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Hematological Markers: An Early Road to Recovery in Sepsis

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Abstract

Objective: To investigate the clinical value of hematological parameters neutrophil NEUT-X, NEUT-Y, and NEUT-Z and monocyte MONO-X, MONO-Y, and MONO-Z in the detection of sepsis and compare their values with that of C-reactive protein (CRP).

Methodology: This is a cross-sectional study that was conducted at Chughtai Institute of Pathology and Mayo Hospital, Lahore, from October 2025 to January 2026. A total of 175 patients, both male and female, were recruited in the study. The normal group consisted of 65 individuals (30 males, 35 females; age range 14–85 years) who underwent routine physical examination and showed no evidence of illness or inflammation. The sepsis group consisted of 110 individuals (70 males, 40 females; age range 14–95 years). Their SOFA score was calculated. The CRP and NEUT-X, NEUT-Y, NEUT-Z, MONO-X, MONO-Y, and MONO-Z were analyzed for everyone using the analyzers, Sysmex XN-9000 (for hematology parameters) and Abott Alinity C (for CRP with cut-off >5 mg/L). The cut-off for total leukocyte counts 10x109/L was taken. The data was analyzed using SPSS. The median and Interquartile range for all parameters were calculated. Mann-Whitney U test and Shapiro-Wilk test were used to assess the data. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance (including sensitivity and specificity) of these parameters in distinguishing between septic and non-septic patients along with overall model quality to help in predictability.

Results: Median values of NEUT-X, NEUT-Y, NEUT-Z, MONO-X, MONO-Y, MONO-Z, and CRP in the sepsis group were significantly higher than those in the normal group. The area under the receiver operating characteristic curve (AUC) of NEUT-X, NEUT-Y, NEUT-Z, MONO-X, MONO-Z, and CRP for the diagnosis of sepsis was 0.719 (sensitivity 92.7%, specificity 20.0%), 0.856 (97.3%, 27.7%), 0.854 (98.2%, 40.0%), 0.922 (83.6%, 89.2%), 0.616 (87.3%, 18.5%), and 0.965 (94.5%, 81.5%), respectively. While the area under the receiver operating characteristic curve (AUC) of MON-Y 0.140 showed low predictability.

Conclusion: The findings collectively indicate that while MONO-Y is not discriminative, neutrophil-related variables (NEUT-X, NEUT-Y, NEUT-Z) and monocyte variables (MONO-X, MONO-Z) may be sepsis biomarkers.

Key words: C-reactive protein, hematological parameters, Sepsis.

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Introduction

Sepsis is a life-threatening clinical condition associated with multiple physiological and biochemical disturbances. It is currently defined as “organ dysfunction caused by a dysregulated host response to infection”.[1] Approximately 49 million individuals are affected by sepsis annually, with nearly 11 million deaths reported worldwide, contributing to about 19.7% of total global mortality.[2] Sepsis represents a severe systemic infection that demands immediate medical attention. In the absence of timely and appropriate management, mortality rates can rise to 30–35%.[3] It has been reported that if treatment is delayed beyond 72 hours from onset, the survival rate decreases by nearly 7.7% per hour.[4] Hence, early identification and prompt management of sepsis are essential. Nevertheless, diagnosing sepsis remains challenging due to the absence of specific clinical signs and symptoms.

Blood culture remains the gold standard for diagnosing sepsis; however, it is time-intensive and may yield false positive or false negative outcomes.[5] C-reactive protein (CRP), an acute-phase reactant, is widely utilized as a sensitive indicator of inflammation and tissue injury and is commonly used in the evaluation of sepsis. However, CRP levels may also be significantly elevated in cases of tissue damage unrelated to infection, potentially leading to misinterpretation in the diagnosis of sepsis.[6]

Therefore, there is an urgent need to identify reliable biomarkers that can facilitate the early detection of sepsis and improve patient outcomes. Among these, parameters such as NEUT-X, NEUT-Y, NEUT-Z, MONO-X, and MONO-Y have shown potential utility. These

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indices reflect morphological alterations occurring in neutrophils and monocytes during septic conditions. Sepsis induces several structural changes in peripheral neutrophils and monocytes, including toxic granulation, a left shift, and increased chromatin density in neutrophils, while monocytes exhibit increased cell volume and nucleic acid content.[7]

NEUT refers to neutrophils and MONO to monocytes, whereas X represents the center of gravity of the sideward scatter light signal, indicating cellular complexity. Y denotes the center of gravity of the sideward fluorescence signal, reflecting nucleic acid content within the cells. Z is calculated as the sum of X and Y values. The Sysmex XN-9000 is an automated hematology analyzer capable of measuring these parameters without the need for additional reagents, thereby providing rapid and cost-effective support in the detection of sepsis.

