

Prevalence and risk factors for COPD in subjects with preserved ratio impaired spirometry

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ABSTRACT

Background Chronic obstructive pulmonary disease (COPD) has been found to be caused by impairment of lung development. Preserved ratio impaired spirometry (PRISm) is thought to be a subtype of lung growth impairment and is associated with COPD. PRISm is heterogeneous and the prevalence and progression to COPD are not yet clear. To prove this, we examined the association by using the medical check-up data.

Methods This retrospective study included medical check-up subjects who visited the Kochi Medical Check-up Clinic at least twice for both period 1 (P1) (2014–2016) for the first visit and period 2 (P2) (2017–2019) for the final visit. The mean duration between visits was 1042±323 days. COPD was defined as a forced expiratory volume in 1 s (FEV₁):forced vital capacity (FVC) ratio <lower limit of normal (LLN), and PRISm was defined as an FEV₁:FVC ratio >LLN and per cent forced expiratory volume in 1 s (%FEV₁) (FEV₁/predicted FEV₁) of <80% without bronchodilators in this study.

Results Of 1672 subjects (mean age±SD 56.5±9.5), 976 (58.4%) were male. The prevalence of PRISm was 10.5% in P1 and 8.9% in P2. The percentage of subjects who progressed to COPD was higher in PRISm than in the normal lung function group (OR 2.62, p=0.014). In logistic regression analysis, PRISm was an independent risk factor for developing COPD (OR 3.75, p<0.001). The best cut-off value of %FEV₁ for prediction of progression to COPD was 86%. The proportion of the PRISm group increased (23.6%) in this cut-off.

Conclusion The prevalence of PRISm was around 10% but increased up to 23.6% at the best cut-off for progression to COPD, and careful follow-up is necessary in these groups even if FEV₁/FVC is normal.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide.^{1–4} Death and increased medical costs due to many complications and exacerbations caused by COPD are also important problems.^{5–8}

COPD has been mainly accepted as a self-inflicted condition caused by tobacco smoking. Recently, it has been proposed that impaired lung growth leads to COPD even if there is no rapid lung function decline.^{9–11}

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Preserved ratio impaired spirometry (PRISm) is caused by a growth disturbance in the lungs and carries the risk of developing chronic obstructive pulmonary disease (COPD) in the future. PRISm is also known to have a poor prognosis and is a disease that deserves attention.

WHAT THIS STUDY ADDS

⇒ This study clarified the prevalence and risk of developing COPD in Japan. It also clarified the cut-off of % forced expiratory volume in 1 s (FEV₁) for progression to COPD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Until now, the definition of PRISm has been a normal FEV₁:FVC ratio and per cent forced expiratory volume in 1 s (%FEV₁) of <80%, but even more than that is at risk of becoming COPD. It should be recognised that a low %FVC and %FEV₁ should be followed carefully even if the FEV₁:FVC ratio is normal on medical check-up examination.

The preserved ratio impaired spirometry (PRISm) can be caused by a various factor such as childhood asthma, infections and obesity and has been proposed as the concept of low lung growth or early COPD. The PRISm is the condition of proportional decreases in forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC), which result in a normal FEV₁:FVC ratio. PRISm is a product of two binary variables, which increases the risk of error. Therefore, there is an opinion that PRISm is uncertain.¹² Recently, PRISm has been considered as a subtype that is prone to the development of COPD or acute exacerbation, and it has been reported that 32.6% progressed to COPD in 4–5 years of observational studies.^{13 14} PRISm is heterogeneous, and the prevalence, sex differences and mortality of PRISm are not clear, with reports varying by region and race. Therefore, we examined the prevalence of



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PRISm and risk of progression from PRISm to COPD in this study.

METHODS

Study design

A longitudinal retrospective study was conducted on 1679 health check-up subjects who visited our institution (Kochi Medical Check Clinic, Kochi, Japan) for medical check-ups at least twice between April 2014 and December 2019. First visit was during 2014–2016 defined as period 1 (P1) and final visit during 2017–2019 as period 2 (P2). Mean duration from first and final visits was 1042 ± 323 days.

