

DIAGNOSTIC UTILITY OF IMMATURE PLATELET FRACTION, IMMATURE RETICULOCYTE FRACTION AND IMMATURE GRANULOCYTE PERCENTAGE COMPARED WITH SERUM PROCALCITONIN IN EARLY DIAGNOSIS OF SEPSIS: A CROSS-SECTIONAL COMPARATIVE STUDY

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ABSTRACT

Background: Sepsis is a life-threatening condition requiring early diagnosis and timely intervention. Serum procalcitonin is commonly used as a biomarker for bacterial sepsis; however, its cost and limited availability may restrict routine use in resource-limited settings. Immature platelet fraction, immature reticulocyte fraction and immature granulocyte percentage are automated complete blood count-derived parameters that may reflect early bone marrow response to systemic infection and inflammation. **Materials and Methods:** This cross-sectional comparative observational study was conducted in the Department of General Medicine, SMS Hospital, Jaipur. A total of 159 participants were included and divided into three equal groups: 53 critically ill adult patients with sepsis fulfilling Sepsis-3 criteria, 53 critically ill non-septic adult patients, and 53 age- and sex-matched healthy controls. Blood samples were collected within 24 hours of admission for automated complete blood count, immature platelet fraction, immature reticulocyte fraction, immature granulocyte percentage and serum procalcitonin. **Results:** The three groups were comparable with respect to age and gender. The mean age was 52.66 ± 18.48 years in septic patients, 53.25 ± 20.98 years in non-septic patients and 47.91 ± 13.15 years in healthy controls. Gender distribution was also not significantly different among groups. Blood culture findings differed significantly among groups, with pathogenic isolates mainly observed in the sepsis group. Total leukocyte count and neutrophil percentage were significantly higher in septic patients compared with non-septic patients and healthy controls. Serum procalcitonin was markedly elevated in septic patients, with a mean value of 6.73 ± 10.38 ng/mL, compared with 0.12 ng/mL in both non-septic patients and healthy controls. Immature platelet fraction was also significantly higher in septic patients at $11.72 \pm 4.03\%$, compared with $3.36 \pm 1.16\%$ in non-septic patients and $2.28 \pm 0.56\%$ in healthy controls. Immature reticulocyte fraction was 19.03% in septic patients, compared with 7.88% in non-septic patients and 7.20% in healthy controls. Immature granulocyte percentage was 2.23% in septic patients, compared with 0.27% in non-septic patients and 0.17% in healthy controls. These findings indicate significant elevation of CBC-derived immature cell indices among patients with sepsis. **Conclusion:** Immature platelet fraction, immature reticulocyte fraction and immature granulocyte percentage were significantly elevated in septic patients compared with critically ill non-septic patients and healthy controls. These CBC-derived hematological markers may serve as rapid, accessible and cost-effective adjuncts to serum procalcitonin for early diagnosis of sepsis, particularly in settings where procalcitonin testing may be delayed or costly.



INTRODUCTION

Sepsis is a life-threatening clinical syndrome caused by a dysregulated host response to infection, leading to organ dysfunction and high mortality if not recognized and treated early.^[1] Early diagnosis remains challenging because clinical features may be nonspecific, particularly in critically ill patients, and conventional markers such as total leukocyte count and neutrophil percentage may reflect inflammation but lack adequate specificity for sepsis diagnosis.^[2] Therefore, reliable biomarkers that can support early differentiation of septic and non-septic illness are clinically important. Serum procalcitonin has been widely used as a biomarker for bacterial sepsis and has shown diagnostic value in distinguishing septic patients from non-septic inflammatory conditions.^[3] However, its routine use may be limited by cost, availability and requirement of specific laboratory platforms, especially in resource-limited healthcare settings. This has encouraged interest in newer hematological parameters that are rapidly generated through automated complete blood count analysis.^[4] Immature platelet fraction is one such marker that reflects active thrombopoiesis and increased platelet turnover. Previous studies have shown that IPF is significantly elevated in patients with sepsis and may help in differentiating sepsis from non-septic illness.^[1-3]

