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Research Article

Association between Multidrug-Resistant Bacterial Infections, Inflammatory Hematological Indices, and Physiological Outcomes: A Predictive Analysis of Neutrophil-to-Lymphocyte Ratio, Platelet Indices, and Physiological Parameters in Bacterial Sepsis

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ABSTRACT

Background: Bacterial sepsis is still one of the most common causes of morbidity and mortality in intensive care units (ICUs) and the increasing emergence of multidrug-resistant (MDR) microorganisms only adds to the problem of prognosis and management. Identification of high risk patients early in the process is important for timely intervention. This study aimed to evaluate the predictive value of the Neutrophil to Lymphocyte Ratio (NLR), the Mean Platelet Volume (MPV), the Platelet Distribution Width (PDW) and the physiological parameters (heart rate, mean arterial pressure, respiratory rate) in the assessment of disease severity and outcome among patients with bacterial sepsis to further investigate the relationship between these variables and the presence of MDR infection.

Methods: The methods employed included a prospective cohort study at Abbottabad District Headquarters (DHQ) Hospital from January 2024 to December 2025. There were 150 adult patients diagnosed with bacterial sepsis who were enrolled. Demographic data and physiological parameters and hematological indices (NLR, MPV and PDW) were noted. To culture the blood for the presence of bacterial pathogens and their susceptibility to antimicrobial agents, blood cultures were ordered. In-hospital mortality and the development of septic shock were the main outcomes.

Resuls: The median age of the cohort was 58 years (IQR: 45-71), and there was a male predominance (58%). Acinetobacter baumannii and Klebsiella pneumoniae were the most prevalent MDR organisms, which were found in 41.3% (n=62) of patients. The NLR, MPV and PDW of patients with MDR infections were significantly higher than those with non-MDR infections (p=0.001, p=0.003 and p=0.01 respectively). A significant correlation was found between physiological parameters like increased heart rate, decreased mean arterial pressure and increased NLR and MPV. On multivariate analysis, an NLR > 12.5 (OR: 3.8, 95% CI: 2.1-6.9) and an MPV > 11.2 fL (OR: 2.9, 95% CI: 1.6-5.2) were identified as independent predictors of 28-day mortality. When added to physiological parameters (qSOFA score), NLR and MPV together showed the best predictive performance for mortality (AUC: 0.86) vs either of them alone.

Conclusion: The inflammatory hematological indices were significantly correlated with MDR infections and poor physiological status in sepsis, especially NLR and MPV. When used with clinical physiological markers, these simple, affordable markers can be used as a powerful tool for risk stratification and early identification of those patients at the highest risk for mortality, particularly in resource limited areas such as DHQ Abbottabad.

Keywords: Sepsis, Multidrug-Resistant Infections, Neutrophils-To-Lymphocytes Ratio, Platelet Indices, Biomarkers.

INTRODUCTION

Sepsis, a life-threatening organ dysfunction resulting from a dysregulated response by the host to infection, is a global health emergency and is a major cause of death in patients in critical condition.(1) Sepsis is a complex condition with a strong inflammatory response mediated by both a pro-inflammatory and anti-inflammatory response that results in endothelial dysfunction, coagulopathy and multi-organ failure.(2) A high prevalence of antimicrobial resistance (AMR), inadequate intensive care bed availability and delayed presentation makes sepsis a greater burden in Pakistan.(3) AMR is among the top ten global public health threats according to the World Health Organization and is especially worrying in situations such as DHQ Abbottabad where antibiotic prescriptions are made on a trial-and-error basis and infections are hard to control.(4) The early recognition of sepsis, and accurate estimation of the clinical course of sepsis, is of paramount importance in improving outcomes in the patient with sepsis.(5) Traditional physiological parameters, such as heart rate (HR), mean arterial pressure (MAP) and respiratory rate (RR) are essential for initial assessment, but may not be sufficiently specific to distinguish infection from sterile inflammatory response or to predict the severity of the host response, such as in scoring systems like the quick Sequential Organ Failure Assessment (qSOFA).(6, 7) In addition, infections with multidrug-resistant (MDR) bacteria bring about a more severe inflammatory response, slower effective treatment and poorer outcome.(8)

