

Original Article

Blood Urea Nitrogen to Albumin Ratio is a Predictor of Mortality among Hospitalized Geriatric Patients with COVID-19.

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ABSTRACT:

Aim: This study aims to determine predictors of mortality among hospitalized geriatric patients with COVID-19 with a particular concern about the predictive value of blood urea nitrogen to albumin ratio (BAR). **Methods:** A retrospective cohort study included 114 geriatric patients (aged ≥ 60 years) admitted to a geriatrics hospital for isolation. A review of the medical files of participants was conducted to extract data regarding age, sex, comorbidities, clinical manifestations of COVID-19 and laboratory data including haematology, biochemistry and inflammatory markers on admission. BAR and Charlson comorbidity index (CCI) were calculated. The primary outcome was in-hospital mortality. Appropriate statistical analyses were operated. **RESULTS:** 59 (51.8%) patients died at the hospital. Comorbidities associated with mortality included diabetes mellitus, old stroke, hypertension, and cardiac disease besides higher CCI. Reporting of fever, fatigue, sore throat and delirium /altered mental status were also associated with mortality. Significant biomarkers included lower hemoglobin and serum albumin, higher total leukocyte count, serum creatinine, blood urea nitrogen, lactate dehydrogenase, D-dimer, c-reactive protein (CRP) and BAR. BAR at a cutoff of 12.92 mg/gm had the best predictive performance for mortality. Serum BAR > 12.92 mg/gm, albumin < 3.05 g/dl and CRP > 108 mg/l were independent predictors of in-hospital mortality **CONCLUSION:** Serum BAR > 12.92 mg/gm, albumin < 3.05 g/dl and CRP > 108 mg/l are independent predictors of mortality among hospitalized geriatric patients with COVID-19. BAR is a convenient biomarker and has the best predictive performance to early pick up COVID-19 geriatric patients at high risk of mortality.

Keywords: Blood Urea Nitrogen to Albumin ratio, Older adults, SARS-CoV-2

INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic is a worldwide health problem with a high risk of progression to severe illness and mortality in geriatric patients [1]. Concerns are essential for the management of COVID-19 geriatric patients in comparison to the younger population [2].

Aging is associated with a state of chronic, low-grade inflammation in a condition known as inflammaging. This condition is a major culprit in immunosenescence which briefs the overall alterations in the immune system of the aged and explains the increased vulnerability to various infections among seniors [3]. Poor immunological responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in geriatric patients could drive excessive inflammatory response, enhanced morbidity, and severe form of COVID-19 [2].

Accordingly, COVID-19 among older adults is characterized by a higher rate of hospitalization, respiratory insufficiency, and even death [2]. Eminent attempts were exerted to early expect outcomes of COVID-19, admirably at the beginning of hospitalization [4].

Certain manifestations, chronic diseases and laboratory markers are associated with a high risk of death among COVID-19 geriatric patients [2]. These factors include older age, severe initial presentations, multi-morbidity, increased D-dimer and elevated inflammatory markers such as Interleukin-6 (IL-6) and C-reactive protein (CRP) [2]. Blood Urea Nitrogen (BUN) was a predictor of mortality among critically ill cases [5]. It is also involved in the CURB-65 scoring system for patients with pneumonia [6]. Albumin is a negative acute-phase reactant [7]. Recently, the blood urea nitrogen to albumin ratio (BAR) was considered a

predictor of in-hospital mortality in geriatric patients with pneumonia in emergency departments [8]. In addition, BAR was a predictor of in-hospital mortality among COVID-19 patients with better reliability than serum BUN and albumin [9].

We did not come across previous studies assessing the predictive value of BAR among geriatric patients with COVID-19. Here we researched the association between different clinical and laboratory parameters with mortality. The study aims to determine predictors of in-hospital mortality and assess the predictive performance of BAR compared to serum BUN, albumin and CRP among a sample of hospitalized geriatric patients with COVID-19.

