

# The Prognostic Performance of Lung Diffusing Capacity in Preserved Ratio Impaired Spirometry: An Observational Cohort Study

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**Purpose:** Similar to chronic obstructive pulmonary disease (COPD), the diffusing capacity of the lung ( $D_{LCO}$ ) might be decreased and associated with poor prognosis in preserved ratio impaired spirometry (PRISm), a clinical entity as a prodromal phase of COPD. The aims of the present study were to evaluate the distributions of  $D_{LCO}$  and to assess the association between  $D_{LCO}$  and mortality among subjects with PRISm.

**Patients and Methods:** We conducted an observational cohort study at the National Hospital Organization Fukuoka National Hospital. We classified the 899 patients  $\geq 40$  years of age with an assessment of  $D_{LCO}$  into five groups based on spirometry: preserved spirometry, PRISm, mild COPD, moderate COPD, and severe/very severe COPD. The prevalence of low  $D_{LCO}$  ( $< 80\%$  per predicted) was compared among the five groups. Using PRISm patients with follow-up data, we further investigated the association of low  $D_{LCO}$  with all-cause mortality.

**Results:** The prevalence of low  $D_{LCO}$  in the PRISm group (58.8%) was significantly higher than that in the preserved-spirometry group (21.8%), the mild-COPD group (23.5%), and the moderate-COPD group (36.0%) (all  $P < 0.01$ ), and it was comparable to that in the severe/very severe-COPD group (63.2%). The results remained unchanged after adjusting for potential confounders. Among the PRISm subjects, the overall survival rate was significantly lower in the low- $D_{LCO}$  group than in the preserved- $D_{LCO}$  group ( $P < 0.01$ ). The multivariable-adjusted hazard ratio (HR) for all-cause mortality was significantly higher in the low- $D_{LCO}$  group than in the preserved- $D_{LCO}$  group (HR = 10.10 (95% confidence interval 2.33–43.89)).

**Conclusion:** Diffusing capacity was more impaired in PRISm subjects than in those with preserved spirometry or mild to moderate COPD. Regarding PRISm, low  $D_{LCO}$  was a significant risk factor for all-cause mortality. Clinicians should assess  $D_{LCO}$  in the management of PRISm to predict the future risk of overall death.

**Keywords:** preserved ratio impaired spirometry, chronic obstructive pulmonary disease, diffusing capacity of the lungs, all-cause mortality

## Introduction

Preserved ratio impaired spirometry (PRISm), also referred to as restrictive pattern or unclassified spirometry, is a clinical entity associated with an increased risk of developing chronic obstructive pulmonary disease (COPD).<sup>1,2</sup> Epidemiological studies worldwide revealed that 3.7–22.3% of the general population were compatible with PRISm,<sup>3–11</sup> indicating that PRISm is a common disease condition. Considering its high prevalence and clinical aspects as a prodromal phase of COPD, PRISm, whose pathophysiology is still largely unknown, is an increasing threat to public health. Since the diffusing capacity of the lung for carbon monoxide ( $D_{LCO}$ ), a useful biomarker for evaluating the gas transfer properties of the respiratory system,<sup>12</sup> is generally deficient in COPD,<sup>13</sup> it might be also impaired in cases of PRISm. However, this issue has not yet been investigated.

PRISm has been demonstrated to be associated with an increased risk of premature mortality,<sup>2,3,11,14</sup> although little is known about the predictive biomarkers for death in PRISm. Since a deficit in  $D_{LCO}$  is a strong risk factor for a poor prognosis in COPD,<sup>15</sup>  $D_{LCO}$  may also be inversely associated with morbidity and mortality in PRISm. However, there has been no study assessing the influence of  $D_{LCO}$  on mortality in subjects with PRISm; therefore, the verification of this hypothesis could be of great benefit for improving the clinical management for such patients.

Based on these considerations, we conducted the present study to evaluate the prevalence of reduced  $D_{LCO}$  in subjects with PRISm and to compare it with that in cases of normal spirometry or COPD. We also assessed the clinical implication of  $D_{LCO}$  impairment as a biomarker for all-cause mortality among subjects with PRISm.

