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Interstitial lung disease in systemic sclerosis: challenges in early diagnosis and management

Małgorzata Chowaniec[1,2], Marta Skoczyńska[1], Renata Sokolik[1], Piotr Wiland[1]

[1]Department of Rheumatology and Internal Diseases, University Hospital in Wrocław, Poland
[2]Department of Hygene, Wrocław Medical University, Poland

Abstract

Interstitial lung disease (ILD) is a group of lung diseases characterized by thickening of the interstitium surrounding pulmonary alveolar walls. It is related to specific radiographic features in lung imaging and/or the presence of restrictive disorders in pulmonary function tests (PFTs). ILD is one of the leading causes of death in systemic sclerosis patients. Major risk factors of ILD associated with SSc (SSc-ILD) include male sex, diffuse type of cutaneous SSc and presence of anti-Scl-70 antibodies.

SSc-ILD is challenging to diagnose at an early stage as the symptoms are non-specific. The greatest risk of its development is during the 4–5 years after the initial diagnosis of systemic sclerosis. Clinical vigilance at the time, including regular pulmonary function tests and/or high-resolution computed tomography (HRCT), is needed. The aim of this paper is to summarize the current knowledge on early diagnostic methods and progression risk factors for SSc-ILD.

Key words: systemic sclerosis, interstitial lung disease, early diagnosis, progression risk factors.

Introduction

Systemic sclerosis (SSc) is a chronic, progressive autoimmune disease leading to vasomotor disturbances, fibrosis and subsequent atrophy of small arteries of the skin and internal organs.

In systemic sclerosis patients, among many organ manifestations, pulmonary involvement – particularly interstitial lung disease (ILD) – is the leading cause of death [1–3]. Although the pathogenesis of SSc-associated ILD (SSc-ILD) is still unknown, it is considered to be a result of both alveolar and vascular damage [4, 5]. Major risk factors that influence risk of ILD development in SSc patients include male gender, diffuse type of cutaneous SSc and presence of anti-Scl-70 antibodies [4].

Screening and management of early SSc-ILD is very complex. Various diagnostic tools and progression risk factors have been defined over the last years with the purpose of distinguishing between progressive and clinically insignificant SSc-ILD. The aim of this paper is to summarize the current knowledge of early diagnosis methods and progression risk factors of SSc-ILD.

Diagnosis of interstitial lung disease

ILD is a group of lung diseases characterized by thickening of interstitium surrounding pulmonary alveolar walls. It is related to specific radiographic features in lung imaging and/or the presence of restrictive disorders in pulmonary function tests (PFTs) [6]. The incidence of ILD in the course of systemic sclerosis varies depending on the diagnostic method. Pulmonary function tests detect restrictive ventilatory defects in 40–75% of patients while HRCT detects interstitial changes in 90% of patients [4, 7].

In high-resolution computed tomography (HRCT) images, there are two main types of ILD in the course of systemic sclerosis: nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP). The NSIP pattern is more frequent in systemic sclerosis, and concerns about 78% of patients, compared to the UIP pattern, which develops in about 10–15% of patients [8]. In the NSIP type, the dominant changes include basal ground-glass opacities, while in UIP, most commonly reticular changes and honeycombing with mainly pe-

Address for correspondence:
Małgorzata Chowaniec, Department of Rheumatology and Internal Diseases, University Hospital in Wrocław, 213 Borowska St., 50-556 Wrocław, Poland, e-mail: malgorzata.chowaniec@onet.pl
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ripheral and basilar distribution are observed [7, 9]. Furthermore, appearance of UIP on HRCT is associated with a poorer prognosis [10, 11].

The problem of early detection of interstitial lung disease in systemic sclerosis

SSc-ILD is challenging to diagnose at an early stage because of the lack of specific symptoms. It is considered that the greatest risk of its development is during the 4–5 years after the initial diagnosis of the systemic sclerosis. Therefore, clinical vigilance at the time, including performing a pulmonary function test every 3–6 months, is needed [1, 4, 5, 12].

