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Original Research

Characterizing the preserved ratio impaired spirometry phenotype in all severities of asthma

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ABSTRACT

Introduction: The preserved ratio impaired spirometry (PRISm) phenotype is characterized by a maintained FEV_1/FVC ratio ≥70 but an abnormal FEV_1<80 % predicted. Small airways dysfunction (SAD) is common amongst asthmatics and is associated with poorer clinical outcomes. SAD can be assessed using oscillometry as resistance between 5 and 20Hz (Rrs5-20), reactance at 5Hz (X5) and area under the reactance curve (AX). We aimed to investigate the prevalence of PRISm and its relationship with SAD in all severities of asthma with the primary outcome of annual exacerbation rate.

Methods: Data from the Oscillometry Asthma Registry comprising 937 adults with GINA-defined persistent asthma were retrospectively collected from two specialized asthma centres in UK and Italy. Multivariate analyses were performed using binary logistic regression to obtain adjusted odds ratios for the association between PRISm and exacerbation frequency and symptom control.

Results: PRISm had a 19.6 % prevalence in moderate-to-severe asthma and was associated with a greater likelihood of ≥1 exacerbation [OR 95 %CI 3.00 (1.80,5.00) $p < 0.001$], ≥2 exacerbations [4.00 (1.86,8.59) $p < 0.001$] and uncontrolled symptoms [14.04 (4.87,40.50) $p < 0.001$] compared to patients with normal spirometry. Conversely, patients with PRISm were prescribed significantly lower ICS doses and had fewer exacerbations compared to those with airway obstruction.

Conclusion: The PRISm asthma phenotype is associated with greater exacerbation frequency, poorer symptom control and a higher SAD prevalence compared to patients with normal spirometry. Future research should focus on longitudinal follow-up to confirm the progression of PRISm to obstructive patterns and assess potential therapeutic interventions to modify this trajectory.

1. Introduction

The preserved ratio impaired spirometry (PRISm) phenotype is traditionally characterized by a maintained forced expiratory volume (FEV_1) to forced vital capacity (FVC) ratio ≥70 but an abnormal FEV_1<80 % predicted [1]. The prevalence of PRISm ranges between 4 %

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and 48 % depending on the studied population [1]. In a large observational study of 53,701 unselected US adults, the presence of PRISm was significantly associated with increased all-cause mortality alongside elevated cardiovascular and respiratory morbidity compared to normal spirometry [2]. In community-based adults with undiagnosed respiratory symptoms, those identified with PRISm experienced the greatest impact of dyspnea [3]. Another study investigating unselected patients attending clinic for annual check-ups found that asthma prevalence was higher in those with PRISm [4]. However, few studies have examined the prevalence and clinical relevance of PRISm in patients with persistent asthma.

Moreover, patients with PRISm demonstrate evidence of oscillometry defined small airways dysfunction (SAD) which, in turn, is associated with poorer symptom control and more frequent asthma exacerbations [5,6]. In this regard, oscillometry is a tidal breathing test used to evaluate peripheral airway resistance between 5 and 20Hz (Rrs5-20), alongside peripheral airway compliance as area under the reactance curve (AX) or reactance at 5Hz (X5) [7]. Therefore, understanding the clinical associations with PRISm in asthma could help refine treatment strategies and improve patient outcomes. We also aimed to investigate the relationship between PRISm and SAD in moderate-to-severe asthmatics with the primary outcome of annual severe exacerbation rate.

A recent scoping review of 38 studies revealed an association between PRISm with lower education level amongst other demographical factors, comorbidities such as diabetes and asthma, and even radiological features such as the percentage of lung affected by emphysema [8]. Another recent meta-analysis including 690,015 patients revealed 70 %, 95 % and 470 % increased risk of all-cause, cardiovascular and respiratory related death respectively [9]. Due to its clinical relevance, our primary research question was whether PRISm is associated with an increased likelihood of poor asthma control defined by severe exacerbation frequency and symptom burden compared to patients with normal or obstructive spirometry. We also sought to determine the prevalence of PRISm in asthma and identify any relationship with type 2 (T2) inflammation.