METHODS

Study Design, Place and Patients

A single-Centre retrospective study retrieved the demographic, clinical and laboratory data of all geriatric patients (aged ≥ 60 years) who were admitted to the geriatric's hospital at Ain Shams University for isolation throughout the period from December 2020 to April 2021. All patients had confirmed infection with SARS-CoV-2. Patients with known chronic kidney disease (CKD)/end-stage renal disease (ESRD) and chronic liver disease/hepatic cirrhosis were excluded from this study. Patients missing a documented outcome or discharged before completion of the recommended treatment regimen because of a transfer to another hospital or discharge on personal demand were also excluded from the study.

Extraction of Demographic and Clinical characteristics

Upon hospital admission, each patient was subjected to a detailed history taking to identify personal demographics such as age

and gender and clinical data as chronic diseases, clinical presentations and manifestations of COVID-19. Reviewing of medical files was performed for each participant to extract these data. Estimation of CCI was also performed [10]. Length of hospital stay (LOS) in days was determined according to the date of hospital admission and discharge as documented in the administrative data section of the hospital.

Laboratory data collection

Reverse transcription-polymerase chain reaction (RT-PCR) laboratory testing was essential to diagnose infection with SARS-CoV-2. Blood samples were collected from each patient on admission and analyzed at the central laboratories of Ain Shams University hospitals. Laboratory results included complete blood count (CBC), liver function tests, kidney function tests, D-dimer level, serum CRP, ferritin, IL-6, and procalcitonin. Reviewing of medical files was performed for each participant to extract these data. BAR was calculated by dividing serum BUN mg/l over Albumin g/l [11]. According to the hospital management protocol, serum levels of IL-6 and procalcitonin were not routinely performed upon admission. These markers were requested for selected cases and special situations as the presence of severe disease and before starting specific treatments. Accordingly, we utilized the available results of these markers during hospitalization.

Determination of Hospital Outcome

The primary outcome was in-hospital mortality. It was based on the documented status at the time of discharge through reviewing the administrative data of the hospital.

Statistical analysis

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data were summarized using mean and standard deviation for normally distributed quantitative variables or median and range for non-normally distributed quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t-test in normally distributed quantitative variables while non-parametric Mann-Whitney test was used for non-normally distributed quantitative variables [12]. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5 [13]. A receiver operating characteristic (ROC) curve was constructed with area under curve (AUC) analysis performed to detect the best cutoff value of selected markers for detection of mortality. Logistic regression was done to detect independent predictors of mortality [14]. P-values less than 0.05 were considered statistically significant.

Ethical Approval

The study protocol was checked and approved by the ethics review members at the geriatrics hospital and Research Ethics Committee (REC) at the Faculty of Medicine, Ain Shams University. The study got an approval code: FMASU R 108 / 2021. The approval date was 26/4/2021. REC works under Federal Wide Assurance No. FWA 000017585. The investigators ensured the privacy of all participants in the study.

RESULTS

A total of 114 patients with a mean age of 71.32 ± 8.23 years were included. 59 (51.8%) patients died at the hospital. Mean BAR was 15.05 ± 12.77 mg/gm. Based on the primary outcome of the study; the two

groups of patients were compared regarding demographics, clinical and laboratory information. Chronic diseases including diabetes mellitus (DM), hypertension, old stroke, and cardiac disease were significantly more frequent among non-survivors. There were statistically significant differences in mean values of the Glasgow Coma Scale (GCS), hemoglobin, and serum albumin upon admission (Tables 1, and 2). Median values of CCI, LOS, total leukocyte count (TLC), serum levels of creatinine, BUN, lactate dehydrogenase (LDH), D-dimer, CRP and BAR were significantly associated with in-hospital mortality as described in (Table 3 and Figure 1).

Shortness of breath was the most frequently reported COVID-19 symptom among participants (72 patients), followed by fever (63 patients), cough (56 patients), delirium/altered mental status (31 patients), fatigue (30 patients), sore throat (14 patients), gastrointestinal symptoms (13 patients), bony aches (11 patients), headache (2 patients), and chest pain (1 patient). Associations between these symptoms and mortality are presented in (Table 4)

ROC curves showed the predictive performance of serum BAR, BUN, albumin and CRP for in-hospital mortality. It provided the optimal cut-off point of each variable. BAR showed better prognostic utility than the mentioned markers. At a cutoff 12.92 mg/gm, BAR had sensitivity of 72.1% and specificity of 92.5% with AUC of 0.870 (95% CI of 0.795-0.946, P value of < 0.001) as described in (Table 5 and Figure 2).

