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Impact Of Pulmonary Rehabilitation and Smoking Cessation on Clinical and Spirometric Outcomes in Smokers with Preserved Ratio Impaired Spirometry: A 12-Month Prospective Follow-Up Study

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KEYWORDS

PRISm, pulmonary rehabilitation, smoking cessation, spirometry, COPD

ABSTRACT:

Background

Preserved ratio impaired spirometry (PRISm) represents a distinct spirometric phenotype characterised by reduced forced expiratory volume in one second (FEV_1 <80% predicted) with a preserved FEV_1/FVC ratio (≥0.70). Individuals with PRISm frequently demonstrate respiratory symptoms, impaired quality of life, and increased risk of progression to chronic obstructive pulmonary disease (COPD). Evidence regarding early intervention strategies in this population remains limited.

Objective

To evaluate the impact of pulmonary rehabilitation in addition to smoking cessation on symptom burden and spirometric outcomes among smokers with PRISm over a twelve-month follow-up period.

Materials and Methods

A prospective follow up study was conducted in a tertiary care centre. Smokers aged 25–55 years diagnosed with PRISm were enrolled and received structured pulmonary rehabilitation along with intensive smoking cessation. Participants underwent clinical assessment and spirometry at baseline and every two months for twelve months. Symptom burden was assessed using the COPD Assessment Test (CAT), modified Medical Research Council (mMRC) dyspnoea scale, and St George's Respiratory Questionnaire (SGRQ). Spirometric outcomes included post-bronchodilator FEV_1% predicted, FVC% predicted, and FEV_1/FVC ratio.

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Results

Seventy-one participants completed the twelve-month follow-up and were included in the analysis. Significant improvement was observed in CAT score (13.09 ± 2.83 to 9.30 ± 4.74), mMRC grade (1.31 ± 0.47 to 0.48 ± 0.75), and SGRQ score (24.67 ± 5.84 to 17.35 ± 10.25). Spirometric parameters also improved, with post-bronchodilator FEV_1% predicted increasing from 65.04 ± 6.38 to 77.92 ± 14.98 and FVC% predicted improving from 63.47 ± 7.80 to 78.10 ± 13.22.

Conclusion

Pulmonary rehabilitation in addition to smoking cessation significantly improves symptoms, quality of life and lung function in smokers with PRISm. Early intervention may modify disease trajectory and potentially prevent progression to COPD.

INTRODUCTION

Preserved ratio impaired spirometry (PRISm) has recently gained recognition as an important intermediate spirometric phenotype within the spectrum of smoking-related lung disease. It is defined by a reduction in forced expiratory volume in one second (FEV_1 <80% predicted) with a preserved FEV_1/FVC ratio ≥0.70[1]. Although individuals with PRISm do not fulfill the spirometric criteria for chronic obstructive pulmonary disease (COPD), they frequently exhibit respiratory symptoms, reduced exercise tolerance, and impaired quality of life[2].

Large population based and smoker cohort studies have demonstrated that individuals with PRISm phenotype show higher rates of respiratory symptoms, increased healthcare utilisation, and greater risk of disease progression compared with smokers with normal spirometry[3]. Longitudinal analyses have further revealed that a significant proportion of individuals with PRISm eventually develop airflow obstruction consistent with COPD, whereas others remain stable or revert to normal spirometry, highlighting the heterogeneous nature of this phenotype[4].

The global prevalence of PRISm has been estimated to range between 6% and 20% depending on population characteristics, smoking exposure, and diagnostic criteria used in spirometric evaluation[5]. PRISm has also been associated with systemic inflammation, metabolic abnormalities, and cardiovascular comorbidities, suggesting that it represents a clinically relevant phenotype rather than a simple spirometric variation[6].

Smoking remains the principal modifiable risk factor contributing to lung function decline in individuals with PRISm. Cigarette smoke exposure leads to chronic airway inflammation, oxidative stress, and structural changes within the lung parenchyma that ultimately result in impaired pulmonary function[7]. Smoking cessation therefore represents the most effective intervention for preventing further lung damage and slowing the decline in FEV_1.

Pulmonary rehabilitation is another important therapeutic strategy in chronic respiratory disease. It consists of structured exercise training, breathing exercises, education, and behavioural modification. Numerous studies have demonstrated that pulmonary rehabilitation improves exercise tolerance, reduces dyspnoea, and enhances quality of life in patients with COPD[8].

