

Clinical significance of cough intensity and frequency in patients with interstitial lung disease: a cross-sectional study

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Abstract

Background The intensity and frequency of cough remain unclear in interstitial lung disease (ILD). The aim of this study was to evaluate the intensity and frequency of cough in idiopathic interstitial pneumonias (IIPs), connective tissue disease-associated interstitial lung disease (CTD-ILD), and chronic hypersensitivity pneumonia (CHP), and examine their associations with clinical indices. **Methods** In this cross-sectional study, the intensity and frequency of cough were evaluated using a 100-mm visual analogue scale. Scores on the Leicester Cough Questionnaire, chronic dyspnoea scale, and a frequency scale for symptoms of gastro-oesophageal reflux disease (FSSG) were collected. The correlations of cough intensity and frequency with potential predictor variables were tested using bivariate and multiple logistic regression analysis. **Results** The study included 70 patients with IIPs, 49 with CTD-ILD, and 10 with CHP. Patients with IIPs had the most severe cough intensity among the three patient groups. In patients with IIPs, both the intensity and frequency of cough were negatively associated with diffusing capacity of the lung for carbon monoxide and positively with the Composite Physiologic Index (CPI). In CTD-ILD, both the intensity and frequency of cough correlated with a higher FSSG score. In multivariate analysis of patients with ILD, IIPs and the FSSG score was independently associated with both components of cough, and CPI tended to be independently associated with cough frequency alone. Finally, we examined the features of differences between cough intensity and frequency in all patients with ILD. Patients in whom cough frequency was predominant had greater impairment of health status relative to other patients. **Conclusions** The intensity of cough was greater in IIPs than in other ILDs. Different clinical indices were associated with cough intensity and frequency according to the subtype of ILD. The frequency of cough was more strongly associated with health status than was the intensity of cough. These findings suggest that medical staff could manage patients with ILD by considering cough-related factors when assessing the intensity and frequency of cough.

Background

Nonproductive cough is a prominent symptom of interstitial lung disease (ILD) [1], and it has been suggested that cough associated with ILD should be assessed in clinical trials [2]. The prevalence of cough has been reported to be as high as 84% in patients with idiopathic pulmonary fibrosis (IPF) [3], 73% in those with scleroderma-related ILD [4], and 83% in those with chronic hypersensitivity pneumonitis (CHP) [5]. Although cough is an important defense mechanism that serves to remove foreign material from the airways, chronic cough is associated with impairment of health-related quality of life (HRQoL) [6, 7]. Several studies in patients with ILD have shown associations of objective measurements of cough frequency and subjective visual analogue scale (VAS) cough scores with HRQoL [5, 8].

In addition to impairment of HRQoL, cough in patients with ILD may correlate with disease progression or augment activation of profibrotic mechanisms [9, 10]. Ryerson et al. reported that cough in patients with IPF was an independent predictor of disease progression and might predict time until death or need for lung transplantation [3]. Moreover, Theodore et al. and Tashkin et al. found that increasing frequency of

cough in patients with scleroderma-related ILD correlated with the extent of fibrosis on high-resolution computed tomography (HRCT) images [4, 11].

The Leicester Cough Questionnaire (LCQ) [8] and cough frequency monitoring [12] are used to assess cough in patients with IPF and focus on its frequency. However, Froese et al. confirmed that both the intensity and frequency of mechanical stress-related breathing impacted activation of key fibrogenic mediators, particularly transforming growth factor beta-1, in rat fibrotic tissue [13]. This suggests the importance of evaluation of cough intensity as well as its frequency in patients with ILD. However, there is a paucity of data focusing on the two components of cough, i.e., intensity and frequency, separately in patients with ILD and their correlations with baseline clinical indices representing disease activity.

The aims of this study were to evaluate both the intensity and frequency of cough in patients with ILD and to examine their association with clinical indices that include data representing disease activity.

Methods

Study design and population

To minimise selection bias, consecutive new patients with ILD, i.e., idiopathic interstitial pneumonias (IIPs), connective tissue disease-associated interstitial lung disease (CTD-ILD), or CHP were invited to participate in this cross-sectional study. The study was performed at Kyoto University Hospital between August 2015 and March 2018. IIPs were diagnosed as previously described [14-16]. IPF was diagnosed by surgical lung biopsy or HRCT according to the guidelines [17]. CHP was diagnosed in multidisciplinary team discussions according to the established criteria [18]. Patients who had had a respiratory tract infection in the preceding month, those who had lung cancer, postnasal drip, rhinitis, catarrhal symptoms, or a history of adult asthma, and those younger than 20 years of age were excluded.