Hematological indices have had a surge of interest as proxy measures of systemic inflammation in recent years.(9) A simple blood test called the neutrophil to lymphocyte ratio (NLR) is a measure of the ratio of the innate (neutrophil) immune system to the adaptive (lymphocyte) immune system.(10) A raised NLR indicates a tendency towards a pro-inflammatory status and is related to worsening severity of diseases of infectious and non-infectious origin. Likewise, indices of platelet activation and turnover such as mean platelet volume (MPV) and platelet distribution width (PDW) have been identified as markers.(11) Platelets have emerged as immune effector cells whose activation and consumption play a major role in the immunothrombosis that underlies sepsis, and are central to the microvascular dysfunction and organ failure.(12)

The role of NLR and platelet indices together with the standard physiological parameters has never been thoroughly investigated in the Pakistani population in sepsis. Furthermore, their exclusive association with MDR infections that are prevalent in our setting should be explored further.(13) This study was thus set up to evaluate the correlation of these novel inflammatory hematological parameters (NLR, MPV, PDW) with presence of MDR infections, and physiological parameters prospectively in patients of bacterial sepsis at DHQ Abbottabad. The major intent is to identify the predictive ability of these composite markers for in-hospital mortality and for severe disease outcomes and eventually to develop a clinically applicable simple, effective, and affordable risk stratification tool in resource-limited settings.

MATERIALS AND METHODOLOGY

Study Design and Setting

This study was conducted as a prospective observational cohort study conducted in Department of Internal Medicine from Abbottabad District Headquarters (DHQ) hospital from 01/01/2024 to 31/12/2025 for a period of 24 months. DHQ Abbottabad is a tertiary care hospital with a wide population of patients representing the entire Hazara division and is a representative hospital for studying severe infections in a resource-limited environment.

Study Population

Fifteen hundred adult patients (age ≥ 18 years) were enrolled who satisfied the Sepsis-3 criteria for bacterial sepsis. Patients were recruited within 24 hours of admission to medical intensive care unit (MICU) or high dependency unit (HDU). Excluded were patients who had hematological malignancies, had a history of bone marrow transplantation and were on immunosuppressive therapy (including long-term steroid use), or had a known diagnosis of chronic liver or renal disease associated with renal replacement therapy. Additionally, patients who did not give informed consent were excluded.

Data Collection

A proforma that was structured was used to gather data at the point of enrolment.

Demographic and clinical data included age, sex, co-morbidities (e.g. diabetes mellitus,

hypertension, coronary artery disease), source of infection (e.g. pneumonia, urinary tract infection, intra-abdominal), and in-hospital mortality.

Physiological Parameters: At the time of the diagnosis of sepsis, the following parameters were measured: Heart Rate (HR), Respiratory Rate (RR), and Mean Arterial Pressure (MAP). For each patient a qSOFA (range 0–3) score was computed.

Laboratory Investigations: On admission, blood samples were taken for complete blood count (CBC) using Sysmex XN series analyzer, and absolute counts of neutrophils, lymphocytes and platelets were obtained. From these, the Neutrophil-to-Lymphocyte Ratio (NLR), Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW) were computed.

Microbiological Analysis: BACT/ALERT® blood culture system was used. The microorganisms were isolated by using general biochemical tests and automated Vitek 2 system. An antimicrobial susceptibility testing (AST) was carried out on all isolates using Kirby Bauer disk diffusion and Vitek 2 according to the clinical and laboratory standards institute (CLSI) 2024 guidelines. MDR was considered to be Non-susceptibility to three or more antimicrobial categories acquired.

Outcome Measures

Primary outcome was mortality from any cause in hospital. The primary outcome was septic shock defined by the requirement for vasopressors to maintain a MAP ≥ 65 mm Hg and a serum lactate level > 2 mmol/L after at least 30 minutes of adequate fluid resuscitation, as recommended in the Sepsis-3 guidelines.

Ethical Considerations

The study has received approval from the institutional ethical review committee of DHQ Hospital, Abbottabad (Approval No: DHQ/IRB/2023/42). All patients/legal guardians signed informed consent prior to participation. All data on the patients were anonymized and confidential.

Statistical Analysis

SPSS 26.0 was used for analysis of the data. Continuous variables were checked for normality with the Shapiro-Wilk test and are reported as mean ± standard deviation (SD) or median ± interquartile range (IQR) depending on the normality. Categorical variables were displayed as frequencies and percentages. The Student's t-test or Mann-Whitney U test was used to compare continuous variables between groups (MDR vs. non-MDR, survivors vs. non-survivors). The Chi-square test was used for categorical variables. The optimal cut-off values for NLR, MPV and PDW for predicting mortality were obtained by Receiver Operating Characteristic (ROC) curve analysis. Receiver Operating Characteristic (ROC) curve analysis was used to obtain the optimal cut-off values of NLR, MPV and PDW for predicting mortality. Two logistic regression models were developed: univariate and multivariate logistic regression models to determine independent mortality predictors. A p-value of <0.05 was deemed as statistically significant.

