ORIGINAL ARTICLE

Composite inflammatory indices for the differentiation of tuberculosis, sarcoidosis, and reactive lymphadenopathy in patients undergoing EBUS-TBNA

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ABSTRACT

Background: Differentiating mediastinal lymphadenopathy (LAP) due to tuberculosis, sarcoidosis, and reactive causes remains challenging because of overlapping clinical and radiological features. This study aimed to evaluate the diagnostic value of the systemic inflammation composite index (SICI), the platelet inflammation composite index (PICI), and other hematological indices for this differentiation.

Methods: This retrospective study included 223 patients who underwent endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) for mediastinal LAP between 2020 and 2025. Pre-procedural laboratory data were used to calculate the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and the newly defined SICI and PICI.

Results: PLR, NLR, SII, SICI, and PICI levels were highest in the tuberculosis group and were significantly higher in patients with granulomatous LAP than in those with reactive LAP ($p < 0.001$ for all). In differentiating tuberculosis from sarcoidosis, a SICI cut-off value of 10966.6 yielded a sensitivity of 83% and a specificity of 63%, while a PICI cut-off value of 2.2 yielded a sensitivity of 85% and a specificity of 60%. For distinguishing granulomatous from reactive LAP, the optimal cut-off values were 77.4 for PLR (sensitivity 98%, specificity 67%), 2721.5 for SICI (sensitivity 89%, specificity 63%), and 0.69 for PICI (sensitivity 87%, specificity 61%). Pairwise comparisons of ROC curves using the DeLong method further supported the diagnostic performance of the composite indices.

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Conclusion: SICI and PICI, introduced for the first time in the literature, are readily available composite indices that may aid in differentiating tuberculosis-, sarcoidosis-, and reactive LAP–related mediastinal LAP.

Keywords: systemic inflammation composite index (SICI), platelet inflammation composite index (PICI), tuberculosis, sarcoidosis

Introduction

Tuberculosis is a chronic infectious disease caused by Mycobacterium tuberculosis and remains one of the leading causes of granulomatous inflammation worldwide (1). Sarcoidosis, in contrast, is a multisystem inflammatory disease characterized by the formation of non-caseating granulomas of unknown etiology (2). Mediastinal and hilar lymphadenopathy (LAP), defined as enlargement of lymph nodes within the mediastinum or hilar regions, represents a common clinical manifestation of several inflammatory and infectious diseases, including tuberculosis and sarcoidosis (3). Owing to overlapping clinical and radiological features, differentiating these conditions can be challenging. Although endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) is widely used for diagnostic evaluation, it is an invasive procedure and may not always provide definitive results in granulomatous diseases (4). Therefore, the identification of simple and non-invasive parameters to support differential diagnosis remains clinically important (5). Systemic inflammatory responses differ between granulomatous and reactive lymph node diseases and are reflected in peripheral blood parameters. In tuberculosis, increased interleukin-6 (IL-6) levels stimulate hepatic thrombopoietin production, promoting reactive thrombocytosis, while elevated fibrinogen during the acute-phase response facilitates erythrocyte rouleaux formation, leading to an increased erythrocyte sedimentation rate (6-8). In contrast, sarcoidosis is an immune-mediated disease in which hematological alterations are generally more heterogeneous and less pronounced, depending on disease activity and extent (2). Reactive LAP typically represents a transient inflammatory condition and is less frequently associated with marked or persistent systemic inflammatory findings (9). In line with these findings, our previous studies demonstrated that patients with tuberculous lymphadenitis diagnosed by mediastinoscopy or EBUS-TBNA had significantly higher platelet counts, erythrocyte sedimentation rates, and systemic immune-inflammation index (SII) levels compared with patients with sarcoidosis-related lymphadenitis (9). Moreover, SII was shown to be a potentially useful marker in distinguishing granulomatous lymphadenitis from reactive LAP. In contrast, a recent meta-analysis reported that the neutrophil-to-lymphocyte ratio (NLR) does not provide adequate discriminative performance in differentiating tuberculosis from sarcoidosis (10). To better capture both cellular inflammation and acute-phase activity, we focused on composite indices integrating hematological parameters with erythrocyte sedimentation rate. In this context, we developed two novel indices: the Systemic Inflammation Composite Index (SICI) and the Platelet Inflammation Composite Index (PICI). To the best of our knowledge, these indices have not been previously described in the literature. By incorporating erythrocyte sedimentation rate alongside conventional hematological parameters, these composite indices may provide a more comprehensive reflection of systemic inflammatory burden than commonly used ratios such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). In this study, we evaluated whether these indices could improve the differentiation of tuberculosis-, sarcoidosis-, and reactive LAP–related mediastinal lymphadenopathy using pre-procedural laboratory data.

