

# Impact of Baseline Lung Function on Future Exacerbations in Patients with Moderate-to-Severe Asthma

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## Introduction

Asthma is a chronic inflammatory disease characterized by reversible and variable expiratory airflow obstruction.<sup>1</sup> It is well known that abnormalities of airway structure and hyperresponsiveness contribute to impaired lung function.<sup>2</sup> Airway remodeling and hyperinflation are also associated with accelerated decline in lung function.<sup>3</sup> In addition, severe asthma exacerbations are correlated with a rapid decline in lung function and reduction in airway reversibility, leading to the progression of irreversible airflow limitation over time.<sup>4</sup> Although reduced lung function is associated with worsened outcomes and increased mortality risk,<sup>5,6</sup> limited real-world evidence exists on the effect of forced expiratory volume in 1 second percent predicted (FEV<sub>1pp</sub>) on exacerbations in patients with moderate-to-severe asthma.<sup>7,8</sup> In this retrospective database study, we aimed to determine the baseline distribution of FEV<sub>1pp</sub> in patients with moderate-to-severe asthma and the association between baseline FEV<sub>1pp</sub> and risk of severe asthma exacerbations in a large UK dataset.

## Methods

### Study Design

This retrospective cohort study was performed using the Clinical Practice Research Datalink (CPRD) database linked to Hospital Episode Statistics inpatient, outpatient and accident and emergency data. The CPRD is an anonymized, longitudinal research database that derived data from nearly 700 primary-care practices in the UK when this study was conducted and provided healthcare data of 60 million patients.<sup>9</sup> Patients were identified from 1st January 2010 to 31st December 2012 and followed up for 36 months from the index date. The index date was defined as the date of the first asthma medication prescription during the study period. A variable-length period from the registration date of patients (from up-to-standard CPRD practices) in the database to the index date was identified as a pre-index baseline period and was used to capture comorbidities.

### Patients

Patients aged  $\geq 18$  years at the index date, with ICD-10<sup>10</sup> clinical diagnosis and Read codes for asthma were identified. Patients with a diagnosis of COPD were excluded. Asthma severity (moderate-to-severe) was determined using the prescription criteria consistent with the British Thoracic Society (BTS) 2011 guideline Steps 3–5 (medium-high dose inhaled corticosteroid [ICS] and long-acting  $\beta$ -agonist plus additional controller medications or oral corticosteroids [OCS], as needed for asthma control).<sup>11</sup>

## Outcomes

Baseline FEV<sub>1</sub> values were taken as the observation nearest to the index date within  $\pm 180$  days. Observed FEV<sub>1</sub> values were compared with the normal range accounting for age, gender and height and were categorized as Group 1: FEV<sub>1pp</sub>  $\geq 80\%$ ; Group 2: FEV<sub>1pp</sub> 50–79%; Group 3: FEV<sub>1pp</sub>  $< 50\%$ . The FEV<sub>1pp</sub> values could be either pre- or post-bronchodilator FEV<sub>1</sub>. Exacerbations in the year prior to the index date were considered as baseline. Severe asthma exacerbations during the follow-up period were identified by an acute course of OCS for  $< 7$  days or an asthma-related emergency hospital contact (A&E diagnosis code 251) or inpatient admission with a primary diagnosis (ICD10 J45, J45.0, J45.1, J45.8, and J45.9) in non-OCS-dependent patients. For OCS-dependent patients (BTS step 5), a severe exacerbation was defined as above but without the criteria for an acute course of OCS use.

## Statistical Analysis

Descriptive statistics were used to analyze baseline demographics and clinical characteristics. Univariate analyses were compared using *t*-test and chi-squared tests for continuous data and categorical variables, respectively. Multivariable regression models were used to estimate the risk of severe asthma exacerbations after adjusting for covariates, including age at the index date, smoking, body mass index, gender, rhinitis, presence of chronic sinusitis, nasal polyps, atopic dermatitis, diabetes, anaphylaxis, ischemic heart disease, heart failure, food allergy, anxiety, depression, and psoriasis. The incident rate ratio (IRR) for severe asthma exacerbation was calculated over the 12 months using the Poisson regression. The Cox proportional hazard model was used to determine hazard ratios (HR) for the risk of severe exacerbation (time-to-first exacerbation) over the 3-year follow-up. Additional sensitivity analyses were performed by adjusting for severe baseline exacerbations as a covariate in addition to the covariates listed above.

