Original article

Prognostic Value of Blood Urea Nitrogen to Albumin Ratio in Patients Admitted with Sepsis: A Retrospective Cohort Study

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ABSTRACT

Background: Sepsis has a high mortality rate and an effective and inexpensive clinical indicator is important to determine prognosis in these patients. The objective of the study was to study serum blood urea nitrogen to albumin ratio as a prognostic factor for in-hospital mortality in patients admitted with sepsis.

Subjects and methods: A retrospective cohort study was conducted at Mayo Hospital Lahore. One-hundred and sixty-eight adult patients admitted between March 2022 to March 2023 were included. Data was obtained from medical records. Blood urea nitrogen to albumin ratio was noted along with other co-morbidities and probable infection source. Outcome was noted in the form of discharge or expiry. Univariable and receiver operating characteristics curve analysis was carried out. The results were further verified by multivariate logistic regression analysis to evaluate the independent predictive value of the ratio.

Results: Among 168 participants, majority were males with a mean age of 55 years. One-hundred and seven patients were discharged and 61 expired. All-cause mortality was seen higher in patients with higher blood urea nitrogen to albumin ratio (p-value<0.028). The area under the receiver operative (ROC) curve (AUC) was 0.682 [95% CI=0.600-0.765]. A cut-off value of the BUN to albumin ratio was >9.524 calculated from the ROC curve was found to have a sensitivity of 77.0% and specificity of 44.1%. This AUC for BUN-to-albumin ration was more than BUN or albumin alone.

Conclusion: Blood urea nitrogen to albumin ratio at admission is significantly associated with in-hospital mortality in patients with sepsis.

Keywords:

Sepsis, Albumin, Blood Urea Nitrogen, Prognosis

INTRODUCTION

Sepsis is a serious and potentially lethal medical condition resulting from the systemic exaggerated inflammatory changes in the body, triggered by an infectious etiology.[1] Although, recent years have seen marked improvements in the diagnostic and management guidelines for these patients, it still remains a highly prevalent disorder with high mortality and morbidity rates. The problem is even more cumbersome in countries like pakistan where recent studies have suggested mortality rate of sepsis ranging from 36.6% to 51%.[2] With such high numbers, it has been stressed time and again to identify predictors of morbidity and mortality in these patients. A few scoring systems have been devised like Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE II) scores. But they are practically onerous as they require multiple parameters assessment.[3] Other studied potential predictors of mortality in sepsis are thrombocytopenia, raised C-Reactive Protein (CRP), requirement of invasive ventilatory support, International Normalized Ratio (INR), Interleukin-6 (IL-6), pro-Brain Natriuretic Peptide (pro-BNP), Lactate to Albumin ratio (Lac/Alb) and Lactate Dehydrogenase to Albumin ratio (LDH/Alb).[4,5] However; to date, no single factor or parameter has been accepted as a standard prognostic biomarker in this regard.

In this regard, Blood Urea Nitrogen (BUN) and serum albumin are economical and easily available laboratory tests in ICU and emergency settings. However, both BUN and albumin levels are not reliable as they are affected by other factors often coexisting in patients with sepsis.[5-7] A composite indicator has been recently studied in the form of BUN to Albumin ratio (BAR) to evaluate its prognostic value in patients with sepsis. However, most of the

ARTICLE INFO

Article History

Received: 26.03.2024, | Accepted: 10-01-2025

Conflict of Interest: The authors declared no conflict of interest exists.

Funding: None

Citation: Suhail A, Bangash AF, Suhail M, Masood S, Tahir I, Rathore R. Prognostic value of blood urea nitrogen to albumin ratio in patients admitted with sepsis: A retrospective cohort study. J Fatima Jinnah Med Univ. 2024; 18(4): 153-157.

DOI: https://doi.org/10.37018/WASE8856

recently published studies have been conducted in the developed world and data in developing countries is scarce.[3,7-9] To the best of our knowledge, no such study has been conducted in Pakistan to date. The objective of our study was to assess the association between BAR and in-hospital mortality in patients with sepsis.