Measurements

Data were obtained from patient-completed questionnaires and electronic patient records. The intensity and frequency of cough were evaluated using a 100-mm VAS (0, no cough; 100, unbearable), which is the tool most commonly used to assess subjective severity of cough [19]. Patients were asked to place a vertical mark on the scale reflecting the intensity of cough and another vertical mark indicating the frequency of their cough. To explore the features underlying any difference between the VAS score for cough intensity and that for cough frequency, we stratified patients into three categories using the following formula: (cough intensity) – (cough frequency), defining a cough frequency-dominant group, ≤ -10 mm; an equal cough severity group, -9 mm to 9 mm; and a cough intensity-dominant group, ≥ 10 mm. We assessed cough-specific HRQoL using the Japanese version of the LCQ [20]. The total score on the LCQ ranges from 3 to 21, with lower scores indicating greater impairment of health status as a result of cough. The LCQ was demonstrated to have appropriate feasibility and sensitivity so can be considered an appropriate clinical outcome tool for use in clinical trials that include patients with ILD [21]. Permission was obtained from the developer (Dr Surinder Biring) and translators (Drs Akio Niimi and

Haruhiko Ogawa) to use the LCQ. Dyspnoea was assessed using the Medical Research Council (MRC) chronic dyspnoea scale. The symptoms of gastro-oesophageal reflux disease (GORD) were assessed using a frequency scale for symptoms of GORD (FSSG) developed by Kusano et al. [22], which has been already used in studies of cough [23, 24]. This questionnaire consists of 12 questions; the total score on the FSSG ranges from 0 to 48, with higher scores indicating more severe symptoms of GORD. We simultaneously collected data on the intensity and frequency of cough, LCQ, MRC chronic dyspnea scale, and FSSG scores. Additional data, including for age, sex, body mass index, smoking history, anamnesis, medication, and pulmonary function tests performed within three months of the assessment of cough intensity and frequency, were obtained from the clinical records. The pulmonary function tests were performed using the CHESTAC system (Chest M.I. Inc., Tokyo, Japan), and diffusing capacity of the lung for carbon monoxide (D_{LCO}) was determined by the single-breath technique. The Composite Physiologic Index (CPI) was used to predict the extent of fibrosis on HRCT. The formula used to calculate the CPI is as follows: $CPI = 91.0 - (0.65 \times \text{percent predicted } D_{LCO}) - (0.53 \times \text{percent predicted forced vital capacity [FVC]}) + (0.34 \times \text{percentage of predicted forced expiratory volume in 1 s [FEV}_1])$ [25].

Statistical analysis

The sample size was determined by the correlation between severity of cough and %FVC in patients with IPF based on previous data [3]. However, there were few reports available on the correlation between severity of cough and %FVC in patients with ILD until the present study. Therefore, we hypothesised a mild effect size of 0.3 with an alpha level of 5% and a power of 90% and calculated that a minimum sample size of 113 would be required for this study.

The data were compared between the three groups using the chi-square test or Fisher's exact test for categorical variables and one-way analysis of variance or the Kruskal-Wallis test for continuous variables. If the one-way analysis of variance or Kruskal-Wallis test result was significant, the three groups were compared using Tukey's test or a Bonferroni-corrected significance level of 1.6%. The correlations of cough intensity and frequency with potential predictor variables were tested using the Mann-Whitney *U* test or Spearman's rank correlation coefficient as appropriate. After conversion of the cough intensity and frequency data to a dichotomous variable using the median value, multiple logistic regression analysis was performed to identify independent variables predicting cough intensity and frequency. Only one variable in a set of variables with a correlation coefficient >0.5 was used in the multivariate logistic regression analysis because of multicollinearity. Potential predictive variables were age, sex, pack-years of smoking, body mass index, FSSG score, MRC chronic dyspnoea scale, CPI, glucocorticoid medication, and type of ILD. Variables were selected using forward selection method based on the likelihood ratio test. The goodness of fit of the model was assessed using the Hosmer–Lemeshow test. Missing data were not included in the analyses. The data are expressed as the number and percentage, mean and standard deviation, or median with the interquartile range. All statistical analyses were performed using SPSS software (version 25; IBM Corp., Armonk, NY, USA). A *p*-value <0.05 for a two-tailed test was considered statistically significant.

