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PLATELET LYMPHOCYTE RATIO IN PREDICTING THE SEVERITY OF SARCOIDOSIS IN OUR POPULATION

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Abstract

Sarcoidosis is a systemic granulomatous disease with diverse clinical phenotypes and natural histories, so there needs to identify potential biomarkers of disease severity. The aim of the study was to investigate the role of the platelet-to-lymphocyte ratio (PLR) as a biomarker to stop progressive treatment. PLR was found as a readily available haematological index relating to systemic inflammation in different chronic conditions; however, results were not uniform among studies conducted on sarcoidosis. In order to overcome these shortcomings, a prospective observational cohort study was carried out in the Department of Pulmonology Tertiary Care Hospital Karachi from January 2023 to June 2024. Eighty-two treatment-naïve, newly diagnosed sarcoidosis patients aged 18–70 years were recruited according to the ATS/ERS/WASOG diagnostic criteria. Detailed demographics, clinical presentation and laboratory findings were recorded on predesigned proformas. PLR was determined by the complete blood count, disease severity scoring, and staging Scadding using chest imaging and FVC/DLCO. Statistical analysis consisted of t-test, ANOVA, correlation, logistic regression and ROC curve analysis using SPSS version 27. PLR was higher in severe versus mild cases (214.3 ± 61.2 vs 138.6 ± 49.8, $p < 0.001$). PLR was positively correlated with ESR ($r = 0.51$, $p < 0.001$), CRP ($r = 0.47$, $p < 0.001$) and ACE ($r = 0.36$, $p = 0.002$), and negatively correlated with FVC ($r = –0.58$, $p < 0.001$) and DLCO ($r = –0.55$, $P < .001$). Logistic regression analysis revealed that both baseline PLR (OR = 1.012; $p = 0.002$) and CRP OR = 1.145; $p = 0.021$) were independently associated with severe sarcoidosis. A ROC analysis corroborated the accuracy of the diagnosis (AUC = 0.812; 95% CI 0.720–0.904) considering a best cut-off value equal to 176.5 that corresponded to a sensitivity – specificity set at 78.4 % and 74.6 %. These findings support PLR as an easily applicable and non-invasive tool for systemic action and severity of the disease that might have added value in less privileged settings.

INTRODUCTION

Sarcoidosis is an idiopathic, systemic, granulomatous disease characteristically affecting the lungs and mediastinal lymph nodes. The clinical course and the natural history are highly heterogeneous, with some patients recovering after removal from exposure while others progress to chronic organ damage including irreversible lung fibrosis (Tana et al., 2021). This heterogeneity complicates the clinical decision-making, and stresses the relevance of stable and easy markers to monitor disease activity. Because of the unpredictable nature of sarcoidosis, research has been conducted that culminated in the development of various diagnostic and prognostic markers that can better detect disease severity and risk for worse outcomes as well as guide therapy (Kraaijvanger et al., 2020).

At histopathological level, the diagnosis of sarcoidosis is defined by non-caseating epithelioid cell granulomas containing multinucleated giant cells and $CD4^+$ T lymphocytes (Starshinova et al., 2024). The immunopathogenesis of the disease is believed to initiate as a hyperreactive cell-mediated immune response against unidentified antigens in genetically predisposed patients. Cytokines within the granuloma are numerous, and a number of these are produced by activated macrophages and T-helper 1 (Th1) cells, like interferon-gamma (IFN-γ), interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNF-α) which promote additional granuloma generation perpetuating chronic inflammation (Ramalingam *et al.*, 2024). Chronic inflammation can lead to tissue remodelling and scar formation, especially in the lungs, leading to deterioration of pulmonary function and worse clinical outcomes.

Immune dysregulation and inflammation play a key role in the pathogenesis of sarcoidosis, and several biomarkers have been suggested for monitoring disease. Serum angiotensin-converting enzyme (ACE), soluble interleukin-2 receptor (sIL-2R), chitotriosidase and serum amyloid A are established markers that have been found to correlate with disease activity (Ramalingam *et al.*, 2024). Nevertheless, some high specificity, expensive and laboratory specific tests are at present not applicable for routine clinical practice. Recently, focus has been placed on finding simpler and cheaper surrogate easily accessible markers that could reflect the systemic inflammatory status without the need for specific assays.

Among these indexes, there is the platelet-to-lymphocyte ratio (PLR), which can be easily calculated by components of a standard Complete blood count (CBC). PLR is obtained by dividing the platelet count to lymphocyte count; thus, representing two vital arms of immune components such as platelet-mediated inflammatory activity with lymphocyte-dependent immune regulation. High platelet counts can reflect generalized inflammation, as activated platelets release pro-inflammatory cytokines and adhesion molecules, which then contribute to tissue damage (Prabawa *et al.*, 2019). Alternatively, lymphopenia can be the result of immune exhaustion or sequestration of lymphocytes to inflamed lesions. Thus, higher PLR indicates an out-of-balance between pro-inflammatory and regulatory immune mechanisms in many chronic inflammatory disorders.

PLR has been revealed to be a promising prognostic indicator in many diseases, including cardiovascular diseases, cancers, and chronic airway diseases such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). It has been associated with disease severity, progression and mortality and frequently portrayed as more predictive than traditional markers (Man *et al.*, 2021). In sarcoidosis, which is in part overlapping with the aforementioned diseases casted by some common inflammatory pathways, PLR has been proposed as a candidate marker of disease activity and severity. Previous studies have demonstrated increased PLR in patients with sarcoidosis when compared to healthy individuals, and found associations between higher PLR and radiographic advanced stages especially which include lung parenchymal involvement.

The attractiveness of PLR is its simplicity and cheapness. This is quantifiable from routine hematologic studies performed in almost all clinical settings and it comes with great benefits especially in resource-limited areas. In addition,

given that PLR does not entail any special equipment or reagents, it may represent a convenient supplement in the clinical follow-up of patients with sarcoidosis, especially for those who have poor availability to sophisticated molecular biomarkers (Li & Xu, 2024). The recognition of such easily accessible indexes might assist in early risk stratification, therapy guide and focused monitoring of high-risk individuals for disease progression.

Accordingly, we evaluated the role of PLR as a predictor marker to define sarcoidosis severity in the current study. The present study is thus of particular interest for assessment if the basal PLR at time of diagnosis has an association with pulmonary involvement, radiographic staging (according to Scadding) and clinical outcomes. Subsidiary analyses will investigate associations of PLR with classical inflammatory indices such as ESR and CRP and established biomarkers as ACE and sIL-2R. Through exploring those methodological gaps including threshold for the inclusion and lack of longitudinal assessment previously, we hope that this study can help to provide a clearer conclusion as to whether PLR is able not only to monitor disease but also predict prognosis (Katsanos *et al.*, 2017).

Review of Literature

There is emerging literature over the past decade examining easily derived haematologic indices like NLR (neutrophil: lymphocyte ratio) and PLR in sarcoidosis. (Islam *et al.*, 2024) concluded that while NLR (and consequently related indices) may vary by radiological severity and stage, there was significant heterogeneity across studies and consistent results were absent enough to establish a clinical guideline. Such review emphasized that the usual methodologic drawbacks such as paucity of subjects, retrospective nature, lack of uniform end points are common in PLR studies as well.