## Materials and Methods

### Study Population

The current study was conducted as an observational cohort study through a review of medical records at the National Hospital Organization Fukuoka National Hospital. The entire cohort consisted of 899 patients  $\geq 40$  years of age who had a  $D_{LCO}$  assessment from June 1, 2017, to May 31, 2020, regardless of department, with complete information on all relevant covariates. We classified the subjects into five groups based on the results of spirometry: preserved spirometry, PRISm, mild COPD, moderate COPD, and severe/very severe COPD. PRISm was defined as the coexistence of two major criteria: (i) post-bronchodilator forced expiratory volume in 1 second to forced vital capacity (post-BD FEV<sub>1</sub>/FVC)  $\geq 70\%$ ; and (ii) reduction in FEV<sub>1</sub>, that is, post-BD FEV<sub>1</sub> per predicted (FEV<sub>1</sub>% pred)  $< 80\%$ .<sup>3</sup> According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria,<sup>16</sup> the severity of COPD was defined as follows: mild, FEV<sub>1</sub>% pred  $\geq 80\%$ ; moderate,  $50\% \leq$  FEV<sub>1</sub>% pred  $< 80\%$ ; severe and very severe, FEV<sub>1</sub>% pred  $< 50\%$ .

The distribution of  $D_{LCO}$  per predicted ( $D_{LCO}$  % pred) and the prevalence of low  $D_{LCO}$  by lung function category were evaluated as a cross-sectional analysis using the total cohort. With regard to PRISm, we further investigated the association of low  $D_{LCO}$  with all-cause mortality using 111 patients (the PRISm cohort), excluding 8 patients with no follow-up data. For each case in the PRISm cohort, mortality data were collected from June 1, 2017, to December 31, 2021.

### Assessment of the Diffusing Capacity and Transfer Coefficient of the Lungs

$D_{LCO}$  and  $D_{LCO}$  per alveolar volume ( $D_{LCO}/V_A$ ) were measured via the single-breath method using a CHESTAC-8900 spirometer (Chest MI, Inc., Tokyo, Japan) in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.<sup>17</sup>  $D_{LCO}$  % pred and  $D_{LCO}/V_A$  % pred were calculated using the predicted values of  $D_{LCO}$  and  $D_{LCO}/V_A$  for a person of the same age, gender, and body surface area.<sup>18</sup> In accordance with the clinical review article,<sup>13</sup> low  $D_{LCO}$  was defined as  $D_{LCO}$  % pred  $< 80\%$ . In the same manner, low  $D_{LCO}/V_A$  was defined as  $D_{LCO}/V_A$  % pred  $< 80\%$ . When dividing the PRISm cohort into three groups based on the tertile distribution of  $D_{LCO}$  % pred, the cut-off values were as follows: lowest,  $< 64.0\%$ ; middle,  $64.0\text{--}85.4\%$ ; and highest,  $\geq 85.5\%$  for  $D_{LCO}$  % pred.

### Clinical Evaluations

For each case, respiratory physicians reviewed the patient's medical records and assessed the demographic and clinical characteristics: age, gender, height, weight, smoking exposure, and spirometry. Body mass index (BMI;  $\text{kg}/\text{m}^2$ ) was calculated as weight divided by height squared. Taking into consideration the guidelines for diagnosing obesity in Japanese subjects,<sup>19</sup> obesity, normal weight, and underweight were defined as BMI  $\geq 25.0$   $\text{kg}/\text{m}^2$ ,  $18.5$  to  $< 25.0$   $\text{kg}/\text{m}^2$ , and  $> 18.5$   $\text{kg}/\text{m}^2$ , respectively. Spirometry was performed before and 15 minutes after BD administration (ie, 200  $\mu\text{g}$  of salbutamol), in line with the guidelines of the Japanese Respiratory Society,<sup>20</sup> using CHESTAC-8900. Bronchial reversibility was defined as  $\geq 12\%$  and  $\geq 200$  mL reversibility in post-BD FEV<sub>1</sub>. The predicted values of FEV<sub>1</sub> and slow vital capacity (SVC) for a person of the same age, gender, and height were estimated with the equation for the Japanese population.<sup>21</sup>