Thus, the present study aims to evaluate the clinical significance of hematological parameters including neutrophil NEUT-X, NEUT-Y, NEUT-Z and monocyte MONO-X, MONO-Y, and MONO-Z in the diagnosis of sepsis, and to compare their values with those of C-reactive protein (CRP).

Methodology

This is a cross-sectional study that was conducted at Chughtai Institute of Pathology and Mayo hospital, Lahore after getting approval from the ethical and research committee of the institute. The duration of the study was from October 2025 to January 2026. A total of 175 patients were recruited in the study after taking their informed consent. The sample size was calculated with WHO sample size calculator. The confidence level was taken as 95%, margin of error 5%. The prevalence of sepsis in Pakistan was considered 43%.[8] These patients were admitted in the medical ward of Mayo Hospital, with suspicion of sepsis. Both male and female patients, of all age group were included in the study. Their SOFA score was calculated. The SOFA (Sequential Organ Failure Assessment) score is a tool used in critical care to track organ dysfunction by scoring six systems (respiratory, cardiovascular, hepatic, coagulation, renal, neurologic); a higher score indicates worse function and higher mortality risk, with a rise of ≥2 points signaling organ dysfunction.

For this investigation, we gathered data from two groups in the past. Group 1 comprised 30 males and 35 females, ages 14 to 85, with an average age of 38.5 years (SD = 17.7), who underwent routine physical examinations and showed no evidence of illness or inflammation (n = 65). Group 2 comprised 110 sepsis patients (70 men and 40 females) with positive culture results, ages ranging from 14 to 95, with an average age of 58.8 years (SD = 19.4).

Then venous blood sample was taken from each patient in Ethylenediamine tetra acetic acid (EDTA) tube and clotted vials following standard sampling procedures for analysis of CRP and hematological parameters. The CRP was analyzed using clotted samples on Alinity C module following all Standard operating procedures of the laboratory. The EDTA sample was run on Sysmex XN-9000 for hematological parameters. No additional reagent was used to calculate NEUT-X, NEUT-Y, NEUT-Z, MONO-X, MONO-Y, AND MONO-Z.

All values were noted, and the data was entered in the excel work sheets, checked manually and logically corrected where needed. The Shapiro-Wilk test was used to determine whether the data was normal. The medians and interquartile ranges (IQR) of NEUTX, NEUT-Y, NEUT-Z, MONO-X, MONO-Y, MONO-Z and CRP between the septic and normal groups were compared using the Mann-Whitney U test. Additionally, Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance (including sensitivity and specificity) of these parameters in distinguishing between septic and non-septic patients along with overall model quality to help in predictability. Statistical analyses were performed with the software SPSS 26.0 using a significance level of $p<0.05$.

Results

Using the Shapiro-Wilk test the normality of the data was found, the data did not follow a normal distribution, according to the results ($P<0.05$) (Table I). The Mann-Whitney U test was used to compare the two groups using 65 results from the normal group and 110 data from the septic group. Median values for all variables with interquartile ranges are presented in table II. Table III displays the outcomes for NEUT-X, NEUT-Y, NEUT-Z, MONO-X, MONO-Y, and MONO-Z and CRP. The Mann-Whitney U test showed that NEUT-X, NEUT-Y, NEUT-Z, MONO-X, MONO-Y, and MONO-Z and CRP in the sepsis

Table I: Tests of normality using Shapiro-Wilk test.

Tests of Normality							
	Pathogensis	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
NeutX	Septic	.100	110	.009	.962	110	.003
	Normal	.131	65	.008	.925	65	.001
NeutY	Septic	.141	110	.000	.920	110	.000
	Normal	.068	65	.200*	.991	65	.933
NeutZ	Septic	.058	110	.200*	.986	110	.284
	Normal	.117	65	.028	.922	65	.001
MonoX	Septic	.127	110	.000	.946	110	.000
	Normal	.139	65	.003	.916	65	.000
MonoY	Septic	.065	110	.200*	.972	110	.021
	Normal	.215	65	.000	.881	65	.000
MonoZ	Septic	.111	110	.002	.942	110	.000
	Normal	.131	65	.007	.954	65	.018

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Table II: Descriptive statistics for the variables.

Descriptive Statistics								
	N	Mean	Std. Deviation	Min	Max	Percentiles		
						25th	50th (Median)	75th
NeutX	175	153.835	6.2183	136.1	166.7	149.600	152.900	158.200
NeutY	175	55.498	6.3980	43.6	79.3	50.600	54.600	57.700
NeutZ	175	76.986	7.3052	63.0	93.0	71.500	77.800	82.900
MonoX	175	120.893	3.9941	115.0	135.1	117.500	120.500	123.500
MonoY	175	107.521	11.2122	76.9	138.2	98.300	109.700	115.600
MonoZ	175	59.320	6.6166	41.7	87.6	55.300	58.900	62.200
Pathogensis	175	3.37	.485	3	4	3.00	3.00	4.00

Table III: Independent-Samples Mann-Whitney U Test.

