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Association of neutrophil/lymphocyte ratio with the degree of interstitial lung disease in systemic sclerosis

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Background/aim: Determining the severity of systemic sclerosis related interstitial lung disease (SSc-ILD) is based on clinical and radiological findings, inflammation marker levels, and carbon monoxide diffusing capacity of the lung (DLCO). Recently studies are ongoing for objective and easy markers. Neutrophil/lymphocyte ratio (NLR) is shown to be a good marker for inflammation in recent clinical trials. In this study, we aimed to identify the possible relationship between NLR and carbon monoxide transfer coefficient (KCO) of SSc-ILD patients.

Materials and methods: Fifty-nine patients with systemic sclerosis (SSc) were enrolled in the study. We used high-resolution computed tomography for diagnosis and used DLCO to evaluate degree of lung involvement. Complete blood cell counts and acute phase reactants were included as laboratory assessments.

Results: NLR values were significantly higher in the SSc-ILD group (3.66 ± 1.32 vs. 2.85 ± 1.12, P = 0.01) and correlated negatively with KCO. The NLR cut-off value was 3.21, its sensitivity was 81%, and its specificity was 81%.

Conclusion: NLR level may serve as a marker of lung involvement in the presence of ILD in patients with SSc.

Key words: Inflammation, neutrophil/lymphocyte ratio, systemic sclerosis, interstitial lung disease

1. Introduction

Systemic sclerosis (SSc) is an autoimmune disease that can potentially affect gastrointestinal, renal, cardiovascular, and pulmonary systems by disease-specific autoantibodies and overproduction of collagen (1). Although pulmonary thromboembolic disease, aspiration pneumonitis, pleural disease, airways disease, lung cancer, and drug-induced pneumonitis might also be seen, interstitial lung disease (ILD) is the most common and worrisome lung involvement form of SSc (2).

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are commonly used biomarkers of the inflammatory response status in patients with SSc. CRP level is elevated in one-quarter of SSc patients, especially at the onset of the disease (3). It is correlated with disease activity, severity, poor pulmonary function, and shorter survival (3). Recent studies showed that neutrophil/lymphocyte ratio (NLR) is also a marker of inflammation such as CRP and ESR (4). Carbon monoxide transfer coefficient (KCO) is an important indicator of parenchymal destruction and shows the rate of uptake of carbon monoxide (CO) from alveolar gas. The aim of the present study was to investigate possible relationships between NLR and KCO in systemic sclerosis related interstitial lung disease (SSc-ILD) patients.

2. Materials and methods

This study was designed and performed in the Department of Rheumatology of the Kahramanmaraş Sütçü İmam University Faculty of Medicine, Turkey. In total, 82 SSc patients were retrospectively screened. Exclusion criteria were active infection, and the presence of any hematological (included anemia), cardiovascular, and metabolic disorders. Thus we excluded 23 patients, and 59 patients were enrolled in the study. SSc-ILD was present in 34 of them and there was no pulmonary involvement in the remaining 25. We compared the groups with and without lung involvement.

Venous blood was drawn from each patient into tubes with and without anticoagulant. The standard laboratory workup included counts of white blood cells (WBC), neutrophils (NEU), and lymphocytes (LYM), and

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calculation of the NLR. ESR was measured immediately after blood collection. CRP levels were measured by nephelometric methods.

High resolution computed tomography (HRCT) was used for the diagnosis of ILD. Ground-glass opacification and honeycomb reticular shadowing were accepted as ILD. We used the diffusing capacity of the lungs for carbon monoxide (DLCO) and KCO to evaluate the degree of ILD. A value ≥ 81 for DLCO and KCO is considered normal (5).

Student's t-test was used for comparison of averages. Correlations among variables were assessed by Pearson's correlation testing. A P-value < 0.05 was considered to indicate a significant difference. ROC analysis was used for determining the cut-off value of the NLR.

3. Results

Thirty-four SSc patients with ILD and 25 SSc patients without ILD as a control group were enrolled in the present study. The demographics and clinical and laboratory characteristics of the patients and controls are summarized in Table 1. There were 25 female and 9 male patients in the ILD group and 19 female and 6 male patients in the control group (P = 0.08). The median disease duration in the ILD and control groups was 4.3 ± 2.3 and 3.1 ± 2.9 years, respectively (P = 0.88). There was no statistically significant difference between the two groups with regard to sex, age, or disease duration.

