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Obese, non-eosinophilic asthma: frequent exacerbators in a real-world setting

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ABSTRACT

Objective: In the UK, asthma deaths are at their highest level this century. Increased recognition of at-risk patients is needed. This study phenotyped frequent asthma exacerbators and used machine learning to predict frequent exacerbators.

Methods: Patients admitted to a district general hospital with an asthma exacerbation between 1st March 2018 and 1st March 2020 were included. Patients were organized into two groups: “Infrequent Exacerbators” (1 admission in the previous 12 months) and “Frequent Exacerbators” (≥ 2 admissions in the previous 12 months). Patient data were retrospectively collected from hospital and primary care records. Machine learning models were used to predict frequent exacerbators.

Results: 200 patients admitted for asthma exacerbations were randomly selected (73% female; mean age 47.8 years). Peripheral eosinophilia was uncommon in either group (21% vs 19%). More frequent exacerbators were being treated with high-dose ICS than infrequent exacerbators (46.5% vs 23.2%; $P < 0.001$), and frequent exacerbators used more SABA inhalers (10.9 vs 7.40; $P = 0.01$) in the year preceding the current admission. BMI was raised in both groups (34.2 vs 30.9). Logistic regression was the most accurate machine learning model for predicting frequent exacerbators (AUC = 0.80).

Conclusions: Patients admitted for asthma are predominately female, obese and non-eosinophilic. Patients who require multiple admissions per year have poorer asthma control at baseline. Machine learning algorithms can predict frequent exacerbators using clinical data available in primary care. Instead of simply increasing the dose of corticosteroids, multidisciplinary management targeting Th2-low inflammation should be considered for these patients.

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Introduction

Asthma exacerbations cause significant morbidity and mortality. Despite recent advances in asthma management, asthma deaths in the UK are at their highest level this century (1). Furthermore, asthma exacerbations are associated with increased lung function decline and disease progression (2,3). A history of previous exacerbations increases the risk of future exacerbations, even after adjusting for confounding factors (such as asthma control and demographics) (4). In addition, asthma exacerbations impose a considerable economic burden on healthcare systems (5).

Despite the considerable burden of asthma exacerbations on patients and healthcare systems, relatively few studies have phenotyped patients presenting with exacerbations. Phenotypes (sets of observable characteristics in patients) are a recognized feature of asthma

and can be broadly categorized as Th2-high and Th2-low (6). A cohort study of severe asthma patients showed that peripheral eosinophilia, high BMI and gastro-esophageal reflux disease (GERD) were associated with increased exacerbation frequency (7). However, this study focused on patients with a diagnosis of severe asthma, and so it is unclear if these results are generalizable for all exacerbating patients. Likewise, most cluster analysis studies, which form the basis of asthma phenotypes, have analyzed severe asthma cohorts (8). This is pertinent as there is a significant exacerbation burden in patients with “mild” asthma (9).

Of the few studies which have included mild-moderate asthmatics when comparing frequent and infrequent exacerbators, there have been mixed results. Some have shown that frequent exacerbators

have several differences compared to infrequent exacerbators, such as increased use of glucocorticoids, worse asthma control and lung function at baseline, and more severe type 2 airway inflammation (10–12). However, other studies have shown no difference in baseline characteristics between frequent and infrequent exacerbators (when comparing asthmatics with the same baseline asthma severity) (13).

To our knowledge, there are no studies that have used machine learning algorithms to identify frequent exacerbators. Machine learning has predominately been used to diagnose asthma and predict risk of future exacerbation (14). Furthermore, very few studies have taken a holistic approach when comparing frequent and infrequent asthma exacerbators. For example, there is a lack of data regarding medication compliance and follow-up in these two groups. This is important as follow-up by an asthma specialist is associated with fewer future asthma exacerbations and improved baseline asthma control (15–17).

The aim of this study is to phenotype patients presenting with asthma exacerbations to a district general hospital, using a multi-dimensional assessment of each patient, including clinical, inflammatory, radiological and behavioral features. We also aimed to identify differences between frequent and infrequent exacerbators. To our knowledge, this is the first study to use machine learning algorithms to predict frequent exacerbators. This will allow clinicians to identify patients at-risk of exacerbations, and to identify deficiencies in the asthma care of these patients. We hypothesized that frequent exacerbators would have more severe peripheral eosinophilia than infrequent exacerbators.

