ORIGINAL ARTICLE

Validity of Blood Urea Nitrogen to Serum Albumin Ratio as an Independent Biomarker to Predict Severity and Mortality of Community-acquired Pneumonia

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Abstract

Background and objective: Certain serum biomarkers have been reported to predict the severity and mortality of community-acquired pneumonia (CAP). There is a dearth of studies on this subject in the Indian population in patients with CAP. The present prospective observational study was conducted to find the utility of the blood urea nitrogen (BUN)/serum albumin (B/A) ratio as a biomarker to predict the severity and mortality in patients with CAP.

Materials and methods: All 90 patients aged ≥ 18 years of either sex, with a new radiographic infiltrate, were included. Various biochemical parameters such as BUN, serum albumin, and procalcitonin were tested. The serum B/A ratio was calculated. A chest radiograph was obtained. Patients were followed up for the duration of their stay in hospital till discharge or death.

Results: The sensitivity and specificity of the B/A ratio at the optimum cut-off value of 10.66 to predict the severity of CAP was about 79.0%, whereas the sensitivity and specificity of the procalcitonin at the optimum cut-off value of 1.50 ng/dL to predict the severity of CAP were 71.15 and 84.21%, respectively. The sensitivity and specificity of the B/A ratio at the optimum cut-off value of 19.8 to predict the mortality of CAP was about 99.0%, whereas the sensitivity and specificity of the procalcitonin at the optimum cut-off value of 5.55 ng/dL to predict the mortality of CAP was about 92.0%.

Conclusion: The B/A ratio and procalcitonin are simple but independent predictors of mortality and severity of CAP.

Keywords: Blood urea nitrogen, Community-acquired pneumonia, Procalcitonin, Sensitivity, Serum albumin, Specificity.

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Highlights

- The study finds the utility of the blood urea nitrogen (BUN)/serum albumin (B/A) ratio and procalcitonin to predict the severity and mortality in community-acquired pneumonia (CAP) patients.
- We conclude that the B/A ratio and procalcitonin on admission are simple but reliable predictors of severity and mortality from CAP.

Introduction

About 23% of the worldwide pneumonia patients and 36% of those in World Health Organization Southeast Asia are present in India.[1] Between 14 and 30% of cases result in death, and streptococcus pneumoniae has been identified as the most predominant bacterial cause.[1] The annual occurrence of CAP is estimated to be four million in India, with 20% of those cases necessitating hospitalization. In intensive care units (ICUs), the death rate for patients with CAP can reach up to 25%, while in outpatient settings it ranges from 1 to 5%. The hospitalization rates for CAP, including ICUs, have steadily increased in the past few years, particularly among elderly people.[2] Worldwide, CAP is a critical illness that frequently causes indisposition and death.

Since primary care physicians treat the vast majority of CAP patients, it is crucial that they appropriately diagnose and treat CAP patients. The management of CAP includes a special emphasis on prompt recognition of risk for severe illness and timely administration of the proper anti-microbial therapy while acknowledging the possibility of developing anti-microbial resistance (AMR). Individual components of the history or physical examination are unreliable in correctly diagnosing pneumonia, even when the presence of multiple symptoms aids in clinical judgment. Few clinical scales are available to increase the possibility of CAP diagnosis in primary care.[3]

In both primary care settings and hospitals, respiratory tract infections are the most frequent cause of unneeded and inappropriate antibiotic prescriptions, which greatly aids in the emergence of AMR.[4] Numerous clinical decision support systems based on a mix of complaints and simple blood tests are available in situations when a radiograph is not frequently available. When CAP

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is severe, it progresses from a local to a systemic infection, and a variety of sepsis-related consequences necessitate admission to the ICU. Assessment of severity is essential in the management of CAP patients to choose the right site of care, an empirical antibiotic, and adjuvant therapy.[3] Due to the growing number of multidrug-resistant pathogens, patients with life-threatening illnesses are treated with combination antibiotic therapy.[5] Identification of organ dysfunctions and illness severity is essential during the assessment of pneumonia because even a minor dysfunction is linked to an increased death rate of 10%.[6]