2. Methods

The Oscillometry Asthma Registry (OAR) comprised 937 consecutive adults with all severities of Global Initiative for Asthma (GINA) defined persistent asthma. 617 patients exhibited moderate-to-severe asthma whereas 320 had mild disease.

Data were collected from two specialized asthma centres: Ninewells Teaching Hospital, Dundee, UK and the Allergy and Pneumology Outpatient Clinic, Bergamo, Italy. Participants with COPD or moderate-to-severe bronchiectasis were excluded. Ethical approval was obtained by the local institutional review board (NP3364) and Caldicott Guardian (IGTCAL-2024-314).

Impulse oscillometry [Masterscreen (CareFusion, Hoechberg, Germany or Sentry Suite, Vyaire Medical)] was performed in triplicate according to European Respiratory Society (ERS) technical standards [10]. Fractional exhaled nitric oxide (FeNO) was measured with NIOX VERO (Circassia, Oxford, UK) or a chemiluminescence analyzer (HypAir FeNO, Medi-Soft, Sorinnes, Belgium) at a standard expiratory flow rate of 50 mL/s according to the manufacturer's instructions and American Thoracic Society (ATS) guidelines. Spirometry [Micromedical, Chatham, UK or Vyntus PNEUMO-PC Spirometer (VyAire Medical, Chicago, Ill)] was conducted following joint ERS and ATS guidelines using Global Lung Initiative 2012 reference equations [11]. Oscillometry, FeNO and spirometry were performed on the same day in that order.

PRISm was defined as both FEV_1/FVC ratio$\geq$70 and FEV_1<80 % predicted [12]. Normal spirometry was defined as both $FEV_1\geq$80 % and $FEV_1/FVC\geq$70, whereas obstructive spirometry was defined as FEV_1/FVC<70. SAD was defined as the presence of both Rrs5-20 $\geq$ 0.10 kPa/L/s and AX$\geq$1.0 kPa/L [13]. The number of severe asthma exacerbations requiring at least a three-day course of oral corticosteroids (OCS) over the previous 12 months was recorded [14]. Type 2 (T2) biomarker data, including peripheral blood eosinophils (PBE) and FeNO and lung function measurements were collected prior to any biologic initiation. T2 high inflammation was defined as PBE$\geq$300 cells/μL and FeNO$\geq$25 ppb [15] whereas T2 low disease was characterized by PBE<300 cells/μL and FeNO<25 ppb. Patients were considered to be taking extra fine inhaler therapy if their inhalers contained particles with a mass median aerodynamic diameter less than 2 μm [16].

Statistical analyses were conducted using SPSS v28 (IBM, Armonk, USA). One-way analysis of variance (ANOVA) was performed on normally distributed data and presented as means (95 %CI), whereas Kruskal-Wallis tests were applied to non-normally distributed data and presented as medians (interquartile ranges, IQR). Binary logistic regression was applied to obtain odds ratios (OR) for the association between PRISm with severe exacerbation frequency or uncontrolled symptoms. OR were subsequently adjusted for potential confounders such as age, sex, BMI, ICS dose and smoking status. In analyses involving two comparison groups, independent T tests were used. Chi-squared analysis was implemented to detect significant differences between categorical variables. Bonferroni corrections were applied to all analyses to account for multiple testing, in order not to confound the alpha error threshold of 0.05 (two-tailed). Median imputation was implemented for missing data (<5 %) across all the cohorts.

3. Results

In moderate-to-severe asthma (n = 617), patients with PRISm or airflow obstruction were both significantly older and were prescribed higher daily ICS doses compared to those with normal spirometry (Table 1). The PRISm (n = 121) and obstructive (n = 223) phenotypes were also associated with significantly more frequent severe exacerbations, a lower incidence of extrafine ICS use, worse oscillometry outcomes (Rrs5-20, X5 and AX), as well as higher FeNO levels than the normal phenotype (n = 273). Conversely, patients with PRISm required significantly lower ICS doses and had fewer severe exacerbations compared to those with airway obstruction (Table 1). Multivariate analyses revealed a significant relationship between PRISm with $\geq$1 and $\geq$ 2 severe exacerbations in the previous year and uncontrolled symptoms (Table 2).

