Original Article

TANAFFOS

Association of Neutrophil to Lymphocyte Ratio and Pulmonary Hypertension in Sarcoidosis Patients

Mehdi Mirsaeidi [1], **Esmaeil Mortaz** [2,3],
Hesham R. Omar [3], **Enrico M. Camporesi** [5],
Nadera Sweiss [6]

[1] Division of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, University of Miami, FL, USA, [2] Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, The Netherlands, [3]Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Disease (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [4] Internal Medicine Department, Mercy Medical Center, Clinton, Iowa, USA, [5] Professor of Surgery/ Anesthesiology, Professor of Molecular Pharmacology and Physiology, University of South Florida, FGTBA and TEAM Health, Tampa, Florida, USA., [6] Division of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, University of Illinois at Chicago, IL, USA

Correspondence to: Mirsaeidi M
Address: Division of Pulmonary, Critical Care,
Sleep and Allergy, Department of Medicine,
University of Miami, Miller School of Medicine1600
NW 10th Ave # 7060A Miami, FL 33136
Email address: msm249@med.miami.edu

Background: The neutrophil-to-lymphocyte ratio (NLR) has emerged as a new marker of inflammation associated with the severity of several respiratory and cardiac diseases.

Materials and Methods: We investigated whether the degree of systemic inflammation in sarcoidosis patients as measured by the NLR is associated with pulmonary hypertension (PH).

Results: A NLR > 3.5 occurred with a significantly higher frequency in sarcoidosis patients with PH (50% vs. 24%, P=0.016) yielding a sensitivity of 50%, specificity of 78%, positive predictive value (PPV) of 41.9% and negative predictive value (NPV) of 81.4% and remained independently associated with PH in multivariate analysis (OR: 3.254, 95% CI: 1.094– 9.678, P=0.034).

Conclusion: We conclude that level of inflammation in sarcoidosis patients may be associated with the development of PH. Owing to the relatively good specificity and NPV, NLR may be a good negative test, which is a simple, inexpensive and widely available in office-based setting to predict the risk of PH in sarcoidosis patients.

INTRODUCTION

The neutrophil-to-lymphocyte ratio has been recently emerged as a new marker of inflammation and was found to be associated with the severity and prognosis of several respiratory and cardiac diseases (1-4). Sarcoidosis is a systemic inflammatory disease characterized by formation of granulomas in different affected organs (5,6). Pulmonary hypertension is a feared complication in patients with sarcoidosis as it is an important negative prognostic factor, which is reflected in the added priority given to these subjects for orthotopic lung transplantation (7,8). Pulmonary hypertension is considered a vasculopathy caused by excessive vascular cell growth with inflammation playing a major role (8). Previous studies showed that NLR was significantly elevated in PH patients

compared with healthy volunteers (9) and may be useful for the assessment of disease severity (10). The increased prevalence of PH in systemic inflammatory diseases such as sarcoidosis is well known (7,8). Although the gold standard in diagnosing PH is the direct measurement of the pulmonary artery pressure with right heart catheterization (RHC), RHC needs highly skilled personnel and advanced technology that are not available in many settings with limited resources (11). Instead, echocardiography is widely used to estimate pulmonary artery systolic pressure (12). Echocardiography is not a simple and easy tool to be considered as a point-of-care test in primary care setting. We hypothesized that the degree of systemic inflammation (as measured by NLR) would be significantly higher in sarcoidosis subjects with PH compared to those without PH and could be an appropriate test for primary care setting. Herein, we aimed to assess the relationship between NLR and PH in sarcoidosis patients.

MATERIALS AND METHODS

An IRB-approved retrospective chart review (approval number 20130195001) was conducted at University of Illinois in Chicago from January 2010 through January 2015 on adult patients diagnosed with sarcoidosis. Cases were divided into two groups based on presence or absence of PH, which was diagnosed when the pulmonary artery systolic pressure was >25 mmHg using transthoracic echocardiogram. Patients with left ventricular systolic dysfunction (EF≤40 mmHg) were excluded. In subjects with more than one complete blood count during hospitalization, the average of the highest and lowest absolute neutrophil and lymphocyte counts was used.