There have been reports of specific blood biomarkers indicating the severity of CAP and predicting death.[7] Among these are inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin, blood urea, and serum albumin. Previous research on these biomarkers revealed that non-survivors of CAP had elevated BUN levels and lesser serum albumin levels than survivors.[8–11] It was reported that confusion, uremia, respiratory rate, blood pressure, and age 65 years or older (CURB-65) criteria utilize BUN for predicting mortality in CAP.[12] Blood urea nitrogen and serum albumin are routinely used for evaluation of both hospitalized as well as outpatients, it is conveniently and rapidly available. Hence, BUN divided by serum albumin levels (B/A) can be used as a veritable blood marker to prognosticate patients with CAP. There is a dearth of studies on this subject in the Indian population in patients with CAP. Therefore, we have conducted a prospective observational study to find the utility of the B/A ratio as a biomarker to forecast the severity and death in patients with CAP.

Materials and Methods

This prospective observational study was carried out from February 2023 to January 2024 in a tertiary care hospital in Western India. After clearance from the institutional review board (Letter #ADM/2022-2023/94), written informed consent was taken from all the patients. We included 90 patients of either sex who were at least 18 years old, had a new radiological infiltrate, and displayed at least two clinical manifestations that were compatible (e.g., fever or chills, productive cough, chest pain, shortness of breath, crackles on auscultation).[13] Patients diagnosed with hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP), patients known to be human immunodeficiency virus (HIV) positive, immunosuppressed, having advanced liver or renal disease, and undergoing hemodialysis were excluded.

A new or altered infiltrate as seen on radiography, signs or symptoms specific to the respiratory system (cough, increased sputum production, shortness of breath, chest pain, or abnormal pulmonary examination), and evidence of infection (fever or chills and leukocytosis) comprised the triad that was used to define CAP for this study.[11] A sample size of 90 patients was calculated by a formula, $n = (Z_\alpha)^2 Sp\ (1 - Sp)/L^2\ (1 - Prevalence)$.[14] Ugajin et al.[7] reported a specificity of 97.4% = 0.97, and mortality of 10.9% = 0.11. Hence, the sample size was $(Z_\alpha)^2 Sp(1 - Sp)/L^2(1 - Prevalence) = 2.58 \times 2.58 \times 0.97 \times 0.03/0.05 \times 0.05 \times 0.89 = 87$.

Following selection, the patients or their family members provided a thorough medical history. Preliminary symptoms, the family's socioeconomic background, and a clinical evaluation were all performed. The findings were noted in the pre-tested study proforma. At the time of diagnosis, venous blood samples of patients were collected and sent for the measurement of biochemical tests such as BUN, serum albumin, and procalcitonin.

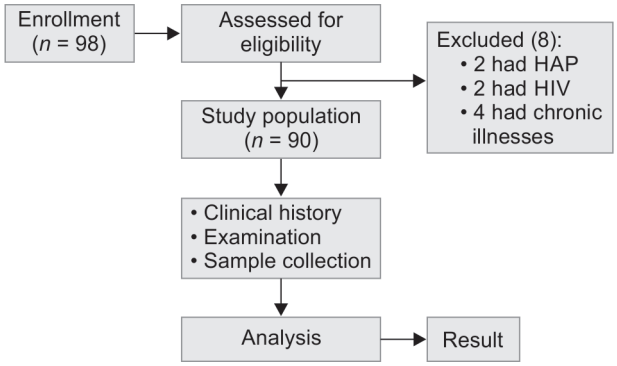

Fig 1: Flow diagram

A chest radiograph was obtained for new infiltrates (opacities) as described in the radiograph reports or directly observed on the film. The serum albumin was measured using the Bromocresol purple method. The serum urea was measured using the Urease L-glutamate dehydrogenase method. Blood urea nitrogen value (in mg/dL) = 0.467*blood urea levels. B/A ratio = BUN (mg/dL)/Serum albumin (gm/dL).

