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Are inflammatory and malnutrition markers associated with metabolic syndrome in patients with sarcoidosis?

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SUMMARY

OBJECTIVE: The study aimed to investigate the use of Neutrophil/lymphocyte ratio, C-reactive protein/albumin ratio, controlling nutritional status, and prognostic nutritional index immune, inflammatory, and malnutrition markers Metabolic syndrome+ in sarcoidosis patients, as an early-stage marker.

METHOD: This is a single-center and cross-sectional study that determines the association of Metabolic syndrome in patients with sarcoidosis. Patients were evaluated based on the National Cholesterol Education Program's Adult Treatment Panel III criteria. Neutrophil/lymphocyte ratio, C-reactive protein/albumin ratio, controlling nutritional status, and prognostic nutritional index values were simultaneously determined through blood test.

RESULTS: A total of 253 patients diagnosed with sarcoidosis were included in this study. Metabolic syndrome– was detected in 37.2% of patients. The prevalence was significantly higher in females (p<0.001). Any degree of malnutrition assessed by controlling nutritional status had higher Metabolic syndrome (p=0.035). The Neutrophil/lymphocyte ratio cutoff value was 2.24, sensitivity was 70.53, specificity was 60.13, and Area Under the Curve value was 0.663 for predicting Metabolic syndrome in sarcoidosis patients.

CONCLUSION: Neutrophil/lymphocyte ratio and controlling nutritional status are associated with the Metabolic syndrome+ in sarcoidosis patients. Thus, close monitoring of Neutrophil/lymphocyte ratio and controlling nutritional status increase in terms of Metabolic syndrome and immune malnutrition may be important in sarcoidosis patients.

KEYWORDS: Metabolic syndrome. Sarcoidosis. Neutrophils. Lymphocytes. Abdominal obesity. C-reactive protein. Albumin. Prognostic nutritional index.

INTRODUCTION

Sarcoidosis is a chronic systemic granulomatous disease that commonly affects the lungs. In the course of this disease, neurological findings, uveitis, blindness, end-stage pulmonary fibrosis, pulmonary hypertension, arrhythmia, cardiomyopathy, hypercalcemia, and renal failure may develop; approximately one-third of these side effects progresses as a chronic disease[1].

Metabolic syndrome (MetS) is a heterogeneous disease that develops on the basis of insulin resistance and involves the combination of systemic disorders such as abdominal obesity,

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glucose intolerance or diabetes mellitus, dyslipidemia, hypertension, and coronary artery disease (CAD)[2]. The neutrophil/lymphocyte ratio (NLR) is a systemic inflammatory marker that can be easily measured and used in the prognosis of several chronic diseases.

In a recent study by Gülhan et al., the coexistence of MetS and insulin resistance was evaluated in patients with sarcoidosis and was found to be increased[3]. Due to MetS components, the risk of early atherosclerosis and the presence of abdominal obesity are particularly important in terms of cardiovascular complications. Our study investigated the predictive value of NLR in predicting the incidence of MetS and the presence of MetS in sarcoidosis patients.

METHODS

The study was designed as an observational, cross-sectional study. The patients who were consecutively admitted as outpatient to the pulmonary medicine department were enrolled. The study was approved by the Local Ethics Committee.

All 345 patients diagnosed with sarcoidosis were screened cross-sectionally to evaluate MetS association and NLR according to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) criteria. Those who had received or were planning to receive steroid therapy within the past six months, pregnant women, emergency patients, terminal-stage malignancies, and those with active and suspected infectious diseases were excluded from the study. Finally, a total of 253 patients, 94 sarcoidosis with MetS patients and 159 sarcoidosis without MetS patients, were included in the study.

The presence of diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), and cardiovascular disease (CVD) was questioned. Based on additional examinations and follow-ups, those who were diagnosed for the first time had DM, HT, HL, and CVD.

Diagnosis of sarcoidosis

Definite diagnosis of sarcoidosis was established through fiber optic bronchoscopy (FOB) in 21.3% (n=53) of patients, endobronchial ultrasonography (EBUS) in 34.1% (n=85) of patients, mediastinoscopy in 38.2% (n=95) of patients, lung biopsy (wedge) in 4% (n=10) of patients, skin biopsy in 2% (n=5) of patients, and lymph node excisional biopsy in the remaining 0.4% (n=1) of patients.