Based on the sample size and clinical preferences of the study, serum BAR, BUN, CRP and albumin at their optimal cut-offs were selected for univariate analysis to determine their association with in-hospital mortality. The strength of association was

expressed as odds ratio (OR) as described in (Table 6). Significant variables were entered into a multivariate regression analysis and showed the independent predictors of mortality; BAR >12.92 mg/gm, CRP >108 mg/l, and albumin < 3.05 g/dl with an OR of 16.317 (95% CI of 3.483- 76.438, P value of < 0.001), 5.681 (95% CI of 1.393- 23.168, P value of 0.015), and 4.452 (95% CI of 1.100- 18.012, P value of 0.036), respectively. The model was able to explain 64.0 % of the variability of mortality as indicated by Nagelkerke R Square value. Also, it was able to correctly predict mortality by 85.9 % (Table 7).

DISCUSSION

The current study found that serum BAR, CRP and albumin at particular cut-offs were independent predictors of in-hospital mortality among COVID-19 geriatric patients. BAR was more valuable than BUN, CRP, and albumin in predicting in-hospital mortality. BAR had the best predictive performance with an AUC of 0.87 at an optimal cut-off point of 12.92 mg/gm with a sensitivity of 72.1 % and specificity of 92.5% among participants. This study showed the values of 38 mg/dl, 108 mg/l and 3.05 g/dl as the optimal cut-offs of BUN, CRP, and albumin, respectively. These findings supported the potential role of BAR as a mortality predictor in geriatric patients with COVID-19. It is also consistent with another study describing BAR as a more trustworthy indicator of in-hospital mortality than serum BUN and albumin [9]. A previous study of a sample of geriatric patients at the emergency department showed that serum albumin < 3.5 g/dl, BUN > 23 mg/dl, and BAR > 6.25 mg/gm have an increased risk of in-hospital mortality. Additionally, BAR was a more powerful predictor of in-hospital mortality than serum BUN, albumin, creatinine, and estimated

glomerular filtration rate among these patients [15].

For a more specific discussion regarding the role of BAR in COVID-19, Huang et al. showed that increased BAR (AUC of 0.82 at optimal cutoff 3.78 mg/g with a sensitivity of 69.0 % and specificity of 78.6 %) on admission was a predictor of critical illness in patients with COVID-19 [16]. Huang et al. also presented BAR in a novel predictive nomogram with a superior predictive utility among these patients [16].

The proportion of deaths in the current study was high, representing 51.8 % of the included patients, which supports the high fatality rates among geriatric patients with COVID-19 [17]. However, it is much higher than the observed proportions in other studies [17, 18]. This difference could be related to differences in settings of different studies, differences in the threshold severity required for hospital admission and racial discrepancies.

The study did not show a significant difference regarding age and gender among the two groups of patients despite their prognostic roles in other studies [18, 19]. Mostaza et al. reported older age as a predictor of mortality and female gender as a factor associated with survival among COVID-19 geriatric patients hospitalized in two hospitals in Spain [18]. Inflammaging, frailty and multi-morbidity are determinants of survival among geriatric patients [3, 20], as these conditions could predict worse outcomes of COVID-19 irrespective of chronological age [21, 22]. Frailty has particular importance in older adults with COVID-19; previous studies stated that frailty status per the clinical frailty scale was significantly associated with mortality rather than the age-adjusted CCI [4].

In this study, frailty assessment was lacking due to its absence in participants' medical records. Multi-morbidity was determined per CCI [10]. A higher median of CCI scores was significantly related to mortality. Frequently observed comorbidities among non-survivors included DM, hypertension, old cerebrovascular stroke and cardiac disease. It coincides with previous studies reporting that multi-morbidity with particular conditions such as DM, hypertension, old stroke and heart disease are predictive factors of worse prognosis, higher morbidity and mortality in geriatric patients [23-26]

The current study assessed the clinical impact of COVID-19 clinical manifestations on hospital outcomes. Shortness of breath, fever and cough were the most frequently reported symptoms. It correlates with other studies describing these symptoms as the most common among geriatric patients with COVID-19 [17, 18]. Additionally, the sequential manifestations of COVID-19 in geriatric patients usually begin with fever and cough, followed by dyspnea and possible hospitalization within 2–7 days after the appearance of initial symptoms. Then, after admission, some patients could develop respiratory insufficiency, acute respiratory distress syndrome, and even death within the next few days [18].