Patients were followed up for the duration of their stay in hospital till discharge or death, whichever was prior. Patients were followed up telephonically in case of discharge before 28 days. In this study, the severity of CAP was defined as per the standards of the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) recommendations.[15] According to the IDSA/ATS guidelines, the patients that met at least 1 of 2 major severity criteria or 3 of 9 minor severity criteria were defined as severe CAP.[16] The primary and secondary objectives were to study the sensitivity and specificity of the B/A ratio and procalcitonin to predict the severity and mortality of CAP, respectively.

Statistical Analysis

The discrete and quantitative variables are shown as *n* (%) and the mean and standard deviation (SD) respectively. The comparison of the discrete and quantitative variables was done using the Chi-squared test/Fisher's exact probability test and the Mann–Whitney *U* test, respectively. The independent factors of the severity of CAP were found by the multivariate logistic regression analysis. To find the cut-off value B/A and procalcitonin in forecasting the occurrence of the severity of CAP, the receiver-operating characteristic (ROC) curve analysis was used. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were determined. The $p < 0.05$ were considered to be statistically significant. The Statistical Package for Social Sciences (SPSS version 24.0, IBM Corporation, USA) for MS Windows was used to analyze the data.

Results

In the present prospective observational study, 98 patients were assessed for eligibility. Eight patients were excluded (2 VAP, 2 HAP, and 4 chronic illnesses). In all 90 patients were included (Fig. 1). The baseline characteristics of the study participants are evident from Table 1. Of 90 patients included in the study, 52 (57.8%) had severe CAP, 35 (38.8%) patients needed ICU admission whereas 10 (11.1%) died in the hospital. There was no noteworthy association of the severity of CAP with age, gender, co-morbidities (hypertension, diabetes mellitus, H/O tuberculosis), and habits such as smoking

and alcohol consumption. There was no noteworthy association of the severity of CAP with signs and symptoms such as fever, cough with expectoration, chest pain, breathlessness, and crepitations.

The severity of CAP was significantly associated with serum albumin < 3.4 gm/dL and procalcitonin > 0.5 ng/dL. There was no statistically significant association between BUN with the severity of CAP. The patients who had a B/A ratio ≥ 10 had more chances of getting severe CAP (Table 2). The median B/A ratio and the median procalcitonin were significantly associated with the severity of CAP, ICU admission, and mortality (Table 3). Multivariate logistic regression analysis showed that the B/A ratio > 12.5 was independently associated with increased odds (>5.25 folds) of having severe CAP. The ROC curve analysis of the B/A ratio for the prediction of the incidence of severity of CAP is depicted in Figure 2, whereas the ROC curve analysis of procalcitonin for the prediction of the incidence of severity of CAP is shown in Figure 3. The optimal cut-off value of B/A ratio and procalcitonin to anticipate the severity of CAP, ICU requirement, and mortality are depicted in Table 4. The sensitivity, specificity, PPV, NPV, and accuracy of B/A ratio and procalcitonin are also shown in Table 4.

Table 1: Demographic and clinical profile of the study participants

Variables	*n (%)*
Age-groups in years	
42–50	11 (12.2)
51–60	24 (26.7)
61–70	25 (27.8)
71–80	19 (21.1)
80–91	11 (12.2)
Mean age in years ± SD	65.2 ± 12.3
Gender	
Males	44 (48.9)
Females	46 (51.1)
Comorbidities	
Diabetes mellitus	30 (33.3)
Hypertension	20 (22.2)
History of tuberculosis	7 (7.7)
Nil	48 (53.3)
Habits	
Smoking	10 (11.1)
Alcohol consumption	25 (27.7)
Nil	64 (71.1)
Symptoms	
Cough with expectoration	77 (83.0)
Chest pain	66 (73.0)
Fever	81 (90.0)
Breathlessness	68 (75.0)
ICU care	35 (38.9)
Mortality	10 (11.1)