Medical information was obtained through a questionnaire which included previous and current medical history, as well as habits such as smoking, alcohol consumption, diet and exercise.

Patient and public involvement

Patients and public were not involved in this study design and planning. They would be informed of our study plan including the recruitment criteria and timing via a notice on the website of clinic because this was retrospective study. When they offered not to participate, we removed them from participation.

Spirometry

Spirometry (FVC, FEV₁ and FEV₁:FVC ratio) was performed using a spirometer (Spiroshift SP-770 COPD; Fukuda Denshi, Tokyo, Japan) in accordance with the American Thoracic Society recommendations.¹⁵ Spirometry was performed without the use of bronchodilators. COPD was defined as an FEV₁:FVC ratio <lower limit of normal (LLN). PRISm was defined as an FEV₁/FVC ratio >LLN and per cent forced expiratory volume in 1 s (%FEV₁) (FEV₁/predicted FEV₁) of <80%. The predicted values of FVC and FEV₁ were calculated according to the recommendations of the Japanese Respiratory Society.¹⁶

Statistical analyses

The Quantitative data of characteristics were presented as mean±SD. Multiple linear regression analysis was performed to determine the factors that contributed to progression of COPD. The explanatory variables were age, gender, body mass index (BMI), smoking history and the presence of PRISm. The cut-off of %FEV₁ that progresses to COPD was examined by the receiver operating characteristic (ROC) curve. Missing values were excluded. A p value of <0.05 was considered significant. Statistical analyses were performed using open-source free software R (GNU General Public License).

RESULTS

Prevalence and characteristics of each group in P1

The prevalence of PRISm was 10.5% in P1 and 8.9% in P2, respectively.

The characteristics of subjects with PRISm, COPD and normal spirometry in P1 are shown in [table 1](#).

Table 1 Subject characteristics

	Period 1 (2014–2016)		
	Normal	PRISm	COPD
Subjects, n	1409	176	87
Age (years)*	56.1±9.5	60.1±9.2	56.3±9.2
Male sex (%)	805 (57.1%)	112 (63.6%)	59 (67.8%)
BMI (kg/m ²)*	23.6±3.4	23.9±4.6	22.7±2.9
Current smoker, n (%)	207 (14.7)	42 (23.9)	23 (26.4)
Former smoker, n (%)	386 (27.4)	53 (30.1)	31 (35.6)
Never-smoker, n (%)	816 (57.9)	81 (46.0)	33 (37.9)
FEV ₁ (litre)*	2.70±0.62	2.03±0.44	2.31±0.67
FVC (litre)*	3.32±0.78	2.61±0.60	3.41±0.94
FEV ₁ /FVC (%)*	81.4±5.0	78.4±5.6	67.6±3.6
%FEV ₁ (%)*	96.8±10.0	73.1±7.2	78.4±16.2
%FVC (%)*	95.0±10.3	74.0±8.4	92.2±16.8
Drinking habit			
Everyday	454 (32.2)	75 (42.6)	34 (39.1)
Sometime	594 (42.5)	47 (26.7)	34 (39.1)
Never	361 (25.6)	54 (30.7)	19 (21.8)

*Values are given as mean±SD or number (%).
BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PRISm, preserved ratio impaired spirometry.

The average age of the subjects was 56.5 ± 9.5 in P1. The number of men was 976 (58.3%). The smoking history was more in the order of COPD, PRISm and normal group. BMI of women tended to be lower than men. The proportion of non-smokers was significantly higher in women (588 subjects, 84.5%) than in men (342 subjects, 35%). The proportion of PRISm in P1 was 11.5% in men and 9.2% in women, with no significant sex-specific difference.

Transition from P1 to P2 of each group

Transition from P1 to P2 of each group is shown in [figure 1](#). In the normal lung function group in P1, 25 subjects (1.8%) progressed to COPD in P2, whereas in the PRISm group, 11 subjects (6.3%) progressed to COPD, in which incidence was significantly higher.

Logistic regression analysis on the risk of progressing to COPD

The risk of developing COPD in P2 from normal lung function group and PRISm in P1 was examined by logistic regression analysis ([table 2](#)).