The clinical course of SSc-ILD differs widely, ranging from a mild disease that is clinically asymptomatic and stable, to an aggressive disease that progresses rapidly and can shorten life significantly [1, 6]. The most common clinical manifestations of ILD in SSc patients include exertional dyspnea and nonproductive cough [4]. Since these symptoms are nonspecific and can be shared with many other cardiovascular and respiratory system diseases, careful differential diagnosis should be carried out. Furthermore, ILD is often suspected in the absence of any clinical symptoms while fine bibasilar crackles are revealed at lung auscultation [1].

Taking the above into account, to detect SSc-ILD in the beginning, early and regular screening should be carried out. ILD screening tools include PFTs, diffusing capacity of the lung for carbon monoxide (DLCO) and, lastly, HRCT of the chest, which is the gold diagnostic standard [13].

High-resolution computed tomography advantages and drawbacks

HRCT of the chest is the principal and most sensitive noninvasive diagnostic method of SSc-ILD. The most common abnormal findings are ground-glass opacities (GGOs) [14, 15]. GGOs predominantly indicate an active and potentially reversible disease. However, GGOs are considered to be nonspecific and have a broad etiology. Differential diagnosis should include pulmonary edema, pneumonia, chronic pulmonary thromboembolism and alveolar hemorrhage [16]. Other ILD patterns in HRCT images include reticular changes, honeycombing pattern, septal and nonseptal marks and micronodules [14].

Also worth a mention is mediastinal lymphadenopathy, which occurs quite often in SSc-ILD patients (41–74%) [10, 17]. Although enlarged mediastinal lymph nodes in the course of SSc-ILD are mostly a reactive process (resulting from lung inflammation or reflux), they may also indicate the coexistence of other diseases such as sarcoidosis, tuberculosis or lymphoma [10, 18]. Distinguishing between pathologic and nonpathologic lymph nodes is crucial in everyday clinical practice. Data from the Evison et al. study [18] provide strong evidence that mediastinal lymph nodes size > 2 cm are associated with higher risk of a pathological process. Furthermore, detailed medical history and physical examination (sudden weight loss, fever) play an important role in determining the likely pathological cause of lymph node enlargement [18].

Despite the fact that HRCT is a gold diagnostic standard for SSc-related ILD, its potential risk connected with radiation is the major limiting factor for regular screening. In order to reduce the radiation exposure, a technique with a reduced number of slices was attempted by Frauenfelder et al. [13] in their prospective study. By limiting the number of slices to nine, the risk connected with radiation was significantly reduced compared to conventional HRCT. The observed results were encouraging, showing a sensitivity of 88.3% and specificity of 93%. However, it was implied that some small interstitial changes may go unnoticed [13].

The role of PFTs and DLCO

Pulmonary functional tests are used to assess the severity of the ILD and monitor its course. However, since the rate of false-negative results of PFTs is high, they seem to be best suited to the monitoring rather than early detection of the disease. In a study from Suliman et al., among 64 patients with significant ILD on HRCT, as many as 40 (62.5%) had a normal forced vital capacity (FVC) value. Furthermore, as many as 5 patients with a normal FVC result had severe lung fibrosis on HRCT. The overall FVC testing sensitivity for detecting SSc-ILD was only 38%, and no more than 72% when using FVC, total lung capacity (TLC) and DLCO testing at the same time. Patients with normal FVC results and fibrosis on HRCT were more often anti-Scl-70-positive and ACA-negative compared with patients who had normal HRCT results. Because of the significant risk of missing SSc-ILD when performing only PFTs, the authors concluded that early imaging, such as chest HRCT or lung ultrasonography, should be considered especially in ACA-negative patients with normal FVC results [19].

