ORIGINAL ARTICLE

C-reactive Protein, Albumin, Urea, CRP/Albumin Ratio, and Urea/Albumin Ratio: A Retrospective Evaluation in COVID-19 Patients

Nor Amirah Mohammad Nazri[1], Wan Norlina Wan Azman[1], Norsyuhadah Musa[1], Tuan Salwani Tuan Ismail[1], Azian Harun[2], Najib Majdi Yaacob[3], Sarina Sulong[4], Sirajudeen K.N.S[5], Mahaya Che Mat[6], Hani Ajrina Zulkeflee[7], Siti Sarah Mustapa[8]

[1] Department of Chemical Pathology, School of Medical Sciences, Universiti Sains Malaysia (Health Campus) Kelantan, Malaysia
[2] Department of Medical Microbiology and Parasitology, Universiti Sains Malaysia (Health Campus) Kelantan, Malaysia
[3] Unit of Biostatistic and Research Methodology, Universiti Sains Malaysia (Health Campus) Kelantan, Malaysia
[4] Human Genome Centre, Universiti Sains Malaysia (Health Campus) Kelantan, Malaysia
[5] Department of Basic Medical Sciences, Kuliyyah of Medicine, International Islamic University Malaysia, Kuantan Campus, Malaysia
[6] Department of Pathology, Hospital Raja Perempuan Zainab II, Kelantan, Malaysia
[7] Department of Medical Sciences II, Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia
[8] Department of Pathology, Hospital Ampang, Selangor, Malaysia

ABSTRACT

Introduction: C-reactive protein (CRP), urea, albumin, CRP/albumin ratio (CAR) and urea/albumin ratio (UAR) could be valuable biomarkers for determining the severity of illness in patients with COVID-19. This study aimed to determine the association between these markers and disease severity in COVID-19 patients on admission and days five to seven after admission. **Methods:** This retrospective study includes 153 adult COVID-19 patients admitted to Hospital Raja Perempuan Zainab II and Hospital Ampang from January 2021 to December 2021. Patients' serum CRP, urea, albumin and creatinine levels were recorded on admission and on days five to seven after admission. The patients were categorised based on the Annex 2e guidelines published by the Ministry of Health, Malaysia and further classified as mild to moderate disease (stages 1-3) and severe to critical illness (stages 4-5). **Results:** On admission, urea, creatinine, CRP, UAR and CAR were significantly higher in the severe to critical group ($p<0.001$). The optimal cut-off value for the UAR was 0.16; the area under the curve (AUC) was 0.760, and sensitivity and specificity were 63.6% and 85.7%, respectively. The AUC of the CAR was 0.752, with 54.2% sensitivity and 91.4% specificity at an optimal cut-off value of 1.63. In severe to critical COVID-19 patients, albumin levels decreased significantly on days five to seven after admission, while urea levels remained significantly higher in this group ($p<0.001$, $p<0.05$, respectively). **Conclusion:** CRP, urea, albumin, CAR and UAR are promising biomarkers for predicting the severity of disease in COVID-19 patients.
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Keywords: COVID-19; c-reactive protein; albumin; urea; CRP/albumin ratio; urea/albumin ratio

Corresponding Author:
Wan Norlina Wan Azman, MPath
Email: dr_wannorlina@usm.my
Tel: +6097676489/6504

INTRODUCTION

In late December 2019, an outbreak of a strange pneumonia characterised by fever, dry cough, fatigue, and occasional gastrointestinal symptoms occurred in the Huanan Seafood Wholesale Market in Wuhan, Hubei, China (1). Even though the lungs are the primary target, this disease affects many other organs, including the cardiovascular system, the kidneys and the liver. Despite many advances in the treatment and prevention of the disease, it is still challenging to accurately predict its severity, progression and the risk of mortality.

The laboratory parameters commonly utilised for COVID-19 patients include C-reactive protein (CRP), urea, and albumin. Some previous studies have suggested that urea levels can predict the prognosis of critically ill patients, regardless of creatinine levels and even after accounting for confounding factors such as renal failure (2).

