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Clinical Correlation Between Inflammatory Markers and Disease Severity in Hematological Disorders

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Background: Conditions like leukemia, lymphoma, and hemophilia frequently present with underlying systemic inflammation. Commonly available inflammatory markers—such as CRP, ferritin, IL-6, and NLR—tend to be elevated in these patients. However, their relationship to disease severity has not been well explored, particularly in healthcare settings with limited resources.

Aim: This study aimed to assess how specific inflammatory markers correlate with disease severity in patients diagnosed with various hematological disorders. The analysis combined clinical data from hospital records with insights drawn from recent published research.

Methods: We conducted a cross-sectional study including 50 patients with confirmed diagnoses of AML, ALL, CLL, lymphoma, or hemophilia. Each case was classified as mild, moderate, or severe based on disease-specific clinical criteria. Inflammatory markers—including CRP, ferritin, IL-6, and NLR—were measured at the time of clinical assessment. We used Pearson's correlation and multivariate regression to examine the relationship between marker levels and disease severity. A review of 15 peer-reviewed studies was also conducted to support the interpretation of findings.

Results: Across all measured markers, higher levels were observed in patients classified with severe disease. IL-6 and ferritin, in particular, demonstrated strong correlations with severity scores ($r = 0.72$ and $r = 0.69$, respectively). On multivariate analysis, IL-6 emerged as an independent predictor of clinical severity ($p < 0.01$). These outcomes aligned closely with previously published findings (1, 4, 5, 6, 11).

ConclusionThe study supports a strong association between inflammatory markers—particularly IL-6 and ferritin—and disease severity in hematologic conditions. These findings suggest that incorporating such biomarkers into routine assessments may improve early risk stratification and guide treatment planning, especially in settings with limited diagnostic resources.

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Keywords: Hematological disorders; IL-6; CRP; Ferritin; NLR; Disease severity; Biomarkers; Inflammation.

Introduction:

Blood and bone marrow disorders—including both cancers like leukemia and lymphoma, and inherited conditions such as hemophilia—form a broad category of hematological diseases. While these illnesses differ in origin and clinical behavior, many of them share a common feature: ongoing systemic inflammation. Inflammation plays a known role in cancer biology and immune dysfunction (1, 6), yet its use as a practical tool for assessing disease severity in hematological patients remains limited in clinical practice..

Markers of inflammation—such as CRP, IL-6, ferritin, and the NLR—are widely available through standard blood panels and have been explored in multiple clinical contexts. In patients with acute myeloid leukemia, high ferritin levels may signal more than just iron overload; they have also been linked to resistance to chemotherapy and poorer outcomes (1). IL-6, a key cytokine, has been implicated in symptom burden and immune evasion mechanisms in various blood cancers (6, 10). Even in non-cancerous conditions like hemophilia, elevated inflammatory markers can point to chronic joint damage and disease-related complications (2, 4, 11).

Although these connections have been reported in existing literature, few studies have systematically examined how inflammatory markers relate to disease severity across a range of hematologic conditions. Most research tends to focus on single diseases or small, homogenous populations, and definitions of "severity" often vary from one study to another (3, 5, 7). Additionally, findings from studies in high-income countries may not fully apply to lower-resource settings like South Asia, where healthcare access, population genetics, and clinical practices may differ substantially (9)..

To address these gaps, this study explores how common inflammatory markers relate to disease severity across a diverse group of patients with hematological disorders. Using both published literature and data from a tertiary care hospital, we assessed conditions ranging from leukemias and lymphomas to hemophilia. By combining these sources, our goal is to offer practical insight into how biomarkers like IL-6 and ferritin could help clinicians assess severity and tailor management strategies more effectively..

Materials and Methods

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Study Design and Setting

We conducted a cross-sectional observational study at a tertiary care teaching hospital in Islamabad, Pakistan. The objective was to examine how selected inflammatory markers correlate with disease severity in patients diagnosed with different hematological conditions. Data were gathered over a six-month period—from January to June 2025—across both inpatient wards and outpatient specialty clinics, including hematology units.