Although the general manifestations of COVID-19 among geriatric patients are distinctly similar to that of younger ones [18], the following differences mandate special attention for these patients. First, the time interval between onset and confirmed diagnosis of COVID-19 is longer than in younger patients. Second, atypical presentations of both clinical symptoms and radiological findings could be misleading [27]. Geriatric patients are more likely to be

asymptomatic and without fever despite having a similar viremia to symptomatic ones [28]. Also, these patients are more likely to have atypical changes in chest computed tomography scans [27].

Besides describing fever, fatigue and sore throat as significant clinical symptoms for mortality prediction, the study highlighted the clinical impact of delirium among older adults with COVID-19 [29]. The study showed that 31 patients had delirium/altered mental status before hospitalization. The presence of delirium/altered mental status was significantly associated with the occurrence of mortality which is consistent with other studies [29, 30]. Special attention has to be devoted to delirium in geriatric patients with COVID-19, as older age poses a high risk for delirium and COVID-19-related mortality [29].

Regarding the hematological parameters, lower hemoglobin levels and higher TLC were associated with mortality because of marked disease severity coinciding with other studies [31, 32].

Unfortunately, inflammation markers like procalcitonin and IL-6 face multiple economic limitations. Accordingly, serum ferritin, LDH and CRP are more feasible in lower-income settings [33]. In the current study, serum procalcitonin and IL-6 were frequently missing in patients' medical files. Additionally, these markers were not routinely requested on hospital admission. It could explain the contrary between the results of this study and other studies regarding the significance of procalcitonin and IL-6 in mortality prediction [4]. Serum CRP, LDH and ferritin levels were more frequently available in our analysis. Both serum CRP and LDH were significantly higher in non-survivors, representing the

cytokine storm associated with moderate to severe COVID-19 illness [33].

The study also revealed significantly higher median values of serum levels of D-dimer, BUN and creatinine among non-survivors coinciding with other studies [2, 4]. As patients with a history of CKD/ESRD were excluded from our analysis, the elevated serum creatinine and BUN levels were more likely to be related to acute kidney injury (AKI) in COVID-19. AKI could be related to different causes including direct viral effects on kidney tissue, septicemia, medication side effects and the systemic inflammatory response to COVID-19 [34]. AKI is more common among geriatric patients with COVID-19 and commonly associated with a higher risk of mortality [35]

Strengths, Limitations, and suggestions

As far as we know, it is the first study investigating the predictive utility of BAR in hospitalized geriatric patients with COVID-19. The study provides age-specific cut-off values of serum BAR, CRP, albumin and BUN for predicting in-hospital mortality among this vulnerable category of patients at the beginning of hospitalization. Study limitations include the relatively small sample size in a single hospital. The missing data in some variables is another limitation due to the retrospective design and the incomplete documentation system of the hospital. Also, the study lacks analysis of radiological data and frailty assessment which could have a confounding effect on our results. Future longitudinal multicentric studies are appreciated.

Conclusion

A combination of simple and easily obtainable clinical and laboratory parameters on admission may be beneficial to the early prediction of in-hospital

mortality among geriatric patients with COVID-19. Serum BAR, albumin and CRP on hospital admission are predictors of in-hospital mortality. BAR had the best predictive performance among the studied markers. Overall, the study supports the value of novel biomarkers to provide an early risk stratification of hospital outcomes among hospitalized geriatric patients with COVID-19.

Conflicts of Interest: The authors declare no conflict of interest.

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Author's Contribution: All authors have contributed to the study through data collection during their work at the geriatric's hospital for isolation with subsequent data entry and data analysis. Khalid E. Elsorady¹ has also contributed to study conceptualization/design, data acquisition and manuscript writing besides coordinating investigator's tasks. All authors approved the article.

