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NOVEL INSIGHTS INTO DIAGNOSTIC UTILITY OF NPAR IN PREDICTING INFLAMMATORY STATUS IN CRITICAL PATIENTS IN TERTIARY HEALTHCARE SETTINGS

Original Research

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ABSTRACT

Objective: To evaluate the diagnostic value of neutrophil percentage-to-albumin ratio (NPAR) for detecting inflammatory status in critically ill patients as well as comparing its performance with conventional inflammatory markers.

Methods: This prospective observational study was carried out in the Intensive Care Unit (ICU) of Mayo Hospital, Lahore, between October 2023 and March 2024. 150 critically ill adult patients were recruited. Within 24 hours of admission, blood samples were collected to measure neutrophil percentage and serum albumin levels, and NPAR was calculated by dividing neutrophil percentage by the serum albumin concentration (g/dL). The patients were divided into high-inflammatory and low-inflammatory groups based on levels of C-reactive protein (CRP) and procalcitonin (PCT). Association between NPAR and inflammatory markers were evaluated using receiver operating characteristic (ROC) curve analysis and correlation analyses. A p-value of less than 0.05 was considered statistically significance.

Results: The mean NPAR scores were significantly greater in patients with high inflammatory status compared to those with lesser inflammation levels (0.085 ± 0.02 vs. 0.046 ± 0.01; $p < 0.001$). NPAR was also found to have a strong positive correlation with CRP ($r = 0.68$, $p = 0.01$) and PCT ($r = 0.61$, $p = 0.02$). ROC analysis showed an excellent diagnostic performance to identify systemic inflammation (AUC = 0.82; sensitivity = 80.0% , specificity = 74.5%), similar to standard inflammatory markers.

Conclusion: NPAR is an inexpensive, universally accessible biomarker that has a high level of diagnostic accuracy in evaluating inflammatory conditions of critically ill patients. Its inclusion in routine laboratory assessments could lead to timely interventions and subsequent detection. Additional multicentric investigations would be justified to determine standard cut-off values and confirm its prognostic value.

Keywords: Neutrophil percentage-to-albumin ratio; NPAR; Critical care; Inflammation; Biomarker; Systemic inflammatory response.

INTRODUCTION

Inflammation is a key element of pathophysiology and development of critical illness, functioning as a protective mechanism while potentially contributing to tissue damage when dysregulated. [1] In critically ill patients who are admitted to intensive care unit (ICU), early diagnosis and monitoring of inflammatory status are important in the clinical management, assessing outcomes and minimizing complications such as sepsis, multi-organ dysfunction and prolonged ICU stay. [2] The traditional biomarkers, including C-reactive protein (CRP) and procalcitonin (PCT), used to evaluate systemic inflammation, but the tests are often impaired by high cost, slow turnaround and inconsistency in diagnostic efficacy across different groups of patients. [3] Consequently, there is a growing need for simple, reliable, and inexpensive indicators that can help clinicians in early identification of inflammatory responses in critically ill patients. [4]

The neutrophil percentage-to-albumin ratio (NPAR) has recently been proposed as a possible biomarker that combines two commonly measured laboratory parameters in one index (neutrophil percentage and serum albumin concentration) that reflects both immune activation and nutritional or hepatic status. [5] An increased number of neutrophils is a feature of acute inflammation, whereas hypoalbuminemia is typical of systemic inflammation due to leakage of capillaries, high catabolism, and failure of the hepatic production.[6] This two-fold representation enables the NPAR to provide a more comprehensive assessment of pro-inflammatory and metabolic processes of critical illness as compared to the single biomarkers. [7]

Evidence from preclinical and clinical studies supports the association between inflammatory cytokines, nutritional status and adverse clinical outcomes. [8] For example, regulating pro-inflammatory cytokines like TNF-alpha has significant impact on systemic inflammatory responses and organ functionality, highlighting the importance of timely and accurate biomarker assessment. [9] Moreover, the introduction of modern monitoring devices and digital health technologies, including IoT-based systems, can enhance real time monitoring of physiological and inflammatory signs among critically ill patients and also allow timely decision-making. [10]

