Original Article

The Diagnostic Value of Automated Neutrophil and Monocyte Parameters in Early Recognition of Sepsis

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Abstract

Background: Sepsis is a medical emergency. Treatment for sepsis is effective only if started early, and a critical lapse of time may be detrimental. The existing blood biomarkers for sepsis, like CRP and Procalcitonin, suffer from cost-ineffectiveness and an additional sample to be handled. The Leukocyte Cell Population Data (CPD) include NEU-X, NEU-Y, MON-X, and MON-Y. NEU-X measures the structural complexity of neutrophils by sideward scatter (SSC), while NEU-Y measures the DNA and RNA content by sideward fluorescence light. Our study aimed to evaluate the utility and significance of NEU-X and NEU-Y in the early diagnosis of sepsis.
Methods: It was a prospective, observational study done over a period of one month at a tertiary care hospital, which included 300 participants admitted in the ICU: 150 adults with suspected sepsis and 150 healthy controls. Blood samples were collected in EDTA vials and run on a Sysmex XN-1000 automated hematology analyser for CBC (complete blood counts) and values of NEU-X, NEU-Y, MON-X, and MON-Y parameters.
Results: The median value of NEU-X, NEU-Y, and MON-Y demonstrated a significant p-value of <0.0001 between cases and controls. NEU-X had a sensitivity of 79.33% and specificity of 91.33% at a cut-off of >339, while NEU-Y exhibited sensitivity and specificity of 93.33% each at a cut-off of >727. MON-Y and MON-X had a cut-off value of ≤ 90.3 and ≤ 118.9, respectively.
Conclusion: The leukocyte CPD parameters—NEU-X, NEU-Y, and MON-Y—represent a promising set of data and can be helpful in the early diagnosis of sepsis.

Keywords: Sepsis; Cell Population data; NEU-X; NEU-Y; MON-X; MON-Y

Introduction

Sepsis is a medical emergency. It is an overwhelming, life-threatening condition due to infection, marked by an exaggerated immune response, leading to multiorgan dysfunction. Deaths due to sepsis account for 11–14 million per year out of an estimated 50 million cases annually, accounting for 20% of global deaths [1]. Treatment for sepsis is effective if started early; a critical lapse of time may be detrimental. Since the management of sepsis requires a multidisciplinary approach, treatment is always costly. The existing blood biomarkers for sepsis, like C-Reactive Protein (CRP), Interleukin-6 (IL-6), and Procalcitonin, suffer from cost-ineffectiveness, lack of specificity and sensitivity, and an additional sample to be handled [1]. Conventionally, manual microscopy is done to look for the morphological features of neutrophils and monocytes which are activated during infection; however, it is very subjective and labor-intensive. Hence, there is an emergent need for developing robust, cost-effective markers for the early and rapid diagnosis of sepsis. The newer five-part and seven-part automated cell analysers provide both quantitative and qualitative data about leukocyte differentials. They use fluorescence and flow cytometry to assess each individual cell for its functional properties in an accurate, fast, and cost-effective manner. The WDF channel of the analyser uses a surfactant to lyse the red blood cells (RBCs) and platelets and analyses each individual leukocyte cell for its volume, internal structural complexity, and nucleic acid content. Infection by a microorganism causes

activation of neutrophils, which are attracted by the Pathogen-Associated Molecular Patterns (PAMPs), chemokines, and cytokines released by the injured endothelial cells and other inflammatory cells. The activated neutrophils synthesize reactive oxygen species and other cytokines to kill the pathogen [2]. Due to activation, the nucleic acid content of the neutrophils increases along with structural complexity, like toxic granules and cytoplasmic vacuoles. Monocytes are heterogeneous inflammatory cells involved since the early stages of infection. Their role in the progression of sepsis involves decreased antigen presentation capacity and decreased pro-inflammatory cytokine release due to the polarization of the monocyte phenotype from a classical pro-inflammatory state to an immunosuppressive state [3]. The Leukocyte Cell Population Data include NEU-X, which measures the structural complexity of neutrophils by sideward scatter (SSC), while NEU-Y measures the DNA and RNA content by sideward fluorescence light [4]. Hence, NEU-X and NEU-Y represent the side scatter light distribution width and fluorescent light distribution width of the neutrophil, respectively. Likewise, MON-X and MON-Y represent the side scatter light distribution width and fluorescent light distribution width of monocytes, respectively. Our study aimed to evaluate the utility and significance of NEU-X, NEU-Y, MON-X, and MON-Y in the early diagnosis of sepsis.