Methods

Study design and participants

In this retrospective observational study, patients admitted to Watford General Hospital with a physician-confirmed diagnosis of asthma exacerbation between 1st March 2018 and 1st March 2020 were included. Patients were aged ≥ 18 years, and had a physician-confirmed diagnosis of asthma, as per the British Thoracic Society (BTS) guidelines (18). Since all patients were hospitalized, they met the joint American Thoracic Society/European Respiratory Society (ATS/ERS) definition for “severe asthma exacerbation” (19). Including the current admission, infrequent exacerbators were defined as having one admission for asthma in the previous 12 months, and frequent exacerbators were defined

as having two or more admissions in the previous 12 months (20).

Data collection

Data regarding age, gender, ethnicity, body mass index (BMI) and smoking history were collected from electronic health records. Obesity was defined as a BMI ≥ 30 .

Blood results from the admission were not used, as the eosinophil levels may have been suppressed by corticosteroid use, and neutrophil levels may have been confounded by the presence of bacterial infection. Therefore, the most recent blood result during a stable state was used to analyze blood eosinophils and blood neutrophils. A stable state was defined as no use of oral corticosteroids (OCS) within the last 4 weeks (or no increase in OCS dose if the patient was on long-term OCS therapy), and no visits to a physician for their asthma within the last 4 weeks. Peripheral eosinophilia was defined as blood eosinophils $\geq 0.5 \times 10^9/L$, and peripheral neutrophilia was defined as blood neutrophils $\geq 7.2 \times 10^9/L$ (21). As per local guidelines, elevated IgE was defined as defined as serum IgE ≥ 81 kU/L.

Forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were assessed during a stable state, as per the ATS guidelines (VIASYS Healthcare, Hochberg, Germany) (22). Obstructive lung function was defined as FEV1/FVC ratio below the lower limit of normal (18). Fractional exhaled nitric oxide (FeNO) was measured, as per the ATS guidelines (NIOX Vero, Circassia, UK) (23). Elevated FeNO was defined as FeNO >40 ppb (24).

Axial imaging with a CT chest was assessed for radiological signs of severe airways disease by an experienced radiologist and respiratory specialist. These signs included bronchial wall thickening, bronchial lumen narrowing, air trapping and subsegmental bronchiectasis (25).

Primary care records were used to identify co-morbidities, and to quantify the number of documented asthma exacerbations managed in the community. Primary care prescription records provided information about the patients' medication history. The dose of inhaled corticosteroids (ICS) was quantified as “low,” “medium” or “high,” based on National Institute for Health and Care Excellence (NICE) guidelines (26). We quantified the number of short-acting beta-agonist (SABA) inhalers and OCS courses dispensed in the last 12 months prior to the current admission. Due to inconsistencies in the primary care prescription records, for some patients it

was unclear if OCS's was prescribed for asthma or another condition. In these instances, the OCS course was excluded from the analysis. SABA overuse was defined as the use of ≥ 3 SABA inhalers in 12 months (27). The medication possession ratio (MPR) was used to assess adherence to ICS. The MPR was defined as the number of days' worth of ICS prescribed, divided by the number of days between ICS prescriptions (28). Good adherence to ICS was defined as $\text{MPR} \geq 0.8$; poor adherence was defined as $\text{MPR} \leq 0.5$ (29).

Online health records were used to assess if a patient was referred to a respiratory physician or asthma specialist nurse within 4 weeks post-discharge, as stipulated in the BTS guidelines (18).

Machine learning analysis

We applied a multivariate logistic regression on the dataset by developing a model in Python (version 3.6.7), using the pandas, NumPy, scikit-learn and matplotlib libraries in a Google Colaboratory environment. Variables included were divided into categorical (age, sex, smoking status, CT evidence of airway morphology changes, long-term use of OCS, presence of COPD, GERD and depression) and continuous (FEV1/FVC ratio, FeNO, blood eosinophils, neutrophils, total IgE, number of exacerbations, number of OCS courses, number of SABA dispensed in 1 year and BMI). The data was pre-processed by an imputer, in order to identify and replace missing values with the mean for each variable. Subsequently, feature scaling was performed by applying mean normalization. The dataset was divided into four groups: training features, training labels, test features and test labels. 25% of the initial dataset was used for validation of the model, while the remaining 75% was used to train the logistic regression model. The predicted model was tested by k-fold cross-validation ($k=10$) to improve the robustness of the results. Other models tested as classifiers included decision tree analysis and neural network classifiers. Analysis was performed by a clinician-scientist trained in data science.