Anthropometric measurements

Each patient underwent a physical examination and a detailed medical examination. Anthropometric measurements and blood pressure measurements were noted. Waist circumference was measured with a tape at the level midway between the lower rib margin and the iliac crest. Blood pressure was measured in the sitting position using a mercury sphygmomanometer with the patients' arm at the level of the heart after they had rested for 15 min in the outpatient clinic.

All patients were evaluated for MetS according to the NCEP-ATP III criteria[4]. The presence of at least three of the five factors defined by ATP III for MetS was accepted as a diagnosis of MetS. European criteria (male ≥94 cm; female ≥80 cm) were used for waist circumference measurement.

Biochemical analysis

Blood samples were collected after 12 h of fasting. Fasting blood glucose, cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, HbA1C, insulin, angiotensin-converting enzyme (ACE), hemogram, albumin, and C-reactive protein (CRP) were analyzed. Neutrophil/lymphocyte and CAR (CRP/albumin ratio) were used for NLR. Prognostic nutritional index (PNI) was calculated as follows: PNI=10×serum albumin (g/dL)+0.005×total lymphocyte count. A value exceeding 2.5 for the homeostasis model assessment of insulin resistance (HOMA-IR) (fasting blood glucose×fasting insulin/22.5) ratio indicates insulin resistance.

Statistical analysis

Variables were investigated using analytical and visual methods (Shapiro–Wilk test and histogram) to determine whether or not they are normally distributed. Continuous variables were presented as mean±SD; if the variables are non-normally distributed, they are presented as median and interquartile range (IQR) 25–75%. Categorical variables were depicted as percentages and numbers. Group comparisons were tested using independent sample t-test or the Mann–Whitney U test, according to distribution of the numerical variables; the chi-square test or the Fisher's exact test was used for the categorical variables. The association between MetS (outcome variable: MetS with sarcoidosis presence) and the CAR, PNI, NLR, age, LDL, and HOMA-IR variables was evaluated using the univariable and multivariable logistic regression models. In addition, receiver operating characteristic (ROC) curve analysis was used to determine whether NLR had discriminative ability for MetS. The independent contribution of each variable to the variance of outcome was estimated. In this regard, the relative importance of each predictor in the model was estimated with a partial 2′ value for each predictor. In addition, correlation analysis was performed for PNI, CAR, HOMA-IR, ACE, and NLR. In all statistical analyses, $p<0.05$ was considered statistically significant. R software version 4.00 (Vienna, Austria) was used for the statistical analysis.

RESULTS

The study population comprised of 253 patients (190 female patients). There was no statistically significant difference between the groups in terms of age, LDL cholesterol, waist circumferences, lymphocyte, insulin, PNI, and ACE. The MetS+ patients had higher neutrophil, CRP, CAR, and NLR than the MetS- patients, other baseline characteristics were described in Table 1.

In sarcoidosis patients, the LDL cholesterol value was 134±33.7 mg/dL, serum triglyceride value was 125 (96–186) mg/dL, HDL cholesterol value was 45±11.2 mg/dL, fasting blood glucose value was 98 (90–190) mg/dL, HbA1c was 6%, waist circumference was 96±11.9 cm, lymphocyte value was 1800 10^3/μL (1400–2300), neutrophil value was 3900 10^3/μL (3100–5000), CRP was 4.2 mg/dL (3.2–7.0), albumin was 4.3 g/L (4.1–4.5), and insulin was 11.4 mIU/L (8.1–17); 28.9% (n=73) of patients had HT, 19% (n=48) had DM, and 49.4% (n=125) had elevated triglyceride levels. Waist circumference was increased in 80.3% of women (n=151) and was statistically significant compared with men (p<0.001). It was increased in 19.7% (n=12) of the male patients, and the median waist circumference was 96 cm; 37.2% (n=94) of patients had MetS. In terms of distribution, 89.3% (n=84) of women and 10.7% (n=10) of men had MetS (p<0.001). The median duration of disease in MetS+ patients with sarcoidosis was found to be four years. Out of 94 MetS+ patients, 57 (60.6%) had HT, and 25 (26.5%) had DM. Out of the 159 MetS- patients, 16 (10%) had HT, and 23 (14.4%) had DM. Fasting blood glucose level was 111 (97–125) mg/dL in MetS+ patients, whereas it was 94 (87–101) in MetS- patients. In MetS+ patients, the neutrophil value was 4700´10^3/μL (3685–5900), CAR was 11.8 (8.01–20.6), NLR was 2.64 (2.09–3.48), and HOMA-IR was 6.73 (3.83–10.2), which were statistically significant (p<0.001).