Continuous variables were compared using Student t-test and categorical variables were compared using the Chi-square test. To determine the ideal cutoff value of NLR, receiver operating characteristic (ROC) curve was used. To assess whether NLR was independently associated with PH in sarcoidosis patients, multivariate regression analysis with backward stepwise elimination was performed.

RESULTS

A total of 107 cases diagnosed with sarcoidosis were included in the study, among which 28 patients (26%) had PH. The mean age of the study population was 53.4±9.4 years; 76.9% were females, 70% were African Americans and the average duration of sarcoidosis was 12 years.

Characteristics of sarcoidosis patients with and without PH are summarized in Table 1.

Compared to sarcoidosis patients without PH, those with PH were significantly older (57.1±8.8 vs. 51.9±9.3 years, P=0.011), had a higher frequency of bronchiectasis (21.4% vs. 5.1%, P=0.012), lower FVC% (84.1±24.8% vs. 96.4±18.4%, P=0.014), lower FEV1% (74.5±27.9% vs. 92.8±22%, P=0.002) and a trend towards lower DLCO% (60.8±18.2% vs. 69.3±20.7%, P=0.088). Also, sarcoidosis patients with PH had a trend towards higher neutrophil count (5.5±2.4 vs. 4.7±1.8, P=0.098), lower lymphocyte count (1.6±0.6 vs. 1.8±0.8, P=0.221) and higher NLR (4.1±2.9 vs. 3.2±2.4, P=0.120). A NLR > 3.5 occurred with significantly higher frequency in sarcoidosis patients with PH (50% vs. 24%, P=0.016). The value of 3.5 was determined as the most appropriate cutoff value for NLR for distinction between sarcoidosis patients with and without PH, which yielded a sensitivity of 50%, specificity of 78%, PPV of 41.9% and NPV of 81.4% with an area under curve of 0.619. In the multivariate model, NLR >3.5 remained independently associated with PH (OR 3.254, 95% CI 1.094–9.678, P=0.034). We found no significant association between PH and CRP or ESR. Figure 1 is a forest plot of the variables used in the multivariate model.

Table 1. Baseline demographic, clinical and laboratory characteristics among sarcoidosis cases with and without pulmonary hypertension