Table 1. Sociodemographic attributes and laboratory characteristics of patients with SSc.

	SSc patients (n=59)
Age (years), mean ± SD	48 ± 12.7
Sex (M/F)	15/44
Age at onset of SSc (years)	40 ± 14.5
Disease duration (years), mean ± SD	3.7 ± 2.6
WBC count (K/μL), mean ± SD	7395 ± 1697
Hb count (g/dL), mean ± SD	13.4 ± 1.33
PLT count (K/μL), mean ± SD	306 ± 78
NLR, mean ± SD	3 ± 1.2
ESR (mm/h), mean ± SD	28 ± 19.4
CRP value (mg/dL), mean ± SD	4.7 ± 7.9

SSc, systemic sclerosis; SD, standard deviation; WBC, white blood cell; Hb, hemoglobin; PLT, platelets; NLR, neutrophil to lymphocyte ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

White blood cell (WBC) counts of the ILD and control groups were 7576 ± 1715 and 7262 ± 1697 K/μL respectively (P = 0.48). Mean hemoglobin (Hb) values were 13.3 ± 0.9 g/dL in the ILD group and 13.5 ± 1.5 g/dL in the control group (P = 0.53). Mean platelet counts (PLT) were 306 ± 78 K/μL in the ILD group and 305 ± 95 K/μL in the control group. SSc patients with and without ILD had similar WBC, Hb, and PLT counts. The mean NLR of the ILD and control patients was 3.6 ± 1.35 and 2.8 ± 1.08, respectively, using Student's t-test (P = 0.001). The serum NLR of ILD patients was significantly higher than that of the controls. We used Student's t-test for comparing the groups (KCO ≥ 81 vs. KCO ≤ 80). The mean NLR of patients with KCO ≥ 81 and KCO ≤ 80 was 2.11 ± 0.8 and 4.05 ± 1.48, respectively (P = 0.00).

The correlation analysis between NLR and ESR, CRP, DLCO, and KCO is summarized in Table 2. There was no significant difference between the ILD and control groups with regard to ESR (P = 0.07) or DLCO (P = 0.3) values. NLR values correlated negatively with the KCO values (P = 0.04, r = −0.32) and correlated positively with CRP values of SSc patients (P = 0.04, r = 0.32) (Table 3). ROC analysis was done for determining NLR cut-off level and found to be 3.21; its sensitivity was 81% and specificity was 81% (Figure).

4. Discussion

The main finding of our study relates to the identification of the NLR as a novel noninvasive marker of disease severity in SSc-ILD. We showed that the NLR levels were positively correlated with CRP and negatively correlated with KCO.

HRCT is the standard method for noninvasive diagnosis of SSc-ILD and can detect mild abnormalities. The HRCT pattern seen in SSc patients is generally nonspecific interstitial pneumonia (NSIP), with a greater proportion of ground-glass opacities and a lower degree of coarse reticulation. However, a usual interstitial pneumonia

Table 2. Correlation analysis between NLR and ESR, CRP, DLCO, and KCO values.

		CRP value (mg/dL)	ESR (mm/h)	DLCO	KCO
NLR	r value	0.32	0.28	-0.16	-0.32
	P value	**0.04**	0.07	0.3	**0.04**

NLR, neutrophil to lymphocyte ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DLCO, transfer factor of the lung for carbon monoxide; KCO, coefficient factor of the lung for carbon monoxide.

Table 3. NLR values for SSc-ILD patients according to KCO.

		NLR	P value
KCO	≤80	4.05 ± 1.48	0.00
	≥81	2.11 ± 0.8	

NLR, neutrophil to lymphocyte ratio; KCO, coefficient factor of the lung for carbon monoxide.