Statistical analysis

Baseline characteristics were expressed as relative frequencies for categorical variables, and as mean and standard deviation for continuous variables. The D'Agostino-Pearson test was used to assess the distribution of the data. To assess differences between frequent and infrequent exacerbators, the Student's *t*-test

and Mann-Whitney U test were used for normally distributed data and non-normally data respectively. Categorical variables were compared using the chi-squared test. Degrees of statistical significance was defined as $P < 0.05$ (*), $P < 0.01$ (**) and $P < 0.001$ (***). Data analysis was performed using GraphPad Prism software (version 8; GraphPad Software, California, USA) and Python (version 3.9.2, California, USA).

Results

A total of 100 frequent exacerbators and 100 infrequent exacerbators were randomly selected, using a computer-generated randomization list. Their baseline characteristics are shown in Table 1. Of the patients in the study, 73.0% were female, and 63.5% of participants were obese.

Frequent exacerbators had more exacerbations managed in primary care in the year preceding the current admission (1.92 vs 0.79; $P < 0.001$). Frequent exacerbators were prescribed more regular ICS-LABA (88.9% vs 60.6%; $P < 0.001$) and high-dose ICS (46.5% vs 23.2%; $P < 0.001$). Frequent exacerbators required more OCS courses (10.1% vs 3.0%; $P = 0.005$) and SABA inhalers (10.9 vs 7.4; $P = 0.01$) in the 12 months preceding the current admission. More frequent exacerbators met the ATS/ERS definition for "severe asthma" than infrequent exacerbators (23.2% vs 46.5%; $P < 0.001$) (30). 44.0% of patients in the study demonstrated good adherence to ICS (there were no differences in adherence between the two groups).

More frequent exacerbators had symptomatic GERD than infrequent exacerbators (46.5% vs 30.6%; $P = 0.02$). There were no differences in BMI or smoking history between the groups. 39.5% of patients were not followed up by an asthma specialist within 4 weeks of their discharge.

Table 2 shows the investigation results for frequent and infrequent exacerbators. There were no differences in FEV1/FVC or FeNO between the two groups. There were no differences in blood eosinophils or blood neutrophils between the two groups. 20% of patients in the study had peripheral eosinophilia, whereas 47% had peripheral neutrophilia. CT scan changes were prevalent in both groups (78.0% vs 90.2%).

Logistic regression was the most accurate model for predicting frequent exacerbators, with an area-under-the-curve (AUC) of 0.83 for the training set, and an AUC of 0.80 on the validation set (Figure 1). Similarities in the two AUC values excluded the possibility of the model overfitting. K-fold cross-validation ($k=10$) was applied to the logistic regression. The overall accuracy was 74% ($\pm 4\%$),

Table 1. Baseline characteristics of patients admitted with asthma exacerbations.

	Infrequent exacerbators	Frequent exacerbators	P value
N	100	100	
Age, years	46.5 ± 20.9	49.0 ± 17.5	0.25
Female (%)	69	77	0.20
Ethnicity (%)	Caucasian 82	Caucasian 83	0.85
	Asian 15	Asian 13/	0.68
	Afro-Caribbean 1	Afro-Caribbean 1	1.00
Exacerbations managed in primary care in the last 12 months	0.79 ± 1.15	1.92 ± 1.83	<0.001***
ICS-LABA (%)	60.6	88.9	<0.001***
High-dose ICS (%)	23.2	46.5	<0.001***
Long-term OCS (%)	3.03	10.1	0.04*
OCS courses in past year	0.99 ± 1.21	2.06 ± 2.34	0.005**
SABA dispensed in past year	7.40 ± 7.89	10.94 ± 9.39	0.01*
SABA overuse (%)	64.8	78.6	0.58
ICS MPR	0.72 ± 0.44	0.72 ± 0.40	0.66
Good ICS adherence (%)	48.3	40.0	0.35
Poor ICS adherence (%)	36.7	30.8	0.49
Past Medical History			
COPD (%)	5.10	3.03	0.46
GERD (%)	30.6	46.5	0.02*
Depression (%)	29.6	32.3	0.68
Ex or current smoker (%)	64.5	69.9	0.51
BMI	30.9 ± 6.06	34.2 ± 9.48	0.14
Obese (%)	63.4	63.6	0.98
Follow-up within 4 weeks (%)	54.0	67.0	0.06

Note. Data presented as mean ± standard deviation, unless stated differently.