In the 1st clinical comparison study of patients with mediastinal lymphadenopathy (stage 1 pulmonary disease), which was a small and preliminary work, (Özdemir *et al.*, 2018) reported NLR and PLR as biomarkers for differentiating stage 1 sarcoidosis from that due to tuberculous lymphadenitis and healthy controls. They retrospectively enrolled 55 subjects of Stage 1 sarcoidosis, 19 subjects with tuberculosis lymphadenitis and 32 healthy individuals. The results showed that NLR and PLR were both remarkably higher in Stage 1 sarcoidosis patients than in controls, and that PLR was also higher in TB than in the control group. NLR and PLR, however, were an unreliable tool to distinguish sarcoidosis from TB lymphadenitis. The study highlights two common findings: (1) consistently high PLR in sarcoidosis when compared with healthy controls, and (2) PLR is not a sensitive parameter in situations like that where other granulomatous or infectious causes such as TB are prevalent (Özdemir *et al.*, 2018). Limitations to this study were the small sample size and the retrospective nature of data collection, with varying inflammatory markers performed between subjects.

(Korkmaz & Demircioglu, 2020) presented one of the first comprehensive cohort analyses that explicitly dealt with PLR and NLR among disease stages. Both NLR and PLR were increased in patients compared to controls in the study of (Korkmaz & Demircioglu, 2020) (75 sarcoidosis cases, 92 controls), and the results tended to be elevated especially for Scadding stages 2–3 when compared with stage 1 or stage 4 among their cohort. Receiver operating characteristic (ROC) curves had the following characteristics: PLR sensitivity 72%, specificity 67% for sarcoidosis in this cohort. (Korkmaz & Demircioglu, 2020) also observed poor positive correlations of PLR (and NLR) with CRP and stressed that hematologic indices, although they were linked to radiographic extent in their patients, did not predict pulmonary hypertension, spontaneous remission, treatment response or overall prognosis. The authors claimed that PLR/NLR could help to direct suspicion of pulmonary parenchymal involvement and needed prospective validation for prognosis prediction.

(Yalnız *et al.*, 2019) investigated a much larger retrospective study (310 sarcoidosis subjects versus 220 controls) and found that PLR was significantly higher in patients, higher values of PLR were present in patients with lung involvement staged as stages 2–3–4 compared to stage 1 and that there was a positive correlation between PLR and erythrocyte sedimentation rate (ESR). The latter study suggested the use of

PLR for parenchymal involvement, and a PLR cut-off value of approximately 158 was recommended to predict sarcoidosis diagnosis in their population. Strengths of this study were the sample size and performing additional ROC analysis, however it was limited by its retrospective nature as many previous reports, and lack of longitudinal prognostic endpoints.

This is not true for all series, as some do not report high or consistent diagnostic/prognostic performance. (Drăgoescu *et al.*, 2025) study analyzing a panel of hematologic inflammation indices (including PLR) showed that although PLR was significantly higher in patients than controls, the diagnostic performance of this ratio was modest with an area under the ROC curve (AUC) ~ 0.60 and employing a cut-point >171 yielded high specificity (≈94.6%) but low sensitivity (≈36%) when sufficient capacity to distinguish sarcoidosis from healthy controls). The implication is practical with some PLR thresholds being specific (rare false positives) but missing very many true cases (insensitive), which would hinder clinical utility as a sole screening indicator. That investigation also described associations of PLR with some clinical presentations, but again the same was true for a relatively small sample size and single-center design.

Recent, larger cohorts have also clouded the utility of PLR. (Korkmaz & Demircioglu, 2020) prospectively followed over a median 12 months that described clinical course at about six months found the absolute baseline PLR (and for that matter, NLR and LMR), were not strongly associated with short-term (six-month) clinical trajectory: regression/stability/progression. In that analysis (369 patients, diagnosed 2020–24) an additional composite ratio, lactate dehydrogenase to albumin ratio, had also emerged as a weak predictor of progression; PLR did not. The authors made a specific point to mention that although PLR had previously been correlated with disease stage, it did not predict early progression in their cohort and they concluded that hematologic indices need more prospective evaluation and standardization before hemograms can be used as guides for prognosis. (Vornicu *et al.*, 2025) focusing on NLR (with many instances of referencing to the PLR literature) noted substantial heterogeneity among studies, and concluded both that NLR /PLR might represent radiological severity, and also that lack of consistency and variation in methodology precluded strong recommendations for routine practice. The review emphasized that patient selection (treatment naïve vs pretreated patients), concomitant infections, steroid treatment, and comorbidities with impact on blood values are important confounders in retrospective CBC-based studies and should be considered for the future prospective cohorts.

Mechanism wise, the basis of PLR in sarcoidosis depends on two biologic findings. First, platelets become an active player in inflammation beyond haemostasis: they secrete cytokines and chemokines, interact with leukocytes and take part in the recruitment to sites of tissue inflammation therefore reactive thrombocytosis or platelet activation may reflect systemic inflammatory load (Korkmaz & Demircioglu, 2020). Second, patients with sarcoidosis often reflect relative lymphopenia in peripheral blood, perhaps due to lymphocyte infiltration into granulomatous tissue and/or aberrant immune responses; therefore, the numerator (platelets) may increase and denominator (lymphocytes) may decrease affecting PLR. These pathways may render PLR a feasible composite index of granulomatous inflammation, however, they do not ensure specificity, as the same haematological alterations are observed with numerous inflammatory, neoplastic and infectious conditions (Islam *et al.*, 2024).

Several methodological limitations reemerge throughout the literature and rationalize controversial findings. Most reports are retrospective and originate from single centres; studies differ in size, various inclusion/exclusion criteria (most notably with regard to concomitant infection and corticosteroid treatment), radiologic staging is not uniformly applied to diagnose, and follow-up duration for prognostic evaluation remains poorly defined. The proposed cut-off values for PLR by various authors (e.g., 158 in (Yalnız *et al.*, 2019)), are widely separated and the sensitivity/specificity trade-offs differ by indication (diagnosis vs detecting parenchymal disease vs predicting progression). Prior studies lack the prospective

evaluation of PLR in conjunction with established biomarkers of sarcoidosis (sACE, sIL-2R, chitotriosidase) and high-resolution CT criteria or functional outcomes within the same cohort thereby undermining appraisal of added value signed.

Research Methodology

This chapter describes the methodological approach used to assess whether PLR represents a biomarker for predicting sarcoidosis severity. It describes the research design, population under investigation, sampling method, data collection and statistical methods used to maintain validity and reliability of findings. As sarcoidosis is a highly heterogeneous condition, a prospective observational cohort design was chosen to capture differences in clinical, radiological and functional phenotypes at presentation. All methodological aspects, such as participant recruitment and laboratory testing, and the analytical model were designed in compliance with international consensus guidelines for sarcoidosis research. This institution ensured the measurement of the inflammatory and hematologic parameters was sufficiently reliable and has allowed provision for actual interpretation of PLR in both disease activity as well as its severity.

3.1 Study Design and Setting

This prospective observational cohort was conducted at the Pulmonology Unit of Jinnah Postgraduate Medical Centre (JPMC) Karachi, which is one of the largest teaching tertiary care centres in Pakistan. The purpose of this study was to evaluate whether the platelet-to-lymphocyte ratio (PLR) is a potential biomarker in predicting sarcoidosis severity at onset (Yalnız et al., 2019). The study took place from January 2023 to June 2024, or over an 18-month period. Written informed consent was taken from every patient following Declaration of Helsinki.

