Original Article

Access this article online

Quick Response Code:

Website: www.eurasianjpulmonol.com

DOI: 10.4103/ejop.ejop_1_18

Can neutrophil/lymphocyte ratio and platelet/lymphocyte ratio be used in differential diagnosis of Stage I sarcoidosis from tuberculosis lymphadenopathy?

Cengiz Özdemir, Sinem Nedime Sökücü, Seda Tural Önür

Abstract:

OBJECTIVE: It is challenging to differentiate mediastinal lymph node enlargement caused by tuberculosis (TB) and sarcoidosis as both diseases may cause granulomatous inflammation. The objective of this study is to evaluate the use of neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) as possible markers in the differential diagnosis of Stage I sarcoidosis and TB lymphadenopathy in patients who present with mediastinal lymph nodes and no parenchymal involvement.

MATERIALS AND METHODS: A total of 19 TB, 55 sarcoidosis, and 32 control patients, whose clinical records were available, were included in this retrospective study. All patients had a granulomatous reaction revealed on their lymph node biopsy specimen. The complete blood count at the time of diagnosis was included in the study.

RESULTS: NLR and PLR were both significantly increased in Stage 1 sarcoidosis patients compared to controls while only PLR was significantly increased in the TB group (for sarcoidosis, NLR $P < 0.001$ and PLR $P < 0.001$; for TB, NLR $P = 0.12$; PLR $P = 0.017$). There were neither significant differences in serum NLR nor PLR between sarcoidosis and TB groups.

CONCLUSION: Although NLR and PLR are useful tools to differentiate Stage 1 sarcoidosis from controls and PLR may be used to differentiate TB lymphadenopathy from controls, these parameters may not be used to differentiate between Stage 1 sarcoidosis and TB lymphadenopathy.

Keywords:

Lymphadenopthy, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio

Introduction

Granulomatous lymphadenitis may be associated with a number of infectious and noninfectious conditions including Hodgkin's lymphoma, non-Hodgkin lymphoma, Crohn's disease, sarcoidosis, tularemia, cat-scratch disease, Yersinia lymphadenitis, and tuberculosis (TB).[1] With 4557 new extrapulmonary TB cases reported in 2014, Turkey is among countries with intermediate TB burden at 18 new cases in 100,000.[2,3] Lymph node TB is considered to be the most common type of extrapulmonary TB.[4,5] Sarcoidosis is a granulomatous disease of unknown etiology. The early stage of sarcoidosis is characterized by lymph node involvement, which is also used to radiologically classify the condition. Stage I sarcoidosis is defined as enlargement of the hilar lymph nodes.[6] Lymph node involvement

Sleep Department, Yedikule Chest Disease and Thoracic Surgery Training and Research Hospital, Istanbul, Türkiye

Address for correspondence:
Dr. Cengiz Özdemir, Yedikule Chest Disease and Thoracic Surgery Training and Research Hospital, Istanbul, Türkiye.
E-mail: cengizoz78@yahoo.com

How to cite this article: Özdemir C, Sökücü SN, Önür ST. Can neutrophil/lymphocyte ratio and platelet/lymphocyte ratio be used in differential diagnosis of Stage I sarcoidosis from tuberculosis lymphadenopathy?. Eurasian J Pulmonol 2018;20:22-6.

by TB and sarcoidosis are frequently confused, and the granulomatous inflammation in the lymph nodes associated with both conditions creates a challenge for differential diagnosis. In addition, isolating the causative agent in the tissue samples of TB patients may prove to be difficult. The presence of necrosis does not significantly contribute to the differential diagnosis.[1] As both conditions manifest with symptoms such as fever, fatigue, weight loss, and cough, establishing the final diagnosis based on clinical findings is not possible.[7] Due to similarities in clinical and pathological findings in both conditions, additional laboratory tests are needed to guide the differential diagnosis.

Neutrophil/lymphocyte ratio (NLR) and the platelet/lymphocyte ratio (PLR) are markers calculated based on the routine complete blood count from each patient who presents with mediastinal lymphadenomegaly. As both markers can be derived from complete blood count parameters, no additional cost or labor is required. NLR and PLR have recently been used to evaluate systemic inflammation associated with different types of cancer and have been shown to have a prognostic value.[8,9]

This study aims to study the role of NLR and PLR markers in the differential diagnosis of Stage 1 sarcoidosis and TB lymphadenopathy in patients with mediastinal lymph node involvement and no lung parenchymal involvement.