Elevated cytokine levels in COVID-19 patients imply a cytokine storm and an aggravating immunological

response to a viral infection, which contribute to the severity of COVID-19. Recent findings suggest that CRP is not just a biomarker of infection and inflammation but also an inflammatory mediator (3). A correlation has been observed between elevated CRP levels and the severity of COVID-19 (4). There is also a strong association between CRP with acute kidney injury and mortality in COVID-19 patients (5).

The CRP/albumin ratio (CAR) can function as a prognostic indicator for other diseases, including cardiovascular, cerebrovascular and other infectious diseases (6). This is because CRP levels increase during the acute inflammatory response to viruses, while albumin synthesis decreases under the same conditions (7). Apart from that, the urea/albumin ratio (UAR) is a novel measure of the systemic inflammatory response and is linked to mortality in pneumonia patients (8). However, these derived biomarkers, CAR and UAR, have not been extensively investigated in COVID-19 patients, and the results are debatable.

Early recognition and prompt treatment of COVID-19 are critical elements in preventing adverse clinical outcomes and easing the strain on limited healthcare resources that would result if high numbers of patients were admitted to intensive care units. Incorporating these clinical laboratory indicators into standard testing would enable healthcare workers to prioritise care for COVID-19 patients who need it most. Hence, we evaluated these valuable parameters in patients hospitalised with COVID-19 on day one of admission and days five to seven after admission and explored the association between these parameters and disease severity.

MATERIALS AND METHODS

Study design, participants and data collection

This was a retrospective study of adult COVID-19 patients aged 18 to 80 admitted to Hospital Raja Perempuan Zainab II (HRPZ II) and Hospital Ampang from January 2021 to December 2021. The patients were categorised into five stages based on the Annex 2e clinical management guidelines for confirmed COVID-19 cases in adults published by the Ministry of Health, Malaysia. The patients were further divided into two categories: mild to moderate disease (stages 1-3) and severe to critical illness (stages 4-5). The patients were confirmed positive for COVID-19 using an Antigen Rapid Test Kit (RTK-Ag) or Reverse Transcription-Polymerase Chain Reaction (RT-PCR). The sample size requirement was calculated using G*power software version 3.1.9.2, with the calculation based on a t-test. Cao Z et al.,2020 (9). To be significant at 5% alpha error probability, 80% power (1-beta error probability), and the two groups, the largest sample size required is 62. By anticipating a 10% dropout due to preanalytical error, the corrected sample size was 68 patients. Therefore, the total sample size required was 136. In the first stage, 228 patients confirmed with COVID-19 were reviewed. As a result, 153 individuals were included in the study. We excluded patients with missing CRP, urea, or albumin data on admission. After hospitalisation, the patient can enter the pulmonary and hyperinflammation phase, as stated by Diab AM et al. The patient may develop life-threatening complications, including sepsis between days two and three of hospital admission, acute respiratory distress syndrome on day four, acute kidney injury and acute heart injury on day eight (10). Given this information, it is best to describe the data collection on admission and days five to seven after admission. The study flow chart is shown in (Fig.1). Clinical and laboratory data were obtained from the hospital's electronic medical system.

