



# Extra-Parenchymal Chest HRCT Findings in Patients with Systemic Sclerosis at the Time of Initial Diagnosis

## Sistemik Sklerozlu Hastaların Tanı Anında Akciğer Parankimi Dışı Toraks Yüksek Çözünürlüklü Bilgisayarlı Tomografi Bulguları

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### ABSTRACT

**Objective:** In systemic sclerosis (SS) patients who are receiving treatment, findings of extra-parenchymal chest involvement (such as thymic abnormality, mediastinal lymph node enlargement) have been previously examined. However, these findings may be affected by medical treatment. Our aim was to evaluate the extra-parenchymal chest high-resolution computed tomography (HRCT) findings of patients with SS at the time of initial diagnosis.

**Methods:** We retrospectively analyzed medical database of patients with SS. Chest HRCT images within 1 month after initial diagnosis of these patients were re-evaluated for the presence of distal esophageal dilatation, thymic hyperplasia, mediastinal lymph node enlargement, pleural or pericardial abnormalities (effusion or thickening). Intergroup comparisons were performed using independent t-test or a Mann-Whitney U test. To detect the relationship between continuous variables, Spearman's correlation coefficients and univariate correlations were used.

**Results:** A total of 51 patients (45 women and 6 men, mean age + STD; 49.2 years+13.9) with SS were included in the study. Esophageal dilatation (88.2%) was the most common finding. Six patients (11.8%) had thymic enlargement. Mediastinal lymph node enlargement (11.8%) and pleural abnormalities (11.8%) were significantly more common in patients with SS diagnosed at late age ( $p<0.05$ ).

### ÖZ

**Amaç:** Tedavi altındaki sistemik skleroz (SS) hastalarında parankim dışı göğüs tutulumu (timik anormallik, mediastinal lenf nodu genişlemesi gibi) daha önce incelenmiştir. Bununla birlikte, bu bulgular tıbbi tedaviden etkilenebilmektedir. Amacımız tanı anındaki SS hastalarının parankim dışı göğüs tutulumu bulgularını yüksek çözünürlüklü bilgisayarlı tomografi (YÇBT) ile değerlendirmektir.

**Yöntemler:** SS. tanılı hastaları tıbbi veri tabanından geriye dönük olarak inceledik. Bu hastaların başlangıç tanısından 1 ay sonraki göğüs YÇBT görüntüleri; distal özofagus dilatasyonu, timik hiperplazi, mediastinal lenf nodu büyümesi, plevral veya perikardiyal anormalliklerin (efüzyon veya kalınlaşma) varlığı açısından yeniden değerlendirildi. Gruplar arası karşılaştırmalar, bağımsız t-testi veya bir Mann-Whitney U testi kullanılarak yapıldı. Sürekli değişkenler arasındaki ilişkiyi saptamak için Spearman korelasyon katsayıları ve tek değişkenli korelasyonlar kullanıldı.

**Bulgular:** Çalışmaya SS tanısı olan toplam 51 hasta (45 kadın ve 6 erkek, ortalama yaş + STD; 49,2 yıl+13,9) alındı. Özofagus dilatasyonu (%88,2) en sık görülen bulguydu. Altı hastada (%11,8) timik büyüme vardı. Mediastinal lenf nodu genişlemesi (%11,8) ve plevra anormallikleri (%11,8) geç yaşta tanı alan hastalarda anlamlı olarak daha sık görülmekteydi ( $p<0,05$ ).

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**Conclusion:** The extra-parenchymal findings are common in patients with SS at the time of initial diagnosis. Esophageal dilatation is usually present at the time of diagnosis in most patients with SS regardless of age.

**Keywords:** Systemic sclerosis, scleroderma, high-resolution computed tomography, thymus, lymph node

**Sonuç:** Parankim dışı göğüs tutulumu bulguları tanı sırasında SS hastalarında sık görülmektedir. Özofagus dilatasyonu çoğu SS hastasında tanı konulduğunda yaştan bağımsız olarak yüksek sıklıkta görülmektedir.

