# Productive cough associated with patient-reported outcomes and computed tomography analysis results in idiopathic pulmonary fibrosis: a single centre cross-sectional study



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*To the Editor:*

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic pulmonary disease that causes mortality in most patients [1, 2]. Cough and dyspnoea are the most common symptoms of IPF. However, the effect of cough on the pathophysiology of IPF has not been extensively investigated. Although the cough of patients with IPF is often described as dry [3], mucus hypersecretion and ciliary impairment in the conducting airway are reported to be common among these patients [4].

This study aimed to determine the frequency of dry and productive cough in patients with IPF and reveal the relationship with clinical parameters, patient-reported outcomes (PROs) and imaging.

This study followed the amended Declaration of Helsinki and received approval from the Ethics Review Board of Nagoya City University Hospital (approval number: 60-23-0002). Written informed consent was obtained from all participants. IPF diagnoses were confirmed adhering to international guidelines [1, 2]. Screening of stable outpatients with IPF had been performed between March 2023 and December 2023 at Nagoya City University Hospital, Japan. We included patients who were capable of undergoing pulmonary function tests and of understanding PRO questionnaires. Exclusion criteria were recent acute exacerbations or acute respiratory infections in the previous 1 month. Common causes of coughing were determined through patient questionnaires and chart reviews, encompassing: smoking history; current treatment with an angiotensin-converting enzyme inhibitor; upper airway cough syndrome (UACS); and diagnoses of asthma, COPD, or gastro-oesophageal reflux disease (GORD). Relevant diagnostic tests were conducted at the discretion of the treating physician.

Cough presence was noted with a yes/no response to the question, “Do you have chronic coughs?” Additionally, patients with productive coughs were asked to respond yes/no to the question “Does sputum accompany it?” The impact of cough on quality of life (QOL) was evaluated using the Leicester Cough Questionnaire (LCQ) [5] and the Cough and Sputum Assessment Questionnaire (CASA-Q) [6]. The LCQ shows a good correlation with objective 24-h cough frequency. It also contains a question about sputum (question 2). The CASA-Q was validated with the association of subjective sputum questions and objective sputum volumes in patients with chronic airway diseases [6]. Breathlessness was evaluated using the modified Medical Research Council (mMRC) dyspnoea scale. Health-related QOL were evaluated using the St George’s Respiratory Questionnaire (SGRQ) [7]. We used a modified frequency scale to measure GORD [8].

Chest high-resolution computed tomography images comprising 1-mm-thick slices at 1-mm intervals were used for analysis. Image analyses were conducted using specialised software (SYNAPSE VINCENT; Fujifilm Medical Systems, Tokyo, Japan). Following whole-lung extraction, areas of the lung with normal attenuation, defined as −950 Hounsfield unit to −701 Hounsfield unit, were identified. The resulting normally attenuated lung volume as a percentage of the whole-lung volume (NL%) was calculated as described previously [9, 10].

Shareable abstract (@ERSpublications)
**The high frequency of productive cough in idiopathic pulmonary fibrosis (IPF) impacts quality of life. Reduced normal lung volume is linked to cough severity, predicting poorer outcomes. Insights could enhance IPF management and patient wellbeing.** https://bit.ly/4bPOCzC

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All statistical analyses were conducted using SPSS Version 28 (IBM Corp., Armonk, NY, USA).

48 outpatients were enrolled; the mean±SD age was 74.3±8.2 years, the mean±SD % predicted forced vital capacity (%FVC) was 84.9±13.9%, and the median (interquartile range) diffusion capacity of the lung for carbon monoxide (%$D_{LCO}$) was 67.7% (60.1–88.6%). Patients experiencing GORD, asthma, COPD, and UACS comprised 54%, 6%, 4%, and 6% of the population, respectively. No patient was administered angiotensin-converting enzyme inhibitors. Among the patients, 63% (n=36) exhibited cough symptoms, with 56% (n=27) presenting with productive cough. The median total LCQ score was 18.3 (15.9–19.8). Median values for the four CASA-Q domains were 75 (60–92) for cough symptoms, 95 (82–100) for cough impact, 75 (6.7–100) for sputum symptoms, and 96 (88–100) for sputum impact. The median NL% was 80.6% (76.0–83.9%). SGRQ scores, LCQ scores, CASA-Q score (sputum symptoms), and NL% were compared among the non-cough, dry cough, and productive cough groups, with the results illustrated in figure 1. From the analysed results of question 2 of the LCQ, the yes/no question "Does sputum accompany it?" is considered credible.