Binary logistic regression analysis showed that NLR (OR 1.80 [1.21–2.68], p<0.001), LDL (OR 1.49 [1.04–2.15], p=0.003), and HOMA-IR (OR 1.37 [1.04–1.85], p=0.02) were statistically significant compared with MetS-, while the other variables were not (Table 2).

The relative importance of each predictor in the model was presented in Figure 1A; the important variables such as NLR and HOMA-IR were used to predict the presence of MetS in

Table 1. Baseline demographic and clinical variables.

	All (n=253)	MetS– (n=159)	MetS+ (n=94)	p-value
Age (years)	48.6±11.4	49.4±11	47.1±12	0.13
Gender (female %)	190 (75.1)	106 (66.6)	84 (89.3)	<0.001
DM presence (%)	48 (19)	23 (14.4)	25 (26.5)	0.02
HT presence (%)	73 (28.9)	16 (10)	57 (60.6)	<0.001
Glucose (mg/dL)	98 (90–109)	94 (87–101)	111 (97–125)	<0.001
LDL (mg/dL)	134±33.7	133±34.7	139±31.9	0.17
HDL (mg/dL)	45±11.2	49.9±12	43.9±8.5	<0.001
Triglyceride (mg/dL)	125 (96–186)	109 (85.5–138)	179 (141–227)	<0.001
Waist circumference (cm)	96±11.9	96.5±12	97.5±11.7	0.56
Albumin (g/L)	4.3 (4.1–4.5)	4.3 (4.13–4.50)	4.3 (4.10–4.50)	0.46
Lymphocyte (10^3/μL)	1800 (1400–2300)	1800 (1375–2308)	1800 (1400–2200)	0.94
Neutrophil (10^3/μL)	3900 (3100–5000)	3600 (2805–4400)	4700 (3685–5900)	<0.001
CRP (mg/L)	4.2 (3.2–7.0)	3.70(3.20–6.27)	5.20 (3.20–8.74)	0.003
Insulin (mIU/L)	11.4 (8.1–17)	10.9 (8.3–14.5)	13.4 (8.30–18.8)	0.053
CAR	9.76 (7.38–17.8)	8.46 (7.27–13.9)	11.8 (8.01–20.6)	<0.001
NLR	2.25 (1.67–3.15)	2.10 (1.56–2.75)	2.64 (2.09–3.48)	<0.001
PNI	52.2 (49–55.5)	52.0 (49–56)	52.5 (49–55.3)	0.96
HOMA-IR	5.12 (3.69–7.86)	4.76 (3.51–6.42)	6.73 (3.83–10.2)	<0.001
ACE (U/L)	56.8 (37.1–87.5)	58.6 (42.6–87.9)	54.7 (29.1–85.4)	0.29

MetS: Metabolic syndrome; DM: diabetes mellitus; HT: hypertension; LDL: low-density lipoprotein; HDL: high-density lipoprotein; CRP: C-reactive protein; CAR: C-reactive protein/albumin ratio; NLR: neutrophil/lymphocyte ratio; PNI: prognostic nutritional index; HOMA-IR: homeostatic model assessment-insulin resistance; ACE: angiotensin-converting enzyme. All patients and MetS+ and MetS–.

Table 2. Multivariable logistic regression for predict Metabolic syndrome presence in sarcoidosis.

