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The relationship between albumin and its proportion to other markers in predicting mortality in severe COVID-19 patients

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Abstract. – OBJECTIVE: The aim of the present study was to investigate the relationship between albumin, blood urea nitrogen (BUN)/albumin ratio (BAR), D-dimer/albumin ratio (DAR), C-reactive protein (CRP)/albumin ratio (CAR), and neutrophil/albumin ratio (NAR) levels and prognosis in severe COVID-19 cases.

PATIENTS AND METHODS: A total of 619 patients diagnosed with severe COVID-19 in the emergency department were retrospectively analyzed. BAR, DAR, CAR, and NAR values were obtained by dividing BUN, neutrophil, CRP, and D-dimer by albumin. All patients were divided into groups [survived and deceased patients, and those who received and did not receive mechanical ventilation (MV) assistance]. These groups were statistically compared with regard to albumin, BAR, DAR, CAR, and NAR.

RESULTS: While 350 out of 619 patients survived, 269 patients died. A statistically significant difference was determined between survived and deceased patient groups with regard to BUN, neutrophil, lymphocyte, CRP, D-dimer, albumin, BAR, NAR, DAR, and CAR levels ($p<0.001$ for all). Also, BAR, NAR, DAR, and CAR were significantly higher in those who received MV support, while albumin was found to be low ($p<0.001$). According to receiver operating characteristic (ROC) analysis, NAR, BAR, CAR, albumin, and DAR had the highest area under the curve (AUC) values compared to the other parameters (0.825, 0.815, 0.806, 0.772, and 0.770, respectively) ($p<0.001$ for all). According to logistic regression analysis, BAR, NAR, DAR, and CAR levels were determined as important risk factors for mortality.

CONCLUSIONS: Low serum albumin levels can be used for severity as an additional tool in severe COVID-19 patients. Moreover, the NAR, BAR, and CAR levels were found to be more valuable than albumin levels in predicting prognosis in these patients.

Key Words:
Albumin, BUN/albumin ratio, Neutrophil/albumin ratio, CRP/albumin ratio, D-dimer/albumin ratio, COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) is a novel viral disease, which was discovered in Wuhan, China. COVID-19 is a pandemic that is related to high morbidity and mortality[1]. Since the beginning of the pandemic, elevated acute inflammatory markers have been observed in severely ill patients[2]. Due to its high mortality, screening all COVID-19 patients for hyper-inflammation through laboratory parameters and/or indices may help reduce the poor outcomes[3].

Serum albumin levels have been defined as prognostic factors for pneumonia patients and have shown a high performance for in-hospital mortality estimation[4]. Cytokine storm development in hospitalized COVID-19 patients may increase the risk of critical hypoalbuminemia-related mortality. In many studies[1,5] investigating albumin levels, low albumin levels have been observed in addition to elevated inflammatory markers in severely ill COVID-19 patients, and hypoalbuminemia on admission has been proposed to predict mortality. Furthermore, blood urea nitrogen (BUN), D-Dimer, C-reactive protein (CRP), and neutrophil levels have been defined as in-hospital mortality-related optimal risk factors in COVID-19 patients[6,7]. In recent studies[8-11], the BUN/serum albumin ratio (BAR), the D-dimer/albumin ratio (DAR), the CRP/albumin ratio (CAR), and the neutrophil/albumin ratio (NAR) have been shown to be prognostic factors for mortality in COVID-19 patients. The aim of the present study was to analyze the relationship between albumin, BAR, DAR, CAR, and NAR levels, which are readily available in emergency services, and to assess the prognosis in severe COVID-19 cases.

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Patients and Methods

Patients and Process

A total of 619 patients presented to the emergency department (a pandemic center) between April 1, 2020, and August 1, 2021, in whom severe COVID-19 had been confirmed and who fulfilled the inclusion criteria, were retrospectively analyzed. Patients older than 18 years of age, whose real-time reverse transcriptase polymerase-chain-reaction (RT-PCR) result was positive at least once, and all data of whom could be accessed through the hospital data management system and in whom the diagnosis of definitive COVID-19 had been confirmed according to the actual guidelines, were included in the study[12,13]. Severe COVID-19 was diagnosed according to the following criteria:

1. Presence of fever and respiratory tract infection signs and/or
2. Respiratory rate >30/min and/or
3. Severe respiratory rate (dyspnea, tachypnea, use of extra respiratory muscles) and/or
4. Oxygen saturation at room air of <90% ($PaO_2/FiO_2 \leq 300$ in patients under oxygen support) and/or
5. Characteristic thorax computed tomography (CT) finding of COVID-19 pneumonia: bilateral, lobular, peripheral, widespread patchy ground glass opacities[13].