	Null Hypothesis	Test	Sig	Decision
1	The distribution of NeutX is the same across categories of Pathogenesis.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.
2	The distribution of NeutY is the same across categories of Pathogenesis.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.
3	The distribution of NeutZ is the same across categories of Pathogenesis.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.
4	The distribution of MonoX is the same across categories of Pathogenesis.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.
5	The distribution of MonoY is the same across categories of Pathogenesis.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.
6	The distribution of MonoZ is the same across categories of Pathogenesis.	Independent-Samples Mann-Whitney U Test	.011	Reject the null hypothesis.
7	The distribution of CRP is the same across categories of Pathogenesis.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.

group were significantly higher than those in the normal control group (P<0.001). CRP level significantly higher in the sepsis group, with a significant difference (P<0.001).

As shown in the table IV. The Mann Whitney U test indicates that all hematological parameters are different

between two groups (Septic and control). The negative Z value indicate that the first group tends to have lower values for these parameters, so the sepsis group has higher values. All the p-values are<0.05 (Most are <0.001), which means these differences are statistically significant. Mono Z is also significant (p=0.011), but the difference is less significant than others.

The graphs show the distribution of each parameter (Neut-X, Neut-Y, Neut-Z, Mono-X, Mono-Z and CRP) for septic (blue, N=110) and normal (red, N=65) groups. The septic patients have higher values for all parameters and

Table IV: test statistics for Mann-Whitney U test.						
Test Statistics						
	NeutX	NeutY	NeutZ	MonoX	MonoY	MonoZ
Mann-Whitney U	2012.000	1027.000	1040.500	556.000	1000.000	2747.000
Wilcoxon W	4157.000	3172.000	3185.500	2701.000	7105.000	4892.000
Z	-4.827	-7.869	-7.827	-9.326	-7.953	-2.558
Asymp. Sig. (2-tailed)	.000	.000	.000	.000	.000	.011
a. Grouping Variable: Pathogensis						

Table V. Area under the ROC curve.					
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
CRP	.965	.014	.000	.938	.992
NeutX	.719	.038	.000	.645	.792
NeutY	.856	.027	.000	.803	.910
MonoZ	.616	.043	.006	.532	.699
MonoY	.140	.030	.000	.082	.198
MonoX	.922	.020	.000	.883	.961
NeutZ	.854	.032	.000	.792	.917

have higher mean ranks. The normal controls clusters at lower values. The separation between blue and red bar visually supports the Mann-Whitney U test results: sepsis patients have significantly higher bars than normal controls The Mono-Y shows higher values and mean

rank in normal group (Red) than the septic group, opposite to the other markers. This suggests Mono-Y is lower in sepsis and higher in controls

To assess how well these measures performed in the diagnosis of sepsis, ROC analysis was carried out and the area under the ROC curve (AUC) was computed (Table V). After determining the ideal cutoff values using Youden's index (sensitivity + specificity − 1), the diagnostic sensitivity and specificity were computed. (Figure 1) illustrates how well NEUT-X, NEUT-Y, NEUT-Z, MONO-X, MONO-Z and CRP performed as diagnostic tools for sepsis. Whereas MONO-Y showed very low diagnostic characteristic.

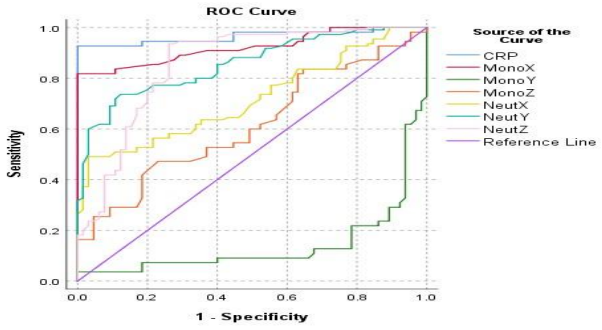

Figure 1. Showing ROC curve with reference line.

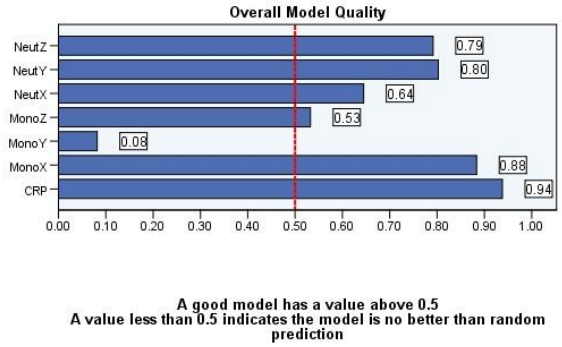

Figure 2. Showing overall model quality with predictability.