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TABLES

Table 1. Participant characteristics and their associations with In-hospital mortality

Participant's characteristics		In-hospital Mortality				P value
		Yes		No		
		Count	%	Count	%	
Sex	Male	28	47.5%	24	43.6%	0.682
	Female	31	52.5%	31	56.4%	
Diabetes Mellitus	Yes	43	72.9%	29	52.7%	0.026
	No	16	27.1%	26	47.3%	
Cardiac disease (HF, ISHD, AF)	Yes	35	59.3%	22	40.0%	0.039
	No	24	40.7%	33	60.0%	
Old stroke	Yes	12	20.3%	4	7.3%	0.045
	No	47	79.7%	51	92.7%	
Chronic respiratory disease	Yes	4	6.8%	6	10.9%	0.518
	No	55	93.2%	49	89.1%	
Dementia	Yes	4	6.8%	2	3.6%	0.680
	No	55	93.2%	53	96.4%	
Hypertension	Yes	47	79.7%	29	52.7%	0.002
	No	12	20.3%	26	47.3%	
Malignant disease	Yes	7	11.9%	5	9.1%	0.630
	No	52	88.1%	50	90.9%	

* **Bold numbers mean significant**

Abbreviations: Heart failure (HF), ischemic heart disease (ISHD), Atrial fibrillation (AF)

Table 2. Participant characteristics and their associations with In-hospital mortality

Participant's characteristics	In-hospital Mortality				P value
	Yes		No		
	Mean	Standard Deviation	Mean	Standard Deviation	
Age	72.41	8.32	70.15	8.04	0.143
Glasgow Coma Scale	12.73	3.27	14.56	1.63	0.002
Albumin	2.83	0.60	3.34	0.43	< 0.001
Sodium level	135.73	5.42	133.13	19.25	0.504
Total proteins	6.50	0.42	6.68	1.18	0.722
Hemoglobin	10.40	2.33	12.33	2.16	< 0.001

* **Bold numbers mean significant**

Normal range of Hemoglobin (12-15g/dl), Albumin (3.5-5.7g/dl), Sodium (136-145 mmol/L), Total proteins (6-8.3 g/dl)

Table 3. Participant characteristics and their associations with In-hospital mortality

Participant's characteristics	In-hospital Mortality						P value
	Yes			No			
	Median	Minimum	Maximum	Median	Minimum	Maximum	
CCI	6.00	2.00	14.00	4.00	2.00	10.00	0.001
Creatinine	1.20	0.50	5.90	1.00	0.50	6.60	0.001
LOS (days)	9.00	2.00	46.00	13.00	4.00	31.00	0.006
BUN	54.00	10.00	144.00	22.00	8.00	57.00	< 0.001
BAR	20.90	4.35	62.50	6.39	2.25	21.53	< 0.001
AST	42.00	10.00	210.00	40.00	15.00	371.00	0.613
ALT	36.00	5.00	177.00	27.00	9.00	319.00	0.220
Ferritin level	540.50	54.70	4406.00	587.50	49.80	3465.00	0.799
LDH	450.00	211.00	649.00	300.50	146.00	970.00	0.011
TLC	12.00	2.30	26.80	7.90	2.90	16.80	< 0.001
Platelets	197.00	11.00	870.00	208.00	107.00	585.00	0.200
Total bilirubin	0.80	0.20	1.60	0.60	0.20	23.30	0.226
D-dimer	1.84	0.20	5000.00	0.80	0.04	18.10	< 0.001
C-reactive protein	144.25	9.70	368.00	44.20	0.62	482.00	< 0.001
Interleukin-6	26.00	25.00	129.00	34.70	2.80	63.00	0.629
Procalcitonin	0.28	0.13	0.35	0.11	0.02	0.50	0.157

* **Bold numbers mean significant**

Abbreviations: Charlson comorbidity index (CCI), Length of stay (LOS), Blood Urea Nitrogen (BUN), Blood Urea Nitrogen / Albumin ratio (BAR), Aspartate transaminase (AST), Alanine aminotransferase (ALT), Lactate dehydrogenase (LDH), Total Leucocyte Count (TLC)