### Statistical Analysis

R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) was used to perform all statistical analyses. Two-sided  $P < 0.05$  was considered to indicate statistical significance. For baseline characteristics, the

heterogeneity in each variable among the lung function categories was evaluated using the analysis of variance (ANOVA), chi-square test, or Kruskal–Wallis test. Tukey’s test, logistic regression analysis, or the Mann–Whitney *U*-test with Bonferroni correction was used to assess the statistical difference between the PRISm group and any of the other groups. The heterogeneity in the distribution of  $D_{LCO}$  % pred and  $D_{LCO}/V_A$  % pred across the lung-function categories was also analyzed using an ANOVA. Stratified analysis was performed according to BMI levels or smoking status. The prevalences of low  $D_{LCO}$  and low  $D_{LCO}/V_A$  were calculated for each lung-function group and compared using unadjusted and multivariable-adjusted logistic regression models and estimated as odds ratios (ORs) with 95% confidence intervals (95% CIs). Adjustments were made for age, gender, BMI, and smoking exposure. We performed a sensitivity analysis after excluding subjects with bronchial reversibility in order to exclude asthmatic patients. Kaplan–Meier curves were constructed to show the overall survival by the levels of  $D_{LCO}$  % pred and  $D_{LCO}/V_A$  % pred. Log rank testing was performed to study the influence of low  $D_{LCO}$  and low  $D_{LCO}/V_A$  on all-cause mortality. The trend in overall survival according to the tertile groups of  $D_{LCO}$  % pred was assessed with a Cox proportional hazards model. The multivariable-adjusted hazard ratios (HRs) with their 95% CIs of each level of  $D_{LCO}$  % pred or  $D_{LCO}/V_A$  % pred for all-cause death were estimated using a Cox proportional hazards model adjusted for all aforementioned potential confounders. The same model was used to assess the linear trends in the risk of all-cause death across the tertile groups of  $D_{LCO}$  % pred.

## Ethical Considerations

The study was approved by the National Hospital Organization Fukuoka National Hospital Institutional Review Board for Clinical Research (#F4-2). The study was conducted in accordance with the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study. All the data was anonymized for covering the patient data confidentiality and participant privacy.

## Results

### Level of $D_{LCO}$ % Pred and Prevalence of Low $D_{LCO}$ for Each Lung-Function Group

The prevalence of PRISm was 13.2% among the entire cohort. [Table 1](#) lists the demographic and clinical characteristics of the total cohort. Among the five lung function groups, the prevalence of male gender, the mean age, the mean BMI, and the amount of smoking exposure were not prominent in the PRISm group. Meanwhile, the mean values of absolute SVC and SVC % pred were lowest in the PRISm group.

[Figure 1](#) shows the level of  $D_{LCO}$  % pred for each lung-function group. The mean values of  $D_{LCO}$  % pred were 98.4%, 73.9%, 99.3%, 89.4%, and 71.0% in the preserved-spirometry group, the PRISm group, the mild-COPD group, the moderate-COPD group, and the severe/very severe-COPD group, respectively. In the PRISm group,  $D_{LCO}$  % pred was significantly lower than in the other lung function groups except for in the severe/very severe-COPD group. Likewise, the prevalence of low  $D_{LCO}$  was significantly higher in subjects with PRISm than in those with preserved spirometry, mild COPD, or moderate COPD (all  $P < 0.01$ ); it was as high as about 60% in the PRISm group and the severe/very severe-COPD group ([Figure 2](#)). The results were substantially similar after adjustments for potential confounders; there was a significant increase in OR in the PRISm group as compared to the preserved-spirometry group, the mild-COPD group, and the moderate-COPD group (all  $P < 0.01$ ) ([Table 2](#)). Broadly similar results were obtained in the analysis stratified by BMI levels ([Supplementary Figures S1](#) and [S2](#)) or smoking status ([Supplementary Figures S3](#) and [S4](#)). The results were not substantially changed after excluding asthmatic subjects ([Supplementary Figures S5](#) and [S6](#)). Further, there was no significant decrease in the level of  $D_{LCO}/V_A$  % pred or increase in the prevalence of low  $D_{LCO}/V_A$  in the PRISm group compared to the group with preserved spirometry, mild COPD, or moderate COPD (all  $P > 0.05$ ) ([Supplementary Figures S7](#) and [S8](#)).