We examined factors for productive cough through univariate and multiple regression analyses. Age (OR 1.087, 95% CI 1.006–1.175; p=0.034), body mass index (OR 0.822, 95% CI 0.677–0.999; p=0.049), and NL% (OR 0.895, 95% CI 0.801–1.000; p=0.049) were associated with productive cough, although %FVC or %$D_{LCO}$ were not. Multivariate regression analysis revealed NL% as an independent factor associated with productive cough (OR 0.860, 95% CI 0.745–0.992; p=0.039), even after adjusting for treatments such as pirfenidone, nintedanib and proton pump inhibitors (OR 0.858, 95% CI 0.743–0.992; p=0.038).

Multiple linear regression analysis was conducted to determine the relationship between productive cough and PROs. Productive cough emerged as an independent factor contributing to mMRC (p=0.024), SGRQ total (p=0.029) and LCQ total (p=0.007) scores. Conversely, age, %FVC, %$D_{LCO}$ and smoking history

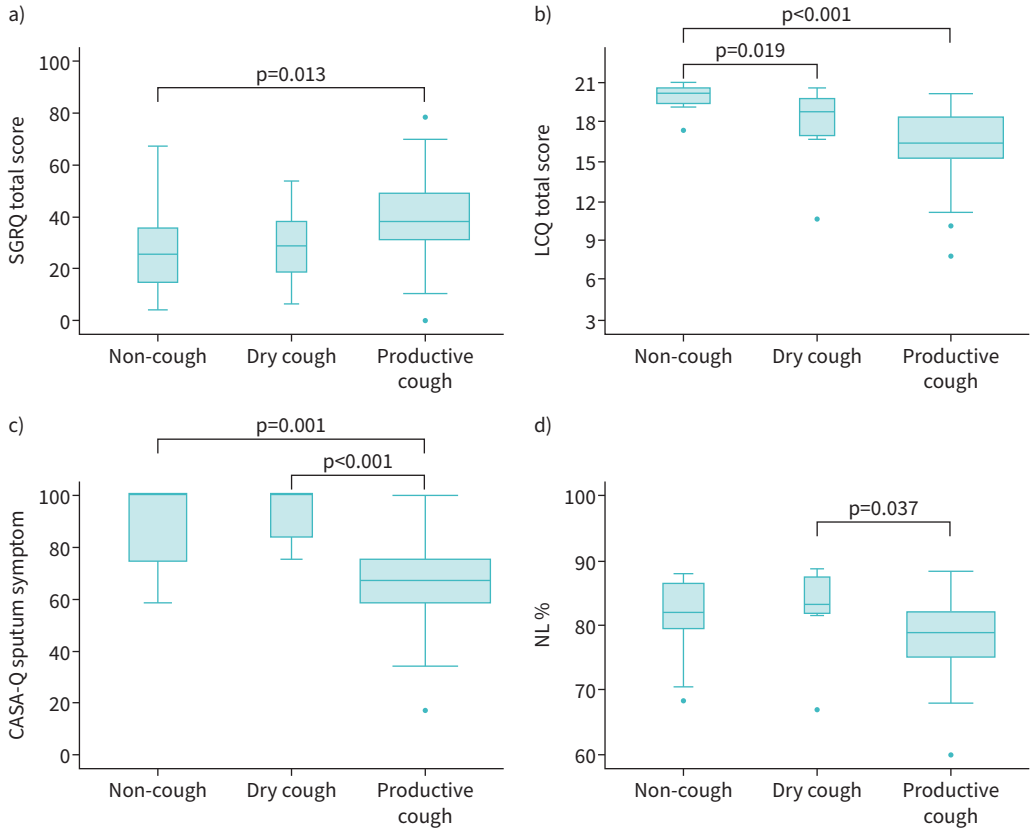


FIGURE 1 Comparison of a) St George's Respiratory Questionnaire (SGRQ), b) Leicester Cough Questionnaire (LCQ), c) the Cough and Sputum Assessment Questionnaire (CASA-Q), and d) normally attenuated lung volume as a percentage of the whole lung volume (NLs%) among non-cough, dry cough, and productive cough groups of patients with idiopathic pulmonary fibrosis.

did not exhibit independent predictive significance. A similar analysis was conducted for the presence of cough, including dry cough; however, cough did not emerge as a significant predictor of the mMRC and SGRQ total scores.

