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RESEARCH ARTICLE
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SERUM UREA TO ALBUMIN RATIO AS A SIGNIFICANT PREDICTOR OF MORTALITY AMONG PATIENTS OF COVID-19 PNEUMONIA IN THE EARLY DAYS OF ICU ADMISSION

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ABSTRACT

Background; Covid-19 pneumonia was a pandemic which lead to relentless acute respiratory failure caused by SARS-CoV2 virus. The cytokine storm is responsible for hypoxia and multiorgan failure. Various serum markers have been identified as key factors in the progression to COVID-19 pneumonia. Although pandemic is over after worldwide vaccination by messenger RNA vaccine yet there are still cases being reported to death in few countries of world. Therefore, it is important to further elaborate the key factor like elevated serum urea to albumin ratio for risk stratification and allocation of resources to avoid mortality in COVID-19 pneumonia.

Objective: To evaluate the association between the serum urea-to-albumin ratio and the mortality risk in the early days of ICU admission among patients with COVID-19 pneumonia.

Methods: This retrospective study was conducted on eighty-two COVID-19 patients hospitalized in the ICU. These patients were admitted to the ICU for at least four days with COVID-19 pneumonia between March 1 and July 30, 2021, at Lahore Health Care Hospital. Diagnosis was confirmed by RT-PCR on nasal swab along with characteristic opacities in both lower lung zones on radiological imaging. Patients were on high-flow oxygen via rebreathing mask, non-invasive positive pressure ventilator support, or mechanical ventilator. Serum albumin levels and urea were measured daily from the first day to the fourth day of ICU admission.

Results: Out of 82 patients of COVID-19 pneumonia who remained admitted in the ICU for four days, 38 patients expired. The mean age was 59.1 ± 13.1 years, and 62% (n = 52) were male. Nearly half of the patients (n = 42) were aged 60 years or older. The mean U/A ratio for discharged patients

was 13.60 on day 1 and 12.30 on day 4, while for expired patients it was 21.09 on day 1 and 35.06 on day 4. An increased U/A ratio was significantly associated with a higher risk of death ($p < 0.001$) on both day 1 and day 4, with a stronger correlation observed on day 4 ($r = 0.55$) compared to day 1 ($r = 0.29$). Increased age was not correlated with mortality, and no significant association was found between gender and mortality.

Conclusion: Elevated serum U/A ratio at admission is a strong predictor of disease severity and mortality in COVID-19 pneumonia. Its routine assessment may aid in early risk stratification and clinical decision-making.

Keywords: COVID-19, (U/A ratio) urea to albumin ratio, (RT-PCR) Reverse transcriptase polymerase chain reaction, Intensive Care Unit (ICU)

INTRODUCTION

The COVID-19 pandemic, caused by SARS-CoV-2, has led to significant morbidity and mortality worldwide, with pneumonia being a major complication[3]. Although the pandemic is over after messenger RNA COVID vaccination but there are still cases being reported with morbidity and mortality in different countries, evident in the report of the World Health Organization[4].

That's why the WHO is keeping an eye on emerging COVID variants and their associated mortality[5]. Similarly, CDC is also closely monitoring the morbidity and mortality due to COVID-19 variants[6]. Identifying early prognostic markers is crucial for risk stratification and optimizing resource allocation for the treatment of COVID-19 pneumonia. Several biomarkers, like C-reactive protein and serum ferritin, have been studied as key factors in COVID-19 progression[7] Similarly, D-dimer level at the time of admission to a health facility is associated with poor prognosis in COVID-19 pneumonia[8].

An elevated U/A ratio has been linked to poor outcomes in sepsis, heart failure, and other critical illnesses[9]. However, its role in COVID-19 pneumonia in the ICU remains underexplored. This study investigates the U/A ratio as a prognostic marker in COVID-19 pneumonia in the early days of ICU admission.

Methods:

This retrospective study was conducted on eighty-two COVID-19 patients hospitalized in the ICU. These patients remained admitted at least for four days in the ICU with COVID-19 pneumonia, from March 1, 2021 to July 30, 2021 in Lahore Health Care Hospital. The hospital is recognized by the Punjab Health Care Commission. The ICU has a central Oxygen supply, ICU beds, Ventilators, BIPAP machines, Cardiac monitors, and round-the-clock dedicated staff.

Ethical clearance: The study was approved by the institutional review board of Lahore Care Hospital via letter No.02-Art/ICU-IRB/LCH dated 15-8-2021.

Inclusion Criteria;

Patients were on high-flow oxygen via rebreathing mask, non-invasive positive pressure ventilator support, or mechanical ventilator. Patients were labelled as COVID-19 pneumonia by RT-PCR on nasal swab and characteristic opacities in both lower radiological zones[1, 2].

Demographic, clinical, and laboratory data were collected, including serum urea and albumin levels on admission day 1 and day 4 of ICU admission.

