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Role of blood urea nitrogen and serum albumin ratio in predicting severity of community acquired pneumonia (CAP)

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Abstract

Blood urea nitrogen and serum albumin levels are independent risk factors for poor clinical outcome in CAP. However, there is a paucity in the literature on the role of blood urea nitrogen and albumin ratio (B/A) in CAP. This was a prospective observational study in which 112 admitted patients with the diagnosis of CAP underwent routine blood examinations, ABG, procalcitonin and chest X-ray. Univariate analysis among various risk factors, CURB-65 scores, blood parameters including B/A ratios and clinical outcomes were carried out followed by multiple logistic regression. Cox regression was done to look at B/A values and time to mortality. In the logistic regression, age, CURB-65 score, B/A ratio and procalcitonin came out to be independent risk factors for ICU admission and mortality. Odds ratio of B/A in predicting mortality and ICU admission came out to be 67.8(49.2-95.4) and 11.2 (8.4-14), respectively. Cox regression showed B/A values were also found to have a statistically significant relationship with time to mortality (p=0.001). B/A ratio has the potential to become a veritable predictor of poor clinical outcomes in patients with CAP.

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Introduction

Community-acquired pneumonia (CAP) is one of the leading causes of mortality and morbidity in the world. A recent systemic analysis revealed that 2.4 million deaths occur every year among all ages due to lower respiratory tract infections (LRTIs) [1]. In recent years, there has been a steady increase in the hospitalization rates including intensive care units (ICU) due to CAP, especially in the older population [2]. Scoring systems have been developed over the years to ascertain the risk factors associated with worse clinical outcomes in patient with CAP. One such extremely popular and easy to carry out test is CURB-65, advocated by the British Thoracic Society and includes parameters like presence of confusion, serum urea levels, respiratory rate, blood pressure and age of the patient [3]. An issue with this scoring system is the parameter of confusion which is quite difficult to judge, especially in aged patients with dementia and other neurological disorders and as a result the score might vary between clinicians [4,5]. In numerous studies it has been shown that blood urea nitrogen and serum albumin levels are independent risk factors for poor clinical outcome in CAP [3,6,7]. Hence blood urea nitrogen divided by serum albumin levels (B/A) can be used as a veritable blood marker to prognosticate CAP patients. Other than a few studies [8,9], in general, there is a paucity of literature on the role of B/A in CAP, especially from a resource constrained country like India. Hence, we carried out a prospective study aimed to look at the predictive power of B/A ratio and also to compare it with a standard scoring system like CURB -65 in CAP.

Materials and Methods

This was a prospective observational study in which consecutive patients with the diagnosis of CAP and requiring indoor admission from June 2019 to December 2019 were enrolled after due consent. Study was carried out in a tertiary level hospital in the Indian State of Rajasthan and the study was approved by the Institute Ethical Committee. Refusal to consent to take part in the study was the only exclusion criteria. Study period was of 6 months and the patients were followed up for up to 30 days of admission.

Following enrolment after due consent, all patients underwent a thorough clinical examination and clinical history taking. Clinical risk factors that can predict worse clinical outcomes were also tabulated. Comorbidities like respiratory ailments (including COPD, ILD, post tubercular sequelae), cardiac ailments (including ischaemic heart disease, hypertension), chronic kidney disease, diabetes mellitus were noted. Routine blood parameters like CBC, LFT, KFT, serum electrolytes, procalcitonin, sputum pyogenic and fungal culture, Ziehl Neelsen staining, mycobacterial culture and chest X-ray were done for all patients at admission. Routine ABG at time of admission and procalcitonin was done for all patients. If clinically indicated, nasopharyngeal swabs were taken and sent for H1N1 RT-PCR. Other tests like CT scan or bronchoscopy guided respiratory sample collection were carried out as per the decisions of the treating physician. All patients were followed up for a period of 30 days to look for mortality and requirement of ICU admission.

Statistical analysis

Patient parameters were put into Microsoft Excel and then fed into R studio v. 1.2.5019. Univariate analysis among various risk factors and clinical outcomes were carried out followed by multiple logistic regression; p-value <0.05 was taken to be significant. ROC curve was done for CURB-65 scores (Figures 1 and 2) and B/A ratios (Figures 3 and 4) with respect to mortality and ICU admission rates AUC was calculated for both CURB-65 and B/A ratios. Cox regression method was also used to investigate B/A values with the time to mortality. Appropriate Ethical Clearance was taken from the IEC of the respective institute.

