	.250
0.30-0.45	166	1.19 (0.71-1.99)	.516	0.90 (0.43-1.85)	.767
>0.45	321	1.66 (1.04-2.66)	**.035**	1.44 (0.72-2.88)	.307

Values highlighted in bold are P values <.05.
95% CI, 95% confidence interval.
*Hospital and assessment year also achieved statistical significance in our univariable analysis and were included as independent variables in our multivariable regression model.

comorbidities are a significant cause of difficult-to-control asthma. A combined search of the U.K. Optimum Patient Care Research Database and Clinical Practice Research Database registries for patients with mild to severe asthma showed blood eosinophil count was the best predictor of frequent exacerbations. Other risk factors in this primary care population included older age, female gender, obesity, reflux, rhinitis, and anxiety/depression.21 Results were similar in the SARP-3 cohort, which included children and adults on various levels of asthma treatment.7 These risk factors were identified in populations that included those with mild asthma and were not specific to severe asthma. A smaller prospective study of mild/moderate and severe asthma patients showed ACQ score greater than 1.36, FeNO greater than 45 ppb, and a history of smoking were significantly associated with increased risk of two or more exacerbations during the follow-up year.[10] Only those who had at least one

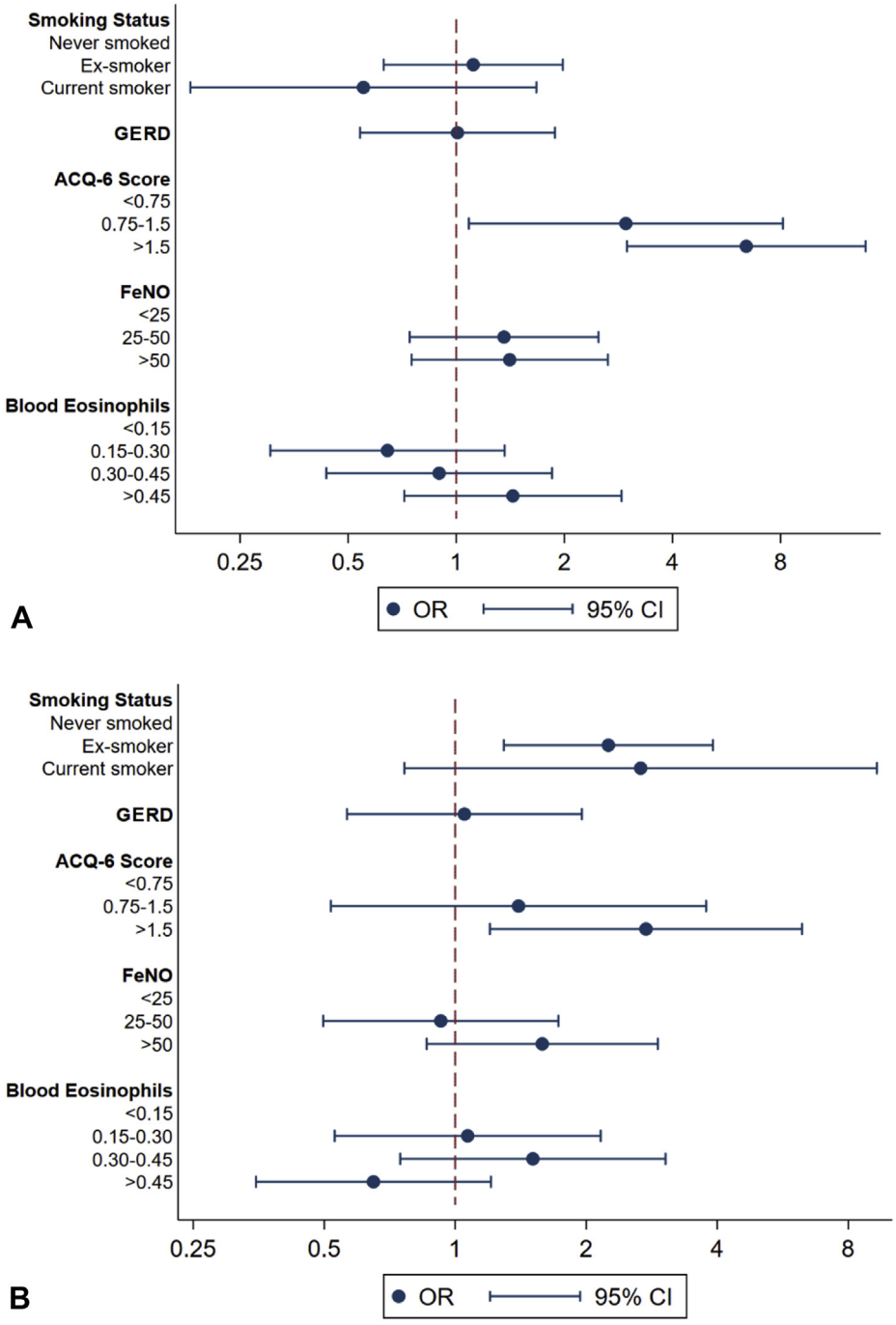

FIGURE 2. (**A**) Factors associated with frequent exacerbations in patients not on maintenance oral corticosteroids—multivariable logistic regression. (**B**) Factors associated with frequent exacerbations in patients on maintenance oral corticosteroids—multivariable logistic regression. GERD, gastroesophageal disease.

exacerbation in the preceding year were included and the majority of patients had severe asthma. These findings were confirmed in the present study, which further elucidated the relationship between FeNO and frequent exacerbations. The difference between our findings and those from previous studies is likely due to disparity in asthma cohorts. Our study suggests in an asthma population with severe disease, good adherence to high-dose inhaled corticosteroids, and adequately managed comorbidities, symptom control then becomes the main indicator for frequent exacerbations.

