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ROLE OF UREA TO ALBUMIN RATIO AS A PREDICTOR OF IN - HOSPITAL MORTALITY IN SEVERE PNEUMONIA PATIENTS

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ABSTRACT

Background: Urea to albumin ratio (UAR), as a marker of renal dysfunction along with systemic inflammation and nutrition has been suggested as a potential prognostic marker in critically ill patients.

Objective: To determine the role of urea-to-albumin ratio as a predictor of in-hospital mortality among patients with severe pneumonia admitted to intensive care units.

Methods: Prospective cohort study was carried out at the intensive care units of Jinnah Postgraduate Medical Centre, Karachi over a period of six months. Consecutive sampling method was used to recruit a total of 80 adult patients with severe pneumonia, who were divided into high UAR (>0.2555) and low UAR (<0.2555) groups according to the UAR value. Demographic data, clinical data and CURB-65, APACHE II and SOFA scores were collected. Relative risk analysis, receiver operating characteristic (ROC) curve analysis, and multivariable Cox regression were used to evaluate the association of UAR with in-hospital mortality.

Results: In 24 patients (30.0%) death occurred within the hospital. The high UAR group had significantly higher mortality rate than the low UAR group (45.0% vs. 15.0%, respectively, p=0.004). A higher UAR was linked to higher mortality risk (RR=3.00, 95% CI: 1.38–6.51). The ROC analysis showed that the UAR had good predictive ability for in-hospital death (AUC=0.78; 95% CI: 0.67–0.89) when the cut-off value was 0.2555, with a sensitivity of 75.0% and a specificity of 70.0%.

Conclusion: Increased urea/albumin ratio is a predictor of the in-hospital mortality of severe pneumonia independent of other factors.

KEYWORDS: Albumin, Biomarkers, Mortality, Pneumonia, Urea Nitrogen.

INTRODUCTION

Severe pneumonia continues to be a great contributor to hospitalization, intensive care unit (ICU) admission and in-hospital death, especially in older age and people with multiple comorbidities. The clinical course may be acute due to secondary respiratory failure, systemic inflammatory response, septicemia and multiorgan dysfunction. It is therefore crucial to identify patients who are at high risk of being at risk of death early, so that they can be appropriately trialled, monitored closely and treatment escalated swiftly. There are a number of clinical severity scores and laboratory markers available but many of these are complex and not necessarily easily available in resource-limited settings. This ratio of the urea/albumin (UAR) has been identified as a simple and cheap biomarker that integrates markers of metabolic stress, renal hypoperfusion, systemic inflammation and nutrition. Tian et al. showed that UAR was strongly related to in-hospital mortality among severe pneumonia patients, indicating that it could be applied as an early risk stratification tool [1].

During severe infection, a rise in serum urea can occur due to dehydration, decreased renal blood flow, increased protein breakdown, gastrointestinal bleeding or renal failure. However, serum albumin is often low in conditions that involve systemic inflammation, capillary leakage, decreased hepatic production, malnutrition, and increased metabolism. Thus, the ratio may be a better prognostic than either parameter separately. In the patients with aspiration pneumonia, the blood urea nitrogen to serum albumin ratio was independently associated with death

and was also useful as an easily available indicator of prognosis [2]. Likewise, the ratio was shown to be helpful in the treatment of non-HIV patients with pneumocystis pneumonia along with the A-DROP severity score [3].
The urea-to-albumin ratio is also raised in CAP severity and may be useful in determining those needing intensive management [4] of the disease. It also has been reported as a predictor of mortality among patients with pneumonia treated with glucocorticoid [5]. The ability of BUN/ALB to predict pneumonia was also confirmed by a meta-analysis in a wide variety of clinical settings and patient cohorts [6].
This ratio has also been widely studied as a predictor in viral pneumonia. A higher BUN: ALB was associated with a higher mortality rate for moderate to severe COVID-19 pneumonia patients in the intensive care unit [7]. Emergency department data also revealed that the ratio could help to predict early death of COVID-19 patients [8]. Furthermore, high levels were linked to the severity of the disease and to 30-day mortality, which gave some additional evidence for its association with the bad short-term prognosis [9]. Further evidence has shown that the ratio was able to identify COVID-19 patients that had an increased risk of death and could be used in conjunction with the usual clinical and laboratory evaluation [10].
Although several studies have been published, some local hospital populations do not have sufficient data to evaluate the prognostic value of UAR in severe pneumonia. Knowing its association with in-hospital mortality may help to offer a fast, objective and cost-effective way to identify those who are at high risk. So, the present study is aimed at assessing the predictive role of the ratio of urea/albumin in in-hospital mortality of severe pneumonia patients.

