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ASSOCIATION BETWEEN RED CELL DISTRIBUTION WIDTH TO ALBUMIN RATIO AND PROGNOSIS IN PATIENTS ADMITTED WITH SEPSIS

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Abstract

Background: *Sepsis is a life-threatening condition caused by a dysregulated host immune response to infection, leading to high global mortality. Early risk stratification remains essential, particularly in resource-limited settings where advanced biomarkers are often unavailable, highlighting the need for simple and cost-effective prognostic tools. This study evaluates the Red Cell Distribution Width-to-Albumin Ratio (RAR) as an easily accessible biomarker for predicting in-hospital mortality in patients with sepsis.*

Materials and Methods: *This prospective observational study enrolled adult patients with sepsis admitted to FGPC Hospital Islamabad to evaluate the association of Red Cell Distribution Width-to-Albumin Ratio (RAR) with disease severity and in-hospital mortality. RAR was calculated from baseline laboratory parameters obtained within 24 hours of admission. Statistical analyses were performed to assess its relationship with clinical severity scores and its predictive value for in-hospital mortality using multivariable logistic regression.*

Results: *A total of 200 adult patients with sepsis were included in the study, with in-hospital mortality of 29.0%. Respiratory tract infection was the most common source of sepsis, and non-survivors demonstrated significantly higher SOFA scores along with elevated RDW and reduced serum albumin levels compared to survivors. The mean Red Cell Distribution Width-to-Albumin Ratio (RAR) was significantly higher in non-survivors (7.04 ± 1.31 vs 4.56 ± 0.92, p<0.001), and on multivariable analysis, higher RAR remained an independent predictor of in-hospital mortality along with SOFA score and age.*

Conclusion: *Elevated Red Cell Distribution Width-to-Albumin Ratio (RAR) is independently associated with increased in-hospital mortality in sepsis. RAR may*

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serve as a simple, cost-effective biomarker for early risk stratification and improved prognostication in septic patients.

INTRODUCTION:

Sepsis is a severe and potentially fatal clinical syndrome that arises from an abnormal and dysregulated host immune response to infection, resulting in acute organ dysfunction.[1] It is associated with profound physiological, biochemical, and pathological abnormalities that may rapidly progress to hemodynamic instability and circulatory failure.[2] Despite notable improvements in intensive care management and antimicrobial therapy, severe sepsis and septic shock continue to be major causes of morbidity and mortality across the globe. Current estimates indicate that sepsis contributes to nearly 20% of all global deaths and remains the leading cause of mortality related to infectious diseases, particularly in cases where diagnosis and initiation of treatment are delayed.[3]

The underlying mechanisms of sepsis are highly complex and involve a dynamic interaction of pro-inflammatory and anti-inflammatory pathways, endocrine disturbances, cellular injury, immune dysregulation, and alterations in systemic hemodynamics.[1] Early recognition of high-risk patients, combined with timely monitoring and therapeutic intervention, plays a crucial role in improving patient outcomes.[4] Consequently, there is an increasing demand for simple, rapid, and cost-effective approaches that can assist clinicians in early risk assessment and prompt management of septic patients.[5]

An essential aspect of sepsis care involves the early identification of individuals who are more likely to develop adverse outcomes. Prompt initiation of evidence-based therapies, particularly early antibiotic administration and aggressive fluid resuscitation, has been associated with improved survival rates.[6] To facilitate early bedside assessment, several clinical scoring systems and track-and-trigger tools have been introduced for evaluating disease severity and organ dysfunction. Among these, the Sequential Organ Failure Assessment (SOFA) score and qSOFA is one of the most widely utilized tools in intensive care settings, as it provides an objective measure of the extent of organ dysfunction and helps predict clinical outcomes in patients with sepsis.[2,6] Similarly, biomarkers such as serum lactate, procalcitonin, interleukin-6, and C-reactive protein have demonstrated prognostic significance, but their routine utilization may be restricted by cost, availability, and limited accessibility in many developing countries.