3.2 Study Population

Adults from 18 to 70 years were recruited as study participants, who haven't been previously diagnosed for having sarcoidosis on clinical, radiological and histopathological criteria. Consecutive cases presenting to pulmonology and internal medicine outdoor/indoor were enrolled in the study. Sarcoidosis diagnosis was based on the American Thoracic Society (ATS)/European Respiratory Society (ERS)/World Association for Sarcoidosis and Other Granulomatous Disease criteria (Giwa et al., 2020). This required that there was a recognizable complete clinical and imaging picture with histological proof of non-caseating granulomas and exclusion of other causes of granulomatous diseases like tuberculosis or fungal infections (Rosen, 2022).

3.3 Sample Size and Sampling Technique

A total of 82 patients were included in the study using consecutive non-probability sampling. The statistical power of the test was 80% and an alpha level of 5% (two tailed) to calculate the sample size using Open Epi software (version 3.01). We assumed a conservative correlation between PLR and the severity of sarcoidosis based on prior investigations (r = 0.35). A 10% oversampling was applied to compensate for potential attrition, resulting in a total sample size of 82 participants (Kraaijvanger et al., 2020). This number of samples was adequate for detecting clinically relevant differences in PLR between different groups of illness severities.

3.4 Inclusion and Exclusion Criteria

The study subjects included patients who were newly diagnosed with sarcoidosis by histopathology examination and HRCT findings, aged between 18 and 70 years old, without any history of steroids or immunosuppressants at the time of blood sampling.

Other patients with comorbidities which could affect hematologic indices, like autoimmune disorders (rheumatoid arthritis or systemic lupus erythematosus), chronic infections (tuberculosis and hepatitis B and C), cancers, hematologic disorders or recent major surgeries were excluded from the study (Sankar & Villa, 2021). Patients receiving drugs that may impact on bone marrow function (e.g. corticosteroids, cytotoxic agents or immunomodulation) were excluded. The aim was to prevent the differences in PLR that reflected sarcoidosis-related inflammation alone, and not also other confounders.

3.5 Data Collection Procedure

All subjects underwent written informed consent and a comprehensive baseline evaluation. Data were filled on a predesigned proforma containing demography (age, sex, place of residence, smoking history) and clinical details about duration of symptoms, involvement of organ systems and presence of extrapulmonary features. A full examination was performed searching for lymphadenopathy, cutaneous lesions and ocular or cardiac manifestations.

Complete aseptic blood collection was obtained at presentation by venepuncture before any treatment drugs were given. Laboratory studies included complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum angiotensin-converting enzyme (ACE), and serum calcium. CBC was analyzed with Sysmex XN-1000 automated hematology analyzer (Sysmex Corporation, Japan) within 2 hours from sampling in order to reduce pre-analytical variation. Quality control was carried out on a daily basis according to laboratory requirements (Verma *et al.*, 2023).

3.6 Estimation of platelet-lymphocyte ratio (PLR)

Platelet to lymphocyte ratio was determined and analyzed as previously reported by (Cai *et al.*, 2025) with some modifications. The PLR was determined by finding the ratio of absolute platelet count to absolute lymphocyte count in a given CBC report. In each case both parameters were used as cell counts per microliter ($\times 10^9$/L). Because the day of blood sampling was before treatment, the PLR values reflected baseline systemic inflammation associated with sarcoidosis. All data processes were repeated twice for the accuracy of the recorded results before statistical entry.

3.7 Assessment of Disease Severity

The severity was assessed radiologically and functionally. Radiological evaluation was also conducted via HRCT of the chest by two radiologists blinded to laboratory results (Cardinale *et al.*, 2014). The radiologic staging was based on the Scadding classification system:

- Stage I-bilateral hilar lymphadenopathy alone
- Stage II: hilar lymphadenopathy with parenchymal infiltrates
- Stage III: parenchymal disease with no involvement of hilar lymph nodes
- Stage IV-pulmonary fibrosis

The functional severity was evaluated with Pulmonary Function Tests (PFTs) performed with a Spirolab III spirometer (MIR, Italy) and meeting the ATS/ERS criteria. The main parameters were the Forced Vital Capacity (FVC) and the Diffusing Capacity for Carbon Monoxide (DLCO), reported as percentages of their respective predicted values (Vongvivitpatana & Nambiar, 2024). Patients with FVC < 70% or D LCO < 65% fall into significant pulmonary function damage.

3.8 Study Variables

The main factor of interest was represented by platelet lymphocyte ratio (PLR). For radiation dose-response analyses, the primary endpoint was disease severity at diagnosis quantified by radiographic stage and degree of pulmonary function deficit. Secondary variables were age, sex, ESR, CRP, ACE and serum calcium levels as well as extrapulmonary disease. Associations of PLR with these variables were further analyzed for independent effect (Vongvivitpatana & Nambiar, 2024).

3.9 Statistical Analysis

All data were introduced in Microsoft Excel 2021 software and analyzed through the IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data and median (interquartile range) for skewed data. Normality was tested using the Shapiro–Wilk test.

The comparisons between the two independent groups (mild vs severe diseases) were made by an independent t-test and Mann–Whitney U test for normally distributed and non-normally distributed data, respectively. Within group comparisons between several stages of diseases were conducted using one-way ANOVA or Kruskal–Wallis test, as appropriate. The relationship between the PLR and continuous

variables (percent predicted FVC, percent predicted DLCO, ACE value, ESR and CRP) was assessed in terms of Pearson's or Spearman's correlation coefficient (Onyilmaz *et al.*, 2025).

Binary logistic regression analysis was carried out to determine the independent predictors of severe sarcoidosis after controlling for confounding factors including age, gender, history of smoking and CRP. The Receiver Operating Characteristic (ROC) curve was generated to evaluate the diagnostic performance of PLR for severe disease, and Area Under the Curve (AUC), sensitivity, specificity, and optimal cut-off values were derived. A p-value of < 0.05 was considered as statistically significant.

3.10 Ethical Considerations

Comprehensive consent was secured with explanation of their data confidentiality prior to patient enrollment. Informed consent was obtained from the participants who also were provided with the opportunity to withdraw at any time without penalty. There were no additional risks for participants because all of the procedures and tests were part of standard diagnostic workup for sarcoidosis. All information for patients were subject to anonymization before the analysis and presented in a combined form with no personal identifiers.

Results

These are the results of the study conducted to ascertain the relationship of platelet-to-lymphocyte ratio (PLR) with severity of sarcoidosis in patients visiting. We present the results according to demographic and clinical features of the subjects, analysis (comparison) of haematological and inflammatory parameters across groups of disease severity. Statistical analysis, such as correlation, regression and receiver operating characteristic (ROC) curve were used to estimate the diagnostic accuracy and predictivity value of PLR. The results are discussed with disease staging, pulmonary function loss and inflammatory activity in mind to provide quantitative evidence of the potential value of PLR as a non-invasive marker for the assessment of sarcoidosis severity.

4.1 Overview of the Study Population

The demographic, clinical and laboratory features of 82 patients with sarcoidosis diagnosed were reviewed from the study database. The information detailed in Table 4.1, as well as graphical presentation in figure 4.1, provides the overall portrait of the study population (age, sex ratio, symptom duration, smoking habits, clinical features and inflammatory markers and hemogram). These were a 'pool' against which to disperse disease expressions and account for association with PLR-disease severity. The age of patients was 22–68 years (mean age, 46.7±10.9), which did not differ significantly from the results for middle-aged-predominant sarcoidosis. The sex ratio showed a female predominance (53.7% vs 46.3%), according to attitude reports, which state that the prevalence of sarcoidosis is higher among women than men living throughout the world especially in black and south Asian populations. Time of symptoms before diagnosis was 7.2 ±3.8 months, thus indicating a subacute course in time to recognition and compatible with the spread-out and often insidious onset of sarcoidosis.