Fig. 1 depicts the subject distribution according to their FEV_1 and FEV_1/FVC values, with a PRISm prevalence of 19.6 %. Individuals with both PRISm and SAD were older and exhibited significantly more frequent severe exacerbations, whilst also less likely to be taking extra fine ICS (Table S1). In patients with T2 high disease, PRISm was associated with intermediate daily ICS doses and severe exacerbations compared to those with normal or obstructive spirometry (Table S2). No significant differences were observed in daily ICS doses or severe exacerbation frequency across the normal, PRISm and obstructive phenotypes in the T2 low cohort (Table S3).

In mild asthma (n = 320), a PRISm analysis was not possible since only n = 9 patients fulfilled this criterion (Table S4). Patients with missing values, where median imputation was implemented, were as follows: n = 8 for Rrs5-20; n = 13 for AX; n = 15 for FeNO; n = 131 for PBE.

4. Discussion

Our findings highlight several important aspects. First, PRISm in moderate-to-severe asthma is a relatively prevalent phenomenon affecting 20 % of individuals in our cohort. Multivariate analyses revealed a significantly greater likelihood of exacerbations and poor symptom control in PRISm compared to patients with normal spirometry. We propose that the PRISm phenotype represents an intermediate stage between normal and obstructive spirometry. This observation is supported by its association with intermediate ICS doses and severe

Table 1
Demographics and clinical outcomes in moderate-to-severe asthma (n = 617).

	Normal (n = 273) $FEV_1 \geq 80$ % and $FEV_1/FVC \geq 70$	PRISm (n = 121) $FEV_1 < 80$ % and $FEV_1/FVC \geq 70$	Obstructive (n = 223) $FEV_1/FVC < 70$
Age (yrs)	49 (47,52)	56 (53,59)***	55 (53,57)***
BMI (kg/m^2)	26.3 (25.5,27.1)	27.8 (26.6,29.0)	29.0 (28.1,30.0)***
Female (n, %)	160 (58.6 %)	75 (62.0 %)	137 (61.4 %)
Ex-smokers (n, %)	12 (4.4 %)	10 (8.3 %)	53 (23.8 %)*†
ICS dose (μg)	1154 (1098,1209)	1486 (1306,1667)***	1718 (1655,1782)***††
Severe exacerbations	0 (1)	1 (1)***	1 (4)***†
ACQ	2.3 (1.9,2.6)	2.3 (2.0,2.7)	2.3 (2.2,2.5)
	(n = 49)	(n = 26)	(n = 182)
GINA symptom control	(n = 224)	(n = 95)	(n = 41)
Well controlled (n,%)	98 (43.8 %)	10 (10.5 %)*	9 (22.0 %)*
Partially controlled (n,%)	83 (37.1 %)	33 (34.7 %)	11 (26.8 %)
Uncontrolled (n,%)	43 (19.2 %)	52 (54.7 %)*	21 (51.2 %)*
FEV_1 (%)	99.8 (98.2,101.3)	68.4 (66.7,70.1)***	77.9 (75.0,80.8)***†††
FEF_{25-75} (%)	82.8 (79.6,86.0)	41.2 (38.7,43.7)***	41.5 (38.5,44.5)***
FVC (%)	108.5 (101.1,116.0)	81.7 (79.5,84.0)***	100.6 (98.1,103.2)†††
FEV_1/FVC	92.7 (91.7,93.8)	80.7 (79.4,82.1)***	64.1 (62.5,65.6)***†††
SAD prevalence (n, %)	108 (41.9 %)	93 (76.9 %)*	122 (54.7 %)*†
Rrs5-20 (kPa/L/s)	0.09 (0.12)	0.17 (0.14)***	0.12 (0.17)***†
X5 (kPa/L/s)	−0.13 (0.10)	−0.22 (0.15)***	−0.19 (0.19)***
AX (kPa/L)	0.80 (1.27)	2.05 (2.05)***	1.15 (2.54)***††
Extra fine therapy (n, %)	94 (42.0 %)	20 (21.1 %)*	12 (29.3 %)
	(n = 224)	(n = 95)	(n = 41)
FeNO (ppb)	21 (25)	32 (30)**	26 (29)**††
PBE (cells/μL)	340 (148)	340 (303)	340 (300)