**Anahtar Sözcükler:** Sistemik skleroz, skleroderma, yüksek çözünürlü bilgisayarlı tomografi, timus, lenf nodu

## Introduction

Systemic sclerosis (SS), also known as scleroderma, is an autoimmune collagen vascular disease and it causes abnormal collagen growth in tissues such as skin, lung, heart and digestive tract. SS is usually characterized by swelling in the fingertips, joint pain and excessive tension and hardness of skin (1). Chest high-resolution computed tomography (HRCT) significantly increases the diagnostic sensitivity of lung involvement in SS (1-4). Also, mediastinal lymph node enlargement (MLNE), pleural disease or thymic enlargement may be seen in patients with SS at any time during the illness (5-10). However, the extra-parenchymal findings of SS may change with medical treatment. For example, thymus gland size decreases in response to use of corticosteroids or immunosuppressants. However, the risk of MLNE and pleural disease (pleural effusion or thickening) increases because of the increased frequency of infection in patients using corticosteroids or immunosuppressants (11,12). To the best of our knowledge, there is no study that evaluates extra-parenchymal chest CT findings in newly diagnosed patients with SS. Therefore, our aim was to evaluate the extra-parenchymal chest HRCT findings in newly diagnosed patients with SS and compare with literature. We also aimed to demonstrate the relationship between the age at initial diagnosis and extra-parenchymal HRCT findings.

## Methods

This single-center retrospective study was approved by our institutional local ethics committee. This single-center retrospective study received approval from Pamukkale University, Medical Ethics Committee (03.10.2017/13).

## Patients

The patients diagnosed as having SS according to the criteria of the American Rheumatism Association 1980 (13) or ACR/EULAR 2013 classification criteria (14) for SS, between January 2009 and August 2017 were retrospectively analyzed.

The patients with SS who underwent HRCT scan within one month after the initial diagnosis were included in the study. Having respiratory symptoms was indication for performing HRCT. Patients with history of malignancy, esophageal-gastric surgery or smoking and patients with additional rheumatologic disease (such as rheumatoid arthritis, Sjögren syndrome) or patients with overlap syndromes (such as SS and Sjögren syndrome overlap syndrome) were excluded from the study.

Patients without HRCT screening within one month after initial diagnosis were not included in the study.

## High-Resolution Computed Tomography (HRCT) Scanning Protocol and Radiological Evaluation

All HRCT scans were obtained in the supine position with using a multi-detector CT system (Brilliance 16; Philips Healthcare, Best, the Netherlands) with full inspiration and the following parameters: Kv, 140; mAs, 280; detector collimation, 16x0.8/0.4 mm; slice thickness, 1 mm; slice interval, 10 mm; field of view (FOV), 35 cm and matrix, 512x512. Expiratory scans at least three selected levels (aortic arch, 2 cm above the diaphragm and tracheal carina) were obtained.

All HRCT images of the patients with SS were evaluated by two radiologists by consensus. Axial HRCT images of the chest were evaluated in the lung window for the presence of distal esophageal dilatation (with a maximum esophageal diameter  $\geq 9$  mm). Also HRCT images were evaluated in the mediastinal window for the presence of thymic hyperplasia (TH) (increased thymic thickness with  $\geq 13$  mm), MLNE (MLNE) (increased short-axis diameter with  $\geq 10$  mm), pleural or pericardial abnormalities (effusion or thickening).

## Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 19.0: SPSS Inc. IBM Corp, Chicago, IL, USA). Continuous and categorical data were reported as mean  $\pm$  standart deviation (SD), frequency and percentage. Intergroup comparisons were performed using independent t-test or a Mann-Whitney U test for continuous variables. Spearman's correlation coefficients and univariate correlations were used to detect the relationship between continuous variables.  $P < 0.05$  was considered to indicate statistical significance.

## Results

Medical database analysis revealed a total of 101 patients who were newly diagnosed as having SS between January 2009 and August 2017. Among these patients, 4 patients with history of malignancy (2 breast, 1 lung, 1 rectum cancer), 9 patients with additional rheumatic disease or overlap syndromes (4 Sjögren syndrome, 2 rheumatoid arthritis, 2 dermatomyositis, 1 systemic lupus erythematosus) and 9 patients with smoking history were excluded from the study. In addition, 26 patients with  $>1$ -month interval between imaging and initial diagnosis, 2 patients with

severe artifacts on HRCT. Totally, 51 patients [88.2% (n=45) females, 11.8% (n=6) males]; whose mean age  $\pm$  STD was 49.2 years  $\pm$  13.9 (range 18-71 years) and who met the appropriate conditions were included in the study. The median time between SS diagnosis and HRCT examination was 8 days (range: 1-23 days).

The HRCT findings (thymic enlargement, MLNE, esophageal dilatation, pleural-pericardial abnormalities) and frequencies are shown in Table 1 and 2. Also, correlations of variables are shown in Table 3. The HRCT images of the patients are shown in Figures 1-4.

Four patients had pericardial effusion (7.8%). Pericardial thickening was not seen in any patient. Six patients (11.8%) had pleural abnormality, including effusion (n=4), and focal pleural thickening (n=2).