Exclusion Criteria:

1. Patients who stayed in the ICU for less than four days.
2. Patients who were on dialysis before admission or initiated dialysis within the first four days of ICU admission.
3. Those patients who had CLD, Nephrotic syndrome, and Diabetic Nephropathy were excluded from the study.

Statistical Analysis

Age was normally distributed while the U/A ratio on Day 1 and 4 was not normally distributed. We compared discharged patients with expired patients using Mann-Whitney U test and U/A ratio of the same group for day 1 and 4 using the Wilcoxon signed-rank test. Normality was confirmed using the Shapiro-Wilk test. ROC analysis determined the U/A ratio's predictive performance. Multivariate logistic regression identified independent predictors of severity. A p-value <0.05 was considered significant. The data was analyzed using SPSS version 26.

Results:

A total of 82 patients were included in the study, of whom 44 (53%) survived. The mean age was 59.1 ± 13.1 years, and 62% (n = 52) were male. Nearly half of the patients (n = 42) were aged 60 years or older. The U/A ratio was 17.1 ± 12.62 on day 1 and 22.8 ± 20.77 on day 4. Median (IQR) values were 13.24 (9.74) and 16.05 (18.93), respectively. Demographic characteristics and outcomes are summarized in Table 1.

			Outcome					
			Discharged			**Expired**		
			Count	**Mean (median)**	**Standard deviation (IQR)**	**Count**	**Mean (median)**	**Standard deviation (IQR)**
Number	**Gender**	**Male**	24			28		
		Female	20			10		
		subtotal	44			38		
Age	**Gender**	**Male**		55	15		62	13
		Female		59	11		62	12
		Subtotal		57	13		62	12
U/A ratio Day1	**Gender**	**Male**		13.22 (9.73)	8.34 (7.73)		19.26 (14.49)	14.63 (8.29)
		Female		14.25 (10.70)	9.27 (9.24)		26.19 (24.54)	16.39 (16.28)
		Subtotal		13.68 (10.53)	8.69 (8.39)		21.09 (14.77)	15.20 (15.61)
U/A ratio day4	**Gender**	**Male**		11.79 (9.24)	8.47 (4.34)		30.58 (23.79)	21.52 (17.90)
		Female		12.91 (9.30)	6.49 (8.07)		47.62 (34.40)	28.48 (47.65)
		subtotal		12.30 (9.30)	7.57 (6.64)		35.06 (28.52)	24.35 (19.35)

Table 1. Patient demographics, including patients' age, gender distribution, and Urea Albumin Ratio (U/A ratio) means, median, Standard deviation, and IQR on the first and fourth day for discharged and expired patients.

The mean U/A ratio was 13.60 on day 1 and 12.30 on day 4 for discharge patients, while 21.09 on day 1 and 35.06 on day 4 for expired respectively.

The mean U/A ratio on day 1 and day 4 differed significantly between discharged and expired patients ($p = 0.003$). Among discharged patients, the U/A ratio did not change significantly over the four days ($p > 0.05$). However, expired patients showed a significant rise in U/A ratio during this period ($p < 0.001$).

An increased U/A ratio was significantly associated with a higher risk of death ($p < 0.001$ on both day 1 and day 4), with a stronger correlation observed on day 4 ($r = 0.55$) compared to day 1 ($r = 0.29$). A higher U/A ratio on day 4 was significantly associated with increased mortality. Patients with a U/A ratio ≥17.7 had 33.8 times higher odds of dying compared to those with lower ratios on day 4 (OR: 33.78; 95% CI: 9.92–115.03; $p < 0.001$). Increased age was not correlated with mortality, and no significant association was found between gender and mortality. An ROC curve was generated to identify the optimal U/A ratio cutoff value on day 4 for predicting mortality. The best cutoff value

was 17.7 (units), with a sensitivity of 0.852 and a specificity of 0.864, and the area under the curve is 0.865 (CI 95%:0.776-0.952) (Figure 1).

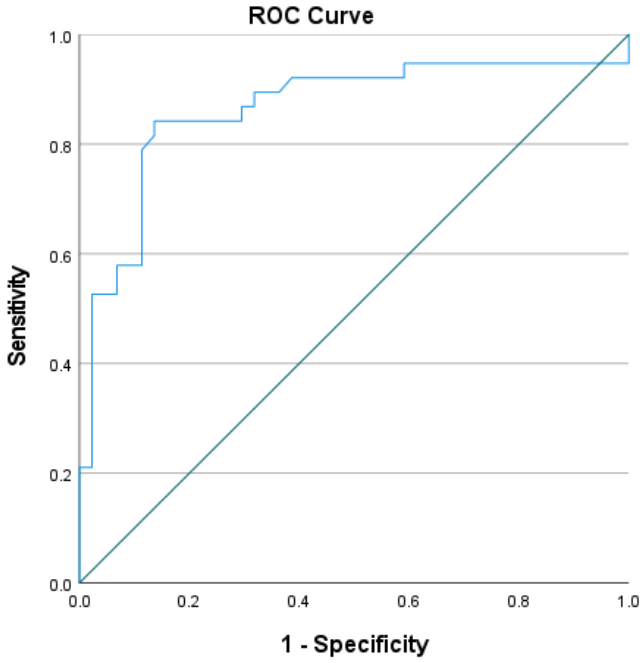

Figure 1. ROC curve showing the optimal U/A ratio cutoff value on day 4 of ICU admission for predicting mortality (sensitivity on y-axis).