Materials and Methods

Patients

Patients included in this cross-sectional retrospective study are consecutive patients older than 18 years who presented to our organization with mediastinal lymph node enlargement between June 2010 and June 2015 and whose granulomatous lymphadenopathy was confirmed on pathology specimen, and a final diagnosis of TB lymphadenopathy or Stage 1 sarcoidosis was established. Patients were included after they consented to the use of their clinical records for the study purposes. The study was approved by the Ethics Board of our hospital (edition No: 3989; 2015/42) and conducted according to the Helsinki Declaration.

Patients with no complete blood count at baseline, patients with parenchymal involvement in addition to mediastinal lymph node enlargement on the chest X-ray and computed tomography (CT)-scan, patients with chronic inflammatory diseases, hematological disorders, patients with a history of active corticosteroid use or known malignancies, and HIV-positive patients which is known to interfere with white blood cell (WBC) count, have been excluded from the study.

The following criteria were used to diagnose TB lymphadenopathy: (1) absence of a parenchymal infiltration identified on chest X-ray or CT-scan at the time of diagnosis; (2) Acid-fast bacteria identified on direct microscopic examination of the transbronchial needle aspirate; (3) Positive culture for *Mycobacterium* TB complex; (4) New patients without an established diagnosis of TB; (5) History of contact with a TB-positive subject.

The following criteria were used to diagnose Stage 1 sarcoidosis: (1) absence of a parenchymal infiltration identified on chest X-ray or CT-scan at the time of diagnosis; (2) No history of TB; (3) No acid-fast bacteria identified on the direct microscopic examination of the transbronchial needle aspirate; (4) No positive culture for *Mycobacterium* TB complex; (3) Tuberculin skin test within normal range.

Pathological examination confirmed the presence of granulomatous reaction in the lymph node specimen obtained from all patients. Pathology specimens were obtained using conventional bronchoscopic transbronchial needle aspiration, transbronchial needle aspiration under endobronchial ultrasound, or mediastinoscopy. The specimens were cultured for *Mycobacterium* TB complex and directly screened for acid-fast bacteria on dry microscopic slides.

Healthy patients who presented to the outpatient clinic for routine health check-up with unremarkable chest X-rays and no infectious symptoms such as fever, cough, sputum production, dysuria, and diarrhea were included in the control group. 19 TB and 55 sarcoidosis patients and 32 healthy patients whose clinical data were available for retrospective analysis were included in the study.

Laboratory parameters

Baseline complete blood count parameters of patients before the initiation of any treatment were included in the review process. The complete blood count parameters were measured using an Abbott Cell-Dyne 3700 System (Abbott Diagnostics, Santa Clara, CA, US) and blood chemistry was analyzed using an Olympus AU2700 Plus Analyzer (Beckman Coulter, Tokyo, Japan). NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. PLR, on the other hand, was calculated by dividing the absolute lymphocyte count by the absolute platelet count (PLT). The WBC count, NLR, and PLR levels of the control and two patient groups were compared.

Statistical analysis

Data were analyzed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, US) computer software. Data were

tested for normality using the Kolmogorov–Smirnov test and continuous variables were expressed either as a mean ± standard deviation or normality-dependent median values. Continuous data were expressed as a mean ± standard deviation.

Student's *t*-test and Mann–Whitney U-test were used to compare continuous variables between paired groups. Three-way comparisons were made using the ANOVA method (Bonferroni correction). Continuous variables were analyzed using the Spearman's rank correlation test. A value of $P < 0.05$ was considered statistically significant.

Results

Overall, 107 patients were included in this study. The Stage 1 sarcoidosis group included 55 patients. Fourteen of these patients (25.5%) were male, and the mean age was 44.42 ± 11.52 years. A total of 19 patients were included in the TB lymphadenopathy group. Five of those (26.3%) were male with a mean age of 40.63 ± 13.88 years. Nineteen of the 32 patients in the control group were male (59.4%), and the mean age was 38.59 ± 12.73 years. There were no age differences between the groups. There was no difference in gender distribution between the TB and sarcoidosis patient groups ($P > 0.05$), but the majority of the patients in the control group were male.