METHODS

The prospective cohort study was conducted in Jinnah Postgraduate Medical Centre (JPMC), Karachi, ICUs. This study was conducted for 6 months. A non-probability consecutive sampling technique was used to enroll adult patients (aged 18–65 years) admitted to the ICU with severe pneumonia. Severe pneumonia was characterized as pneumonia that needed to be treated in an intensive care unit (ICU) with severe respiratory failure (SRF) and/or a PaO_2/FiO_2 ratio ≤200. All participants or legally acceptable representatives signed informed consent forms prior to being placed in the study. The anonymity of the data collected was ensured by anonymization.
After admission to the ICU, patients were classified into 2 groups, based on urea-to-albumin ratio (UAR) values obtained within the first 24 hours. The UAR was determined as the ratio of serum urea nitrogen (mg/dl) to serum albumin (g/dl). Patients with UAR >0.2555 were put into the high UAR (exposed) group, and those with UAR <0.2555 were assigned to the low UAR (unexposed) group. Patients with chronic kidney disease, end-stage renal disease, chronic liver disease or cirrhosis, and those who had abnormal urea or albumin levels such as severe dehydration or continued parenteral feeding were excluded from the study.There were patients who were excluded from the study, such as those with chronic kidney disease, end-stage renal disease, chronic liver disease/cirrhosis, and those with abnormal urea and/or albumin levels including those patients who were severely dehydrated or receiving ongoing parenteral feeding.
Demographic and Clinical parameters such as age, sex, BMI, smoking, diabetes mellitus, and Hypertension was noted from medical records. The severity of the clinical condition on admission was rated by employing available clinical scores. The CURB-65 score was derived on the basis of confusion, blood urea level, respiratory rate, blood pressure and age >65 years with a score of 0–5. Acute Physiology and Chronic Health Evaluation II (APACHE II) score was also determined to measure the severity of disease and risk of mortality in ICUs.

Blood samples were drawn in the first 24 hours after admission to the ICU by trained healthcare workers under aseptically using the sterile technique. Blood urea nitrogen (BUN), and albumin were determined in the serum by standard laboratory methods. The two enzymes were used to determine serum urea and the bromocresol green method was used to measure serum albumin. All the results obtained were accurate and reliable which was followed by laboratory quality control procedures. The main outcome measured was in-hospital death (defined as death during the same hospital stay as the admission for severe pneumonia). Secondary outcomes were 30-day mortality (medical records or telephone follow-up after discharge). All patients were followed during their hospitalisation and complications such as secondary infections, sepsis, respiratory failure, renal failure and multiorgan failure were recorded.
The data were entered in double entry system with regular checks to reduce error in data entry. Restriction in selection of participants and multivariable regression analysis were used to control for potential confounding factors. Standardization of inclusion criteria, objective outcome assessment, and standardization of procedures for data collection minimized bias.
Data were analysed statistically with SPSS version 30 or R software. Continuous data such as age, BMI, BUN, serum albumin, UAR, CURB-65, APACHE II and SOFA were presented as a mean ± SD or median (interquartile range) depending on data distribution. Categorical variables such as gender, presence of comorbidities, smoking status, requirement for oxygen or mechanical ventilation, characteristics of admission to the intensive care unit and death outcomes were described using frequencies and percentages. High and low UAR groups were compared

to determine the association between UAR and in-hospital mortality. Two-by-two contingency tables were used to compute relative risk (RR) and the chi-square test was used for categorical comparisons.
Receiver operating characteristic (ROC) curve analysis was used to assess the predictive performance of the UAR, CURB-65 scores and APACHE II scores for in-hospital mortality. The area under the curve (AUC) was computed and compared between the predictive markers. Youden's index was used to determine the best UAR cutoff value and diagnostic performance was evaluated by sensitivity, specificity, PPV, and NPV. Survival difference between high and low UAR groups were expressed using Kaplan–Meier survival curves and a log-rank test was used to determine statistical significance. To assess whether there is independent relationship between UAR and in-hospital mortality, Cox proportional hazards regression analysis was conducted adjusting for possible confounders such as age, gender, comorbidities, CURB-65, APACHE II, and SOFA scores. Hazard ratios (HR) and 95% confidence intervals (CI) were provided. All statistical tests were performed for both tails of the curve, and a p-value of < 0.05 was regarded as statistically significant.