Nevertheless, as emphasized by Steen et al. [5], abnormal FVC early in the course of the disease is one of the most important risk factors for developing end-stage lung disease. Therefore, the authors propose performing PFTs every six months during the first five years of the disease. They also recommend further tests in all patients with FVC values that are abnormal at baseline and/or decreasing over time, regardless of whether they are symptomatic, as patients with severe lung disease

often develop pulmonary symptoms only after FVC is significantly reduced [5].

Since FVC is likely to be in the normal range in early stages of ILD, as mentioned by Degano et al. [19], another functional parameter that may be of use in early detection is functional residual capacity (FRC), which measures relaxation volume in subjects without intrinsic positive expiratory pressure. Also parameters such as TLC reflecting mild increases in lung elastic recoil and DLCO, decreasing in pulmonary vascular destruction, may be more sensitive than FVC in early ILD [19].

The diffusing capacity of the lungs for carbon monoxide (DLCO) is a test measuring the difference in partial pressure between inspired and expired carbon monoxide, and, indirectly, the extent to which oxygen passes from the alveoli to the bloodstream. The DLCO value is considered normal when > 75%, mildly impaired when 74–60%, moderately impaired when 59–50% and severely impaired when < 50% of the predicted value.

DLCO values decrease in states related to decreased effective alveolar surface area, such as restrictive disorders and pulmonary arterial hypertension (PAH). DLCO usually reflects the decrease in VC (vital capacity) and should not be considered in isolation from VC in SSc patients. The vascular component affects the diffusing capacity, and therefore DLCO might not be a good early marker of fibrosis when considered alone. At the same time, DLCO is the most important marker of vasculopathy causing PAH. An isolated decreased DLCO value, even at a normal FVC/DLCO ratio of over 1.4–1.6, may indicate PAH [1, 7].

Both FVC and DLCO are prognostic factors for mortality in patients with SSc-ILD, and therefore a close clinical follow-up including PFTs should be carried out every 3–6 months in symptomatic patients and every 12 months in the absence of clinical symptoms [6].

Lung ultrasound

Although lung ultrasound (LUS) has not been widely used for lung assessment, several studies have shown that it is a promising tool for early detection and monitoring of interstitial lung disease [20–24]. The essence of this diagnostic method in ILD screening is evaluation of artifacts called B lines. B lines, also known as "comet tails", are vertical hyperechogenic lines derived from the pleura line that move with breathing. The increase in their number is associated with thickening of the lung parenchyma, which is a result of the presence of fluid or fibrous tissue [25, 26].

The major advantage of LUS is that it is a noninvasive diagnostic technique, with no radiation exposure. Furthermore, it is quick, low-cost, repeatable and may be performed at bedside. However, LUS also has some limitations such as being a subjective, operator-dependent examination. Also, B lines are nonspecific patterns and aside from interstitial changes may be present e.g. in pulmonary edema. Furthermore, there is no general approved scoring system to detect B lines in SSc-ILD patients [26].

In conclusion, LUS is relatively new technique for lung diagnosis and despite its limitations should be considered as an alternative to HRCT in ILD early diagnosis and monitoring. Further investigations are needed to establish the exact scheme of lung examination and the scoring system of ILD.

Interstitial lung disease screening issues

A number of concerns have been expressed regarding the SSc-ILD screening tools. The pulmonary function tests are non-invasive and easy to access but their major limitation is low sensitivity [27]. On the other hand, HRCT has high sensitivity but is associated with radiation exposure [28].

Although there are no official guidelines for early detection of ILD in SSc patients, some screening algorithms have been proposed [4, 7, 28]. For example, Cappelli et al. [28] have proposed a diagnostic algorithm for SSc-ILD using lung ultrasound. According to their recommendations, every patient should undergo PFTs, DLCO, HRCT and lung ultrasound at baseline. Patients without diagnosed ILD should be screened for this disease using PFTs, DLCO and lung ultrasound, if accessible, every 1–2 years. If the results of screening tests indicate deterioration, HRCT chest scans should be performed [28]. Similar recommendations, including baseline HRCT in all patients followed by annual control of PFTs, have been proposed by Solomon et al. [7]. In contrast, Schoenfeld et al. [4] recommend performing HRCT only in patients with progression of clinical symptoms or PFT changes.