SUBJECTS AND METHODS

This was a single-center observational retrospective cohort study conducted at the inpatient department of general medical units of Mayo Hospital Lahore, Pakistan. The study was approved by Institutional Review Board of King Edward Medical University (IRB number: 904/RC/KEMU). The Institutional Review Board waived off consent of study population. Data was collected from March 2022 to March 2023. A total of 168 patients; of both genders above 18 years of age; who had been admitted with a diagnosis of sepsis and fulfilling Systemic Inflammatory Response Syndrome (SIRS) criteria; were included in the study.[1] Patients were excluded if they were pregnant or had a history of malignancy or malabsorption syndrome. Patients who left against medical advice or whose' attendants denied resuscitation; or patients with a hospital stay of less than 8 hours were also not included in the study. Patients whose BUN and albumin levels were not documented at admission were also excluded from the study. Non-purposive convenience sampling method was used for selection. Sample size was calculated using formula $n_o = Z_{1-\frac{\alpha}{2}}^2 \frac{p(1-P)}{d^2}$ where n_o is the sample size. P is the prevalence rate. Level of significance was 95% and 7% was the margin of error. Prevalence rate of sepsis used was 69%.[10]

Data was collected from records of patients admitted with a diagnosis of sepsis; at the time of admission in medical wards. It included demographic details including name, age, gender and address. Presence of any co-morbidities, vital signs including spO2 measurements, oxygen requirement and laboratory values at presentation were also documented. The source of infection in sepsis patients was documented as per physicians' diagnoses in the medical record files supported by investigations like Chest X-rays, blood and urine cultures, cerebrospinal fluid (CSF) examination and cultures, ultrasound abdomen or any other investigation available in the medical record. Analyzed laboratory factors included Hemoglobin (Hb), White Blood Cell count (WBC), Platelets count (Plt), BUN in mg/dL and serum albumin in g/dL. BAR was calculated by dividing the BUN with serum albumin. All the laboratory values were recorded according to the initial admission data. The primary outcome of the patients was noted in the form of either discharged or expired. All findings were noted on a pre-designed proforma.

Data was analyzed using SPSS version 22. Categorical variables were analyzed using Chi-square test while for continuous variables, student t-test and descriptive frequencies were used. Categorical variables were expressed in percentages and continuous variables in median and inter-quartile range. Univariate analysis followed by multivariate logistic regression analysis was performed to identify significant mortality indicators (considering p-value<0.05 as significant). Univariate regression analysis was used to analyze the relationship of patient's sociodemographic and clinical variables with the dependent prognostic variable and further multiple regression analysis was performed to predict the prognostic value of BAR. Receiver operator characteristic (ROC) curve analysis was composed for these 3 variables. ROC Curve was used to further analyze the predictive performance of the dependent variables (BUN, Albumin and BAR). A cut-off value using Youden index for BAR was obtained from the curve. Sensitivity and specificity for this cut-off value as mortality predictors was also derived from the curve.

RESULTS

Out of the 168 patients with sepsis recruited in the study; 61 (36.3%) died and remaining 107 (63.7%) were discharged. Among the enrolled patients, mean age was 55 years (interquartile range 38-66 years) with a male/female ratio of 1.63:1. Respiratory tract infection (RTI) was the commonest source of sepsis leading to admission in these patients (76%). It was followed by urinary tract infection (UTI) (23.8%) and intra-abdominal infections (13.7%). The most common co-morbid conditions seen in septic patients were hypertension (51.8%) followed by Diabetes Mellitus (DM) (29.8%) and Chronic Kidney Disease (CKD) (20.2%).

Univariate regression analysis revealed DM, CKD and Ischemic Heart Disease (IHD) to be significant co-morbidities affecting mortality (p-values of 0.016, 0.024 and 0.002 respectively). Among the patients with a fatal outcome, RTI was the most common cause (50.2%) while the least common percentage was of patients suffering from intrabdominal infection as suspected source of infection (3.3%). However, only the patients with intra-abdominal infections had significantly low probability of in-hospital mortality (p-value=0.003). Similarly, body temperature (p-value < 0.001) and oxygen saturation (p-value < 0.001) at the time of admission were also found to be significantly different among surviving and non-surviving groups. Biochemical and hematological factors significantly associated with survival included WBC count,

Table 1: Univariate analysis of baseline characteristics between discharged and expired patients; and multivariate regression analysis of prognostic variables and factors for in-hospital mortality.