However, pulmonary rehabilitation is traditionally recommended for individuals with established COPD, and relatively few studies have examined its potential benefits in individuals with early spirometric impairment such as PRISm. Given that PRISm may represent an early stage of smoking-related lung disease, interventions targeting reversible factors such as physical deconditioning and smoking behaviour may provide substantial clinical benefit.

Early identification of PRISm through spirometric screening may therefore offer a valuable opportunity for preventive intervention before the development of irreversible airflow obstruction. In this context, evaluating the effectiveness of pulmonary rehabilitation and smoking cessation in individuals with PRISm is of considerable clinical importance.

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The present study was undertaken to evaluate the impact of pulmonary rehabilitation combined with smoking cessation on symptom burden, health-related quality of life, and spirometric parameters among smokers with PRISm during a twelve-month follow-up period.

AIM AND OBJECTIVES

To evaluate the impact of pulmonary rehabilitation in addition to smoking cessation on symptom burden and spirometric outcomes among smokers with PRISm over a twelve-month follow-up period.

MATERIALS AND METHODS

Study Design

This study represents a prospective follow-up analysis of participants from a previously conducted randomized controlled trial carried out in the Department of Respiratory Medicine at a tertiary care teaching hospital.

Study Population

Smokers with PRISm aged 25-55 from the intervention arm who underwent pulmonary rehabilitation and smoking cessation in the parent study were included in the present analysis.

Inclusion Criteria

- Current smokers
- Age between 25–55 years
- Post-bronchodilator FEV_1 <80% predicted
- Post-bronchodilator FEV_1/FVC ratio ≥0.70
- Willingness to participate in pulmonary rehabilitation and follow-up visits

Exclusion Criteria

- Significant systemic comorbidities
- Active pulmonary pathology on chest imaging
- Occupational lung disease
- Inhaled substance abuse
- Inability to provide informed consent

Study Procedure

Participants underwent a structured pulmonary rehabilitation program that included breathing exercises, supervised physical activity training and education on respiratory health. Smoking cessation was implemented throughout the study period to reduce ongoing tobacco exposure and support improvement in lung function.

Follow-up

Participants were evaluated at:

- Baseline
- 2 months
- 4 months
- 6 months
- 8 months
- 10 months
- 12 months

Clinical Assessment

Symptom severity and quality of life were assessed using:

- COPD Assessment Test (CAT)
- Modified Medical Research Council (mMRC) dyspnea scale
- St George's Respiratory Questionnaire (SGRQ)

Spirometry

Spirometry was performed using standardized procedures and calibrated equipment.

Parameters recorded included:

- Post-bronchodilator FEV_1 % predicted
- Post bronchodilator FVC % predicted
- Post bronchodilator FEV_1/FVC ratio

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation. Changes in clinical scores and spirometric parameters across follow-up visits were analysed using appropriate repeated measures statistical methods. Repeated measures analysis was performed to

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evaluate changes over time. A p-value <0.05 was considered statistically significant.

Ethical Considerations

This study was conducted using data derived from participants who had been enrolled in a previously approved institutional research protocol in the Department of Pulmonary Medicine. The present study represents secondary analysis of previously collected data .All procedures were performed in accordance with institutional ethical guidelines. Patient confidentiality was strictly maintained throughout the study, and all personal identifiers were removed prior to data analysis to ensure anonymity and protection of participant privacy.

RESULTS

Participant Flow

A total of 753 smokers were screened using spirometry. Among them, individuals fulfilling the criteria for preserved ratio impaired spirometry were enrolled in the parent randomized study. Participants allocated to the pulmonary rehabilitation and smoking cessation arm who completed follow-up (n = 71) were included in the present analysis.

Baseline Characteristics

Table 1: Baseline Characteristics of Study Group

Variable	Mean ± SD
Age	41.35 ± 7.00
Smoking index	326.62 ± 191.16
CAT score	13.09 ± 2.83
mMRC grade	1.31 ± 0.47
SGRQ score	24.67 ± 5.84
Post FEV_1 % predicted	65.04 ± 6.38
Post FVC % predicted	63.47 ± 7.80

