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Chan, Rory; Lipworth, Brian

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Rory Chan, MBChB, and Brian J. Lipworth, MD

Clinical Implications

Amalgamating forced expiratory volume in 1 second with oscillometry, peripheral blood eosinophilia, or total immunoglobulin E is associated with increased risk of poor control and severe exacerbations in moderate-to-severe asthma.

Asthma patients remain susceptible to severe exacerbations even when their condition is seemingly brought under control,[1] potentially suggesting an element of disconnect between exacerbations and asthma control. It has recently been shown that combining oscillometry and spirometry measurements of pulmonary function identifies patients with worse asthma control and more frequent severe exacerbations requiring oral corticosteroids (OCS).[2] Moreover, those with combined elevation of peripheral blood eosinophil (PBE) counts and fractional exhaled nitric oxide (FeNO) subsequently have higher asthma exacerbation rates across all asthma severities but especially in those with more severe disease.[3]

However, to date, there are no available data looking at combining measurements of airway physiology with type 2 (T2) biomarkers. Here we, therefore, aim to calculate odds ratios (ORs) in association with poor asthma control and severe exacerbations in a real-life setting based on combinations of spirometry (forced expiratory volume in 1 second [FEV_1]), oscillometry (reactance area [AX] and resistance heterogeneity [R5-R20]) and T2 biomarkers (PBE, FeNO, and total immunoglobulin E [IgE]).

Data on 193 moderate-to-severe asthma patients attending the hospital clinic were included in this retrospective cohort study. The FeNO was measured using NIOX VERO (Circassia, Oxford, UK) according to the manufacturer's instructions and American Thoracic Society (ATS) guidelines. Spirometry (Micromedical, Chatham, UK) was performed according to European Respiratory Society (ERS)/ATS guidelines. Oscillometry was measured prior to spirometry using IOS Masterscreen (Carefusion, Hoechberg, Germany) with measurements performed in triplicate according to the ERS technical standards. Heterogeneity of resistance between 5 and 20Hz (R5-R20) and heterogeneity of reactance as area under the curve between 5Hz and resonant frequency (AX) were measured. Both R5-R20 and AX reflect changes in small airways resistance and capacitance, respectively. Blood testing was performed for PBE and total IgE. Poor asthma control was defined by an Asthma Control Questionnaire (ACQ) score of 1.5 or greater and the number of OCS-requiring exacerbations over the past year was retrieved from medical records. The FeNO, oscillometry, spirometry, and ACQ were carried out contemporaneously whereas PBE counts were averaged over the preceding year owing to temporal variability. All data were obtained before appropriate patients were commenced on biologic therapy.

Statistical analysis using SPSS v27 involved logistic regression to obtain ORs for the specified determinant associated with poor asthma control and 2 or more exacerbations in the past year compared with all other variables. The ORs were subsequently adjusted for important characteristics such as age, gender, body mass index, smoking history, presence of nasal polyps, and those taking long-acting beta agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and leukotriene receptor antagonists (LTRAs).[4] Values are presented as adjusted OR (95% CI) in which the lower CI exceeding unity denotes significance. Caldicott approval was obtained prior to data collection.

Mean or proportion (%) demographics were as follows: females: 65%, age 50 years (range 17−85 years); body mass index 31 kg/m^2 (range 15.4−58.4); inhaled corticosteroids (ICS) beclomethasone dipropionate (BDP) equivalent dose 1,693 μg; LABA 83%; LAMA 47%; LTRA 53%; theophylline 19%; oral antihistamines 19%, nasal polyps 21%; current smokers 6%; exsmokers 22%; FEV_1 85% predicted; AX 2.02 kPa/L; R5-R20 0.16 kPa/L/s; PBE 347 cells/μL; FeNO 34 ppb (range 0−237 ppb); total IgE 387 kU/L (range 3−5,000 kU/L); ACQ 2.3 (range 0−6.0); number of severe exacerbations/y 2.1 (range 0−8).