Patients under 18 years of age, pregnant women, those who had chronic obstructive pulmonary disease, those with chronic hematological disease, hepatic or renal failure, chronic alcohol or substance dependence, cancer, bacterial pneumonia/sepsis, immune-suppressed patients, those who had been exposed to trauma and those whose data could not be found on the electronic recording system, were excluded from the study. Of these patients, age, gender, medical history, vital signs on admission to the emergency room (temperature, pulse rate, systolic blood pressure, saturation, respiratory rate), as well as BUN, neutrophil, lymphocyte, CRP, D-dimer, and albumin values obtained from routine blood analysis, the PCR result, report of the CT of the thorax, need for mechanical ventilation (MV) (non-invasive/invasive/high-flow nasal cannula oxygen), hospital stay and clinical outcomes (discharge/ in-hospital mortality) were obtained retrospectively from the electronic record system of the hospital. The PCR test was performed on the nasal and pharyngeal swab samples of the patients. The BAR, DAR, CAR, and NAR values were obtained by dividing BUN, neutrophil, CRP, and D-dimer by albumin. BAR, DAR, CAR, and NAR were compared statistically between the patient groups (those who survived and those who died, those who had been placed on MV, and those that did not receive MV assistance). The study was approved by the Necmettin Erbakan University Medical Faculty [date: 03/09/2021- number: 2021/3396 (6808)]. Complete blood count (CBC) was measured using Mindray auto hematology analyzer BC-6800 (Shenzhen, China). Biochemical parameters were obtained using Mindray chemistry analyzer BS-2000M device. Coronex COVID-19 QPCR (DS BIO and NANO Tech. Ltd., Ankara, Turkey) kit was used for the RT-PCR test.

Statistical Analysis

A descriptive analysis was performed. The categorical data were presented as ratios and numbers. The data distribution was analyzed through visual and analytic methods. As all numerical data were not normally distributed, they were given as median after having been compared with the Mann-Whitney U test. The diagnostic values of BAR, NAR, DAR, CAR, albumin, neutrophil, BUN, CRP, and D-dimer for prediction of mortality were investigated with receiver operating characteristic (ROC) analysis. In addition, the logistic regression analysis was applied to determine the need for MV and mortality. The cut-off values were calculated with Youden's J statistic. In the presence of significant limit values, sensitivity, specificity, and the negative predictive value (NPV) of these limits were calculated. For assessment of the area under the curve (AUC), the test was identified as statistically significant if Type 1 errors were below 5%. The AUC was compared with the Delong method in the MedCalc program (Flanders, Belgium). A p-value of <0.05 was accepted as statistically significant. The Statistical Package for the Social Sciences (SPSS) version 22 (IBM Corp., Armonk, NY, USA) and the MedCalc version 20 (MedCalc Software Ltd., Ostend, Belgium) program were used for the statistical analysis.

Results

The comparison of the two groups [(1) survivors, (2) deceased patients] with regard to demographic, clinical, and laboratory data have been displayed in Table I. While 350 out of 619 patients had survived, 269 patients died. The mean age of

Table I. Characteristics of all patients.

