

ACE/LYMPHOCYTE RATIO AND CONUT SCORE: KEY PREDICTORS OF EXTRAPULMONARY INVOLVEMENT AND RECURRENCE IN SARCOIDOSIS

Kadir Canoglu¹, Omer Ayten², Gokce Kulah³, Hasan Furkan Avcı⁴, Ilyas Kocabag¹, Erhan Ogur¹, Insa Gul Ekiz Iscanli⁵

¹Sultan 2. Abdulhamid Han Training and Research Hospital, Pulmonology, Istanbul, Türkiye; ²Liv Vadi Istanbul Hospital, Pulmonology, Istanbul, Türkiye; ³Umraniye Training and Research Hospital, Pulmonology, Istanbul, Türkiye; ⁴Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Immunology and Allergy, Istanbul, Türkiye; ⁵Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Respiratory Intensive Care Unit, Istanbul, Türkiye

ABSTRACT. *Background and aim:* Extrapulmonary involvement is associated with high morbidity and mortality in sarcoidosis. Sarcoidosis recurrence rates vary between 37-75% in the literature. In this study, we aimed to investigate the association of ACE/lymphocyte ratio and The Controlling Nutritional Status (CONUT) score with systemic involvement and recurrence in sarcoidosis. *Methods:* 156 adult patients diagnosed with sarcoidosis was conducted in this retrospective, single-center study between 01.09.2016 - 31.12.2021 in the pulmonology clinic of Sultan 2. Abdulhamid Han Training and Research Hospital in Istanbul/Türkiye. The ACE/lymphocyte ratio was calculated by dividing the serum ACE level by lymphocyte count. CONUT score was calculated according to serum albumin, lymphocyte count and total cholesterol levels. *Results:* Fifty (32%) patients had systemic involvement. In patients with systemic involvement, serum ACE and ACE/lymphocyte ratio were higher and lymphocytes were lower than those without systemic involvement ($p < 0.05$). 24 (15.4%) patients had recurrence. Serum ACE and ACE/lymphocyte ratio were found to be higher in patients with recurrence compared to those without recurrence ($p < 0.05$). There was no statistically significant difference between the groups in terms of CONUT score ($p = 0.232$). In Spearman's Rho correlation, systemic involvement and recurrence were positively correlated with ACE/lymphocyte ratio ($p < 0.05$). In Binary Logistic Regression, ACE/lymphocyte ratio was not associated with recurrence and systemic involvement ($p > 0.05$). In ROC curve analysis, the sensitivity, specificity and AUC of ACE/lymphocyte ratio in predicting systemic involvement were 78%, 39.8% and 0.644, respectively with a cut-off value of 19.55; and in predicting recurrence were 79.2%, 44.8% and 0.714, respectively with a cut-off value of 22.41. *Conclusions:* The ACE/lymphocyte ratio, which was evaluated for the first time in the literature, was found to be higher in patients with systemic involvement in sarcoidosis than in those without, and higher in patients with recurrence than in those without. Therefore, it can be used to predict extrapulmonary involvement, which can have high mortality and morbidity, as well as recurrence in post-treatment follow-up.

KEY WORDS: ace/lymphocyte ratio, conut score, extrapulmonary sarcoidosis, recurrence predictors, angiotensin converting enzyme, nutritional status, sarcoidosis outcomes, disease recurrence

INTRODUCTION

Sarcoidosis is a chronic inflammatory disease of unknown etiology, characterised by non-caseating granulomas, which frequently involves the lung but can also involve all organs and tissues (1). Extrapulmonary involvement, particularly cardiac and neurological, is associated with morbidity and mortality

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Correspondence: Dr. Kadir Canoglu

Sultan 2. Abdulhamid Han Training and Research Hospital,
Pulmonology, Istanbul, Türkiye.

E-mail: kadircano@gmail.com

ORCID: 0000-0003-1579-3392

(2). Corticosteroids are the mainstay of treatment, discontinuation after 6-12 months of use has been tried. The duration of treatment is decided on the basis of benefit/harm (3). However, recurrence can be observed especially in the first 3 years after discontinuation of treatment. Sarcoidosis recurrence rates vary between 37-75% in the literature (4). The Controlling Nutritional Status (CONUT) score is a marker of nutritional status. In the literature, the CONUT score has been investigated for nutritional status in various malignancies (5). Serum angiotensin converting enzyme (ACE) indicates granuloma burden and disease activation; mostly used in patient follow-up (1). Lymphopenia is also a common hematologic change in sarcoidosis. Jones et al. reported that lymphopenia may be associated with the presence of uveitis in new-diagnosed sarcoidosis (6). Furthermore, Niederer et al. reported that elevated serum ACE levels and lymphopenia were associated with an increased risk of systemic sarcoidosis (7). In this study, we investigated the association of ACE/lymphocyte ratio as a novel biomarker with systemic involvement and recurrence in sarcoidosis. Furthermore, the role of the CONUT score, which indicates nutritional status, was investigated in sarcoidosis.