Methods

Study design

This study was designed as a retrospective analysis of patients who underwent EBUS-TBNA for mediastinal LAP between January 2020 and 2025. During the study period, a total of 1312 patients underwent EBUS-TBNA at our institution. Routine laboratory blood tests were obtained from all patients prior to the procedure, and no additional laboratory investigations were requested specifically for this study. Only patients whose diagnoses of granulomatous or reactive LAP were confirmed after at least one year of follow-up were included in the analysis. As the data were analyzed retrospectively, no additional informed consent was obtained beyond the standard pre-procedural consent.

Study population

During the study period, 1312 patients underwent EBUS-TBNA for mediastinal LAP. Of these, 1089 patients were excluded due to the presence of malignancy, non-diagnostic pathology, other specific diagnoses, missing pre-procedural laboratory data, or repeat EBUS procedures. After applying these exclusion criteria, a total of 223 patients were included in the final analysis (Figure 1). The study population consisted of patients with a confirmed diagnosis of tuberculosis, sarcoidosis, or reactive LAP, with diagnostic confirmation established after at least one year of clinical follow-up. Patients classified as having reactive LAP based on EBUS-TBNA findings were included only if no alternative pathological diagnosis emerged during the follow-up period (Figure 1). For patients diagnosed with sarcoidosis, radiographic staging was performed according to the Scadding classification based on chest radiography findings. Stage 1 was defined as isolated bilateral hilar lymphadenopathy, whereas stage 2 included patients with both hilar lymphadenopathy and parenchymal lung involvement.

Endobronchial ultrasonography application procedure

Patients who were admitted to our outpatient clinic for various reasons and whose thoracic computed tomography showed a LAP of 10 mm or more were evaluated as pathologic LAP and subjected to EBUS procedure. Before the procedure, all patients gargled with 5 ml of 2% lidocaine (Jetmonal %2®) and received 3 puffs of lidocaine spray (Vemcaine 10%®) to the posterior pharynx for local anesthesia. All patients were sedated using midazolam (for patients ≤60

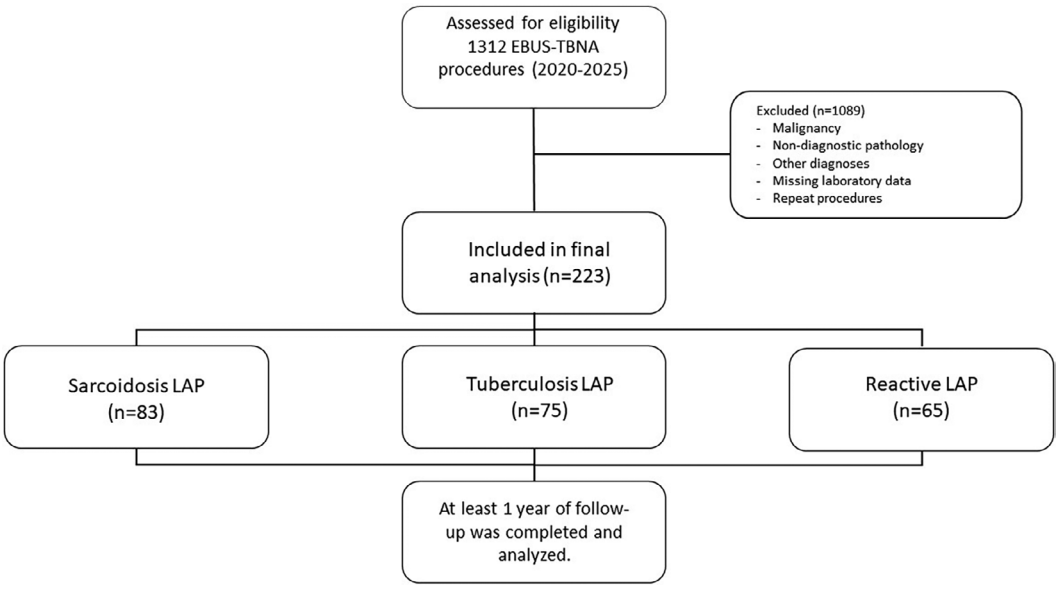

Figure 1. Patient flow diagram.

years old: initial dose of 2–2.5 mg increasing to total dose of 7.5 mg as needed; for patients >60 years old, initial dose of 0.5–1 mg increasing to total dose of 3.5 mg as needed). Oxygen therapy was initiated according to the patients' randomly assigned groups. The EBUS (Olympus BF-UC160F-0L8) procedure was performed via oropharyngeal approach.

