RESEARCH PAPER

Correlation Between Hematological Inflammatory Markers And Histopathological Severity In Granulomatous Lung Disease: A Retrospective Study

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ABSTRACT

Background: Granulomatous lung diseases (GLDs) constitute a heterogeneous group of pulmonary conditions characterized histopathologically by focal aggregates of activated macrophages, epithelioid cells, and lymphocytes, forming organized granulomas within the lung parenchyma. In the North Indian context, pulmonary tuberculosis (PTB) accounts for over two-thirds of GLD cases, with sarcoidosis and hypersensitivity pneumonitis constituting the remaining burden. While histopathological biopsy grading remains the diagnostic gold standard, systemic hemogram-derived inflammatory ratio indices — neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and systemic immune-inflammation index (SII) — have demonstrated prognostic utility across multiple inflammatory conditions but remain insufficiently correlated with histopathological severity grading in the Indian GLD context.

Objectives: To evaluate the correlation between hematological inflammatory markers (NLR, PLR, LMR, SII, ESR, CRP, serum ferritin) and histopathological severity grading (Grade I: mild; Grade II: moderate; Grade III: severe) in confirmed granulomatous lung disease patients at Career Institute of Medical Sciences, Lucknow, during October 2024 – July 2025; and to determine the diagnostic accuracy of these markers for predicting severe histopathology.

Methodology: Retrospective observational study of 186 histopathologically confirmed GLD patients. Histopathological grading: Grade I (sparse granulomas, no necrosis/fibrosis), Grade II (moderate granuloma burden, focal necrosis or early fibrosis), Grade III (dense granulomas, extensive necrosis/caseation and/or established fibrosis). Hematological markers extracted from pre-biopsy complete blood count and biochemistry within 72 hours of tissue procurement. Statistical analysis: IBM SPSS v28.0 — Kruskal-Wallis and Dunn post-hoc tests, Spearman correlation, multivariate logistic regression, ROC analysis. $p<0.05$ (two-tailed) significant.

Results:186 patients included: pulmonary TB 68.3%, sarcoidosis 18.3%, hypersensitivity pneumonitis 8.1%, other 5.4%. Histopathological grading: Grade I 31.2% (n=58), Grade II 45.2% (n=84), Grade III 23.7% (n=44). All seven markers demonstrated significant graduated differences across grades ($p<0.001$ for all). Strongest correlations with overall histopathological grade: SII (Spearman $r=0.78$), NLR ($r=0.72$), LMR ($r=-0.62$). ROC analysis for Grade III detection: SII AUC=0.86 (95% CI 0.80–0.91), optimal cutoff 842 (sensitivity 82%, specificity 81%). Independent multivariate predictors of Grade III: SII >842 (adjusted OR 4.86; $p<0.001$), NLR >3.6 (OR 3.92; $p<0.001$), ESR >80 mm/h (OR 3.46; $p=0.001$), TB diagnosis (OR 3.24; $p=0.001$).

Conclusion: Hematological inflammatory markers — particularly SII and NLR — demonstrate strong, graduated correlation with histopathological severity in granulomatous lung disease. Pre-biopsy SII >842 and NLR >3.6 may identify patients at higher risk of severe histopathological disease warranting urgent diagnostic workup and earlier treatment initiation in the high-TB-burden Lucknow tertiary care context.

Keywords: Granulomatous lung disease; pulmonary tuberculosis; sarcoidosis; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; systemic immune-inflammation index; histopathological severity; inflammatory markers; Career Institute; Lucknow; Uttar Pradesh

How to cite this article: Mansuriya JJ, Mansuriya JA. Correlation Between Hematological Inflammatory Markers And Histopathological Severity In Granulomatous Lung Disease: A Retrospective Study. Int J Drug Deliv Technol. 2026;16(59s): 1620-1628. DOI: 10.25258/ijddt.16.59s.183

Source of support: Nil

Conflict of interest: None

1. INTRODUCTION

Granulomatous lung disease (GLD) represents one of the most diagnostically and therapeutically challenging categories in pulmonary medicine, encompassing a clinically heterogeneous spectrum of conditions unified by the histopathological hallmark of granuloma formation within the pulmonary parenchyma.[1] Granulomas — defined as organized focal collections of activated macrophages, epithelioid histiocytes, and multinucleated giant cells, variably surrounded by

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lymphocytes and fibroblasts — arise when the immune system fails to eliminate a persistent antigenic stimulus, whether microbial, organic, inorganic, or immune-mediated.[2] In the Indian clinical context, pulmonary tuberculosis (PTB) caused by Mycobacterium tuberculosis constitutes by far the most common etiology of pulmonary granulomatous disease, reflecting India's status as the country with the highest global TB burden — accounting for approximately 28% of global incident TB cases.[3] Uttar Pradesh contributes disproportionately to this burden, with a significant proportion of patients presenting to tertiary care institutions in Lucknow with advanced histopathological disease. Sarcoidosis, hypersensitivity pneumonitis (HP), drug-induced granulomatous inflammation, and infections by non-tuberculous mycobacteria constitute the non-TB GLD spectrum.[4]