## Results

### Baseline Demographics and Patient Characteristics

Of 36,164 patients identified, 1865 had baseline FEV<sub>1pp</sub> values reported and were included in this analysis. Mean (SD) age was 47.5 (16.5) years in the overall population and 1130 (60.6%) were women. Based on the FEV<sub>1pp</sub> values, 1106 (59.3%) patients were categorized in Group 1 (FEV<sub>1pp</sub>  $\geq 80\%$ ), 644 (34.5%) in Group 2 (FEV<sub>1pp</sub> 50–79%) and 115 (6.2%) in Group 3 (FEV<sub>1pp</sub>  $< 50\%$ ). Baseline FEV<sub>1pp</sub> measurements occurred within approximately 50 days of the index date. The average pre-index date baseline period, when comorbidities were captured, was 8 years. The number of patients on BTS Step 5 were 83 (7.5%) in Group 1, 58 (9.0%) in Group 2, and 22 (19.1%) in Group 3. Baseline demographics and patient characteristics are described in [Table 1](#).

### Exacerbations

Rates of severe asthma exacerbations over 12 months in patients in Groups 1–3, and in patients with  $\geq 1$  severe asthma exacerbation at baseline in these groups are presented in [Figure 1](#).

The annual IRR of severe exacerbations was significantly higher for Group 2 (1.46 [1.27 to 1.68];  $P < 0.0001$ ) and 3 (2.03 [1.59 to 2.54];  $P < 0.0001$ ) versus Group 1 ([Figure 2](#)) over 12 months following index date. The risk of severe asthma exacerbation was significantly greater in patients in Group 2 ( $P = 0.0018$ ) and 3 ( $P < 0.0001$ ), compared with those in Group 1 during the 36-month follow-up period ([Figure 2](#)). In sensitivity analysis, similar results were observed after adjusting for baseline severe exacerbations. The annual IRR of severe exacerbation was significantly higher for Group 2 (1.61 [1.27 to 2.05];  $P < 0.0001$ ) and 3 (1.78 [1.22 to 2.54];  $P = 0.0029$ ) versus Group 1; however the risk of severe exacerbation was significantly greater for Group 3 versus Group 1 (1.45 [1.04 to 2.03];  $P = 0.0308$ ) but not for Group 2 (1.11 [0.91 to 1.34];  $P = 0.3011$ ).

## Discussion

In asthma, permanent structural changes in the airway can lead to a progressive loss of lung function, increasing airflow obstruction.<sup>12</sup> These structural changes can include subepithelial fibrosis (thickening of the membrane), airway smooth muscle hypertrophy and hyperplasia. Clinically, decreased lung function can result in reduced treatment efficacy, is

**Table 1** Baseline Demographics and Patient Characteristics

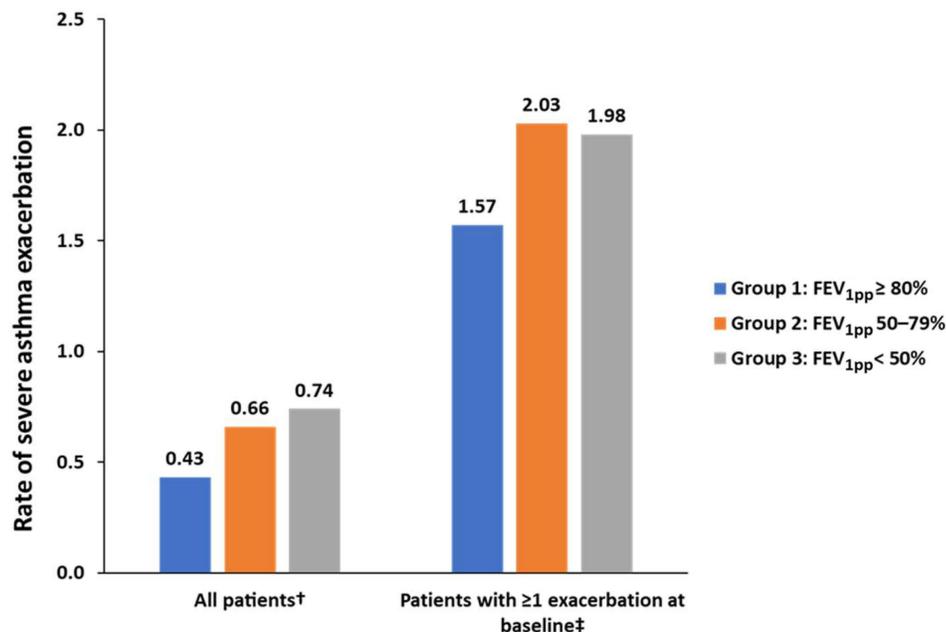
Characteristic	Group 1 (FEV <sub>1pp</sub> ≥ 80%) (N = 1106)	Group 2 (FEV <sub>1pp</sub> 50–79%) (N = 644)	Group 3 (FEV <sub>1pp</sub> < 50%) (N = 115)	Overall Population (N = 1865)
Age (years), mean ± SD	48.5 ± 15.7	46.2 ± 17.5	45.0 ± 17.7	47.5 ± 16.5
Women	736 (66.5%)	341 (53.0%)	53 (46.1%)	1130 (60.6%)
BMI (kg/m <sup>2</sup> ), mean ± SD	29.5 ± 6.7	29.7 ± 7.0	29.4 ± 7.0	29.6 ± 6.8
Prior smoking	401 (36.3%)	203 (31.5%)	36 (31.3%)	640 (30.3%)
FEV <sub>1pp</sub> , mean ± SD	95.6 ± 10.9	68.2 ± 8.2	40.8 ± 7.3	82.7 ± 19.3
Average number of severe exacerbations in the year before index date	0.36	0.47	0.50	0.41
<b>Comorbidities</b>				
Eczema	337 (30.5%)	203 (31.5%)	31 (27.0%)	571 (30.6%)
Nasal polyps	29 (2.6%)	30 (4.7%)	4 (3.5%)	63 (3.4%)
Rhinitis	229 (20.7%)	120 (18.6%)	21 (18.3%)	370 (19.8%)