Table I presents the adjusted ORs for impaired spirometry or oscillometry and elevated T2 biomarkers that were associated with ACQ of 1.5 or greater and 2 or more exacerbations/y. One hundred twelve of 161 patients had an ACQ of 1.5 or greater and 82 of 166 had 2 or more exacerbations in the previous year. Table E1 (available in this article's Online Repository at www.jaci-inpractice.org) shows crude ORs. Table E2 (available in this article's Online Repository at www.jaci-inpractice.org) presents ORs for univariate analyses of baseline characteristics. As individual variables, FEV_1 less than 80%, AX of 1.0 kPa/L or greater, and PBE of 300 cells/μL or greater had a significantly increased risk of poor control whereas AX of 1.0 kPa/L or greater and R5-R20 of 0.10 kPa/L/s or greater were significantly associated with exacerbations. When combined with FEV_1 less than 80%, the addition of AX, R5-R20, and PBE were all significant in being associated with both control and exacerbations, while the addition of FeNO and IgE were only significant for control (Figure 1).

These analyses suggest that combining spirometry as FEV_1 with oscillometry measures indicative of small airways dysfunction as either R5-R20 or AX confers the greatest likelihood of being significantly associated with both poor control and frequent asthma exacerbations. For example, FEV_1 + AX was associated with an 86% and a 73% increased likelihood of poor control and frequent exacerbations, respectively, whereas FEV_1 + R5-R20 had an 83% and a 72% increased likelihood. The 95% CIs were wide and overlapping when comparing FEV_1 in combination with either AX or R5-R20 versus either measure alone.

Our data are also in keeping with previous findings when combining spirometry and oscillometry as forced expiratory flow between 25% and 75% of forced vital capacity ($FEF_{25\%-75\%}$) and R5-R20 in patients with mild-to-moderate asthma being

TABLE I. Adjusted ORs for pulmonary function and T2 biomarkers associated with asthma control and Exac*

Characteristic	ACQ ≥ 1.5 (n = 112/161) OR (95% CI)	Characteristic	≥2 Exac/y (n = 82/166) OR (95% CI)
FEV_1 (n = 63/161)	3.45 (1.45−8.21)†	FEV_1 (n = 65/166)	1.95 (0.97−3.94)
AX (n = 83/159)	4.07 (1.73−9.55)‡	AX (n = 76/161)	2.37 (1.14−4.94)†
R5-R20 (n = 92/161)	2.13 (0.98−4.64)	R5-R20 (n = 88/166)	2.33 (1.17−4.63)†
PBE (n = 79/154)	2.55 (1.02−6.36)†	PBE (n = 91/161)	1.31 (0.63−2.73)
FeNO (n = 69/135)	0.95 (0.39−2.30)	FeNO (n = 63/129)	1.26 (0.56−2.81)
IgE (n = 72/128)	1.41 (0.55−3.64)	IgE (n = 84/155)	0.82 (0.40−1.67)
FEV_1 + AX (n = 44/159)	7.41 (2.40−22.86)§	FEV_1 + AX (n = 44/161)	3.69 (1.59−8.55)‡
FEV_1 + R5-R20 (n = 46/161)	5.78 (2.02−16.56)‡	FEV_1 + R5-R20 (n = 46/166)	3.55 (1.60−7.90)‡
FEV_1 + PBE (n = 31/154)	3.85 (1.19−12.45)*	FEV_1 + PBE (n = 35/161)	2.87 (1.17−7.05)*
FEV_1 + FeNO (n = 31/135)	5.20 (1.52−17.76)‡	FEV_1 + FeNO (n = 28/129)	2.21 (0.86−5.69)
FEV_1 + IgE (n = 30/128)	3.93 (1.14−13.54)*	FEV_1 + IgE (n = 37/155)	2.30 (1.00−5.31)‖

BDP, Beclomethasone dipropionate; *BMI,* body mass index; *Exac,* exacerbations.
*Adjusted for age, gender, ICS BDP dose, presence of nasal polyps, BMI, smoking, LABA, LAMA, and LTRA. Cut points used: FEV_1 < 80%, AX ≥ 1.0 kPa/L, R5-R20 ≥ 0.10 kPa/L/s, PBE ≥300 cells/μL, FeNO ≥ 25 ppb, total IgE ≥ 100 kU/L.
†$P < .05$.
‡$P < .01$.
§$P < .001$.
‖$P = .05$.