Calculation of hematological and composite inflammatory indices

Pre-procedural blood parameters of all patients were obtained from peripheral venous blood samples collected at the time of admission prior to EBUS-TBNA. Blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA) and analyzed using an automated hematological analyzer in accordance with the routine procedures of our hospital laboratory (Coulter LH 780 Analyzer, CA, USA). No additional blood samples were obtained specifically for this study.

Based on these measurements, the following hematological and composite inflammatory indices were calculated:

Neutrophil-to-Lymphocyte Ratio (NLR)

NLR = Neutrophil count (10^3/μL) / Lymphocyte count (10^3/μL)

Platelet-to-Lymphocyte Ratio (PLR)

PLR = Platelet count (10^3/μL) / Lymphocyte count (10^3/μL)

Systemic Immune-Inflammation Index (SII)

SII = [Platelet count (10^3/μL) x Neutrophil count (10^3/μL)] / Lymphocyte count (10^3/μL)

Systemic Inflammation Composite Index (SICI)

SICI = [SII x Erythrocyte sedimentation rate (mm/hour)] / 1000

Platelet Inflammation Composite Index (PICI)

PICI = [PLR x Erythrocyte sedimentation rate (mm/hour)] / 1000

The division by 1000 in the calculation of SICI and PICI was applied to improve numerical stability and interpretability of the composite indices.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA) and MedCalc Statistical Software (MedCalc Software Ltd, Ostend, Belgium). Continuous variables were assessed for normality using visual (histograms and Q–Q plots) and analytical methods. As most variables showed non-normal distribution, data were expressed as median (minimum–maximum). Categorical variables were presented as number and percentage. Comparisons among more than two independent groups (sarcoidosis, tuberculosis, and reactive LAP) were performed using the Kruskal–Wallis test. When a statistically significant difference was detected, pairwise comparisons were conducted using appropriate post-hoc analyses. Comparisons between two independent groups (stage 1 vs. stage 2 sarcoidosis) were performed using the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The diagnostic performance of hematological and composite inflammatory indices in differentiating granulomatous from reactive LAP, tuberculosis from sarcoidosis, and stage 1 from stage 2 sarcoidosis was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) with 95% confidence intervals was calculated for each index. Optimal cut-off values were determined using the Youden index, and corresponding sensitivity and specificity values were reported. Pairwise comparisons of ROC curves were performed using the DeLong method. A p value < 0.05 was considered statistically significant.

Results

The median age of patients in the study was 35 (18 – 77), with 33 (18 – 71) in the sarcoidosis group, 31 (18 – 73) in the tuberculosis group, and 48 (18 – 77) in the reactive LAP group. Age comparisons showed no significant differences between the groups (p = 0.71).

59 patients (71.1%) in the sarcoidosis group, 44 patients (58.7%) in the tuberculosis group, and 7 patients (10.8%) in the reactive LAP group were female. A statistically significant difference was observed between the groups based on gender (p < 0.001). Comparison of laboratory data across the groups is shown in Table 1. Platelet and neutrophil levels were higher in patients with granulomatous LAP than in those with reactive LAP, whereas lymphocyte levels were lower (p = < 0.001, <0.001, 0.007, respectively). The erythrocyte sedimentation rate was highest in the tuberculosis group. It was also higher in patients with granulomatous LAP than in those with reactive LAP (p < 0.001). Similarly, PLR, NLR, SII, SICI, and PICI levels were highest in the tuberculosis group. These indices were also higher in patients with granulomatous LAP than in those with reactive LAP (p < 0.001 for all). Table 2 presents the comparison of age and laboratory parameters between patients with stage 1 and stage 2 sarcoidosis. Accordingly, no statistically significant difference was observed in median age between stage 1 and stage 2 patients (p = 0.31). 31 (77.5%) of stage 1 patients and 28 (65.1%) of stage 2 patients were women. No significant difference was observed between the groups in terms of gender (p = 0.16). Leukocyte levels were higher in stage 1 patients, whereas platelet count, sedimentation rate, PLR, NLR, SII, SICI, and PICI were statistically higher in stage 2 patients (p < 0.001, 0.01, 0.001, < 0.001, < 0.001, < 0.001, < 0.001, < 0.001, and < 0.001, respectively). Figure 2 and Table 3 show the ROC curve analysis of hematological and composite indices for differentiating granulomatous and reactive LAP. The area under the curve (AUC) was 0.857 for PLR, 0.829 for SICI, and 0.828 for PICI. For PLR, with a cutoff value of 77.4, the sensitivity was 98% and the specificity was 67%; for SICI, with a

Table 1. Comparison of age and laboratory data for patients diagnosed with sarcoidosis, tuberculosis, and reactive lymphadenitis after pathological and clinical evaluation