The lack of generally approved guidelines for SSc-ILD screening proceedings was the motivation for a study based on a questionnaire sent to 1032 doctors, including 356 SSc experts around the world. Significant diversity of ILD-SSc screening strategies between different countries was found in this study. One of the interesting observations was that HRCT screening was ordered significantly more frequently by respondents from Europe (45 of 57) compared to experts from Australia (0 of 5), Canada (2 of 6) and the USA (28 of 47) [29].

Risk factors for progressive SSc-ILD

The clinical course of SSc-ILD can be very diverse. Some patients tend to have rapid progression of symptoms while others may have mild and stable disease for a long time [30, 31]. A fundamental difficulty in scleroderma-related interstitial lung disease is identi-

Table I. Risk factors of worse prognosis of SSc-ILD [1, 4, 31, 32–35]

• Occupied lung area more than 20% of total lung area on HRCT
• Decrease in DLCO
• Decline of FVC in an early stage of ILD
• High baseline plasma CRP levels
• Co-occurrence of gastro-esophageal reflux
• Co-occurrence of pulmonary arterial hypertension
• Older age
• Male gender

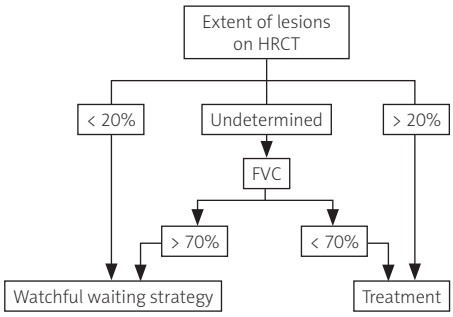

Fig. 1. Management of SSc-ILD depending on the extent of lung changes on HRCT and FVC values [31, 32, 36, 37].

fying which patients require immunosuppressive therapy and which may benefit from an active surveillance strategy. This observational method, also known as the watchful waiting strategy, involves regular monitoring (pulmonary function tests, measuring DLCO and chest imaging) of the SSc-ILD patients at low risk of future progression with the expectation to start therapy if the disease progresses. The aim of this strategy is to avoid the side effects of therapy that may not be necessary and to preserve quality of life. Therefore, predicting SSc-ILD progression may be more clinically important than merely detecting the disease in SSc patients, and the knowledge of individual risk factors for progressive ILD in SSc patients during the diagnostic and therapeutic process is necessary [30, 32, 33].

The major progression risk factors in SSc-ILD include the extent of interstitial changes on HRCT, the decrease in DLCO, the decline of FVC in early stages of ILD, high baseline plasma CRP levels, co-occurrence of gastro-esophageal reflux, pulmonary arterial hypertension, older age and male gender (Table I) [1, 4, 32, 34–36].

The extent of SSc-ILD on HRCT is one of the most important determinants of the further course of the disease. It has been shown that patients with involvement of more than 20% of the lung area on HRCT had a significantly worse prognosis and higher risk of death compared to the group in which the occupied area was less than 20% [32, 37]. These data indicate that the HRCT scoring system based on the extent of interstitial changes is useful for predicting the clinical course of SSc-ILD and also for sub-classifying patients into two groups: with limited disease (< 20% of occupied lung area) and with diffuse disease (> 20% of occupied lung area). The first group consists of patients with low risk of ILD progression who may benefit from active surveillance as a management strategy. In patients with an undetermined extent of ILD on HRCT, the FVC threshold of 70% of the predicted value may be useful for deciding to treat (FVC < 70% of predicted FVC) or not to treat (FVC > 70% of the predicted value) (Fig. 1) [32, 33, 37, 38].

Dynamic decreases in FVC and DLCO also have essential prognostic significance. A decrease in FVC by more than 10% and/or a DLCO decrease above 15% during one year are associated with worse prognosis [39].