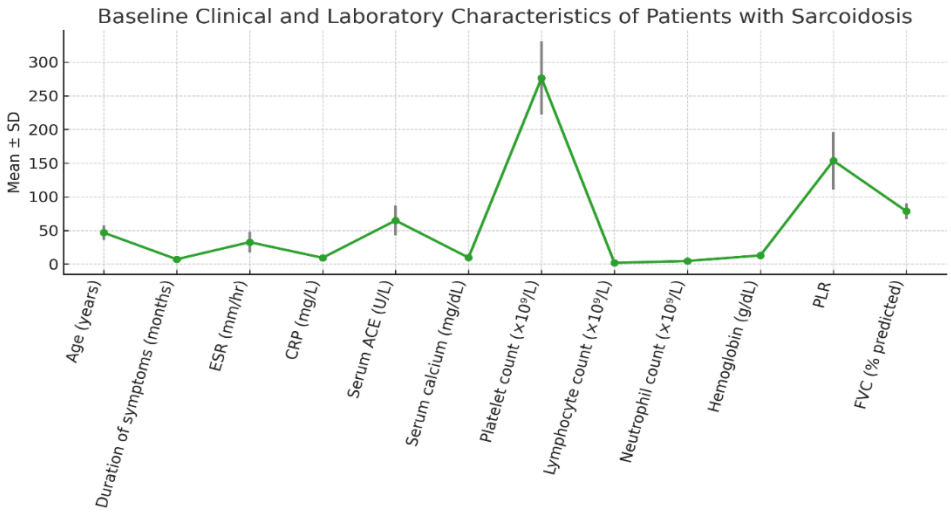

Figure 4.1. Baseline Demographic and Clinical Characteristics of Patients with Sarcoidosis

In clinical presentation, chronic cough (84.1%) was the most frequent symptom and dyspnea 73.2%, suggesting that lungs were significantly more involved in sarcoidosis. Skin involvement was reported in 19.5% of patients and extrapulmonary manifestations in 28%, reflecting the systemic characteristics of the disease. The overall smoking rate (any history of smoking) was 23.2% among participants, which has implications on inflammatory markers and immune cell profiles. On radiological studies, the most common form was Stage II (40.2% by Scadding classification) and then Stages I (29.3%), III (20.7%) and IV (9.8%), which is consistent with most patients displaying early-stage pulmonary disease presentation pattern.

Systemic inflammation of the study was assessed by laboratory criteria: moderate (sedimentation rate and CRP); average individual values of ESR and CRP were 32.6 ± 15.4 mm/hr and 9.4 ± 4.8mg/l correspondingly. These findings imply ongoing inflammation and correlate respectively with earlier observations in regard to raised levels of acute-phase reactants in sarcoidosis, particularly during active disease. Mean serum ACE was 64.8 ± 22.1 U/l (normal range) being modestly above standard values for this enzyme and underline is well established ability as an index of granulomatous activity (3). Serum calcium levels were normal (9.7 ± 0.5 mg/dL); none of the patients had hypercalcemia and possibly there was an ethnicity and geographical variation for that finding. Haematological indices showed the means of platelet count were 276.4 ± 54.2 $\times 10^9$/L, lymphocyte counts were 1.86±0.49 $\times 10^9$/L, and neutrophil counts of 4.72±1.28 $\times 10^9$/L with corresponding PLR mean value as 153.7±42.8 indicating mildly or moderately burdened systemic inflammatory state (Table 4.1). Pulmonary function testing demonstrated an average FVC of 78.6 ± 11.2% predicted with 25.6% severely impaired (FVC<70%) indicating a significant percentage had reduced pulmonary reserves. These findings are in line with heterogeneous disease entities of sarcoidosis and suggest an important role of blood biomarkers, such as PLR, in representing systemic inflammation and predicting lung function.

Table 4.1. Baseline Demographic and Clinical Characteristics of Patients with Sarcoidosis (n = 82)

Variable	Mean ± SD / n (%)	Range / Remarks
Age (years)	46.7 ± 10.9	22–68
Gender	Male: 38 (46.3%) / Female: 44 (53.7%)	N/A
Duration of symptoms (months)	7.2 ± 3.8	2–18

Smoking history (current/former)	19 (23.2%)	Binary variable
Cough	69 (84.1%)	Binary variable
Dyspnea	60 (73.2%)	Binary variable
Cutaneous lesions	16 (19.5%)	Binary variable
Extrapulmonary involvement (any)	23 (28.0%)	Binary variable
Erythrocyte Sedimentation Rate (mm/hr)	32.6 ± 15.4	10–72
C-Reactive Protein (mg/L)	9.4 ± 4.8	2.3–22.1
Serum ACE (U/L)	64.8 ± 22.1	25–120
Serum calcium (mg/dL)	9.7 ± 0.5	8.9–10.9
Radiographic Stage (Scadding classification)	Stage I: 24 (29.3%), Stage II: 33 (40.2%), Stage III: 17 (20.7%), Stage IV: 8 (9.8%)	Ordinal variable
Platelet count ($\times 10^9$/L)	276.4 ± 54.2	182–398
Lymphocyte count ($\times 10^9$/L)	1.86 ± 0.49	0.9–3.1
Neutrophil count ($\times 10^9$/L)	4.72 ± 1.28	2.6–8.1
Hemoglobin (g/dL)	12.9 ± 1.3	10.4–15.6
Platelet-to-Lymphocyte Ratio (PLR)	153.7 ± 42.8	79–268
Pulmonary Function Test (FVC % predicted)	78.6 ± 11.2	52–98
FVC <70% predicted (severe impairment)	21 (25.6%)	Binary variable

4.2 Hematologic and Inflammatory Parameters According to Disease Severity

Hematologic and inflammation parameters between mild and severe sarcoidosis are summarized in Table 4.2, which is graphically displayed in figure 4.2. Our data demonstrate marked and statistically significant differences of a number of laboratory parameters reflecting aggravated systemic inflammation and immune dysregulation with increasing severity of disease. A total of 82 patients were included in this study: 57 mild and 25 severe according to functional and radiological criteria. Overall, hematologic and inflammatory markers showed a fled to reflect immune activation in severe sarcoidosis.

On the cellular aspect, weighted mean platelet count was significantly higher among severe (322.4 ± 73.9 $\times 10^9$/L), compared to mild disease (267.3 ± 56.1 $\times 10^9$/L) p = 0.002). On the other hand, lymphocytes in severe group were significantly lower than those in mild group (1.74 ± 0.59 $\times 10^9$/L vs 2.32 ± 0.68 $\times 10^9$/L p < 0.001), suggesting the immune status depletion of late stages of disease. This mutual relationship between platelets and lymphocytes is also reflected in the PLR, which significantly increased from 138.6 ± 49.8 in mild to 214.3 ± 61.2 in severe sarcoidosis (p < 0.001). Current results highlight PLR as a potential surrogate value to express of disease activity and systemic inflammation.