RESULTS

In total, 80 patients with severe pneumonia were enrolled in the study who were admitted to intensive care units. Patients were randomly allocated in two groups based on UAR value, the high UAR group (>0.2555) and the low UAR group (<0.2555) with 40 patients in each group. The average age of the study population was 56.8 ± 12.4 years and 51 (63.8%) of the patients were male. The mean UAR was significantly higher in the high UAR group compared with the low UAR group (0.39±0.10 vs. 0.18±0.05, p<0.001).
Data on demographic characteristics of the study subjects are shown in **Table 1**. There were no differences between the two groups in terms of age, sex, diabetes mellitus, hypertension and smoking (p>0.05). Patients with high UAR, however, had significantly higher CURB-65, APACHE II and SOFA scores than those in the low UAR group (p<0.05).
The clinical outcomes according to UAR categories are shown in **Table 2.** Twenty-four (30.0%) patients died in the hospital. The mortality rate was significantly higher in the high UAR group than in the low UAR group: 18 (45.0%) vs. 6 (15.0%) respectively, p=0.004. Patients with high UAR also had a higher frequency of mechanical ventilation requirement (55.0% vs. 22.5%, p=0.002), septic complications (42.5% vs. 17.5%, p=0.015), and longer ICU stay (12.4±5.6 vs. 8.1±4.2 days, p<0.001).
Table 3 shows the association between UAR and mortality-related outcomes. Patients with high UAR were three times more likely to die during their hospital stay than those with a low UAR (RR=3.00; 95% CI: 1.38-6.51; p=0.004). Similarly, high UAR was significantly associated with 30-day mortality (RR=2.67, 95% CI: 1.08–6.59, p=0.034).
The receiver operating characteristic (ROC) curve analysis was used to assess the predictive value of UAR, CURB-65 and APACHE II for in-hospital mortality. The UAR showed good predictive ability with an area under the curve of 0.78 (95% CI: 0.67–0.89) as illustrated in **Figure 1.** APACHE II showed the highest predictive accuracy (AUC=0.84, 95% CI: 0.75–0.93), followed by UAR and CURB-65 (AUC=0.73, 95% CI: 0.62–0.84). The best cut-off point for UAR was 0.2555 and had a 75.0% sensitivity and a 70.0% specificity for in-hospital mortality.
The results of multivariable Cox regression analysis are shown in **Table 4.** High UAR was an independent predictor of in-hospital mortality after adjusting for age, gender, comorbidities, CURB-65, APACHE II and SOFA scores (adjusted HR=2.65, 95% CI: 1.12–6.28, p=0.026).

Table 1: Baseline demographic and clinical characteristics of patients according to UAR groups (n=80)

Variables	Low UAR <0.2555 (n=40)	High UAR >0.2555 (n=40)	p-value
Age (years), mean±SD	54.2±11.8	59.4±12.6	0.061
Male gender, n (%)	24 (60.0%)	27 (67.5%)	0.474
Diabetes mellitus, n (%)	13 (32.5%)	16 (40.0%)	0.486
Hypertension, n (%)	15 (37.5%)	19 (47.5%)	0.370
Smoking history, n (%)	14 (35.0%)	18 (45.0%)	0.365
UAR, mean±SD	0.18±0.05	0.39±0.10	<0.001
CURB-65 score, mean±SD	1.8±0.8	3.0±0.9	<0.001
APACHE II score, mean±SD	15.6±6.2	23.5±7.4	<0.001
SOFA score, mean±SD	5.1±2.5	8.7±3.2	<0.001

Table 2: Clinical outcomes according to UAR groups (n=80)

Outcomes	Low UAR <0.2555 (n=40)	High UAR >0.2555 (n=40)	p-value

In-hospital mortality, n (%)	6 (15.0%)	18 (45.0%)	0.004
30-day mortality, n (%)	7 (17.5%)	19 (47.5%)	0.005
Mechanical ventilation required, n (%)	9 (22.5%)	22 (55.0%)	0.002
Septic complications, n (%)	7 (17.5%)	17 (42.5%)	0.015
Acute kidney injury, n (%)	8 (20.0%)	16 (40.0%)	0.044
ICU stay (days), mean±SD	8.1±4.2	12.4±5.6	<0.001

Table 3: Association between UAR categories and mortality outcomes

Outcome	Risk in Low UAR n (%)	Risk in High UAR n (%)	Relative Risk (95% CI)	p-value
In-hospital mortality	6 (15.0%)	18 (45.0%)	3.00 (1.38–6.51)	0.004
30-day mortality	7 (17.5%)	19 (47.5%)	2.67 (1.08–6.59)	0.034
Mechanical ventilation	9 (22.5%)	22 (55.0%)	2.44 (1.29–4.62)	0.002