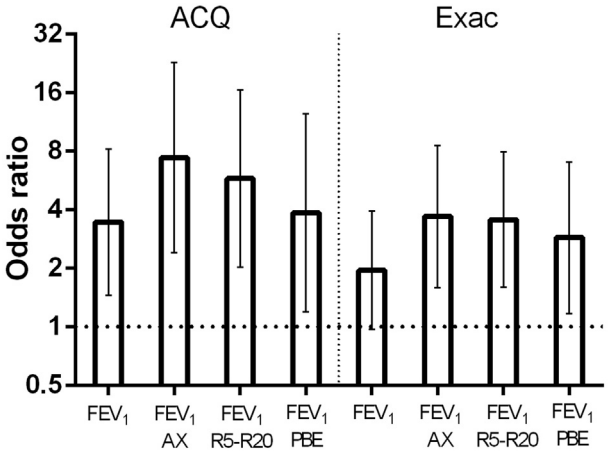

FIGURE 1. Adjusted ORs (95% CI) for AX, R5-R20, or PBEs combined with FEV_1 as risk factors for poor asthma control (ACQ ≥ 1.5) and severe exacerbations (Exac ≥ 2/y). The interrupted line represents the level of unity that the lower CI must exceed for a statistically significant effect. Cut points used: FEV_1 < 80%, AX ≥ 1.0 kPa/L, R5-R20 ≥ 0.10 kPa/L/s, and PBE ≥ 300 cells/μL.

associated with long term OCS and salbutamol use.[5] Traditionally, the small airways have been considered the quiet zone of the lungs because it is difficult to measure changes in the peripheral lung. Moreover, it has been shown that those with combined impairment of low-frequency resistance or reactance with FEV_1 have worse asthma control and more frequent severe exacerbations,[2] perhaps providing more evidence that the small airways are closely associated with symptoms in moderate-to-severe asthma. The present results, therefore, emphasize the potential role for performing both effort dependent (spirometry) and effort independent (oscillometry) tests of pulmonary function to comprehensively define physiological patient variables with severe asthma and define their risk of poor control and exacerbations.

We were surprised to find that none of the raised T2 biomarkers on their own were significantly associated with exacerbation risk. This might be related to the fact that patients were receiving ICS therapy in a nonrandomized fashion and such discrepancy between real-world data and findings from placebo arms of randomized controlled trials is well recognized. Nevertheless, it is clear that biomarkers are prognostic but also predictive of a treatment response to biologics as shown in landmark studies.[6] However, amalgamation of T2 biomarkers with impaired FEV_1 exhibited an increased likelihood of frequent exacerbations, amounting to a 65% higher risk with PBE and 55% with total IgE. However, we did show that raised PBE counts alone were associated with poor asthma control in line with previous literature.[7] Hence, we postulate that perhaps PBE counts more accurately reflect the future risk of asthma exacerbations,[8] whereas our data were looking at retrospective exacerbations. Nonetheless, when impaired FEV_1 was combined with raised T2 biomarkers, we observed an 81% likelihood of poor control with FeNO, 75% with IgE, and 74% with PBE. In this regard, ACQ has been shown to be a strong independent predictor of future exacerbation risk.[9]

We appreciate our study has limitations including its retrospective nature and, therefore, prior adherence to medication cannot be accurately determined. In particular, our limited patient cohort likely resulted in wide 95% CIs, although we still managed to demonstrate the numerically and significant additive effects of combining FEV_1 with oscillometry or T2 biomarkers on asthma control. These results can be considered exploratory in nature with larger studies required to increase power. Indeed, if the study sample size was larger, a multivariate analysis providing effect sizes could be carried out rather than individual logistic regressions. Notably, we did not have any measurement of adherence to ICS therapy, which may be important in determining the relationship between T2 biomarkers and exacerbations. We look forward to seeing larger replication studies with the aim of producing an application-based algorithm for

clinicians to facilitate asthma risk assessment in a real-life clinic setting in terms of the phenotypic interaction between airway physiology and T2 biomarkers.