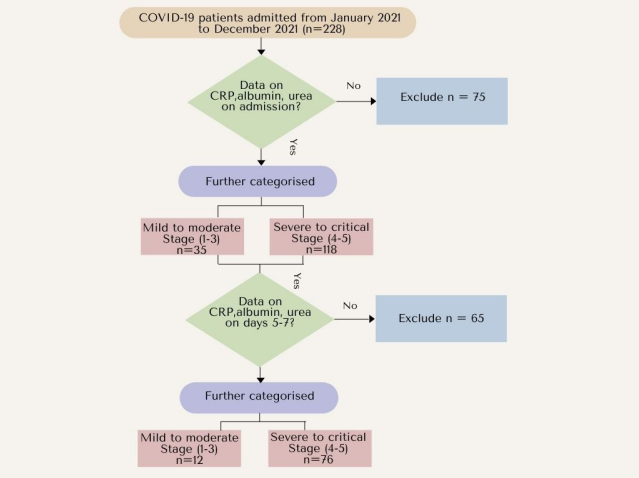

Figure 1: Flow diagram of the study population

Statistical analyses

The data were analysed using SPSS version 27. Categorical data are presented as frequency and percentage and analysed using a chi-squared test. Numerical data with normal distribution are expressed as mean and standard deviation (mean ± SD), while numerical variables with skewed distribution are expressed as the median and interquartile range (IQR). The two groups (mild to moderate illness and severe to critical illness) were compared and the numerical variables were calculated using the independent t-test for data with a parametric distribution and the Mann–Whitney U test for data with a non-parametric distribution. A receiver operating characteristic (ROC) curve analysis was used to determine the CAR and UAR cut-off values for severity in COVID-19 patients. The highest Youden index was used to establish the optimal cut-off. This cut-off was then used to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and odds ratio (OR). For all analyses, $p < 0.05$ was considered statistically significant.

Ethics approval

This study was approved by The Human Research Ethics Committee of USM (JEPeM-USM) protocol code

USM/JEPeM/21100691 and Ministry of Health Malaysia protocol code NMRR-21-762-58458 (IIR).

RESULTS

A total of 153 COVID-19-positive patients who met the inclusion criteria were included in this study. Of these, 35 had mild to moderate illness, while 118 had severe to critical illness. The characteristics of the COVID-19 patients are summarised in Table I.

Table I: Characteristics of COVID-19 patients

Variables	Mild to moderate group	Severe to critical group	p-value
Number (n)	35	118	
	mean ± SD	**mean ± SD**	
Age in years	49.8 ±16.8	57.8 ± 12.7	**0.003**[a]
	n (%)	**n (%)**	
Gender			
Male	8 (22.9%)	65 (55.1%)	**0.001**[b]
Female	27 (77.1%)	53 (44.9%)	
Vital status			
Alive	34 (97.1%)	86 (72.9%)	**0.002**[b]
Deceased	1 (2.9%)	32 (27.1%)	

[a] Independent sample t-test, [b] χ^2 test

The two groups (mild to moderate illness and severe to critical illness) differed significantly in gender and vital status. The Pearson chi-squared test also showed a significant association between COVID-19 severity and some pre-existing conditions: type 2 diabetes mellitus (T2DM) and hypertension (HPT) were associated with mild to moderate illness and severe to critical illness, respectively. The frequency and percentage of these associations are as follows: T2DM: eight participants (10%) vs. 72 participants (90%) (p<0.001); HPT: six participants (12%) vs. 43 participants (87.8%) (p=0.024). We found no significant association between COVID-19 severity and other comorbidities, such as chronic kidney disease, underlying lung disease, malignancy or autoimmune disease.

Table II shows the laboratory results for both groups on admission. Urea, creatinine, CRP, UAR and CAR on admission were significantly higher in patients with severe to critical illness than in those with mild to moderate illness (p<0.001). There was no significant difference in albumin level between the groups.

A receiver operating characteristic (ROC) curve analysis was used to evaluate the ability of UAR and CAR on admission to predict the severity of COVID-19 illness (Fig. 2). As shown in Table III, at the optimal cut-off value of 0.16 for the UAR, AUC was 0.760, and sensitivity and specificity were 63.6% and 85.7%, respectively. At the optimal cut-off value of 1.63, the AUC of the CAR was 0.752, with 54.2% sensitivity and 91.4% specificity.