The explanatory variables were age, sex, BMI, smoking history and presence of PRISm. It was found that low BMI and PRISm are independent risk factors that progress to COPD (OR 4.58, 95% CI 2.22 to 9.40, $p<0.001$). It analysed for sex-specific differences, PRISm was a risk factor for developing COPD in men ($p<0.05$) but not in women ($p=0.787$, date not shown).

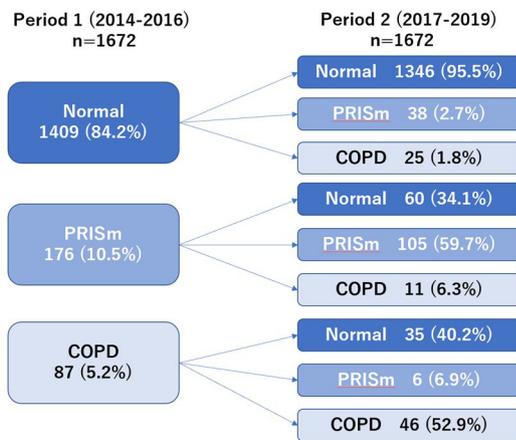


Figure 1 Transitions of lung function categories between period 1 and period 2. COPD, chronic obstructive pulmonary disease; PRISm, preserved ratio impaired spirometry.

Determination of the best %FEV₁ cut-off for prediction of progression to COPD

In previous reports, PRISm was defined as %FEV₁ less than 80%, and that definition was used in this study. However, the rationale for setting %FEV₁ to 80% in PRISm is not clear. The best cut-off of %FEV₁ for progression to COPD was investigated using ROC curve (figure 2). The sensitivity and specificity were best when %FEV₁ was 86% (area under the curve=0.706, 95% CI 0.617 to 0.794). If this is used, the proportion of the normal group, PRISm group or COPD group is in P1 and P2, as shown in figure 3. The proportion of the PRISm group increased (23.6%). Logistics regression analysis for the risk for progress from PRISm to COPD showed that low BMI, smoking history and PRISm were significant risk factors (model 2, table 2).

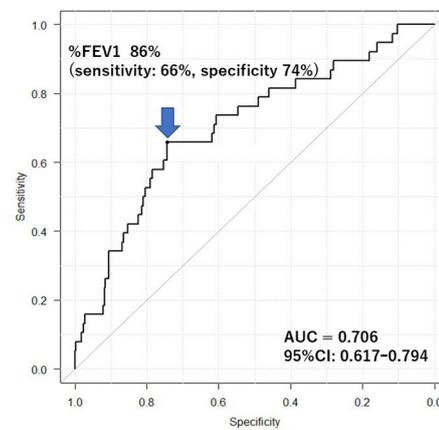


Figure 2 Receiver operating characteristic curve for progression from PRISm to COPD. The %FEV₁ cut-off for progression to COPD in subjects with a 1 s rate of 70% or greater (normal lung function group and PRISm). AUC, area under the curve; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; %FEV₁, per cent forced expiratory volume in 1 s PRISm, preserved ratio impaired spirometry.

DISCUSSION

This study demonstrated that the prevalence of PRISm in Japan is around 10%, and the PRISm is an independent risk factor for COPD progression. The most predictable cut-off value of %FEV₁ to develop to COPD was 86%. This finding may indicate that if %FEV₁ is <86%, there is a risk of COPD progression and careful follow-up is necessary.

The prevalence of PRISm was 12.4%–12.5% in the COPD gene study, 5.3%–7.0% in the Rotterdam study and 11.7% in the other study.^{13 14 17} The difference in prevalence of PRISm may be due to background differences such as age, BMI and smoking history, but it is around 10% in all studies, which is similar to our study. The COPD gene study and the study from Korea included smokers only. In the Rotterdam study, the average age