SD, standard deviation

Discussion

The current prospective observational research was carried out on 90 patients to find the sensitivity and specificity of the B/A ratio and procalcitonin to forecast the severity and mortality of CAP. The sensitivity and specificity of the B/A ratio at the optimum cut-off value of 10.66 to predict the severity of CAP were 78.84 and 78.95 % respectively, whereas the sensitivity and specificity of the procalcitonin at the optimum cut-off value of 1.50 ng/dL to anticipate the severity of CAP were 71.15 and 84.21%, respectively.

In many conditions, serum albumin seemed to be a trustworthy prognostic indicator. Transport of endogenous substances, scavenging of oxidizing agents, and preservation of a normal colloid osmotic pressure are all made possible by serum albumin, which is

Table 2: Association of severity of CAP with various biochemical parameters

	Severity of CAP			
Parameters (normal values)	*Not severe* n (%)	*Severe* n (%)	*Total* n (%)	*p-value*
Blood urea level (15–40 mg/dL)				
Normal	5 (83.3)	1 (16.7)	6 (100.0)	0.079*
>40 mg/dL	33 (39.3)	51 (60.7)	84 (100.0)	
Serum albumin (3.4–5 gm/dL)				
Normal	17 (68.0)	8 (32.0)	25 (100.0)	0.002**
<3.4 gm/dL	21 (32.3)	44 (66.7)	65 (100.0)	
Serum PCT (<0.5 ng/dL)				
Normal	7 (77.8)	2 (22.2)	9 (100.0)	0.033*
>0.5 ng/dL	31 (38.3)	50 (61.7)	81 (100.0)	
B/A ratio mg/g				
<7.5	15 (100.0)	0 (0.0)	15 (100.0)	0.001*
7.5 < 10	13 (61.9)	8 (38.1)	21 (100.0)	
10.0 < 12.5	6 (40.0)	9 (60.0)	15 (100.0)	
12.5 < 15	4 (28.6)	10 (71.4)	14 (100.0)	
≥15.0	0 (0.0)	25 (100.0)	25 (100.0)	

B/A, blood urea nitrogen/serum albumin levels; CAP, community-acquired pneumonia; PCT, procalcitonin; *Fisher's exact test was used; **Chi-squared test was used

Table 3: Association of mean B/A ratio and procalcitonin with severe disease, ICU requirement and mortality in CAP

	CAP			*ICU required*			*Mortality*		
Variables	*Severe*	*Not severe*	*p-value*	*Yes*	*No*	*p-value*	*Yes*	*No*	*p-value*
Median B/A ratio mg/g	14.78	8.16	0.001	18.13	9.20	0.001	21.21	10.39	0.001
(IQR)	(8.26)	(3.17)		(6.67)	(3.49)		(2.80)	(5.13)	
Median procalcitonin ng/dL	2.20	0.60	0.001	4.50	0.90	0.001	6.90	1.20	0.001
(IQR)	(4.58)	(0.70)		(4.50)	(0.70)		(1.15)	(1.38)	

B/A, blood urea nitrogen/serum albumin levels; CAP, community-acquired pneumonia; ICU, intensive care unit; IQR, inter quartile range. Mann–Whitney *U* test was used

essential for physiological homeostasis. Nicholson et al.[17] in their review on the role of albumin in critical illness delineated the various mechanisms by which there is a decrement in albumin levels in response to systemic inflammatory response. Protein catabolism and low hydration status, both of which are seen in critically ill patients are responsible for elevation in BUN levels. Hence, it can be inferred that the B/A ratio is linked with serious illness.