Furthermore, many investigators are now focusing on researching biomarkers from samples that can be collected without any significant risk (such as plasma, urine or exhaled breath) and could help identify patients at high risk of SSc-ILD progression. Currently, serum levels of mucin-like glycoprotein KL-6, surfactant protein-D (SP-D) and CC-chemokine ligand 18 (CCL18) represent a promising group of serum progressive SSc-ILD biomarkers [40–42].

It is also worthwhile to point out the conflicting reports as to the association between anti-Scl-70 antibodies and worse prognosis of ILD in scleroderma patients. Some authors assert that the presence of anti-Scl-70 antibodies and diffuse type of SSc are risk factors for ILD development but not for its progression [2, 5, 43]. However, the results of a study performed by Sánchez-Cano et al. [36] show that diffuse type of SSc and presence of Scl-70 antibodies are both associated with higher risk of decline of FVC < 70%.

According to EULAR recommendations published in 2016, SSc-ILD, in particular progressive lung disease, may be treated with cyclophosphamide or cyclosporine. Drugs should be administered at an individualized dose and therapy duration after considering potential risks. In selected patients with rapidly progressive SSc and at risk of organ failure, another viable option is hematopoietic stem cell transplantation (HSCT). It is however connected with increased risk of death in the course of Epstein-Barr virus reactivation, lymphoma, acute respiratory distress syndrome, myocardial infarction and heart failure. Several therapeutic agents, such as mycophenolate mofetil and tocilizumab, are still under evaluation in SSc lung involvement. Promising preliminary effects have been observed, but further studies concerning these medications are needed before drawing conclusions. The efficacy of methotrexate is proved with regards to the skin but uncertain in organ involvement [44].

Conclusions

SSc-ILD is a leading cause of death in SSc patients. The problem of SSc-ILD deserves particular clinical vigilance, especially in newly diagnosed SSc patients and SSc patients with risk factors such as male gender, diffuse type of cutaneous SSc and presence of anti-Scl-70 antibodies.

The diagnosis of SSc-ILD may be difficult as its manifestations vary from patient to patient, are nonspecific, and may have an insidious beginning and oligo-symptomatic course despite rapid progression on HRCT.

Major risk factors of SSc-ILD progression include the extent of involved lung area on HRCT, the decrease in DLCO and/or FVC, high baseline plasma CRP levels, co-occurrence of gastro-esophageal reflux or pulmonary arterial hypertension, older age and male sex.

HRCT and FVC can be used to stratify patients for treatment. The results of HRCT, which is the gold diagnostic standard, may help determine the time of therapy introduction. If HRCT is not available or its results are inconclusive, PFTs may guide the decision to initiate treatment.

The monitoring of SSc patients should include auscultation on every visit and PFTs every 3–6 months in symptomatic, and 12 months in asymptomatic patients, followed by HRCT in the case of abnormal PFT results and/or progression of symptoms and/or at baseline. Clinicians should take into account limitations of such follow-up, especially low sensitivity of PFTs and HRCT-related radiation exposure.

The authors declare no conflict of interest.