Type 2 inflammatory biomarkers were associated with frequent exacerbations in the present study, but the strength of this association was subject to influence by other factors such as asthma treatments. Previous studies identified elevated FeNO and blood eosinophilia as independent risk factors for frequent exacerbations; however, results were inconsistent.[7,10,21]

TABLE IV. Factors associated with frequent exacerbations in patients on maintenance OCS—univariable and multivariable logistic regression

	Univariable model (n = 828)			Multivariable model* (n = 412)	
	n	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male	326	0.86 (0.64-1.16)	.322	1.22 (0.73-2.05)	.446
Age at first assessment, y					
18-34	119	1		1	
35-54	352	0.65 (0.40-1.05)	.077	0.52 (0.22-1.24)	.141
55-79	362	0.52 (0.32-0.85)	.008	0.37 (0.16, 0.88)	.024
Ethnicity					
Caucasian	672	1		1	
Southeast Asian	31	1.31 (0.58-2.97)	.523	1.43 (0.33-6.13)	.633
Northeast Asian	24	0.76 (0.33-1.76)	.518	0.63 (0.16-2.51)	.510
African	28	0.82 (0.37-1.80)	.619	0.91 (0.30-2.71)	.860
Mixed	8	0.15 (0.03-0.76)	**.021**	0.17 (0.01-2.11)	.170
Other	65	0.95 (0.55-1.64)	.861	1.57 (0.69-3.56)	.280
BMI, kg/m^2					
<24.9	162	1		1	
25-29.9	242	0.82 (0.54-1.25)	.354	0.64 (0.32-1.28)	.206
≥30	418	1.08 (0.73-1.59)	.711	0.86 (0.45-1.63)	.643
Smoking status					
Never smoked	578	1		1	
Ex-smoker	211	1.54 (1.08-2.19)	**.017**	2.25 (1.29-3.91)	**.004**
Current smoker	24	1.59 (0.62-4.06)	.335	2.67 (0.76-9.31)	.124
Nasal polyps	169	0.81 (0.57-1.16)	.245	0.76 (0.42-1.36)	.350
GERD	140	1.49 (0.98-2.25)	.061	1.05 (0.56-1.95)	.878
Depression or anxiety	58	1.13 (0.63-2.03)	.679	0.57 (0.23-1.41)	.222
ACQ-6 score					
Well-controlled (score 0.0-0.75)	62	1		1	
Gray zone (score 0.75-1.5)	83	1.11 (0.57-2.15)	.756	1.40 (0.52-3.77)	.508
Poorly controlled (score > 1.5)	586	2.20 (1.30-3.74)	**.003**	2.74 (1.20-6.26)	**.017**
FEV_1 % predicted (%)					
<50	163	1		1	
50-70	246	1.24 (0.80-1.92)	.329	1.80 (0.96-3.40)	.068
70-90	185	0.88 (0.56-1.38)	.583	1.49 (0.76-2.93)	.244
>90	88	0.80 (0.46-1.38)	.415	1.11 (0.48-2.54)	.809
FeNO (ppb)					
Low (<25)	180	1		1	
Intermediate (25-50)	171	0.69 (0.44,-1.06)	.091	0.93 (0.50-1.73)	.810
High (>50)	265	0.96 (0.64-1.44)	.859	1.58 (0.86-2.92)	.140
Blood eosinophil count ($\times 10^9$ cells/L)					
≤0.15	231	1		1	
0.15-0.30	100	1.03 (0.63-1.69)	.912	1.07 (0.53-2.16)	.855
0.30-0.45	200	1.18 (0.79-1.77)	.424	1.51 (0.75-3.04)	.251
>0.45	289	1.23 (0.85-1.78)	.272	0.65 (0.35-1.21)	.173