Similarly, immature reticulocyte fraction reflects early erythropoietic marrow response and has been evaluated as a supportive marker in critically ill patients with sepsis.^[5] Immature granulocyte percentage represents premature release of granulocytic precursors into peripheral blood during infection-related emergency granulopoiesis and has also shown diagnostic and prognostic relevance in sepsis.^[6]

These CBC-derived immature cell indices are clinically attractive because they are rapidly available, cost-effective and do not require additional blood sampling. Automated hematology analyzers can provide these parameters as part of routine laboratory evaluation, making them useful potential adjuncts in early sepsis assessment.^[7,8]

However, comparative evaluation of immature platelet fraction, immature reticulocyte fraction and immature granulocyte percentage vis-à-vis serum procalcitonin remains limited. Therefore, the present study was conducted to evaluate the diagnostic significance of immature platelet fraction, immature reticulocyte fraction and immature granulocyte percentage in comparison with serum procalcitonin for early diagnosis of sepsis among critically ill adult patients and healthy controls.

MATERIALS AND METHODS

Study Design and Setting: This was a hospital-based, cross-sectional comparative study conducted

in the Department of General Medicine, SMS Hospital, Jaipur, Rajasthan, India. The study was carried out from August 2023 to August 2024.

Study Participants: A total of 159 participants was enrolled and categorized into three equal groups: critically ill adult patients with sepsis (n=53), critically ill adult patients without sepsis (n=53), and age- and sex-matched healthy controls (n=53). Critically ill patients were recruited from admitted patients evaluated in the Department of General Medicine. Healthy controls were selected from the general population.

Case Definition: Sepsis was diagnosed according to Sepsis-3 criteria and defined as life-threatening organ dysfunction due to infection, identified by an acute increase in Sequential Organ Failure Assessment (SOFA) score of ≥ 2 . Critically ill patients fulfilling Sepsis-3 criteria were included in the sepsis group, while critically ill patients not fulfilling these criteria were included in the non-sepsis group.

Sample Size: The sample size was calculated at a 95% confidence level, 5% alpha error and 80% study power. Based on previously reported mean immature reticulocyte fraction values among septic patients, critically ill patients and controls, and considering a minimum detectable mean difference of 2.5 with a standard deviation of 4.17, the required sample size was calculated as 53 participants in each group. Therefore, the final sample size was 159 participants.

Eligibility Criteria: Critically ill adult patients with sepsis fulfilling Sepsis-3 criteria, critically ill adult patients without sepsis, and healthy age- and sex-matched controls who provided written informed consent were included. Patients with immunodeficiency, autoimmune disorders, immune thrombocytopenia, malignancy, history of chemotherapy, chronic kidney disease, anemia receiving hematinics, or history of blood transfusion were excluded.

Laboratory Measurements: Blood samples were collected from critically ill patients within 24 hours of admission. Samples were also collected from healthy controls at enrolment. Automated complete blood count-derived parameters, including immature platelet fraction (IPF), immature reticulocyte fraction (IRF) and immature granulocyte percentage (IG%), were measured using the Sysmex XN-1000 automated hematology analyzer (Kobe, Japan). Serum procalcitonin was measured using Cobas e411. Blood culture and other relevant investigations, including urine culture, pus culture, body fluid culture, X-ray and CT scan, were performed where clinically indicated to support diagnosis and identify the source of infection.

Outcome Measures: The primary outcome was comparison of IPF, IRF and IG% among septic patients, non-septic critically ill patients and healthy controls. The secondary outcome was comparison of these CBC-derived markers with serum procalcitonin for their diagnostic relevance in early sepsis evaluation.