Materials and Methods

It was a prospective, observational study done over a period of one month at a tertiary care hospital in Delhi, which included 300 participants admitted in the ICU: 150 adults (aged 18 and older) with suspected sepsis (cases) based on Sepsis-3 criteria, following the Surviving Sepsis Guidelines [5], and 150 healthy controls (controls). Healthy controls were defined as subjects 18–65 years old presenting with CBC counts within the normal range and without any severe liver, kidney, cardiovascular, or hematological disease. The study collected all eligible cases during a predefined one-month period, and as such, no sample size was calculated.

Blood samples were collected in ethylenediamine tetraacetic acid (EDTA) vials and run on a Sysmex XN-1000 automated hematology analyser for CBC (complete blood counts) and values of NEU-X, NEU-Y, MON-X, and MON-Y parameters. Sysmex XN-1000 calibration and quality control procedures met manufacturer and ISO-15189 requirements. All the tests were completed within 4 hours of sample collection. Standard biomarkers, such as procalcitonin, lactate, and CRP, were also measured. Sensitivity, specificity, diagnostic accuracy, and correlation coefficient of all these parameters were statistically analyzed in comparison to traditional biomarkers. Due to some technical issues, the values of MON-X and MON-Y were analyzed only for 40 cases and 40 controls.

Statistical Analysis: Quantitative data with a non-normal distribution were presented as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using the Shapiro-Wilk test. In the cases in which the data was not normal, non-parametric tests were used. The following statistical tests were applied for the results. The comparison of the variables which were quantitative and not normally distributed in nature was analyzed using the Mann-Whitney Test.

A receiver operating characteristic curve was used to assess the cut-off point, sensitivity, specificity, positive predictive value, and negative predictive value of MON-X, MON-Y, NEU-X, NEU-Y, CRP, Procalcitonin, and Lactate for predicting sepsis.

The data entry was done in a Microsoft Excel spreadsheet, and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software (IBM manufacturer, Chicago, USA, version 25.0). For statistical significance, a p-value of less than 0.05 was considered statistically significant.

Results

The study included 150 cases and 150 healthy controls. The mean TLC of cases was 22,390/µl, whereas it was 7,386/µl for controls. Table 1 shows the median values of NEU-X, NEU-Y, MON-X, and MON-Y along with traditional biomarkers: CRP, Procalcitonin, and Lactate. The median value of NEU-X in cases was 384, while in controls, it was 306, demonstrating a significant p-value of <0.0001. NEU-Y, with a median value of 901 in cases and 626 in controls, also showed a significant difference (p-value <0.0001). The median values of MON-Y in cases was 93.6 and 97.6 for controls, with a significant p-value of 0.004. MON-X, however, did not show any significant difference between cases and controls (Table 2). With an Area Under the ROC Curve (AUC) of 0.928, a sensitivity of 79.33%, and a specificity of 91.33% at a cut-off of >339, NEU-X achieved a diagnostic accuracy of 85%. NEU-Y performed even better; it exhibited an AUC of 0.985, sensitivity and specificity of 93.33% each at a cut-off of >727, resulting in a diagnostic accuracy of 93.33% (Table 3, Fig. 1–2). Traditional biomarkers, including CRP, procalcitonin, and lactate, showed 100% sensitivity, specificity, and diagnostic accuracy, further confirming their reliability in diagnosing sepsis. In the prediction of sepsis, NEU-Y had a sensitivity of 93.33%, followed by NEU-X (79.33%). Also, NEU-Y had a specificity of 93.33%, followed by NEU-X (91.33%). The cut-off values used were >339 for NEU-X and >727 for NEU-Y. NEU-Y showed higher sensitivity (93.33%, 95% CI: 88.1–96.8%) compared to NEU-X (79.33%, 95% CI: 72.0–85.5%). Specificity was also higher for NEU-Y at 93.33% (95% CI: 88.1–96.8%) than for NEU-X at 91.33% (95% CI: 85.6–95.3%). MON-X and MON-Y had an AUC of 0.599 and 0.689, respectively. MON-Y had