RESULTS

A final analysis was performed on 150 patients. The baseline characteristics and outcomes are summarized in Table 1. The median age was 58 years (IQR 45-71), and 58% (n=87) were male. Lower respiratory tract (n=61, 40.7%) and urinary tract (n=38, 25.3%) and intra-abdominal sepsis (n=24, 16%) were the most common sites of infection. Overall, 32.7% (n=49) of patients died in the hospital.

Table 1: Baseline Demographics, Clinical Characteristics, and Outcomes of the Study Cohort

Parameter	Total (N=150)	Non-MDR (n=88)	MDR (n=62)	p-value*
Age, median (IQR)	58 (45-71)	56 (43-69)	61 (48-74)	0.08
Sex, Male, n (%)	87 (58%)	50 (56.8%)	37 (59.7%)	0.72
Comorbidities, n (%)				
- Diabetes Mellitus	54 (36%)	29 (33%)	25 (40.3%)	0.35
- Hypertension	62 (41.3%)	33 (37.5%)	29 (46.8%)	0.25
- Coronary Artery Disease	28 (18.7%)	15 (17%)	13 (21%)	0.54

Source of Infection, n (%)				
- Respiratory	61 (40.7%)	32 (36.4%)	29 (46.8%)	0.20
- Urinary Tract	38 (25.3%)	26 (29.5%)	12 (19.4%)	0.16
- Intra-abdominal	24 (16%)	16 (18.2%)	8 (12.9%)	0.38
- Skin/Soft Tissue	19 (12.7%)	10 (11.4%)	9 (14.5%)	0.56
- Other/Unknown	8 (5.3%)	4 (4.5%)	4 (6.5%)	0.60
qSOFA Score ≥ 2, n (%)	71 (47.3%)	34 (38.6%)	37 (59.7%)	0.01
In-Hospital Mortality, n (%)	49 (32.7%)	21 (23.9%)	28 (45.2%)	0.006
Septic Shock, n (%)	54 (36%)	24 (27.3%)	30 (48.4%)	0.007

Bold indicates statistical significance ($p<0.05$). *p-value compares MDR vs. Non-MDR groups.

As indicated in Table 1, patients with MDR had significantly higher qSOFA scores (p=0.01), higher incidence of septic shock (p=0.007) and significantly higher mortality (45.2% vs. 23.9%, p=0.006) compared to the non-MDR group.

Table 2: Comparison of Inflammatory Hematological Indices and Physiological Parameters

Parameter	**Total (N=150)**	**Survivors (n=101)**	**Non-Survivors (n=49)**	**p-value***
NLR, median (IQR)	8.4 (5.2-14.1)	6.9 (4.5-10.2)	14.8 (9.8-19.5)	<0.001
MPV (fL), mean ± SD	10.5 ± 1.8	9.9 ± 1.5	11.6 ± 1.9	<0.001
PDW (%), mean ± SD	15.3 ± 2.9	14.5 ± 2.5	16.9 ± 3.1	<0.001
Platelet Count ($x10^9$/L), median (IQR)	138 (89-198)	155 (102-210)	98 (65-145)	<0.001
Heart Rate (beats/min), mean ± SD	112 ± 18	108 ± 15	120 ± 20	0.002
MAP (mmHg), mean ± SD	72 ± 11	75 ± 10	66 ± 12	<0.001
Respiratory Rate (breaths/min), mean ± SD	24 ± 5	23 ± 4	27 ± 6	0.001

Bold indicates statistical significance ($p<0.05$). *p-value compares Survivors vs. Non-Survivors.

Table 2 shows that there is a difference between survivor and non-survivor group in all measured hematological and physiological parameters; the difference is evident and statistically significant. The non-survivors showed significantly higher NLR, MPV and PDW and were found to have fewer platelets. They were also hyperdynamic, with increased heart rates, increased breathing rates and much lower MAPs (which suggested a more severe hemodynamic compromise). The optimum NLR value for prediction of mortality was 12.5 (Sensitivity: 76%, Specificity: 81%), for MPV, it was 11.2 fL (Sensitivity: 72%, Specificity: 74%) and for PDW, it was 16.5% (Sensitivity: 68%, Specificity: 70%).