METHODS

One hundred and fifty-six adult patients diagnosed with sarcoidosis was conducted in a retrospective, single-center study between 01.09.2016 and 31.12.2021 in the pulmonology clinic of Sultan 2. Abdulhamid Han Training and Research Hospital in Istanbul/Türkiye. Patients diagnosed with malignancy that may affect the CONUT score were excluded from the study. Age, gender, serum ACE, urinary calcium, sedimentation, neutrophil and lymphocyte counts, albumin, cholesterol, forced expiratory volume (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) values were recorded. Since blood tests such as serum ACE and lymphocytes may be affected by steroid treatment, blood results obtained at the time of initial presentation were used prior to diagnosis and treatment. CONUT score was calculated according to serum albumin, lymphocyte count and total cholesterol levels. 0-1 points are classified as normal, 2-4 points as mild, 5-8 points as moderate and 9-12 points as severe (5). The ACE/lymphocyte ratio was calculated by dividing the serum ACE level by lymphocyte count.

Skin, eye, cardiac, neurological involvement and hypercalciuria were recorded as systemic involvement. We use the WASOG sarcoidosis organ assessment instrument for extra-pulmonary disease (8). Recurrence was defined as clinical, radiological and respiratory deterioration requiring a new course of steroids treatment in patients who were followed up after treatment discontinued for more than 1 month (9). The follow-up after study entry was two years. Relapses typically occur 1 month to 1 year after steroid treatment discontinuation (10). Therefore, follow-up period was at least one year after steroid discontinuation. Descriptive analyses (frequency distributions, percentage, mean, standard deviation, 95% confidence intervals) were used as statistical methods to analyze the data. The t-test was used when the data were normally distributed and Mann Whitney U test was used when the data were not. Spearman's rho correlation and Binary Logistic Regression analysis were used for correlations. ROC curve analysis was used for the cut-off point. The results were evaluated at 95% confidence interval and $p < 0.05$ significance level. SPSS 22.0 package program was used for data analysis.

RESULTS

A total of 156 patients with sarcoidosis were included in the study. 50 (32%) patients had systemic involvement. In patients with systemic involvement, serum ACE and ACE/lymphocyte ratio were higher, and lymphocytes were lower than those without systemic involvement ($p=0.034$, $p=0.004$, $p=0.029$; respectively). There was no statistically significant difference between the groups in terms of CONUT score ($p=0.232$) (Table 1). In Spearman's Rho Correlation test, systemic involvement was positively correlated with serum ACE ($r=0.170$, $p=0.034$), ACE/lymphocyte ratio ($r=0.234$, $p=0.004$) and negatively correlated with lymphocyte ($r=-0.177$, $p=0.029$) (Table 2). Although ACE, ACE/lymphocyte ratio and lymphocytes were found to be statistically correlated with systemic involvement in univariate analysis; no association was found in Binary Logistic Regression multivariate analysis ($p > 0.05$) (Table 3). In ROC curve analysis, the sensitivity, specificity and area under the curve (AUC) of ACE/lymphocyte ratio in predicting systemic involvement were 78%, 39.8% and 0.644, respectively with a cut-off value of 19.55 (Figure 1).

Table 1. Baseline characteristics of patients and differences according to systematic involvement and recurrence

	Systemic involvement		p value
	No (n=106)	Yes (n=50)	
Age, mean ± SD	45.58±14.36	44.94±14.95	0.797*
Gender			
Female	58 (54.7)	35 (70.0)	
Male	48 (45.3)	15 (30.0)	0.049 †
Involvement			
Skin	-	23 (46.0)	0.000 †
Eye	-	13 (26.0)	0.000 †
Hypercalciuria	1(0.9)	4 (8.0)	0.037 †
Neurological	-	1 (2.0)	0.323†
Cardiac	-	1 (2.0)	0.321†
Other	2 (1.9)	20 (40.0)	0.000 †
Treatment	51 (49.5)	31 (64.6)	0.059†
Recurrence	12 (11.5)	12 (25.0)	0.033 †
CONUT score			
Mild	95 (95.0)	43 (89.6)	
Moderate	4 (4.0)	5 (10.4)	0.232‡
Severe	1 (1.0)		
Serum ACE	59.10±42.98	75.71±51.04	0.034 §
Urine Ca	153.84±129.22	153.34±108.00	0.982§
Sedimentation	24.74±21.94	30.71±27.04	0.304§
Neutrophile	4.31±1.57	4.65±1.91	0.454§
Lymphocyte	1.88±0.60	1.76±0.89	0.029 §
Albumin	4.22±0.48	4.13±0.47	0.274§
Cholesterol	204.75±35.65	202.38±49.49	0.775*
FVC lt	3.52±1.02	3.04±0.81	0.047 *
DLCO lt	7.47±2.37	6.24±2.09	0.063*
ACE/Lymphocyte	35.20±33.90	53.95±49.46	0.004 §
	Recurrence		p value
	No (n=132)	Yes (n=24)	
Age, mean ± SD	44.92±14.74	48.25±11.76	0.298*
Gender			
Female	75 (58.6)	18 (75.0)	0.098†
Male	53 (41.4)	6 (25.0)	
Involvement			
Skin	17 (13.3)	4 (16.7)	0.432†
Eye	8 (6.3)	5 (20.8)	0.035 †
Hypercalciuria	3 (2.3)	2 (8.3)	0.177†
Neurological	1 (0.8)	-	0.841†
Cardiac	-	1 (4.2)	0.158†