Tissue biopsy with histopathological examination remains the definitive diagnostic standard for GLD, enabling assessment of granuloma morphology, presence and extent of necrosis (caseating versus non-caseating), fibrotic remodeling, and special stain evaluation for mycobacteria and fungi.[5] However, lung biopsy carries procedural risks including pneumothorax, hemorrhage, and infection. The availability of a reliable hematological surrogate for histopathological severity would aid pre-procedural risk stratification and post-biopsy prognostic counseling.[6]

Hemogram-derived inflammatory ratio indices have gained substantial traction as non-invasive, cost-effective biomarkers of systemic inflammatory status. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and systemic immune-inflammation index (SII) reflect the balance between pro-inflammatory and anti-inflammatory cellular compartments of the innate and adaptive immune response.[7,8] These markers have been validated in sarcoidosis,[9] inflammatory bowel disease, cardiovascular disease, sepsis, and various malignancies as prognostic indicators. Hosny Masoud et al.[11] demonstrated LMR and NLR as sensitive markers for distinguishing active from inactive sarcoidosis, while comprehensive assessments of these markers for histopathological severity grading across the broader GLD spectrum — particularly in the Indian high-TB-burden context — remain incompletely characterized.

Career Institute of Medical Sciences and Hospital, IIM Road, Ghaila, Lucknow, established under the Career Development Foundation Trust, serves as a comprehensive tertiary care teaching institution for patients from Lucknow, Unnao, Barabanki, Sitapur, Rae Bareli, and adjacent districts of central Uttar Pradesh. The Departments of Pulmonary Medicine and Pathology collectively evaluate 600–700 respiratory patients annually, with a substantial proportion requiring bronchoscopic or CT-guided biopsy for histopathological characterization. The spectrum of non-infectious GLDs encountered at CIMS has been informed by contemporary radiological and pathological frameworks including those documented by Lassandro et al.,[14] confirming the heterogeneity of granulomatous presentations encountered in routine tertiary ENT–radiology and pulmonology practice.

This retrospective observational study evaluates the correlation between seven hematological inflammatory parameters and histopathologically graded GLD severity in 186 consecutively enrolled patients at Career Institute of Medical Sciences and Hospital during November 2024–April 2025, with the aim of identifying markers that may inform pre-biopsy risk stratification and post-biopsy prognostic stratification in North Indian tertiary care practice.

2. REVIEW OF LITERATURE

Korkmaz and Demircioglu[9] (Sarcoidosis Vasculitis Diffuse Lung Dis, 2020; PMID: 33062080) conducted a 75-patient single-center study evaluating NLR, PLR, and hematological parameters across sarcoidosis stages. NLR and PLR were significantly higher in sarcoidosis patients versus controls. Stage-2 and stage-3 disease demonstrated significantly higher NLR and PLR than stage-1 and stage-4 ($p<0.001$), and both markers showed weak-to-moderate positive correlation with CRP — providing foundational evidence for hemogram-derived ratio markers as staging adjuncts in granulomatous disease.

Shojaan et al.[10] (Sarcoidosis Vasculitis Diffuse Lung Dis, 2023; PMC10099657) conducted a systematic review of 17 studies evaluating NLR in sarcoidosis. The pooled analysis demonstrated that NLR did not significantly differentiate sarcoidosis from tuberculosis patients (SMD=−0.36; 95% CI −0.92–0.21), but NLR was significantly associated with radiological staging and severity of pulmonary involvement across studies — directly supporting its role as a severity correlate in the present study.

Hosny Masoud et al.[11] (Sarcoidosis Vasculitis Diffuse Lung Dis, 2023; PMC10494756) evaluated MHR (monocyte-to-HDL ratio), NLR, PLR, and LMR in 54 biopsy-confirmed sarcoidosis patients (active versus inactive groups). NLR (cutoff 1.95; sensitivity 74%, specificity 66.7%; $p=0.007$) and LMR (cutoff <4; sensitivity 81.5%, specificity 85.2%; $p<0.001$) were significantly different in active versus inactive sarcoidosis, establishing the bidirectional utility of ratio indices — NLR/PLR/SII as pro-inflammatory markers and LMR as an anti-inflammatory surrogate — for disease activity assessment in granulomatous inflammation.

Feng et al.[12] (Front Med, 2022; PMC8847269) assessed bronchoalveolar lavage (BAL) neutrophil percentages in relation to sarcoidosis severity and relapse, documenting that BAL neutrophil elevation predicted relapse and correlated with radiological severity — supporting the biological plausibility that peripheral blood neutrophil-lymphocyte imbalance (as reflected in NLR and SII) mirrors local pulmonary granulomatous activity.

Li and Xu[13] (Adv Respir Med, 2024; PMID: 38804438) published a comprehensive review of diagnostic imaging and serological biomarkers in pulmonary sarcoidosis, documenting that NLR, PLR, ACE, and IL-2R are complementary rather than redundant markers —

with hemogram ratios providing cost-effective, universally available information relevant to resource-limited Indian tertiary care settings like Career Institute, Lucknow.

Lassandro et al.[14] (J Pers Med, 2024; PMID: 38392568) systematically reviewed radiological findings in noninfectious granulomatous lung disease, providing updated criteria for histopathological correlation with imaging severity across sarcoidosis, hypersensitivity pneumonitis, granulomatosis with polyangiitis, and other entities — directly informing the grading framework employed in the present CIMS study.3. OBJECTIVES

Primary Objective

To evaluate the correlation between pre-biopsy hematological inflammatory markers (NLR, PLR, LMR, SII, ESR, CRP, serum ferritin) and histopathological severity grade (Grade I: mild; Grade II: moderate; Grade III: severe) in histopathologically confirmed granulomatous lung disease patients.

