ORIGINAL ARTICLE

Blood Urea Nitrogen/Albumin Ratio and Mortality Risk in Patients with COVID-19

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Abstract

Introduction: We researched blood urea nitrogen (BUN), albumin and their ratio (BAR), and compared them with C-reactive protein (CRP), D-dimer, and computed tomography severity scores (CT-SS), to predict inhospital mortality.

Methods: One-hundred and thirty-one coronavirus disease-2019 (COVID-19)-confirmed patients brought to the emergency department (ED) were dispensed to the survivor or non-survivor group, in light of inhospital mortality. Information on age, gender, complaints, comorbidities, laboratory parameters, and outcome were gathered from the patient's record files.

Results: The median BUN, mean total protein, mean albumin, median BAR, median creatinine, median CRP, and median D-dimer were recorded. CT-SS were utilized in categorizing the patient as mild, moderate, and severe. Inhospital mortality occurred in 42 (32.06%) patients (non-survivor group) and did not occur in 89 (67.94%) patients (survivor group). The median BUN (mg/dL) and BAR (mg/g) values were significantly raised in the non-survivor group than in the survivor group [BUN: 23.48 (7.51–62.75) and 20.66 (4.07–74.67), respectively ($p = 0.009$); BAR: 8.33 mg/g (2.07–21.86) and 6.11 mg/g (1.26–23.33); ($p = 0.0003$)]. The mean albumin levels (g/dL) in the non-survivor group were significantly lower than in the survivor group [2.96 ± 0.35 and 3.27 ± 0.35, respectively ($p < 0.0001$)]. Albumin with an odd's ratio of 6.14 performed the best in predicting inhospital mortality, followed by D-dimer (4.98). BAR and CRP had similar outcome of 3.75; BUN showed an OR of 3.13 at the selected cutoff value.

Conclusion: The BUN, albumin, and BAR were found to be dependable predictors of inhospital mortality in COVID-19 patients, with albumin (hypoalbuminemia) performing even better.

Keywords: Blood urea nitrogen/albumin ratio, COVID-19, COVID-19 mortality, C-reactive protein, D-dimer, Hypoalbuminemia.

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Introduction

The second wave apart from a steep rise in coronavirus disease-2019 (COVID-19) cases has been characterized by unprecedented demand for medical-grade oxygen and hospital beds. According to World Health Organization data, 171 million cases of COVID-19 have been confirmed worldwide as of this writing. The overall crude fatality rate is 2.3% which rises to 49% among critical cases.[1] In India with a population of billion plus people, the absolute number of COVID-19 patients and associated mortality is large. Till date, there is no established treatment protocol for COVID-19. Early recognition and supportive care can effectively decrease the incidence of prolonged clinical illness and inhospital mortality.

Many laboratory markers, like D-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, procalcitonin (PCT), and cytokine tests particularly interleukin-6 (IL-6) have been studied for their prognostication and therapeutic guidance in COVID-19 cases. High-resolution computed tomography (HRCT) scan–based semi-quantitative score of pulmonary involvement is also being considered for predicting short-term mortality. However, due to sociodemographic factors, adequate laboratory facilities may not be available to one and all, and focusing on simple laboratory markers would be more practically feasible.

Blood urea nitrogen (BUN), a nitrogenous end product of protein metabolism, is commonly used as biomarker for kidney function and hypovolemia. CURB-65 criteria utilize BUN for predicting mortality in community-acquired pneumonia (CAP) and infection of any site.[2] A multicentric study reported that BUN can be used as a predictor of mortality in critically ill patients[3] and for predicting persistent organ failure after 48 hours of hospital admission.[4,5] Studies have associated higher BUN with mortality in COVID-19 patients.[6,7]

Albumin is a negative acute-phase reactant protein,[8] commonly assessed for malnutrition and liver function. Systemic inflammation is common in severe COVID-19.[9] Inflammation begets increased capillary permeability causing the escape of serum albumin into interstitial space.[10] There are studies that have shown hypoalbuminemia in COVID-19 patients,[11,12] but limited literature is available on its role in COVID-19 progression and mortality.

BUN/albumin ratio (BAR) has been projected as a predictor of inhospital mortality in older (>65 years of age) emergency department (ED) patients[13] and pneumonia patients.[14] One study has found BAR to be a more reliable predictor of inhospital mortality than BUN or albumin, in COVID-19 patients.[7] We did not come

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across any literature comparing BAR with other more established prognosticators, like CRP, D-dimer, and HRCT, in COVID-19.