Red Cell Distribution Width (RDW), a routinely reported parameter in complete blood count analysis, reflects the variability in erythrocyte size and has traditionally been used in the evaluation of anemia. In recent years, elevated RDW has emerged as a potential marker of systemic inflammation, oxidative stress, impaired erythropoiesis, nutritional deficiencies, and chronic physiological stress.[7]

Serum albumin is another widely available laboratory marker that has important prognostic implications in critically ill patients. Albumin plays a vital role in maintaining plasma oncotic pressure, antioxidant defense, endothelial stability, and transport of endogenous and exogenous substances.[8] Hypoalbuminemia is frequently observed in sepsis due to increased vascular permeability, inflammatory-mediated capillary leakage, reduced hepatic synthesis, malnutrition, and accelerated catabolism.[9]

Recently, the Red Cell Distribution Width-to-Albumin Ratio (RAR) has emerged as a novel composite inflammatory biomarker that combines the prognostic significance of both RDW and serum albumin.[10] Furthermore, because RDW and serum albumin are routinely measured in hospitalized patients, RAR represents a simple, inexpensive, and readily accessible biomarker with particular utility in resource-limited healthcare settings.[11]

Local data from Pakistan and other developing countries remain limited to support the prognostic value of RAR in sepsis. The present study aims to determine the association between Red Cell

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Distribution Width-to-Albumin Ratio and prognosis in patients admitted with sepsis. Additionally, the study seeks to evaluate the utility of RAR as an early prognostic marker for predicting in-hospital mortality and adverse clinical outcomes among septic patients in a resource-limited tertiary care hospital.

MATERIALS AND METHODS:

This prospective observational study was conducted in the Department of Medicine, at Federal Government Polyclinic Hospital, (FGPC) Islamabad after approval by the Institutional Ethics Committee. The study was carried out over six months, from January 2024 to June 2024. All data were anonymized to maintain participant confidentiality.

A total of 200 adult patients admitted with sepsis were enrolled using non-probability consecutive sampling. Sepsis was diagnosed according to the Sepsis-3 criteria, defined as suspected or confirmed infection associated with organ dysfunction represented by an increase in Sequential Organ Failure Assessment (SOFA) score of ≥2 points. Patients aged 18 years or older of either gender were included in the study. Patients with hematological malignancies, chronic liver disease, recent blood transfusion within the previous three months, end-stage renal disease on dialysis, active chemotherapy, pregnancy, severe trauma or burns, and those with incomplete clinical records were excluded from the study.

After obtaining informed consent from the patient or attendant, demographic and clinical data including age, gender, comorbidities, and source of infection were recorded on a structured proforma. Baseline laboratory investigations including complete blood count, serum albumin, and other routine biochemical parameters were obtained within the first 24 hours of admission. Red Cell Distribution Width (RDW) values were obtained from automated hematology analyzer reports, while serum albumin levels were measured using standard hospital laboratory techniques. The Red Cell Distribution Width-to-Albumin Ratio (RAR) was calculated using the formula: RDW (%) divided by serum albumin (g/dL). SOFA and qSOFA scores were calculated at admission for assessment of disease severity.

Patients were followed throughout their hospital stay until discharge or death. Data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 23. Quantitative variables were expressed as mean ± standard deviation, whereas categorical variables were presented as frequencies and percentages. Independent sample t-test or Mann–Whitney U test was applied for comparison of continuous variables between groups as appropriate, while Chi-square test was used for categorical variables. Multivariable logistic regression analysis was performed to identify independent predictors of in-hospital mortality. A p-value of <0.05 was considered statistically significant.

RESULTS:

A total of 200 patients diagnosed with sepsis were included in the study. The mean age of the study population was 56.8 ± 15.2 years, with a male predominance (59.0%). Diabetes mellitus and hypertension were present in 41.0% and 38.0% of patients, respectively. The most common source of sepsis was respiratory tract infection (37.0%), followed by urinary tract infection (23.0%) and abdominal infections (19.5%). The overall in-hospital mortality was 29.0% (58/200). The mean RDW of the cohort was 15.9 ± 2.3%, while the mean serum albumin level was 3.1 ± 0.6 g/dL. The mean Red Cell Distribution Width-to-Albumin Ratio (RAR) was 5.28 ± 1.42. Baseline demographic, clinical, and laboratory characteristics are summarized in Table 1.

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Table 1: Baseline characteristics of the study population (n = 200)

VARIABLE	TOTAL (n=200)
Age (years), mean ± SD	56.8 ± 15.2
Male gender, n (%)	118 (59.0)
Diabetes mellitus, n (%)	82 (41.0)
Hypertension, n (%)	76 (38.0)
Chronic kidney disease, n (%)	29 (14.5)
Ischemic heart disease, n (%)	34 (17.0)
Respiratory source of sepsis, n (%)	74 (37.0)
Urinary source of sepsis, n (%)	46 (23.0)
Abdominal source of sepsis, n (%)	39 (19.5)
SOFA score, mean ± SD	7.1 ± 2.9
qSOFA score, mean ± SD	2.1 ± 0.7
Hemoglobin (g/dL), mean ± SD	10.4 ± 2.1
RDW (%), mean ± SD	15.9 ± 2.3
Serum albumin (g/dL), mean ± SD	3.1 ± 0.6
RAR, mean ± SD	5.28 ± 1.42
In-hospital mortality, n (%)	58 (29.0)