a cut-off value of ≤90.3 with a diagnostic accuracy of 66.25%, and MON-X had a cut-off value of ≤118.9 with a diagnostic accuracy of 67.5% (Fig. 3, 4). The positive predictive value (PPV) for NEU-Y was 93.3% (95% CI: 88.1–96.8%), while NEU-X had a slightly lower PPV at 90.2% (95% CI: 83.7–94.7%). Negative predictive values (NPVs) were notably different, with NEU-Y achieving 93.3% (95% CI: 88.1–96.8%) compared to NEU-X's 81.5% (95% CI: 74.8–87.1%). In terms of overall diagnostic accuracy, NEU-Y achieved better performance with a diagnostic accuracy of 93.33%, while NEU-X had a diagnostic accuracy of 85.33%. A significant weak positive correlation was seen between NEU-X and procalcitonin (ng/mL) with a correlation coefficient of 0.244. A non-significant, very weak positive correlation was seen between NEU-X and C-reactive protein (mg/L) with a correlation coefficient of 0.095. A non-significant, very weak positive correlation was seen between NEU-Y and CRP (mg/L) and procalcitonin (ng/mL) with correlation coefficients of 0.126 and 0.072, respectively (Table 4).

Table 1: Comparison of traditional biomarkers of sepsis and NEU-X, NEU-Y parameters between cases and controls.

Parameters	Cases (n=150)	Controls (n=150)	Total	P value
NEU-X	384 (349.25-403)	306 (295.25-321)	333.5 (306-387)	<.0001*
NEU-Y	901 (820-1074)	625.5 (608-664)	727.5 (626.25-901)	<.0001*
C-reactive protein (mg/L)	380 (290-510)	1.2 (0.8-2.675)	94.15 (1.2-380)	<.0001*
Procalcitonin (ng/mL)	5 (4.225-6)	0.05 (0.04-0.07)	1.1 (0.05-5)	<.0001*
Lactate (mmol/L)	6 (4.6-6.6)	1.3 (1.125-1.675)	2.55 (1.3-6)	<.0001*

*Mann Whitney test

Table 2: Comparison of MON-X & MON-Y parameters between cases and controls.

Parameters	Cases (n=40)	Controls (n=40)	Total	P value
MON-X	121.85 (118.475-124.85)	122.25 (120.4-125.5)	122 (119.225-125.15)	0.127*
MON-Y	93.6 (87.225-99.175)	97.6 (94.35-101.725)	95.35 (91.3-100.7)	0.004*

*Mann Whitney test

Table 3: Receiver operating characteristic curve (ROC) of NEU-X, NEU-Y, C-reactive protein, Procalcitonin and Lactate for predicting sepsis.

Variables	NEU-X	NEU-Y	C-reactive protein (mg/L)	Procalcitonin (ng/mL)	Lactate (mmol/L)
Area under the ROC curve (AUC)	0.928	0.985	1	1	1
Standard Error	0.0141	0.00493	0	0	0
95% Confidence interval	0.900 to 0.955	0.975 to 0.994	1.000 to 1.000	1.000 to 1.000	1.000 to 1.000
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Cut off	>339	>727	>8.3	>0.09	>2.2
Sensitivity (95% CI)	79.33% (72.0 - 85.5%)	93.33% (88.1 - 96.8%)	100% (97.6 - 100.0%)	100% (97.6 - 100.0%)	100% (97.6 - 100.0%)
Specificity (95% CI)	91.33% (85.6 - 95.3%)	93.33% (88.1 - 96.8%)	100% (97.6 - 100.0%)	100% (97.6 - 100.0%)	100% (97.6 - 100.0%)
PPV (95% CI)	90.2% (83.7 - 94.7%)	93.3% (88.1 - 96.8%)	100% (97.6 - 100.0%)	100% (97.6 - 100.0%)	100% (97.6 - 100.0%)
NPV (95% CI)	81.5% (74.8 - 87.1%)	93.3% (88.1 - 96.8%)	100% (97.6 - 100.0%)	100% (97.6 - 100.0%)	100% (97.6 - 100.0%)
Diagnostic accuracy	85.33%	93.33%	100.00%	100.00%	100.00%

Table 4: Correlation of NEU-X and NEU-Y with C-reactive protein and Procalcitonin.