Values highlighted in bold are *P* values <.05.
95% CI, 95% confidence interval.
*Hospital and assessment year also achieved statistical significance in our univariable analysis and were included as independent variables in our multivariable regression model.

Similarly, we showed, in a large severe asthma registry cohort, blood eosinophilia correlated with frequent exacerbations prior to adjustment for other variables, but the association between high FeNO and frequent exacerbations only became significant when other variables were taken into account. The relationship between type 2 biomarkers and exacerbation risk became clearer when we performed subgroup analyses based on maintenance OCS use. Individually, FeNO and blood eosinophils were associated with increased exacerbations in those not on maintenance OCS. In patients on maintenance OCS, type 2 biomarkers added little value for exacerbation prediction. Even in those not exposed to maintenance OCS, type 2 biomarkers were not superior to symptoms control when adjusted for confounding factors. The dissociation between exacerbation rates and T2

biomarkers, particularly in patients on maintenance OCS, may reflect the prevalence of infective non-T2 events that are known to occur in severe asthma.[22-24]

Interpretation of the present study findings need to take several factors into account. This is a registry study that collected spirometry results obtained in a clinical setting. Lung function was generally measured while on treatment because patients were not routinely asked to withhold asthma treatments prior to testing. Interpretation of the relationship between lung function and frequent exacerbations should take this into consideration. Second, the UKSAR population is enriched with patients who later received biological therapy. Patients not on maintenance OCS need four or more exacerbations over the past year to qualify for biological treatment in the United Kingdom. The present study cohort will, as a result, represent the most severe cohort of asthma patients, of whom many will have an eosinophilic and/or atopic phenotype. Third, the number of current smokers recruited into the UKSAR was very small; therefore, this should have limited effect on suppressing FeNO levels. The majority of patients went on to receive biological therapy after specialist assessment. However, 7.3% of patients were on omalizumab at baseline, and biological treatment was not included in our multivariable model. Finally, and perhaps most important, this is a retrospective analysis that used historical exacerbations for stratification of the FE and non-FE groups. The correlations identified between frequent exacerbations and other factors in our study do not, therefore, directly translate to causation. There may also be a dissociation between baseline type-2 biomarkers and exacerbation frequency, given treatment changes made during the exacerbation year can affect type-2 inflammatory marker measurements.[25] Nevertheless, we identified a clear association between uncontrolled asthma symptoms and frequent exacerbations. A real-world prospective study is required to confirm the causative effect of uncontrolled asthma symptoms on future exacerbation risk.