The baseline characteristics of participants included in the study group are summarised in Table 1. Baseline demographic characteristics including age, gender distribution, smoking index, spirometric parameters, and symptom scores. The mean age of the study population was 41.35 ± 7.00 years, indicating that most participants belonged to the middle-aged adult group. Gender-wise distribution showed a marked male predominance in the study group, with males accounting for 95.80% (n = 68) and females 4.20% (n = 3). The mean smoking index was 326.62 ± 191.16, reflecting substantial cumulative tobacco exposure among the study participants. At baseline, the mean COPD Assessment Test (CAT) score was 13.09 ± 2.83, suggesting a moderate level of respiratory symptom burden. Similarly, the mean modified Medical Research Council (mMRC) dyspnea grade was 1.31 ± 0.47**,** indicating mild to moderate exertional breathlessness among the participants. The mean St George's Respiratory Questionnaire (SGRQ) score was 24.67 ± 5.84, reflecting impairment in health-related quality of life associated with respiratory symptoms. Spirometric evaluation demonstrated reduced lung function, with a mean post-bronchodilator FEV_1 of 65.04 ± 6.38% predicted and FVC of 63.47 ± 7.80% predicted, consistent with the diagnostic criteria for preserved ratio impaired spirometry (PRISm). These findings indicate that the study cohort consisted of smokers with moderate smoking exposure, symptomatic respiratory disease, and impaired pulmonary function at baseline despite a preserved FEV_1/FVC ratio.

Table 2: Bimonthly Follow-up of Clinical Scores

Visit	CAT score (Mean ± SD)	mMRC grade (Mean ± SD)	SGRQ score (Mean ± SD)
Baseline	**13.09 ± 2.83**	**1.31 ± 0.47**	**24.67 ± 5.84**
2 Months	**12.58 ± 2.80**	**1.31 ± 0.47**	**23.04 ± 6.39**
4 Months	**11.77 ± 2.84**	**1.31 ± 0.47**	**21.75 ± 7.14**

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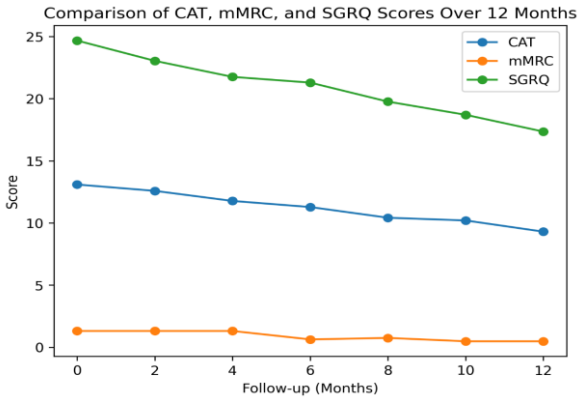
6 Months	**11.28 ± 3.35**	**0.63 ± 0.57**	**21.29 ± 7.33**
8 Months	**10.42 ± 3.52**	**0.75 ± 0.71**	**19.76 ± 7.77**
10 Months	**10.20 ± 4.10**	**0.48 ± 0.75**	**18.70 ± 8.66**
12 Months	**9.30 ± 4.74**	**0.48 ± 0.75**	**17.35 ± 10.25**
Overall p-value	**<0.001***	**<0.001***	**<0.001***

Table 2 presents the longitudinal changes in symptom scores among participants undergoing pulmonary rehabilitation and smoking cessation over the 12-month follow-up period. At baseline, the mean COPD Assessment Test (CAT) score was 13.09 ± 2.83, indicating a moderate level of respiratory symptom burden. Over the course of follow-up, a progressive decline in CAT scores was observed, decreasing to 12.58 ± 2.80 at 2 months**,** 11.77 ± 2.84 at 4 months, and 11.28 ± 3.35 at 6 months, with further reduction to 10.42 ± 3.52 at 8 months**,** 10.20 ± 4.10 at 10 months, and 9.30 ± 4.74 at 12 months, suggesting gradual improvement in respiratory symptoms. Similarly, the modified Medical Research Council (mMRC) dyspnoea grade demonstrated improvement during follow-up. The mean baseline mMRC score was 1.31 ± 0.47, which remained similar at 2 and 4 months, but showed a marked reduction thereafter, declining to 0.63 ± 0.57 at 6 months**,** 0.75 ± 0.71 at 8 months, and 0.48 ± 0.75 at both 10 and 12 months, reflecting improvement in perceived breathlessness. Quality of life assessed using the St George's Respiratory Questionnaire (SGRQ) also showed a consistent downward trend over time. The mean SGRQ score decreased from 24.67 ± 5.84 at baseline to 23.04 ± 6.39 at 2 months and 21.75 ± 7.14 at 4 months, followed by further reductions to 21.29 ± 7.33 at 6 months, 19.76 ± 7.77 at 8 months**,** 18.70 ± 8.66 at 10 months**,** and 17.35 ± 10.25 at 12 months. Overall, these findings demonstrate a sustained improvement in respiratory symptoms, dyspnea severity, and health-related quality of life over the 12-month follow-up period among participants receiving pulmonary rehabilitation and smoking cessation.