### $D_{LCO}$ % Pred and Risk of All-Cause Mortality in PRISm

In the PRISm cohort, all-cause death occurred in 27 of 111 individuals (24.3%) with a median follow-up of 899 days (interquartile range 335–1378). As shown in [Figure 3A](#), the overall survival rate was significantly lower in the low- $D_{LCO}$

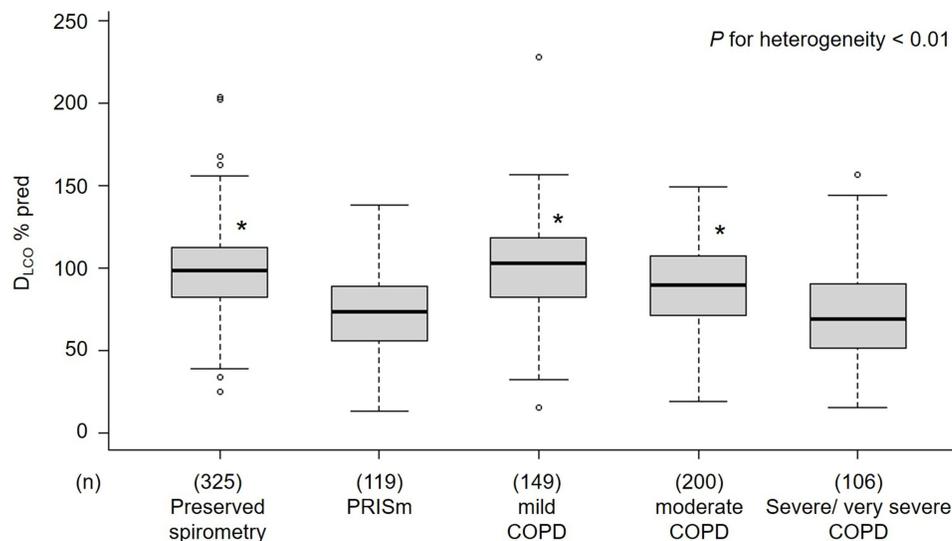
**Table 1** Demographic and Clinical Characteristics of Study Subjects by Lung Function Category

Variables	Preserved Spirometry (n = 325)	PRISm (n = 119)	Mild COPD (n = 149)	Moderate COPD (n = 200)	Severe/Very Severe COPD (n = 106)	P for Heterogeneity
Male gender (%)	53.2	59.7	77.2 <sup>†</sup>	70.5*	83 <sup>†</sup>	< 0.01
Age (years)	67 (12)	68 (10)	70 (9)	70 (10)	72 (9)*	< 0.01
Height (cm)	161 (9)	161 (9)	163 (7)	162 (9)	161 (9)	0.07
Weight (kg)	60.4 (12.1)	59.4 (17.3)	61.4 (10.3)	61.6 (10.7)	55.8 (11.7)	< 0.01
BMI (kg/m <sup>2</sup> )	23.3 (3.9)	22.8 (5.6)	23.0 (3.2)	23.4 (3.5)	21.4 (3.4)	< 0.01
Obesity (%)	30.5	24.4	20.8	28.0	16.0	0.02
Smokers (%)	58.2	63.9	78.5 <sup>†</sup>	77.5 <sup>†</sup>	89.6 <sup>†</sup>	< 0.01
Smoking history (pack/year)	10 (0–32)	24 (0–44)	35 (8–49)	38 (10–57)*	41 (25–61) <sup>†</sup>	< 0.01
FEV <sub>1</sub> (l)	2.44 (0.64)*	1.64 (0.45)	2.36 (0.49) <sup>†</sup>	1.66 (0.41) <sup>†</sup>	0.95 (0.31) <sup>†</sup>	< 0.01
FEV <sub>1</sub> per predicted (%)	98.3 (12.3) <sup>†</sup>	66.4 (11.9)	91.7 (8.6) <sup>†</sup>	65.8 (8.2)	37.9 (8.9) <sup>†</sup>	< 0.01
FEV <sub>1</sub> /FVC (%)	79.6 (6.3)*	82.0 (9.2)	63.9 (4.6) <sup>†</sup>	56.9 (8.5) <sup>†</sup>	37.5 (10.6) <sup>†</sup>	< 0.01
Bronchial reversibility (%)	3.7	5.0	10.7	10.5	4.7	< 0.01
SVC (l)	3.05 (0.82) <sup>†</sup>	2.01 (0.63)	3.62 (0.76) <sup>†</sup>	2.86 (0.77) <sup>†</sup>	2.42 (0.71) <sup>†</sup>	< 0.01
SVC per predicted (%)	92.4 (13.8) <sup>†</sup>	60.9 (14.4)	103.9 (11.2) <sup>†</sup>	84.1 (13.8) <sup>†</sup>	71.3 (15.3) <sup>†</sup>	< 0.01