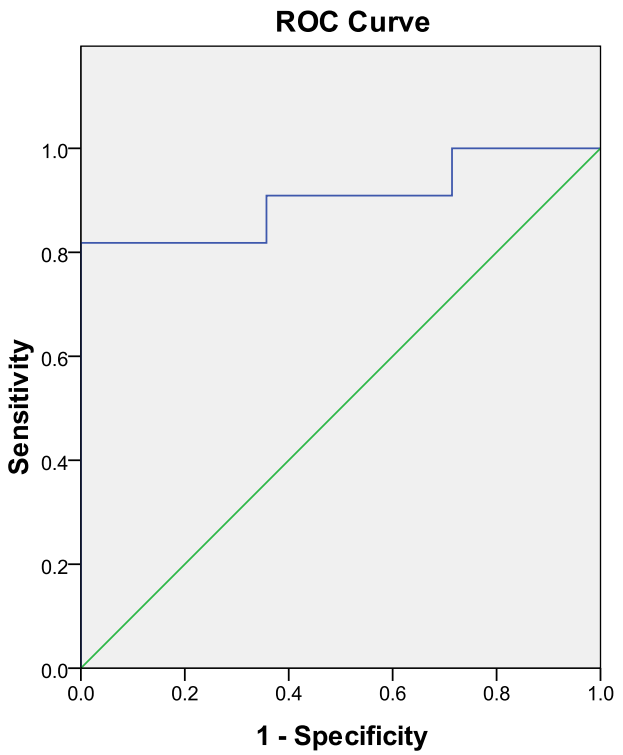

Figure. ROC analysis for NLR cut-off value.
NLR, neutrophil to lymphocyte ratio

(UIP) pattern and honeycomb cysts can also be seen (6). Although forced vital capacity (FVC) and DLCO are both identified as prognostic markers in SSc-ILD, a declining DLCO is the single most significant marker of poor outcome and correlates with the extent of lung disease on HRCT (7). The DLCO measures the capacity of the lungs to transfer gas from air to the red blood cells in pulmonary capillaries. The DLCO test is more convenient and easier and takes less time than spirometric tests and there are no contraindications or adverse effects. Because of these reasons we use DLCO for follow-up of SSc-ILD patients in our clinic.

The value calculated from DLCO/alveolar volume (VA) is related to Krogh's constant, K, and for this reason DLCO/VA is also known as KCO. KCO is useful for distinguishing the reason for total lung capacity (TLC) decrease as intraparenchymal or extraparenchymal. This means that when TLC is reduced but the lung tissue is normal, which would be the case with neuromuscular diseases or chest wall diseases, then KCO should be increased. Interstitial involvement in restrictive lung disease is often complicated and there can be multiple reasons for a decrease in DLCO. Scarring and a loss of elasticity cause the lung to become stiffer and harder to expand, which decreases TLC. The alveolar membrane can thicken, which increases resistance to the transfer of gases. Moreover, probably, most commonly there is destruction of the alveolar capillary bed, which decreases the pulmonary capillary blood volume and the functional alveolar capillary surface area. This means that when TLC is reduced and there is interstitial involvement, a normal KCO (in terms of percent predicted) is actually abnormal. The components of DLCO (KCO and VA) may largely vary in ILD while DLCO appears constant. The magnitudes of KCO and VA values might indicate distinct disease mechanisms and thereby bear a relative prognostic value in addition to giving clues to the pathogenesis of these diseases. There are several studies confirming clinicians should take into account not only DLCO but also VA and KCO when seeking to assess ILD (8). Because of its high sensitivity in ILD we used KCO in our study.

Both ESR and CRP are acute-phase reactants. CRP is produced by hepatocytes upon stimulation by interleukin-6 (IL-6) and has been utilized as a marker of infection and inflammation (9). ESR is a biomarker for increased morbidity and mortality in SSc (10,11). However, data are limited about the impact of CRP associations with SSc activity and severity. CRP level was found elevated in 35%–54% of Japanese patients with SSc in two studies, but the sample size was small (40 patients in each study) (12,13).

The current study showed that elevated CRP levels are correlated with lung involvement rated according to KCO in SSc-ILD.

The NLR, differentially (and readily) calculated from complete blood count data, has recently been shown to be a novel marker of infection and inflammation (14,15). An increase in the NLR has been noted to be common in patients with cancer, cardiovascular disease, active rheumatoid arthritis, and active ulcerative colitis (16–19).

The present study had some limitations including the cross-sectional design and the relatively small sample size; SSc-ILD was not evaluated separately as honeycombing and ground glass and our study was not designed to elucidate the mechanistic pathways that lead to higher NLR in patients with SSc.

In conclusion, NLR values can serve as useful markers of SSc-ILD in the absence of a rise in the ESR and CRP level.

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