ACQ: Asthma Control Questionnaire, AX: Area under the reactance curve, BMI: Body Mass Index, FeNO: Fractional Exhaled Nitric Oxide, FEF_{25-75}: Forced Expiratory Flow at 25–75 % of FVC, FEV_1: Forced Expiratory Volume in 1 s, FEV_1/FVC: Forced Expiratory Volume to Forced Vital Capacity ratio, FVC: Forced Vital Capacity, ICS: Inhaled Corticosteroid, PBE: Peripheral Blood Eosinophils, PRISm: Preserved Ratio Impaired Spirometry, Rrs5-20: Respiratory Resistance at 5–20 Hz, SAD: Small Airways Dysfunction.
*cf normal *$p < 0.05$ **$p < 0.01$ ***$p < 0.001$.
†cf PRISm †$p < 0.05$ ††$p < 0.01$ †††$p < 0.001$.
Bonferroni corrected.
Age, BMI, ICS dose, ACQ and Spirometry presented as mean (95%CI).
Exacerbations, Oscillometry, FeNO and PBE presented as medians (IQR).

Table 2
Multivariate odds ratios (95 %CI) for the association between PRISm versus normal spirometry in relation to asthma outcomes in moderate-to-severe asthma.

	≥1 severe exacerbations (n = 394)	≥2 severe exacerbations (n = 394)	GINA-U (n = 203)
Univariate			
Age	1.01 (1.00,1.03)*	1.01 (0.99,1.02)	1.03 (1.01,1.05)***
ICS dose	1.00 (1.00,1.00)***	1.00 (1.00,1.00)***	1.00 (1.00,1.00)***
Sex	0.52 (0.34,0.78)**	0.42 (0.22,0.81)*	0.39 (0.22,0.69)**
BMI	1.11 (1.07,1.15)***	1.13 (1.08,1.19)***	1.25 (1.16,1.36)***
Smoking	1.57 (1.01,2.44)*	1.01 (0.49,2.05)	4.41 (2.36,8.24)***
Multivariate			
PRISm	3.00 (1.80,5.00)***	4.00 (1.86,8.59)***	14.04 (4.87,40.50)***

exacerbation frequency. Notably, only 9 patients from our mild asthmatic cohort exhibited PRISm. If externally validated and confirmed, these findings could support earlier therapeutic interventions to prevent longitudinal lung function decline and adverse systemic effects of cumulative OCS. In this regard, a previous study also identified an association between longitudinal FEV_1 decline and elevated FeNO in patients with stable controlled asthma [17]. The potential utility of combining PRISm with FeNO to predict future lung function deterioration therefore warrants further investigation. Moreover, it has been shown that SAD is closely associated with airway remodelling on thoracic imaging [18], begging the question whether PRISm might also be linked to bronchial wall thickening.

Second, subgroup analyses revealed that the combination of PRISm with SAD carried significantly greater severe exacerbation frequency compared to PRISm without SAD. This perhaps supports SAD as the predominant factor driving exacerbations. It is noteworthy here that in all analyses, a greater proportion of asthmatics without PRISm or SAD were taking extra fine ICS. In this regard, smaller therapeutic inhaler particles have been associated with better peripheral lung deposition and improved small airway function [19,20]. A meta-analysis of 33,453 subjects has also shown that the use of extra fine particle ICS is associated with a greater likelihood of better asthma control compared to the use of fine particle ICS [21]. Previous data using biologics including anti-IL5Rα benralizumab, anti-IL4Rα dupilumab and anti-thymic stromal lymphopoietin (TSLP) tezepelumab all have illustrated clinically relevant improvements in airflow obstruction and/or small airways dysfunction [22–25]. The next logical question that could perhaps be answered with post hoc analyses of large phase III trials is whether extra fine ICS and anti-T2 biologics can potentially reverse or mitigate the progression of PRISm.