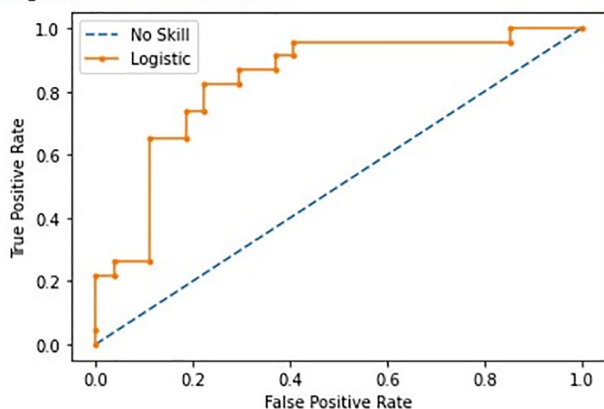
Table 2. Biochemical, radiological and lung function results of patients admitted with asthma exacerbations.

	Infrequent exacerbators	Frequent exacerbators	P value
N	100	100	
FEV1/FVC, %	71.0 ± 13.4	70.9 ± 16.8	0.96
Obstructive lung function (%)	34.5	39.1	0.60
FeNO, ppb	42.3 ± 57.1	24.8 ± 13.6	0.97
High FeNO (%)	27.3	12.5	0.44
Blood eosinophils, x10 ⁹ /L	0.27 ± 0.39	0.32 ± 0.41	0.45
Eosinophilia (%)	19.0	21.0	0.72
Blood neutrophils, x10 ⁹ /L	7.91 ± 3.87	7.70 ± 3.11	0.87
Neutrophilia (%)	45.0	49.0	0.57
Total IgE, kU/L	470.3 ± 870.3	378.9 ± 755.1	0.18
High IgE (%)	68.2	52.9	0.11
Patients with CT scan changes (%)	78.0	90.2	0.09

Note. Data presented as mean ± standard deviation, unless stated differently.

No Skill: ROC AUC=0.500

Logistic: ROC AUC=0.802

**Figure 1.** Receiver-operating characteristics (ROC) curve for the logistic regression model used to predict frequent exacerbators.

with an accuracy range of 70%–80% within the individual subsets. Decision tree regression had an AUC of 0.96 for the training set, which decreased to 0.74 for the validation set. Neural network classifier had an accuracy of 99% for the training set, which decreased to 80% for the validation set, and this model demonstrated significant overfitting.

Discussion

This study comprehensively assessed the clinical, inflammatory, radiological and behavioral characteristics of patients presenting with asthma exacerbations to a district general hospital. Furthermore, this is the first study to identify a machine learning algorithm which predicts frequent exacerbators. Asthma exacerbators are predominately female, obese and

non-eosinophilic. The management of the obese, non-eosinophilic asthma phenotype remains sub-optimal, despite being identified over a decade ago (31).

The lack of peripheral eosinophilia contradicts our hypothesis, but is replicated in other studies. A recent cluster analysis of asthma exacerbators showed that two clusters (comprising 61.2% of the study's population) were characterized by female, neutrophilic patients (similar to our study) (32). A recent prospective study of severe asthmatics showed that blood eosinophils did not differ between frequent and infrequent exacerbators, and 60% of frequent exacerbators did not have eosinophilia (33). However, other studies have shown that frequent exacerbators do have increased blood eosinophils (12). This discrepancy could be due to differences in the populations studied. The studies which did not identify differences in blood eosinophils often featured patients with average BMIs greater than 30 (similar to the patients in our study), whereas the studies which identified differences in blood eosinophils often featured patients with average BMIs less than 30 (12,33). Therefore, the inflammatory characteristics of the exacerbation-prone asthma phenotype may differ between populations, depending on the degree of metabolic dysfunction in these populations. International, multi-centre trials of frequent exacerbators are needed to further investigate this.

Our finding that asthma exacerbators are mostly obese is pertinent as obesity is a known risk factor for asthma exacerbations (7,33). Obese asthmatics have more exacerbations than non-obese asthmatics, even after adjusting for confounding factors (such as smoking history, demographics and presence of GERD) (34). Obesity's effect on asthma exacerbations can be explained by several mechanisms, including increased airway hyper-responsiveness (35), reduced FRV and ERV (36), and up-regulated Th17 inflammation (37). These mechanisms may explain why peripheral eosinophilia was largely absent in our study's patients.