Variables	C-reactive protein (mg/L)	Procalcitonin (ng/mL)
NEU-X		
Correlation coefficient	0.095	0.244
P value	0.248	0.003
NEU-Y		
Correlation coefficient	0.126	0.072
P value	0.125	0.382

Discussion

Sepsis remains the prominent cause of mortality in critically ill patients. Every hour of delay of the therapy can cause an increase in the mortality rate by 7–10% [6]. Early diagnosis and treatment, therefore, have improved outcomes. The immune

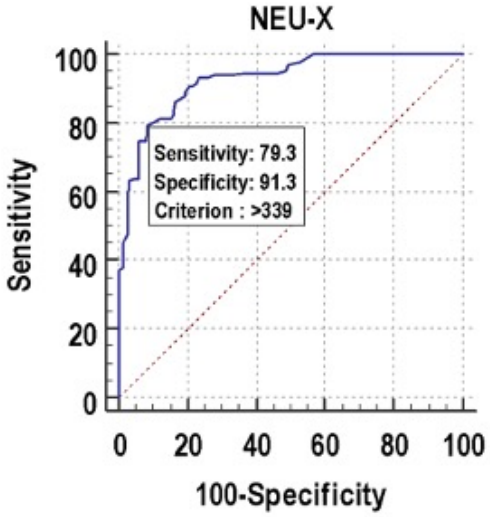

Figure 1: Receiver operating characteristic curve of NEU-X for predicting sepsis.

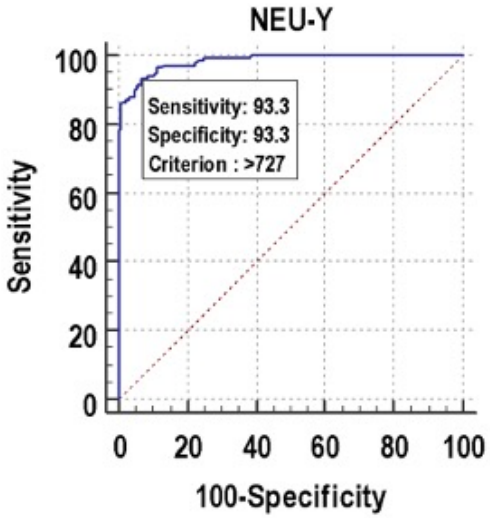

Figure 2: Receiver operating characteristic curve of NEU-Y for predicting sepsis.

system, with its defenders—neutrophils and monocytes—releases cytokines and plays an important role in mounting a protective response against the evading pathogen. Hence, the quantitative and qualitative assessment of these parameters with automated hematology analysers can aid in the early diagnosis of sepsis with no additional sample requirement, 24/7 availability, and more objectivity. This was a pilot study to assess the efficacy and performance of newer CPD parameters, namely NEU-X, NEU-Y, MON-X, and MON-Y, in sepsis, as well as to compare their diagnostic performance with traditional biomarkers like Procalcitonin and CRP. The results in the study showed that NEU-X and NEU-Y were significantly increased in the sepsis group as compared to controls. MON-X and MON-Y were studied in only 40 cases; however, MON-Y had a significant difference between cases and controls. Out of all the CPD parameters studied, NEU-Y had the best diagnostic performance, with a sensitivity and specificity of 93.33% and a higher AUC of 0.985 (95% CI: 0.975 to 0.994, SE: 0.00493). The cut-off values used were >339 for NEU-X and >727 for NEU-Y. Our study found a significant weak positive correlation between NEU-X and procalcitonin (ng/mL) with a correlation coefficient of 0.244. A non-significant, very weak positive correlation was seen between NEU-X and C-reactive protein (mg/L) with a correlation coefficient of 0.095. Our results were comparable to those achieved by Zhang et al. [1], who also found a significant difference between the median values of NEU-X, NEU-Y, MON-X, and MON-Y between sepsis patients and controls. A study by Shalini et al. [7] enrolled 100 healthy subjects and 100 sepsis patients. They also found a significant difference ($p<0.001$) in NEU-X, NEU-Y, MON-X, and MON-Y among healthy subjects versus cases. A study by Urrechaga et al. [8] found the cut-off value of NEU-Y, NEU-X, MON-X, and MON-Y as 632.5, 335.7, 118.8, and 121.7, respectively. However, NEU-X had a diagnostic accuracy of only 77.2 compared to NEU-Y (90.9). Procalcitonin, a precursor of calcitonin, is produced by the thyroid. However, when