Results

A total of 112 patients were enrolled in our study out of whom 40 (35.7%) required ICU care and 22 (19.6%) succumbed to their disease at 30 days following admission. Univariate analysis of the various risk factors predicting ICU admission and mortality were carried out and the results are tabulated in Table 1 and Table 2. Out of the 112 patients, 15 (13.4%) patients had comorbidities, the commonest being cardiac ailments (9.7%), followed by diabetes (8%), COPD (7.1%) and chronic kidney disease (3.6%). On univariate analysis, COPD emerged as a risk factor for mortality on univariate analysis while both COPD and cardiac ailments came out to be risk factors for ICU admission. Out of the eight patients with COPD, sputum culture yielded significant

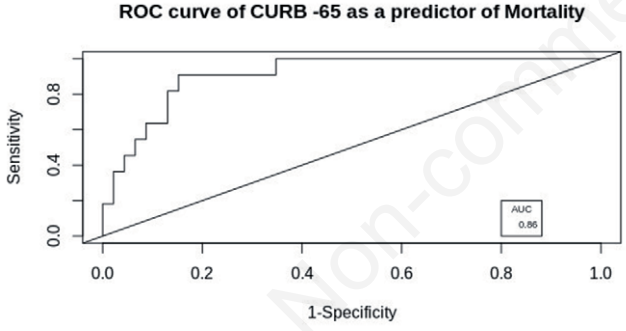

Figure 1. ROC curve of CURB-65 as a predictor of mortality.

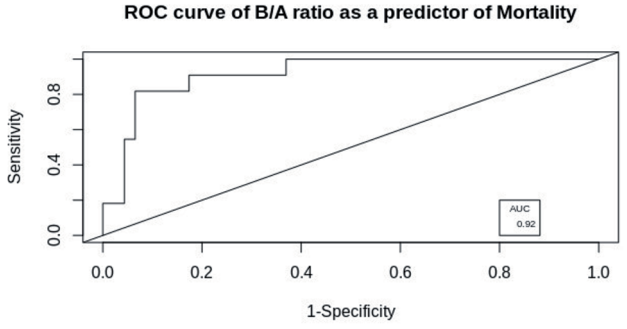

Figure 3. ROC curve of B/A ratio as a predictor of mortality.

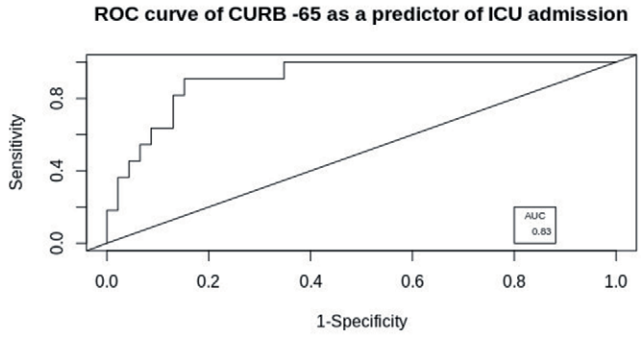

Figure 2. ROC curve of CURB-65 as a predictor of ICU admission.

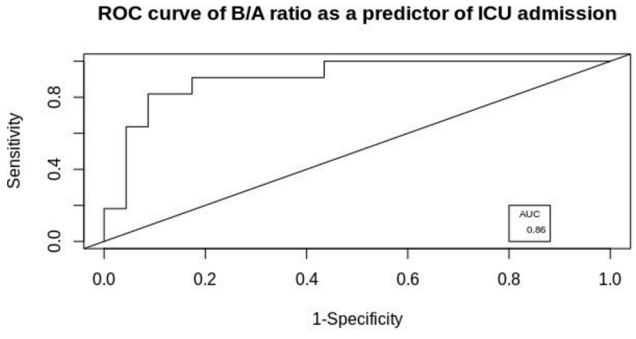

Figure 4. ROC curve of B/A ratio as a predictor of ICU admission.

growth in 5 (62.5%), 3 (60%) out of which had a growth of *Pseudomonas* spp, while the rest 2(40%) had a growth of *Klebsiella* spp.

Multiple logistic regression was then carried out on the risk factors that came out to be statistically significant in the univariate analysis. In the logistic regression age, CURB-65 score, B/A ratio and procalcitonin levels at admission came out to be the independent risk factors that predict risk of ICU admission and mortality within 30 days of admission (Table 3). ROC curves were carried out for B/A and CURB-65 and further AUC were calculated. AUC

Table 1. Risk factors between patients who survived and expired.