Results

Patient characteristics and intensity and frequency of cough

Twenty-one of 150 patients examined for eligibility were excluded (9 with a respiratory tract infection in the preceding month, 1 with lung cancer, 6 with rhinitis, 3 with a history of adult asthma, 1 with an acute exacerbation of IPF in the previous month, and 1 with pneumoconiosis). Seventy patients with IIPs, 49 with CTD-ILD, and 10 with CHP were included in the study. The 70 patients with IIPs included 36 (51.4%) with IPF, 2 (2.9%) with idiopathic nonspecific interstitial pneumonia, 2 (2.9%) with respiratory bronchiolitis-associated ILD, 1 (1.4%) with desquamative interstitial pneumonia, 2 (2.9%) with cryptogenic organising pneumonia, 5 (7.1%) with idiopathic pleuroparenchymal fibroelastosis, and 22 (31.4%) with unclassifiable idiopathic interstitial pneumonia. The 49 patients with CTD-ILD included 15 (30.6%) with systemic sclerosis (SSc), 10 (20.4%) with polymyositis or dermatomyositis, 8 (16.3%) with Sjögren's syndrome, 11 (22.4%) with rheumatoid arthritis, 1 (2.0%) with systemic lupus erythematosus, and 4 (8.2%) with microscopic polyangiitis. None of the patients were using angiotensin-converting enzyme inhibitors.

Table 1 shows the characteristics and intensity and frequency of cough in patients with IIPs, CTD-ILD, and CHP. Patients in the IIPs group were more likely to be male and less likely to be using a glucocorticoid than those in the CTD-ILD and CHP groups. The patients with CTD-ILD had a less extensive pack-year smoking history, higher FSSG scores, and better pulmonary function test results than those with IIPs. The patients with CTD-ILD also had a greater total lung capacity than those with CHP. Among the three subtypes of ILD, the patients with IIPs showed the greatest intensity of cough. The LCQ score was not affected by the subtype of ILD.

[[Insert Table 1 about here]]

Factors associated with cough intensity and frequency

The unadjusted factors associated with intensity and frequency of cough in ILD are shown in Tables 2 and 3, respectively. In patients with IIPs, both the intensity and frequency of cough were negatively associated with the D_{LCO} and positively with the CPI. For patients with CTD-ILD, the D_{LCO} and CPI were associated with frequency of cough only, and both the intensity and frequency of cough were associated with FSSG and the MRC chronic dyspnoea scale score. However, the association between cough frequency and D_{LCO} or MRC chronic dyspnoea scale score was rather weak (Spearman $\rho = -0.287$ for D_{LCO} and $\rho = 0.291$ for the MRC chronic dyspnoea scale score) in patients with CTD-ILD. Of note is that the association of cough intensity and frequency with CPI (Fig. 1) was numerically weaker and that with the FSSG score (Fig. 2) was stronger in patients with CTD-ILD than in those with IIPs. There was no significant association of intensity or frequency of cough with any variable in patients with CHP.

[[Insert Tables 2 and 3 about here]]

Table 4 shows the results of the multiple logistic regression analysis of factors associated with the intensity and frequency of cough in all patients with ILD. IIPs and the FSSG score was independently associated with both the intensity and frequency of cough. Furthermore, CPI tended to be independently associated with the frequency only of cough ($p=0.052$).

[[Insert Table 4 about here]]

Features of differences between cough intensity and frequency

Finally, we examined the features of the differences between cough intensity and frequency in all patients with ILD ($n=129$). There was a positive correlation between cough intensity and cough frequency (Spearman $\rho=0.801$, $p<0.001$), but notably, the cough frequency-dominant group had significantly lower total and subdomain LCQ scores than the equal cough severity group or cough intensity-dominant group (Table 5). The Spearman's correlation coefficients between total LCQ scores and intensity and frequency of cough were -0.675 and -0.762 , respectively (both $p<0.001$).