Discussion:

Serum urea to albumin ratio has already been demonstrated to deteriorate mortality in patients with severe pneumonia. Elevated urea reflects renal dysfunction and catabolic state, while serum albumin indicates nutritional status and systemic inflammation, elaborating their role in critical illness (9).On the other hand, elevated serum urea to albumin ratio has also been observed in pulmonary embolism with poor prognosis[10].

In case of COVID-19 pneumonia, acute kidney injury has been established in various studies. Profound hypoxia is the main culprit responsible for acute kidney injury in COVID-19 pneumonia [11]. Happy hypoxia is a characteristic feature of COVID pneumonia in which patients have no hunger for oxygen[12]. Patients continue their usual activity without dyspnoea, which leads to hypoxic kidney injury. This hypoxic kidney injury is further aggravated by hypovolemia due to the use of intravenous diuretics prescribed by some physicians to avoid pulmonary edema.

Hypoalbuminemia indicates inflammation and malnutrition, worsening prognosis in COVID Pneumonia[13]. This hypoalbuminemia further reduced the effective intravascular volume and contributed to aggravating the hypoxic kidney injury.

Rodrigues et al revealed that the value of the U/A ratio was lower among survivors of ICU admission, and a U/A ratio ≥12.17 increased the risk of mortality by 2.00-fold in their study without a specific day of post admission[14].

Whereas in our study, the best cutoff value for the U/A ratio was 17.7 on day 4, and they had 33.8 times higher odds of dying compared to those with lower ratios on day 4.

This study manifests that elevated U/A ratio at admission significantly predicts severe COVID-19 outcomes, aligning with prior findings in sepsis and critical illness[9]

There are other serum markers like procalcitonin level to predict the risk of death in severe COVID-19 Pneumonia, but these markers are costly and not available in each lab in an underdeveloped country[15].

On the other hand, the serum urea to albumin ratio is a simple, cost-effective serum marker that can be used as a prognostic tool in COVID Pneumonia as supported by this study. Serum urea is a

indicator of renal function but it also represent the degree of dehydration. In ARDS patient it is recommended to keep patient in negative fluid balance but in case of COVID-pneumonia dehydration lead to aggravation of renal hypoxia thus It is also obvious to avoid hypoxia by maintenance of intravascular volume to prevent the hypoxic kidney injury in COVID-19 Pneumonia.

Limitations:
This study has several limitations due to its retrospective design, which may introduce biases in data collection and patient selection. Since the analysis relies on pre-existing medical records, unmeasured confounding factors could influence the results. The sample size, though sufficient for initial observations, could be expanded to enhance statistical power and generalizability. A larger, multicentre study would improve reliability by incorporating diverse patient demographics and clinical practices. Additionally, this study only assessed the U/A ratio on day one and day four, which, while useful for acute phase evaluation, may not capture later disease progression. Future research should include measurements on day six or eight to determine whether the ratio remains predictive in subacute or resolving stages of COVID-19 pneumonia.

The single centre design limits the external validity of the findings, as regional variations in treatment protocols and patient populations were not accounted for. Moreover, the study did not account for potential differences in laboratory techniques across institutions, which could affect urea and albumin measurements. The lack of serial measurements beyond day four also means that dynamic changes in the ratio over time could not be fully analysed. Finally, while the elevated serum U/A ratio shows promise as a prognostic marker, its clinical utility must be validated prospectively in randomized controlled settings. Addressing these limitations in future studies would strengthen the evidence and support broader implementation in risk stratification protocols.

Conclusion:
The study concludes that the elevated serum urea-to-albumin (U/A) ratio is a highly reliable and independent marker for predicting disease severity and mortality in COVID-19 pneumonia. By assessing this ratio, clinicians can identify high-risk patients early, allowing for timely interventions and improved outcomes. Integrating the U/A ratio into routine clinical practice could enhance risk stratification, helping healthcare providers allocate resources more efficiently. Additionally, this simple and cost-effective biomarker may serve as a valuable tool for monitoring disease progression and tailoring treatment strategies. Its widespread adoption could lead to better patient management, particularly in resource-limited settings. Overall, the findings highlight the elevated U/A ratio as a promising prognostic tool in the fight against COVID-19 pneumonia.

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Conflicts of Interest: no conflict of interest

AUTHORS' CONTRIBUTION:
MY conceptualized, did data collection & editing of manuscript MMAB conceptualized, did data collection, review and final approval of manuscript.
MI did data collection & editing of manuscript.
TT did data analysis, data interpretation, &manuscript writing.
ZN did statistical analysis & editing of manuscript.
ARZB did data analysis, data interpretation, manuscript writing.
All authors approved the final version of the manuscript.

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