A major strength of this study is our findings are applicable to patients with severe asthma in clinical practice, given the lack of entry criteria. The ACQ-6 is an accessible questionnaire that has been so far limited to use in specialist clinics and research for evaluation of current asthma control and benefits of therapeutic interventions. In contrast to other biomarkers, ACQ-6 can also be measured remotely.[26] The ACQ-6 can be utilized in clinical practice to help identify patients most at risk of frequent exacerbations alongside other clinical assessments. Focus had previously been given to the comorbidities as the key risk factors for frequent exacerbations. However, we have demonstrated in patients with severe asthma, on or off maintenance OCS, poor control of asthma had the strongest correlation with frequent exacerbations. Successful management of poorly controlled symptoms with biological therapy, macrolides or other novel treatments can prevent future exacerbations, thus reducing morbidity and mortality.

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REFERENCES

1. Mukherjee M, Stoddart A, Gupta RP, Nwaru BI, Farr A, Heaven M, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. BMC Med 2016;14:113.
2. Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM, British Thoracic Society Difficult Asthma Network. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. Thorax 2010;65:787-94.
3. O'Neill S, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, et al. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. Thorax 2015;70:376-8.
4. de Groot JC, Amelink M, de Nijs SB, Plaat R, Reitsma BH, Storm H, et al. Risk factors for frequent severe exacerbations in late-onset eosinophilic asthma. Am J Respir Crit Care Med 2015;192:899-902.
5. Walsh CJ, Zaihra T, Benedetti A, Fugere C, Olivenstein R, Lemiere C, et al. Exacerbation risk in severe asthma is stratified by inflammatory phenotype using longitudinal measures of sputum eosinophils. Clin Exp Allergy 2016;46:1291-302.
6. Westerhof GA, de Groot JC, Amelink M, de Nijs SB, Ten Brinke A, Weersink EJ, et al. Predictors of frequent exacerbations in (ex)smoking and never smoking adults with severe asthma. Respir Med 2016;118:122-7.
7. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. Am J Respir Crit Care Med 2017;195:302-13.
8. Calhoun WJ, Haselkorn T, Mink DR, Miller DP, Dorenbaum A, Zeiger RS. Clinical burden and predictors of asthma exacerbations in patients on guideline-based steps 4-6 asthma therapy in the TENOR cohort. J Allergy Clin Immunol Pract 2014;2:193-200.
9. ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J 2005;26:812-8.
10. Kupczyk M, ten Brinke A, Sterk PJ, Bel EH, Papi A, Chanez P, et al. Frequent exacerbators—a distinct phenotype of severe asthma. Clin Exp Allergy 2014;44:212-21.
11. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.
12. Bateman ED, Reddel HK, Eriksson G, Peterson S, Ostlund O, Sears MR, et al. Overall asthma control: the relationship between current control and future risk. J Allergy Clin Immunol 2010;125:600-8. 608.e1-8.e6.
13. Meltzer EO, Busse WW, Wenzel SE, Belozeroff V, Weng HH, Feng J, et al. Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. J Allergy Clin Immunol 2011;127:167-72.
14. Jackson DJ, Busby J, Pfeffer PE, Menzies-Gow A, Brown T, Gore R, et al. Characterisation of patients with severe asthma in the UK Severe Asthma Registry in the biologic era [published online ahead of print December 9, 2020]. Thorax, https://doi.org/10.1136/thoraxjnl-2020-215168.
15. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
16. Heaney LG, Busby J, Bradding P, Chaudhuri R, Mansur AH, Niven R, et al. Remotely monitored therapy and nitric oxide suppression identifies nonadherence in severe asthma. Am J Respir Crit Care Med 2019;199:454-64.
17. LeDell E, Petersen M, van der Laan M. Computationally efficient confidence intervals for cross-validated area under the ROC curve estimates. Electron J Stat 2015;9:1583-607.
18. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393.
19. Jackson DJ, Trujillo-Torralbo MB, del-Rosario J, Bartlett NW, Edwards MR, Mallia P, et al. The influence of asthma control on the severity of virus-induced asthma exacerbations. J Allergy Clin Immunol 2015;136:497-500.e3.
20. Bateman ED, Buhl R, O'Byrne PM, Humbert M, Reddel HK, Sears MR, et al. Development and validation of a novel risk score for asthma exacerbations: the risk score for exacerbations. J Aallergy Clin Immunol 2015;135:1457-1464.e4.
21. Price D, Wilson AM, Chisholm A, Rigazio A, Burden A, Thomas M, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. J Asthma Allergy 2016;9:1-12.
22. Ghebre M, Pang PH, Diver S, Desai D, Bafadhel M, Haldar K, et al. Overlapping biologic exacerbation clusters in asthma and chronic obstructive