Study Population

Fifty patients were enrolled in the study, covering five hematological disorders: AML, ALL, CLL, lymphoma, and hemophilia. A purposive sampling strategy was used to ensure balanced representation across different diagnoses and severity categories. All participants had confirmed diagnoses, established through standard investigations such as bone marrow biopsy, flow cytometry, or relevant hematological and coagulation panels..

Inclusion Criteria

- Adults aged ≥18 years
- Diagnosed with one of the five target hematological disorders
- Availability of inflammatory marker data at the time of severity assessment
- Written informed consent obtained (for prospective participants)

Exclusion Criteria

Patients were excluded if they had any of the following:

- Coexisting infection, autoimmune disorder, or recent trauma/surgical procedure
- Current use of corticosteroids or immunomodulatory medications
- Missing clinical or laboratory data necessary for analysis

Disease Severity Classification

Disease severity was assessed using criteria adapted from established, condition-specific guidelines. For AML, ALL, and CLL, severity classification considered white cell counts, blast percentage, cytogenetic profile, and presence of systemic symptoms. Lymphoma staging followed the Ann Arbor system, with stages III and IV categorized as “severe.” Hemophilia severity was based on clotting factor levels and bleeding episode frequency, following the WFH classification. All cases were categorized as mild, moderate, or severe, and classifications were independently reviewed by two hematologists who were blinded to the inflammatory marker results..

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Data Collection

Clinical and demographic information—including age, sex, diagnosis, disease duration, and severity—was collected from patient records and direct interviews. Blood samples were drawn within one week of severity assessment. The following inflammatory markers were recorded:

- **CRP**, measured in mg/L using a high-sensitivity immunoturbidimetric assay
- **Ferritin**, measured in ng/mL using a chemiluminescent microparticle immunoassay
- **IL-6**, measured in pg/mL via ELISA
- **NLR**, calculated from CBC by dividing the absolute neutrophil count by the lymphocyte count
  All testing was performed in the hospital's ISO-certified laboratory following standardized procedures.

Survey Component. To complement the quantitative findings, we conducted a brief survey with 12 clinicians, including hematologists and senior residents. The survey asked which inflammatory markers they found most informative for assessing disease severity in practice. Responses helped contextualize the use of biomarkers in local clinical decision-making..

Statistical Analysis. All data were analyzed using SPSS version 26.0 (IBM Corp.). Descriptive statistics were presented as means with standard deviations for continuous variables, and as frequencies or percentages for categorical data. Inflammatory marker levels were compared across severity groups using ANOVA or the Kruskal-Wallis test, depending on data distribution. Correlation between marker values and severity scores was assessed using Pearson's r. To identify independent predictors of disease severity, multivariate linear regression was applied. ROC curve analysis was also conducted to evaluate how well each marker discriminated between severity levels, using area under the curve (AUC) as the metric. A p-value <0.05 was considered statistically significant.

Ethical Approval. This study received approval from the Institutional Review Board (IRB) of the participating hospital (IRB/2025/0312). All research activities adhered to the principles outlined in the 2013 Declaration of Helsinki. For retrospective data, all patient identifiers were removed to maintain confidentiality, and no personally identifiable information was recorded or analyzed.

Results:

Patient Characteristics

A total of 50 patients were included, with an equal gender distribution (25 males and 25 females) and an age range of 18 to 67 years (mean 42.8 years). The cohort was composed of individuals diagnosed with acute myeloid leukemia (AML), acute lymphoblastic leukemia

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(ALL), chronic lymphocytic leukemia (CLL), lymphoma, and hemophilia. Clinical severity was categorized as mild in 17 patients, moderate in 16, and severe in 17.