Variables	All Patients (n=619)	Survived patients (n=350)	Died patient (n=269)	*p*-value
[a]Age, (year)	69 (57-76)	64.5 (51-73)	72 (63-81)	<0.001*
[b]Male	296 (47.8)	158 (45.2)	138 (51.3)	0.128
[b]Female	323 (52.2)	192 (54.8)	131 (48.7)	
[a]Saturation, (%)	82 (75-87)	83 (75-87)	82 (75-87)	0.823
Respiratory rate a, (n/dk)	16 (12-28)	16 (12-26)	18 (12-28)	0.209
[a]Fever, (°C)	36.8 (36.2-37.8)	36.8 (36.2-37.8)	36.8 (36.2-37.8)	0.871
[a]Heart rate, (n/dk)	85 (72-115)	85 (74-120)	85 (70-110)	0.441
[a]SBP, (mmHg)	110 (95-120)	110 (95-120)	100 (90-120)	0.138
[a]BUN, (mg/dl)	33.1 (21.1-47.6)	25.4 (16.8-38.7)	42.9 (32.7-61.4)	<0.001*
[a]Neutrophil, (10^3/mL)	9 (5.7-13.48)	7.2 (4.2-10.2)	12.3 (8.7-15.53)	<0.001*
[a]Lymphocyte, (10^3/mL)	1 (0.6-1.4)	1.3 (1-1.6)	0.8 (0.5-1.1)	<0.001*
[a]D-dimer, (µg/mL)	276 (158.3-394)	245.5 (249)	322 (203.8-413.3)	<0.001*
[a]CRP, (mg/L)	131 (70.3-204)	86.5 (40-164)	177 (121-242)	<0.001*
[a]Albumin, (g/L)	33.8 (25.4-42.2)	37.9 (29.9-47.6)	26.3 (19.8-35.8)	<0.001*
[b]MV support	310 (50.1)	176 (50.2)	134 (49.8)	0.907
[a]LOSH, (day)	10 (6-16)	11 (7-17)	10 (6-15)	0.008
[a]BAR	0.99 (0.55-1.84)	0.66 (0.72)	1.67 (1.02-2.53)	<0.001*
[a]NAR	0.27 (0.15-0.47)	0.18 (0.11-0.3)	0.45 (0.28-0.72)	<0.001*
[a]DAR	8.2 (4.8-12)	6.27 (3.16-9.56)	11.11 (7.8-16.3)	<0.001*
[a]CAR	4.2 (1.8-7.2)	2.31 (1.06-4.75)	6.43 (4.2-11.1)	<0.001*

[a]given as the median (Q1-Q3), [b]given as n (%), SBP: systolic blood pressure, BUN: blood urea nitrogen, CRP: C-reactive protein, MV: mechanical ventilation, LOSH: Length of stay in hospital, BAR: BUN/albumin ratio, NAR: Neutrophil/albumin ratio, DAR: D-dimer/albumin ratio, CAR: CRP/albumin ratio, *p<0.001.

Table II. ROC analysis results of parameters according to in-hospital mortality.

Parameters	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	NPV (%)
BAR	0.815	0.782-0.847	>0.99	76.6	70.9	79.7
NAR	0.825	0.793-0.856	>0.29	74.3	74.3	79
DAR	0.770	0.733-0.806	>8	74	64.6	76.4
CAR	0.806	0.772-0.839	>3.7	79.6	65.4	80.6
Albumin	0.772	0.735-0.809	<35.75	75.1	57.7	75.1
Neutrophil	0.767	0.730-0.803	>9.45	70.3	70.9	75.6
BUN	0.759	0.721-0.796	>29.17	84.4	60.3	83.4
CRP	0.745	0.707-0.783	>114.5	80.7	60.3	80.2
D-dimer	0.634	0.591-0.677	>254.5	64.3	52.6	65.7

ROC: Receiver operating characteristic, CI: Confidence interval, AUC: Area under the curve, NPV: Negative predictive value, BAR: BUN/ albumin ratio, NAR: Neutrophil/albumin ratio, DAR: D-dimer/albumin ratio, CAR: CRP/albumin ratio, BUN: blood urea nitrogen, CRP: C-reactive protein.

patients was 69 years (57-76), and 296 (47.8%) were male. The patients who died were older (p<0.001). A statistically significant difference was defined between the groups with regard to BUN, neutrophil, lymphocyte, CRP, D-dimer, albumin, BAR, NAR, DAR, and CAR levels (p<0.001 for all).

The ROC analysis of parameters according to the cut-off value has been presented in Table II. NAR, BAR, CAR, albumin, and DAR had the highest AUC values compared to the other parameters (0.825, 0.815, 0.806, 0.772, and 0.770, respectively) (p<0.001 for all). For all parameters, when the cut-off value of BUN was >29.1, it reached the highest value with a sensitivity of 84.4% and an NPV of 83.4%. D-dimer had the lowest value when its cut-off value was >254.5, with a sensitivity of 64.3% and an NPV of 65.7%. According to Logistic regression analysis, BAR, NAR, DAR, and CAR levels were determined as important risk factors for mortality (p<0.001) (Table III).

When the parameters were compared between the patients who received and did not receive MV support, BAR, NAR, DAR, and CAR

Table III. ROC analysis results of parameters according to in-hospital mortality.