	Multivariable odds ratio	95%CI	p-value
CRP/albumin ratio (from 7.38–17.76)	1.14	0.99–1.32	0.06
Prognostic nutritional index (from 49–55)	1.03	0.,67–1.56	0.89
Neutrophil/lymphocyte ratio (from 1.66–3.14)	1.80	1.21–2.68	0.003
LDL (from 112–154 mg/dL)	1.49	1.04–2.15	0.03
HOMA-IR (from 3.68–7.85)	1.37	1.04–1.85	0.02
Age (from 40–56 years)	0.77	0.51–1.16	0.22

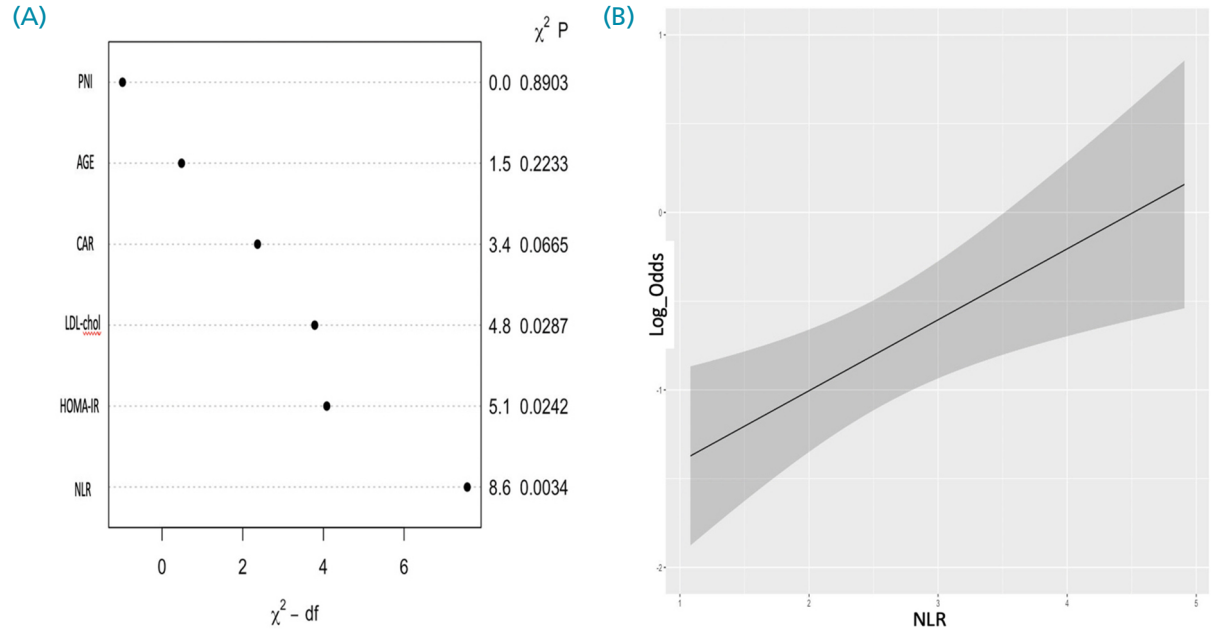
CRP: C-reactive protein; LDL: low-density lipoprotein; CI: Confidence interval; CRP: C-reactive protein; LDL: low-density lipoprotein; HOMA-IR: homeostatic model assessment-insulin resistance. Bold values denote statistical significance at the p<0.05 level.

the sarcoidosis patient. The partial effect plots show the fitted curve on the mean (probability) scale as log-odds (linear predictor) for NLR in Figure 1B.

The NLR cutoff value was 2.24, sensitivity was 70.53, specificity was 60.13, and AUC was 0.663 in predicting MetS in sarcoidosis patients. Herein, a negative correlation existed between NLR and PNI in the correlation analysis [R 0.369 (p<0.001)]. However, there was no correlation between HOMA-IR and NLR, PNI, and CAR.

