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Original Article

Clinical Significance of Delta Neutrophil Index as Diagnostic Indicator for Patients in Sepsis

Nozaif Sarwar, Muhammad Iqbal, Zunera Sajjad, Muhammad Shoaib, Saqib Hussain Korejo, Umer Chaudhary

Department of Haematology, Pakistan Naval Ship Shifa Hospital, Karachi Pakistan

ABSTRACT

Objective: To determine the clinical significance sof Delta Neutrophil Index (DNI) in diagnosing sepsis.
Study Design: Cross-sectional study.
Place and Duration of Study: Department of Pathology, Pakistan Navy Ship, Shifa Hospital, Karachi from Jan to Jun 2020.
Methodology: The study included one hundred and fifty patients with systemic inflammatory response syndrome (SIRS) sadmitted to the medical intensive care unit (ICU). Delta Neutrophil Index (DNI) is the difference in leukocyte sub-fractions recognized by myeloperoxidase reactive cells and nuclear lobularity channels. A specific blood cell analyzer measured DNI, and a cut-off of 2.7% was used to diagnose the sepsis. Positive blood culture was considered the gold standard.
Results: The Delta Neutrophil Index (DNI) showed a sensitivity of 72.2% and a specificity of 97.6%, respectively. The area under the receiver operating characteristics curve (ROC) was determined to be 0.82(0.81–0.94). The threshold efficiency was 2.5 per cent for the highest diagnostic accuracy.
Conclusion: As an early diagnostic measure for evaluating patients with septicemia, the Delta neutrophil index can be a reasonable and effective indicator and should be encouraged in regular screening programs.
Keywords: Delta neutrophil index, Immature granulocyte, Infectious disease, Systemic inflammation, Sepsis.

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INTRODUCTION

Globally, Septicemia accounts for a major proportion of the mortality and socioeconomic burden. Inferring statistics from developed nations, almost 31 million new sepsis patients, with approximately 6 million mortalities annually, are registered worldwide.[1,2] The prevalence and regularity of hospital admissions rise yearly. One of the main causes of referral to intensive care units (ICUs) is sepsis.[3,4] For prompt initiation of antibiotics and elimination of the cause of infection, precise and expeditious evaluation of sepsis is necessary.[5] However, the definition of systemic inflammatory response syndrome (SIRS) must be included in the 2016 Sepsis Guidelines (Sepsis-3).[6]

Several biomarkers have been evaluated to diagnose sepsis. One of the biomarkers is C-reactive protein (CRP), an acute-phase reactant secreted from hepatic sources during inflammation that has been thoroughly researched.[7] While it has strong potential for validity, its characteristic response to infection is that, like in any inflammatory disease, it can rise very fast (occasionally>1000 times).[8] A study performed by Pradhan *et al*., in which it is stated that CRP using 50 mg/L as a cut-off point is highly sensitive (84.3%) but less specific (46.1%) in diagnosing sepsis. Furthermore, the sensitivity and specificity of CRP vary with different cut-off values.[9]

One new inflammatory marker, serum delta neutrophil index (DNI), measures the proportion of circulating immature granulocytes because infectious conditions are known to increase immature granulocytes.[10] There needs to be more published evidence, and less is recognized regarding the medical utility of DNI in diagnosing septicemia. Therefore, this study was conducted to determine the clinical significance of DNI in diagnosing sepsis.

METHODOLOGY

The cross-sectional study was performed at the Pathology Department of PNS Shifa Hospital, Karachi. Institutional Review Board (IRB) approval (ERC/2020/HEM/35) was obtained before conducting the study, and written informed consent from the patient or guardian was taken. The sample size was calculated using the prevalence of sepsis, as 9%.[11]

Inclusion Criteria: Patients admitted to ICU meeting sepsis criteria were included in the study. ACCP/SCCM Consensus Conference Committee 1992 criteria defined the SIRS. SIRS was deemed as positive if at least two of the following conditions were met: a) hyperthermia (>38°C) or hypothermia (<36°C), b) tachypnea (RR 20/min) or PaCO2<32 mmHg, c) tachycardia (heart rate >90 beats/min), d) raised white blood cell count [WBC] >12,000/µL or decreased WBC count as< 4000/µL or >10% of band forms.[12]

Correspondence: Dr Nozaif Sarwar, Department of Haematology, Pakistan Naval Ship Shifa Hospital, Karachi Pakistan
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Exclusion Criteria: Patients aged < 18 years, Glasgow Coma Scale (GCS) <8, pregnancy, pulmonary oedema, myocardial infarction, seizure, trauma, hemorrhagic shock, required immediate surgery or do-not-attempt-resuscitation orders were excluded from the study.