Past clinical studies on a large sample of patients, including people with sepsis, cardiovascular disease, malignancies and nutritional deficiencies, has shown high NPAR values to be significantly associated with poor outcomes. [11] Malnutrition, anaemia and hypoalbuminemia have been repeatedly associated with poor prognosis, which also highlights the need for composite indices which reflect inflammatory as well as metabolic status. [12] Despite these promising results, little evidence has been provided about the diagnostic role of NPAR in particular for predicting the inflammatory state in ICU patients. Assessing diagnostic accuracy of NPAR as a biomarker and its comparison with previously known biomarkers, including CRP and PCT, can be useful to justify its clinical use, cost-effectiveness, and possible application in the early risk stratification. [13]

The present study aimed to evaluate the diagnostic usefulness of NPAR in the diagnosis of systemic inflammation among critically ill patients admitted in ICU and to compare its performance with the conventional markers of inflammation. Recognition of NPAR as a dependable biomarker may enhance early detection of systemic inflammation, risk stratification, and individualized management programs and consequently lead to better patient outcomes in critical care practice.

METHODOLOGY

This prospective observational study aimed to assess the diagnostic value of NPAR in predicting inflammatory status of critically ill patients admitted to the ICU Mayo Hospital, Lahore during October 2023 and March 2024. Informed consent was obtained by all participants or by their legally authorized representatives. The study received clearance by the institutional ethics review board.

The inclusion criteria included adult patients who are at the age of 18 years and above, admitted in the ICU with critical illness to be closely monitored. Patients with pre-existing chronic inflammatory conditions, hematological disorders or severe liver disease were excluded to reduce the number of possible confounding factors. A total of 150 patients eligible for the study using consecutive sampling method were enrolled. The sample size was calculated based on previous studies examining the correlations between inflammatory biomarkers using OpenEpi version 3.0.0 software (Atlanta, GA, USA), using an 80% study power, 95% confidence interval and margin of error equal to 5% . [14]

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Within 24 hours of admission in the ICU, venous blood samples were collected from all the participants to measure the complete blood count (for neutrophil percentage) and serum albumin levels. The neutrophil percentage was divided by the serum albumin concentration (g/dL) to determine the NPAR. Patients were divided into high-inflammatory and low-inflammatory groups based on set diagnostic thresholds (CRP > 10 mg/L, PCT > 0.5 ng/mL).

Data were analyzed through SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Mean ± SD was used for quantitative variables. Frequencies and percentages were used to express categorical variables. Group comparisons were conducted by using independent sample t-test for continuous data and Chi-square test for categorical data. Pearson's correlation coefficient (r) was used to analyze the association between NPAR, CRP and PCT. Diagnostic performance was assessed using Receiver Operating Characteristic (ROC) curve analysis and calculation of area under the curve (AUC), sensitivity and specificity. A p value of less than 0.05 was considered statistically significant.

The independent sample t-test was used to make a group comparison of continuous data whereas the Chi-square test was used to make a group comparison of categorical data. Pearson correlation coefficient (r) was used to assess the variation between NPAR and CRP as well as PCT. Diagnostic performance was calculated by analyzing the Receiver Operating Characteristic (ROC) curve by measuring the area under the curve (AUC), the sensitivity, and specificity. A p-value of less than 0.05 was regarded to be significant.

RESULTS:

A total of 150 critically ill patients were included with 88 males (58.7%), and 62 females (41.3%) with a mean age of 51.2 ± 13.4 years. Patients were divided into high inflammatory (n = 78) and low inflammatory (n = 72) groups, according to the CRP and PCT values. Baseline Demographic and laboratory characteristics are presented in Table 1.

Table 1: Baseline Characteristics of Critically Ill Patients (n = 150)