**Notes:** \* $P < 0.05$  versus the PRISm group. <sup>†</sup> $P < 0.01$  versus the PRISm group. Age, height, weight, BMI, FEV<sub>1</sub>, FEV<sub>1</sub> per predicted, FEV<sub>1</sub>/FVC, SVC, and SVC per predicted are given as the mean with standard deviations. Smoking history is shown as the median with an interquartile range because of the skewed distributions. Other variables are given as percentages. Obesity was defined as BMI  $\geq 25.0$  kg/m<sup>2</sup>. Smokers were defined as past or current smokers. Bronchial reversibility was defined as  $\geq 12\%$  and  $\geq 200$  mL reversibility in post-BD FEV<sub>1</sub>.

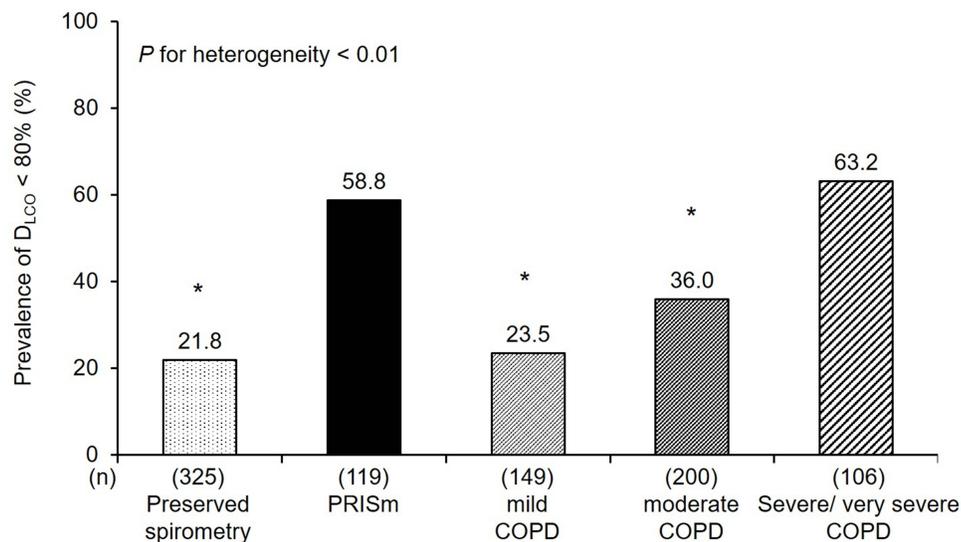
**Abbreviations:** PRISm, preserved ratio impaired spirometry; COPD, chronic obstructive pulmonary disease; BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; SVC, slow vital capacity.

group than in the preserved-D<sub>LCO</sub> group ( $P < 0.01$ ). There was a significant linear trend in the association between D<sub>LCO</sub> % pred and overall survival ( $P < 0.01$  for the trend) (Figure 3B). A more significant increase in multivariable-adjusted HR for all-cause mortality was observed in the low-D<sub>LCO</sub> group than in the others (HR = 10.10 (95% CI 2.33–43.89)) (Figure 4A). In the same analysis, the multivariable-adjusted HR of smoking failed to reach statistical significance ( $P = 0.27$ ). Similarly, the multivariable-adjusted HR for all-cause death was elevated as D<sub>LCO</sub> % pred decreased ( $P < 0.01$  for the trend); as compared with the highest tertile group, the HR was significantly higher in the lowest tertile group (HR =

**Figure 1** Level of D<sub>LCO</sub> % pred by lung-function group.

**Note:** \* $P < 0.01$  versus the PRISm group.

**Abbreviations:** D<sub>LCO</sub> % pred, diffusing capacity of the lung for carbon monoxide per predicted; PRISm, preserved ratio impaired spirometry; COPD, chronic obstructive pulmonary disease.