**Note:** Data presented as n (%), unless otherwise specified.

**Abbreviations:** BMI, body mass index; FEV<sub>1pp</sub>, forced expiratory volume in 1 second % predicted; SD, standard deviation.

associated with poor asthma control, and lower health-related quality of life, and is a more reliable indicator of exacerbation severity<sup>13–15</sup> than symptoms.<sup>1</sup>

We report the prevalence of impaired lung function in a population cohort representative of patients with moderate-to-severe asthma treated in the UK. Although lung function assessment is recommended for diagnosis<sup>1</sup> and periodically after that in asthma, we found that only about 5% of the patients in this cohort had FEV<sub>1</sub> recorded, showing low



**Figure 1** Rates of severe asthma exacerbations over 12 months in patients with moderate-to-severe asthma, categorized by baseline FEV<sub>1pp</sub> values. <sup>†</sup>Group 1, N = 1106; Group 2, N = 644; Group 3, N = 115. <sup>‡</sup>Group 1, N = 302; Group 2, N = 209; Group 3, N = 43.

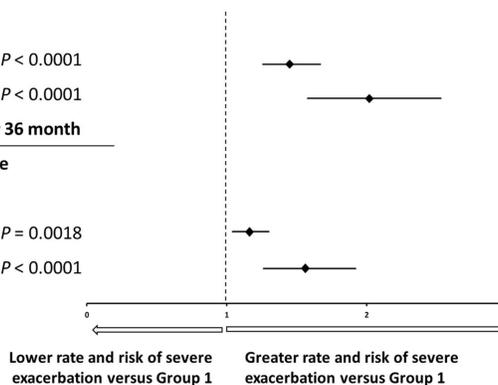
**Abbreviation:** FEV<sub>1pp</sub>, forced expiratory volume in 1 second % predicted.

**A** IRR for severe exacerbations over 12 months

	N	IRR (95% CI); P-value
Group 1 (FEV <sub>1pp</sub> ≥ 80%)	1106	1.00 [reference]
Group 2 (FEV <sub>1pp</sub> 50–79%)	644	1.46 (1.27 to 1.68); P < 0.0001
Group 3 (FEV <sub>1pp</sub> < 50%)	115	2.03 (1.59 to 2.54); P < 0.0001

**B** HR for risk (time-to-first) of severe exacerbation over 36 month

	N	HR (95% CI); P-value
Group 1 (FEV <sub>1pp</sub> ≥ 80%)	1106	1.00 [reference]
Group 2 (FEV <sub>1pp</sub> 50–79%)	644	1.19 (1.07 to 1.33); P = 0.0018
Group 3 (FEV <sub>1pp</sub> < 50%)	115	1.59 (1.29 to 1.95); P < 0.0001



**Figure 2 (A)** Incident rate ratio over 12 months and **(B)** hazard ratio for risk of severe exacerbation over 36 months in patients with moderate-to-severe asthma, categorized by baseline FEV<sub>1pp</sub> values. P-value for Group 2 and 3 were evaluated versus Group 1. Adjusted for age at the index date, smoking status, BMI, gender, rhinitis, chronic sinusitis, nasal polyps, atopic dermatitis, diabetes, anaphylaxis, ischemic heart disease, heart failure, food allergy, anxiety, depression, and psoriasis. Patients without a baseline % predicted FEV<sub>1</sub> measurement were included in the analysis as a categorical variable.