	Univariate analysis				Multivariate analysis		
Baseline characteristic	**Overall (n=168)**	**Discharged (n=107)**	**Expired (n=61)**	**p-value**	**β-value**	**OR (95% CI)**	**p-value**
Age	55 (38–66)	48 (35–65)	60 (55-70)	<0.001*	0.037	1.038 (1.017–1.059)	<0.001*
Gender							
Male	104 (61.9%)	70 (65.4%)	34 (55.7%)	0.214	-0.407	0.666 (0.350–1.267)	0.215
Female	64 (38.1%)	37 (34.6%)	27 (44.3%)				
Co-morbidities							
Hypertension	87 (51.8%)	58 (54.2%)	29 (47.5%)	0.406	-0.267	0.766 (0.408–1.438)	0.406
Diabetes	50 (29.8%)	25 (23.4%)	25 (41.0%)	0.016*	0.823	2.278 (1.155–4.491)	0.017*
Chronic Kidney Disease	34 (20.2%)	16 (15%)	18 (29.5%)	0.024*	0.867	2.381 (1.108–5.116)	0.026*
Chronic Liver Disease	4 (2.4%)	1 (0.9%)	3 (4.9%)	0.103	1.702	5.483 (0.558–53.91)	0.111
Cerebrovascular accident	12 (7.1%)	0 (0%)	5 (8.2%)	0.689	0.243	1.276 (0.387–4.207)	0.691
Ischemic Heart Disease	21 (12.5%)	7 (6.5%)	14 (23%)	0.002*	1.448	4.225 (1.611–11.239)	0.002*
Asthma	6 (3.6%)	4 (3.7%)	2 (3.3%)	0.877	-0.136	0.873 (0.155–4.910)	0.877
COPD	16 (9.5%)	13 (12.1%)	3 (4.9%)	0.125	-0.983	0.374 (0.102-1.369)	0.108
Hepatitis C	8 (4.8%)	5 (4.7%)	3 (4.9%)	0.943	0.054	1.055 (0.243-4.576)	0.943
Suspected Infection Source							
Respiratory tract	76 (45.2%)	45 (42.1%)	31 (50.8%)	0.272	0.353	1.424 (0.757–2.678)	0.273
Urinary tract	40 (23.8%)	24 (22.4%)	16 (26.2%)	0.578	0.207	1.230 (0.593–2.550)	0.580
Intra-abdominal	23 (13.7%)	21 (19.6%)	2 (3.3%)	0.003*	-1.975	0.139 (0.031-0.615)	0.001*
CNS	11 (6.5%)	8 (7.5%)	3 (4.9%)	0.519	-0.446	0.640 (0.163–2.509)	0.511
Others	18 (10.7%)	9 (8.4%)	9 (14.8%)	0.201	0.634	1.885 (0.705–5.038)	0.209
Vital Signs							
SBP (mmHg)	100 [90–130]	100 [90–120]	100 [90-130]	0.309	0.006	1.006 (0.995–1.016)	0.309
DBP (mmHg)	70 [60–80]	70 [60–80]	70 [60–90]	0.192	0.014	1.015 (0.993-1.037)	0.192
Heart rate (/min)	109 [99–114]	106 [98–112]	112 [107–118]	0.152	0.062	1.064 (1.026–1.102)	<0.001
Body Temp. °F	100.50 [100–101]	100 [100–101]	101 [100–102]	<0.001*	0.169	1.184 (0.939–1.492)	0.149
SpO_2 (%)	95 [92–97]	96 [93-97]	92 [91–96]	<0.001*	-0.210	0.810 (0.732–0.897)	<0.001*
Laboratory data							
WBC, /mm^3	16 [13.90–19.68]	15.6 [13.7–18.8]	17.10 [14.45-23.10]	0.040*	0.044	1.045 (1.000–1.091)	0.041*
Hb, g/dl	11.20 [9.20–12.98]	12 [9.8–13]	9.80 [8.85–11.85]	0.006*	-0.177	0.838 (0.736–0.954)	0.006*
Platelets	225.50 [148.25–281.75]	234 [178–320]	178 [108.5–246]	0.040*	-0.003	0.997 (0.995–1.000)	0.033*
Alb, g/dl	2.9 [2.4–3.3]	3.1 [2.6–3.5]	2.7 [2.3–3.1]	0.001*	-0.895	0.409 (0.241–0.693)	<0.001*
Urea, mg/dl	62.50 [46–100]	57 [45–78]	72 [53.5–118.5]	0.055	0.005	1.005 (1.000 –1.011)	0.058
BUN, mg/dl	29.17 [21.47–46.65]	26.6 [21–36.4]	33.6 [24.9–55.28]	0.055	0.011	1.011 (0.999–1.023)	0.059
BAR	9.69 [7.01-17.43]	8.257 [6.56–15.33]	12.76 [9.59–22.61]	0.026*	0.030	1.030 (1.002–1.059)	0.028*

Categorical variables are expressed by number (%) and continuous variables are expressed by median [interquartile range]. COPD=Chronic Obstructive Pulmonary Disease, **Abbreviations:** ILD=Interstitial lung disease; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; WBC=White Blood Cells; Alb=Albumin; BUN = Blood Urea Nitrogen; $Sp0_2$=Oxygen Saturation measured by pulse oximeter; CI=Confidence Interval; OR=Odds Ratio.
A p-value of less than or equal to 0.05 was taken as significant.