Table II: Laboratory results for COVID-19 patients on admission

Laboratory parameters	Mild to moderate group (n=35)	Severe to the critical group (n=118)	Z statistics	p-value
	Median (IQR)			
Urea (mmol/l)	4.0 (3.0)	6.8 (8.0)	-4.433	**<0.001**[a]
Creatinine(mmol/l)	63.0 (42.0)	95.0 (87.0)	-3.649	**<0.001**[a]
CRP (mg/l)	27.0 (24.0)	67.6 (92.0)	-4.626	**<0.001**[a]
UAR	0.1 (0.0)	0.21 (0.0)	-4.657	**<0.001**[a]
CAR	0.73 (1.0)	2.0 (3.0)	-4.513	**<0.001**[a]
	mean ±SD		**t-stats (df)**	
Albumin (g/l)	36.8 ± 5.9	35.4 ± 5.7	1.251 (151)	0.213[b]

[a]Mann–Whitney test, [b]independent sample t-test

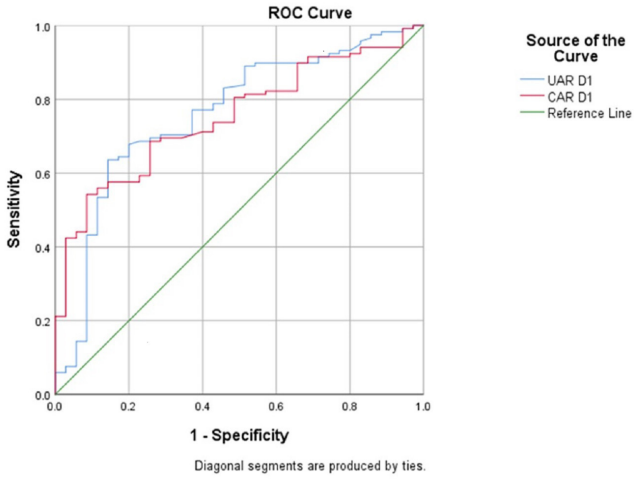

Figure 2: ROC curves for the ability of UAR and CAR to predict disease severity on admission of COVID-19

On follow-up, 88 patients had complete CRP, urea, and albumin data between days five and seven of hospitalisation. The laboratory results for mild to moderate and severe to critical groups on days five to seven after admission were also analysed, as shown in Table IV. Table V shows the comparison of the laboratory results on different days after admission. Urea, CRP, albumin, CAR and UAR levels differed significantly over time in patients with severe to critical illness.

DISCUSSION

This retrospective study has analysed laboratory parameters from 153 patients hospitalised with

Table III: ROC analysis of UAR and CAR on admission of COVID-19 patients

Variable	AUC	95% CI	P	Cut-off	Sens (%)	Spec (%)	PPV(%)	NPV(%)	LR+	LR-	DOR
UAR	0.760	0.667-0.852	<0.001*	0.16	63.6	85.7	92.68	40.85	4.45	0.17	26.69
CAR	0.752	0.671-0.832	<0.001*	1.63	54.2	91.4	95.52	37.21	6.33	0.09	67.50

Abbreviations: AUC: area under the receiver operating characteristic (ROC) Curve; CI: confidence interval; Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio; DOR: diagnostic odds ratio

Table IV: Laboratory results for COVID-19 patients on days five to seven after admission

Laboratory parameters	Mild to moderate group (n=12)	Severe to critical group (n=76)	Z statistics	p-value
	Median (IQR)			
Urea (mmol/l)	3.5 (3.0)	9.3 (15.0)	-4.609	**<0.001**[a]
CRP (mg/l)	34.0 (47.0)	35.2 (68.0)	-0.523	0.601[a]
UAR	0.1 (0.0)	0.3 (1.0)	-4.791	**<0.001**[a]
CAR	1.2 (1.0)	1.3 (3.0)	-0.875	0.381[a]
	mean ± SD		t-stats (df)	
Albumin (g/l)	35.2 ± 5.6	31.1± 5.1	2.585 (86)	**0.011**[b]

[a]Mann–Whitney test, [b]independent sample t-test

COVID-19. Urea, albumin, CRP, UAR and CAR were evaluated on admission and on days five to seven after admission. There was a significant difference in gender between the two groups with majority being males in severe to critical group. The mean age of the severe to critical group was also higher. These outcomes verify the severe impacts of COVID-19 in the elderly and in males, in line with previous research (11,12). Our study also showed a significant association between pre-existing comorbidities such as hypertension and T2DM with COVID-19 severity; patients with these conditions are particularly more prone to severe disease course and progression. This also aligns with previous studies (13,14).