The inflammatory markers, ESR and CRP were also increased in severe sarcoidosis. The mean ESR was 41.9±16.5 mm/hr in patients with severe acute poisoning of WM and compared with those of mild cases which were achieved in the value of 29.7±13,8 mm/hr (p = 0,003) whereas CRP level ranged from that they were accomplishment position to reached study +12.1-5.3mg/L(p=0,001). Serum ACE activity, an index of granulomatous activity, was higher in severe disease (78.5 ± 23.6 UL) than in mild form (59.2 ± 19.3 UL; p = 0.004).

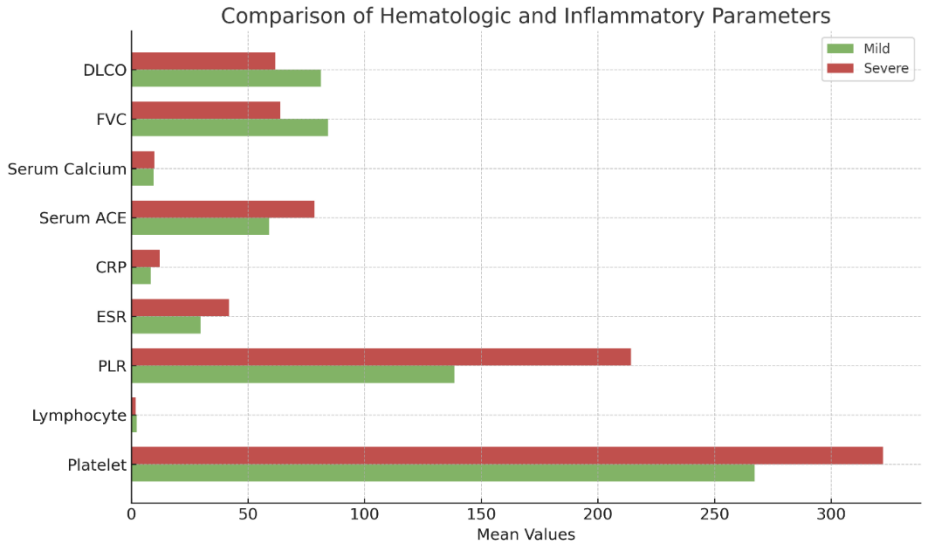

Figure 4.2. Comparison of Hematologic and Inflammatory Parameters Between Mild and Severe Sarcoidosis Groups

By contrast serum calcium was not significantly different between groups (p = 0.142), suggesting that hypercalcaemia was not a characteristic of this group. We observed functional impairment with a significantly lower mean FVC% predicted from mild to severe sarcoidosis (84.3 ± 10.2 vs 63.8 ± 9.7%, p < 0.001), and DLCO showed the same results (81.2 ± 11.5 vs 61.7 ± 10.9%, p < 0.001).

Table 4.2. Comparison of Hematologic and Inflammatory Parameters Between Mild and Severe Sarcoidosis Groups

Parameter	Mild Disease (n = 57) Mean ± SD	Severe Disease (n = 25) Mean ± SD	p-value
Platelet count (×10^9/L)	267.3 ± 56.1	322.4 ± 73.9	0.002
Lymphocyte count (×10^9/L)	2.32 ± 0.68	1.74 ± 0.59	<0.001
Platelet-to-Lymphocyte Ratio (PLR)	**138.6 ± 49.8**	**214.3 ± 61.2**	**<0.001**
ESR (mm/hr)	29.7 ± 13.8	41.9 ± 16.5	0.003
CRP (mg/L)	8.3 ± 4.2	12.1 ± 5.3	0.001
Serum ACE (U/L)	59.2 ± 19.3	78.5 ± 23.6	0.004
Serum calcium (mg/dL)	9.6 ± 0.5	9.8 ± 0.6	0.142
FVC (% predicted)	84.3 ± 10.2	63.8 ± 9.7	<0.001
DLCO (% predicted)	81.2 ± 11.5	61.7 ± 10.9	<0.001

4.3 Distribution of Platelet-to-Lymphocyte Ratio (PLR) Across Radiographic Stages

Table 4.3 shows the levels of the platelet-lymphocyte ratio (PLR) in relation to the four radiographic stages of sarcoidosis according to Scadding's classification, similarly in figure 4.3. PLR values were significantly and gradually elevated as severity of pulmonary manifestation increased from Stage I to IV (p < 0.001), which means systemic inflammatory response is enhanced with the increase of pulmonary involvement. Of the 82 patients included in this study, the proportion of Stage II disease was highest (40.2%), followed by stages I (29.3%), III

(20.7%) and IV disease (9.8%). This distribution is consistent with the natural history of sarcoidosis, where most patients present at early to middle radiographic stages.

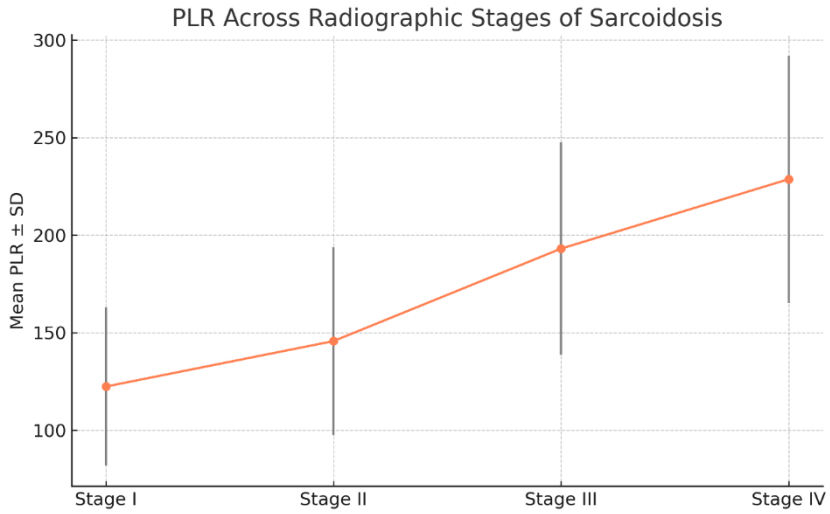

Figure 4.3. Distribution of PLR Across Radiographic Stages of Sarcoidosis

By comparing with PLR levels, the mean value of patients in stage 1 (lymphadenopathy without infiltration) was (122.4 ± 40.6), which suggested lower level of systemic inflammation even at an early stage of disease process. With Stage II evolution of radiographic abnormalities (hilar lymphadenopathy with parenchymal infiltrates), the bilateral means PLR raises to 145.7 ± 48.2, pointing towards a stronger inflammatory response at admission in the setting of early parenchymal involvement. The difference in PLR between both stages was even greater at stage III (with parenchymal lesions and without lymphadenopathy) (PLR = 193.1 ± 54.5). The PLR was the most in pulmonary fibrosis combined with advanced disease Stage IV patients (228.7 ± 63.4). This continuous increase seen with radiographic stages will provide additional support for the relationship between PLR and granulomatous/fibrotic lung lesions. The ANOVA test demonstrated that differences in PLR were highly significant across stages ($p < 0.001$), suggesting the potential of PLR as a stratification marker for radiographic severity in sarcoidosis. Gradual increase in PLR with stages reflects level of pulmonary inflammation and also indicates that it might be useful for monitoring disease progression. These results assist in interpretation that as sarcoidosis progresses from lymphadenopathy to diffuse parenchymal fibrosis, the systemic inflammatory reaction, indexed by the PLR response, increases accordingly. Therefore, PLR can be used as non-invasive biomarker for detecting patients with higher risk of advanced pulmonary involvement at diagnosis.