Frequent exacerbators required more OCS and high-dose ICS than infrequent exacerbators, indicating poorer baseline asthma control. However, our results indicate that non-Th2 inflammation may be prevalent in these patients, which does not typically respond to glucocorticoids (38). Likewise, obese asthmatics tend to be glucocorticoid-resistant (39). Mechanisms for this include a predominance toward Th2-low inflammation in obese asthmatics, or because obesity reduces the ability of glucocorticoids to suppress pro-inflammatory gene expression (40). Thus, instead of simply increasing the dose of ICS or

prescribing more OCS, clinicians may need to consider alternative treatment options for these obese, frequent exacerbators. Management of comorbidities is particularly important, since asthma exacerbators with multiple comorbidities suffer more in-hospital adverse outcomes (32). Weight-loss regimens are associated with improved asthma control and lung function (41–43). Similarly, bariatric surgery results in a 58% reduction in asthma exacerbation risk (44). Also, treatment of symptomatic GERD is associated with reduced asthma exacerbations and improved quality-of-life (45,46); this is pertinent as symptomatic GERD was more prevalent in frequent exacerbators in our study. Moreover, a recent individual patient data meta-analysis showed that long-term macrolide therapy reduces exacerbations in non-eosinophilic asthma (47).

To our knowledge, this is the first study to identify a machine learning algorithm which predicts the risk of being a frequent exacerbator. Previous studies have predicted the risk of future asthma hospitalization, but not the need for multiple hospitalizations (48,49). The benefits of machine learning include the ability to analyze large quantities of data ("big data") and the potential to improve the accuracy of prediction models as more data is added to the algorithm (50). Prospective studies featuring larger patient cohorts are needed to validate the use of machine learning algorithms that identify frequent exacerbators, so that these algorithms can be used in primary care to identify high-risk asthma patients.

Frequent exacerbators experienced more exacerbations managed in the community and used more SABA inhalers, which both indicate that frequent exacerbators have worse baseline asthma control. Frequent exacerbators were dispensed an average of 10.9 SABA cannisters per year, which is particularly striking because the use of 3 cannisters per year is considered to be "overuse" in the GINA asthma guidelines (27). SABA overuse is associated with more frequent exacerbations and increased mortality (51,52). Therefore, SABA overuse is a relatively easy way for clinicians to identify at-risk patients and optimize their management accordingly. For example, primary care physicians could be alerted if a patient dispenses more than 3 SABA cannisters in a year, prompting an asthma review. Similar computerized decision support tools have resulted in improved asthma control and increased uptake of asthma action plans (53).

Our study is one of the few studies to assess medication adherence in asthma exacerbators. Only 44% of patients displayed good adherence to ICS. ICS adherence in asthma ranges from 15% to 69% (54,55),

though it is difficult to compare studies as there is marked heterogeneity in the calculation of adherence (56). Good adherence is associated with a decreased risk of severe asthma exacerbations, while poor adherence is associated with more rapid lung function decline (55,56). Therefore, ICS adherence is a modifiable risk factor for asthma exacerbations. There are multiple reasons for non-adherence. Pertinently, some patients believe that they do not need the daily treatment, or that the treatment does not work (57,58). This may apply to the obese, non-eosinophilic patients identified in our study. Qualitative studies assessing the attitudes of these patients to glucocorticoids are needed.

This is one of the few studies to assess follow-up rates in asthma exacerbators. An insufficient proportion of patients was followed up by an asthma specialist within 4 weeks of discharge, as per the BTS guidelines (18). Follow-up with an asthma specialist improves asthma outcomes and reduces subsequent re-admissions (15,16). National audits of follow-up rates are needed, to assess if this is a wider problem, and to identify reasons for the lack of follow-up.

A strength of this study is its real-world nature, and so it did not solely focus on severe asthmatics. In fact, most of the patients in the study would be classified as mild-moderate asthmatics. This increases the generalizability of the results, as 94%–96% of asthmatics are in the mild-moderate category (depending on which definition of severe asthma is used) (59). However, this study does have some limitations. Asthma control was not assessed formally at baseline using an asthma control questionnaire, as patients were admitted to a busy Acute Admissions Unit, with significant time pressures on the staff there. Also, this was a retrospective study, and so important longitudinal changes could not be identified. For example, a recent prospective study showed that patients with low eosinophils frequently shifted to eosinophilia during a 90-day follow-up (60). Furthermore, the management and disease control of the patients' co-morbidities (such as GERD) were not assessed.

Conclusion

We have shown that patients admitted with asthma exacerbations are mostly female, obese and non-eosinophilic. Rates of medication adherence and follow-up are inadequate. Frequent exacerbators have poorer asthma control at baseline, as shown by increased use of SABA and OCS, which can be easily identified by clinicians. Furthermore, we have shown that machine learning can be used to identify frequent

exacerbators using clinical data available in primary care. Our findings emphasize the crucial need to optimize the management of patients with Th2-low asthma, which is an area of asthma that is largely neglected, despite being prominent in frequent exacerbators. Multi-disciplinary management should be considered for this asthma phenotype, including weight loss regimens, GERD management and long-term macrolides.

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Declaration of interest

The authors report no conflicts of interest.

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