Third, when considering individuals with T2 high asthma, severe exacerbation frequency was broadly similar to the primary analyses. However, in this cohort, we also observed similar prevalence of SAD across normal, PRISm and obstructive phenotypes with largely comparable peripheral airway resistance and compliance. Whilst this could be related to the proposed protective mechanism of extra fine ICS therapy, which a similar proportion of patients from each group used, there is also an acknowledged connection between T2 inflammation and SAD [26].

Another aspect to our study is that many centres do not have access to oscillometry for the detection of SAD. However, we have shown here that the prevalence of SAD was approximately twice in those with PRISm in the overall cohort, using either definition, compared to those with normal spirometry. We therefore suggest that the presence of

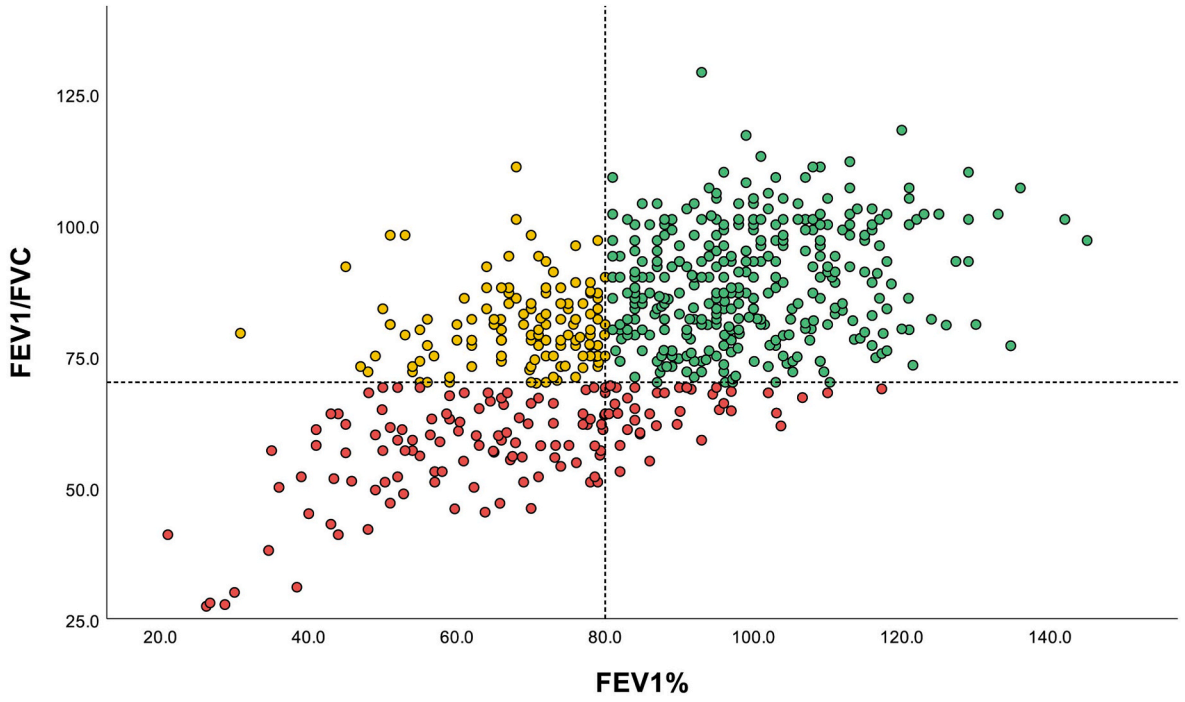

Fig. 1. Distribution of spirometry values according to FEV_1 and FEV_1/FVC. Green, amber and red circles represent patients with normal spirometry, PRISm or obstructive limitation respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

PRISm can be used as part of an exacerbation risk prediction score but also as a potential surrogate test if oscillometry data are not readily available.