**Figure 2** Prevalence of low  $D_{LCO}$  by lung-function group.

**Notes:** \* $P < 0.01$  versus the PRISm group. Low  $D_{LCO}$  was defined as  $D_{LCO} \% \text{ pred} < 80\%$ .

**Abbreviations:**  $D_{LCO}$ , diffusing capacity of the lung for carbon monoxide; PRISm, preserved ratio impaired spirometry; COPD, chronic obstructive pulmonary disease.

15.33 (95% CI 3.39–69.37),  $P < 0.01$ ) (Figure 4B). Statistical significance was also observed in the associations between low  $D_{LCO}/V_A$  and all-cause mortality (multivariable-adjusted HR = 4.23 (95% CI 1.70–10.50)) (Supplementary Figures S9 and S10).

## Discussion

The present study revealed a higher prevalence of low  $D_{LCO}$  in patients with PRISm than in those with normal spirometry, mild COPD, or moderate COPD. The diffusing capacity in PRISm was at the same level as in severe COPD. The results were consistent across BMI levels. Our study also showed that impaired  $D_{LCO} \% \text{ pred}$  was a significant risk factor for all-cause mortality in cases of PRISm. To the best of our knowledge, this is the first study to evaluate the distributions of  $D_{LCO} \% \text{ pred}$  and to investigate the impact of low  $D_{LCO}$  on overall survival in PRISm patients.

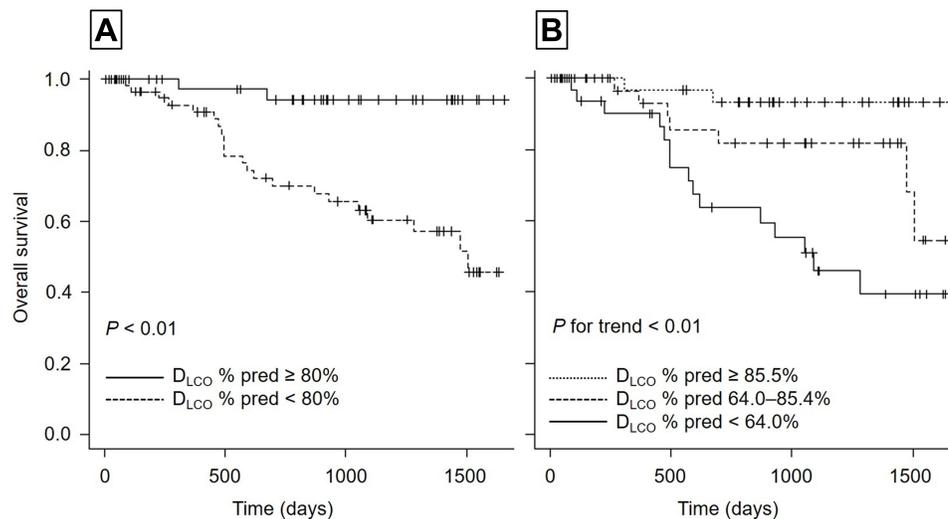
In the current study, PRISm was accompanied by deficits in diffusing capacity. It has been well known that there are inverse associations between  $D_{LCO}$  and disease severity in COPD,<sup>12</sup> since  $D_{LCO}$  decreases by alveolar destruction (lung emphysema) and alveolar microvascular damage preceding emphysematous changes.<sup>22</sup>  $D_{LCO}/V_A$  did not decrease as much as  $D_{LCO}$  in PRISm, probably due to attenuated impairment by obesity-related deficits in  $V_A$ . Recent

**Table 2** Multivariable-Adjusted Regression Analysis for Low  $D_{LCO}$  in the Patient Groups Based on FEV<sub>1</sub> Value

Lung Function Category	Number of Events/Cases (%)	Multivariable-Adjusted OR (95% CI) vs PRISm Group	P value
Preserved spirometry	71/325 (21.8%)	0.21 (0.13–0.34)	< 0.01
PRISm	70/119 (58.8%)	1.00	N/A
Mild COPD	35/149 (23.5%)	0.18 (0.10–0.31)	< 0.01
Moderate COPD	72/200 (36.0%)	0.27 (0.16–0.46)	< 0.01
Severe/very severe COPD	67/106 (63.2%)	0.92 (0.51–1.64)	0.77