In this study, 56% of the patients with IPF exhibited productive cough, which exceeded our expectations. The median score of the sputum symptoms of CASA-Q was 66.7 points in patients with IPF with productive cough (figure 1c), which was lower than that of COPD without sputum (approximately 80 points) and higher than that of COPD with sputum (approximately 50 points) [6]. Although not as severe as COPD, several patients with IPF were considered to have productive cough. We also found that productive cough impacts cough- and health-related QOL and dyspnoea scores. Conversely, dry cough did not impact health-related QOL and dyspnoea scores. These results indicate that productive cough negatively affects patients with IPF.

In the multivariate analysis, NL% emerged as the only significant factor for productive cough. Mechanical stress due to fibrotic tissue tearing in the small airways may contribute to coughing and sputum production in patients with IPF by stimulating receptors in the peripheral airway [11]. Furthermore, structural distortion may cause abnormal ciliary motor function, inducing productive cough [12].

Asthma, COPD and UACS were considered potential comorbidities that could induce productive cough. However, their representation in this study was limited and unlikely to have played a significant role.

This study had several limitations. First, the results were obtained by analysing Japanese patients from a single centre with a small sample size that included only a few severe-stage patients, which may have introduced a selection bias. Second, the definitions of cough and productive cough were noted with yes/no responses to the questions. Objective characteristics such as sputum volumes and objective 24-h cough frequency were not analysed. Instead, we assessed cough and sputum symptoms using multiple validated questionnaires. Third, unlike COPD and asthma, GORD and UACS were not diagnosed by specialists. Finally, NL% cannot identify the specific radiological findings associated with productive cough, as it collectively excludes traction bronchiectasis [13], honeycombing and ground-glass opacities. Artificial intelligence-based quantitative computed tomography image analysis [14] may further clarify the radiological findings associated with productive cough.

In conclusion, we demonstrated the prevalence of productive cough and its association with reduced normal lung volume in patients with IPF. Notably, productive cough is an independent predictor of poor PROs.

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contributed to the manuscript interpretation. Y. Ozawa and T. Murase contributed as radiologists and pathologists, respectively. All the authors have read and approved the final version of this manuscript.

Conflict of interest: The authors declare that they have no competing interests.

## References


1 Raghu G, Remy-Jardin M, Myers JL, *et al.* Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198: e44–e68.

2 Raghu G, Remy-Jardin M, Richeldi L, *et al.* Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2022; 205: e18–e47.

3 American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med* 2000; 161: 646–664.

4 Peng Y, Wang ZN, Xu AR, *et al.* Mucus hypersecretion and ciliary impairment in conducting airway contribute to alveolar mucus plugging in idiopathic pulmonary fibrosis. *Front Cell Dev Biol* 2021; 9: 810842.

5 Birring SS, Prudon B, Carr AJ, *et al.* Development of a symptom-specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003; 58: 339–343.

6 Crawford B, Monz B, Hohlfeld J, *et al.* Development and validation of a cough and sputum assessment questionnaire. *Respir Med* 2008; 102: 1545–1555.

7 Jones PW, Quirk FH, Baveystock CM, *et al.* A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; 145: 1321–1327.

8 Kusano M, Hosaka H, Kawada A, *et al.* Development and evaluation of a modified frequency scale for the symptoms of gastroesophageal reflux disease to distinguish functional dyspepsia from non-erosive reflux disease. *J Gastroenterol Hepatol* 2012; 27: 1187–1191.

9 Ohkubo H, Kanemitsu Y, Uemura T, *et al.* Normal lung quantification in usual interstitial pneumonia pattern: the impact of threshold-based volumetric CT analysis for the staging of idiopathic pulmonary fibrosis. *PLoS One* 2016; 11: e0152505.

10 Ohkubo H, Taniguchi H, Kondoh Y, *et al.* A volumetric computed tomography analysis of the normal lung in idiopathic pulmonary fibrosis: the relationship with the survival. *Intern Med* 2018; 57: 929–937.

11 Mann J, Goh NSL, Holland AE, *et al.* Cough in idiopathic pulmonary fibrosis. *Front Rehabil Sci* 2021; 2: 751798.

12 Harrison NK. Idiopathic pulmonary fibrosis: a nervous cough? *Pulm Pharmacol Ther* 2004; 17: 347–350.

13 Yamamura K, Hara J, Watanabe S, *et al.* Patients with idiopathic pulmonary fibrosis and refractory cough have traction bronchiectasis and distorted airway architecture: a retrospective case review study. *J Thorac Dis* 2024; 16: 2159–2166.

14 Handa T, Tanizawa K, Oguma T, *et al.* Novel artificial intelligence-based technology for chest computed tomography analysis of idiopathic pulmonary fibrosis. *Ann Am Thorac Soc* 2022; 19: 399–406.