Data regarding age, gender, infection site and bacteria origin was also collected. Blood samples were collected from the venous puncture in the initial 24 hours of ICU registration for evaluating DNI and some other laboratory parameters. Blood samples were collected into an EDTA tube from each individual and were then sent to the pathology department at room temperature. The test was conducted within 1 hour of collecting the blood. Complete blood count cell (CBC) data was collected from an automated haematology analyzer (Abbott cell-Dyn Ruby Hematology analyzer, USA). The DNI was obtained from the following equation: DN (per cent)=(a subfraction of leukocytes assayed by cytochemical reaction in the MPO channel)-(the leukocyte subfraction counted in the nuclear lobularity channel by reflected light beam). An arbitrary cut-off value of >2.7% was used based on previous studies.[12,13] Before antibiotic treatment, a blood culture was performed as a routine practice in ICU work to validate the diagnosis. Blood culture results were determined and finalized in an automated blood culture device after five days of incubation of sample bottles (BacT/Alert 3D; bioMerieux, France).

Statistical Package for Social Sciences (SPSS) ver 21 was used to perform the statistical analyses. Mean± Standard Deviation (SD) was computed for quantitative variables. However, the median values range was calculated when the normality assumption was violated. Frequencies and percentages were computed for qualitative variables. The sensitivity, specificity, positive predictive value and negative predictive value of DNI were calculated using the positive culture as a gold standard for diagnosing sepsis. The sensitivity of DNI was measured as the proportion of the DNI-positive cases in the positive culture. At the same time, the specificity was determined as the proportion of the DNI-negative cases in negative cultures. The positive predictive value and negative predictive value of the DNI were also calculated.

RESULTS

Out of 150 patients, 88 (58.6%) were males, and 62 (41.2%) were females, with an age group ranging between 18 to 85 years. The details of DNI and other laboratory markers of SIRS patients are shown in Table-I. Out of 150 patients with SIRS, 108 (72%) were diagnosed with Sepsis. Therefore, DNI truly diagnosed 78(72%) Sepsis patients. DNI had a sensitivity of 72.2% and specificity of 97.6%, respectively, using a cut-off >2.7%. A comparison between DNI and positive blood culture in diagnosing sepsis is illustrated in Table-II. While diagnostic accuracy parameters for delta Neutrophil Index (DNI) and Blood Culture are shown in the Table-III.

Table-I: Demographics of Patients with Delta Neutrophil Index and other Laboratory Markers (n=150)

Variables	Frequency	Percentage
Age (Mean±SD)	49.03 ± 5.32	
Delta Neutrophil Index parameter		
WBC, 103/uL	11200.00 ± 4700.00	
Absolute neutrophil count,103/uL	8.2 (3.17-11.90)	
DNI values, %	3.06 (1.0-6.0)	
Gender		
Male	88	58.6%
Female	62	41.4%
Primary Site of Infection:		
Lung	58	38.6%
Intra-abdomen	32	21.3%
Genitourinary	38	25.3%
Skin and soft tissue	14	9.3%
Others	8	5.3%
Bacterial Origin, %		
Klebsiella spp	50	19.4%
Acinetobacter baumannii	06	8.9%
Escherichia coli	15	33.4%
Coagulase negative staphylococcus	29	1.2%
Serratia	02	5.1%
Pseudomonas aeruginosa	11	7.4%
Streptococcus pneumonia	02	7.4%
Proteus	02	1.2%
MSSA	13	4.4%
MRSA	08	10.1%
Gram Positive Rods	11	1.2%

MSSA: Methicillin sensitive staphylococcus aureus, MRSA: Methicillin resistant staphylococcus aureus

Table-II: Comparison of Delta Neutrophil Index (DNI) and Blood Culture in Diagnosing Sepsis (n=150)

DNI> 2.7 %	Blood Culture	
	Yes/Positive	No/Negative
Name of Treatment Modality		
Yes/Positive	78(52%)	01(0.66%)
No/Negative	30(20%)	41(27.3%)

Table-III: Diagnostic Accuracy parameters for Delta Neutrophil Index (DNI) and Blood Culture in Diagnosing Sepsis(n=150)

Diagnostic Parameters	Values
Sensitivity=True Positive/(True Positive+False Negative)	72.2%
Specificity=True Negative/(True Negative+FalsePositive)	97.6%
Positive Predictive Value=True Positive/(True Positive+False Positive)	98.7%
Negative Predictive Value= True Negative/(True Negative +False Negative)	57.74%
Diagnostic Accuracy=(True Positive +True Negative)/All Patients	79.3%

The receiver operating characteristic (ROC) curve was plotted, and the area under the curve was found to be 0.82 (0.81–0.94), as presented in the Figure and showed a sensitivity of 73.6% and specificity of 97.9% at a cut-off value of DNI >2.5%.