	All (n=107)	Sarcoidosis with PHTN (n=28)	Sarcoidosis without PHTN (n=79)	P value
Age (mean ± SD)	53.4 ± 9.4	57.1 ± 8.8	51.9 ± 9.3	0.011
Female sex % (n)	76.6% (82)	82.1% (23)	74.7% (59)	0.425
BMI (mean ±SD)	31.9 ± 8	32.2 ± 7.2	31.9 ± 8.3	0.836
Duration of sarcoidosis (y, mean± SD)	12.2 ± 9.1	14.3 ± 10.7	11.5 ± 8.5	0.18
African American % (n)	70.1% (75)	82.1% (23)	65.8% (52)	0.112
Diabetes % (n)	31.4% (33)	17.9% (5)	36.4% (28)	0.077
Dyslipidemia % (n)	24.5% (26)	25% (7)	24.4% (19)	0.946
CKD % (n)	3.7% (4)	3.6% (1)	3.8% (3)	0.957
PCI or CABG % (n)	1.9% (2)	0% (0)	2.5% (2)	0.543
Atrial fibrillation % (n)	5.6% (6)	10.7% (3)	3.8% (3)	0.190
Pulmonary sarcoidosis % (n)	91.9% (91)	96.3% (26)	90.3% (65)	0.347
Extrapulmonary sarcoidosis % (n)	64.5% (69)	60.7% (17)	65.8% (52)	0.628
Rheumatoid arthritis % (n)	3.7% (4)	0% (0)	5.1% (4)	0.291
Asthma % (n)	26.4% (28)	28.6% (8)	25.6% (20)	0.763
OSA % (n)	24.5% (26)	29.6% (8)	22.8% (18)	0.477
Bronchiectasis % (n)	9.3% (10)	21.4% (6)	5.1% (4)	0.018
FVC % (mean ±SD)	93.2 ±20.9	84.1 ± 24.8	96.4 ± 18.4	0.014
FEV1 % (mean ±SD)	88 ± 24.9	74.5 ± 27.9	92.8 ± 22	0.002
TLC % (mean ±SD)	89.1 ±15.6	84.7 ± 16.8	90.7 ± 15	0.114
RV % (mean ±SD)	99.4 ±26.7	102.2 ± 29.8	98.3 ± 25.7	0.605
FRC % (mean ±SD)	97.4 ±22.1	102.5 ± 20.2	95.6 ± 22.7	0.291
DLCO % (mean ±SD)	67 ± 20.3	60.8 ± 18.2	69.3 ± 20.7	0.088
PASP (mmHg, mean ±SD)	35.1 ±17.4	41.1 ± 17.7	21.2 ± 2.3	0.000
EF (mean ±SD)	57.8 ± 4.8	57.5 ± 5	58 ± 4.7	0.672
Neutrophil (mean ±SD)	4.9 ± 2	5.5 ± 2.4	4.7 ± 1.8	0.098
Lymphocyte (mean ±SD)	1.76 ± 0.7	1.6 ± 0.6	1.8 ± 0.8	0.221
Neutrophil/Lymphocyte ratio (mean± SD)	3.4 ± 2.5	4.1 ± 2.9	3.2 ± 2.4	0.120
Neutrophil/Lymphocyte ratio > 3.5 % (n)	30.7% (31)	50% (13)	24% (18)	0.016
CRP (mean ±SD)	2.5 ± 4.2	3 ± 4.1	2.4 ± 4.2	0.562
ESR (mean ±SD)	35.2 ±33.4	45.8 ± 32.6	32.6 ± 33.3	0.160
Oral steroid % (n)	83.3% (85)	88.9% (24)	81.3% (61)	0.372
DMARD % (n)	44.3% (47)	32.1% (9)	48.7% (38)	0.133
Methotrexate % (n)	29.9% (32)	17.9% (5)	34.2% (27)	0.112
Azathioprine% (n)	4.7%(5)	7.1% (2)	3.8%(3)	0.478
Sildenafil% (n)	7.5%(8)	14.3% (4)	5.1% (4)	0.126
Warfarin% (n)	2.8%(3)	7.1% (2)	1.3% (1)	0.150

PHTN: Pulmonary hypertension, BMI: Body mass index, CKD: Chronic kidney disease, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass graft, OSA: Obstructive sleep apnea, PASP: Pulmonary artery systolic pressure, EF: Ejection fraction, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, DMARD: Disease modifying anti-rheumatic drug, y: Year, m: Mean, SD: Standard deviation.
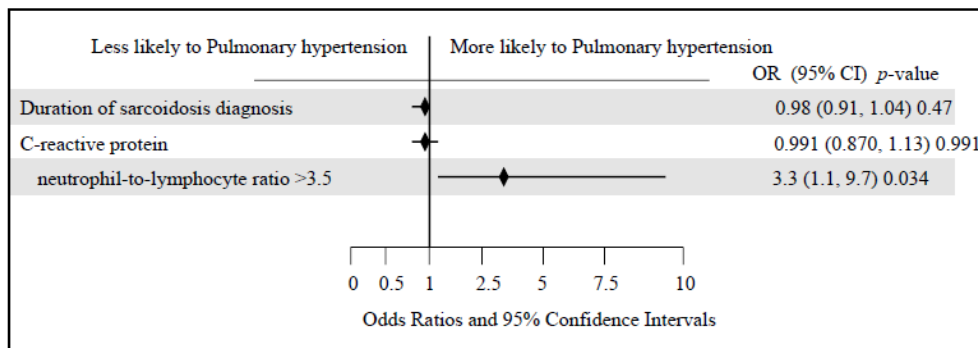

Figure 1. Forest plot of the variables used in the multivariate model among sarcoidosis cases with and without pulmonary hypertension

DISCUSSION

In this retrospective study, we were able to show an independent relationship between NLR, a marker of inflammation, and PH in sarcoidosis patients. It is obvious that patients with a systemic inflammatory disease such as sarcoidosis will have an elevated NLR, and this was in fact demonstrated by Iliaz and colleagues who found a NLR of 2.48±1.1 in sarcoidosis patients compared with 1.73±0.7 in the control group (P<0.001)(13). Nonetheless, as we speculated, a higher NLR (>3.5) in sarcoidosis patients signifies a more intense inflammatory response, which may be the underlying subset and pathophysiological basis for development of PH. These results raise hope and provoke further research to study the utility of this promising marker in sarcoidosis-associated PH. This test is a good negative test owing to the relatively good specificity (78%) and NPV (81.4%). Compared to other inflammatory markers, the NLR is a simple, inexpensive and widely available test that is routinely measured in office-based settings and adds no extra cost. Our study limitations included the single center retrospective design and the relatively small cohort due to rarity of the disease.