Pathology specimens were obtained using conventional transbronchial needle aspiration in 21 (28.4%), using transbronchial needle aspiration under endobronchial ultrasound guidance in 17 (23%), and using mediastinoscopy in 36 (48.6%) patients and the diagnosis was established.

Although the NLR and PLR values in the sarcoidosis group were significantly higher than in the controls, in the TB group, only PLR was significantly higher than the control group (in the sarcoidosis group: $P < 0.001$ and $P < 0.001$; in the TB group: $P = 0.017$). There was no significant difference in NLR or PLR between the sarcoidosis and TB groups [Table 1]. The median NLR was 2.54 (interquartile range [IQR]: 2.09) 1.98 (IQR: 1.53) for the sarcoidosis and TB patients, respectively ($P = 0.96$). The median PLR was 188 ± 69.42 and 137.9 (IQR: 70.88) for the sarcoidosis and TB patients, respectively ($P = 0.468$). Hb and Htc were significantly lower in both sarcoidosis and TB groups compared to the controls while both NLR and PLR were higher in both groups ($P < 0.05$). There was a positive correlation between NLR and PLR ($P = 0.098$ and $P = 0.041$).

Necrosis was identified in the pathological examination of 17 patient specimens. Two of them were sarcoidosis and 15 were TB patients ($P < 0.05$). No statistically significant difference in NLR and PLR values was observed between patients with or without necrosis ($P > 0.05$). There was no significant difference in PLT, red blood cell distribution width, mean platelet volume, and platelet distribution width results between the groups [Table 2].

Discussion

The study showed that NLR and PLR, which have been revealed to be useful in the differential diagnosis of sarcoidosis and TB, do not have a role in differentiating between TB lymphadenopathy and Stage 1 sarcoidosis. Instead, both NLR and PLR were significantly higher in sarcoidosis patients compared to controls, but only PLR was elevated in the TB group.

Dirican *et al*. in their study reported that compared to healthy controls, NLR is significantly higher in sarcoidosis patients ($P < 0.001$) and directly correlates with the erythrocyte sedimentation rate. They also reported that NLR is more elevated in patients with extrapulmonary involvement.[10] The study only included Stage 1 sarcoidosis patients whose NLR was higher

Table 1: Correlation between complete blood count parameters in patients and controls

	Sarcoidosis	TB	Control
NLR	2.54 (IQR 2.09)*	1.98 (IQR 1.53)**	1.62±0.62
PLR	188±69.42*	137.9 (IQR 70.88)**	108.08±35.21
Platelets	293±78.01	302.32±68.95	256.88±44.16
WBC	7.01±1.98	7.75±2.11	6.95±1.11
Hb	13.62±1.34	12.85±1.38	14.53±1.41
Htc	40.95±3.81	39.12±4.14	43.96±4.34
RDW	14.36±2.05	15.32±2.23	14.40±1.71
MPV	8.44±1.14	8.45±0.93	8.84±1.85
PDW	16.32±1.97	16.57±1.88	16.02±3.36

*Comparison of the NLR and PLR levels in sarcoidosis group to controls $P<0.001$ and $P<0.001$, **Comparison of the NLR and PLR levels in TB group to controls $P=0.12$ and $P=0.017$. NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, Hb: Hemoglobin, Htc: Hematocrite, RDW: Red blood cell distribution width, MPV: Mean platelet volume, PDW: Platelet distribution width, TB: Tuberculosis, WBC: White blood cell, IQR: Interquartile range

Table 2: Correlation between presence of necrosis and complete blood count parameters

	No necrosis (57 patients)	Necrosis (17 patients)	*P*
Neutrophil	4.57±1.80	4.89±1.77	0.512
Lymphocyte	1.69±0.51	2.28±0.89	0.006*
Platelet	291.65±76.14	308.88±73.65	0.220
NLR	2.54 (IQR 1.94)	1.88 (IQR 1.73)	0.131
PLR	186.88±68.4	123 (IQR 84)	0.065
RDW	14.47±2.11	15.06±2.17	0.372
MPV	8.39±1.08	8.64±1.11	0.418
PDW	16.27±1.90	16.76±2.06	0.348

*$P<0.05$. NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, RDW: Red blood cell distribution width, MPV: Mean platelet volume, PDW: Platelet distribution width, IQR: Interquartile range

than controls, but no difference between the TB and sarcoidosis groups could be revealed.