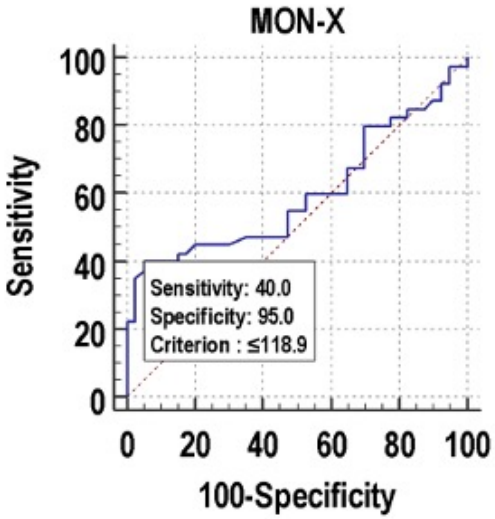

Figure 3: Receiver operating characteristic curve of MON-X for predicting sepsis.

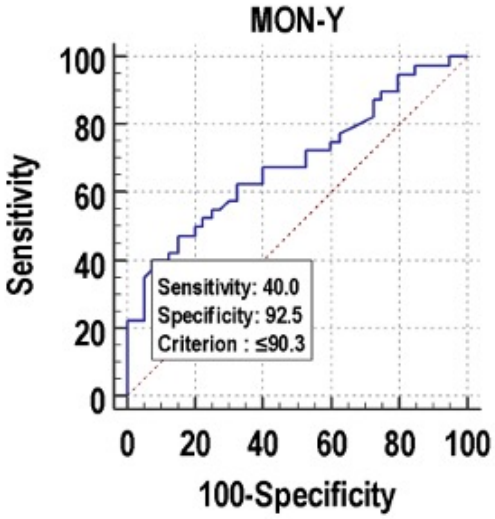

Figure 4: Receiver operating characteristic curve of MON-Y for predicting sepsis.

infected, the body produces procalcitonin from other sources: the liver, pancreas, and kidney [3]. CRP is the most widely used inflammation marker; however, it lacks specificity. It is also elevated in other inflammatory states [9, 10]. Similar to many studies [11, 12], the traditional biomarkers—Procalcitonin and CRP—had the highest diagnostic accuracy in our study.

However, despite their high sensitivity and specificity, the parameters suffer from some limitations. S.PCT levels have a high cost, huge variation with different stages of disease, with the type of pathogenic bacteria, and variation with the detection methods used. Hence, defining a critical value is difficult [13]. Also, it is not an early marker, as its value reaches its peak at about 6–12 hours post-stimulus [14, 15, 16]. Lactate is a marker of hypoperfusion and is elevated in other conditions involving tissue hypoperfusion, like cardiac arrest, trauma, seizure, or increased muscle activity [17]. Hence, it lacks specificity, raising a doubt towards its diagnostic value [18, 19]. The automated CPD parameters are easy, objective, cost-effective, and time-saving data sets which may help in predicting sepsis. The CPD parameters, however, require harmonization among different instruments across clinical laboratories to avoid imprecision errors [20].

The study had certain limitations. The sample size was relatively smaller; also, MON-X and MON-Y were studied only in 40 subjects due to some technical limitations, and hence, the results may not be truly representative. However, the results of the study are significant and promising. A prospective study with a larger sample size may be more contributory.

Conclusion

Sepsis remains a diagnostic dilemma and a challenge to clinicians. The leukocyte CPD parameters—NEU-X, NEU-Y, and MON-Y—represent a promising set of data which can be helpful in the early diagnosis of sepsis. However, larger studies with a greater sample size are required to evaluate their usefulness, performance, and validity in routine clinical practice.

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