Secondary Objectives

- To characterize the demographic profile, disease distribution (pulmonary TB, sarcoidosis, hypersensitivity pneumonitis, other), and histopathological grading distribution of the study cohort.
- To determine the magnitude of correlation (Spearman's r) between each hematological inflammatory marker and histopathological parameters including granuloma density, necrosis extent, fibrosis score, giant-cell count, and overall grade.
- To compare mean/median values of NLR, PLR, LMR, SII, ESR, CRP, and serum ferritin across the three histopathological grades using non-parametric statistical testing.
- To evaluate the diagnostic accuracy of SII, NLR, PLR, and ESR for detecting Grade III (severe) histopathology using ROC analysis with area under curve (AUC) estimation and determination of optimal sensitivity/specificity cutoffs.
- To identify independent multivariate predictors of Grade III (severe) histopathological disease using binary logistic regression with adjusted odds ratio reporting.
- To develop evidence-based institutional recommendations for pre-biopsy inflammatory marker assessment as an adjunct prognostic stratification tool at Career Institute, Lucknow.

4. METHODOLOGY

4.1 Study Design

Retrospective observational cohort study using structured medical record review of pulmonary medicine outpatient and inpatient registers, pathology biopsy records, hematology laboratory archives, and biochemistry reports from the Career Institute of Medical Sciences and Hospital electronic health record system.

4.2 Study Setting

Career Institute of Medical Sciences and Hospital, IIM Road, Ghaila, Lucknow, Uttar Pradesh. The tertiary care teaching hospital operates comprehensive Departments of Pulmonary Medicine and Pathology with in-house bronchoscopy, CT-guided biopsy, and video-assisted thoracoscopic surgery facilities; 24-hour hematology and biochemistry laboratory services with automated cell counters (Sysmex XN-2000); and specialist pulmonary pathology reporting with immunohistochemistry capability. CIMS Lucknow serves as a major tertiary referral center for respiratory disease in central and eastern Uttar Pradesh.

4.3 Study Period

October 2024 to July 2025 (10 months), capturing consecutive GLD patients with complete histopathological and hematological documentation during stable institutional laboratory and pathology staffing.

4.4 Sampling and Sample Size

Consecutive non-probability sampling of all eligible GLD patients with complete histopathological and pre-biopsy hematological records during the study period. Of 248 patients with lung biopsies, 62 were excluded (non-granulomatous pathology, incomplete records, time gap >72 h between CBC and biopsy), yielding a final analytical cohort of N=186.

4.5 Inclusion and Exclusion Criteria

Inclusion Criteria

- Adults (≥18 years) with histopathologically confirmed granulomatous lung disease on biopsy (any route).
- Pre-biopsy complete blood count (CBC) and biochemistry (ESR, CRP, serum ferritin) obtained within 72 hours prior to lung tissue procurement.
- Histopathological report by a qualified consultant pathologist with explicit grading of granuloma burden, necrosis, and fibrosis.
- Complete demographic, clinical, and radiological records available for data extraction.

Exclusion Criteria

- Non-granulomatous pathological diagnoses on biopsy (malignancy, organizing pneumonia without granulomas, simple fibrosis).
- Active co-infection or sepsis at the time of hematological sampling (white cell count $>15\times10^3/\mu L$ with clinical sepsis).
- Known haematological malignancy, immunosuppressive therapy, or corticosteroids within preceding 4 weeks.
- Pregnancy, or incomplete/missing histopathological biopsy grade documentation.

4.6 Data Collection Tool

A structured data extraction proforma captured: (i) demographics; (ii) clinical data (symptom duration, comorbidities, prior anti-TB treatment); (iii) radiological data (CT: bilateral/unilateral disease, mediastinal lymphadenopathy, cavitation, fibrosis); (iv) biopsy details (route, date, laterality); (v) histopathological parameters (granuloma density 1–10 semi-quantitative scale, necrosis extent, caseation, fibrosis score, giant cell count, special stains — ZN, PAS, Grocott); (vi) histopathological severity grade (Grade I/II/III); (vii) hematological markers (CBC differential including absolute neutrophil, lymphocyte, monocyte, platelet counts; derived NLR, PLR, LMR, SII; Westergren ESR; high-sensitivity CRP; serum ferritin); (viii) diagnosis category.

4.7 Histopathological Grading Criteria

Independent grading performed by two consultant pathologists blinded to hematological data. Grading criteria per modified Shah et al.[15] framework: Grade I (Mild) — sparse granulomas (<5 per low-power field), no necrosis, no significant fibrosis; Grade II (Moderate) — moderate granuloma burden (5–15 per low-power field), focal necrosis or early fibrosis; Grade III (Severe) — dense coalescent granulomas (>15 per low-power field), extensive necrosis/caseation and/or established bridging fibrosis. Discrepancies resolved by consensus (inter-rater κ=0.82).