	Sarcoidosis LAP n = 83 Median (Min. - Max)	**Tuberculosis LAP n = 75 Median (Min. - Max)**	**Reactive LAP n = 65 Median (Min. - Max)**	**p**
Age (year)	33 (18 - 71)	31 (18 - 73)	48 (18 -77)	0.71
Hemoglobin (mg/dL)	13.7 (9.8 - 18.6)	13.4 (9.9 - 17.6)	14.5 (10.3 - 17.2)	0.7
WBC (/µL)	7800 (2060 - 17000)	8100 (2350 - 17260)	8300 (3295 - 18045)	0.59
Monocyte (/µL)	540 (220 - 980)	560 (240 -1050)	520 (210 - 1020)	0.71
Eosinophil (/µL)	180 (20 - 620)	160 (10 - 580)	170 (15 - 600)	0.68
Basophil (/µL)	40 (0 - 120)	45 (0 - 130)	38 (0 - 125)	0.74
Lymphocyte (/µL)	1600 (320 - 2680)	1300 (600 - 3500)*	2500 (370 - 4000)	<0.001
Neuthrophil (/µL)	4770 (1500 - 12600)	4700 (1500 - 12000)	4400 (2700 - 12300)	0.007
Platelet (/µL)	277000 (12300 - 803000)	278000 (141000 - 781000)	216000 (126000 - 654000)	<0.001
Sedimentation (mm/h)	11 (2 - 56)	34 (2 - 97)*	4 (2 - 68)	<0.001
PLR	156.5 (72.3 - 892.2)	247.7 (74.2 - 616.7)*	77.1 (69.4 - 467.1)	<0.001
NLR	3.1 (0.7 - 14.9)	4.3 (1.1 - 15.5)*	1.8 (0.9 - 21.7)	<0.001
SII	781875 (108409.1 - 1120000)	1165714.3 (265375 - 5740000)*	334400 (208285.7 - 5750000)	<0.001
SICI	8682.4 (630.2 - 281050)	40800 (592.2 - 556295)*	1337.6 (416.6 - 390718)	<0.001
PICI	1.67 (0.17 - 36.8)	8.4 (0.2 - 59.8)*	0.3 (0.14 - 31.8)	<0.001

p*: Statistically significant difference in comparison of tuberculosis and sarcoidosis LAP patients (p < 0.05), *Abbreviations:* WBC: White blood cell, systemic inflammation composite index (SICI), platelet inflammation composite index (PICI), platelet-to-lymphocyte ratio (PLR), neutrophil -to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII).

Table 2. Comparison of age and laboratory parameters between patients with stage 1 and stage 2 sarcoidosis.

	Sarcoidosis Stage 1 n = 40 Median (Min. - Max)		**p**
Age (year)	31 (18 - 71)	35 (21 - 69)	0.31
Hemoglobin (mg/dL)	13.3 (9.8 - 18.3)	13.8 (10.3 - 18.6)	0.28
WBC (/µL)	7200 (2060 - 13760)	8200 (3785 - 17320)	0.41
Monocyte (/µL)	520 (220 - 950)	560 (260 - 980)	0.62
Eosinophil (/µL)	170 (20 - 600)	180 (25 - 620)	0.67
Basophil (/µL)	38 (0 - 110)	42 (0 - 120)	0.71
Lymphocyte (/µL)	2000 (320 - 3000)	1400 (800 - 3000)	<0.001
Neuthrophil (/µL)	4400 (1500 - 9100)	5100 (2700 - 12600)	0.14
Platelet (/µL)	245500 (123000 - 407000)	290000 (178000 - 803000)	0.01
Sedimentation (mm/h)	10 (2 - 56)	15 (2 -48)	0.001
PLR	125.4 (72.3 - 656.3)	200.8 (82.9 - 892.2)	<0.001
NLR	2.2 (0.7 - 14.9)	3.7 (1.4 - 14)	<0.001
SII	610504.1 (108409 - 3130000)	976500 (315083.3 - 1120000)	<0.001
SICI	5585.7 (630.1 - 175297.5)	18953.9 (712 - 281050)	<0.001
PICI	1.21 (0.2 - 36.75)	3.1 (0.2 - 22.3)	<0.001

Abbreviations: WBC: White blood cell, systemic inflammation composite index (SICI), platelet inflammation composite index (PICI), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII).