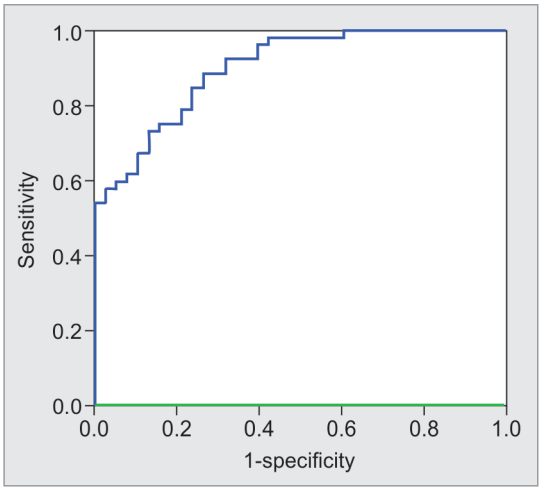

Fig 2: Receiver operating characteristic analyses for B/A ratio as a predictor of incidence of severity of CAP

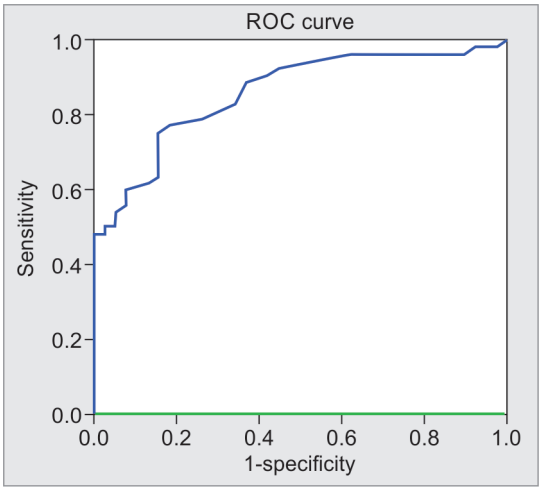

Fig 3: Receiver operating characteristic analyses for procalcitonin as a predictor of severity of CAP

The present research consolidates the accuracy of the B/A ratio in predicting the severity and mortality in CAP over serum albumin and BUN individually. While the pneumonia severity index has been proven more consistent in forecasting CAP-associated deaths, it is painstakingly difficult to calculate, especially in the outpatient department.[18] Therefore, other quicker and simpler markers should be considered in CAP. The use of routine procalcitonin tests in patients is limited by its cost, while both albumin and BUN are available at a comparatively lower price.

A study conducted in Japan by Ugajin et al.[7] reported that the optimal cut-off value of the B/A ratio for anticipating mortality was 12.44 mg/g, with a sensitivity of 57.9%, specificity of 94.5%, a PPV of 57.9%, and an NPV of 94.5%. The study further stated that similarly, the optimal cut-off value for the B/A ratio forecasting the need for intensive care was 9.85 mg/g, with a sensitivity of 62.1%, specificity of 91.8%, a PPV of 60.0%, and an NPV of 92.4%. Jyothi et al.[19] conducted a study in Shivamogga, Karnataka reported that the level of B/A ratio was ≥12.94 for the need for ICU admission. The sensitivity and specificity of the B/A ratio were 91.30 and 65.79% respectively. The study further stated that the diminished albumin level was an independent cause for the requirement of ICU management [odds ratio (OR): 4.152, 95% CI: 0.814–0.971, $p < 0.001$]. Shetty et al.[20] observed that a higher B/A ratio ($p < 0.001$), and higher mortality rate ($p < 0.001$) was found in patients who required ICU admission. The cut-off level of B/A was 5.78 (sensitivity of 89.1% and specificity of 67.7%) in forecasting ICU admission.

Agarwal et al.,[21] using the ROC curve to predict mortality, derived a cut-off value of B/A ratio of 9.84 mg/g for ICU admission and 10.2 mg/g for predicting mortality. They also compared procalcitonin with the B/A ratio for anticipating ICU admission via a multiple logistic regression for risk factors, which showed a *p*-value of 0.0013 for the B/A ratio and 0.048 for procalcitonin.