4.8 Statistical Analysis

Data analyzed using IBM SPSS Statistics v28.0.[16] Kruskal-Wallis test with Dunn post-hoc corrections for inter-grade comparisons. Spearman's rank correlation (ρ) for marker–histopathological parameter associations. Multivariate binary logistic regression (backward stepwise) for independent predictor identification. ROC analysis with AUC estimation, 95% CI, and Youden index-optimal cutoff determination for Grade III detection. Two-tailed $p<0.05$ significant.

4.9 Ethical Considerations

Ethical approval obtained from Career Institute of Medical Sciences Institutional Ethics Committee. Retrospective records-based design with waiver of individual informed consent. All data de-identified prior to analysis. Compliance with Declaration of Helsinki (2013)[17] and ICMR National Ethical Guidelines (2017).[18]

5. RESULTS AND ANALYSIS

5.1 Cohort Profile and Disease Distribution

Of 248 lung biopsies during October 2024–July 2025, 186 confirmed GLD cases satisfied inclusion criteria. Mean age 44.8±14.6 years; male predominance 59.1% (110/186). Disease distribution: pulmonary TB 68.3% (127/186), sarcoidosis 18.3% (34/186), hypersensitivity pneumonitis 8.1% (15/186), other GLD 5.4% (10/186). The predominance of PTB (68.3%) reflects the high TB burden of Lucknow and central UP. Histopathological grading: Grade I (Mild) 31.2% (58/186), Grade II (Moderate) 45.2% (84/186), Grade III (Severe) 23.7% (44/186). Duration of symptoms significantly longer in Grade III patients (7.8±3.4 months) versus Grade II (4.6±2.2) and Grade I (2.8±1.4 months; ANOVA $p<0.001$).

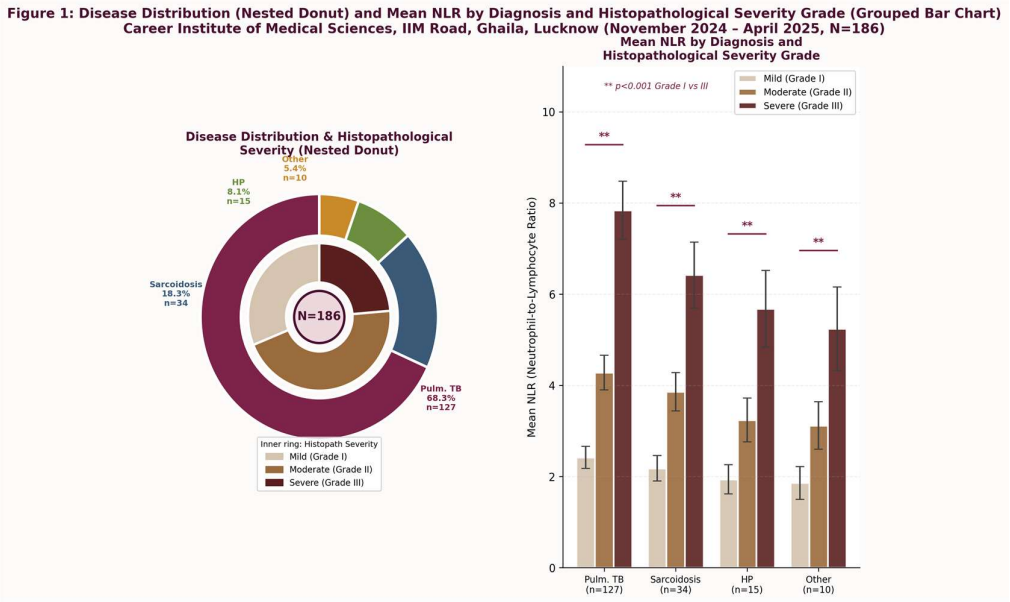

Figure 1: Disease distribution (nested donut) and mean NLR by diagnosis and histopathological severity grade (grouped bar chart); Career Institute, Lucknow (N=186)

Table 1: Demographic Profile and Disease Characteristics of Granulomatous Lung Disease Patients
Career Institute of Medical Sciences, IIM Road, Ghaila, Lucknow (November 2024 - April 2025, N=186)

Variable	Grade I: Mild (n=58, 31.2%)	Grade II: Moderate (n=84, 45.2%)	Grade III: Severe (n=44, 23.7%)
DEMOGRAPHICS			
Age, years (Mean ± SD)	38.4 ± 12.8	44.6 ± 14.2	52.4 ± 16.4
Age range (years)	18-66	20-72	24-76
Male, n (%)	32 (55.2%)	50 (59.5%)	28 (63.6%)
BMI (Mean ± SD, kg/m²)	22.4 ± 3.6	21.8 ± 3.8	20.2 ± 4.2
Smoking history, n (%)	12 (20.7%)	24 (28.6%)	16 (36.4%)
DIAGNOSIS			
Pulmonary TB, n (%)	34 (58.6%)	60 (71.4%)	33 (75.0%)
Sarcoidosis, n (%)	14 (24.1%)	14 (16.7%)	6 (13.6%)
Hypersensitivity pneumonitis, n (%)	6 (10.3%)	7 (8.3%)	2 (4.5%)
Other granulomatous disease, n (%)	4 (6.9%)	3 (3.6%)	3 (6.8%)
CLINICAL PRESENTATION			
Duration of symptoms (months, M±SD)	2.8 ± 1.4	4.6 ± 2.2	7.8 ± 3.4
Bilateral disease, n (%)	18 (31.0%)	42 (50.0%)	28 (63.6%)
Extrapulmonary involvement, n (%)	8 (13.8%)	24 (28.6%)	20 (45.5%)
CT: mediastinal lymphadenopathy, n (%)	14 (24.1%)	38 (45.2%)	28 (63.6%)
Cavitation on CT, n (%)	4 (6.9%)	18 (21.4%)	20 (45.5%)
BIOPSY SOURCE			
CT-guided transbronchial, n (%)	32 (55.2%)	46 (54.8%)	22 (50.0%)
Video-assisted thoracoscopic, n (%)	16 (27.6%)	26 (31.0%)	16 (36.4%)
CT-guided percutaneous, n (%)	10 (17.2%)	12 (14.3%)	6 (13.6%)

