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Preserved Ratio Impaired Spirometry (PRISm) and Serum Matrix Metalloproteinase-9 (MMP-9) Levels as Early Markers of Lung Obstruction in Active Smokers

Fajar Amri Ekahadikusuma[1], Sitti Nurisyah[1,3]*, Jamaluddin Madolangan[1], Muh. Ilyas[1,2], Irawaty Djaharuddin[1,2], Harry Akza Putrawan[1,2]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia
[2]Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia
3Dr. Tadjuddin Chalid Hospital, Makassar, Indonesia
Corresponding Author*: Sitti Nurisyah. Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. Dr. Tadjuddin Chalid Hospital, Makassar, Indonesia. Perintis Kemerdekaan Street, Km 10, Tamalanrea, Makassar, South Sulawesi, Indonesia. Email: ichanurisyah@unhas.ac.id.
ORCID ID: 0009-0004-5375-4954

ABSTRACT: PRISm is defined by reduced forced expiratory volume in one second (FEV1 <80% predicted) with a preserved FEV1/forced vital capacity (FVC) ratio (≥0.70). Recognized as early stage of chronic obstructive pulmonary disease (COPD) in smokers, it remains underdiagnosed. This study compared MMP-9 in Indonesian smokers with PRISm versus non-PRISm and its association with PRISm status. This cross-sectional study enrolled 88 asymptomatic smokers among hospital security personnel in Makassar, Indonesia. Participants underwent interviews, anthropometry, ATS/ERS-standard spirometry, and serum MMP-9 ELISA. They were classified as PRISm or non-PRISm. Groups were compared using Mann-Whitney U/chi-square tests; logistic regression adjusted for age, BMI, Brinkman Index; ROC assessed MMP-9 discrimination. PRISm was identified in 58 of 88 participants (65.9%). Versus the non-PRISm group, the PRISm group had lower FEV1, FVC, and FEF25–75% (all p<0.001), with no difference in FEV1/FVC (p=0.672). Median serum MMP-9 was higher in PRISm (259.50 [IQR 197.00–428.50] vs. 116.50 [IQR 48.75–192.25] ng/mL; p<0.001). ROC analysis showed discrimination (AUC 0.812; 95% CI 0.718–0.906); ≥158 ng/mL gave 77.6% sensitivity, 76.7% specificity, and independent association with PRISm after adjustment (adjusted OR 12.80; 95% CI 4.19–39.12; p<0.001). PRISm was common in active smokers and independently associated with elevated serum MMP-9, supporting a biomarker role in subclinical airway inflammation and remodeling. Serum MMP-9 may complement spirometry for early detection of lung impairment, pending external validation before clinical application.

1. INTRODUCTION

Active smokers are vulnerable to chronic airway disorders, including subtle lung function abnormalities that often escape early detection. One increasingly recognized pattern is Preserved Ratio Impaired Spirometry (PRISm), a phenotype defined by

reduced FEV1 (<80% predicted) with a preserved FEV1/FVC ratio (≥0.70). Because PRISm does not meet the classic spirometric definition of airflow obstruction, it is often overlooked in routine screening, although it reflects small-airway inflammation and remodeling preceding overt obstruction [1,2]. Reviews estimate PRISm affects 7–20% of adults worldwide and is associated with increased all-cause, cardiovascular, and respiratory mortality versus normal spirometry [3,4]. Longitudinal cohorts indicate PRISm is dynamic: many affected individuals progress to persistent airflow obstruction and overt COPD within several years, while others remain stable or revert to normal spirometry [5,6]. Imaging links PRISm to functional small-airway disease and air trapping, supporting early subclinical remodeling and the need for intervention in hospital security personnel [7–9].