Statistical Analysis: Data were entered in Microsoft Excel and analyzed using SPSS software. Categorical variables were expressed as frequency and percentage, while continuous variables were expressed as mean \pm standard deviation. Categorical variables were compared using Pearson Chi-square test. Continuous variables among the three study groups were compared using one-way analysis of variance (ANOVA), followed by Tukey HSD post-hoc test for pairwise intergroup comparisons. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 159 participants were included in the study and divided equally into three groups: 53 critically ill patients with sepsis, 53 critically ill patients without sepsis and 53 healthy controls. The mean age was 52.66 ± 18.48 years in septic patients, 53.25 ± 20.98 years in non-septic patients and 47.91 ± 13.15 years in healthy controls. There was no statistically significant difference in age among the study groups. Gender distribution was also comparable among the groups, with 100 males and 59 females overall. The Chi-square value for gender distribution was 0.701 with a p-value of 0.704, indicating no statistically significant association between gender and study group allocation.

Blood Culture Findings

Blood culture findings showed a statistically significant difference among the three groups. All healthy controls had sterile blood cultures. Among septic patients, 23 had sterile cultures, while pathogenic organisms were isolated in the remaining cases. *Streptococcus pneumoniae* was isolated in 11 cases, *Klebsiella pneumoniae* in 9 cases, *Acinetobacter baumannii* in 5 cases, *Staphylococcus aureus* in 4 cases and *Proteus mirabilis* in 1 case. Among non-septic patients, 49 had sterile blood cultures and 4 showed skin commensals. The association between blood culture findings and study groups was highly significant ($\chi^2 = 80.736$, $p < 0.001$).

Total Leukocyte Count and Neutrophil Percentage

Total leukocyte count was significantly higher in septic patients compared with the other groups. The mean total leukocyte count was $16.87 \pm 3.35 \times 10^3/\mu\text{L}$ in septic patients, $8.37 \pm 4.29 \times 10^3/\mu\text{L}$ in non-septic patients and $6.31 \pm 1.76 \times 10^3/\mu\text{L}$ in healthy controls. Intergroup comparison showed statistically significant differences between septic and non-septic patients, septic patients and controls, and non-septic patients and controls.

Neutrophil percentage was also significantly higher in septic patients. The mean neutrophil percentage

was $89.32 \pm 5.04\%$ in septic patients, $66.71 \pm 11.19\%$ in non-septic patients and $60.06 \pm 3.78\%$ in healthy controls. All intergroup comparisons showed statistically significant differences.

Serum Procalcitonin

Serum procalcitonin was markedly elevated in septic patients compared with non-septic patients and healthy controls. The mean procalcitonin level was 6.73 ± 10.38 in septic patients, while both non-septic patients and healthy controls had a mean value of 0.12 with zero standard deviation. This finding showed a clear discriminatory pattern of procalcitonin elevation in septic patients.

Immature Reticulocyte Fraction

Immature reticulocyte fraction was significantly higher among septic patients. The mean IRF was $19.03 \pm 5.18\%$ in septic patients, $7.88 \pm 4.86\%$ in non-septic patients and $7.20 \pm 3.97\%$ in healthy controls. Post-hoc analysis showed significant differences between septic and non-septic patients ($p = 0.017$) and between septic patients and healthy controls ($p = 0.003$), while the difference between non-septic patients and healthy controls was not significant ($p = 0.736$).

Immature Platelet Fraction

Immature platelet fraction was significantly elevated in septic patients. The mean IPF was $11.72 \pm 4.03\%$ in septic patients, $3.36 \pm 1.16\%$ in non-septic patients and $2.28 \pm 0.56\%$ in healthy controls. Post-hoc comparison showed significant differences between septic and non-septic patients ($p < 0.001$) and between septic patients and healthy controls ($p < 0.001$). The difference between non-septic patients and healthy controls was not statistically significant ($p = 0.061$).

Immature Granulocyte Percentage

Immature granulocyte percentage was also significantly higher in septic patients. The mean IG% was $2.23 \pm 0.95\%$ in septic patients, $0.27 \pm 0.61\%$ in non-septic patients and $0.17 \pm 0.17\%$ in healthy controls. Post-hoc comparison showed significant differences between septic and non-septic patients ($p < 0.001$) and between septic patients and healthy controls ($p < 0.001$), while the difference between non-septic patients and healthy controls was not statistically significant ($p = 0.694$).