For the diagnosis of sepsis, the AUC for NEUT-X, NEUT-Y, NEUT-Z, MONO-X, MONO-Z, and CRP was 0.719, 0.856, 0.854, 0.922, 0.616, and 0.965; the sensitivity findings were 92.7, 97.4%, 98.2%, 83.6%, 87.3%, 94.5% and the specificity was 20.0%, 27.7%, 40.0%, 89.2%, 18.5%, 81.5% respectively. NEUT-X, NEUT-Y, NEUT-Z, MONO-X, MONO-Z, and CRP showed good predictability (above 0.5), whereas MONO-Y showed very low predictability (Figure 2)

Discussion

Sepsis remains a major healthcare challenge worldwide. Elderly individuals are particularly vulnerable to poor outcomes associated with sepsis. Globally, the condition is linked with elevated mortality rates, especially among patients older than 70 years. Hence, strengthening

strategies for early recognition, prevention, and timely management of sepsis is essential.[9]

CRP and procalcitonin are commonly utilized biomarkers for the detection of sepsis; however, certain limitations must be considered. CRP is synthesized in the liver and may provide misleading results in septic patients with impaired hepatic function, thereby reducing its diagnostic reliability in liver disorders. In a similar manner, procalcitonin levels may be elevated in individuals with chronic kidney disease, and this rise is often independent of sepsis.[10,11] Therefore, there is a need for more dependable diagnostic markers for early identification of sepsis, particularly in patients with multiple organ involvement.

A study closely related to ours was performed at the Third People's Hospital of Shenzhen by Zheng et al. According to Zhang et al., NEUT-X, NEUT-Y, and MONO-Y were significantly elevated in septic patients and could serve as early diagnostic indicators. These observations are largely consistent with our findings, except for MONO-Y. In our study, neutrophil indices (NEUT-X, NEUT-Y, NEUT-Z) along with monocyte indices (MONO-X, MONO-Z) were found to be reliable for early detection of sepsis. Furthermore, the ROC analysis reported by Zhang et al. demonstrated that NEUT-Y had an AUC of 0.877, which was considerably higher than CRP (0.790), with sensitivity and specificity of 87.3% and 72.1%, respectively. In contrast, our findings showed that MONO-X exhibited the highest AUC, indicating a sensitivity of approximately 90%.[7]

Another investigation conducted in Spain reported that patients with COVID-19 exhibiting neutrophilia along with lymphopenia showed intermediate values of Neu X and Neu Y, as well as Mon Z. The authors suggested that Neu X, Neu Y, and Mon Z could serve as early warning indicators for clinicians, particularly in cases with unclear clinical history, and may suggest progression toward a cytokine storm.[12]

A further study supported by the National Natural Science Foundation of China evaluated these parameters in patients diagnosed with severe fever with thrombocytopenia syndrome (SFTS). The results indicated that surviving patients had significantly lower Lym-Y values, whereas Neu-Y and Mon-Z levels were markedly elevated ($p < 0.001$), particularly in patients who did not survive. This suggests that increased NEUT-Y and MONO-Z levels are associated with severe disease and may serve as predictors of sepsis outcomes.[13] Our findings similarly demonstrated that NEUT-Y and MONO-Z are promising markers for sepsis.

Another study conducted in China aimed to develop a novel hematological model and assess its clinical utility in the diagnosis and prognosis of severe community-acquired pneumonia. The investigators evaluated the sensitivity of these parameters and found that hematological indices were significantly higher in pneumonia patients compared to controls. Moreover, even greater elevations were observed in severe pneumonia cases compared to mild cases. In addition, NEUT-X, NEUT-Y, and MONO-X showed significant diagnostic performance.[14]

Although peripheral blood smear examination and complete blood count (CBC) analysis remain the initial steps in identifying infections, these advanced hematological parameters can be obtained simultaneously with routine CBC testing and facilitate rapid diagnosis, particularly in emergency settings. These automated analyzers are user-friendly and provide results within a short time frame. Therefore, these advantages highlight the potential of these novel parameters as future tools in diagnostic practice.

Conclusion

We conclude that neutrophil-related parameters (NEUT-X, NEUT-Y, NEUT-Z) and monocyte parameters (MONO-X, MONO-Z) can be used as potential biomarkers for early detection of sepsis. These parameters can be easily obtained along with CBC by automated hematology analyzers which are widely available in laboratories throughout the country and do not require any special sampling or testing pre-requisites. It is a cost-effective test which can lessen the economic burden on the health sector. Furthermore, a prompt diagnosis for septic patients can give them a better chance of survival.

Limitations: A limited number of samples were tested in this study. We recommend that to further evaluate the effectiveness of these parameters a bigger research project should be designed with a larger sample size. This will help to fully assess the effectiveness of these parameters

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