**Abbreviations:** CI, confidence interval; FEV<sub>1pp</sub>, forced expiratory volume in 1 second % predicted; HR, hazard ratio; IRR, incident rate ratio, N, number of patients.

utilization at the primary health care level. Indeed, in a discussion on the national review of asthma deaths,<sup>16</sup> one of the recommendations to reduce the mortality rate due to asthma was a routine measurement of lung function.<sup>17</sup>

FEV<sub>1pp</sub> allows for the comparison of the functional measure of lung function with a population. In the current analysis, ~40% of patients had impaired lung function with FEV<sub>1pp</sub> <80% (FEV<sub>1pp</sub> 50–79%, 34.5%; FEV<sub>1pp</sub> < 50%, 6.2%), while the remaining patients experienced mild airflow obstruction (FEV<sub>1pp</sub> ≥ 80%). Although asthma severity cannot be described by FEV<sub>1pp</sub> alone, it is a marker of disease severity that can be measured objectively and is reproducible.<sup>1,18</sup> In this analysis, 6.2% of the patients had severely impaired lung function with FEV<sub>1pp</sub> < 50% despite treatment with a standard-of-care therapy. We did not assess specialist referrals for these patients; however, this highlights the unmet needs in some patients with moderate-to-severe asthma.

Further, during the follow-up period, we observed that the patients with low FEV<sub>1pp</sub> had increased exacerbation rates and a higher risk of severe exacerbations over the 36-month follow-up, which were about 20% and 60% greater, respectively, in patients in Group 2 (FEV<sub>1pp</sub> 50–79%) and Group 3 (FEV<sub>1pp</sub> <50%), compared with Group 1 (FEV<sub>1pp</sub> ≥80%), respectively. Data from this analysis were in line with previous findings, wherein lower FEV<sub>1pp</sub> values were associated with an increased risk of severe asthma exacerbations.<sup>5,19–21</sup> Assessment of the risk of future exacerbations is an important aspect in the clinical management of asthma, and FEV<sub>1pp</sub> values at baseline can be a reliable predictor of future risks and guide treatment.

In Groups 1–3, severe exacerbations were even higher in patients with ≥1 severe asthma exacerbation at baseline than in the overall population; a formal statistical analysis was not performed to evaluate these differences. This is consistent with published evidence suggesting prior severe exacerbation as a predictor of future severe exacerbations.<sup>22</sup> Exacerbations represent a change in lung function or asthma symptoms. Severe exacerbations can occur in patients with well-controlled or mild asthma symptoms<sup>23</sup> and can be life-threatening.

There are a few limitations that should be considered. Lung function measurement (FEV<sub>1pp</sub>) could be biased as only patients with moderate-to-severe asthma were assessed. The current analysis compares the rate and risk of exacerbations in patients with impaired lung function versus those with mild airflow limitation to evaluate the impact of FEV<sub>1pp</sub> values on exacerbations. Accordingly, a comparison between Group 2 and 3 was out of the scope of this analysis. Further, severe exacerbations were identified by either an acute course of OCS use or asthma-related emergency room or hospital admission in this analysis. For OCS-dependent patients (BTS step 5), an acute course of OCS was not one of the criteria. However, given the low proportion (8.7%) of patients in BTS step 5, this might not impact the overall findings from this analysis. In addition, an analysis combining spirometry and biomarkers at baseline could provide additional predictive value in identifying patients with a greater exacerbation risk.

## Conclusion

Lung function is an important parameter in asthma control; however, as reported in this analysis, only a few patients have this assessed in clinical practice. The data from this analysis showed that low FEV<sub>1pp</sub> is a significant predictor of increased rate and greater risk of severe asthma exacerbations. Lung function in asthma typically declines over time, contributing to an increased risk of exacerbations and further impairment of asthma control. Therefore, it is important to assess lung function in patients with asthma to optimize treatment options in patients with low lung function to improve patient outcomes, including asthma control.

## Data Sharing Statement

The datasets used and/or analysed during the current analysis are available from the corresponding author on reasonable request.

## Ethics Approval

This study is based in part on data from the Clinical Practice Research Datalink (CPRD) obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The anonymized data are provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. The CPRD has ethics approval from the Health Research Authority to support research using anonymized patient data. This study received protocol approval (ISAC 17\_077) from the CPRD Independent Scientific Advisory Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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## Author Contributions

All authors contributed to data analysis, drafting, or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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## Disclosure

Khan AH, Gray C, Eckert L, Amand C and Rowe PJ are employees of Sanofi, may hold stock and/or stock options in the company. Maroni J and Wang Z are employees of Regeneron Pharmaceuticals Inc, may hold stock and/or stock options in the company. Jones B, Berni T and Morgan CL are employees of Pharmatelligence, which was funded by Sanofi to conduct the study. The authors report no other conflicts of interest.

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