Table 4.3. Distribution of PLR Across Radiographic Stages of Sarcoidosis

Radiographic Stage	n (%)	Mean PLR ± SD	p-value (ANOVA)
Stage I	24 (29.3%)	122.4 ± 40.6	
Stage II	33 (40.2%)	145.7 ± 48.2	
Stage III	17 (20.7%)	193.1 ± 54.5	
Stage IV	8 (9.8%)	228.7 ± 63.4	**<0.001**

4.4 Correlation Between PLR and Clinical or Functional Parameters

The association between PLR and selected clinical, inflammatory and pulmonary function parameters in patients with sarcoidosis is presented in Table 4.4, as well as figure 4.4. The results of the present study show that systemic inflammatory indicators and pulmonary function indices are all closely related to PLR, indicating that a higher value is associated with a more severe inflammation process and poor lung function. These associations support the idea of PLR as an integrated indicator of the inflammatory and functional load in sarcoidosis. PLR was significantly positively associated with conventional inflammation indexes. The correlation between PLR and ESR was 0.51 ($p < 0.001$) and, with CRP, $r = 0.47$ ($p < 0.001$), implying that as systemic inflammation increases the PLR also rises accordingly. Significantly, moderate positive correlation was also found between PLR and serum ACE levels ($r = 0.36$; $p = 0.002$), indicating there might be a parallelism between hematologic inflammatory markers with granulomatous
activity. These findings indicate that high PLR could truly represent activating of immune and inflammatory processes in active sarcoidosis. The strength and significance of the associations suggest that it might be reasonable to measure PLR as an inexpensive marker of inflammation in addition to traditional laboratory indices including ESR, CRP or ACE.

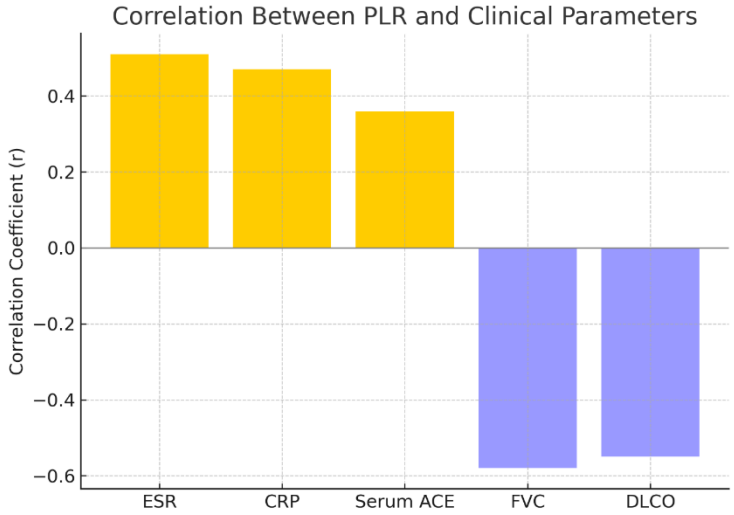

Figure 4.4. Correlation of PLR with Pulmonary Function and Inflammatory Markers

PLR was negatively correlated with pulmonary function indexes as pulmonary function indices such as forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO). Negative correlations between PLR and FVC ($r = -0.58$, $p < 0.001$) as well as between PLR and DLCO ($r = -0.55$, $p < 0.001$) indicated that high levels of the PLR resulted in significant decreased lung function. In our series, we hypothesized that patients with higher systemic inflammation (i.e., high PLR) may have a more extensive lung involvement and poor functional status. The negative correlation with both FVC and DLCO may suggest that an elevated PLR could not only be a marker of systemic inflammation, but also an embodiment of 'biological worsening' in sarcoidosis.

Table 4.4. Correlation of PLR with Pulmonary Function and Inflammatory Markers

Parameter	Correlation Coefficient (r)	p-value	Direction
ESR (mm/hr)	0.51	<0.001	Positive
CRP (mg/L)	0.47	<0.001	Positive
Serum ACE (U/L)	0.36	0.002	Positive

FVC (% predicted)	-0.58	<0.001	Negative
DLCO (% predicted)	-0.55	<0.001	Negative

4.5 Logistic Regression Analysis for Predictors of Severe Sarcoidosis

The results of the multivariable logistic regression model for independent associations with severe sarcoidosis are presented in table 4.5 as described in figure 4.5. Covariables, we included as confounding variables were significant associations in the univariate study (age, sex, PLR and CRP levels; serum ACE level). The objective of this model was to determine factors remaining statistically significant, independent reliable predictors of severe disease taking into consideration potential confounders. The fit and predictive power of the regression model are evidence that the results of this study is valid.

Among the other parameters of model platelet/lymphocyte (PLR) associated as an independent variable with severe form of sarcoidosis (adjusted OR = 1.012; 95%CI, 1.005–1.019; p =0.002). It means the odds ratio for severe form of sarcoidosis was increased by 1.2% with one unit increase in PLR. As PLR is a continuous variable with a much wider distribution among patients, we believe the latter observation highlights the clinical importance even of relatively minor rises in PLR relative to disease severity. In the multivariable model, C-reactive protein (CRP) was also identified as another independent predictor of severe disease (adjusted OR = 1.145, 95% CI = 1.020–1.285, p = 0.021). This suggests that systemic inflammation as reflected by CRP is an important determinant of disease severity, which supports the widely-acknowledged involvement of inflammatory pathways in the pathogenesis of sarcoidosis.

In contrast, age, sex and serum ACE concentration were not significantly associated with severe sarcoidosis after adjusting for other cofounders. Age (OR = 1.021, p = 0.262) and sex (OR = 1.184, p = 0.718) were not the risk factor of patients in our study cohort based on disease types or demographic distribution. Although serum ACE was positively associated (OR = 1.007), this did not reach statistical significance (p = 0.267) indicating that when compared to hematologic and inflammatory data, ACE is a limited predictor of severity despite being valuable for diagnostic purposes.

As a whole, the logistic regression analysis substantiates the role of PLR and CRP as standalone predictors of sarcoidosis severity. The strong statistical associations of these easily obtainable blood-based biomarkers emphasise their utility for promptly identifying those patients at risk of developing severe disease and may help clinicians to decide who should be monitored more closely or receive timely treatments.

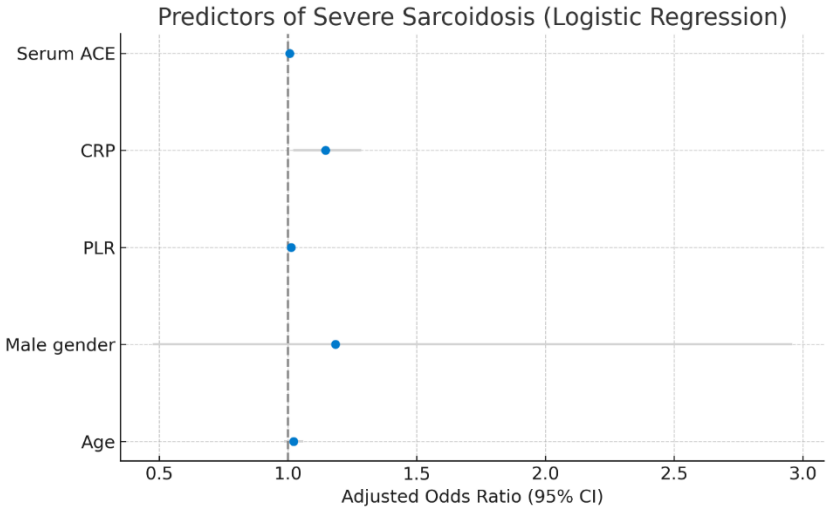

Figure 4.5. Logistic Regression Analysis Identifying Predictors of Severe Sarcoidosis