Scottish Centre for Respiratory Research, School of Medicine, University of Dundee, Ninewells Hospital, Dundee, Scotland, UK

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Corresponding author: Brian J. Lipworth, MD, Scottish Centre for Respiratory Research, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, Scotland, UK. E-mail: b.j.lipworth@dundee.ac.uk.

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ONLINE REPOSITORY

TABLE E1. Crude OR for pulmonary function and type 2 biomarkers associated with asthma control and Exac*

	ACQ ≥ 1.5	≥2 Exac/y
	OR (95% CI)	OR (95% CI)
FEV_1	2.58 (1.22−5.46)†	2.02 (1.07−3.81)†
AX	3.21 (1.58−6.53)‡	2.30 (1.22−4.33)†
R5-R20	2.05 (1.04−4.04)†	2.31 (1.24−4.31)‡
PBE	1.91 (0.94−3.88)	1.53 (0.80−2.91)
FeNO	0.89 (0.43−1.84)	1.32 (0.66−2.63)
IgE	1.29 (0.58−2.87)	0.97 (0.52, 1.83)
FEV_1 + AX	4.83 (1.77−13.19)‡	3.31 (1.57−6.97)‡
FEV_1 + R5-R20	3.98 (1.56−10.17)‡	3.20 (1.55−6.61)‡
FEV_1 + PBE	2.73 (0.98−7.63)	2.88 (1.30−6.40)‡
FEV_1 + FeNO	2.84 (1.01−7.93)†	2.38 (1.02−5.57)†
FEV_1 + IgE	3.55 (1.16−10.88)†	2.28 (1.06−4.89)†

ACQ, Asthma Control Questionnaire; *AX,* resonant frequency; *Exac,* exacerbation; *FeNO,* fractional exhaled nitric oxide; *FEV_1,* forced expiratory volume in 1 second; *IgE,* immunoglobulin E; *OR,* odds ratio; *PBE,* peripheral blood eosinophil; *R5-R20,* resistance heterogeneity.
*Cut points used: $FEV_1 < 80\%$, AX ≥ 1.0 kPa/L, R5-R20 ≥ 0.10 kPa/L/s, PBE ≥ 300 cells/μL, FeNO ≥ 25 ppb, and total IgE ≥ 100 kU/L.
†$P < .05$.
‡$P < .01$.

TABLE E2. ORs for univariate baseline characteristics associated with asthma control and Exac

	ACQ ≥1.5	≥2 Exac/y
Characteristic	OR (95% CI)	OR (95% CI)
Age	0.99 (0.97−1.02)	1.01 (0.99−1.03)
Gender	1.34 (0.67−2.68)	0.82 (0.44−1.55)
BMI	1.00 (0.95−1.05)	1.00 (0.96−1.05)
Smoking	0.66 (0.28−1.54)	0.53 (0.26−1.10)
Nasal polyps	1.07 (0.47−2.38)	0.50 (0.24−1.03)
LABA	1.75 (0.66−4.64)	0.67 (0.27−1.67)
LAMA	0.51 (0.26−1.03)	0.46 (0.25−0.85)*
LTRA	0.41 (0.21−0.82)*	0.90 (0.49−1.66)

ACQ, Asthma Control Questionnaire; *BMI,* body mass index; *Exac,* exacerbation; *LABA,* long-acting beta agonist; *LAMA,* long-acting muscarinic antagonist; *LTRA,* leukotriene receptor antagonist; *OR,* odds ratio; *PBE,* peripheral blood eosinophil; *R5-R20,* resistance heterogeneity.
*$P < .05$.