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References

1. Giacomelli R, Liakouli V, Berardicurti O, et al. Interstitial lung disease in systemic sclerosis: current and future treatment. Rheumatol Int 2017; 37: 1-11.
2. Silver KC, Silver RM. Management of systemic-sclerosis-associated interstitial lung disease. Rheum Dis Clin North Am 2015; 41: 439-457.
3. Strickland G, Pauling J, Cavill C, et al. Mortality in systemic sclerosis-a single centre study from the UK. Clin Rheumatol 2013; 32: 1533-1539.
4. Schoenfeld SR, Castelino FV. Interstitial lung disease in scleroderma. Rheum Dis Clin North Am 2015; 41: 237-248.
5. Steen V. Predictors of end stage lung disease in systemic sclerosis. Ann Rheum Dis 2003; 62: 97-99.
6. Bauer PR, Schiavo DN, Osborn TG, et al. Influence of interstitial lung disease on outcome in systemic sclerosis: A population-based historical cohort study. Chest 2013; 144: 571-577.
7. Solomon JJ, Olson AL, Fischer A, et al. Scleroderma lung disease. Eur Respir Rev 2013; 22: 6-19.
8. Khanna D, Nagaraja V, Tseng C, et al. Predictors of lung function decline in scleroderma-related interstitial lung disease based on high-resolution computed tomography: implications for cohort enrichment in systemic sclerosis–associated interstitial lung disease trials. Arthritis Res Ther 2015; 17: 372.
9. Park SO, Seo JB, Kim N, et al. Comparison of usual interstitial pneumonia and nonspecific interstitial pneumonia: Quantification of disease severity and discrimination between two diseases on HRCT using a texture-based automated system. Korean J Radiol 2011; 12: 297-307.
10. Bastos AL, Corrêa RA, Ferreira GA. Tomography patterns of lung disease in systemic sclerosis. Radiol Bras 2016; 49: 316-321.
11. Okamoto M, Fujimoto K, Sadohara J, et al. A retrospective cohort study of outcome in systemic sclerosis-associated interstitial lung disease. Respir Investig 2016; 54: 445-453.
12. Cappelli S, Guiducci S, Bellando Randone S, et al. Immunosuppression for interstitial lung disease in systemic sclerosis. Eur Respir Rev 2013; 22: 236-243.
13. Frauenfelder T, Winklehner A, Nguyen TD, et al. Screening for interstitial lung disease in systemic sclerosis: performance of high-resolution CT with limited number of slices: a prospective study. Ann Rheum Dis 2014; 73: 2069-2073.
14. Branley HM. Pulmonary fibrosis in systemic sclerosis: Diagnosis and management. Respir Med CME 2010; 3: 10-14.
15. Goldin JG, Lynch DA, Strollo DC, et al. High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. Chest 2008; 134: 358-367.
16. Grzanka P, Bestry I. Choroby układu oddechowego. Badania diagnostyczne. Badania obrazowe. In: Choroby wewnętrzne, Szczeklik A (ed.). Medycyna Praktyczna, Kraków 2011: 553-560.
17. Farrokh D, Abbasi B, Fallah-Rastega Y, et al. The extrapulmonary manifestations of systemic sclerosis on chest high resolution computed tomography. Tanaffos 2015; 14: 193-200.
18. Evison M, Crosbie PA, Morris J, et al. A study of patients with isolated mediastinal and hilar lymphadenopathy undergoing EBUS-TBNA. BMJ Open Respir Res 2014; 1: 11-13.
19. Degano B, Soumagne T, Eberst G, et al. Pulmonary function parameters other than vital capacity should be considered in screening for interstitial lung disease in patients with systemic sclerosis: Comment on the article by Suliman et al. Arthritis Rheumatol 2016; 68: 2346-2347.
20. Gigante A, Rossi Fanelli F, Lucci S, et al. Lung ultrasound in systemic sclerosis: correlation with high-resolution computed tomography, pulmonary function tests and clinical variables of disease. Intern Emerg Med 2016; 11: 213-217.
21. Buda N, Piskunowicz M, Porzezińska M, et al. Lung ultrasonography in the evaluation of interstitial lung disease in systemic connective tissue diseases: criteria and severity of pulmonary