The present study had several strengths, including real-life comprehensive data obtained from two specialized asthma centres as well as phenotypic data from all severities of asthma. However, we appreciate the potential limitations including its retrospective nature. Furthermore, it was not possible to ascertain whether PRISm is truly an intermediary stage between normal and obstructive spirometry as we did not have longitudinal data. In this regard, a longitudinal study identified three potential trajectories in patients with PRISm including (a) the development of COPD; (b) association with high mortality and cardiovascular burden; and (c) persistent PRISm with normal age-related lung function decline [27]. In our study, there was also a considerable proportion of patients with obstructive spirometry who did not have data on whether their inhaler therapy contained extra fine particles thereby limiting interpretation. Future research should focus on longitudinal follow-up of asthmatics to confirm the progression of PRISm to obstructive patterns and assess potential therapeutic interventions to modify this trajectory. In summary, the preserved ratio impaired spirometry (PRISm) asthma phenotype is associated with greater exacerbation frequency, poorer symptom control and a higher prevalence of small airways dysfunction compared to patients with normal spirometry. PRISm was also linked to intermediate clinical outcomes compared to those with normal and obstructive spirometry.

CRediT authorship contribution statement

Marcello Cottini: Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization. **Remo Poto:** Writing – review & editing, Writing – original draft, Methodology. **Atanu Bhattacharjee:** Writing – review & editing, Writing – original draft, Formal analysis. **Stanley Galant:** Writing – review & editing, Writing – original draft, Methodology. **Brian Lipworth:** Writing – review & editing, Writing – original draft, Methodology. **Erol A. Gaillard:** Writing – review & editing, Writing – original draft, Methodology. **Robert Greig:** Writing – review & editing, Writing – original draft, Methodology. **Alvise Berti:** Writing – review & editing, Writing – original draft, Methodology. **Carlo Lombardi:** Writing – review & editing, Writing – original draft, Methodology. **Francesco Menzella:** Writing – review & editing, Writing – original draft, Methodology. **Laura Ventura:** Writing – review & editing, Writing – original draft, Formal analysis. **Pasquale Comberiati:** Writing – review & editing, Writing – original draft, Methodology. **Rory Chan:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MC reports personal fees (talks) from Chiesi, Menarini, GSK, and support attending meetings from Chiesi.RP reports personal fees (talks) from AstraZeneca.BL reports grants, personal fees (consulting, talks and advisory board), other support (attending ATS and ERS) from AstraZeneca; grants, personal fees (talks and consulting) from Sanofi/Regeneron, personal fees (consulting, talks and advisory board) from NIOX in relation to the submitted work; grants, personal fees (consulting, talks, advisory board), other support (attending ERS) from Teva, personal fees (talks and consulting), grants and other support (attending ERS and BTS) from Chiesi, personal fees (consulting and talks) from Lupin, personal fees (consulting) from Glenmark, personal fees (consulting, talks, advisory board), other support (attending BTS) from Boehringer Ingelheim; and the son of BL is presently an employee of AstraZeneca.RG reports personal fees (talks) from AstraZeneca.SG reports no conflicts of interest.EAG has received institutional grants from Gilead, Circassia, Chiesi, Propellar Health, Helicon Health, Adherium Ltd, and AstraZeneca, and personal fees from Circassia and SanofiAlvise Berti reports grants, personal fees (consulting, talks and advisory board) from GSK and Vifor.PC reports no conflicts of interest.CL reports no conflicts of interest.FM reports no conflicts of interest.LV reports no conflicts of interest.Atanu Bhattacharjee reports no conflicts of interest.RC reports institutional grants from Chiesi, AstraZeneca and GlaxoSmithKline to Chair the Scottish Airways Research Network; serving on an advisory board for

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2025.108180.

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