So, here we investigated the inhospital mortality predictive power of BUN, albumin, BAR and compared them with CRP, D-dimer, and HRCT values, in COVID-19 patients.

Materials and Methods

This is a retrospective, single-center, observational study done for the period between April 15, 2021, and May 15, 2021, at Netaji Subhas Medical College and Hospital, Patna. Written informed consent was waived off for retrospective study of emerging infectious diseases.

Patients over the age of 18 years brought to the ED and admitted for the suspicion of COVID-19 and with at least one polymerase chain reaction (PCR) test positive for COVID-19 were included. Patients with a history of chronic renal failure (CRF) with maintenance hemodialysis, chronic liver disease, secondary vasculitis, those who sought leave against medical advice (LAMA), those who were referred to other centers, and/or those who died within 24 hours of admission were excluded. Pre-dialysis CRF and renal transplant patients were included.

Data were collected from the patient's file and hospital information system (HIS) regarding patient's complaints, comorbidities, and laboratory investigations, like total protein, albumin, BUN, creatinine, D-dimer, CRP, HRCT scan, and hospital outcome (discharge, inhospital exitus). The BAR value was calculated by dividing BUN (mg/L) by albumin (g/L). The primary end point was inhospital mortality. All patients were allocated into either of the two groups—survivor or non-survivor, depending on whether they were duly discharged or succumbed to COVID in their case.

Statistical Analysis

Data were analyzed by using statistical software Stata 14.0. Categorical data were expressed as frequency and percentage. Quantitative data were expressed as mean and standard deviation (SD). Those quantitative variables that did not follow normal distribution were expressed as median and range. Independent *t*-test and Mann–Whitney *U* test (rank-sum test) were used to compare quantitative variables between survival and non-survival category of the patient. Chi-square/Fisher's exact test was used to check the association between survival and categorical variable. Receiver operating characteristic (ROC) curve analysis was carried out to find the cutoff value for non-survival in COVID-19 patients for selected parameters (BUN, albumin, BAR, CRP, and D-dimer). Using this cutoff, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and odd's ratio (OR) were calculated. $p < 0.05$ is considered as statistically significant.

Results

After excluding two patients of CRF (requiring dialysis), two patients who died within 24 hours of admission, and 11 patients who sought leave against medical advice (LAMA), a total of 131 patients were included in the study.

Of the 131 patients, 98 (74.81%) were males and 33 (25.19%) were females (Table 1). Fever was the predominant symptom in 121 (92.37%) patients, followed by shortness of breath (103 patients; 78.63%) and cough (101 patients; 77.1%). A small number of patients (11 patients; 8.40%) additionally complained of myalgia, diarrhea, ageusia, and/or anosmia. A total of 40 (30.53%) patients had at least one comorbidity in their medical history, and the most frequent comorbidity was diabetes (32 patients; 24.43%), followed by hypertension (23 patients, 17.56%). The median BUN, mean total protein, mean albumin, median BAR, median creatinine, median CRP, and median D-dimer were recorded as 21.67 (4.07–74.67) mg/dL, 6.67 ± 0.62 g/dL, 3.17 ± 0.38 g/dL, 6.73 (1.26–23.33) mg/g, 0.79 (0.44–3.5) g/dL, 45.75 (1.21–262.66) mg/dL, and 0.89 (0.03–14.81) mg/L, respectively. HRCT was performed in only 89 out of 131 patients as advised by the treating physician and/or patient's consent. CT severity scores (CT-SS) were utilized in categorizing the patient as mild (7 patients, 8.14%), moderate (38 patients, 44.19%), and severe (41 patients, 47.67%). A total of 76 (58%) patients were sent to ward and 55 (42%) were admitted to intensive care unit (ICU), at the time of admission. The median length of hospital stay was 8 (1–39) days in ward and 8 (1–27) days in ICU. Inhospital mortality occurred in 42 (32.06%) patients (non-survivor group) and did not occur in 89 (67.94%) patients (survivor group).