Figure 1: Comparison of symptom scores over the 12-month follow-up among participants undergoing pulmonary rehabilitation and smoking cessation



The graph illustrates the progressive reduction in COPD Assessment Test (CAT) score, modified Medical Research Council (mMRC) dyspnea grade, and St George's Respiratory Questionnaire (SGRQ) score, indicating improvement in respiratory symptoms and health-related quality of life during the study period.

Table 3: Bimonthly Follow-up of Spirometry

Visit	Post FEV_1 % predicted (Mean ± SD)	Post FVC % predicted (Mean ± SD)	Post FEV_1/FVC ratio (%) (Mean ± SD)
Baseline	65.04 ± 6.38	63.47 ± 7.80	80.30 ± 4.98
2 Months	67.08 ± 7.28	67.58 ± 9.08	77.97 ± 6.91
4 Months	69.35 ± 8.18	69.91 ± 7.07	77.49 ± 6.47
6 Months	71.33 ± 9.48	71.07 ± 8.28	78.32 ± 5.84
8 Months	73.60 ± 11.28	75.22 ± 10.07	76.32 ± 6.50
10 Months	75.18 ± 13.06	75.01 ± 11.22	78.08 ± 6.72
12 Months	77.92 ± 14.98	78.10 ± 13.22	77.62 ± 7.05

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Overall p-value	<0.001*	<0.001*	0.08

Table 3 illustrates the longitudinal changes in spirometric parameters among participants undergoing pulmonary rehabilitation and smoking cessation over the 12-month follow-up period. At baseline, the mean post-bronchodilator FEV_1 was 65.04 ± 6.38% predicted, while the mean FVC was 63.47 ± 7.80% predicted, indicating reduced lung function consistent with preserved ratio impaired spirometry (PRISm). During follow-up, a progressive improvement in both FEV_1 and FVC values was observed. The mean FEV_1 increased to 67.08 ± 7.28% predicted at 2 months, 69.35 ± 8.18% at 4 months, and 71.33 ± 9.48% at 6 months, with further improvement to 73.60 ± 11.28% at 8 months, 75.18 ± 13.06% at 10 months, and 77.92 ± 14.98% predicted at 12 months. A similar upward trend was noted for FVC, which improved from 63.47 ± 7.80% predicted at baseline to 67.58 ± 9.08% at 2 months, 69.91 ± 7.07% at 4 months, 71.07 ± 8.28% at 6 months, 75.22 ± 10.07% at 8 months, 75.01 ± 11.22% at 10 months, and 78.10 ± 13.22% predicted at 12 months. In contrast, the FEV_1/FVC ratio remained relatively stable throughout the study period, ranging from 80.30 ± 4.98% at baseline to 77.62 ± 7.05% at 12 months, reflecting the preserved airflow ratio characteristic of PRISm. Overall, these findings indicate a gradual improvement in lung function parameters during the follow-up period among participants receiving pulmonary rehabilitation and smoking cessation.

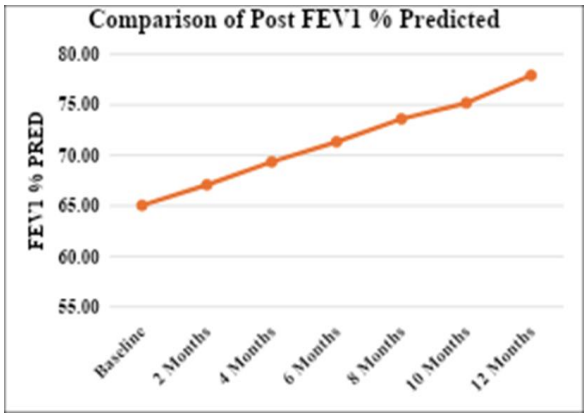

Figure 2: Comparison of Post FEV1% Predicted in participants receiving pulmonary rehabilitation and smoking cessation

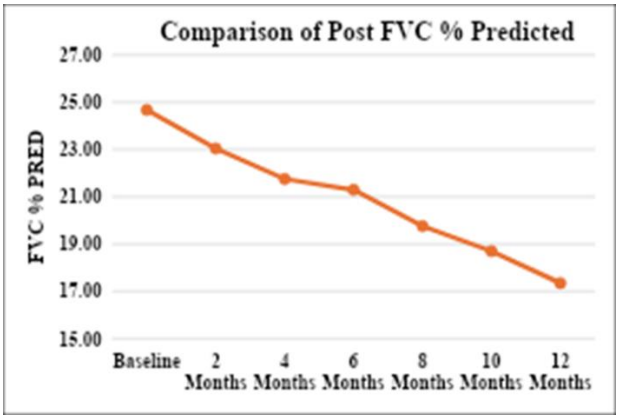

Figure 3: Comparison of Post FVC% Predicted in participants receiving pulmonary rehabilitation and smoking cessation