Matrix metalloproteinase-9 (MMP-9), a zinc-dependent gelatinase produced by activated alveolar macrophages, neutrophils, and bronchial epithelial cells, degrades extracellular matrix components such as elastin and type IV collagen and is central to airway remodeling in smoking-related lung disease [10,11]. Cigarette smoke increases oxidative stress and pro-inflammatory signaling (including IL-1β, TNF-α, and IL-8), which upregulates MMP-9 expression and activity even before airflow obstruction develops [12–14]. Elevated MMP-9 has been reported in active smokers and in patients across the COPD severity spectrum, and an imbalance between MMP-9 and its tissue inhibitor (TIMP-1) has been linked to progressive matrix degradation and disease severity [15,16]. However, evidence is not fully consistent: some reviews note that MMP-9 expression varies across lung compartments and does not always track with structural progression, underscoring the need for context-specific data linking MMP-9 to defined functional phenotypes such as PRISm [3,17].

Despite growing international interest in PRISm as a pre-COPD phenotype, the relationship between PRISm and MMP-9 has rarely been examined in Southeast Asian populations, and local data from Indonesian active smokers, particularly occupational groups with sustained tobacco exposure, are lacking [18,19]. This study was therefore designed to compare serum MMP-9 levels between active smokers with PRISm and non-PRISm spirometric patterns and to evaluate the independent association between serum MMP-9 and PRISm status, with the aim of supporting earlier identification and prevention of progressive lung function impairment in this at-risk population.

2. MATERIALS AND METHODS

2.1 Study design and setting

This study was an observational, analytical, cross-sectional comparison conducted at Dr. Wahidin Sudirohusodo General Hospital and its affiliated hospitals in Makassar, Indonesia, until the target sample size was reached.

2.2 Population and sample

The target population consisted of asymptomatic active smokers of working age employed as hospital security personnel. The accessible population included asymptomatic active smokers with moderate-to-heavy cumulative tobacco exposure, as measured by the Brinkman Index, at the study sites. Participants were recruited through consecutive sampling: eligible individuals underwent a structured interview, provided written informed consent, and were enrolled sequentially until the target sample size was achieved.

The sample size was determined for the comparison of two independent means (serum MMP-9 levels between PRISm and non-PRISm groups), with $\alpha = 0.05$ (two-tailed), a power of 80%, an assumed standard deviation of 80 ng/mL based on previous studies of MMP-9 in smokers, and a minimum clinically meaningful between-group difference of 60 ng/mL. This calculation resulted in a minimum requirement of 28 participants per group; after accounting for an anticipated 20% dropout rate and rounding, 35 participants per group (70 in total) were planned. During the study period, 88 participants met the inclusion and exclusion criteria and had complete data; all were retained for analysis to enhance statistical power.

2.3 Inclusion and Exclusion criteria

Individuals eligible for inclusion were active smokers over the age of 18, employed as security personnel at hospitals in Makassar, who were asymptomatic, meaning they exhibited no significant respiratory complaints such as chronic cough, dyspnea, or wheezing. Additionally, they were required to be willing to undergo spirometry and serum MMP-9 testing and to provide written informed consent.

Exclusion criteria included the presence of active respiratory symptoms, such as chronic cough, dyspnea, or wheezing; a history of chronic, autoimmune, or malignant diseases; use of systemic corticosteroids within the preceding four weeks; inability to perform acceptable spirometric maneuvers according to ATS/ERS criteria; or unwillingness to participate in the study.

2.4 Variables and measurements

The dependent variable was the PRISm status, determined through spirometry. The independent variable was the serum MMP-9 concentration, assessed via ELISA. Potential confounders included smoking intensity, quantified by the Brinkman Index, age, sex, and BMI. Data regarding demographic characteristics, smoking history, and clinical findings were gathered using a structured case report form. Body weight and height were measured using a calibrated digital scale and stadiometer to compute BMI (kg/m²). The Brinkman Index was calculated by multiplying the number of cigarettes smoked per day by the years of smoking, categorized as light (<200), moderate (200–599), or heavy (≥600).