Table 1: Patients characteristics

Number of patients (*n*)	131 (100%)
Age[a]	54 ± 14 years
Gender[b]	
Male	98 (74.81%)
Female	33 (25.19%)
Chief complaints[b]	
Fever	121 (92.37%)
Cough	101 (77.1%)
Shortness of breath	103 (78.63%)
Others	11 (8.40%)
Medical history[b]	
Comorbidity[d]	40 (30.53%)
Diabetes	32 (24.43%)
Hypertension	23 (17.56%)
Hypothyroidism	6 (4.58%)
Cardiovascular disease	2 (1.53%)
Cerebrovascular disease	2 (1.53%)
Pulmonary disease	1 (0.76%)
Laboratory results	
BUN (mg/dL)[c]	21.67 (4.07–74.67)
Total protein (g/dL)[a]	6.67 ± 0.62
Albumin (g/dL)[a]	3.17 ± 0.38
BAR (mg/g)[c]	6.73 (1.26–23.33)
Creatinine (mg/dL)[c]	0.79 (0.44–3.5)
CRP (mg/dL)[c]	45.75 (1.21–262.66)
D-dimer (mg/L)[c]	0.89 (0.03–14.81)
HRCT[e]	89 (100%)
Mild	7 (8.14%)
Moderate	38 (44.19%)
Severe	41 (47.67%)
Length of hospital stay (days)[c]	
Ward	8 (1–39)
ICU	8 (1–27)
Hospital outcome[b]	
Survivor	89 (67.94%)
Non-survivor	42 (32.06%)

[a]Data presented as mean ± standard deviation; [b]Data are presented as *n* (%); [c]Data presented as median (minimum–maximum); [d]Having at least one additional disease in his/her medical history; [e]High-resolution computed tomography (HRCT) done in 86 patients only. CT-SS (CT severity scores) used; mild <7, moderate 8–17, severe 18–25; CRP, C-reactive protein

A detailed intergroup comparison by inhospital mortality is shown in Table 2. No significant difference was observed between the survivor and the non-survivor groups in terms of age, gender, chief complaints, and comorbidities. The median BUN value was observed to be significantly higher in the non-survivor group 23.48 (7.51–62.75) mg/dL than in the survivor group 20.66 (4.07–74.67) mg/dL; $p = 0.009$. Mean total protein (survivor 6.76 ± 0.63 g/L; non-survivor 6.48 ± 0.55 g/dL; $p = 0.0163$) and albumin (survivor 3.27 ± 0.35 g/dL; non-survivor 2.96 ± 0.35 g/dL; $p < 0.0001$) were significantly lower in the non-survivor group than in the survivor group. The median value of BAR (mg/g) was calculated to be significantly higher in the non-survivors 8.33 mg/g (2.07–21.86) than in the survivor group 6.11 mg/g (1.26–23.33); $p = 0.0003$. The median CRP and D-dimer values obtained were also significantly higher in the non-survivor group than the survivor group (CRP survivor 33.72 mg/dL (1.21–180.64); CRP non-survivor 54.11 mg/dL (5.23–262.66); $p = 0.0002$; D-dimer survivor 0.58 mg/L (0.09–10.8); non-survivor 2.25 mg/L (0.03–14.81); $p < 0.0001$). There was no significant difference in creatinine and HRCT scores obtained between the survivor and the non-survivor groups.

Receiver operating characteristic curve analysis was performed to determine the inhospital COVID-19 mortality predictive power of BUN, Albumin, BAR, CRP, and D-dimer levels (Fig. 1). Using a cutoff value of 18.69 mg/dL for BUN, the area under the curve (AUC) was 0.640, sensitivity and specificity were 81% and 46%, respectively (Table 3). The AUC of albumin was 0.727, with 73% sensitivity and 64% specificity, at a cutoff value of 3.03 g/dL. With a cutoff value of 6.23 mg/g for BAR and 38 mg/dL for CRP, similar values for AUC, sensitivity, and specificity were obtained (BAR 0.695; 79%, 54%; CRP 0.699, 79% and 53%). D-dimer had an AUC of 0.767 at a cutoff value of 0.64 mg/L, with sensitivity of 83% and specificity of 53%. To further analyze inhospital mortality predictive power, OR was calculated at the selected cutoff values. Albumin with an OR of 6.14, performed the best, followed by D-dimer (4.98). BAR and CRP had similar outcome of 3.75; BUN showed an OR of 3.13 at the selected cutoff value.