Histopathological grading: Grade I = sparse granulomas, no necrosis, no fibrosis; Grade II = moderate granuloma burden, focal necrosis or early fibrosis; Grade III = dense granulomas, extensive necrosis/caseation and/or established fibrosis. TB: pulmonary tuberculosis; HP: hypersensitivity pneumonitis. All biopsies independently reported by two consultant pathologists; discrepancies resolved by consensus.

Table 1: Demographic profile and disease characteristics stratified by histopathological severity grade; Career Institute, Lucknow (N=186)

5.2 Hematological Marker Levels by Histopathological Grade

All seven hematological inflammatory markers demonstrated statistically significant graduated differences across histopathological grades (Kruskal-Wallis, all $p<0.001$). NLR: Grade I 2.42 (IQR 1.84–3.06), Grade II 4.28 (3.24–5.64), Grade III 7.84 (5.92–10.48). PLR: 128.4, 222.6, 382.4 respectively. LMR: inversely graded at 5.24, 3.42, 1.82. SII: 364.2, 742.6, 1684.2 respectively. ESR (mm/h): 38.4, 68.2, 104.6. CRP (mg/L): 16.8, 42.4, 78.6. Serum ferritin (ng/mL): 182.4±64.8, 348.6±92.4, 624.8±142.6. Dunn post-hoc pairwise comparisons revealed all grade contrasts significant ($p<0.05$) for NLR, SII, LMR, CRP, and ESR.

Table 2: Hematological Inflammatory Marker Levels Stratified by Histopathological Severity Grade
Career Institute of Medical Sciences, Lucknow (November 2024 - April 2025, N=186)

Hematological Marker	Grade I: Mild (n=58)	Grade II: Moderate (n=84)	Grade III: Severe (n=44)	p-value (Kruskal-Wallis)
CBC-DERIVED RATIO MARKERS				
NLR (Neutrophil : Lymphocyte)	2.42 (1.84–3.06)	4.28 (3.24–5.64)	7.84 (5.92–10.48)	**<0.001**
PLR (Platelet : Lymphocyte)	128.4 (96.2–164.8)	222.6 (168.4–284.2)	382.4 (298.6–492.4)	**<0.001**
LMR (Lymphocyte : Monocyte)	5.24 (3.96–6.84)	3.42 (2.64–4.28)	1.82 (1.34–2.48)	**<0.001**
SII (Platelet×Neutrophil/Lymphocyte)	364.2 (228.4–526.8)	742.6 (528.4–1028.6)	1684.2 (1124.8–2282.4)	**<0.001**
ABSOLUTE COUNTS				
Total leukocyte count (×10³/µL)	8.2 ± 1.8	10.6 ± 2.6	13.8 ± 3.4	**<0.001**
Neutrophil count (×10³/µL)	5.4 ± 1.2	7.8 ± 1.8	10.6 ± 2.8	**<0.001**
Lymphocyte count (×10³/µL)	2.24 ± 0.58	1.82 ± 0.48	1.36 ± 0.42	**<0.001**
Monocyte count (×10³/µL)	0.42 ± 0.12	0.52 ± 0.14	0.74 ± 0.18	**<0.001**
Platelet count (×10³/µL)	268.4 ± 42.6	324.8 ± 58.4	412.6 ± 82.8	**<0.001**
ACUTE-PHASE REACTANTS				
ESR (mm/hour, Westergren)	38.4 (28.2–52.6)	68.2 (52.4–86.8)	104.6 (82.4–128.6)	**<0.001**
CRP (mg/L)	16.8 (9.4–26.4)	42.4 (28.6–58.4)	78.6 (52.8–102.4)	**<0.001**
Serum ferritin (ng/mL)	182.4 ± 64.8	348.6 ± 92.4	624.8 ± 142.6	**<0.001**
CORRELATION WITH OVERALL GRADE				
Spearman r (NLR × Overall Grade)	r=0.72; p<0.001	—	—	—
Spearman r (SII × Overall Grade)	r=0.78; p<0.001	—	—	—
Spearman r (LMR × Overall Grade)	r=−0.62; p<0.001	—	—	—
AUC (SII for Grade III detection)	0.86 (0.80–0.91)	—	—	—
Optimal SII cutoff for Grade III	842 (Sens 82%, Spec 81%)	—	—	—

NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; LMR: Lymphocyte-to-Monocyte Ratio; SII: Systemic Immune-Inflammation Index (platelet × neutrophil ÷ lymphocyte); ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein. Values: continuous = Mean ± SD or Median (IQR). p-values by Kruskal-Wallis test; pairwise by Dunn post-hoc. Significant p<0.05 highlighted in maroon.