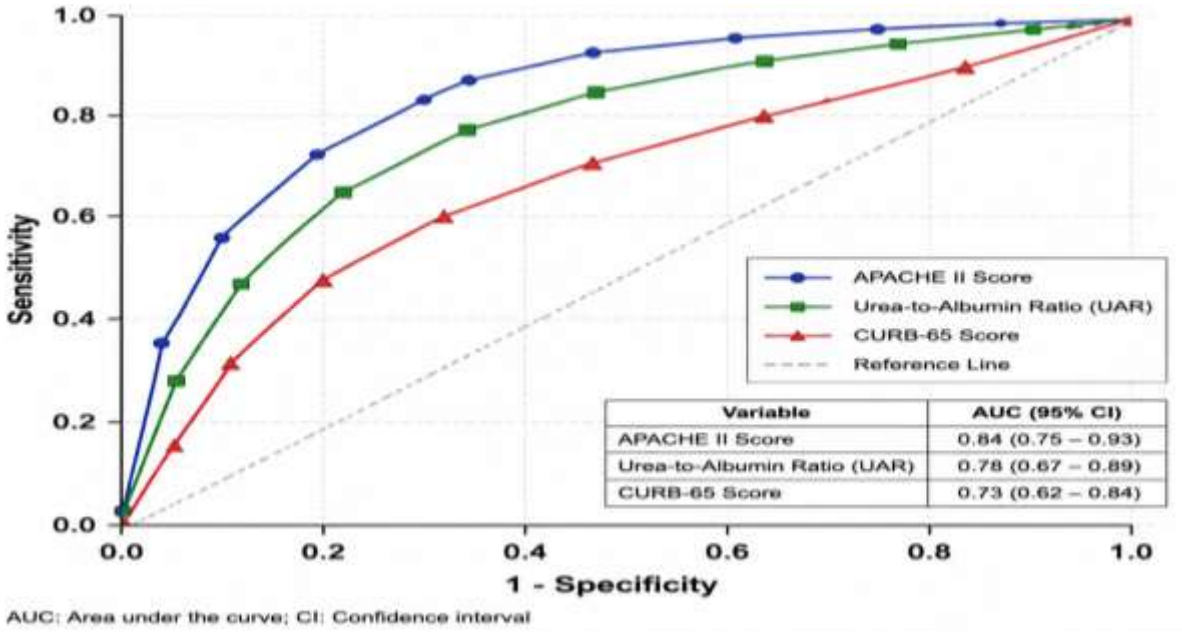

Figure 1: Receiver operating characteristic (ROC) curves of UAR, CURB-65, and APACHE II for prediction of in-hospital mortality

Table 4: Cox proportional hazards regression analysis for predictors of in-hospital mortality

Variables	Adjusted Hazard Ratio (HR)	95% CI	p-value
High UAR (>0.2555)	2.65	1.12–6.28	0.026
Age (per year increase)	1.03	0.99–1.07	0.112
Male gender	1.21	0.52–2.82	0.654
Diabetes mellitus	1.36	0.61–3.04	0.452
CURB-65 score	1.48	1.10–2.00	0.010
APACHE II score	1.08	1.03–1.14	0.002
SOFA score	1.12	1.04–1.21	0.003

DISCUSSION

Despite advances in treatment, severe pneumonia continues to be a significant reason for intensive care unit admission and death from progressive respiratory failure, systemic inflammation, sepsis, and multiorgan dysfunction. It is critical that patients at high risk for mortality are identified early, so that they can receive timely

intervention and optimized critical care management. We found that an elevated urea-to-albumin ratio (UAR) was significantly associated with raised in-hospital mortality in severe pneumonia patients in the present study. Higher UAR (>0.2555) was independently associated with three times the risk of in-hospital death, as compared to lower UAR.

This study is in line with earlier studies that showed the prognostic significance of the BUN/A ratio in infectious and inflammatory diseases. A systematic review and meta-analysis by Ulloque-Badaracco et al. found that high-UAR was linked to poor outcomes in COVID-19 patients, suggesting that UAR may be a comprehensive marker that reflects renal dysfunction and systemic inflammatory response [11]. In the same way, in COVID-19 hospitalized patients, Hung et al. showed in a meta-analysis that higher BUN/albumin ratio was significantly correlated with death suggesting its potential as a promising simple prognostic biomarker [12].