Discussion

This study was undertaken to predict the inhospital mortality of COVID-19 patients utilizing simple parameters, like BUN, albumin, and their ratio (BAR). A comparison of the inhospital mortality predictive power of BUN, albumin and BAR was done with CRP, D-dimer, and HRCT values.

Our study found that albumin (hypoalbuminemia) was more valuable than BUN and BAR in predicting inhospital mortality among COVID-19 admissions. The inhospital mortality predictive power of albumin was even greater than CRP, D-dimer, and HRCT, in our findings.

As the gigantic second wave of the COVID-19 pandemic ripped through India (and the world), there were shortages of testing kits, manpower, and capacities. So, it is important to assess the

Table 2: Evaluation of patients by inhospital mortality

	Survivor (89)	*Non-survivor (42)*	*p value*
Age[a]	52.9 ± 13.6	56.1 ± 14.7	0.234[d]
Gender			
Male (98)	68 (69.39%)	30 (30.61%)	0.540[e]
Female (33)	21 (63.64%)	12 (36.36%)	
Chief complaints[c]			
Fever	81 (91%)	40 (95.24%)	0.395[e]
Cough	68 (76.40%)	33 (78.57%)	0.783[e]
Shortness of breath	68 (76.40%)	35 (83.33%)	0.367[e]
Comorbidity[c]			
None (91)	56 (62.92%)	35 (83.33%)	0.099[e]
One (21)	18 (20.22%)	3 (7.14%)	0.156[e]
Two 17)	13 (14.61%)	4 (9.52%)	0.097[e]
Three or more (2)	2 (2.25%)	0 (0%)	0.085[f]
Diabetes[c] (32)	25 (28.09%)	7 (16.67%)	
Hypertension[c] (23)	19 (21.35%)	4 (9.52%)	
Hypothyroidism[c] (6)	6 (6.74%)	0 (0%)	
Laboratory results			
BUN (mg/dL)[b]	20.66 (4.07–74.67)	23.48 (7.51–62.75)	0.009*[g]
Total protein(g/dL)[a]	6.76 ± 0.63	6.48 ± 0.55	0.0163*[d]
Albumin (g/dL)[a]	3.27 ± 0.35	2.96 ± 0.35	<0.0001*[d]
BAR (mg/g)[b]	6.11 (1.26–23.33)	8.33 (2.07–21.86)	0.0003*[g]
Creatinine (mg/dL)[b]	0.78 (0.44–2.44)	0.85 (0.44–3.50)	0.2878[g]
CRP (mg/dL)[b]	33.72 (1.21–180.64)	54.11 (5.23–262.66)	0.0002*[g]
D-dimer (mg/L)[b]	0.58 (0.09–10.8)	2.25 (0.03–14.81)	<0.0001*[g]
HRCT	6 (8.57%)	1 (6.25%)	0.745[e]
Mild[c]	32 (45.71%)	6 (37.50%)	0.3304[e]
Moderate[c]	32 (45.71%)	9 (56.25%)	
Severe[c]	17 (2–25)	17.5 (4–25)	
Scores[b] (1–25)			

[a]Data presented as mean ± standard deviation; [b]Data presented as median (minimum–maximum); [c]Data presented as *n* (%); [d]Student's *t*-test was used; [e]Chi-square test was used; [f]Fisher's exact test was used; [g]Mann–Whitney *U* test was used; *p value is significant (<0.05)

factors related to COVID-19 to predict prognosis and channelize the resources. A systematic survey including 207 studies expressed 49 demographic and laboratory factors that can give important prognostic data on mortality and/or severe disease COVID-19 patients.[15] However, considering the sociodemographic constraints and to lessen the economic impact, we focused on more commonly available serum markers, like BUN, albumin and their ratio (BAR) for predicting the inhospital mortality.

In our study, age, gender, and presence of comorbidities did not have any significant difference between the survivors and the non-survivors. A current review stated that having at least one comorbidity is connected to increased severity of COVID-19 disease; however, no unmistakable affiliation was created between having these risk factors and hazard of casualty.[16] Another possible explanation could be a small sample size and younger median age of the admitted patients.