fibrosis – analysis of 52 patients. Ultraschall Med 2016; 37: 379-385.
22. Sperandeo M, De Cata A, Molinaro F, et al. Ultrasound signs of pulmonary fibrosis in systemic sclerosis as timely indicators for chest computed tomography. Sand J Rheumatol 2015; 44: 389-398.
23. Pinal-Fernandez I, Pallisa-Nuñez E, Selva-O'Callaghan A, et al. Pleural irregularity, a new ultrasound sign for the study of interstitial lung disease in systemic sclerosis and antisynthetase syndrome. Clin Exp Rheumatol 2015; 33 (Suppl 91): 136-141.
24. Gargani L, Doveri M, D'Errico L, et al. Ultrasound lung comets in systemic sclerosis: a chest sonography hallmark of pulmonary interstitial fibrosis. Rheumatology 2009; 48: 1382-1387.
25. Delle Sedie A, Carli L, Cioffi E, et al. The promising role of lung ultrasound in systemic sclerosis. Clin Rheumatol 2012; 31: 1537-1541.
26. Wang Y, Gargani L, Barskova T, et al. Usefulness of lung ultrasound B-lines in connective tissue disease-associated interstitial lung disease: a literature review. Arthritis Res Ther 2017; 19: 206.
27. Suliman YA, Dobrota R, Huscher D, et al. Pulmonary function tests: High rate of false-negative results in the early detection and screening of scleroderma-related interstitial lung disease. Arthritis Rheumatol 2015; 67: 3256-3261.
28. Cappelli S, Bellando Randone S, Camiciottoli G, et al. Interstitial lung disease in systemic sclerosis: Where do we stand? Eur Respir Rev 2015; 24: 411-419.
29. Bernstein EJ, Khanna D, Lederer DJ. Screening high resolution computed tomography of the chest to detect interstitial lung disease in systemic sclerosis: A global survey of rheumatologists. Arthritis Rheumatol 2018; 70: 971-972.
30. Adler S, Huscher D, Siegert E, et al. Systemic sclerosis associated interstitial lung disease – individualized immunosuppressive therapy and course of lung function: Results of the EUSTAR group. Arthritis Res Ther 2018; 20: 1-12.
31. Herzog EL, Mathur A, Tager AM, et al. Interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: How similar and distinct? Arthritis Rheumatol 2014; 66: 1967-1978.
32. Moore OA, Goh N, Corte T, et al. Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease. Rheumatology (Oxford) 2013; 52: 155-160.
33. Kwon HM, Kang EH, Park JK, et al. A decision model for the watch-and-wait strategy in systemic sclerosis-associated interstitial lung disease. Rheumatology (Oxford) 2015; 54: 1792-1796.
34. Liu X, Mayes MD, Pedroza C, et al. Does C-reactive protein predict the long-term progression of interstitial lung disease and survival in patients with early systemic sclerosis? Arthritis Care Res 2013; 65: 1-11.
35. Winstone TA, Assayag D, Wilcox PG, et al. Predictors of mortality and progression in scleroderma-associated interstitial lung disease: A systematic review. Chest 2014; 146: 422-436.
36. Sánchez-Cano D, Ortego-Centeno N, Callejas JL, et al. Interstitial lung disease in systemic sclerosis: data from the spanish scleroderma study group. Rheumatol Int 2018; 38: 363-374.
37. Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis a simple staging system. Am J Respir Crit Care Med 2008; 177: 1248-1254.
38. Yasuoka H. Recent treatments of interstitial lung disease with systemic sclerosis. Clin Med Insights Circ Respir Pulm Med 2015; 9: 97-110.
39. Moore OA, Proudman SM, Goh N, et al. Quantifying change in pulmonary function as a prognostic marker in systemic sclerosis-related interstitial lung disease. Clin Exp Rheumatol 2015; 33: 111-116.
40. Lota HK, Renzoni EA. Circulating biomarkers of interstitial lung disease in systemic sclerosis. Int J Rheumatol 2012; 2012: 121439.
41. Bonella F, Caramaschi P. The ambitious goal of validating prognostic biomarkers for systemic sclerosis-related interstitial lung disease. J Rheumatol 2013; 40: 1034-1036.
42. Ligon C, Hummers LK. Biomarkers in Scleroderma: Progressing from Association to Clinical Utility. Curr Rheumatol Rep 2016; 18: 17.
43. Steen VD, Conte C, Owens GR, et al. Severe restrictive lung disease in systemic sclerosis. Arthritis Rheum 1994; 37: 1283-1289.
44. Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017; 76: 1327-1339.