We conclude that level of inflammation in sarcoidosis patients may be associated with development of PH. Also, NLR has low sensitivity and PPV for diagnosis of PH in sarcoidosis patients and therefore it is not an ideal screening tool. However, its high NPV makes it an interesting tool to exclude PH in patients with sarcoidosis. Larger studies are required to evaluate the value of NLR in predicting sarcoidosis-associated PH and confirm our findings before being used in the primary care setting.

REFERENCES

1. Uthamalingam S, Patvardhan EA, Subramanian S, Ahmed W, Martin W, Daley M, et al. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. *Am J Cardiol* 2011;107(3):433-8.

2. Korkmaz A, Yildiz A, Gunes H, Duyuler S, Tuncez A. Utility of Neutrophil-Lymphocyte Ratio in Predicting Troponin Elevation in the Emergency Department Setting. *Clin Appl Thromb Hemost* 2015;21(7):667-71.

3. Tasal A, Erturk M, Uyarel H, Karakurt H, Bacaksiz A, Vatankulu MA, et al. Utility of the neutrophil to lymphocyte ratio for predicting in-hospital mortality after levosimendan infusion in patients with acute decompensated heart failure. *J Cardiol* 2014;63(6):418-23.

4. Kayrak M, Erdoğan HI, Solak Y, Akilli H, Gül EE, Yildirim O, et al. Prognostic value of neutrophil to lymphocyte ratio in patients with acute pulmonary embolism: a restrospective study. *Heart Lung Circ* 2014;23(1):56-62.

5. Mortaz E, Sereshki HA, Abedini A, Kiani A, Mirsaeidi M, Soroush D, et al. Association of serum TNF-α, IL-8 and free light chain with HLA-DR B alleles expression in pulmonary and extra-pulmonary sarcoidosis. *J Inflamm (Lond)* 2015;12:21.

6. Mirsaeidi M, Machado RF, Schraufnagel D, Sweiss NJ, Baughman RP. Racial difference in sarcoidosis mortality in the United States. *Chest* 2015;147(2):438-49.

7. Baughman RP, Engel PJ, Meyer CA, Barrett AB, Lower EE. Pulmonary hypertension in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2006;23(2):108-16.

8. Baughman RP. Pulmonary hypertension associated with sarcoidosis. *Arthritis Res Ther* 2007;9 Suppl 2:S8.

9. Yıldız A, Kaya H, Ertaş F, Oylumlu M, Bilik MZ, Yüksel M, et al. Association between neutrophil to lymphocyte ratio and pulmonary arterial hypertension. *Turk Kardiyol Dern Ars* 2013;41(7):604-9.

10. Özpelit E, Akdeniz B, Özpelit ME, Tas S, Bozkurt S, Tertemiz KC, et al. Prognostic value of neutrophil-to-lymphocyte ratio in pulmonary arterial hypertension. *J Int Med Res* 2015;43(5):661-71.

11. Keusch S, Bucher A, Müller-Mottet S, Hasler E, Maggiorini M, Speich R, et al. Experience with exercise right heart catheterization in the diagnosis of pulmonary hypertension: a retrospective study. *Multidiscip Respir Med* 2014;9(1):51.

12. Bossone E, D'Andrea A, D'Alto M, Citro R, Argiento P, Ferrara F, et al. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. *J Am Soc Echocardiogr* 2013;26(1):1-14.

13. Iliaz S, Iliaz R, Ortakoylu G, Bahadir A, Bagci BA, Caglar E. Value of neutrophil/lymphocyte ratio in the differential diagnosis of sarcoidosis and tuberculosis. *Ann Thorac Med* 2014;9(4):232-5.