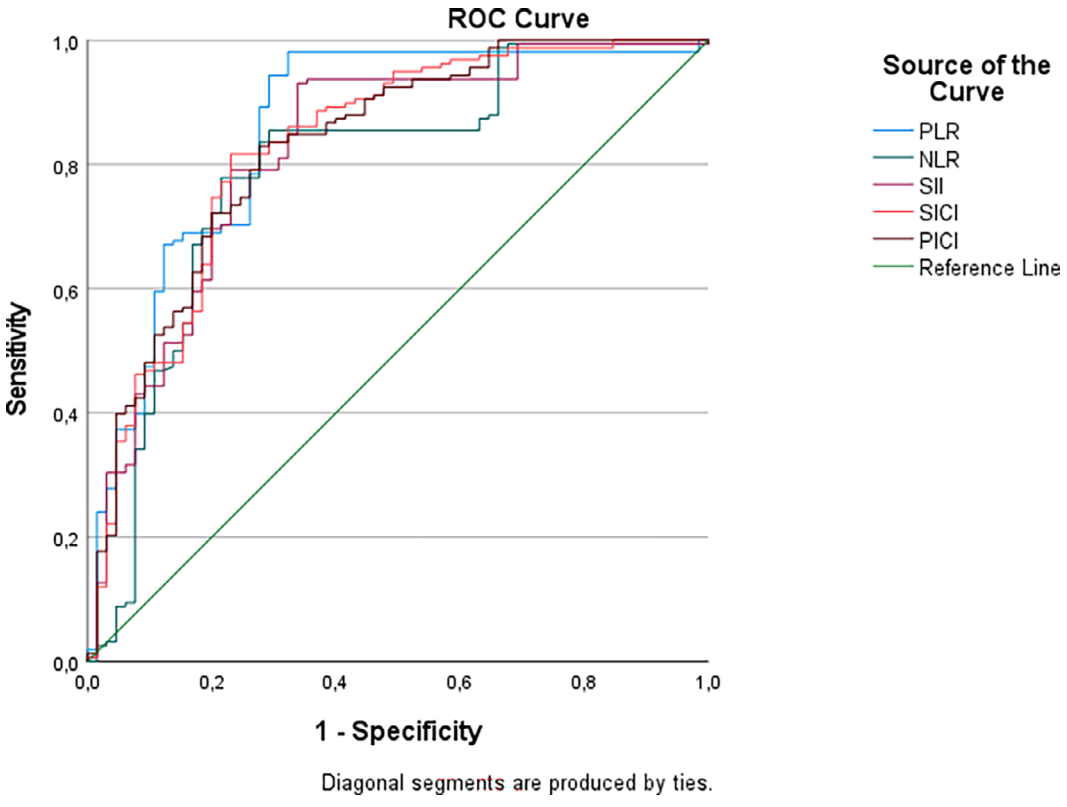

Figure 2. ROC curve analysis of hematological and composite inflammatory indices for differentiating granulomatous and reactive LAP.

Table 3. Pairwise comparison of ROC curves using the DeLong method for differentiating granulomatous and reactive LAP

Test Result Variables	Area	Std. Error	p	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PLR	0.857	0.031	<0.001	0.797	0.917
NLR	0.791	0.037	<0.001	0.719	0.863
SII	0.824	0.033	<0.001	0.76	0.888
SICI	0.829	0.032	<0.001	0.765	0.892
PICI	0.828	0.032	<0.001	0.766	0.89

Pairwise comparison of ROC curves (DeLong test)			
Comparison	**Difference between AUC**	**95% CI**	**p**
PLR vs NLR	0.0674	0.0219–0.113	**0.004**
PLR vs SII	0.0332	0.00393–0.0625	**0.03**
NLR vs SII	0.0342	0.00374–0.0646	**0.03**

Abbreviations: Systemic inflammation composite index (SICI), platelet inflammation composite index (PICI), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII).

cutoff value of 2721.5, the sensitivity was 89% and the specificity was 63%; and for PICI, with a cutoff value of 0.69, the sensitivity was 87% and the specificity was 61%. Pairwise comparisons of ROC curves using the DeLong test demonstrated that PLR had significantly higher diagnostic performance than NLR (p = 0.004) and SII (p = 0.03). Figure 3 and Table 4 show the ROC curve analysis of hematological and composite indices for differentiating tuberculosis from sarcoidosis. The AUC was 0.75 for SICI and 0.779 for PICI. When the SICI cut-off was set at 10966.6, the sensitivity was 83% and the specificity was 63%. When the PICI cut-off was set at 2.2, the sensitivity was 85% and the specificity was 60%. Pairwise comparisons of ROC curves using the DeLong method demonstrated that SICI and PICI showed significantly higher diagnostic performance compared with NLR and SII (p < 0.01 for all comparisons). In addition, PICI showed a significantly higher AUC than PLR (p = 0.003), and SICI also showed a significantly higher AUC than SII (p = 0.0002). Figure 4 and Table 5 show the ROC curve analysis of hematological and composite indices for differentiating patients with stage 1 and stage 2 sarcoidosis. The AUC was 0.788 for PLR, 0.774 for SII, 0.76 for SICI, and 0.761 for PICI. With a cut-off value of 158.3 for PLR, the sensitivity was 79% and the specificity was 83%. With a cut-off value of 702760.9 for SII, the sensitivity was 77% and the specificity was 65%. With a cut-off value of 7541 for SICI, the sensitivity was 72% and the specificity was 67%. With a cut-off value of 1.47 for PICI, the sensitivity was 77% and the specificity was 65%. Pairwise comparisons of ROC curves using the DeLong method did not demonstrate statistically significant differences between the evaluated indices in differentiating stage 1 and stage 2 sarcoidosis.