**Note:** Adjustments were made for age, gender, body mass index, and smoking exposure.

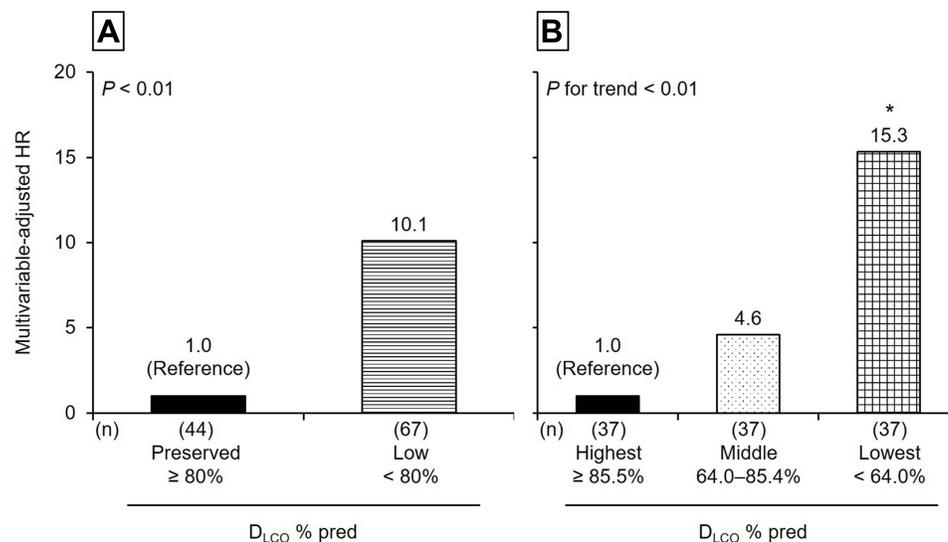
**Abbreviations:**  $D_{LCO}$ , diffusing capacity of the lung for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; 95% CI, 95% confidence interval; PRISm, preserved ratio impaired spirometry; COPD, chronic obstructive pulmonary disease; N/A, not applicable.



**Figure 3** Probability of overall survival according to levels of  $D_{LCO} \% \text{ pred}$  among cases of PRISm.

**Notes:** (A) Preserved and low  $D_{LCO}$  were defined as  $D_{LCO} \% \text{ pred} \geq 80\%$  and  $< 80\%$ , respectively. (B) The cut-off values for  $D_{LCO} \% \text{ pred}$  were  $\geq 85.5\%$  for the highest, 64.0–85.4% for the middle, and  $< 64.0\%$  for the lowest tertile groups.

**Abbreviations:**  $D_{LCO} \% \text{ pred}$ , diffusing capacity of the lung for carbon monoxide per predicted; PRISm, preserved ratio impaired spirometry.



**Figure 4** The multivariable-adjusted HRs for all-cause mortality by levels of  $D_{LCO} \% \text{ pred}$  among cases of PRISm.

**Notes:** \* $P < 0.01$  versus the reference group. Adjustments were made for age, gender, body mass index, and smoking exposure. (A) Preserved and low  $D_{LCO}$  were defined as  $D_{LCO} \% \text{ pred} \geq 80\%$  and  $< 80\%$ , respectively. (B) The cut-off values for  $D_{LCO} \% \text{ pred}$  were  $\geq 85.5\%$  for the highest, 64.0–85.4% for the middle, and  $< 64.0\%$  for the lowest tertile groups.

**Abbreviations:** HR, hazard ratio;  $D_{LCO} \% \text{ pred}$ , diffusing capacity of the lung for carbon monoxide per predicted; PRISm, preserved ratio impaired spirometry.

epidemiological studies have established that PRISm is associated with adverse cardiovascular outcomes and dementia,<sup>2,3,14,23</sup> probably due to potential hypoxia and/or systemic microvascular atherosclerosis.<sup>23</sup> Our results were in accordance with these reports, considering that  $D_{LCO}$  reflects not only lung function impairment but also microvascular damage. Although PRISm has been reported to be at least partly attributed to obesity,<sup>3,5</sup> which can be linked to increased  $D_{LCO} \% \text{ pred}$ ,<sup>24</sup> diffusing capacity was strongly impaired in PRISm at all BMI levels in the present study, indicating that PRISm is not merely a byproduct of obesity. Deficits in diffusing capacity among subjects with PRISm were observed regardless of subjects' smoking status; we believe that decrease in  $D_{LCO}$  in PRISm is unlikely to be explained solely by

smoking exposure. Among PRISm subjects, impairment in  $D_{LCO}$  might have been mainly a reflection of enhanced systemic inflammation and oxidative stress,<sup>2,4</sup> which was considered to result in a high prevalence of cardiovascular disease and diabetes in this population.<sup>3,5,11</sup>