Table 3: Univariate and Multivariate Logistic Regression Analysis for Predictors of In-Hospital Mortality

Variable	**Univariate OR (95% CI)**	**p-value**	**Multivariate OR (95% CI)**	**p-value**
MDR Infection	2.62 (1.32-5.19)	0.006	2.10 (1.15-4.86)	0.02
qSOFA Score ≥ 2	3.45 (1.71-6.98)	0.001	2.55 (1.08-5.99)	0.03

NLR > 12.5	4.21 (2.34-7.56)	<0.001	3.81 (2.11-6.91)	<0.001
MPV > 11.2 fL	3.12 (1.78-5.48)	<0.001	2.91 (1.61-5.25)	<0.001
PDW > 16.5%	2.45 (1.32-4.54)	0.005	1.78 (0.95-3.33)	0.07
Platelet Count < 100	2.98 (1.52-5.84)	0.001	1.67 (0.89-3.14)	0.11
Age > 65 years	1.95 (0.98-3.88)	0.06	1.45 (0.75-2.82)	0.28

Bold indicates statistical significance ($p<0.05$). CI = Confidence Interval; OR = Odds Ratio. On multivariate analysis (Table 3), after adjusting for confounders, MDR infection (OR: 2.10, $p=0.02$), high qSOFA (≥2) (OR: 2.55, $p=0.03$), elevated NLR >12.5 (OR: 3.81, $p<0.001$), and elevated MPV >11.2 fL (OR: 2.91, $p<0.001$) emerged as independent predictors of in-hospital mortality. The univariate analysis showed that these were significant, with PDW being the only factor found to be independent in the multivariate model, while thrombocytopenia (platelet count <100) was not. The combined model with NLR, MPV and qSOFA showed an excellent discriminatory power (AUC: 0.86, 95% CI: 0.80-0.92) for predicting mortality that outperformed the individual parameters.

DISCUSSION

The present study is a prospective cohort study conducted at DHQ Hospital, Abbottabad which gives important insights into the utility of simple hematological inflammatory markers as predictors of prognosis in sepsis patients caused by bacterial infection. Our findings revealed a strong and independent association between higher NLR, MPV levels and incidence of multidrug resistant (MDR) infections and poor physiological outcomes, which suggest these parameters to be good predictors of in-hospital mortality. The value of our work to the clinical community is that these low-cost lab markers combined with bedside clinical measures (qSOFA) significantly enhance predictive ability in a resource-poor environment. This reinforces the concept of multiple dimensions of risk stratification, beyond the clinical gestalt.

On the contrary, the high prevalence of MDR infections (41.3%) in our cohort is alarming but it is in line with the recent surveillance data from Pakistan.(13) A. baumannii and K. pneumoniae were the most commonly isolated MDR pathogens which are known to cause nosocomial outbreaks and are associated with high mortality.(14) Clinical courses were significantly poorer with patients who infected with MDR organisms in our study presented with higher qSOFA score and septic shock more frequently. This may be due to delayed administration of effective antibiotic, inherent virulence factors of these organisms and the excessive inflammatory response that these organisms brings about.(15) In our setting there is insufficient timely access to effective antibiotics, so clinicians have to use a lot of broad-spectrum empiric medicine, which might not be effective against some MDR pathogens, and cause disease expansion. The role of MDR infection as an independent predictor for mortality (OR: 2.10) highlights the need to increase efforts of antimicrobial stewardship, infection prevention and control,(16) and affordability of rapid diagnostic capacity at DHQ Abbottabad for early guidance of treatment in the early course of MDR infection.

One of the major results of our research is that the NLR is a potent prognostic parameter. We set an optimum cut-off value of 12.5, which matches the value of some big meta-analyses on sepsis.(17) The strength of the NLR is the fact that it is a reflection of the immunological state of the host. Neutrophil-mediated hyper-inflammatory response is the first phase of sepsis which is essential for pathogen clearance.(18) An exaggerated and persistent neutrophilia, however, along with lymphocyte apoptosis and immunosuppression (mirrored by a high NLR) is a hallmark of a dysregulated immune response leading to tissue damage and death. This was the reason that patients with elevated NLR also had higher HR and lower MAP levels, as well as higher risk of mortality. The independence of the other variables and the fact that NLR remained a strong predictor (OR: 3.81) even after accounting for the other variables, suggest that it may be a useful dynamic marker to track therapeutic response and disease progression.(19)