Discussion

In our study, we observed higher sedimentation rates, platelet counts, and neutrophil counts in patients with granulomatous inflammation. Consequently, the PLR, NLR, SII, SICI, and PICI indices were higher in patients with granulomatous LAP. To the best of our knowledge, the SICI and PICI indices showed better sensitivity and specificity than other indices in patients with lymphadenopathy due to tuberculosis and sarcoidosis. The PLR ratio showed higher sensitivity and specificity than other indices in differentiating sarcoidosis stages 1 and 2. The two most important causes of mediastinal granulomatous

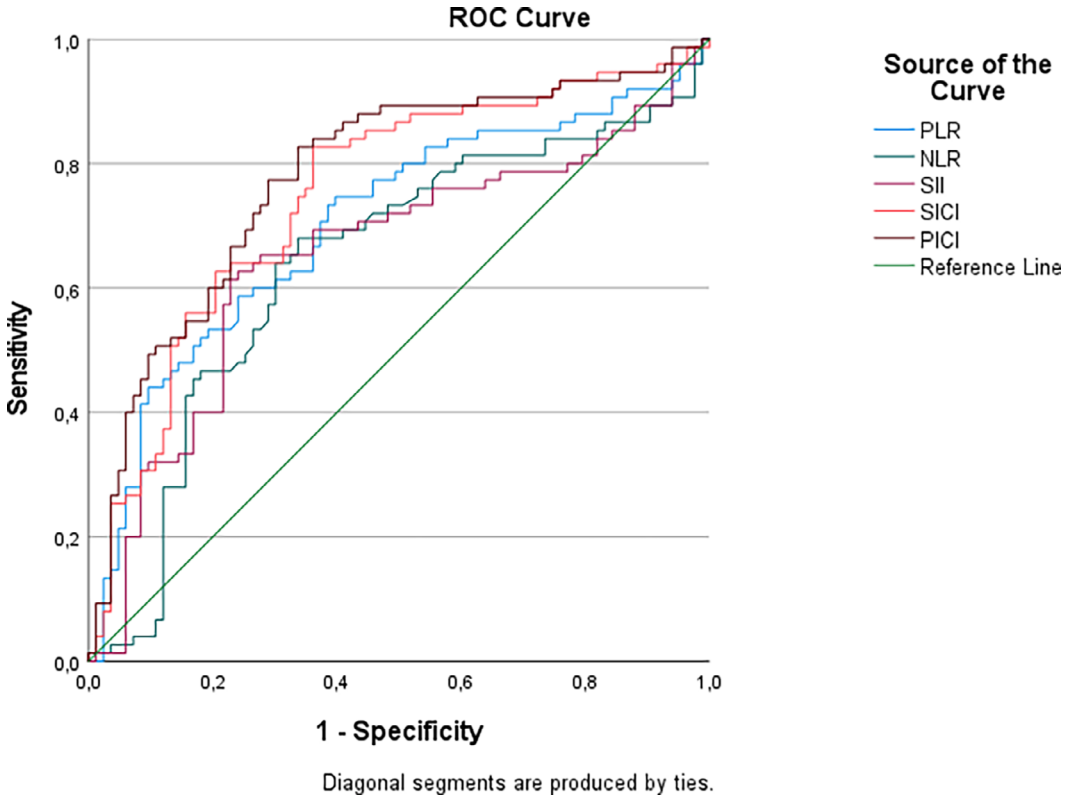

Figure 3. ROC curve analysis of hematological and composite inflammatory indices for differentiating tuberculosis and sarcoidosis.