Overall Biomarker Pattern

The study showed that serum procalcitonin, immature reticulocyte fraction, immature platelet fraction and immature granulocyte percentage were all higher among septic patients compared with non-septic critically ill patients and healthy controls. Among the CBC-derived parameters, IPF, IRF and IG% demonstrated significant elevation in sepsis, supporting their potential role as adjunctive hematological markers in early sepsis diagnosis.

Table 1: Baseline characteristics of study participants

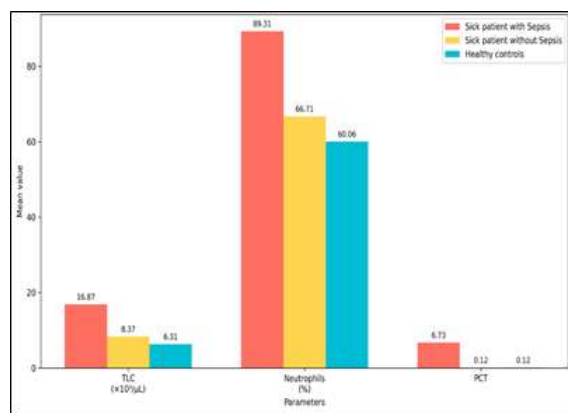
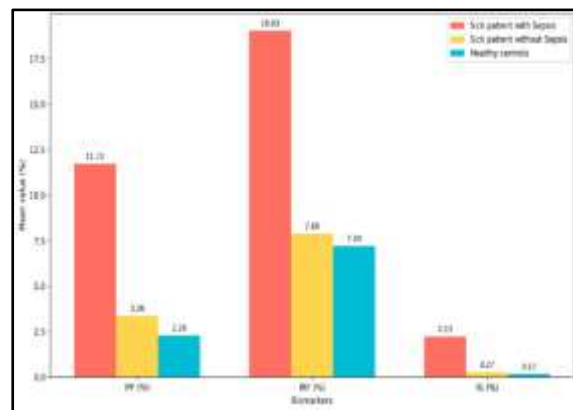
Variable	Sepsis (n=53)	Non-sepsis (n=53)	Healthy controls (n=53)	p-value
Age, years	52.66 ± 18.48	53.25 ± 20.98	47.91 ± 13.15	NS
Male	34	31	35	0.704
Female	19	22	18	0.704

Table 2: Comparison of laboratory parameters among study groups

Parameter	Sepsis (n=53)	Non-sepsis (n=53)	Healthy controls (n=53)	p-value
TLC ($\times 10^3/\mu\text{L}$)	16.87 \pm 3.35	8.37 \pm 4.29	6.31 \pm 1.76	<0.001
Neutrophils (%)	89.32 \pm 5.04	66.71 \pm 11.19	60.06 \pm 3.78	<0.001
Procalcitonin	6.73 \pm 10.38	0.12 \pm 0.00	0.12 \pm 0.00	<0.001
IRF (%)	19.03 \pm 5.18	7.88 \pm 4.86	7.20 \pm 3.97	0.003
IPF (%)	11.72 \pm 4.03	3.36 \pm 1.16	2.28 \pm 0.56	<0.001
IG (%)	2.23 \pm 0.95	0.27 \pm 0.61	0.17 \pm 0.17	<0.001

Table 3: Grade of hepatomegaly according to age and gender

Study group	Total (n)	Mild, n (%)	Moderate, n (%)	Massive/severe, n (%)
Overall	104	36 (34.6)	52 (50.0)	16 (15.4)
Age group				
<5 years	38	14 (36.8)	17 (44.7)	7 (18.4)
5–10 years	37	12 (32.4)	19 (51.4)	6 (16.2)
10–18 years	29	10 (34.5)	16 (55.2)	3 (10.3)
Gender				
Male	60	22 (36.7)	29 (48.3)	9 (15.0)
Female	44	14 (31.8)	23 (52.3)	7 (15.9)