There was no significant difference between male and female patients in terms of thymic enlargement ( $p=0.699$ ), MLNE ( $p=0.351$ ), esophagus dilatation ( $p=0.699$ ), pleural ( $p=0.699$ ) and pericardial abnormalities ( $p=0.457$ ).



**Figure 1.** A 42-year-old female with systemic sclerosis. Axial high-resolution computed tomography image obtained during deep inspiration shows ground-glass opacity areas (arrow heads). Also, distal esophageal dilatation is seen (black arrow)

**Table 1.** High-resolution computed tomography findings in patients with systemic sclerosis

HRCT Finding	Yes n (%)	No n (%)
Thymic enlargement	6 (11.8%)	45 (88.2%)
MLNE	6 (11.8%)	45 (88.2%)
Esophagus dilatation	45 (88.2%)	6 (11.8%)
Pleural abnormalities	6 (11.8%)	45 (88.2%)
Pericardial abnormalities	4 (7.8%)	47 (92.2%)

HRCT: High-resolution computed tomography, MLNE: Mediastinal lymph node enlargement, n: Number of patients

**Table 2.** Comparison of high-resolution computed tomography findings in patients with systemic sclerosis with mean age of the patients

HRCT Finding	Yes Mean Age	No Mean Age	p value
Thymic enlargement	44 years	49.9 years	0.441
MLNE	61.3 years	48.6 years	0.021
Esophagus dilatation	50.2 years	41.8 years	0.166
Pleural abnormalities	64.8 years	47.1 years	0.002
Pericardial abnormalities	62 years	48.1 years	0.054

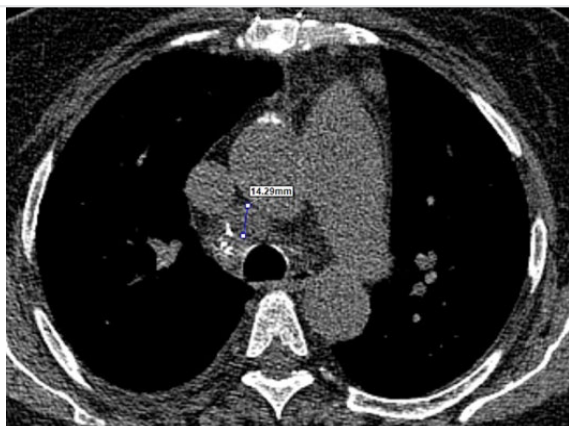
HRCT: High-resolution computed tomography, MLNE: Mediastinal lymph node enlargement, n: Number of patients,  $p<0.05$  means statistical significance

**Table 3.** Correlations of variables

HRCT Finding	1	2	3	4	5
1. Thymic enlargement	1	-0.13	0.13	-0.13	-0.11
2. MLNE	-0.13	1	0.13	0.62**	0.35*
3. Esophageal dilatation	0.13	0.13	1	0.13	0.11
4. Pleural abnormality	-0.13	0.62**	0.13	1	0.35*
5. Pericardial abnormality	-0.11	0.35*	0.11	0.35*	1

\* $p<0.05$ , \*\* $p<0.01$ , MLNE: Mediastinal lymph node enlargement, HRCT: High-resolution computed tomography





**Figure 2.** A 56-year-old female with systemic sclerosis. Axial high-resolution computed tomography image shows right para-tracheal lymph node enlargement with a 14 mm short axis



**Figure 3.** A 48-year-old female with systemic sclerosis. Axial high-resolution computed tomography image obtained during deep inspiration shows pericardial effusion with a 9 mm thickness



**Figure 4.** A 36-year-old male with systemic sclerosis. Axial high-resolution computed tomography image shows thymic enlargement with a 21 mm thickness (white arrows)

## Discussion

According to our results, esophageal dilatation (88.2%) is frequently found in SS patients with respiratory symptoms, at the time of initial diagnosis. MLNE and pleural abnormalities are significantly more common in patients with SS diagnosis at the late age.