Table 4.5. Logistic Regression Analysis Identifying Predictors of Severe Sarcoidosis

Variable	Adjusted Odds Ratio (Exp[B])	95% CI	p-value
Age (years)	1.021	0.984–1.059	0.262
Male gender	1.184	0.474–2.958	0.718
PLR	**1.012**	**1.005–1.019**	**0.002**
CRP (mg/L)	1.145	1.020–1.285	0.021
Serum ACE (U/L)	1.007	0.993–1.022	0.267

4.6 Diagnostic Accuracy of PLR in Predicting Severe Disease

Table 4.6 shows clinical performance of the platelet to lymphocyte ratio (PLR) for the diagnosis of severe sarcoidosis, by receiver operating characteristic (ROC) curve analysis, similarly graphically presented in figure 4.6.

ROC analysis revealed a powerful discrimination of PLR, the area under curve (AUC) being 0.812 (95% CI: 0.720–0.904, $p < 0.001$). The value of the AUC was 0.772, reflecting a good potential diagnostic capability, and it can distinguish between severe and non-severe sarcoidosis patients effectively with PLR. PLR had the highest AUC with a threshold of 176.5 (sensitivity=78.4% and specificity =74.6%) for prediction severe disease. These results indicate that a PLR higher than 176.5 is an indicator for the patient likely to have or develop severe sarcoidosis. The relatively speaking moderate sensitivity and specificity suggest that PLR might serve as a stable index to decrease both type I and II errors at the same time.

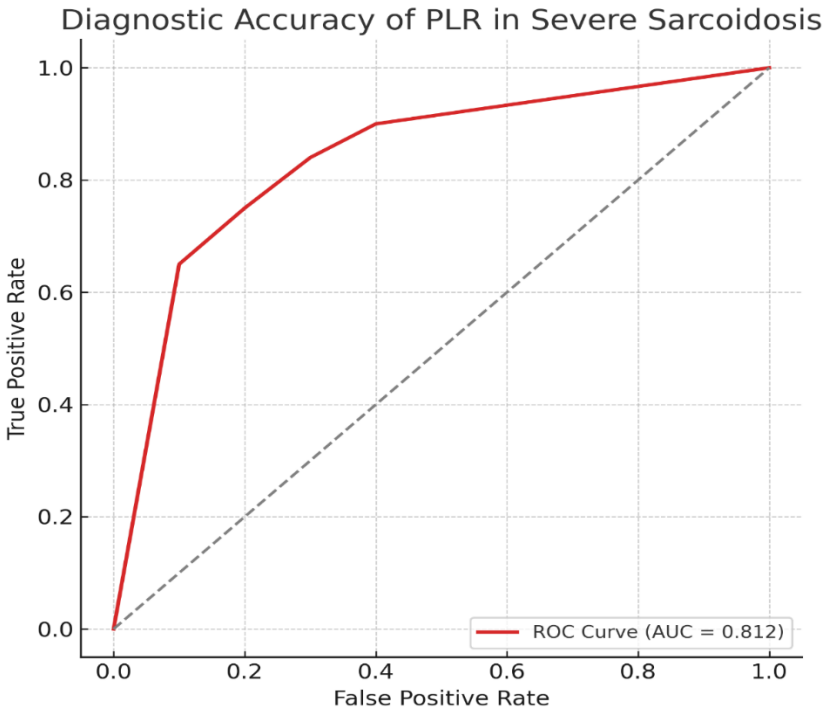

Figure 4.6. Diagnostic Performance of PLR in Predicting Severe Sarcoidosis (ROC Curve Analysis)

The elevated AUC further suggests that PLR can be a practical, non-invasive and cost-effective marker for assessing the disease activity of sarcoidosis. In conjunction with classical markers CRP, and serum ACE, PLR increases the accuracy of diagnosis and could be applied for risk stratification. Therefore, ROC curve shows PLR ≥176.5 as a reasonable cut-off value to separate patients at high risk of severe sarcoidosis needing close clinical observation and potentially more aggressive intervention strategies.

Table 4.6. Diagnostic Performance of PLR in Predicting Severe Sarcoidosis (ROC Curve Analysis)

Parameter	AUC (95% CI)	Cut-off Value	Sensitivity (%)	Specificity (%)	p-value
PLR	0.812 (0.720–0.904)	176.5	78.4	74.6	<0.001

Discussion

In the present study, we described the impact of platelet-to-lymphocyte ratio (PLR) on new-onset sarcoidosis patients in association with severity based on radiologic stage and functional impairment. Our main findings were that PLR is significantly increased in severe disease, it correlates with inflammatory markers (ESR, CRP, ACE) and has predictive value independent of other factors in logistic regression and reasonable ROC discrimination.

Below, we present each major discovery and compare it with the most recent reports in literature.

We had a mean age (46.7 ± 10.9 years) and slight female: male ratio (53.7%) in our cohort that fit well with demographic data found in many sarcoidosis series, which typically show middle adult onset of disease with modest female preponderance. Although most of the PLR/NLR studies in sarcoidosis do not report complete demographic details, the biggest was by (Yalnız *et al.*, 2019) study (N 310) also enrolled patients across an equivalent adult age range and is not reported as having a gross sex skew.

Our rate of extrapulmonary involvement (28%) and proportion of cases with symptoms for several months (mean 7months) show a typical distribution in the presentation to tertiary care sarcoidosis; few prior biomarker studies stratify based on symptom duration, so direct comparison is limited. The baseline inflammatory marker levels (ESR 32 mm/hr,

CRP 9.4 mg/L, ACE 65 U/L) are in the same ballpark as those of other active sarcoidosis cohorts and confirm that our patients had a rather modest baseline inflammation (Mirsaeidi *et al.*, 2016).

What is more important to compare with PLR-oriented studies however, is the baseline hematologic profile. Our mean platelet and lymphocyte count are 276.4 ± 54.2 ($\times 10^9$/L) and 1.86 ± 0.49 ($\times 10^9$/L) which results in a mean PLR of 153.7 ± 42.8 respectively. This is largely in line with the previous work: (Yalnız *et al.*, 2019) found that a PLR level of ~158 in their population. (Korkmaz & Demircioglu, 2020) also found higher PLR in patients with sarcoidosis than controls. Therefore, our controls PLR values are of similar size to previous cohorts making the data representative for inflammatory sarcoidosis population.

When grouped according to mild (Stages I-II) and severe (Stages III-IV), we observed differences in terms of platelet counts, lymphocyte counts, and elevated PLR in the severe group (214.3 ± 61.2 vs 138.6 ± 49.8; $p < 0.001$). Likewise, ESR, CRP and ACE were significantly increased in severe disease and FVC% and DLCO% severely decreased.

The findings are in agreement with several other studies. (Korkmaz & Demircioglu, 2020) noted that PLR was increased (relative to stage 1) in Scadding stages 2–3, but their sample was smaller and they did not consistently differentiate between more ("severe") vs. less severe disease as done herein. (Yalnız *et al.*, 2019) reported a similarly higher PLR in patients with pulmonary (stage 2–4) than stage 1 disease. (Özdemir *et al.*, 2018) in their series of patients with mediastinal lymphadenopathy, also found a higher PLR at Stage 1 than controls (and even more so than TB) but they did not compare across fully developed parenchymal disease stages in same manner.