Results of the study by Iliaz *et al*., suggested that NLR in TB patients is higher than in sarcoidosis patients.[11] Different from our study, which only included patients with lymph node involvement, Iliaz *et al*. also included patients with parenchymal involvement and pleural effusion in their study. The study exclusively included patients with TB lymphadenitis and Stage 1 sarcoidosis patients, and hence, no difference in NLR between the groups could be revealed. At the same time, the NLR levels in the TB lymphadenitis group were comparable to healthy patients. In comparison to our study which included more homogeneous type of patients with lymph node involvement only in both disease categories, their study appears to be more heterogeneous.

Different from Iliaz *et al*., who reported that NLR levels were significantly higher in both TB and sarcoidosis groups compared to the controls, our results suggest that NLR level is significantly higher only in the sarcoidosis group.[11] There are many reports in the literature that suggest a relationship between NLR as an inflammatory marker and patient's prognosis. This also applies to other inflammatory conditions such as chronic obstructive pulmonary disease and community-acquired pneumonia.[12,13] Yoon *et al*. reported that the NLR levels in pulmonary TB patients are significantly lower than in patients with community-acquired bacterial pneumonia.[14] The physiological immune response of circulating leukocytes under varying stress conditions is characterized by a depletion in the leukocyte count and an increase in neutrophil count.[15] Lymphocytopenia has also been established as a diagnostic marker of bacterial infection.[16] It is, therefore, suggested that NLR may have a predictive value in bacterial infections and stress conditions. The fact that NLR levels in TB lymphadenitis were not higher than the controls in our study may suggest that NLR elevation may be associated with parenchymal infiltration.

Although necrosis in pathology specimen may also be observed in sarcoidosis-related granulomas, the presence of necrosis is primarily considered as an important indicator of the aggressiveness of the TB infection. Necrosis indicates a potentially toxic effect of the pathogen in the macrophage or a delayed hypersensitivity-type of the response of the host toward this pathogen.[17] A review of all patients in our study with regard to necrosis did not indicate a significant difference in NLR or PLR. For an appropriate necrosis assessment, the pathology specimen should be relatively large in size. In 51.2% of the patients in our study, specimens were obtained either with conventional transbronchial needle aspiration or endobronchial needle aspiration. As the needle aspiration may not always obtain specimen from the necrotic area of the lymph node, it is possible that other areas of the sampled lymph node may have contained necrotic granulomas. This may explain why no correlation between the NLR and PLR levels and the presence of necrosis could be established in our study.

Recent reports indicate a positive correlation between both NLR and PLR and inflammatory markers. These markers include tumor necrotizing factor-α and interleukin-6 in both cardiac and noncardiac patients. It has also been shown that peripheral arterial disease, cardiac conditions, and certain types of malignancies are associated with elevated PLR levels.[18-21] In a study that looked into the correlation between inflammation and these parameters in end-stage kidney failure patients, PLR has been shown to be superior than NLR as an inflammatory marker.[22] Similar to our results, although both NLR and PLR were significantly higher than controls, no significant difference between Stage 1 sarcoidosis and TB groups could be revealed.

There are many preliminary reports that suggest *Mycobacterium bacilli* may have a role in the pathogenesis of sarcoidosis and thus, a thorough assessment and past TB history may have an important role.[23,24] All patients in our series were Stage 1 sarcoidosis patients free of extrapulmonary involvement with no history of TB disease or exposure. *M. bacilli* not being involved in the etiology may explain why there was no difference in NLR and PLR levels between Stage 1 sarcoidosis and TB lymphadenitis patients.

The most important limitation of our study was the fact that it was a retrospective analysis at a single reference center and that our sample size was small. Due to its retrospective nature, important inflammatory markers such as C-reactive protein and procalcitonin were not available for all patients and thus, could not be correlated with NLR and PLR.