**Figure 1: Comparison of TLC, Neutrophils & PCT across three groups****Figure 2: Comparison of IPF, IRF & IG % across three groups**

DISCUSSION

The findings related to immature platelet fraction are supported by Enz Hubert et al., who reported a significant association of IPF with sepsis diagnosis and severity.^[2] Similar observations were reported by Park et al., who demonstrated the diagnostic utility of IPF in critically ill septic patients.^[1] De Blasi et al. also observed that IPF could predict sepsis in critically ill patients, supporting its role as an early hematological marker.^[3] Di Mario et al. further

reported that IPF was useful in hospitalized patients with neutrophilia and suspected bacterial infection, reinforcing its value in infection-related marrow response.^[4] The biological interpretation of increased IPF is also supported by studies evaluating platelet kinetics in different clinical settings. Briggs et al. demonstrated the usefulness of IPF in peripheral thrombocytopenia, while Kickler et al. evaluated high fluorescent platelet fraction in thrombocytopenic patients and confirmed its role as an indicator of platelet production.^[5,6] Jung et al. established reference intervals and diagnostic utility of IPF in thrombocytopenia, and Cremer et al. showed that IPF could predict the course of neonatal thrombocytopenia.^[7,8] Although these studies were not exclusively focused on adult sepsis, they support the concept that IPF reflects active thrombopoiesis and peripheral platelet consumption, which are relevant mechanisms in sepsis. The findings related to immature reticulocyte fraction are in agreement with Yilmaz et al., who compared immature reticulocyte and platelet fractions with other sepsis markers and found these indices useful in the diagnosis of sepsis among critically ill children.^[10] Hoffmann et al. also demonstrated that immature reticulocyte parameters reflect early erythropoietic activity, supporting the use of IRF as a marker of marrow response.^[15] Zini et al. emphasized the importance of automated hematology analyzer-derived immature cell indices and supported their integration into routine laboratory evaluation.^[16] The findings related to immature granulocyte percentage are supported by Celik et al., who reported that immature granulocyte count and immature granulocyte percentage were useful in the diagnosis of neonatal sepsis.^[12] Nahm et al. also demonstrated that delta neutrophil index, an automated immature granulocyte-related parameter, was useful for assessing disease severity in sepsis.^[13] Han et al. further reported that the immature granulocyte to total neutrophil ratio had prognostic value in septic shock.^[14] These studies support the role of immature granulocyte-related indices as

indicators of emergency granulopoiesis during systemic infection. Regarding serum procalcitonin, the present findings are supported by Park et al. and Yilmaz et al., who included procalcitonin among sepsis biomarkers and demonstrated its diagnostic relevance in septic patients.^[1,10] Urrechaga also reviewed the value of leukocyte cell population data in sepsis management and discussed the role of hematological analyzer-derived parameters alongside established biomarkers.^[11] These studies support the use of procalcitonin as a reference biomarker while highlighting the potential contribution of CBC-derived parameters.

CONCLUSION

The present study supports the diagnostic utility of immature platelet fraction, immature reticulocyte fraction and immature granulocyte percentage in the early evaluation of sepsis. These CBC-derived hematological parameters were useful in differentiating septic patients from non-septic critically ill patients and healthy controls. Among these, IPF and IG% appear particularly useful as rapid indicators of infection-related marrow response, while IRF may serve as an additional supportive marker.

Since IPF, IRF and IG% are generated through routine automated hematology analysis, they are rapidly available, cost-effective and do not require additional blood sampling. These parameters may therefore be used as adjunctive markers along with serum procalcitonin for early diagnosis of sepsis, especially in settings where procalcitonin testing is costly or not immediately available. Larger multicentric studies with ROC-based cut-off values and outcome correlation are recommended to further validate their clinical use.

Limitations: This was a single-center observational study conducted at a tertiary care hospital, which may limit the generalizability of the findings to other healthcare settings. The sample size was adequate as per calculation, but larger multicentric studies would provide stronger evidence.

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