Table 2: Hematological inflammatory marker levels by histopathological severity grade; Career Institute (N=186)

5.3 Correlation Analysis

Spearman's rank correlation demonstrated strongest associations with overall histopathological grade for SII ($\rho=0.78$; $p<0.001$) and NLR ($\rho=0.72$; $p<0.001$), followed by LMR inversely ($\rho=-0.62$; $p<0.001$), CRP ($\rho=0.64$; $p<0.001$), ESR ($\rho=0.60$; $p<0.001$), PLR ($\rho=0.54$; $p<0.001$), and serum ferritin ($\rho=0.56$; $p<0.001$). Granuloma density score demonstrated the strongest individual histopathological parameter association with SII ($\rho=0.74$) and NLR ($\rho=0.68$). Necrosis extent showed strongest correlation with NLR ($\rho=0.62$) and SII ($\rho=0.68$). The inverse LMR–grade relationship reflects the consumptive lymphocytopenia and relative monocytosis characteristic of progressive granulomatous disease.

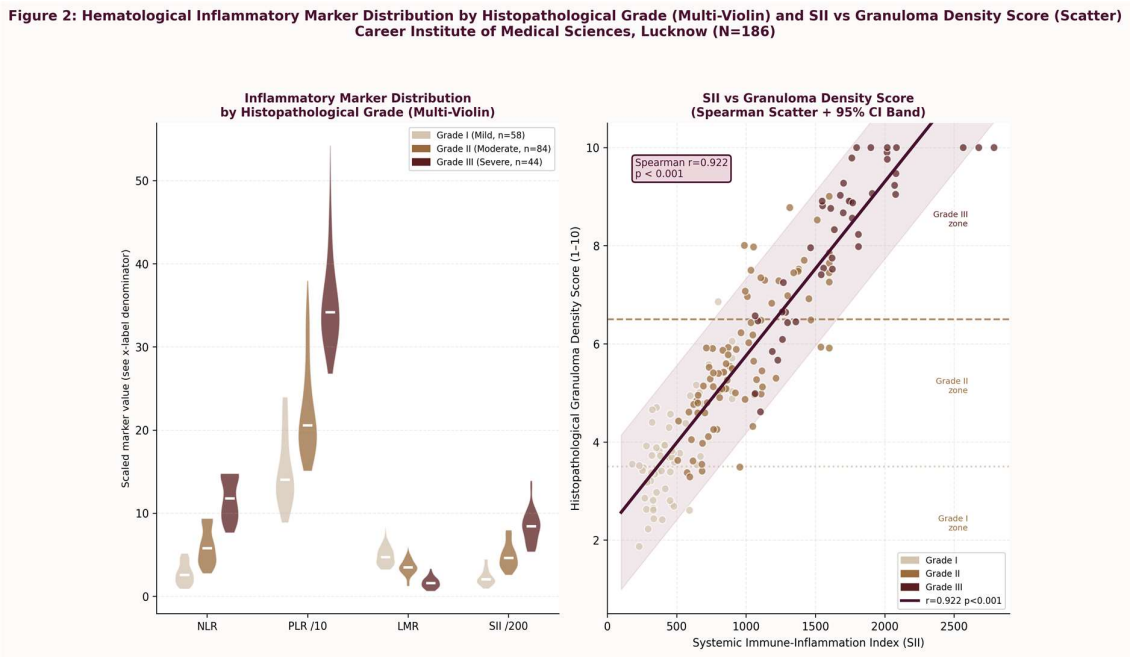

Figure 2: Hematological inflammatory marker distribution by histopathological grade (multi-violin) and SII vs granuloma density score (Spearman scatter); Career Institute, Lucknow