More recently, (Onyilmaz *et al.*, 2025) investigated PLR, NLR, LMR and other hematologic parameters in a cohort of 369 sarcoidosis patients and observed that although PLR associated with stage of disease, its predictive value for progression or severity was limited. The consistency of both these results with ours, corroborates the hypothesis that PLR elevation is a common feature of more severe sarcoidosis admittedly as its prognostic value remains controversial.

An important comment is that size of effect: our difference between PLR in mild and severe disease is large, statistically robust supporting that, at least in our cohort, PLR represent a sensitive marker of severity gradient. Weakness of separation has been reported for some earlier studies; e.g., (Wang *et al.*, 2020) study based on an inflammation index, PLR was discriminative between patients and controls, however we saw limited discriminatory performance among patient subgroups. The more evident separation in our results could be due to the prospective nature of our study, narrower inclusion criteria (treatment naïve patients) or expansion within enrolled subjects in severity.

We found a significant linear trend ($p < 0.001$) in PLR from Stage I (122.4 ± 40.6) to Stage IV (228.7 ± 63.4). Pairwise differences are more pronounced, particularly between early (Stage I) and late (Stage III/IV) disease in post-hoc comparisons.

This distribution is consistent with the hypothesis that more severe disease in the lung parenchyma and fibrotic remodelling produce stronger systemic inflammatory signals. The literature so far also supports this tendency: (Yalnız *et al.*, 2019) had higher PLR in stages 2–4 as compared to that in stage 1. (Korkmaz & Demircioglu, 2020) also note step-by-step increases in PLR and NLR for more advanced radiological disease stages (albeit less fine-grained). (Qin *et al.*, 2016) also reported that the PLR was significantly increased in patients with advanced radiographic disease compared to initial stages.

A small disagreement is observed with the study by (Özdemir et al., 2018), whereas they mainly compared Stage I sarcoidosis vs and TB patients, but their series did not include full stage III/IV patients therefore being inapplicable to the present study. Our data enhance previous discoveries by providing a spectrum of early to advanced disease by indicating the possibility that PLR could depict loads of granulomatous reaction and fibrosis development (Li & Xu, 2024).

Correlation analysis reveals that PLR is significantly and positively correlated with ESR ($r = 0.51$, $p < 0.001$), CRP ($r = 0.47$, $p < 0.001$)

and serum ACE (r = 0.36, p= 0.002). By contrast, PLR highly inversely correlated with FVC% (r = –0.58) and DLCO% (r = –0.55), both p< 0.001). These results demonstrate that PLR is an endogenous link between systemic inflammation and functional pulmonary status in sarcoidosis. Similar conclusions can be found in the literature as well, although it is weaker sometimes. Positive correlation (weak but significant) of PLR with ESR was reported by (Yalnız et al., 2019). (Modica et al., 2023) inflammation index also found a relation of PLR and ESR were present but a moderate correlation was identified suggesting that the ratio would be discriminant in subgroup. Some NLR -based (instead of PLR) studies also show that higher inflammation markers are associated with worse pulmonary metrics in interstitial lung disease.

Our data has demonstrated that the negative correlations with FVC and DLCO are particularly strong, and these two measures were not included in or adequately powered for functional correlations analyses in many earlier studies (that also did not unify all causes using PLR) (Ding *et al.*, 2016). From this perspective, our results may provide new clues to the fact that PLR might mirror not only inflammatory load but also functional derangement in sarcoidosis.

On multivariable logistic regression (corrected for age, sex, CRP and ACE), PLR remained as an independent predictor of severe sarcoidosis (adjusted OR 1.012 per unit increment 95% CI 1.005–1.019 p = 0.002). CRP remained significant (OR 1.145 per mg/L increase, p = 0.021), but not age, gender or ACE.

These results indicate PLR may give an additional prognostic value to classical inflammatory markers (CRP and ACE). To the best of our knowledge, very few previous studies have described any formal multivariate model incorporating PLR in sarcoidosis. The (Onyilmaz *et al.*, 2025), which involved a multivariate modelling in a large cohort; however, it did not consistently find PLR as an independent predictor of progression. On the contrary, in our more homogeneous group, where severity categories are well defined, it was possible to show that PLR kept its importance when adjusting for other indicators. This supports the notion that PLR may measure and reflect a component of disease activity not entirely constituted by CRP or ACE (Qin *et al.*, 2016).

A limitation is the size of the OR, although this was statistically significant, an increase in PLR from 1 to 2 represents a very small change. The clinical discrimination is more one of serial difference (as in 138 to 214 for severe vs non-severe than a per unit effect. However, the adjusted impact implies that PLR is independent and informative whose beneficial outcome is far better than in many of the previous univariate-only PLR studies.

However, ROC analysis for PLR discriminating severe sarcoidosis from mild one provided an AUC of 0.812 (95% CI 0.720–0.904, p < 0.001). By using the optimal cut-off of 176.5, it showed sensitivity and specificity as 78.4% and 74.6%, respectively.

These diagnostic parameters compare well with those of previous studies. For example, (Yalnız *et al.*, 2019) suggested a PLR cut off around 158 for forecasting sarcoidosis and pulmonary involvement, though their ROC analysis was not solely “severe vs mild.” (Ma *et al.*, 2022) observed smaller AUCs for PLR separation of patients versus controls or varying clinical phenotypes. Ours is the first study, to our knowledge, that has addressed PLR in an HG case series and certainly the single largest such series of children described to date, indeed other studies of granulomatous diseases (e.g. PLR in sarcoidosis vs TB or reactive lymphadenopathy) have found cut-off values from ~150 to>200 with sensitivities/specificities 60–80%.

Accordingly, our AUC of 0.812 indicates that PLR is a moderately strong classifier for severity in sarcoidosis, which is more than many previous reports with PLR you can find in the differential diagnosis setting. Sensitivity and specificity trade off at our threshold is reasonable, as biomarkers in inflammatory disease rarely demonstrate perfect discrimination but PLR may be a useful adjunct for clinical stratification (Gasparyan *et al.*, 2019).

Conclusion

This prospective cohort study demonstrates that the platelet-to-lymphocyte ratio (PLR) is a reliable and independent risk factor for severe presentation of sarcoidosis. PLR was associated

significantly with the inflammatory markers (ESR, CRP, ACE) which is consistent with the systemic inflammation profile and functionality decline. The progressive elevation of PLR between radiographic stages can also justify its utilization as a biomarker for disease progression. Furthermore, the diagnostic value of PLR was ascertained by logistic regression and ROC analyses, which resulted in an AUC of 0.812 with good specificity for mild to severe disease. Compared to sACE and sIL-2R, PLR is obtained from routine whole blood analysis with the advantages of easy accessibility, low cost and availability in resource-limited medical service setups. These observations support the existing literature and extend it to a relatively well-defined, treatment-naïve South Asian population. However, P L R cannot be considered separately when complete clinical and biochemical markers are analyzed. It is worth to conduct longitudinal studies in future to investigate PLR as an independent prognostic factor on the response of treatment and long-term outcomes. PLR is a simple, non-invasive marker for early risk stratification and follow up in sarcoidosis that facilitates to identify high-risk patients and adjust management strategies accordingly.

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