	Systemic involvement		p value
	No (n=106)	Yes (n=50)	
Other	15 (11.7)	6 (25.0)	0.085†
Treatment	58 (45.7)	24 (100.0)	0.000 †
Systemic involvement	36 (28.1)	12 (50.0)	0.033 †
CONUT score			
Mild	112 (92.6)	23 (95.8)	
Moderate	8 (6.6)	1 (4.2)	0.741‡
Severe	1 (0.8)	-	
Serum ACE	58.63±39.81	99.33±63.47	0.003§
Urine Ca	145.90±121.50	180.61±125.52	0.299§
Sedimentation	27.54±24.40	23.57±21.51	0.508§
Neutrophile	4.38±1.67	4.64±1.90	0.674§
Lymphocyte	1.89±0.71	1.65±0.73	0.066§
Albumin	4.19±0.50	4.20±0.35	0.695§
Cholesterol	205.88±41.73	199.96±32.88	0.524*
FVC lt	3.43±1.00	3.10±0.88	0.252*
DLCO lt	7.16±2.42	6.42±1.98	0.336*
ACE/Lymphocyte	34.81±28.49	76.93±69.34	0.001§

*Independent Samples t-test, † Fischer's Exact Test, ‡ Chi-Square likelihood ratio, § Mann Whitney U Test, Abbreviations: SD: Standard Deviation.

Table 2. Spearman's rho correlation between systemic involvement/recurrence and significantly different parameters

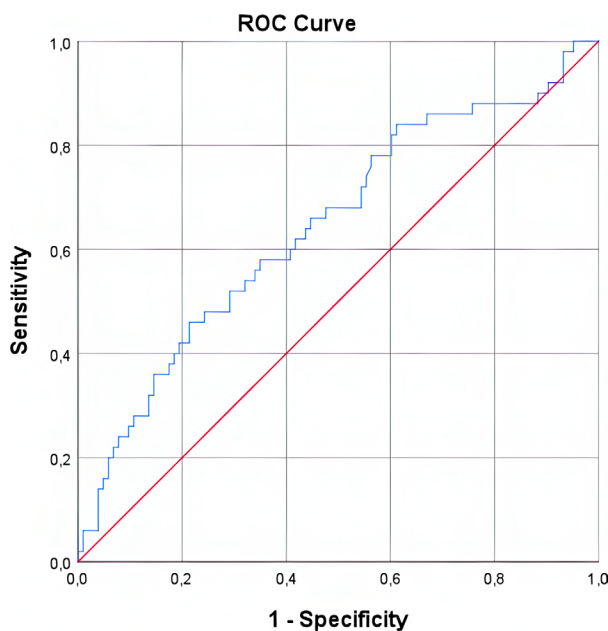
Systemic involvement	r	p
Gender	-0.145	0.070
Recurrence	0.172	0.035*
Serum ACE	0.170	0.034*
Lymphocyte	-0.177	0.029*
FVC lt	-0.210	0.071
ACE/Lymphocyte	0.234	0.004†
Recurrence	r	p
Stage	0.253	0.002†
Systemic involvement	0.172	0.035*
Serum ACE	0.243	0.003†
ACE/Lymphocyte	0.273	0.001†

*p<0.05 † p<0.01

A total of 24 (15.4%) patients had recurrence, requiring a new course of steroids. Time to relapse after the steroid withdrawal was 13 months (mean time; range 1-32). Serum ACE and ACE/lymphocyte ratio