The contribution of platelet indices to the pathogenesis of sepsis has come to be increasingly appreciated. In our study, the MPV and PDW were also significantly elevated in non-survivors and patients with MDR infections. Platelets are not just hemostatic cells, but sentinels of the immune system. Pathogen-associated molecular patterns (PAMPs) and

damage-associated molecular patterns (DAMPs) are bound to platelet Toll-like receptors, which results in activation of the receptors.(20) Activated platelets exude their granules (pro-inflammatory and pro-coagulant mediators) and also create micro-aggregates with neutrophils and monocytes. This process is a core component of immunothrombosis, the process of coagulation and inflammation coalescing together, resulting in microvascular thrombosis and impaired tissue perfusion, and ultimately multi-organ failure A raised MPV suggests that larger, more immature, more hyperreactive platelets are being released from the bone marrow as a result of consumption in the periphery. In the same way, a raised PDW is due to anisocytosis (variation in platelet size) and is another sign of high platelet turnover. (21) These indices were elevated in our MDR group and indicate that exposure to MDR organism's triggers a stronger platelet activation and consumption cycle that leads to worse hemodynamic instability (lower MAP) and mortality.(22)

Hematological indices in combination with physiological parameters were found to be the most powerful tool for the risk assessment. qSOFA is a simple and effective bedside tool, but has a limited sensitivity for early deterioration.(23) We found that after adding the two markers, NLR and MPV, to the clinical picture, the area under the curve (AUC) for prediction of death rose to 0.86. Logically, this synergic effect is not surprising – physiological parameters (HR, MAP) express the cardiovascular reaction to infection, while NLR and MPV give a more profound idea of the inflammatory and thrombotic derangements underlying the instability. If a patient has a high qSOFA score, an NLR >12.5, and an MPV >11.2 fL, this should raise the clinician's level of concern and result in more aggressive resuscitation and early consideration of empiric anti-MDR antibiotics in a busy ED setting such as DHQ. This composite scoring system can be easily accomplished quickly, with minimal extra expense, since both NLR and MPV are derived from a routine CBC. It should be remembered, however, that these are not sepsis-specific indices and may be raised in conditions other than sepsis such as trauma, surgery and myocardial infarction. So, our results apply only to patients with clinically diagnosed sepsis, as we did in our study.

CONCLUSION

This study not only showed that inflammatory hematological indices such as NLR and MPV were significantly high in patients of MDR infections but also these parameters were also seen to be strong and independent predictor of mortality and severity of bacterial sepsis. The elevation of NLR (>12.5) and MPV (>11.2 fL) along with high values of qSOFA have shown significant prognostic accuracy over any single parameter and provides a simple, easy to access and cost-effective approach for early risk stratification and clinical decision making at the resource limited hospital setting in Abbottabad, DHQ Hospital.

Recommendations

Clinical Practice: Measurement of NLR and MPV should be done routinely in complete blood count on all admissions for suspected sepsis. In addition to the qSOFA score, these indicators must be considered as a bedside risk stratification tool to triage patients for early ICU/HDU admission and to initiate broad-spectrum antimicrobial treatment, especially in areas where there is a high prevalence of MDR infections.DHQ Abbottabad must develop its antimicrobial stewardship program (ASP) as the rate of MDR infections and their impact on poor outcomes are high. This involves the establishment of empiric antibiotic guidelines based on local antibiograms, and the establishment of a "fast-track de-escalation of therapy" protocol after a positive culture/sensitivity result.To prevent the spread of these resistant organisms, infection control: Hospital-wide IPC (hand hygiene, environmental cleaning and active surveillance for MDR pathogens) must be emphasized and maintained.

Limitations

The present study was conducted at a single hospital (DHQ Hospital Abbottabad) and may not be representative of other populations or healthcare settings of other demographical backgrounds and resistance pattern.The number of patients in the sample (150) was large enough to achieve the primary objective but may not have been large enough to conduct detailed sub-group analyses (e.g. for specific types of pathogens, site of infection) and the study was designed to examine in-hospital mortality rather than long-term outcomes.The determination of the other hematological parameters (NLR, MPV, PDW) was performed solely at the time of diagnosis of sepsis, and we

did not perform serial evaluations of these parameters to achieve a more dynamic evaluation of these parameters that could give a more fine-grained predictive information, given the course of the illness.

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