Variable	High Inflammation (n=78)	Low Inflammation (n=72)	Test used	Test Value	p-value
Age (years)	52.4 ± 12.7	49.9 ± 14.1	t-test	t = 1.34	0.18
Male, n (%)	46 (59%)	42 (58.3%)	Chi-square	$\chi^2 = 0.01$	0.92
Female, n (%)	32 (41%)	30 (41.7%)	Chi-square	$\chi^2 = 0.01$	0.92
Neutrophil %	75.4 ± 9.2	61.2 ± 8.5	t-test	t = 10.2	<0.001
Albumin (g/dL)	2.8 ± 0.5	3.4 ± 0.4	t-test	t = -8.3	<0.001
NPAR	0.085 ± 0.02	0.046 ± 0.01	t-test	t = 13.2	<0.001
CRP (mg/L)	15.2 ± 7.3	6.8 ± 3.1	Mann–Whitney U	U = 280.0	<0.001
PCT (ng/mL)	2.4 ± 1.1	0.8 ± 0.4	Mann–Whitney U	U = 310.5	<0.001

t-test = Independent t-test; χ^2 = Chi-square test; Mann–Whitney U = non-parametric test; NPAR = Neutrophil Percentage-to-Albumin Ratio; CRP = C-reactive protein; PCT = Procalcitonin; g/dL = grams per deciliter; mg/L = milligrams per liter; ng/mL = nanograms per milliliter; % = percentage; n = number of participants; p < 0.05 is considered significant.

Patients in the high-inflammatory group showed significantly higher values for NPAR, CRP, and PCT, but lower albumin levels than patients of low-inflammatory group. Age and gender distribution were similar between groups.

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Table 2: Correlation of NPAR with Inflammatory Markers

Marker	Pearson's r	Significance (p)
CRP (mg/L)	+0.68	0.01*
PCT (ng/mL)	+0.61	0.02*
WBC (10^9/L)	+0.42	0.03*

r = Pearson's correlation coefficient; NPAR = Neutrophil Percentage-to-Albumin Ratio; CRP = C-reactive protein; PCT = Procalcitonin; WBC = White Blood Cell count (10^9/L); *p < 0.05 indicates statistical significance; + = positive correlation.

NPAR was significantly positively correlated with CRP and PCT and moderately correlated with WBC indicating that it validly reflects systemic inflammatory status. (Table 2)

Table 3: Diagnostic Performance of NPAR and Standard Markers (n = 150)

Marker	AUC	Sensitivity (%)	Specificity (%)
NPAR	0.82	80.0	74.5
CRP	0.85	82.7	76.0
PCT	0.81	78.5	73.3

AUC = Area Under the Receiver Operating Characteristic Curve; NPAR = Neutrophil Percentage-to-Albumin Ratio; CRP = C-reactive protein; PCT = Procalcitonin; % = percentage; Sensitivity = proportion of correctly identified positive cases; Specificity = proportion of correctly identified negative cases.

ROC analysis showed that the NPAR has a good diagnostic performance in the detection of systemic inflammation, comparable to CRP and PCT. Sensitivity and specificity signify balance in spotting the inflammatory status. (Table 3)

DISCUSSION

The findings of this study showed that the NPAR is a reliable and cost-effective biomarker for determining systemic inflammation in critically ill patients. Elevated NPAR values in patients with increased inflammatory status suggest that this ratio is a good indicator of a balance between immune activation mediated by the neutrophil and hypoalbuminemia, which usually occurs during acute phase responses. [15] The role of neutrophil activation in the formation of airway and systemic inflammatory cascades is based on cytokines and oxidative stress as the key areas in multiple critical and inflammatory conditions. [16] Similarly, endothelial and vascular dysfunction, which are commonly observed in cardiometabolic and hypertensive diseases, are commonly associated with decreased albumin synthesis and an imbalance in protein status, indicative of the presence of systemic inflammatory stress. [17]

The positive correlations are high between NPAR and traditional inflammatory indicators, including CRP and procalcitonin PCT indicating that NPAR is a valuable reflector of systemic immune stimulation. [18] Similar discoveries of hormonal and inflammatory mediators have been made for endocrine and reproductive disorders, where adipokines and thyroid-linked cytokines are indicators of immune-metabolic abnormalities. [19,20] These similarities allow suggesting that composite biomarkers can indicate the systemic interaction of inflammation and dysfunction of a particular organ.