[[Insert Table 5 about here]]

Discussion

To the best of our knowledge, this is the first study to examine cough intensity and frequency separately in patients with IIPs, CTD-ILD, or CHP. Cough intensity was greatest in the group containing patients with IIPs; both the intensity and frequency of cough were negatively associated with the D_{LCO} and positively with the CPI in these patients. In patients with CTD-ILD, both components of cough correlated significantly with a higher FSSG score. In all patients with ILD, multiple logistic regression analysis revealed independent associations of IIPs and the FSSG score with both the intensity and frequency of cough and a tendency for an independent association of CPI with the frequency of cough. Furthermore, although cough intensity and frequency behaved similarly overall, the total and subdomain LCQ scores were significantly poorer in the cough frequency-dominant group than in the other two groups.

Cheng et al. recently reported that the VAS score for cough severity was higher in patients with IPF or CHP than in those with CTD (SSc)-ILD [5]. In the present study, we demonstrated that patients with IIPs had more intense cough than those with CTD-ILD or CHP (Table 1) and that IIPs but not the CPI was an independent risk factor for intensity of cough (Table 4). Cough intensity in patients with IIPs in the present study (median 31 mm) was similar to the cough severity in patients with IPF reported by Cheng et al. (median 39 mm) [5] and Key et al. (median 32 mm) [8].

In this study, CPI tended to be independently associated with frequency of cough in patients with ILD. Specifically, in patients with IIPs, both the intensity and frequency of cough were associated with the CPI and D_{LCO} . Both CPI and D_{LCO} reflect the extent of disease seen on computed tomography scans in patients with ILD [25-27], so it is possible that severity of cough may be associated with the extent of the parenchymal lesions in IIPs. When compared with patients with CTD-ILD, there was also a numerically

stronger association of both the intensity and frequency of cough with CPI in patients with IIPs (Fig. 1). Like our findings in patients with IIPs, Cheng et al. reported a significant correlation of cough severity with D_{LCo} in patients with IPF [5]. Although our results do not indicate a causal relationship between intensity and frequency of cough and CPI, Ryerson et al. showed that cough in patients with IPF is an independent predictor of disease progression, which was defined as a 15% decline in D_{LCo} , a 10% decline in FVC, or lung transplantation or death attributable to any cause [3]. Moreover, there is a hypothesis that formation of the fibroblastic foci in IPF may come from stretch injury to the epithelial-mesenchymal interface [28]. It was also found that both the intensity and frequency of mechanical stress-related breathing resulted in activation of transforming growth factor beta-1 in rat fibrotic tissue; when forces of 5–20 mN were applied to fibrotic lung strips, active transforming growth factor beta-1 increased significantly in response to the mechanical stimulus [13]. Therefore, an increase in intensity and frequency of cough that causes mechanical stress may contribute to disease progression, such as an increase in CPI, in patients with IIPs.

Alternatively, cough in patients with IIPs might be a consequence of architectural distortion of the fibrotic lung. Traction bronchiectasis is caused by constriction of the surrounding fibrotic alveolar tissue, and such architectural distortion of the bronchial tree may be involved in activation of rapidly adapting receptors [10, 29], resulting in an exaggerated coughing response, i.e., an increase in cough intensity or frequency. Further studies are required to evaluate the correlation between the extent of disease seen on HRCT and the intensity and frequency of cough in patients with IIPs.

The FSSG score was another independent risk factor for both the frequency and intensity of cough in patients with ILD, and particularly in patients with CTD-ILD. This finding is consistent with that of Tashkin et al., suggesting that frequency of cough relates to the severity of GORD at baseline and declines in parallel with improvement in GORD by treatment for SSc-ILD [11]. Furthermore, a study in patients with SSc-ILD reported a relationship between the degree of pulmonary fibrosis assessed using a validated HRCT score and the number of reflux episodes in the distal and proximal oesophagus [30]. Hence, the well-known interaction between GORD and cough [31] may be closely involved in the pathogenesis of CTD-ILD, particularly SSc-ILD. Meanwhile, FSSG scores were lower in patients with IIPs than those in patients with CTD-ILD, and there was no significant correlation of either intensity or frequency of cough with the FSSG score in patients with IIPs in the present study. Another study found that only 25% of patients with IPF and increased exposure to acid in the oesophagus reported typical reflux symptoms [32]. A further study found no association between GORD and cough in patients with IPF [3]. Therefore, the impact and association of GORD with cough may be weaker in patients with IIPs than in those with CTD-ILD, even though GORD is thought to be involved in the pathogenesis of IIPs [33].