Characteristics (mean±SD)	Survived patients (n=90)	Expired patients (n=22)	p-value
Total number (112)	90(80.35%)	22(19.6%)	
Age (years)	52.8±16.5	71.7±8.3	0.0006
Comorbidities present (%)	5.5% (5/90)	45.5%(10/22)	<0.0001
COPD, n (%)	1/5(20%)	7/10(70%)	0.034
ILD, n (%)	0/5	1/10(10%)	0.46
Post tubercular sequelae, n (%)	1/5(20%)	0/10	0.15
Cardiovascular ailments, n (%)	3/5(60%)	8/10(80%)	0.2
Chronic kidney disease, n (%)	1/5(20%)	3/10(30%)	0.34
Diabetes mellitus, n (%)	2/5(40%)	7/10(70%)	0.13
Procalcitonin(ng/ml)	1.5±2.3	13.4±3.4	0.0001
Total Leukocyte counts (x 10^3/ µL)	16.1±10.6	13.1±6.6	0.38
Blood Urea Nitrogen (mg/dl)	18.2±9.5	37.6± 22.9	<0.0001
Albumin (gm/dl)	3.0± 0.5	2.2±0.25	<0.0001
BUN/Albumin ratio	6.3±3.6	16.4±7.7	<0.0001
PaO2 at admission (mmHg)	66.8±11.35	57.8±10.6	0.02
CURB-65 score	1.36±0.79	2.72±0.44	<0.0001

Students' *t*-test for means or proportions used as appropriate.

Table 2. Risk factors between patients requiring and not requiring ICU admission.

Characteristics (mean±SD)	ICU admission required	ICU admission not required	p-value
Total number (112)	40 (35.7%)	72 (64.28%)	
Age (years)	65.1±12.6	50.9±16.75	0.0009
Comorbidities present (%)	25% (10/40)	6.9% (5/72)	0.004
COPD, n (%)	7/10 (70%)	1/5 (20%)	0.034
ILD, n (%)	1/10 (10%)	0/5	0.46
Post tubercular sequelae, n (%)	0/10	1/5 (20%)	0.15
Cardiovascular ailments, n (%)	9/10 (90%)	2/ 5(40%)	0.02
Chronic kidney disease, n (%)	2/10 (20%)	2/5 (40%)	0.21
Diabetes mellitus, n (%)	6/10 (60%)	3/5 (60%)	0.5
Procalcitonin(ng/ml)	8.4±12.47	1.1±1.3	0.001
Total leukocyte counts (x 10^3 µl)	15.97±9.74	15.4±10.16	0.57
Blood urea nitrogen (mg/dl)	29.6±17.62	17.05±9.09	0.0009
Albumin (gm/dl)	2.5±0.5	3.11±0.45	0.0001
BUN/albumin ratio	12.5±6.63	6.09±3.53	<0.0001
PaO2 at admission (mmHg)	61.92±12.5	67.5±10.27	0.078
CURB-65 score	2.45±0.59	1.13±0.62	<0.0001

Students' *t*-test for means and proportions used as applicable.

Table 3. Risk factors and their association with mortality and ICU admission (multiple logistic regression).

Risk factors	p-value (multiple logistic regression)		Odds ratio (95% CI)	
	Mortality	ICU admission	Mortality	ICU admission
Age (years)	0.03	0.01	1.3 (1.08-1.52)	2.1 (1.5-2.7)
BUN/albumin ratio	7*10-6	0.0013	67.8 (49.2-95.4)	11.2 (8.4-14)
Procalcitonin (ng/ml)	0.026	0.048	1.4 (1.10-1.3)	1.02 (1.01-1.03)
CURB-65 score	0.012	0.007	2.08 (1.5-2.56)	8.9 (6.3-11.5)

for B/A for ICU admission and mortality were 0.86 and 0.92, respectively. AUC for CURB-65 score and B/A for ICU admission and mortality were 0.83 and 0.86, respectively. Cut off values of B/A ratio for predicting mortality came out to be 10.2 mg/g with a sensitivity of 0.7, specificity of 0.92, positive predictive value of 82.3% and a negative predictive value of 91.89%. The optimal cut off value of B/A for ICU admission came out to be 9.84 mg/g with sensitivity of 0.68, specificity of 0.88, positive predictive value of 80% and a negative predictive value of 89%. Out of the 112 enrolled patients, bacteriological confirmation was done in 81 (72.32%) patients. Causative pathogens are enumerated in Table 4, the commonest pathogens isolated being *Streptococcus pneumoniae* (25%) and *Pseudomonas aeruginosa* (16.9%). Cox regression was done which revealed that B/A levels were significantly associated with time to mortality within 30 days of admission (p=0.002 with concordance level 0.94).