In this study, BUN values were higher in the non-survivor group than the survivor group significantly (p <0.01). The ROC analysis performed for inhospital mortality gave an AUC of 0.640 for BUN and an OR of 3.31 using a cutoff value of 18.69 mg/dL. Arihan et al. showed that high BUN at admission displayed a strong association with mortality in critically ill patients, even after rectifying for cofounders like renal failure.[17] Cheng et al. found that raised BUN was an independent risk factor for adverse outcome after adjustment of estimated glomerular filtration rate (eGFR) and could anticipate mortality in COVID-19 patients.[6] Elevated BUN can gauge the seriousness of pneumonia[18] and is used as one of the parameters of CURB-65 score.[2] Regular lung inclusion in COVID-19 patients, with respiratory failure being the main source of death, clarifies the relationship.[19] Acute kidney injury (AKI) is recognizable among COVID-19 patients and connected with higher mortality.[20] This may additionally clarify the connection between raised BUN and in-emergency clinic mortality in COVID-19 patients. Creatinine, in any case, is not considered as a risk factor for more regrettable prognosis in COVID-19 patients.[6] Even in our study, no significant difference was observed for creatinine among the survivors and the non-survivors. An explicit detail may be studied for this difference in BUN and creatinine.

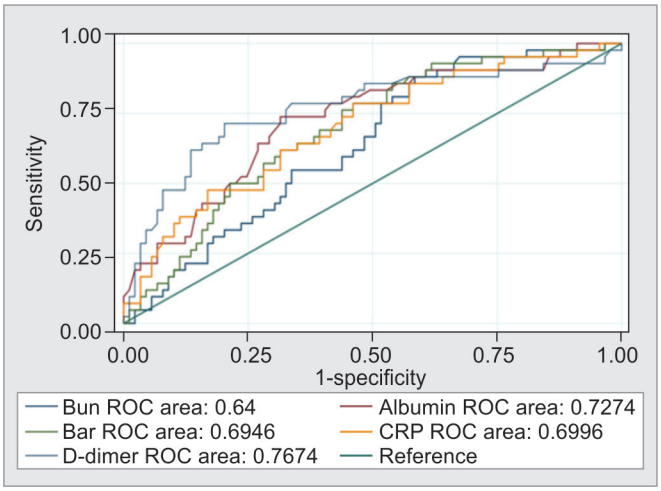

Fig. 1: ROC curve by inhospital mortality

We observed albumin levels to be significantly lower in the non-survivor group than the survivor group (p <0.0001). The ROC analysis revealed an AUC of 0.727. The OR calculated was 6.14 at a cutoff value of 3.03 g/dL. The OR thus observed was best among all the parameters observed, indicating the strongest association of hypoalbuminemia with inhospital mortality in COVID-19 patients. Hypoalbuminemia has been addressed in COVID-19, time and again, but its role in mortality has been less explored, and mechanisms less defined.[7,11,12,15,19] The albumin levels are maintained because of a harmony between pace of albumin synthesis and albumin clearance, through the renal and gastrointestinal route, and catabolism.[20] Following mechanisms have been suggested for hypoalbuminemia—(a) consistent viral replication and viral shedding can cause an extensive depletion of amino acids pool. (b) Decreased levels of branched chain amino acids can reduce (rapamycin-intervened) albumin translation[21] (b) patients without previous liver infection experiencing fever (as in COVID-19 likewise) may have albumin half-life diminished to around 7 days (rather than 21 days), proposing a checked increase in albumin removal.[22] (c) Systemic inflammation (as in COVID-19) results in increased capillary permeability that may cause escape of albumin into interstitial space. There is a likelihood that albumin therapy might be useful in COVID-19 patients through elective components.[23]

Huang et al. studied 299 patients of COVID-19, found hypoalbuminemia (<3.5 g/dL) in 106 (35.5%) patients, and concluded that hypoalbuminemia and lymphopenia were independent predictive factors for mortality (OR 6.39 and 13.13, respectively).[11] Violi et al. studied a cohort of 319 COVID-19 patients and observed that age and human serum albumin (HSA) were independently associated with mortality.[12] Another study with 602 COVID-19 patients advocated that mean albumin in the non-survivor group was significantly lower than that in the survivor group. Albumin had an OR of 6.48 at a cutoff value of 4.01 g/dL.[7]