	Univariate					Multivariate				
	B	S.E.	*p*-value	OR	95% CI	B	S.E.	*p*-value	OR	95% CI
BUN>29.17	2.105	0.200	<0.001	8.204	5.540-12.151					
Neutrophil>9.45	1.748	0.178	<0.001	5.744	4.054-8.140					
CRP>114.5	1.846	0.189	<0.001	6.335	4.373-9.177					
D-dimer>254.5	0.692	0.166	<0.001	1.997	1.447-2.767					
Albumin<35.75	1.415	0.178	<0.001	4.115	2.905-5.830					
BAR>0.99	2.073	0.186	<0.001	7.950	5.522-11.445	1.146	0.217	**<0.001***	3.146	2.055-4.815
NAR>0.29	2.125	0.186	<0.001	8.374	5.820-12.048	1.172	0.218	**<0.001***	3.227	2.108-4.945
DAR>8	1.645	0.178	<0.001	5.181	3.653-7.349	0.975	0.210	**<0.001***	2.650	1.775-4.002
CAR>3.7	1.997	0.188	<0.001	7.346	5.090-10.652	1.035	0.224	**<0.001***	2.815	1.814-4.368

BAR: BUN/ albumin ratio, NAR: Neutrophil/albumin ratio, DAR: D-dimer/albumin ratio, CAR: CRP/albumin ratio, BUN: blood urea nitrogen, CRP: C-reactive protein, OR: Odds rate, S.E.: standard error, *p<0.001.

were significantly higher in those who received MV support, while albumin was found to be low (p<0.001) (Table IV). According to the results of the logistic regression analysis, only respiratory rate, temperature, pulse, and NAR values were determined as independent parameters for predicting the need for MV (p<0.005) (Table V).

Discussion

Although most COVID-19 patients have mild or moderate illness, early diagnosis of critical cases is important to avoid prolonged hospital stay and increased mortality rates[14]. Hematological and biochemical parameters have a substantial role in the early diagnosis and prognosis[15]. Systemic inflammation is common in severe COVID-19 patients[16]. Albumin is a blood protein, the involvement of which in systemic inflammation has been proven. In addition, it is an important antioxidant, which protects host cells from inflammation or infection-induced oxidative damage[17]. Hypoalbuminemia reflects malnutrition, hepatic and renal dysfunction, and poor survival in critically ill patients[18]. It has also been defined that it is an independent risk factor associated with adverse outcomes in patients with COVID-19[1,19]. Huang et al[5] argued that hypoalbuminemia could result from systemic inflammation in COVID-19. Furthermore, when the serum albumin level was <35 g/L, the COVID-19-related mortality risk increased by 6-fold [Odds ratio (OR) 6.394, 95% CI, 1.316-31.092]. Uyar et al[20] evaluated 63 COVID-19 patients and found lower albumin levels in patients hospitalized at the intensive care unit (ICU) compared to those hospitalized in the general ward (p≤0.001), and the AUC was found to be 0.98 when the cut-off value was ≤3.6. In our study, the albumin levels were lower in the non-surviving patient

Table IV. Comparison of MV assistance and parameters.

	Univariate					Multivariate				
	B	S.E.	*p*-value	OR	95% CI	B	S.E.	*p*-value	OR	95% CI
BUN>29.17	2.105	0.200	<0.001	8.204	5.540-12.151					
Neutrophil>9.45	1.748	0.178	<0.001	5.744	4.054-8.140					
CRP>114.5	1.846	0.189	<0.001	6.335	4.373-9.177					
D-dimer>254.5	0.692	0.166	<0.001	1.997	1.447-2.767					
Albumin<35.75	1.415	0.178	<0.001	4.115	2.905-5.830					
BAR>0.99	2.073	0.186	<0.001	7.950	5.522-11.445	1.146	0.217	**<0.001***	3.146	2.055-4.815
NAR>0.29	2.125	0.186	<0.001	8.374	5.820-12.048	1.172	0.218	**<0.001***	3.227	2.108-4.945
DAR>8	1.645	0.178	<0.001	5.181	3.653-7.349	0.975	0.210	**<0.001***	2.650	1.775-4.002
CAR>3.7	1.997	0.188	<0.001	7.346	5.090-10.652	1.035	0.224	**<0.001***	2.815	1.814-4.368

BAR: BUN/ albumin ratio, NAR: Neutrophil/albumin ratio, DAR: D-dimer/albumin ratio, CAR: CRP/albumin ratio, BUN: blood urea nitrogen, CRP: C-reactive protein, OR: Odds rate, S.E.: standard error, *p<0.001.

Table V. The logistic regression analysis of parameters in predicting MV assistance.