Normal range of Creatinine (0.6-1.2mg/dl), BUN (8-20 mg/dl), AST (13-39 IU/L), ALT (7-52 IU/L), Ferritin level (13-150 ng/ml), Lactate dehydrogenase (140-271 IU/L), Total Leucocyte count (4-10 x 10³/μL), Platelets (150-410x 10³/μL), Total bilirubin (0.3-1mg/dL), D-dimer (Up to 0.500 μg/mL), C reactive protein (< 6 mg/l), Interleukin-6 (< 17.4 pg/mL), Procalcitonin (< 0.1 ng/mL)

Table 4. COVID-19 related symptoms and their associations with In-hospital mortality

COVID-19 related symptoms		In-hospital Mortality				P value
		Yes		No		
		Count	%	Count	%	
Fever	Yes	43	74.1%	20	47.6%	0.007
	No	15	25.9%	22	52.4%	
Cough	Yes	34	58.6%	22	51.2%	0.456
	No	24	41.4%	21	48.8%	
Shortness of breath	Yes	43	74.1%	29	67.4%	0.462
	No	15	25.9%	14	32.6%	
Fatigue	Yes	23	41.1%	7	17.9%	0.017
	No	33	58.9%	32	82.1%	
Bony aches	Yes	5	8.9%	6	14.3%	0.522
	No	51	91.1%	36	85.7%	
Headache	Yes	0	0.0%	2	4.8%	0.177
	No	57	100.0%	40	95.2%	
Chest pain	Yes	1	1.8%	0	0.0%	1
	No	56	98.2%	42	100.0%	
Sore throat	Yes	13	22.4%	1	2.4%	0.004
	No	45	77.6%	41	97.6%	
Delirium/altered mental status	Yes	27	45.8%	4	7.5%	< 0.001
	No	32	54.2%	49	92.5%	
Gastrointestinal symptoms (Diarrhea, vomiting, abdominal pain and anorexia)	Yes	8	14.0%	5	10.0%	0.524
	No	49	86.0%	45	90.0%	

* **Bold numbers mean significant**

Table 5. Predictive utilities of selected variables for In-hospital mortality

	Area Under the Curve	P value	95% CI		Cut off	Sensitivity %	Specificity %	PPV %	NPV %
			Lower Bound	Upper Bound					
BAR mg/gm	0.870	< 0.001	0.795	0.946	12.92	72.1	92.5	91.2%	75.5%
BUN mg/dl	0.847	< 0.001	0.767	0.927	38	73.5	91.5	90.0%	76.8%
CRP mg/l	0.732	< 0.001	0.623	0.841	108	67.5	77.8	73.0%	72.9%
Albumin g/dl	0.765	< 0.001	0.662	0.868	3.05	71.7	75	76.7%	69.8%

* **Bold numbers mean significant**

Abbreviations: Blood urea nitrogen / Albumin ratio (BAR), Blood Urea Nitrogen (BUN), C-reactive protein (CRP), 95% Confidence Interval (95% CI), Positive Predictive value (PPV), Negative Predictive Value (NPV).

Table 6. Univariate logistic regression for detection of mortality using BAR, BUN, CRP, Albumin

Variables		P value	OR	95% C.I.	
				Lower	Upper
Mortality	BAR >12.92 mg/gm	< 0.001	31.861	8.242	123.168
	BUN >38 mg/dl	< 0.001	29.769	8.922	99.328
	C-reactive protein >108 mg/l	< 0.001	7.269	2.769	19.085
	Albumin <3.05 g/dl	< 0.001	7.615	2.912	19.915

* **Bold numbers means significant**

Abbreviations: Blood urea nitrogen / Albumin ratio (BAR), Blood Urea Nitrogen (BUN).

Table 7. Multivariate logistic regression for detection of mortality using BAR, BUN, CRP, Albumin

Variable		P value	OR	95% C.I.	
				Lower	Upper
Mortality	BAR >12.92 mg/gm	< 0.001	16.317	3.483	76.438
	C reactive protein >108 mg/l	0.015	5.681	1.393	23.168
	Albumin <3.05 g/dl	0.036	4.452	1.100	18.012

*** Bold numbers means significant**

Abbreviations: Blood urea nitrogen / Albumin ratio (BAR).