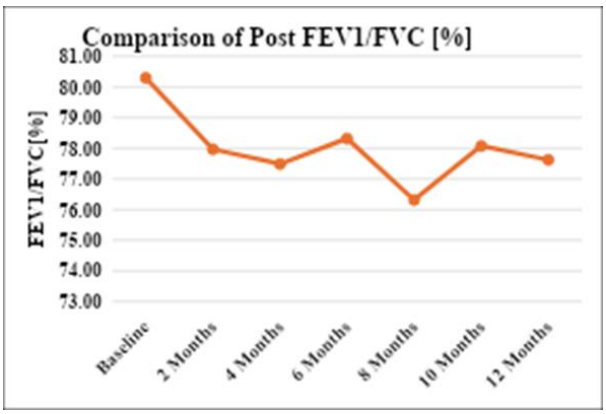

Figure 4: Comparison of Post FEV1/FVC [%] in participants receiving pulmonary rehabilitation and smoking cessation

Table 4: Pulmonary Function Test Outcome in Participants undergoing Pulmonary rehabilitation and Smoking cessation

PFT Outcome	Participants undergoing Pulmonary rehabilitation and Smoking cessation (n = 71)	p-value
Improvement in lung function	60 (84.51%)	<0.001*
Not improved	11 (15.49%)	<0.001*

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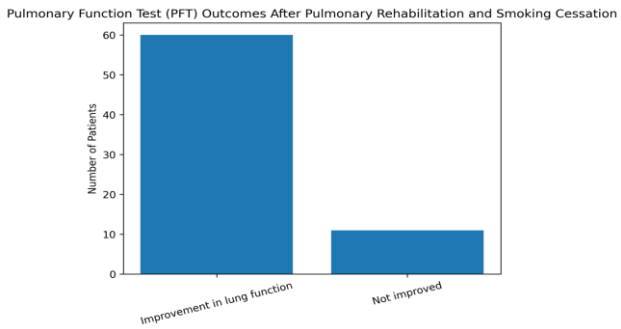
Table 3 summarises the pulmonary function test (PFT) outcomes among participants after the follow-up period. A substantial proportion of participants demonstrated improvement in lung function following pulmonary rehabilitation and smoking cessation. Specifically, 60 participants (84.51%) showed improvement in lung function**,** whereas 11 participants (15.49%) did not demonstrate measurable improvement in spirometric parameters. The observed improvement in pulmonary function was statistically significant ($p < 0.001$), indicating a strong association between the intervention and enhanced lung function outcomes. These findings suggest that pulmonary rehabilitation in addition to smoking cessation may contribute to meaningful improvements in respiratory function among individuals with preserved ratio impaired spirometry (PRISm).

Figure 5: Pulmonary function test (PFT) outcomes among participants undergoing pulmonary rehabilitation and smoking cessation



Pulmonary function test (PFT) outcomes among participants undergoing pulmonary rehabilitation and smoking cessation (n = 71). The majority of participants (84.51%) demonstrated improvement in lung function, whereas 15.49% did not show measurable improvement. The observed improvement was statistically significant ($p < 0.001$).

DISCUSSION

The present study demonstrates that pulmonary rehabilitation in addition to smoking cessation leads to significant improvements in respiratory symptoms, quality of life, and spirometric parameters among smokers with preserved ratio impaired spirometry. These findings highlight the potential importance of early lifestyle-based interventions in modifying the trajectory of smoking-related lung disease.

PRISm has increasingly been recognised as an intermediate phenotype within the continuum of smoking-related respiratory impairment. Although individuals with PRISm do not meet the spirometric definition of COPD, several studies have shown that they experience substantial respiratory morbidity and are at increased risk of developing airflow obstruction in the future[9]. The present findings reinforce the concept that PRISm represents a clinically meaningful phenotype rather than an incidental spirometric pattern.

Participants in the present cohort demonstrated moderate symptom burden at baseline as reflected by CAT, mMRC, and SGRQ scores. Following pulmonary rehabilitation and smoking cessation, significant improvements were observed across all symptom scores. These improvements are consistent with the known physiological benefits of pulmonary rehabilitation, which include enhanced skeletal muscle efficiency, improved ventilatory mechanics, and reduced perception of dyspnoea during physical activity.