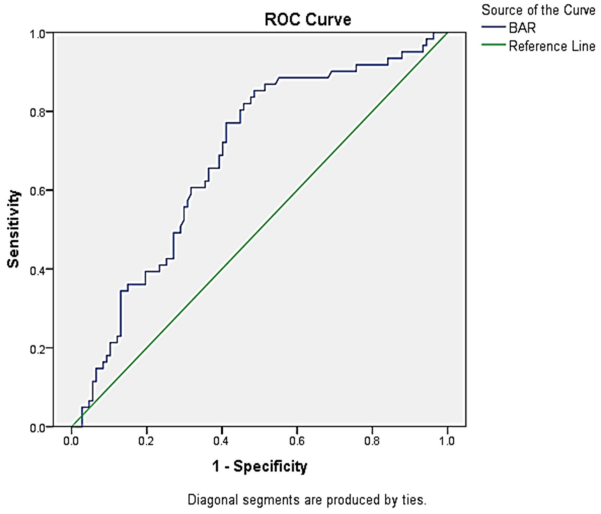

Figure 1: ROC Curve analysis for the predictive performance of BAR (BUN/Albumin ratio) compared to the reference line (purple). BAR (blue) is well above the reference line indicating a reasonable balance between sensitivity and specificity.

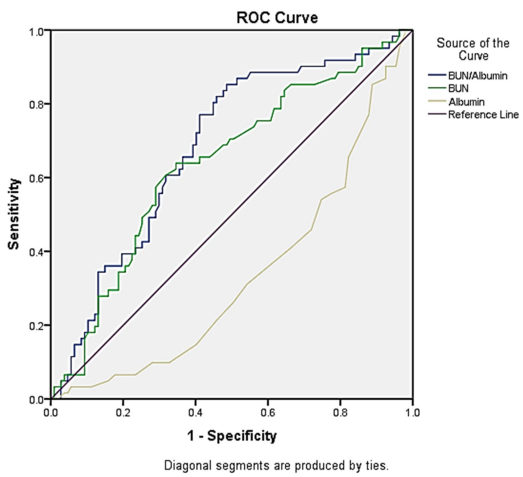

Figure 2: ROC Curve comparing BAR (BUN/Albumin) with BUN (Blood Urea Nitrogen) and Albumin as prognostic factors. BAR (blue) shows highest sensitivity and specificity as compare to BUN (green) and Albumin (yellow). The represented as purple (no predictive value), indicating random guessing.

Table 2: Sensitivity and Specificity of BUN/ALB ratio, BUN and Albumin as a predictor of in-hospital mortality

Variables	Cut off values			AUROC (95% CI)	p-value
	Value	Sensitivity	Specificity		
BUN/Alb	>9.524	77.0%	41.1%	0.682 (0.600-0.765)	<0.001*
BUN	>30	60.7%	31.8%	0.638 (0.551-0.725)	0.003*
Albumin	<2.55	55.7%	77.6%	0.334 (0.250-0.417)	<0.001*

Abbreviations: AUROC=Area Under the Receiver-Operating characteristics Curve; CI=Confidence Interval; BUN=Blood Urea Nitrogen; Alb=Albumin;
A p-value of less than or equal to 0.05 was taken as significant.

Hb, Platelets count, serum albumin and BAR (p-values of 0.040, 0.006, 0.040, 0.001 and 0.028 respectively).

Prognostic variables and factors were further evaluated through multivariate regression analysis, which revealed that with increase in age, there was a rise in in-hospital mortality of patients. Also, the probability of patients with DM, CKD and IHD have increased chances of dying from sepsis and its complications. The OR of BAR was 1.030 (95% confidence interval [CI]:1.002–1.059, p-value=0.0028); indicating BAR as an independent prognostic factor for in-hospital mortality **(Table 1).**

BAR was further analyzed by constructing (ROC). The area under the receiver operator curve (AUROC) for BAR was 0.682 (95% CI: 0.600-0.765, p-value<0.001) **(Figure 1).** Cut-off point of 9.542 calculated by Youden index had a sensitivity of 77% and specificity of 41.1% as mortality predictor **(Table 2).** Area under the receiver operator curves for BUN, albumin and BAR were compared **(Figure 2).** The composite ratio had the highest predictive performance for both specificity and sensitivity as compared to albumin and BUN alone.