Patients with ILD and frequency-dominant cough had greater impairment of health status than those in the other groups. Numerically, there was a stronger correlation between cough frequency and total LCQ scores than between cough intensity and total LCQ scores. Our results concur with a report by Key et al. that demonstrated a strong correlation between the objective cough count and cough-related HRQoL in patients with IPF [8]. Furthermore, given the tendency for an association between frequency of cough and the CPI in patients with ILD in the present study, it is reasonable to assess the frequency of cough in

patients with ILD in a clinical setting. However, we should not neglect cough intensity. The scores in the physical domain of the LCQ were significantly poorer in the cough intensity-dominant group than in the group with equal cough severity (Table 5). Furthermore, the intensity of cough also showed a significant correlation with total LCQ scores in patients with ILD. Finally, in patients with IIPs, cough intensity, which was severest in the three subtypes of ILD, was as significantly associated with D_{LCo} and CPI as cough frequency. These findings highlight the need for assessment of both the intensity and frequency of cough in patients with ILD, particularly for patients with IIPs.

The strengths of this study are that it addressed both the intensity and frequency of cough in patients with ILD and included an analysis of subtypes of ILD (i.e., IIPs, CTD-ILD, and CHP). However, the study also has several limitations. First, we could not carry out a detailed analysis in patients with CHP because of the small sample size, which may reflect our stringent study exclusion criteria. Second, we did not investigate whether or not patients had sputum present. Third, the study had a cross-sectional design that precluded identification of a temporal or causal relationship. Prospective and longitudinal studies that include additional characteristics of cough (e.g., production of sputum and duration) are needed.

Conclusions

We found that the degrees of cough intensity and frequency and their associations with clinical indices representing disease activity were different for each type of ILD. We also found independent associations of IIPs and the FSSG score with both the intensity and frequency of cough and a tendency for an independent association of the CPI with the frequency of cough in patients with ILD. Furthermore, impairment of cough-specific HRQoL was noted in the cough frequency-dominant group. These findings suggest that medical staff could manage patients with ILD by considering cough-related factors when assessing the intensity and frequency of cough.

Abbreviations

CHP: chronic hypersensitivity pneumonia, CPI: Composite Physiologic Index, CTD-ILD: connective tissue disease-associated interstitial lung disease, $DLco$: diffusing capacity of the lung for carbon monoxide, FEV1: forced expiratory volume in 1 s, FSSG: frequency scale for symptoms of gastro-oesophageal reflux disease, FVC: forced vital capacity, GORD: gastro-oesophageal reflux disease, HRCT: high-resolution computed tomography, HRQoL: health-related quality of life, IIPs: idiopathic interstitial pneumonias, ILD: interstitial lung disease, IPF: idiopathic pulmonary fibrosis, LCQ: Leicester Cough Questionnaire, MRC: Medical Research Council, SSc: systemic sclerosis, VAS: visual analogue scale

Declarations

Ethics approval and consent to participate

Subjects gave their written informed consent for participation in the study and publication of their data. The study protocol was approved by the Ethics Committee of the Kyoto University Graduate School of Medicine (registration number R0026) on human research. This study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to limitations on secondary use but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

RS, TH, and HM contributed to the conception and design of the study, data collection, analysis and interpretation of data, drafting and revision of the manuscript for important intellectual content, and approval of the final manuscript. TK and TH contributed to data collection and drafting and approval of the manuscript.

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Tables

Due to technical limitations, tables 1 - 5 are only available as a download in the supplemental files section.