Spirometry was conducted in accordance with ATS/ERS technical standards, with results expressed as FEV1, FVC, FEV1/FVC ratio, and FEF25–75%, referenced against Global Lung Initiative (GLI) predicted values. Participants were classified as PRISm if FEV1 was less than 80% of the predicted value with an FEV1/FVC ratio of ≥0.70, or as non-PRISm if FEV1 was ≥80% of the predicted value with an FEV1/FVC ratio of ≥0.70. Venous blood samples (3–5 mL) were collected, processed into serum, anonymized, and analyzed for MMP-9 concentration using ELISA, with results reported in ng/mL.

2.5 Statistical Analysis

Data processing, which included editing, coding, double entry, and cleaning, was conducted, followed by analysis using SPSS. The normality of continuous variables was assessed via the Shapiro-Wilk test. Data that were normally distributed were presented as mean ± standard deviation and compared using the independent t-test. In contrast, non-normally distributed data were summarized as median with interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical variables were described using frequencies and percentages and analyzed with the chi-square test. To assess the independent association between serum MMP-9 and PRISm status, multivariable logistic regression was employed, adjusting for age, BMI, and Brinkman Index. Variables with a p-value less than 0.25 in bivariate analysis were considered for inclusion in the model. The discriminative performance, optimal cut-off, sensitivity, and specificity of serum MMP-9 for PRISm were evaluated using ROC curve analysis. A p-value of less than 0.05 was deemed statistically significant throughout the study.

3. RESULTS AND DISCUSSION

3.1 Participant characteristics

A cohort of 88 active smokers, all male and employed as hospital security personnel, was enrolled in the study. The participants had a mean age of 30.3 ± 6.2 years, with ages ranging from 20 to 54 years. The majority (86.4%) had completed senior high school education. The mean Body Mass Index (BMI) was recorded at 24.35 ± 3.57 kg/m², with 45.5% of participants classified as having obesity class I and 34.1% as having normal weight; none had a diagnosed comorbidity. In terms of smoking exposure, white (filtered) cigarettes were predominantly used by 60.2% of the participants. The mean age at smoking initiation was 15.5 ± 2.0 years, with a mean smoking duration of 14.8 ± 6.2 years. The mean Brinkman Index was 176.0 ± 89.7, indicating that 68.2% of participants had light exposure and 31.8% had moderate exposure, with no participants experiencing heavy exposure (Table 1). PRISm distribution. Of the 88 active smokers included in the study, 58 (65.9%) met the spirometric criteria for preserved ratio impaired spirometry (PRISm), whereas 30 (34.1%) were classified as non-PRISm.

3.2 Spirometric parameters

In the PRISm group, the FEV1, FVC, and FEF25–75% (% predicted) were significantly lower compared to the non-PRISm group, with all p-values being less than 0.001. However, the FEV1/FVC ratio did not show a significant difference between the two groups (p=0.672) (refer to Table 2). Additionally, smoking exposure, as measured by the Brinkman Index category, was comparable between the PRISm and non-PRISm groups (p=0.323).

Serum MMP-9 levels were assessed, revealing a median concentration of 259.50 ng/mL (interquartile range [IQR] 197.00–428.50; range 104.00–444.00) in the PRISm group. In contrast, the non-PRISm group exhibited a median level of 116.50 ng/mL (IQR 48.75–192.25; range 20.00–444.00). This difference was statistically significant (p<0.001) as shown in Table 3.