Comparison between survivors and non-survivors demonstrated significant differences in several clinical and laboratory parameters. Markers of disease severity were substantially higher in patients who died during hospitalization. Non-survivors had significantly elevated SOFA scores. Regarding hematological and biochemical parameters, non-survivors demonstrated significantly higher RDW values (18.1 ± 2.0% vs 14.9 ± 1.8%, p<0.001) and lower serum albumin levels (2.5 ± 0.4 vs 3.3 ± 0.5 g/dL, p<0.001). Consequently, the mean RAR was markedly elevated in non-survivors compared to survivors (7.04 ± 1.31 vs 4.56 ± 0.92, p<0.001). This is presented in Table 2.

Table 2: Comparison Between Survivors and Non-Survivors

VARIABLE	SURVIVORS (n=142)	NON-SURVIVORS (n=58)	p-VALUE*
Age (years)	54.2 ± 14.8	63.1 ± 14.1	0.001
Male gender, n (%)	81 (57.0)	37 (63.8)	0.381
Diabetes mellitus, n (%)	54 (38.0)	28 (48.3)	0.178
Hypertension, n (%)	50 (35.2)	26 (44.8)	0.213
CKD, n (%)	15 (10.6)	14 (24.1)	0.014
SOFA score	5.9 ± 2.1	10.0 ± 2.6	<0.001

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qSOFA score	1.9 ± 0.6	2.5 ± 0.5	<0.001
Hemoglobin (g/dL)	10.7 ± 2.0	9.6 ± 2.1	0.002
RDW (%)	14.9 ± 1.8	18.1 ± 2.0	<0.001
Serum albumin (g/dL)	3.3 ± 0.5	2.5 ± 0.4	<0.001
RAR	4.56 ± 0.92	7.04 ± 1.31	<0.001

* p ≤ 0.05 was considered statistically significant.

Multivariable logistic regression analysis was performed to identify independent predictors of in-hospital mortality. After adjustment for confounding variables, higher RAR remained an independent predictor of mortality (adjusted odds ratio [AOR]: 2.16, 95% CI: 1.58–2.96, p<0.001). SOFA score was also independently associated with mortality (AOR: 1.41, 95% CI: 1.22–1.63, p<0.001). Increasing age (AOR: 1.03, 95% CI: 1.01–1.06, p=0.012) was additional independent predictor. Chronic kidney disease lost statistical significance after adjustment as shown in Table 3.

Table 3: Multivariable Logistic Regression Analysis for Predictors of In-Hospital Mortality

VARIABLE	Adjusted Odds Ratio (AOR)	95% CI	p-VALUE*
Age	1.03	1.01–1.06	0.012
CKD	1.89	0.94–3.78	0.072
SOFA score	1.41	1.22–1.63	<0.001
RAR	2.16	1.58–2.96	<0.001

* p ≤ 0.05 was considered statistically significant.

DISCUSSION:

The present study evaluated the prognostic significance of Red Cell Distribution Width-to-Albumin Ratio (RAR) among patients admitted with sepsis and demonstrated a strong association between elevated RAR and increased in-hospital mortality. Patients with poor clinical outcomes exhibited significantly higher RDW values, lower serum albumin levels, and markedly elevated RAR compared to survivors. Furthermore, RAR remained an independent predictor of mortality after adjustment for potential confounding variables, suggesting that this readily available biomarker may serve as a valuable tool for early risk stratification in septic patients.

The overall in-hospital mortality observed in our study was 29.0%, which is consistent with previously published international literature on sepsis outcomes. Sakr et al., in the Intensive Care over Nations (ICON) audit, reported ICU and hospital mortality rates of 25.8% and 35.3%, respectively, among patients with sepsis., while

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Rudd et al. estimated that sepsis contributes to approximately 20% of all global deaths annually.[3, 12] The mortality rate observed in our cohort likely reflects the severe nature of sepsis as well as the challenges associated with delayed presentation and limited healthcare resources commonly encountered in developing countries.