Table 4. Pairwise comparison of ROC curves using the DeLong method for differentiating tuberculosis and sarcoidosis

Test Result Variables	Area	Std. Error	p	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PLR	0.703	0.043	<0.001	0.619	0.786
NLR	0.64	0.046	0.002	0.55	0.729
SII	0.651	0.046	0.001	0.562	0.74
SICI	0.75	0.04	<0.001	0.672	0.827
PICI	0.779	0.038	<0.001	0.705	0.854

Pairwise comparison of ROC curves (DeLong test)			
Comparison	**Difference between AUC**	**95% CI**	**p**
NLR vs SICI	0.110	0.042–0.177	0.002
NLR vs PICI	0.139	0.061–0.217	0.0005
PLR vs SII	0.0515	0.003–0.099	0.04
PLR vs PICI	0.0763	0.025–0.127	0.003
SII vs SICI	0.0983	0.046–0.151	0.0002
SII vs PICI	0.128	0.063–0.193	0.0001
SICI vs PICI	0.0295	0.008–0.050	0.006

Abbreviations: Systemic inflammation composite index (SICI), platelet inflammation composite index (PICI), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII).

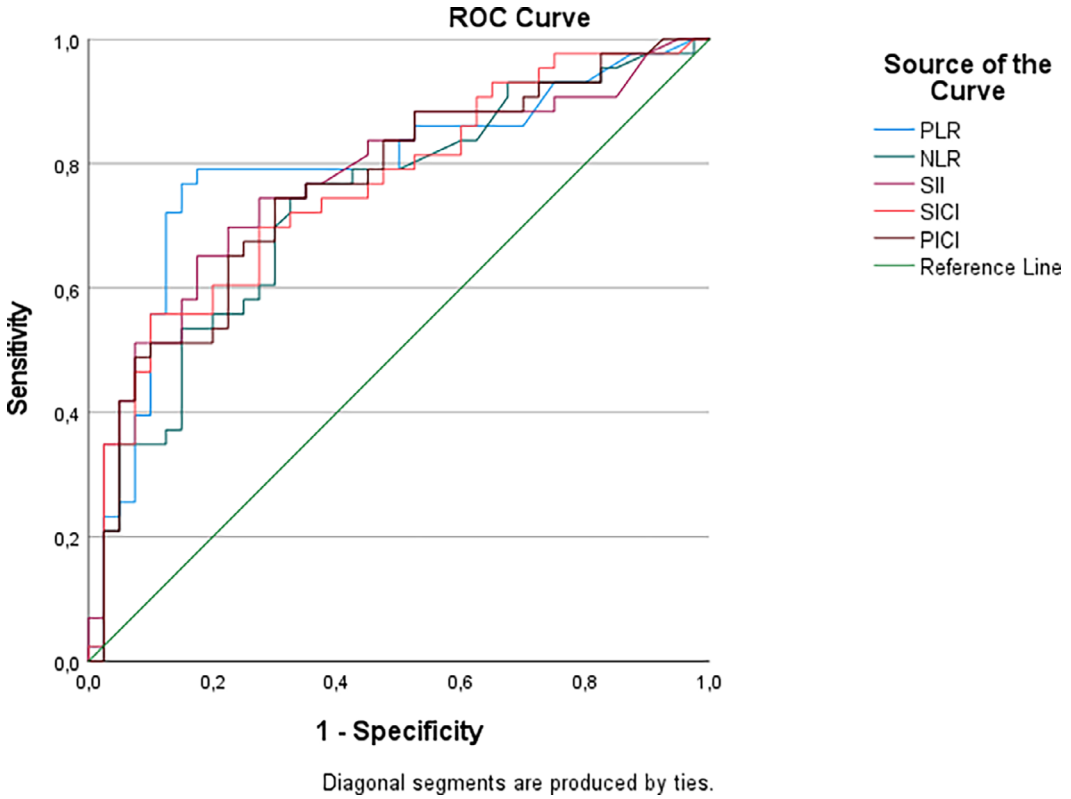

Figure 4. ROC curve analysis of hematological and composite indices for differentiating patients with stage 1 and stage 2 sarcoidosis

Table 5. ROC curve analysis of hematological and composite indices for differentiating patients with stage 1 and stage 2 sarcoidosis

Test Result Variables	Area	Std. Error	p	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PLR	0.788	0.053	<0.001	0.685	0.892
NLR	0.734	0.055	<0.001	0.626	0.842
SII	0.774	0.052	<0.001	0.672	0.877
SICI	0.76	0.053	<0.001	0.657	0.863
PICI	0.761	0.053	<0.001	0.658	0.865

*Abbreviations:*Systemic inflammation composite index (SICI), platelet inflammation composite index (PICI), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII)

LAP are tuberculosis and sarcoidosis. In these diseases, characterized by granulomatous inflammation, there is a significant increase in pro-inflammatory cytokine levels, primarily IL-6, interferon-gamma, and TNF-alpha (6, 11). This excess affects neutrophil activation, induces reactive thrombocytosis, and increases the acute-phase reactant response, leading to a significant rise in the erythrocyte sedimentation rate (8). While increased cytokine levels are more pronounced in tuberculosis, sarcoidosis also leads to elevated cytokine levels, particularly through Th1 lymphocyte and macrophage activation, as the disease progresses