Figures

Fig. 1

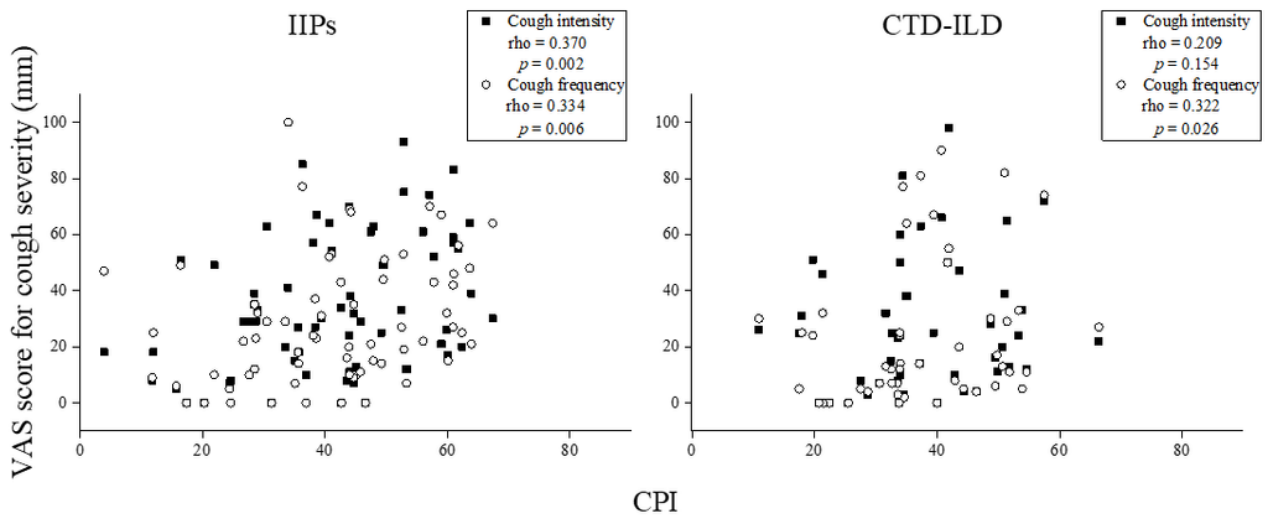


Figure 1

Association of intensity and frequency of cough with CPI. A statistically significant association was observed between intensity and frequency of cough and CPI in patients with idiopathic interstitial pneumonias. However, in connective tissue disease-associated interstitial lung disease, the frequency alone of cough correlated with CPI. CPI, Composite Physiologic Index; CTD-ILD, connective tissue disease-associated interstitial lung disease; IIPs, idiopathic interstitial pneumonias; VAS, visual analogue scale.

Fig. 2

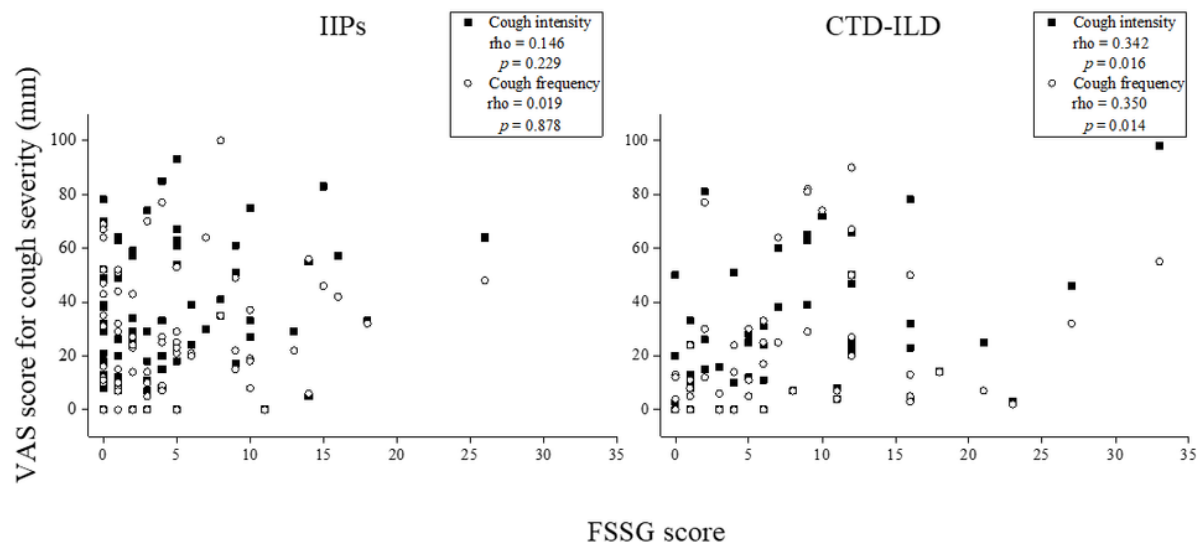


Figure 2

Association of intensity and frequency of cough with the FSSG score. A statistically significant association was observed between cough intensity and frequency and the FSSG score in patients with connective tissue disease-associated interstitial lung disease, but not in idiopathic interstitial pneumonias. CTD-ILD, connective tissue disease-associated interstitial lung disease; FSSG, frequency scale for symptoms of gastro-oesophageal reflux disease; IIPs, idiopathic interstitial pneumonias; VAS, visual analogue scale.

Supplementary Files

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