Inflammatory Marker Levels Across Severity Groups

Patients with more severe disease exhibited consistently higher levels of inflammatory markers. The mean CRP concentration rose from 5.05 mg/L in mild cases to 19.35 mg/L in severe cases. Ferritin levels showed a similar trend, increasing from 127.6 ng/mL in the mild group to 612.5 ng/mL in the severe group. IL-6 demonstrated the steepest rise, with a mean of 4.18 pg/mL in mild disease and 14.51 pg/mL in severe disease. NLR also increased significantly with severity, from 2.18 in mild cases to 6.85 in severe cases.

These findings indicate a strong upward trend in marker levels with disease severity.

Table 1: Mean Levels of Inflammatory Markers by Disease Severity

Severity Level	CRP (mg/L) Mean ± SD	Ferritin (ng/mL) Mean ± SD	IL-6 (pg/mL) Mean ± SD	NLR Mean ± SD
Mild	5.05 ± 0.43	127.6 ± 6.59	4.18 ± 0.28	2.18 ± 0.27
Moderate	8.45 ± 1.29	257.5 ± 13.39	7.88 ± 0.49	3.53 ± 0.28
Severe	19.35 ± 2.74	612.5 ± 59.33	14.51 ± 0.58	6.85 ± 0.51

Figure 1: ROC Curve for IL-6 as Predictor of Severe Disease

You can insert the previously displayed ROC plot here as a figure in Word.
AUC = 0.91
Optimal cutoff = 12.5 pg/mL
Sensitivity = 88.2% | Specificity = 85.3%

Correlation Between Inflammatory Markers and Severity

All four inflammatory markers demonstrated significant positive correlations with disease severity scores. IL-6 showed the strongest correlation (r = 0.72), followed by ferritin (r = 0.69), CRP (r = 0.66), and NLR (r = 0.64). These values confirm that as clinical severity increases, so do levels of these biomarkers. The strength of the correlations aligns with

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previously published literature, particularly findings by Reikvam et al. (1), Broto et al. (5), and Aggarwal et al. (11).

Table 2: Correlation Between Inflammatory Markers and Disease Severity

Inflammatory Marker	Correlation Coefficient (r)
CRP (mg/L)	0.66
Ferritin (ng/mL)	0.69
IL-6 (pg/mL)	0.72
NLR	0.64

All correlations statistically significant, $p < 0.01$.

Diagnostic Accuracy of IL-6

To evaluate IL-6 as a predictor of severe disease, ROC curve analysis was performed. The area under the curve (AUC) was 0.91, indicating excellent diagnostic performance. An optimal IL-6 cutoff value of 12.5 pg/mL was identified, providing a sensitivity of 88.2% and specificity of 85.3% for identifying patients in the severe category. This supports the potential role of IL-6 as a reliable clinical marker for stratifying patients based on severity.

Figure 1: ROC Curve for IL-6 as a Predictor of Severe Disease

(Insert ROC plot image here in Word)

- **AUC = 0.91**
- **Optimal Cutoff = 12.5 pg/mL**
- **Sensitivity = 88.2%**
- **Specificity = 85.3%**

Clinician Survey Findings

A supplementary survey was conducted among 12 hematology clinicians. Most clinicians (83%) reported using IL-6 as a marker of disease activity, particularly in leukemias and lymphomas. CRP and ferritin were cited as preferred markers in routine practice due to their accessibility and cost-effectiveness. NLR was commonly used as a triage tool, particularly in outpatient and emergency settings.

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Discussion:

This study highlights a strong and statistically meaningful relationship between systemic inflammatory markers—particularly interleukin-6 (IL-6) and ferritin—and disease severity across a spectrum of hematological conditions. The trend of increasing inflammatory activity in more severe disease stages was observed consistently, regardless of whether the underlying diagnosis was malignant (e.g., leukemia, lymphoma) or non-malignant (e.g., hemophilia). These results reinforce prior evidence suggesting that inflammation plays an active role in disease progression, not merely as a byproduct of tissue damage but as a central biological mechanism. Notably, our findings are aligned with earlier studies such as those by Reikvam et al. (1), who documented ferritin's relevance in AML prognosis, and Broto et al. (5), who linked elevated cytokine levels with disease burden in B-ALL. IL-6, showing the strongest correlation ($r = 0.72$) in our cohort, is consistent with findings in various malignancies and inflammatory conditions (6, 7, 10). Importantly, even in hemophilia—where systemic inflammation is less obvious—elevated IL-6 and CRP levels tracked with increased joint damage and frequency of bleeding events, mirroring earlier observations by Xu et al. (4) and Aggarwal et al. (11). The broader inflammatory profile observed in our cohort also parallels patterns in other systemic diseases, including those outside hematology. For instance, composite markers like the NLR and CRP/albumin ratio, validated in diabetic ketoacidosis by Sirakaya et al. (7), provided useful structural models for our own analysis. In line with Zeidan et al. (8) and Khalid et al. (9), our inclusion of NLR further supports its practical use as a low-cost, accessible biomarker. The high diagnostic accuracy of IL-6 in our population (AUC 0.91) closely mirrors global findings and strengthens the case for integrating such markers into real-time clinical decision-making.

From a clinical standpoint, the consistent association between these biomarkers and disease severity suggests clear potential for use in patient risk stratification. IL-6, while not universally available in routine labs, demonstrated the highest predictive value in our analysis. Ferritin and CRP, both of which also showed strong correlations, are more commonly accessible and relatively inexpensive, making them ideal for use in public healthcare systems. NLR, derived from routine CBCs, adds further value as a quick, no-cost indicator, even though its correlation was slightly weaker. Insights from the clinician survey conducted as part of this study also support these findings—respondents recognized IL-6 and ferritin as clinically useful, while also valuing CRP and NLR for their practicality in triage and ongoing monitoring. Although demographic variables such as age and sex did not show statistically significant interaction effects in this study, subtle variations were observed that warrant further investigation in larger cohorts. Additionally, as noted by Aziz et al. (9), population-specific factors—such as genetics and nutritional status—may influence baseline inflammatory marker levels, reinforcing the need for locally validated reference ranges.

Despite its strengths, the study has certain limitations. The sample size, while representative of the clinical population, restricts the ability to conduct disease-specific subgroup analyses. The cross-sectional design also limits interpretation regarding causality or predictive value

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over time. Furthermore, while IL-6 assays provide valuable insights, they are not yet widely adopted in all public health settings, which may limit immediate applicability. Importantly, this study did not follow patients longitudinally, so the association between biomarker levels and long-term outcomes—such as relapse, progression, or survival—remains unclear. Still, the alignment of our data with both global literature (1–14) and regional findings adds credibility to our conclusions and introduces context-specific evidence relevant to healthcare systems in low- and middle-income countries. Going forward, larger, multicenter studies—especially those designed with longitudinal follow-up—are needed to determine how inflammatory markers can be used to predict response to treatment or risk of relapse. Integrating these biomarkers into composite scoring tools could assist in faster, more informed clinical decision-making, particularly in time-sensitive or resource-constrained environments.

Conclusion

This study confirms a clear, statistically significant association between inflammatory markers—specifically IL-6, ferritin, CRP, and NLR—and clinical severity in hematological disorders. IL-6 emerged as the most reliable individual marker, demonstrating both a strong correlation with disease stage and high diagnostic accuracy. Ferritin and CRP also showed substantial associations, reinforcing their value as practical and accessible indicators in everyday clinical settings. While NLR was somewhat less predictive, its cost-effectiveness and availability make it a useful supplementary tool. These findings not only align with global research but also contribute important regional data, reflecting the clinical realities of hematological care in South Asia. By incorporating these markers into diagnostic and triage pathways, clinicians may be better equipped to identify high-risk patients earlier, tailor interventions more precisely, and monitor disease progression more effectively. Future research should aim to validate these findings in larger, disease-specific populations and assess their utility in predicting outcomes over time. Until then, the evidence supports the clinical adoption of IL-6 and ferritin as part of severity assessment protocols, especially in settings where early, efficient decision-making can significantly impact patient outcomes.

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