(12). Activation in lymph nodes draws CD4+ T lymphocytes and macrophages to regional lymph nodes, while lymphocyte levels decrease in the peripheral area (12). Because inflammation due to reactive LAP is shorter-lived and does not trigger a systemic immune response, lymphocyte numbers in the peripheral area may be preserved or slightly increased (13). Pathologically, the term granulomatous LAP is observed in many chronic inflammatory diseases, including those mentioned above. This can sometimes lead clinicians to search for a needle in a haystack. Hematological parameters have been chosen as an easily accessible method for clinicians to differentiate between the two diseases (14). Hematological parameters, which vary depending on the secondary consequences of diseases, have been evaluated in many diseases, and positive results have been obtained. In studies examining the PLR ratio in patients with sarcoidosis, it was observed that the PLR ratio increased with disease stage and correlated with the sedimentation rate (9, 15). A similar study of tuberculosis patients found that NLR, PLR, and the monocyte/lymphocyte ratio increased with disease severity (16). Studies on the role of hematological parameters in differentiating between these two diseases have been limited. In our clinic's studies, we observed that the PLR and NLR ratios can be useful in differentiating granulomatous LAP from reactive LAP (17). Another study found that SII levels were higher in patients with tuberculosis than in those with sarcoidosis or reactive LAP (9). In our study, in addition to current literature data, we aimed to develop new composite inflammatory indices, given the importance of sedimentation in diseases presenting with granulomatous LAP. In this evaluation, consistent with the literature, platelet and neutrophil levels were higher, and lymphocyte levels were lower, in patients with granulomatous LAP. Among patients with granulomatous LAP, the tuberculosis LAP group had higher PLR, NLR, SII, SICI, and PICI indices. This finding may reflect the more pronounced lymphopenia observed in tuberculosis compared with sarcoidosis, which could be related to the stronger systemic inflammatory response in tuberculosis. Furthermore, the higher erythrocyte sedimentation rate observed in tuberculosis patients may partially explain the elevated SICI and PICI levels in this group. In stage 1 and 2 sarcoidosis patients, PLR, NLR, SII, SICI, and PICI values were observed to be higher as the stage progressed. This observation may be related to decreased peripheral lymphocyte levels and increased sedimentation rates in patients with more advanced stages of sarcoidosis. When we examined the gender distribution in our study, we found that sarcoidosis patients were predominantly female, consistent with the literature. In the evaluation of composite inflammatory index levels to differentiate between tuberculosis and sarcoidosis LAP, SICI and PICI appeared to demonstrate higher sensitivity and specificity compared with the other indices evaluated in this study. Furthermore, pairwise comparisons of ROC curves using the DeLong method supported these findings, demonstrating that SICI and PICI showed significantly higher diagnostic performance than several conventional inflammatory indices in differentiating tuberculosis from sarcoidosis. In differentiating between granulomatous and reactive LAP, the PLR ratio showed the best sensitivity, followed by SICI and PICI indices. The decreased effectiveness of SICI and PICI levels in differentiating between granulomatous and reactive LAP in tuberculosis and sarcoidosis can primarily be attributed to the lower sedimentation rate in sarcoidosis patients. For this reason, among the sarcoidosis stages, the PLR level has shown slightly higher sensitivity and specificity for SICI and PICI. This study has several limitations. Its retrospective and single-center design may limit the generalizability of the findings. In addition, inflammatory markers were assessed at a single pre-procedural time point, and other acute-phase reactants such as C-reactive protein were not included in the analysis. However, the study population was derived from a well-defined EBUS-TBNA cohort, and diagnoses were confirmed after at least one year of follow-up, which strengthens the validity of the results. Furthermore, all indices were calculated using routine and readily available laboratory parameters, supporting the clinical applicability of the proposed composite indices. In conclusion, the newly defined SICI and PICI indices were found to be useful

in differentiating tuberculosis- and sarcoidosis-related LAP, a distinction that can be particularly challenging in patients with granulomatous LAP. These indices also provided valuable diagnostic contribution in distinguishing granulomatous from reactive LAP. By incorporating erythrocyte sedimentation rate, SICI and PICI may serve as readily available and practical markers to support diagnostic evaluation in diseases characterized by chronic inflammatory activity.

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.

Ethical Approval: This study was approved by the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (approval number: B.30.2.ATA.0.01.00/23). As the study was designed retrospectively and based on anonymized data, informed consent was not obtained from the patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Declaration on the Use of AI: No artificial intelligence tools were used in the preparation of this manuscript.

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