DISCUSSION

This study showed that NLR was higher in sarcoidosis patients with MetS. Chuan-Chuan Liu et al. evaluated patients in six groups using anthropometric, biochemical, and hematological measurements in terms of MetS marker (NLR) in a study including 34,013 subjects. NLR was concluded to be a good predictor, and the risk increased as this ratio increased. NLR and increased values of NLR could be used as a prognostic marker for the development of MetS[5]. In another study, Kaya et al. investigated the relationship between NLR and CAD using syntax score (SS) in 649 patients with stable angina pectoris and CAD; they determined that NLR was a measurable



PNI: prognostic nutritional index; age: years; CAR: C-reactive protein/albumin ratio; LDL: low density lipoprotein; HOMA-IR: homeostatic model assessment–insulin resistance; NLR: neutrophil/lymphocyte ratio.

Figure 1. **(A)** Relative importance of each variable in the multivariable model for predict presence of metabolic syndrome in sarcoidosis. **(B)** Partial effect plot of neutrophil/lymphocyte ratio for predicting presence of metabolic syndrome+.

systemic inflammatory marker. In multivariate analysis, NLR was associated with the presence and severity of CAD[6].

In their studies including 1300 sarcoidosis patients, Güngör et al. investigated the use of NLR as a marker of inflammation in sarcoidosis. It was concluded that NLR could be used as an inflammation marker, and studies with large patient populations were needed for activity and staging in prognosis[7].

In the report of Balta et al., NLR value was suggested as an independent prognostic factor for CAD, which may be affected by vascular disease-associated MetS, DM, HT, and hypercholesterolemia[8]. In their case-control study, Büyükkaya et al. divided MetS+ patients into three groups (based on their components). MetS+ patients had significantly higher NLR values compared with the control group, and it was observed that the NLR increased with increasing severity ($r=0.586$, $p<0.001$)[9]. Similarly, as a result of our study, NLR was statistically significant as predicted by MetS+. In addition, in the study conducted by Bahadır et al, correlation analysis was performed by comparing metabolic and inflammatory markers between the groups, and it was concluded that NLR is not a good marker of inflammation, and leukocyte and hs-CRP values may be more useful biomarkers to indicate inflammation in nondiabetic patients with obesity and MetS[10].

In our study, 37.15% MetS+ and 6.73 (3.83–10.2) HOMA-IR values were higher in women and were statistically significant ($p<0.001$). In the study conducted by Cozier et al., the relationship of obesity and weight gain with the incidence of sarcoidosis was evaluated in 59,000 US black women aged between 21 and 69 years; of these, the development of sarcoidosis was reported in 454 patients during a 16-year follow-up period (1995–2011). The incidence of sarcoidosis increased with increasing body mass index and weight gain[11].

In the study conducted by Moon et al., patients with elevated CAR and DM were at higher risk of all-cause mortality compared with those without elevated CAR and DM[12]. Similarly, significant results were achieved with CAR and NLR values in predicting inflammation in MetS+ patients ($p<0.001$).

Gvozdenovic et al. conducted a case-control study with 184 patients and evaluated the effect of high body mass index (BMI) on patient-reported results in sarcoidosis patients and healthy individuals, and the highest risk (more than three times) was detected in obese women[13]. In this study, MetS+ was more common in women and was statistically significant ($p<0.001$). In the recently published review, the importance of inflammatory parameters was stated, but malnutrition was left out[14]. According to the results of our research, sarcoidosis patients may need to have their inflammation and malnutrition assessed.

Limitations

This study has some limitations. Being a single-center study and its observational nature is one of the limitations of our study. Our findings should be confirmed in prospective and large-scale studies involving other inflammatory biomarkers to clarify the exact mechanistic role of NLR in sarcoidosis with MetS+.

CONCLUSIONS

In addition to classical parameters, NLR can be used in sarcoidosis patients to predict MetS+. The use of NLR, a strong inflammation marker, may be considered for the closer follow-up needed in patients with MetS+ sarcoidosis. Sarcoidosis patients should be followed up closely in terms of possible comorbidities through separate evaluation in terms of MetS components in their long-term follow-up.

AUTHORS' CONTRIBUTIONS

ACI: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. **MK:** Conceptualization, Data curation, Writing – original draft. **SB:** Data curation, Visualization. **AK:** Formal Analysis, Methodology, Visualization, Writing – original draft. **GK:** Formal Analysis, Investigation, Methodology. **NŞ:** Investigation, Methodology, Visualization.

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