We also compared the performance of the B/A ratio with procalcitonin in this study for severity, mortality, and the requirement of ICU admission in CAP patients. We found that while procalcitonin proved to be more specific, the B/A ratio was more sensitive for forecasting the severity of the disease and the need for ICU care. Agarwal M et al. observed that procalcitonin and the B/A ratio were found to be independent risk factors for both death and ICU admission. The OR of the B/A ratio in forecasting death and ICU admission was 67.8 (49.2–95.4) and 11.2 (8.4–14), respectively. The study concluded that the B/A ratio may be a reliable indicator of adverse clinical outcomes for CAP patients.[21] Ugajin et al.[22] reported the predictive utility of various cut-off values of B/A as a severity indicator for mortality in CAP. The study stated that the B/A ratio of 6 mg/gm had the highest sensitivity of 92.9%, whereas the B/A ratio of 12 mg/gm had the highest specificity of 92.8%.

Table 4: Diagnostic efficacy of B/A ratio and PCT for the prediction of severity of CAP, ICU required, and mortality

	Severity of CAP		*ICU required*		*Mortality*	
Diagnostic efficacy measures	*B/A ratio (optimal cut-off 10.66) mg/g*	*Procalcitonin (optimal cut-off 1.50) ng/dL*	*B/A ratio (optimal cut-off 12.46) mg/g*	*Procalcitonin (optimal cut-off 2.25) ng/dL*	*B/A ratio (optimal cut-off 19.80) mg/g*	*Procalcitonin (optimal cut-off 5.55) ng/dL*
Sensitivity	78.84	71.15	97.14	71.43	100.00	90.00
Specificity	78.95	84.21	90.91	96.36	97.50	93.75
PPV	83.67	86.05	87.18	92.59	83.33	64.29
NPV	73.17	68.09	98.04	84.13	100.00	98.68
Accuracy	78.89	76.67	93.33	86.67	97.78	93.33

B/A, blood urea nitrogen/serum albumin levels; CAP, community-acquired pneumonia; ICU, intensive care unit

Limitations

The strength of our study is we used both the B/A ratio and procalcitonin to predict the severity and mortality in patients with CAP. There are some limitations in the present research. The number of patients included was small. The research was a single-center prospective observational with a limited study duration. The study cohort was of advanced age with the youngest individual being 42 years; however, age was not associated with severity in CAP. To evaluate the predictive value of serum biomarkers we did not include patients who had chronic kidney and advanced liver diseases. We did not study individuals with structural lung diseases or the vaccination status of individuals which would have a significant influence on the severity of CAP. Hence, polycentric studies with a large sample size are needed to corroborate the results of this research.

Conclusion

The sensitivity and specificity of the B/A ratio at the optimum cut-off value of 10.66 to predict the severity of CAP were 78.84 and 78.95%, respectively, whereas the sensitivity and specificity of the procalcitonin at the optimum cut-off value of 1.50 ng/dL to predict the severity of CAP were 71.15 and 84.21%, respectively. The sensitivity and specificity of the B/A ratio at the optimum cut-off value of 19.80 to predict the mortality of CAP were 100.0 and 97.5%, respectively, whereas the sensitivity and specificity of the procalcitonin at the optimum cut-off value of 5.55 ng/dL to predict the mortality of CAP were 90.0 and 93.75%, respectively. The median B/A ratio and the median procalcitonin were significantly associated with the severity of CAP, ICU admission, and mortality. Multiple logistic regression analysis showed that the B/A ratio >12.5 was independently associated with increased odds of having severe CAP. In conclusion, the B/A ratio and procalcitonin on admission is a simple but reliable predictor of severity and mortality from CAP. A higher B/A ratio on admission predicts a high mortality rate and a high probability of a need for intensive care in patients with CAP.

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