Table 1. Demographic, clinical, and smoking-exposure characteristics of participants (n = 88)

Variable	Result
Age, years, mean ± SD (range)	30.3 ± 6.2 (20–54)
Male sex, n (%)	88 (100%)
Education: elementary / junior high / senior high, n (%)	8 (9.1%) / 4 (4.5%) / 76 (86.4%)
Occupation: security personnel, n (%)	88 (100%)
Duration of employment, years	6.6 ± 3.4 (0.7–15.0)
Body weight, kg	67.4 ± 10.7 (48–101)
Height, cm	166.3 ± 4.4 (155–176)
BMI, kg/m²	24.35 ± 3.57 (18.29–34.20)
BMI category: underweight / normal / overweight / obesity I / obesity II, n (%)	2 (2.3%) / 30 (34.1%) / 13 (14.8%) / 40 (45.5%) / 3 (3.4%)
Comorbidity: none, n (%)	88 (100%)
Cigarette type: white / kretek (clove) / mixed, n (%)	53 (60.2%) / 33 (37.5%) / 2 (2.3%)
Age at smoking initiation, years	15.5 ± 2.0 (12–21)
Smoking duration, years	14.8 ± 6.2 (3–39)
Cigarettes per day	12.3 ± 4.6 (6–24)
Brinkman Index	176.0 ± 89.7 (40–504)
Brinkman Index category: light (<200) / moderate (200–599) / heavy (≥600), n (%)	60 (68.2%) / 28 (31.8%) / 0 (0%)

Table 2. Spirometric parameters (% predicted) by PRISm status

Parameter	PRISm, median (IQR)	Non-PRISm, median (IQR)	P value
FEV1	70.0 (65.0–75.0)	86.0 (82.0–92.0)	<0.001
FVC	69.0 (64.0–74.0)	83.0 (78.0–88.0)	<0.001
FEV1/FVC	0.90 (0.86–0.94)	0.91 (0.88–0.93)	0.672
FEF25–75%	66.0 (58.0–77.0)	85.0 (79.0–93.0)	<0.001

Mann-Whitney U test.

Table 3. Serum MMP-9 levels by PRISm status

Group	n	Median (IQR), ng/mL	P value
PRISm	58	259.50 (197.00–428.50)	<0.001
Non-PRISm	30	116.50 (48.75–192.25)	

Mann-Whitney U test.

3.3 Discriminative performance of serum MMP-9

The ROC analysis indicated that serum MMP-9 effectively distinguished PRISm from non-PRISm, achieving an AUC of 0.812 (95% CI 0.718–0.906; p<0.001). The optimal threshold was determined to be ≥158 ng/mL, which resulted in a sensitivity of 77.6%, a specificity of 76.7%, and a Youden Index of 0.543 (Table 4).

3.4 Multivariable analysis

Following adjustments for age, BMI, and the Brinkman Index, a serum MMP-9 level of ≥158 ng/mL was independently associated with PRISm status, with an adjusted odds ratio of 12.80 (95% CI 4.19–39.12; p<0.001). In the adjusted model, age, BMI, and the Brinkman Index did not demonstrate independent associations with PRISm (refer to Table 5).

Table 4. ROC analysis of serum MMP-9 for discriminating PRISm status

Parameter	Result
AUC	0.812
95% CI	0.718–0.906
Optimal cut-off	≥158 ng/mL
Sensitivity	77.6%
Specificity	76.7%
Youden Index	0.543
P value	<0.001

Table 5. Multivariable logistic regression for PRISm status

Variable	Adjusted OR	95% CI	P Value
Serum MMP-9 ≥158 ng/mL	12.80	4.19–39.12	<0.001
Age, years	1.01	0.90–1.13	0.906
BMI, kg/m²	0.87	0.75–1.01	0.074
Brinkman Index	1.00	0.99–1.01	0.636

3.5 Discussion

This study demonstrated a high prevalence of PRISm (65.9%) among asymptomatic active smokers, substantially exceeding the 7–20% prevalence reported in population-based studies. This discrepancy is likely attributable to the homogeneous high-risk characteristics of the study population, comprising exclusively male smokers with prolonged tobacco exposure and a high prevalence of overweight and obesity, both recognized risk factors for impaired lung function. These findings are consistent with those reported by Kim et al. (2022) and Choi et al. (2024), who identified smoking exposure and metabolic factors as important determinants of PRISm, while Robertson et al. (2025) emphasized that its prevalence varies considerably according to population characteristics and risk profiles [4,6,19].