Although the actual role of thymic abnormalities on imaging studies in patients with SS is still unclear, the possible involvement of the immune-mediated SS pathogenesis at an early stage may be presumed (7,8,14). When the increased thymic thickness was accepted as a threshold value of greater than 13 mm, Colaci et al. (15) reported that the frequency of abnormalities in thymus size was 9.5% (19 of 200 patients) in patients with SS with a mean of 5-year (0-38 years) disease duration. Ferri et al. (7) found that, radiological thymic enlargement were correlated with SS disease duration and thymic enlargement more common in patients with short disease duration ( $\leq 5$  years or  $> 5$  years;  $p=0.007$ ). They detected thymic enlargement in 9 of 34 cases (26%). We found that thymic enlargement was present in 11.8% (6 of 51) of patients with SS, at the time of initial diagnosis. In addition, studies showed that patients with SS with thymic enlargement were found at a younger age. For this reason, it has been argued that thymic enlargement is due to insufficient involution of the thymus gland (16-18). In our study, although the mean age of cases with thymic enlargement was lower than that of without thymic enlargement, there was no statistically significant difference between the age of initial diagnosis and presence of thymic enlargement (44 vs 49.9 years;  $p=0.441$ ). This may be due to a small number of cases in our study. In our study, unlike previous studies, the HRCT findings of newly diagnosed patients with SS were evaluated. We suggest that the duration of the disease and the medications may cause thymic abnormalities. There is a need for more extensive studies in order to explain this situation.

MLNE has been reported to be a common finding in patients with SS (9). In patients with SS, Santos et al. (5) demonstrated that, MLNE was present in 5 of 23 patients (21%), Yamakawa et al. (17) found that MLNE was seen in 20% ( $n=40$ ), and Farrokh et al. (18) found that 30% ( $n=40$ ) of patients with SS had MLNE on HRCT. Wechsler et al. (19) and Garber et al. (20) found that MLNE was present in %50 and 32% of patients with SS, respectively. In those studies, examining the prevalence of MLNE, the duration of the disease and medical treatment were not considered (5,9,17-20). In our study, MLNE was present in 11.8% of newly diagnosed SS patients ( $n=51$ ). The mean age of the patients with MLNE was significantly higher than those without MLNE ( $p=0.021$ ). It is more likely that elderly patients have more SS disease duration and risk of infectious lung diseases than younger ones.

Another common finding in patients with SS is esophageal involvement. Esophageal involvement is common in SS and it can occur from 58 to 80% in different studies (9,21,22). Vonk et al. (21) reported that, esophageal dilation in patients with interstitial lung disease suggests a diagnosis of SS with a high sensitivity and specificity on HRCT (63% and 88%, respectively). In our study,

we demonstrated that esophageal dilation is a frequent HRCT finding in patients with SS at the time of initial diagnosis, with a rate of 88.2% (45/51).

It has been reported that pleural abnormalities are rarely present in patients with SS. Pleural abnormalities may be seen as, diffuse or focal pleural thickening, pleural effusion, and pseudo-plaques (22). Farrokh et al. (18) reported that pleural abnormality was present in 30% of patients (12 of 40) with SS and they found 4 patients had pleural effusion, 8 patients had pleural thickening. Yamakawa et al. (17) found that, pleural abnormality (thickening or effusion) was present in 10% of patients with SS (n=40). Pleural effusion in patients with SS is an uncommon finding that requires a complete evaluation to exclude different causes of pleural effusion such as heart failure, side effects of medication and pneumonia (23). Similar to Yamakawa et al. (17), we also detected that 11.8% of SS patients had pleural abnormalities on HRCT. We also found that, as expected, the age of the patients with pleural abnormality was significantly higher than the age of the patients without pleural abnormality ( $p=0.002$ ). This may be due to the fact that elderly patients are more likely to develop empyema or hemothorax than younger patients. Also, pleural abnormality may occur due to long disease duration or heart failure in the elderly.

This study has some limitations. First, the HRCT images were evaluated by two observers by consensus so the differences between the observers could not be assessed. Second, it was a retrospective study that involved a relatively small number of cases. Third, there was also sampling bias since only patients with positive respiratory symptoms were included in the study. So, we could not evaluate the extra-parenchymal chest CT findings in patients without respiratory symptoms. Finally, we did not have histopathological findings and we could not make a radiological-histopathological comparison.

## Conclusion

Despite these limitations, our study suggests that esophageal dilatation is frequently found in patients with SS with respiratory symptoms at the time of initial diagnosis. MLNE and pleural effusion are more common in newly diagnosed patients with SS at the late age, probably due to long disease duration and advanced age.

## Ethics

**Ethics Committee Approval:** This single-center retrospective study received approval from Pamukkale University, Medical Ethics Committee (03.10.2017/13).

**Informed Consent:** Written informed consent was not obtained from participants due to retrospective nature of study.

**Peer review:** Externally peer-reviewed.

## Authorship Contributions

Concept: F.U., P.Ç., Design: F.U., E.S., Data Collection or Processing: F.U., Analysis or Interpretation: F.U., Literature Search: E.S., P.Ç., Writing: F.U., B.Y.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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