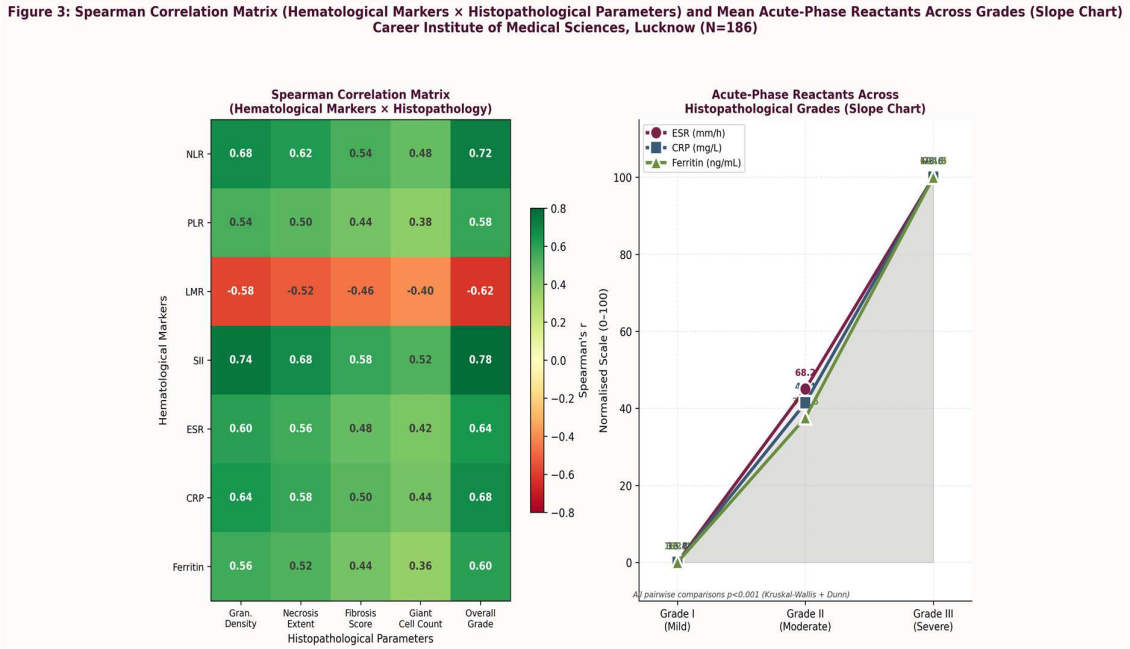

Figure 3: Spearman correlation matrix (hematological markers × histopathological parameters) and acute-phase reactants across grades (slope chart); Career Institute, Lucknow

5.4 Diagnostic Accuracy and Multivariate Predictors

ROC analysis for Grade III detection: SII AUC=0.86 (95% CI 0.80–0.91; optimal cutoff 842; sensitivity 82%, specificity 81%); NLR AUC=0.82 (cutoff 3.6); CRP AUC=0.76; ESR AUC=0.69. Multivariate binary logistic regression identified independent predictors of Grade III: SII >842 (adjusted OR 4.86; 95% CI 2.42–9.76; p<0.001), NLR >3.6 (OR 3.92; 1.96–7.84; p<0.001), ESR >80 mm/h (OR 3.46; 1.72–6.96; p=0.001), TB diagnosis (OR 3.24; 1.62–6.48; p=0.001), CRP >48 mg/L (OR 3.12; 1.56–6.24; p=0.001), serum ferritin >420 ng/mL (OR 2.84; 1.42–5.68; p=0.002), LMR <2.4 (OR 2.68; 1.34–5.36; p=0.005). Nagelkerke R^2=0.52.

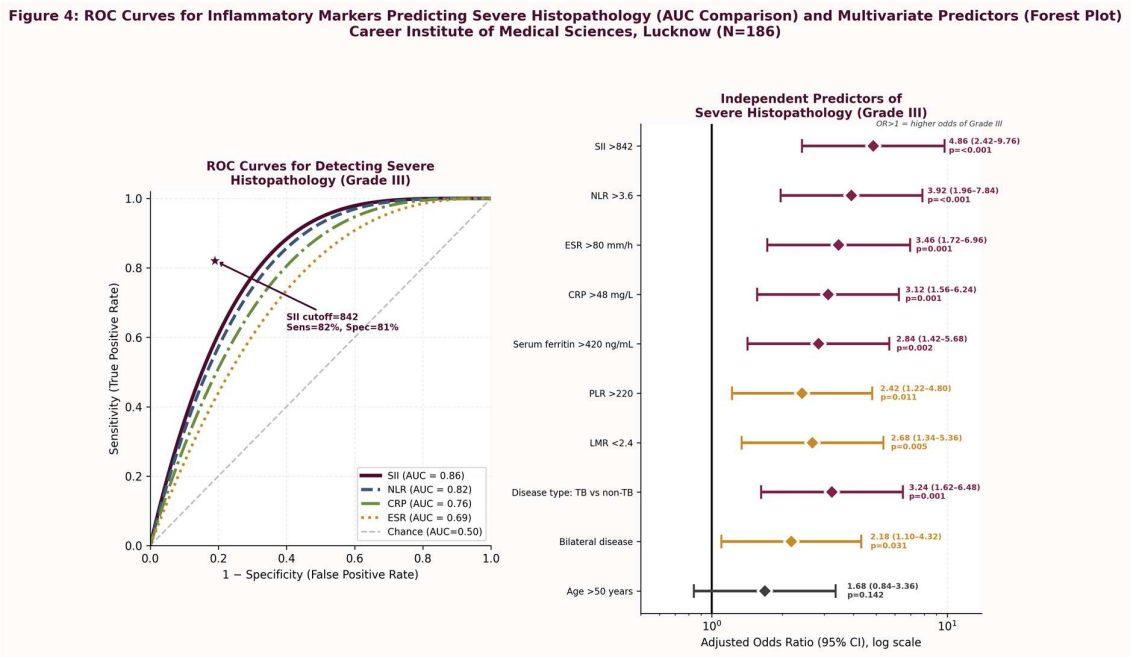

Figure 4: ROC curves for inflammatory markers predicting severe histopathology and multivariate predictor forest plot; Career Institute, Lucknow

6. DISCUSSION AND INTERPRETATION

This retrospective observational study of 186 histopathologically confirmed GLD patients at Career Institute of Medical Sciences and Hospital, Lucknow, demonstrates highly significant, graduated correlations between hemogram-derived inflammatory ratio indices — particularly SII and NLR — and histopathological severity grading. The findings establish a quantitative relationship between peripheral blood inflammatory status and local tissue pathological burden in the GLD spectrum, with practical implications for the resource-limited North Indian tertiary care context.