Table 2 Logistic regression analysis on the risk of progression to COPD

	Model 1			Model 2		
	OR	95 %CI	P value	OR	95% CI	P value
Female*	0.63	0.26 to 1.51	0.3	0.61	0.27 to 1.38	0.23
Age	0.98	0.95 to 1.02	0.28	0.99	0.95 to 1.02	0.47
BMI	0.88	0.79 to 0.98	0.024	0.88	0.79 to 0.98	0.015
Ever smoker †	1.69	0.76 to 3.76	0.19	2.48	1.16 to 5.34	0.019
PRISm	3.75	1.78 to 7.97	<0.001	4.07	2.06 to 8.07	<0.001

Model 1: PRISm defined as FEV₁:FVC >70%, %FEV₁ >80%.
 Model 2: PRISm defined as FEV₁:FVC >70%, %FEV₁ >86%.
 *Risk of women developing COPD for men.
 †Risk of current smoker and former smoker developing COPD for never-smoker.
 BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PRISm, preserved ratio impaired spirometry.

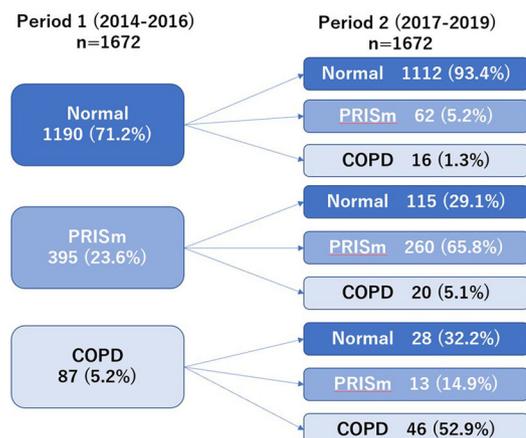


Figure 3 Transitions of lung function categories as the cut-off %FEV₁ is set to 86% between period 1 and period 2. COPD, chronic obstructive pulmonary disease; %FEV₁, per cent forced expiratory volume in 1 s PRISm, preserved ratio impaired spirometry.

of the subjects was around 70 years old, which was older than those in the other studies. BMI was higher in the Rotterdam and COPD gene studies than in our study. The value of FVC could be reduced by obesity.^{18–20} Although subjects with PRISm (low FVC) in Europe and the USA are influenced by obesity, those with PRISm in our study may suggest more likely to be due to lung growth impairments.

PRISm is considered as a subtype that is more likely to progress to COPD.^{13 14} In our study, the transition from PRISm to COPD was also significantly higher than in the normal lung function group, but the incidence was clearly lower than that in the Rotterdam or COPD gene studies. We believe that this is largely due to differences in patient background, such as smoking history, age and race. Patients with COPD in Europe and the USA tend to be obese and non-emphysematous, whereas emphysematous and lean type are more common in East Asia. In our study, multivariate analysis showed that low BMI is a risk for progression to COPD, which is still controversial.

There are several limitations in our study. There were subjects with COPD at P1 who transitioned to PRISm or normal lung function at P2. In this study, the history of asthma and the history of treatment by bronchodilators could not be obtained. Therefore, it is possible that some of the subjects improved with bronchodilators. Because of the variability of symptoms in patients with bronchial asthma, pulmonary function tests may improve without therapeutic intervention. Impaired lung growth such as PRISm can be caused by bronchial asthma in childhood.¹¹ However, it is difficult to completely exclude asthma in cohort studies. Second, it was performed by pulmonary function tests without bronchodilators in this study. The values of postbronchodilator spirometry are necessary to diagnose COPD. In this study, we recruited subjects who visited the clinic for medical check-up; thus, bronchodilators could not be used. Lastly, there may be survivor bias. This study retrospectively included those who were able to perform pulmonary function tests at both P1 and P2. Those who died were not included, and the annual decline in lung function may have been estimated to be lower than previously reported.

In conclusion, it was revealed that subjects with low %FEV₁ are a subtype that is more likely to progress to COPD, even if FEV₁:FVC is preserved. Subjects with low %FEV₁, even if FEV₁:FVC is maintained, need to be aware of the risk of progression to COPD.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the ethics committee of Kochi Medical School, Kochi University (number 31–82, 15 August 2019). Because of retrospective study, subject consent was based on opt-out. Those who refused to participate in the study by opt-out were excluded.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Not applicable.

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