The mean age of the study population was 56.8 ± 15.2 years, and non-survivors were significantly older than survivors (p=0.001). Increasing age also remained independently associated with mortality on multivariable logistic regression analysis (p=0.012). Martin et al. demonstrated significantly higher mortality rates among elderly septic patients.[13] Likewise, Mayr et al. reported that advanced age is strongly associated with increased susceptibility to organ dysfunction and adverse outcomes in septic patients.[14] Elderly patients often exhibit altered inflammatory responses and reduced compensatory mechanisms, which may explain the poorer prognosis observed with advancing age.

Chronic kidney disease (CKD), was significantly more prevalent among non-survivors compared to survivors (p=0.014). These findings are supported by study conducted by Sarnak et al. who demonstrated increased susceptibility to severe infections and higher mortality rates among patients with renal dysfunction.[15,] CKD is associated with chronic inflammation, impaired immune function, endothelial dysfunction, and metabolic disturbances, all of which may predispose patients to worse outcomes during sepsis. Nevertheless, CKD lost statistical significance following multivariable adjustment in our study, suggesting that its effect on mortality may be mediated through greater disease severity and organ dysfunction rather than acting as an independent predictor.

Disease severity scores demonstrated strong associations with mortality in our study. Non-survivors had significantly higher SOFA scores (10.0 ± 2.6 vs 5.9 ± 2.1, p<0.001) and qSOFA scores (2.5 ± 0.5 vs 1.9 ± 0.6, p<0.001) compared to survivors. Furthermore, SOFA score remained independently associated with mortality on multivariable analysis (AOR: 1.41, 95% CI: 1.22–1.63, p<0.001). These findings are in agreement with the Sepsis-3 consensus established by Singer et al.[16]

Hemoglobin levels were significantly lower among non-survivors compared to survivors (p=0.002). Similar observations were reported by Piagnerelli et al.[17] Reduced oxygen-carrying capacity may further contribute to tissue hypoxia and organ dysfunction, thereby worsening prognosis during sepsis.

A key finding of the present study was the significant elevation of RDW among non-survivors (18.1 ± 2.0% vs 14.9 ± 1.8%, p<0.001). Braun et al. first demonstrated an association between elevated RDW and increased mortality among hospitalized patients, while Jo et al. later reported that higher RDW independently predicted mortality in patients with severe sepsis and septic shock.[18,19] Similarly, Kim et al. observed that elevated RDW was associated with prolonged hospitalization and increased ICU mortality in septic patients.[20] The mechanisms underlying RDW elevation during sepsis are believed to involve inflammatory cytokine-mediated suppression of erythrocyte maturation, oxidative stress, altered iron metabolism, and impaired red blood cell deformability.

Serum albumin levels were significantly lower among non-survivors in our cohort (p<0.001). Vincent et al. demonstrated that low serum albumin is independently associated with increased mortality, prolonged hospitalization, and greater organ dysfunction in sepsis.[21] During sepsis, decreased albumin levels may result from increased capillary permeability, systemic inflammation, reduced hepatic synthesis, and enhanced catabolism.

The most important finding of our study was the strong association between elevated RAR and mortality in septic patients. Non-survivors demonstrated markedly higher RAR values compared to survivors (7.04 ± 1.31 vs 4.56 ± 0.92, p<0.001). Moreover, RAR remained independently associated with mortality after adjustment for confounding variables (AOR: 2.16, 95% CI: 1.58–2.96, p<0.001). Huang et al. demonstrated that elevated RAR independently

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predicted increased 28-day mortality among critically ill septic patients.[22] Likewise, Shan et al. reported that higher RAR values were significantly associated with increased mortality and greater disease severity in patients with sepsis.[23] By integrating these two parameters, RAR may better represent the overall inflammatory and metabolic status of septic patients, thereby enhancing its prognostic utility.

Despite these findings, certain limitations should be acknowledged. This was a single-center study with a relatively modest sample size, which may limit generalizability of the results. Additionally, only baseline RAR values obtained at admission were evaluated, while serial measurements during hospitalization were not assessed. Larger multicenter studies are required to further validate the prognostic utility of RAR across diverse patient populations and healthcare settings.

CONCLUSION:

This study demonstrated that an elevated Red Cell Distribution Width-to-Albumin Ratio (RAR) is significantly associated with increased in-hospital mortality among patients admitted with sepsis. Furthermore, RAR remained an independent predictor of mortality after adjustment. These findings suggest that RAR may serve as a simple, inexpensive, and readily available prognostic biomarker for early risk stratification in septic patients. Incorporation of RAR into routine clinical assessment may assist clinicians in identifying high-risk patients at an earlier stage, thereby facilitating timely intervention and improved clinical decision-making.

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