pulmonary disease have distinct sputum mediator and microbiome profiles. Eur Respir J 2018;52:PA5468.

23. Ghebre MA, Pang PH, Desai D, Hargadon B, Newby C, Woods J, et al. Severe exacerbations in moderate-to-severe asthmatics are associated with increased pro-inflammatory and type 1 mediators in sputum and serum. BMC Pulm Med 2019;19:144.
24. McDowell PJ, Diver S, Yang F, Borg C, Busby J, Brown V, et al. A prospective observational study of the inflammatory profile of Mepolizumab EXacerbations in participants with severe refractory eosinophilic asthma (the MEX study). Lancet Respir Med 2021.
25. Busby J, Holweg CTJ, Chai A, Bradding P, Cai F, Chaudhuri R, et al. Change in type-2 biomarkers and related cytokines with prednisolone in uncontrolled severe oral corticosteroid dependent asthmatics: an interventional open-label study. Thorax 2019;74:806-9.
26. Gruffydd-Jones K, Hollinghurst S, Ward S, Taylor G. Targeted routine asthma care in general practice using telephone triage. Br J Gen Pract 2005;55:918-23.

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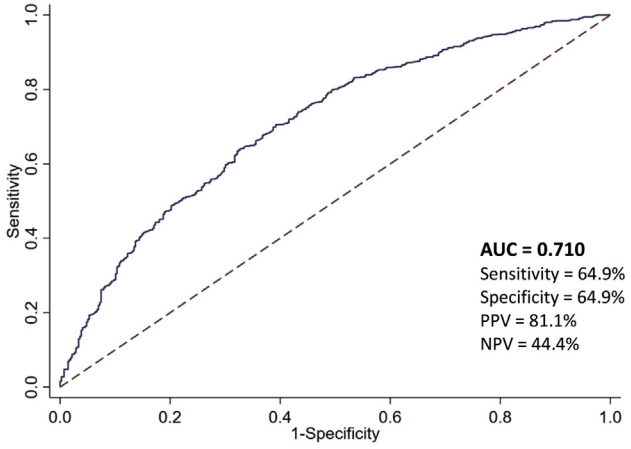

FIGURE E1. ROC curve for ACQ-6. NPV, negative predictive value; PPV, positive predictive value.

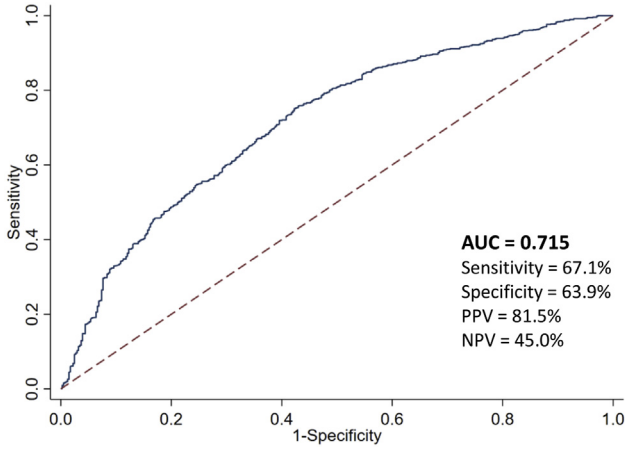

FIGURE E2. ROC curve for ACQ-7. NPV, negative predictive value; PP, positive predictive value.