Discussion

Blood urea nitrogen (BUN) levels are determined by the complex balance between urea production, urea metabolism and urea excretion. The serum level of BUN is determined by many factors which can be renal or non-renal. These factors include glomerular filtration, tubular reabsorption of urea, dietary protein intake, parenteral hyperalimentation therapy, catabolism of endogenous proteins, exogenous glucocorticoid dependent catabolism, volume status and upper gastrointestinal bleeding [10]. Due to this complex interplay of modulatory factors, BUN is generally used as a surrogate marker of systemic illness rather than a specific marker of renal dysfunction. In patients with CAP there is an infective focus which may lead to sepsis and systemic inflammatory response, and this leads to worse clinical outcomes. The high rates of mortality in this subgroup of patients may also be due to the neurohormonal response to arterial underfilling due to systemic vasodilatation following septicaemia. The neurohormonal response includes activation of the renin-angiotensin cycle and production of AVP [11]. High plasma AVP concentrations can result in increased urea reabsorption in the collecting duct, resulting in an increased BUN [12]. Angiotensin and adrenergic stimulation increase proximal tubular sodium and water reabsorption, decreasing distal fluid delivery which increases flow-dependent urea reabsorption [13]. In the study by Farr et al., in which 245 patients with CAP were studied, BUN was shown to be an independent risk factor for mortality (p<0.0001) [14]. In the study by Raz *et al*., in which 320 patients were enrolled, mortality was found in 14.4% patients within 1 month. BUN>30mg/dl was found to be found to be an independent risk factor for mortality in this study too with Odds ratio of 7.8 (3.7-16.4) [15].

Low albumin level has been shown to predict poor outcome in many patients including CAP. The quantity of albumin production is markedly decreased in the acute phase of inflammation. Many of the patients of pneumonia are infected with gram negative bacteria. These bacteria promote the release of cytokines, interleukins and chemokines as mediators of inflammation. These mediators increase the membrane permeability and lead to escape of albumin from the capillary vessels. In the study by Lee et al, in which 424 patients were enrolled, serum albumin emerged as an independent risk factor for 28-day mortality with a hazard ratio of 0.37 (0.19- 0.73) [7].

In recent years, studies have shown B/A ratio to be an important marker to predict short term mortality and morbidity in patients with CAP. In the study by Jyothi *et al*., the optimal level of BUN/Albumin to establish the necessity for ICU management was ≥12.94 mg/g. The sensitivity 91.30% and specificity being 65.79% [16]. In the study by Ugajin *et al*. [8], B/A ratio had an AUC of 0.83 (95% CI 0.73–0.94) for mortality and an AUC of 0.86 (95% CI 0.79–0.94) for ICU admission. The optimal cut-off value of the B/A ratio for predicting mortality was 12.44 mg/g and ICU admission was 9.85 mg/g. In comparison, the AUC of CURB -65 with respect to ICU admission was 0.81 (95% CI 0.71–0.91) and for mortality was 0.84 (95% CI 0.77–0.91) [8]. In our study too, B/A outperformed CURB 65 score as a better differentiator for predicting ICU admission (0.86 *vs* 0.83) and mortality (0.92 *vs* 0.86).

Patients with structural lung diseases, especially COPD are a higher risk of developing CAP and suffering worse clinical outcomes, including need for ICU admission and 30-day mortality [17,18]. In our study too, it was found to be a significant risk factor for ICU admission and mortality. This significance disappeared on multiple logistic regression, maybe due to the fact that only eight of the 112 enrolled patients had a spirometric diagnosis of COPD at time of admission. Prevalence of COPD in India is vastly underestimated, determined to be 4.2%, in comparison to USA where the prevalence is around 10-21% [19]. This is mostly due to lack of information and less availability of diagnostic centres. Also, we believe that along with presence of COPD, the severity of obstruction would be a strong risk factor in predicting clinical outcomes which was not included in our study.

B/A ratio has the benefit of being easily calculated and not dependent on operator capacity to correctly gauge the level of confusion in a patient as required in the CURB-65 score. We believe that instead of cumbersome scoring systems like PSI (Pneumonia Severity Index) or APACHE-II, B/A ratio has the potential to become an important surrogate marker for complications in patients with CAP. It will help the treating clinician to streamline patients who are at a higher risk and start intensive care at an earlier stage of the disease process. This would lead to better utilisation of resources and better clinical outcomes in patients.

We acknowledge a few limitations of our study. Our sample size was small, consisting of only 112 patients. Hence we believe to correctly calculate the optimal cut off value of B/A ratio, larger studies should be conducted. In patients with renal diseases, the values of B/A could be falsely elevated. However, role of B/A ratio as a prognosticator in patients with pre-existing renal disease could not be properly studied as patients with CKD formed a small proportion of the patients. The role of B/A ratio at the time of admission was used in our study but we believe that serial B/A ratios over a period would better reflect the trend of the disease. Further studies to look at persistently raised B/A ratios in predicting mortality and morbidity would better help us to understand its role in CAP.

Table 4. Causative pathogens.

Microorganisms	n (%)
Streptococcus pneumoniae	23 (20.5%)
Pseudomonas aeruginosa	19 (16.9%)
Klebsiella pneumoniae	10 (13.4%)
Staphylococcus aureus	9 (8.03%)
Haemophilus influenzae	5 (4.4%)
Escherichia coli	4 (3.6%)
Moraxella catarrhalis	1 (0.9%)
H1N1	10 (12.3%)

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