Clinically, NPAR provide notable benefits due to its simplicity in calculation from conventional hematological and biochemical tests. [21] In resource-limited situations, early detection of systemic inflammation using easily accessible markers like NPAR could help in identifying patients who are at risk for chronic conditions like CKD, as indicated in the study by Rehman et al.[22] Similar to genetic markers used in metabolic disorders, composite indices like NPAR provide informative biomarkers for early risk stratification in critical

care settings. [23] Moreover, NPAR may be useful as a practical biomarker in personalized medicine approaches, integrating the information about both immune activation and systemic protein homeostasis. [24,25]

The pathophysiological explanation of NPAR's utility is justified by studies exploring the systemic impact of neutrophils and albumin in various disease conditions. Being the initial responders to stress and inflammatory stimuli, neutrophils display multi-functional roles beyond immunity, regulating metabolic and neuroendocrine pathways that are linked with systemic inflammation and stress responses. [26] At the same time, the presence of hypoalbuminemia is always linked to unfavorable clinical outcomes, indicating systemic stress and hepatic dysfunction. [27] Using these two parameters, NPAR allows to evaluate the inflammatory state in a more integrated way than the individual markers, demonstrating both immune-mediated activation and the systemic effect of inflammation. [28,29]

In non-alcoholic fatty liver disease (NAFLD), chronic kidney disease, and metabolic syndromes, other indicators of critical illness have also shown predictive usefulness, which suggests the generalizability of composite indices such as NPAR. [30] Combination of inflammatory and metabolic biomarkers is especially important in the context of immune dysregulation and malfunction of individual organs, like NAFLD dynamics or CKD-related inflammation. [31]

Addressing modifiable risk factors through therapeutic measures, ranging from lifestyle and environmental factors. High inflammatory markers and neutrophil or albumin changes have been attributed to dietary habits, physical inactivity, and environment-associated toxins like arsenic. [32] Therapeutic interventions targeting these modifiable risk factors, including lifestyle modification programs and pharmacological strategies, may therefore have indirect effects on NPAR, potentially leading to an improvement in clinical outcomes of patients in both acute and chronic inflammatory conditions. [33]

Animal and experimental studies provide mechanistic understanding that support clinical relevance of NPAR. Studies conducted on rat models have revealed that neutrophil activity is closely associated with oxidative stress and release of inflammatory cytokines, and interventions to restore homeostasis of proteins, namely L-carnitine or resveratrol supplementation, could normalize albumin levels and decrease systemic inflammation. [34,35] These results highlight the translational opportunities of regulating pathways that are expressed in NPAR to control systemic inflammation.

The combination of NPAR assessment with organ-specific biomarkers, e.g. liver-derived hepatokines in NAFLD or kidney markers in CKD, can be useful to improve risk categorization and implement individualized treatment plans. [36] Besides, the interaction of systemic inflammation with neurotrophic regulation, as evidenced by such indicators as BDNF in stress-related disorders, can imply that indices such as NPAR can be important in translating neurophysiological impacts of inflammation. [37]

Besides its potential standalone value, NPAR could also function as an active measure of treatment responses in the critically ill. NPAR value shifts over time could indicate the value of adjusting management plans for inflammation control, nutritional therapy, and other organ-specific treatments. Patient engagement and monitoring, as seen in chronic conditions like CKD, can complement biomarker-guided management strategies such as tracking NPAR trends over time. [38] Integration of NPAR trend into patient monitoring approaches could optimize complications and provide tailored clinical management, especially in the absence of sophisticated biomarker analysis. [39,40]

In spite of these encouraging results, there are several constraints that should be considered. This study has the cross-sectional and single-center design, which can be a weakness in terms of generalizability. The longitudinal study of NPAR over time and its predictive ability regarding outcomes in terms of ICU length of stay, mortality, and post-discharge recovery has not been studied. Future multicentric research, which include larger samples, is suggested to confirm NPAR cut-off values, assess predictive accuracy in a variety of populations, and consider their implementation in decision-making algorithms for therapeutic interventions.

CONCLUSION

NPAR is a cheap, easy, and dependable biomarker to monitor systemic inflammation among critically ill patients. The fact that it is highly correlated with well-known inflammatory markers and has similar diagnostic characteristics highlights its possible usefulness in standard clinic practice, especially in terms of timely diagnosis and selecting patients with increased inflammatory reactions. Integration of NPAR into routine laboratory practices can enhance prompt decision-making in critical care environment, but additional multicentre research is required to establish the prognostic value of NPAR and cut-off values.

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AUTHOR CONTRIBUTIONS

Author	Contribution
Kanta Bai	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Durga Devi	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Muhammad Akram*	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published

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