Smoking cessation likely played a critical role in the improvement observed in lung function parameters. Chronic exposure to cigarette smoke induces airway inflammation and oxidative injury that accelerate decline in FEV_1. Removal of this exposure may allow partial recovery of airway function and stabilisation of lung mechanics. The increase in post-bronchodilator FEV_1% predicted and FVC% predicted suggests that early intervention may influence lung function trajectory in individuals with PRISm.

These findings support the hypothesis that PRISm may represent a potentially modifiable stage of smoking-related lung disease. Early identification through spirometric screening could therefore allow targeted intervention before the development of irreversible airflow obstruction. Integration of pulmonary rehabilitation programs into early disease management pathways may represent a promising strategy for preventing progression to COPD.

The study also highlights the importance of lifestyle-based interventions in respiratory medicine. Unlike pharmacological therapies, pulmonary rehabilitation and smoking cessation address the

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underlying behavioural and physiological factors contributing to disease progression. Implementing these interventions at an early stage may therefore yield substantial long-term benefits.

LIMITATIONS

Nevertheless, several limitations should be considered. The study was conducted at a single tertiary care centre and included a relatively modest sample size. Larger multicentre studies are required to confirm these findings and determine whether early intervention in PRISm can reduce long-term risk of COPD and other smoking-related respiratory diseases.

Despite these limitations, the present study provides important evidence supporting early intervention strategies in smokers with PRISm. The findings suggest that pulmonary rehabilitation combined with smoking cessation can lead to meaningful improvements in clinical outcomes and lung function in this high-risk population.

CONCLUSION

Pulmonary rehabilitation in addition to smoking cessation significantly improves respiratory symptoms, quality of life, and lung function among smokers with preserved ratio impaired spirometry. Early identification and intervention in this population may help modify disease trajectory and potentially prevent progression to chronic obstructive pulmonary disease.

REFERENCES

1. Wan ES, Hokanson JE, Regan EA, Young KA, Make BJ, DeMeo DL, Mason SE, Estepar RS, Crapo JD, Silverman EK. Significant spirometric transitions and preserved ratio impaired spirometry among ever smokers. Chest. 2022 Mar 1;161(3):651-61.
2. Wijnant SRA, de Roos E, Kavousi M, Stricker BH, Terzikhan N, Lahousse L, Brusselle GG. Trajectory and mortality of preserved ratio impaired spirometry: the Rotterdam Study. *Eur Respir J.* 2019;55(1):1901217.
3. Gao F, He S, Li J, Wang X, Chen X, Bu X. Association between preserved ratio impaired spirometry and 1-year clinical outcomes in patients with bronchiectasis: a cohort study. *Respir Investig.* 2024;63(1):163–169.
4. Backman H, Myrberg T, Hedman L, Stridsman C, Rönmark E, Lindberg A. PRISm is an important risk factor for development of COPD, also in non-smokers. CHEST. 2025 Mar 8.
5. Zheng J, Zhou R, Zhang Y, Su K, Chen H, Li FR, Hukportie DN, Niu F, Yiu K, Wu X. Preserved ratio impaired spirometry in relation to cardiovascular outcomes: A large prospective cohort study. *Chest.* 2022;162(5):1178–1188.
6. Wu J, Wang G, Gan J, Yang L, Zhang H, Xian J, Li Y, Li W. Nomogram to predict progression from preserved ratio impaired spirometry to chronic obstructive pulmonary disease. Scientific Reports. 2025 Mar 26;15(1):10447.
7. Agustí A, Hughes R, Rapsomaki E, Make B, del Olmo R, Papi A, et al. The many faces of COPD in real life: a longitudinal analysis of the NOVELTY cohort. *ERJ Open Res*. 2023;9(5):00895-2023. doi:10.1183/23120541.00895-2023
8. Choi H, Oak C, Jung M, Jang TW, Nam SJ, Yoon T. Trend of prevalence and characteristics of preserved ratio impaired spirometry (PRISm): Nationwide population-based survey between 2010 and 2019. *PLoS One.* 2024;19(4):e0307302.
9. Kim T, Choe J, Im Y, Heo J, Park HY, Kang D, Shin SH. Increased risk of lung cancer in individuals with preserved ratio impaired spirometry: a nationwide cohort study. Scientific Reports. 2025 Jul 1;15(1):1-9.