Table 3. Binary Logistic Regression analysis results for systemic involvement

	B	S.E.	Wald	df	p	Exp(B)	95% C.I. for EXP (B)	
							Lower	Upper
Recurrence	-0.532	0.497	1.144	1	0.285	0.588	0.222	1.557
Serum ACE	0.000	0.008	0.001	1	0.970	1.000	0.984	1.016
Lymphocyte	0.081	0.336	0.058	1	0.810	1.084	0.561	2.096
ACE/Lymphocyte	0.011	0.011	0.885	1	0.347	1.011	0.988	1.034
Constant	-0.897	0.867	1.070	1	0.301	0.408		
	B	S.E.	Wald	df	p	Exp(B)	95% C.I. for EXP (B)	
							Lower	Upper
Systemic involvement	-0.335	0.580	0.333	1	0.564	0.716	0.230	2.229
SerumACE	0.002	0.009	0.077	1	0.781	1.002	0.986	1.019
ACE/Lymphocyte	0.017	0.010	2.819	1	0.093	1.017	0.997	1.037
Constant	-1.844	0.835	4.873	1	0.027	0.158		



Diagonal segments are produced by ties.

Figure 1. ROC analysis for predictive value of ACE/Lymphocyte on systemic involvement

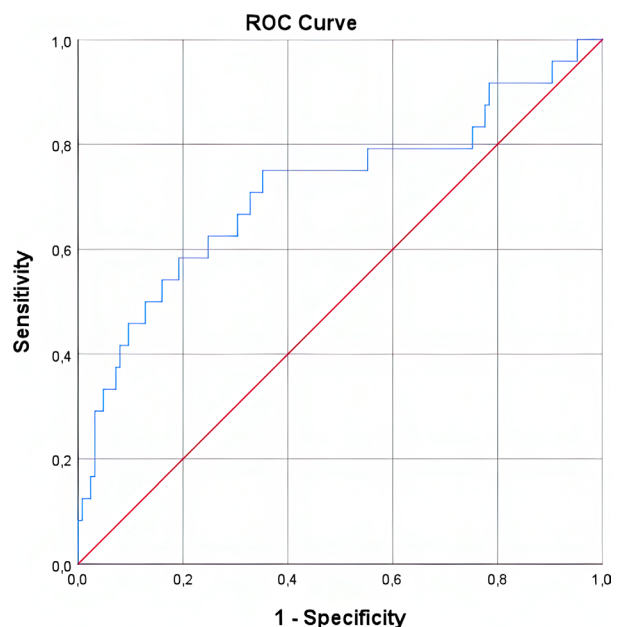


Figure 2. ROC analysis for predictive value of ACE/Lymphocyte on recurrence

were found to be higher in patients with recurrence compared to those without recurrence ($p=0.003$, $p=0.001$, respectively). No significant difference was found between the groups in terms of CONUT score ($p=0.741$) (Table 1).

In Spearman's Rho correlation test, recurrence was correlated with serum ACE ($r=0.243$, $p=0.003$) and ACE/lymphocyte ratio ($r=0.273$, $p=0.001$) (Table 2).

Although ACE and ACE/lymphocyte ratio were significantly correlated with recurrence in univariate analysis, no association was found in Binary Logistic Regression analysis ($p>0.05$) (Table 3).

In ROC curve analysis, the sensitivity, specificity and AUC of ACE/lymphocyte ratio in predicting recurrence were 79.2%, 44.8% and 0.714, respectively with a cut-off value of 22.41 (Figure 2).

DISCUSSION

This study described the sensitivity and specificity of serum ACE/lymphocyte ratio in predicting systemic involvement and recurrence in sarcoidosis. CONUT score had no effect in both conditions.

Mirsaeidi et al. found a correlation between hypoalbuminemia with sedimentation and CRP, while no correlation was found with body mass index (BMI). Therefore, the authors concluded that hypoalbuminemia may be related to inflammation rather than malnutrition (11). Dumas et al. found a relationship between BMI and the risk of developing sarcoidosis. Therefore, overweight (BMI 25-29.9 kg/m²) and obese (BMI ≥30 kg/m²) patients had an increased risk of developing sarcoidosis (12). In our study, CONUT score was used as a nutritional index and no association was found with systemic involvement and recurrence of sarcoidosis. Biomarkers such as serum ACE and chitotriosidase are parameters that can be used to indicate sarcoidosis activity (13). Furthermore, neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), which are cheap and easily accessible parameters, have been studied in sarcoidosis in recent years. NLR and PLR were found to be higher in sarcoidosis patients compared to the control group and may be related to the stage of the disease (14-16). In the current study, the ACE/lymphocyte ratio, which was evaluated for the first time in the literature, was found to be higher in patients with systemic involvement in sarcoidosis than in those without, and higher in patients with recurrence than in those without. Therefore, it can be used to predict extrapulmonary involvement, which can have high mortality and morbidity, as well as recurrence in post-treatment follow-up. The study has some limitations. First, no BMI comparison was made between patient groups when evaluating the CONUT score. This may have affected the assessment of the CONUT score. Second, since the study was retrospective, it cannot be generalized to all sarcoidosis patients and should be supported by prospective studies.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership,

equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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