DISCUSSION

As kidneys are the one of the major organs affected by septicemia; serum urea is expected to be raised in these patients. However, it has been demonstrated that serum urea levels in septic patients can be influenced by other factors like nutritional status especially protein intake, baseline glomerular filtration, hypovolemia, and upper gastrointestinal hemorrhage.[6,7] Nonetheless, recently conducted studies have confirmed increased BUN levels in septic patients to be associated with worse prognosis.[3] In our study, the mean BUN level in expired patients was higher (33.6 mg/dL) than that in the discharged patients (26.6 mg/dL). However, this difference was not significant (p-value=0.055).

In our study, decreased serum albumin was significantly associated with in-hospital mortality (p-value<0.001). These findings are consistent with previously published studies, as it has been described that early serum albumin supplementation in septic patients may lead to better therapeutic outcomes.[11] The mechanism by which serum albumin levels are decreased in septic patients is multi-fold and complex. One possible explanation is the extravascular leakage of albumin due to the enhanced capillary permeability; which in turn is mediated by inflammatory cytokines released in sepsis.[3] Secondly, patients with septicemia have often reduced albumin synthesis by the liver.[11] However; albumin levels like BUN, may be affected by other factors like malnutrition, baseline hepatic disease and amino acid supplementation frequently given in these patients.[5,12]

The relevance of BAR in predicting outcomes in critically sick patients has been evaluated in recent past. In a study by Zeng Z et al., the relationship between BAR and in-hospital as well as 90-day all-cause mortality was studied in patients with acute exacerbation of COPD. A higher BAR was found in non-survivor group vs. survivor group (p-value<0.001). However, no categorization of patients on the basis of sepsis was made in the study.[13]

Our study results showed BAR to be independently associated with in-hospital mortality in sepsis (OR with 95% CI=1.038, p-value=0.028). These results are in agreement with most of recent studies. In 2022, Han T et al. conducted a similar retrospective cohort study where BAR was identified as an independent biomarker to predict mortality in sepsis. In this study, BAR values were also demonstrated to have a strong correlation with the more commonly used APACHE II and SOFA scores.[3] No such comparison was made in our study.

Yet another study was done in China with a larger sample size admitted in ICU with sepsis. BUN and serum albumin levels were recorded at admission and the patients were divided into high BAR group and low BAR group based on optimal cut-off value of BAR as 7.39. Mortality rate in high BAR group was significantly higher than that in low BAR group (20.38% vs. 11.64%, p-value<0.001).[8]

In addition to BAR at admission, our study also identified some other risk factors that increase the likelihood of a fatal outcome in sepsis patients. These include age, DM, CKD and IHD. Similarly patients with tachycardia and hypoxia at admission were at greater risk of mortality. In a large sample-size retrospective study conducted at Boston USA, almost similar results were seen. However, the overall mortality rate of sepsis reported was much lower (18.9%) as compared to our study.[9]

The authors recognize that our study has some limitations. This was a single-center study with a small

sample size. Selection bias was inevitable due to non-purposive convenience sampling technique and retrospective design of the study. Also, the values of BUN and albumin were measured at a single point in time and fluctuation during the course of illness was not accounted for. Similarly, patients' nutritional status which may impact both BUN and albumin levels, was not documented. Another restraint in our study is that patients with sepsis were studied regardless of the etiological organism.

Although elevated BUN may independently be a feature of CKD, it is not a reliable marker for glomerular filtration, and thus renal function. This is owing to the fact that the small uncharged urea nitrogen molecules are readily filtered from the glomeruli and reabsorbed in the renal tubules by specific transporters.[14] Moreover, studies have demonstrated the prognostic significance of BUN in critically sick patients independent of creatine level.[15] Although we did not exclude CKD cases in our study, we propose that more specific studies be done to determine the significance of BUN in septic patients with CKD, as an independent prognostic biomarker.

Despite these limitations, our study has some positive aspects too. The study was done at Mayo Hospital, Lahore which is one of the busiest medical facilities at the second largest populous city of the country. Secondly, both BUN and serum albumin are cost-effective and easily manageable in resource-limited settings. Thirdly, BAR value documented only at a single instance at admission was assessed, making it lesser complex and system-friendly as an initial investigation.

In conclusion, BAR is independently associated with in-hospitality mortality of patients with sepsis. The authors suggest that more research needs be conducted before BAR could be included in the initial assessment as a prognostic marker in these patients.

Acknowledgements

The authors would like to acknowledge Prof. Dr. Adil Iqbal for the critical appraisal of research proposal.

Author Contributions

AS: Conceptualization, manuscript drafting, data curation, and manuscript editing.
AFB: Conceptualization, manuscript drafting, data curation, and manuscript editing.
MS: Data Analysis, drafting the manuscript, editing and revision of manuscript.
SM: Data analysis, literature search, manuscript writing.
IT: Data collection and analysis.
RR: Literature search, manuscript writing, final review of the draft.

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