The observed reductions in FEV1, FVC, and FEF25–75%, despite preservation of the FEV1/FVC ratio, reflect the characteristic physiological pattern of PRISm and support the presence of early small-airway dysfunction before the development of overt airflow obstruction. These findings are in line with Zhao et al. (2022), who demonstrated that PRISm is associated with small-airway dysfunction and reduced lung capacity, and with Lu et al. (2022) and Verleden et al. (2024), who linked this spirometric phenotype to airway remodeling and structural abnormalities detected by quantitative imaging [2,8,9].

The principal finding of this study was the significantly higher serum MMP-9 concentration in participants with PRISm, which remained independently associated with the phenotype after adjustment for age, BMI, and smoking burden. This observation is biologically plausible because cigarette smoke induces inflammatory cell activation and extracellular matrix degradation through increased MMP-9 expression, thereby promoting airway remodeling. These findings are consistent with previous studies demonstrating elevated MMP-9 in smoking-related lung disease and COPD severity [15,16], and extend existing evidence by suggesting that MMP-9 elevation occurs before spirometric airflow obstruction becomes evident. Similarly, Christopoulou et al. (2023) and Lindberg et al. (2025) reported that inflammatory biomarkers are already increased during the pre-obstructive stages of chronic lung disease [17,20].

The ROC analysis further demonstrated good discriminative performance, with an AUC of 0.812 and an optimal cut-off of ≥158 ng/mL. Although external validation is required before clinical implementation, these findings suggest that serum MMP-9 may complement spirometry for identifying individuals with subclinical lung impairment, particularly in high-risk smoking populations. This supports recent evidence highlighting the growing role of circulating biomarkers in improving early detection and risk stratification of pre-COPD [21,22].

Several limitations should be acknowledged. The cross-sectional design precludes causal inference, the study population was limited to male hospital security personnel from a single center, and PRISm classification relied solely on spirometry without confirmatory physiological or imaging assessments. In addition, serum MMP-9 was measured only once, and the proposed cut-off was internally derived, requiring external validation before routine clinical use [23]. Despite these limitations, this study provides one of the first clinical evaluations of the association between serum MMP-9 and PRISm in an Indonesian smoking population, supporting its potential utility as an early biomarker of smoking-related airway remodeling.

4. CONCLUSION

In individuals who actively smoke and are employed in environments with high exposure, PRISm was prevalent and showed an independent association with increased serum MMP-9 levels, even after controlling for age, BMI, and smoking intensity. Serum MMP-9 exhibited strong discriminative ability for PRISm and could potentially act as an adjunctive biomarker alongside spirometry for the early detection of active smokers at risk of subclinical lung function impairment within the pre-COPD spectrum. However, longitudinal studies that include external validation of the suggested cut-off, involve larger and more diverse populations, and employ multimodal assessments (such as imaging and additional biomarkers like TIMP-1 or the MMP-9/TIMP-1 ratio) are necessary before serum MMP-9 can be recommended for routine clinical application.

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AUTHOR CONTRIBUTIONS

F.A.E.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. S.N.: Methodology, Supervision, Validation, Writing – review & editing. J.M.: Methodology, Supervision, Validation, Writing – review & editing. M.I.: Investigation, Data curation, Validation, Writing – review & editing. I.D.: Validation, Visualization, Writing – review & editing. H.A.P.: Validation, Project administration, Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The Health Research Ethics Committee of the Faculty of Medicine at Universitas Hasanuddin granted approval for this study (approval No. 536/UN4.6.4.5.31/PP36/2026). Prior to the collection of data and samples, all participants were thoroughly informed about the study's objectives and procedures, and they provided written informed consent.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are not publicly available because they contain confidential patient information. De-identified data may be made available from the corresponding author upon reasonable request and with permission from the participating institutions and ethics committee.

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