BAR is again an accessible parameter in the ED and we found its level to be significantly raised in the non-survivor than the survivor group (p = 0.0003) With an AUC of 0.695 and OR 3.75, at a cutoff value of 6.23 mg/g, BAR arises as a solid pointer of inhospital mortality in COVID-19 patients. Albumin (hypoalbuminemia) was a more robust predictor of inhospital mortality than BAR or BUN, according to our findings. Küçükceran et al. utilized a cutoff of 3.9 mg/g for BAR and acquired an OR of 10.45. They presumed that BAR was a more trustworthy indicator of inhospital mortality than

Table 3: ROC analysis result by inhospital mortality

	BUN	*Albumin*	*BAR*	*CRP*	*D-dimer*
Cutoff level	≥18.69 mg/dL	≤3.03 g/dL	≥6.23 mg/g	≥38.00 mg/dL	≥0.64 mg/L
AUC (95% CI)	0.640 (0.544–0.736)	0.727 (0.634–0.821)	0.695 (0.601–0.788)	0.699 (0.603–0.796)	0.767 (0.671–0.864)
Sensitivity (%)	81	73	79	79	83
Specificity (%)	46	64	54	53	53
Odds ratio (95% CI)	3.13 (1.36–7.19)	6.14 (2.73–13.8)	3.75 (1.66–8.42)	3.75 (1.66–8.42)	4.98 (2.1–11.7)

CI, confidence interval; AUC, area under the curve; OR, odd's ratio

BUN and albumin levels.[7] Ryu et al. considered BAR as an indicator of mortality in patients with aspiration pneumonia. AUC for BAR was 0.70, OR 3.40 at a cutoff of 7.0 mg/g, and they inferred that BAR is a basic and possibly helpful prognostic factor of mortality in such patients.[14] Feng et al. significantly associated a high BUN to albumin ratio (cutoff 0.165 mg/g) with a worse survival in 1,158 hospital-acquired pneumonia cases.[24] Huang et al. stated that elevated BAR (AUC 0.821 at optimal cutoff 3.7887 mg/g) at admission be an independent risk factor for critical illness among 113 (8.2%) of 1,370 COVID-19 patients.[25] Gemcioglu et al. found neutrophil–albumin ratio (NAR), BAR, albumin–globulin ratio (AGR), aspartate aminotransferase platelet ratio index (APRI), and age to be independent predictors of severe COVID-19.[26]

C-reactive protein, D-dimer, and HRCT are mainstream parameters for risk stratification of COVID-19 patients and treatment direction in clinical practice.[15,27–31] Our results reflected that BAR and CRP performed equally in predicting inhospital mortality (OR 3.75) and marginally over BUN (OR 3.15). D-dimer has been closely studied as a prognostic variable in COVID-19.[6,26] We elucidated that D-dimer levels were significantly higher in non-survivors than survivors (p <0.0001). Thus, it is a robust predictor of mortality with an OR of 4.98, at a cutoff value of 0.64 mg/L. Nevertheless, albumin (hypoalbuminemia) had a still higher inhospital mortality predictive power (OR = 6.14) in COVID-19 patients, as per our findings. There was no significant difference observed in HRCT values (CT-SS scores) between survivors and non-survivors. Chest CT plays a paramount role to identify both complications and alternative diagnoses of COVID-19 (acute respiratory distress syndrome, pulmonary embolism, and heart failure), while its job for prognostication requires further examination with a bigger sample size.[32]

Limitations

The results were based on initial BUN, albumin, CRP, and D-dimer levels, and the kinetic assessment of these parameters was not done. Therefore, the relationship between prognostic significance and time-dependent changes could not be deciphered. Second, only CRF patients on dialysis were excluded and there could be a possibility of other CKD patients to have higher than baseline values for BUN. Nutritional status of the patients could be another confounding factor that was not taken into consideration in the emergency setting. Third, only patients alluded to the ED were incorporated, so this study cannot mirror the genuine mortality of COVID-19. We cannot comment on the mortality of those vaccinated against COVID-19, since only two of the admitted patients were partially vaccinated. Finally, a restricted sample size and a single-center study result may additionally scrutinize the replicability of the outcomes got.

Conclusion

A combination of simple laboratory data from the ED may be useful to predict the severity and mortality of COVID-19. Serum BUN, albumin and their ratio (BAR) at affirmation were dependable predictors of inhospital mortality in COVID-19 patients, with albumin (hypoalbuminemia) playing out the best in foreseeing result.

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