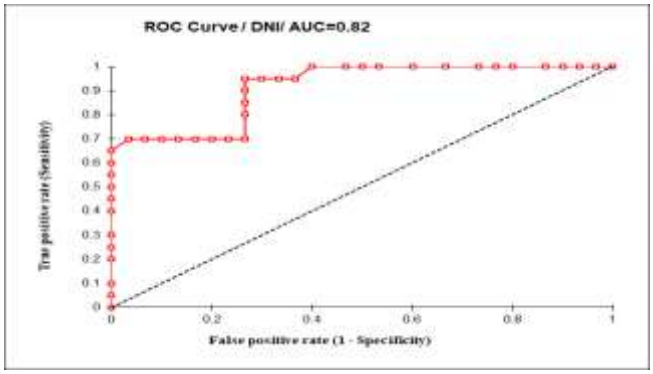

Figure: Receiver Operating Characteristic (ROC) Curve for the Accuracy of Delta Neutrophil Index (DNI) for Diagnosing Sepsis

DISCUSSIONS

Sepsis is among the leading reasons for mortality in severely sick patients. Globally, its incidence is rising each year.[14,15] Early diagnosis and prompt intervention of sepsis patients are important to enhance the recovery outcome. Indicators like CRP, procalcitonin and different cytokines are raised in sepsis. Hence in severe septicemia, these indicators are often utilized as predictive and analytical indicators. More appropriate and accurate biomarkers for diagnosing sepsis need to be identified.[16] The DNI is a recognized indicator of infection.

The CBC count is regularly and commonly tested at a considerably lower expense than other diagnostic indicators in patients with suspected infection or sepsis. Computing and documenting the delta neutrophil index is simple without added expenses. Our findings show that DNI can be used easily to diagnose Sepsis.

From this study, using 2.7 as a cut-off value, DNI was found to be sensitive for sepsis (72.2%) and specific (97.6%), with an AUC of 0.82 (CI, 0.81–0.94). Therefore, the optimal value of DNI to diagnose the sepsis obtained from the ROC curve was 2.5% in our study. Thus our results represent that DNI may conveniently be used for diagnosing sepsis. Comparable to our outcomes, a former study by Seok *et al*. also illustrated that DNI is 73.4% sensitive and 97.7% specific with the area under a curve of 0.88 (CI, 0.83–0.94) in diagnosing sepsis using a cut-off of 2.7%10. Park *et al*. recorded that DNI had 81.3% sensitivity, 91.0% specificity, 88.6% positive predictive value and 84.7% negative predictive value in distinguishing the occurrence and absence of extreme sepsis/septic shock with a >6.5 per cent threshold.[16] Subsequently, the authors recommended that for the percentage of immature granulocytes, high cut-off values may be needed to expect infection or positive blood culture outcomes reliably. However, the authors of that research determined the clinical utility of DNI in assessing the severity of disease in critically ill patients of septicemia. On the contrary, we assessed the experimental effectiveness of DNI in diagnosing septicemia. Different sensitivity, specificity, and ideal threshold limits for DNI may have resulted due to different inclusion criteria.

Other studies done on to determine the DNI reference interval (RI) in healthy dogs and to evaluate its diagnostic and prognostic significance in dogs with sepsis, they concluded that the DNI was significantly higher in dogs with sepsis compared to healthy dogs which also supports our findings.[17,18]

LIMITATIONS OF STUDY

We did not evaluate the comparative advantage of using DNI over other markers, which may have a role in reducing antibiotic exposure of ill patients and serve as a useful complementary comparator for predicting survival outcomes in sepsis patients.

CONCLUSION

This study has confirmed Delta neutrophil index (DNI) as a diagnostic indicator of Sepsis in victims of SIRS. DNI findings can be obtained easily and rapidly due to the latest advancements in testing tools. However, multi-centre prospective studies using different cut-offs are needed to yield more interpretation.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

NS & MI: Data analysis, drafting the manuscript, critical review, approval of the final version to be published.

ZS & MS: Data acquisition, concept, approval of the final version to be published.

HK & UC: Study design, drafting the manuscript, data interpretation, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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