Interestingly, severe to critical patients had significantly higher urea, CRP, CAR and UAR values on admission than patients with mild to moderate illness. The albumin levels of the two patient groups did not differ significantly. However, in patients with severe to critical COVID-19, albumin levels decreased significantly on days five to seven after admission. This is probably because feverish patients (as is usually the case in patients with COVID-19) without a history of liver infection may have a shorter-than-usual albumin half-life (approximately seven days rather than 21 days) due to higher energy expenditure and modification in the internal body environment (15). There are several possible causes for the inverse relationship between hypoalbuminaemia and COVID-19 severity. Albumin is an anti-inflammatory and antioxidant protein; it can therefore help ward off cytokine storms and subsequent multi-organ damage (16). Hypoalbuminaemia in COVID-19 patients could have many causes, such as capillary leakage, an intense systemic inflammatory response, tissue ischaemia, or a weak immune response (17). Moreover, hypoalbuminaemia is associated with poor prognosis and mortality in COVID-19 patients (18).

Our study also demonstrated a significant increase in urea from admission to days five to seven in severe to critical COVID-19 patients. This is because certain patients' systemic immune responses to a COVID-19 infection might be harmful, resulting in a so-called cytokine storm. Furthermore, Arihan et al. demonstrated that elevated urea on admission had a robust connection with mortality in critically sick patients, even after adjusting for confounders such as renal failure (2). SARS-CoV-2 RNA has also been detected in the kidney tissue and urine of COVID-19 patients (19).

CRP is an acute phase reactant. Secretion begins 4 to 10 hours after an inflammatory insult and peaks 48 hours after the insult. CRP's half-life is only 19 hours (20). Elevated CRP is uncommon in most viral infections. However, one study of 1,099 COVID-19 patients in China found that 60.7% had CRP values ≥10 mg/L (21). A high CRP value is not only a biomarker of disease

Table V: Comparison of laboratory results of the COVID-19 patients on admission and days five to seven after admission

Laboratory parameters	Mild to moderate group (n=12)			Severe to critical group (n=76)		
	mean ± SD	t stats (df)	p-value	mean ± SD	t stats (df)	p-value
Urea (mmol/l)						
Admission	3.6 ± 1.7			11.6 ± 11.7		
Days 5-7	4.1 ± 1.9	-1.364 (11)	0.200	15.3 ± 12.3	-2.836 (75)	**<0.05***
CRP (mg/ml)						
Admission	39.7 ± 29.7			99.1 ± 77.2		
Days 5-7	50.6 ± 42.9	-1.009 (11)	0.334	63.4 ± 58.6	3.515 (75)	**<0.05***
Albumin (g/L)						
Admission	38.1 ± 7.0			35.0 ± 6.0		
Days 5-7	35.2 ± 5.6	1.927 (11)	0.080	31.2 ± 5.1	8.582 (75)	**<0.001***
UAR						
Admission	0.1 ± 0.0			0.4 ± 0.4		
Days 5-7	0.1 ± 0.1	-2.211 (11)	**0.049***	0.5 ± 0.4	-3.728 (75)	**<0.001***
CAR						
Admission	1.0 ± 0.5			3.0 ± 2.4		
Days 5-7	1.5 ± 1.3	-1.506 (11)	0.160	2.2 ± 2.0	2.690 (75)	**<0.05***

*Paired t-test

severity but also an independent risk factor for death in patients with severe COVID-19 (22). However, our study found significant reductions in CRP levels in severe to critical COVID-19 patients at days five to seven after admission. Still, the treatment of the disease was not the primary focus of this study; instead, we examined CRP as a potential predictor of disease severity in COVID-19. Future research may investigate the impact of corticosteroids or other anti-inflammatory drugs on COVID-19 severity, as higher CRP levels indicate more systemic inflammation.