Figures Legends:

Figure 1: Association between Blood Urea Nitrogen to Albumin ratio and In-hospital mortality

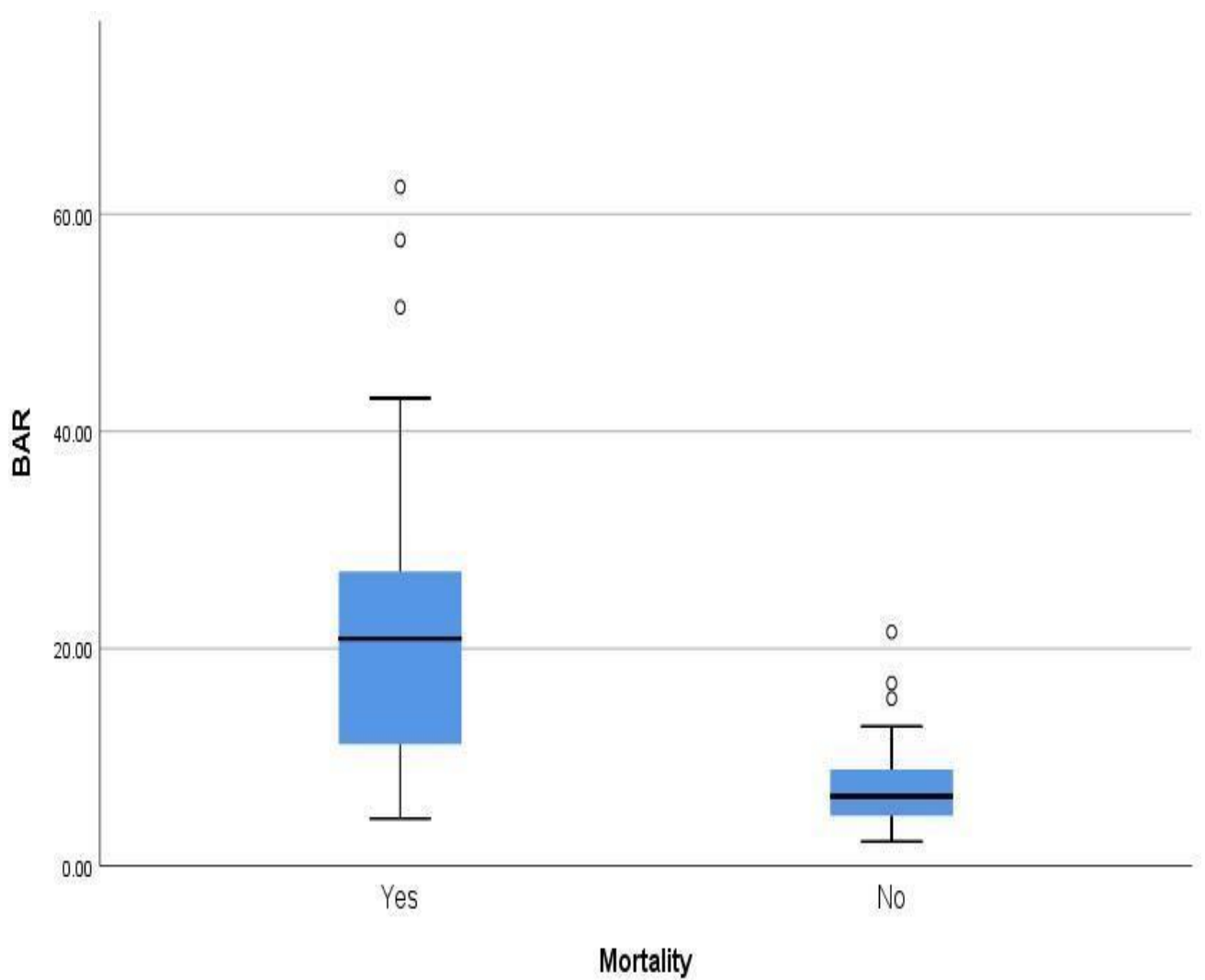


Figure 2: ROC curves of different laboratory markers with In-hospital Mortality