In the present research, low  $D_{LCO}$  was an independent risk factor for all-cause death in PRISm. As for COPD, several cohort studies have demonstrated that impaired diffusing capacity is one of the most robust risk factors for morbidity and mortality.<sup>15,25</sup> This can be explained by  $D_{LCO}$ 's potential as a promising candidate for estimating exercise intolerance and physical functioning in patients with COPD.<sup>15</sup> The current outcome extends these findings to subjects with PRISm. To expand the utility of  $D_{LCO}$  in the management of PRISm, we are planning a prospective cohort study to investigate the associations of  $D_{LCO}$  with the cardiovascular burden and incidence of dementia in a future work.

The strengths of our study were the relatively large sample size with  $D_{LCO}$  assessment, the uniformity in measurements of  $D_{LCO}$  by virtue of the single-center survey, the use of regression models adjusting for multiple confounders to evaluate the independent effects of  $D_{LCO}$ , and the longitudinal study design to minimize the potential of reverse causation. However, some potential limitations should be noted. First, the  $D_{LCO}$  values were based on a single measurement. This may cause misclassification of the levels of  $D_{LCO}$ , which could have weakened the associations found in the present study, biasing the results toward a null hypothesis. Second, the present outcomes might lack external validity and generalizability due to the study design as a single-center analysis, although the lung functions of the study population were substantially comparable to those of other PRISm cohorts.<sup>3,5,6,14,26</sup> Third, we did not have access to prescription data of the study population; it was possible that the increase in the  $D_{LCO}$  value was due to BD use. However, long-acting bronchodilators have reportedly been unable to contribute to significant improvements in  $D_{LCO}$ .<sup>27</sup> In addition, there have been no established treatment options, including BD, for PRISm;<sup>12,28</sup> we speculate that few cases of PRISm received such treatment, as another survey has demonstrated.<sup>6</sup> Hence, this limitation may not have altered our conclusions. Fourth, we might have included some asthmatic subjects in the present study. However, the results of sensitivity analysis using only the subjects without bronchial reversibility were comparable to those from the primary analysis. We therefore speculate that this limitation did not alter the conclusion. Fifth, we did not have access to radiographic information for each subject; some of the individuals with PRISm might have had restrictive lung diseases such as interstitial pneumonia rather than pre-COPD or obesity. Considering the very low prevalence of clinically apparent interstitial lung disease,<sup>29</sup> however, the majority of PRISm subjects were unlikely to show evidence of interstitial pneumonia.<sup>3,30,31</sup> Lastly, we were unable to investigate the associations of impaired diffusing capacity with cause-specific mortality due to a lack of data concerning the cause of death.

## Conclusion

The diffusing capacity of the lung was more impaired in subjects with PRISm than in those with preserved spirometry or mild to moderate COPD. More than half of the cases of PRISm presented with low  $D_{LCO}$ . Additionally, low  $D_{LCO}$  was an independent risk factor for all-cause mortality, and there was a linear trend in the risk of death across the levels of  $D_{LCO}$  % pred. In managing PRISm, clinicians should assess the diffusing capacity of the lung in order to predict each patient's future risk of death.

## Abbreviations

PRISm, preserved ratio impaired spirometry; COPD, chronic obstructive pulmonary disease;  $D_{LCO}$ , diffusing capacity of the lung for carbon monoxide; BD, bronchodilator; FEV<sub>1</sub>/FVC, forced expiratory volume in 1 second to forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; % pred, percent predicted;  $V_A$ , alveolar volume; ATS/ERS, American Thoracic Society/European Respiratory Society; BMI, body mass index; SVC, slow vital capacity; ANOVA, analysis of variance; OR, odds ratio; 95% CIs, 95% confidence intervals; HR, hazard ratio.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethics Approval and Informed Consent

This study was approved by the National Hospital Organization Fukuoka National Hospital Institutional Review Board for Clinical Research (#F4-2). Given the retrospective nature of the study, written informed consent was not requested by the ethics committee.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare that they have no competing interests in this work.

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