CAR has recently received attention as a new inflammatory marker, and its potential role in predicting the outcome of COVID-19 has not been well studied. Some recent studies have suggested that CAR is a more accurate indicator of sepsis than either CRP or albumin alone (23). According to Torun A et al., CAR may also be an early warning sign of COVID-19 severity (24). Like Torun A et al., our study has reported significant CAR elevation in patients with severe COVID-19 compared to the non-severe group on admission. Another study found that CAR had the strongest positive correlation with the sequential organ failure assessment score and length of hospital stay in COVID-19 survivors. Approximately 95 % of COVID-19-induced mortality and morbidity correlate with greater CAR concentrations (25).

Ilzdemir S found that CAR can predict 30-day mortality of COVID-19 patients during the initial presentation at the emergency department, whereby CAR exhibited 92.86% sensitivity and 94.9% negative predictive value at the cut-off $\geq$ 0.049. The value of CAR was also higher in non-survivors compared to COVID-19 survivors (26). Our study, however, assigned a higher CAR cut-off value at 1.63 with ROC curve analysis to differentiate severe COVID-19 and CAR demonstrated high specificity (91.4%) and positive predictive value (95.5%), underscoring its capacity to effectively identify individuals with severe COVID-19 cases while minimising false positives. These findings are supported by other studies (27,28,29). Our cut-off is also found to be higher than other studies, ranging from 0.73 to 0.9 (27,30,31).

Our study observed the UAR cut-off value of 0.16 on admission in predicting the progression of COVID-19 disease. In contrast, other cut-off values were higher than ours, ranging from 3.79 (28) to 4.83 (32). One explanation for this discrepancy is that other studies used the blood urea nitrogen (BUN) to albumin ratio (BAR) instead of UAR. Hence, cut-off values varied. Studies also reported that an elevated UAR on admission had been identified as an independent risk factor for critical illness in COVID-19 patients and was a significant predictor of in-hospital mortality (28,32,33). Our study observed that the UAR ratio exhibited 85.7% specificity and a positive predictive value of 92.68%. Yet, limited data are available regarding the predictive value of the UAR for identifying critical illness in patients with COVID-19.

In both of patient groups, UAR on admission differed significantly from that on days five to seven after admission. Our study demonstrated high UAR in a patient with severe to critical illness compared to mild to moderate COVID-19. Thus, consistent with the literature, the UAR was lower in survivors compared to non-survivors on day one of hospitalisation for COVID-19 infection (33,27). However, limited studies has been done on serial monitoring of UAR during hospital admission.

Thus, this study has demonstrated an association between urea, CRP, CAR, and UAR values on admission and severe COVID-19 disease. Urea and albumin are routine biomarkers that show significant association with disease severity in COVID-19 patients. In clinical practice, the use of CAR for early differentiation of patients with severe COVID-19 can serve as a reliable prognosticator of unfavourable clinical consequences in individuals afflicted with COVID-19. The observed variations in cut-offs for UAR and CAR further highlight the need for harmonisation in reporting the results. Selection of population studies: criteria to define the severity of illness and exclusion criteria must also be considered. This study is retrospective and has a small sample size. In addition, participants' underlying comorbidities and medications may contribute as confounding factors and affect the study's results. Additional multicentre studies with larger sample sizes that consider possible confounding factors are needed to overcome these limitations. Therefore, further research is required to determine the optimal cut-off values, such as the UAR and CAR, for effectively stratifying the severity risk in COVID-19 patients.

CONCLUSION

Baseline and serial monitoring of (CRP, urea, albumin, CAR and UAR) may help clinicians anticipate the likelihood of disease progression in COVID-19 patients. The effects of inflammation in COVID-19 patients necessitates the search for more stable markers that can effectively predict the severity and likely course of the disease. Early detection of a severe infection can enable early treatment and intervention, leading to improved outcomes.

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