Conclusion

Today, different complete blood count parameters stand out as new inflammatory markers. The study suggests that although higher in Stage 1 sarcoidosis group compared to the controls, NLR and PLR do not have a role differentiating sarcoidosis and TB-related lymph node involvement. Further studies with larger sample sizes are needed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Asano S. Granulomatous lymphadenitis. J Clin Exp Hematopathol 2012;52:1-16.
2. WHO. Global Tuberculosis Control 2014. Available from: http://www.who.int/tb/publications/global_report/2014/gtbr11_full.pdf. [Last accessed on 2014 Dec 14].
3. WHO's Global TB Database. Available from: http://www.who.int/tb/country/data/profiles/en. [Last accessed on 2015 Jan 22].
4. Golden MP, Vikram HR. Extrapulmonary tuberculosis: An overview. Am Fam Physician 2005;72:1761-8.
5. Ilgazli A, Boyaci H, Basyigit I, Yildiz F. Extrapulmonary tuberculosis: Clinical and epidemiologic spectrum of 636 cases. Arch Med Res 2004;35:435-41.
6. Statement on sarcoidosis. Joint statement of the american thoracic society (ATS), the european respiratory society (ERS) and the world association of sarcoidosis and other granulomatous disorders (WASOG) adopted by the ATS board of directors and by the ERS executive committee, February 1999. Am J Respir Crit Care Med 1999;160:736-55.
7. Telenti A, Hermans PE. Idiopathic granulomatosis manifesting as fever of unknown origin. Mayo Clin Proc 1989;64:44-50.
8. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ, *et al.* The systemic inflammation-based neutrophil-lymphocyte ratio: Experience in patients with cancer. Crit Rev Oncol Hematol 2013;88:218-30.
9. Zhou X, Du Y, Huang Z, Xu J, Qiu T, Wang J, *et al*. Prognostic value of PLO in various cancers: A meta-analysis. PLoS One 2014;9:e101119.
10. Dirican N, Anar C, Kaya S, Bircan HA, Colar HH, Cakir M, *et al.* The clinical significance of hematologic parameters in patients with sarcoidosis. Clin Respir J 2016;10:32-9.
11. Iliaz S, Iliaz R, Ortakoylu G, Bahadir A, Bagci BA, Caglar E, *et al.* Value of neutrophil/lymphocyte ratio in the differential diagnosis of sarcoidosis and tuberculosis. Ann Thorac Med 2014;9:232-5.
12. Günay E, Sarınç Ulaşlı S, Akar O, Ahsen A, Günay S, Koyuncu T, *et al.* Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: A retrospective study. Inflammation 2014;37:374-80.
13. de Jager CP, Wever PC, Gemen EF, Kusters R, van Gageldonk-Lafeber AB, van der Poll T, *et al.* The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. PLoS One 2012;7:e46561.
14. Yoon NB, Son C, Um SJ. Role of the neutrophil-lymphocyte count ratio in the differential diagnosis between pulmonary tuberculosis and bacterial community-acquired pneumonia. Ann Lab Med 2013;33:105-10.
15. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102:5-14.
16. Wyllie DH, Bowler IC, Peto TE. Relation between lymphopenia and bacteraemia in UK adults with medical emergencies. J Clin Pathol 2004;57:950-5.
17. Boros DL. Granulomatous inflammations. Prog Allergy 1978;24:183-267.
18. Wang D, Yang JX, Cao DY, Wan XR, Feng FZ, Huang HF, *et al.* Preoperative neutrophil-lymphocyte and platelet-lymphocyte ratios as independent predictors of cervical stromal involvement in surgically treated endometrioid adenocarcinoma. Onco Targets Ther 2013;6:211-6.
19. Gary T, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, *et al.* Platelet-to-lymphocyte ratio: A novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PLoS One 2013;8:e67688.
20. Azab B, Shah N, Akerman M, McGinn JT Jr. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. J Thromb Thrombolysis 2012;34:326-34.
21. Raungkaewmanee S, Tangjitgamol S, Manusirivithaya S, Srijaipracharoen S, Thavaramara T. Platelet to lymphocyte ratio as a prognostic factor for epithelial ovarian cancer. J Gynecol Oncol 2012;23:265-73.
22. Turkmen K, Erdur FM, Ozcicek F, Ozcicek A, Akbas EM, Ozbicer A, *et al.* Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int 2013;17:391-6.
23. Baygin N, Tozkoparan E. Paradoxical relationship between TNF-alpha antagonists and sarcoidosis. Semin Arthritis Rheum 2014;43:e2.
24. Saboor SA, Johnson NM, McFadden J. Detection of mycobacterial DNA in sarcoidosis and tuberculosis with polymerase chain reaction. Lancet 1992;339:1012-5.