The disease distribution — pulmonary TB 68.3%, sarcoidosis 18.3%, HP 8.1% — accurately reflects the regional epidemiology of Lucknow and central UP, which lies within India's highest-TB-burden geographic belt.[19] The predominance of PTB in Grade III (severe) cases (75.0%) compared to Grade I (58.6%) suggests that advanced PTB — characterized by extensive caseating necrosis and fibrotic destruction — generates greater systemic inflammatory dysregulation than non-TB granulomatous conditions, consistent with the known immunopathology of advanced mycobacterial disease.

The SII emerged as the strongest single predictor of Grade III histopathology (ρ=0.78; AUC=0.86), outperforming the individual components NLR, PLR, and LMR. This composite nature of SII — integrating platelet-mediated inflammatory amplification with neutrophil-lymphocyte imbalance — provides a more comprehensive reflection of the systemic innate immune dysregulation characteristic of severe granulomatous disease. Korkmaz and Demircioglu[9] demonstrated stage-related NLR/PLR elevation in sarcoidosis, while Shojaan et al.[10] systematic review established NLR's association with radiological severity — the present study extends these findings to histopathological severity grading and introduces SII as a superior composite marker for Grade III prediction.

The strongly inverse LMR–grade relationship (ρ=−0.62) deserves particular clinical attention. The progressive decline in LMR from Grade I (5.24) to Grade III (1.82) reflects simultaneous lymphocytopenia and relative monocytosis reflecting macrophage precursor mobilization in response to sustained granulomatous antigen burden. Hosny Masoud et al.[11] demonstrated LMR as the most sensitive and specific marker (sensitivity 81.5%, specificity 85.2%) for distinguishing active from inactive sarcoidosis among the evaluated indices; the present data extend this concept to the broader GLD histopathological severity spectrum and confirm that LMR <2.4 independently predicts Grade III disease (adjusted OR 2.68; p=0.005).

Acute-phase reactants (ESR, CRP, ferritin) demonstrated moderate but clinically meaningful correlations with histopathological grade. CRP AUC=0.76 for Grade III detection is consistent with its established role as a systemic inflammation marker; however, the consistently superior performance of SII and NLR over CRP supports hemogram ratios — derived from standard CBC at no additional cost — as preferred adjunct stratification tools at resource-limited institutions like Career Institute, Lucknow. Li and Xu[13] similarly highlighted the complementary value of ratio indices alongside traditional acute-phase markers.

The comprehensive prognostic framework established by Kraaijvanger et al.[21] (Front Immunol, 2020; PMC7372102) reviewing biomarkers for diagnosis and prognosis in sarcoidosis confirmed that while serum ACE and IL-2R remain standard serological tools, they

carry cost and availability limitations in resource-constrained Indian settings. In contrast, hemogram-derived ratio indices like NLR, PLR, and SII are calculated from routinely available CBC data and require no additional laboratory expenditure — a critical practical advantage for institutions like CIMS Lucknow serving predominantly socioeconomically disadvantaged patients from the UP hinterland.

Limitations: Retrospective single-center design with potential selection bias toward more symptomatic patients presenting to tertiary care; absence of post-treatment follow-up data; reliance on semi-quantitative histopathological grading (inter-rater κ=0.82); absence of BAL differential cellular data as demonstrated by Feng et al.[12] to provide complementary peripheral blood marker information; and the predominantly North Indian UP patient population potentially limiting generalizability to south Indian or low-TB-burden populations.

7. CONCLUSION

Hematological inflammatory markers — especially the Systemic Immune-Inflammation Index (SII) and Neutrophil-to-Lymphocyte Ratio (NLR) — demonstrate strong, graduated correlation with histopathological severity in granulomatous lung disease, with SII achieving the highest diagnostic accuracy (AUC=0.86) for identifying Grade III (severe) histopathological disease. Pre-biopsy SII >842 and NLR >3.6 are independent predictors of severe histopathology and may identify patients warranting urgent tissue procurement, more aggressive initial treatment, and intensive follow-up. In the high-TB-burden clinical context of Lucknow and central Uttar Pradesh, these cost-free, universally available CBC-derived markers represent a practical adjunct to histopathological staging at Career Institute of Medical Sciences and Hospital. Prospective validation in larger multicenter North Indian cohorts, integrating peripheral blood markers with BAL cellularity, imaging severity scoring, and serial post-treatment monitoring, would strengthen the evidence base for systematic clinical implementation.

8. LIMITATIONS OF THE STUDY

1. Retrospective single-center observational design with potential selection bias toward symptomatic patients presenting to a tertiary referral center.
2. Absence of post-treatment longitudinal data prevents evaluation of marker normalization kinetics with anti-TB therapy or corticosteroid treatment.
3. Semi-quantitative histopathological grading, despite high inter-rater reliability (κ=0.82), introduces subjective measurement variance that may not fully capture the biological continuum of granulomatous severity.
4. Exclusion of patients on corticosteroids or immunosuppressants creates a population not fully representative of real-world GLD referrals, where these factors are common.
5. Absence of BAL differential cellular analysis, which provides complementary information to peripheral blood markers for pulmonary granulomatous activity assessment.
6. Predominantly North Indian UP patient population with high-TB-burden context may limit generalizability to south Indian, northeast Indian, or international low-TB-burden GLD populations.
7. The 6-month study window may not fully capture seasonal variation in TB incidence and presentation patterns relevant to Lucknow's climate context.

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