The UAR was significantly higher in the current study in patients with elevated UAR, reflecting heightened levels of physiological disturbance and disease severity, as evidenced by the increased CURB-65, APACHE II, and SOFA scores. The results are similar to Kaeley et al., who found that BUN/albumin ratio is positively associated with mortality in patients with moderate to severe COVID-19 pneumonia [13]. The relationship between BUN-to-albumin ratio and in-hospital death, too, was confirmed, with Zhou and Pan showing that this ratio was still independently predictive after adjusting for clinical variables [14].

This association between higher UAR and mortality is multifaceted. In severe infection, elevated urea could result due to renal hypoperfusion, increased protein catabolism, dehydration, or renal dysfunction. On the other hand, lowered serum albumin is an indicator of systemic inflammation, endothelial dysfunction, capillary leakage and malnutrition. Thus, this ratio of these parameters combined together may give a better idea of the severity of the disease than either of the markers would individually. In patients with septic shock, Pereira et al. showed that UAR was independent of other factors associated with mortality, thus confirming its connection with systemic inflammatory states and circulatory dysfunction [15].

This link between UAR and poor clinical outcomes has also been shown in septic patients in critical condition. Using the MIMIC-IV database, Cai et al. reported that a higher BUN/Alb ratio was an independent predictor of mortality in patients admitted to the ICUs with sepsis [16]. Likewise, Han et al. reported that UAR was useful for predicting mortality in septic patients, and was a potential readily available prognostic factor in a critical illness setting [17]. In addition, Wang et al. also demonstrated that the prognostic value of UAR in sepsis remained significant even after adjusting for clinical variables as higher ratios correlated with higher short-term mortality risk [18].

The present study also revealed that UAR had good predictive ability for in-hospital mortality with an AUC value of 0.78, sensitivity of 75% and specificity of 70%. While APACHE II showed marginally better discrimination UAR was able to give a similar predictive value with only routine laboratory measurements. This finding lend support to the clinical applicability of UAR, especially in clinical settings where complex clinical scoring systems might not always be possible or feasible. Kocasaban et al. also found a similar result in geriatric ICU patients with a higher risk of death with higher UAR [19].

These observations are corroborated by previous work in respiratory and critical care patients. Among acute exacerbations of chronic obstructive pulmonary disease (COPD), Zeng et al. showed that the BUN-to-albumin ratio (BUN/Alb) was an independent predictor of in-hospital and 90-day mortality, supporting the concept that BUN/Alb is potentially applicable in other respiratory failure syndromes [20]. In a further study, Nguyen et al found a positive correlation between early elevation of BUN/Albumin and long-term mortality of critically ill surgical patients, strengthening their appearance as a marker of systemic physiological stress [21].

Further, the prognostic value of UAR has been noted in various populations of ICUs. In addition to infectious diseases, Zhang et al. found BUN-to-albumin ratio as an independent predictor of mortality in patients hospitalized in an ICU with CHD [22]. Likewise, Shi et al. found that UAR was an important entity associated with all-cause mortality among patients with acute kidney injury, which also indicated that the ratio reflected the interaction between renal dysfunction, inflammation and overall physiological reserve [23].

The present study has a number of strengths. First, it employed a prospective cohort design with a standardized enrollment of severe pneumonia patients in the ICU. Second, UAR was assessed early, within 24 hours of admission, to assess its prognostic value at the early critical stage of the illness. Third, UAR was compared with other severity scoring systems such as CURB-65, APACHE II and SOFA scores, and after accounting for potential confounders in multivariable analysis.

However, some limitations should be considered. The study was carried out at a single tertiary care centre, which could prevent the results from being generalised to other healthcare settings. Secondly, the limited sample size could have limited statistical power for subgroup analysis. Third, the UAR values were only measured at baseline, without looking at any changes in UAR within the hospital. Continuous measurement might give further prognostic information on disease progression. Last, the possibility of residual confounding from unmeasured factors, like inflammatory markers, nutritional status, and treatment variation cannot be ruled out. Future multicentre studies with larger cohorts are recommended to confirm the UAR cut-off value identified, and to evaluate the feasibility of incorporating the UAR value into current pneumonia severity scoring systems. Further

studies are also needed to determine if serial monitoring of UAR can be used to better predict death and inform clinical decision making in patients with severe pneumonia.

CONCLUSION

The present study showed that a U/A ratio>1.27 was significantly correlated with the in-hospital mortality rate of severe pneumonia. After adjustment for clinical severity scores and other potential confounding factors, high UAR was an independent predictor of mortality. Because of its ease of use, low cost, and common laboratory data, UAR may prove to be a valuable marker for early identification of risk for critically ill pneumonia patients, especially in resource-constrained settings in which the use of more sophisticated predictive tools is limited.

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