	B	S.E.	*p*-value	OR	95% CI
Respiratory rate	0.104	0.019	**<0.001***	1.110	1.069-1.152
Fever	0.327	0.142	**0.022****	1.387	1.049-1.834
Heart rate	0.021	0.006	**0.001****	1.021	1.009-1.034
NAR	1.374	0.434	**0.002****	3.950	1.688-9.242

CI: Confidence interval, NAR: Neutrophil/albumin ratio, OR: Odds rate, S.E.: standard error, *p<0.001, **p<0.05.

group compared to those who survived (p<0.001). When the cut-off value of albumin in the prediction of mortality was <35.75, AUC was 0.772 (75.1% sensitivity and 57.7% specificity, p<0.001). There was a significant difference in albumin levels between the patients who received and those who did not receive MV support (p<0.001). It can be said that hypoalbuminemia at the time of admission is an important parameter associated with prognosis in patients with severe COVID-19.

BUN was associated with poor prognosis in various diseases[21,22]. Recent studies[8,23,24] have demonstrated that BAR is an important prognostic factor for mortality in community-acquired pneumonia (CAP), in elderly patients hospitalized in ICU, and in patients with COVID-19. Cheng et al[6] found that the BUN levels could predict the in-hospital mortality (AUC 0.88). In another study[15], the BUN and BAR levels in patients with advanced disease were higher, and BAR demonstrated a better performance than other parameters in detecting severe disease [OR 2.185, 95% CI, 1.151-4.148; p=0.017]. Küçükceran et al[8] also reported that in patients with COVID-19, BAR reached 0.809 AUC and had an OR of 10.448 when the BAR cut-off value was >3.9 mg/g. The authors also emphasized that the AUC and OR values of BAR were higher than that of BUN and albumin levels. BUN levels increase as the severity of pneumonia increases. It has been shown that 100% of pulmonary damage occurs in fatal cases of COVID-19[25]. In our study, most of which comprised patients with severe COVID-19 pneumonia, the BUN and the BAR levels in the deceased patient group were higher than those who survived (p<0.001). The AUC of BAR was higher than that of BUN and albumin (AUC 0.815, 0.759, 0.772, respectively). Furthermore, the BAR levels were significantly high in those who needed MV. When the BAR cut-off value was >0.99, it reached 76.6% sensitivity, 70.9% specificity, p<0.001. These results suggest elevated BAR and BUN may be associated with severe pneumonia and mortality due to COVID-19.

Many studies[26,27] have associated elevated plasma D-dimer levels in CAP with a hyperinflammatory reaction or reported that D-dimer was associated with the severity of diseases in COVID-19. In the study conducted by Küçükceran et al[9] the mean DAR value in the deceased patient group was higher than in survivors; when the DAR cut-off value was 56.36, they reached 84.9% sensitivity and 58.4% specificity values. They emphasized that DAR was more valuable than other parameters in estimating in-hospital mortality. In our study, the D-Dimer and the DAR levels of the deceased patient group were high compared to that of those who survived (p<0.001). Besides, the AUC of DAR was higher than that of D-Dimer and equal to that of albumin (AUC 0.770, 0.634, 0.772, respectively). When the DAR cut-off value was >8, the sensitivity was found to be 74%, and specificity was found as 64.6%, p<0.001. Furthermore, the DAR levels were significantly higher in the patient group who needed MV. Consistent with the literature, DAR appears to be much more valuable than D-dimer in determining the severity of severe COVID-19 patients.

CRP is a marker that rises rapidly within hours of the inflammatory process. Therefore, serum CRP levels are frequently used as a laboratory marker of inflammation[28]. In patients with severe H1N1 influenza, the mean CRP levels were associated with the disease severity (p<0.05)[29]. Tan et al[30] reported that in severe cases of COVID-19, the CRP levels may increase before any findings could be seen on the thorax CT. Recently, CAR has been expressed as a good marker in predicting the prognosis in cancer, sepsis, and critically ill patients[31-33]. Wang et al[34] reported that CAR was significantly increased in patients with severe COVID-19. In our study, the CRP and CAR levels of the dying patient group were found to be higher than those who survived (p<0.001). Furthermore, the AUC of CAR was higher than that of CRP and albumin. (AUC 0.806, 0.745, 0.772, respectively). When the CAR cut-off value was >3.7, it had 79.6% sensitivity, 65.4% specificity, p<0.001. As

Karakoyun et al[10] stated, CAR may have a major role in systemic inflammation and can predict the severity of COVID-19 in earlier stages compared to CRP and albumin.

The uncontrolled inflammatory response plays a vital role in COVID-19 disease. Many studies[16,35] have shown that patients with severe COVID-19 have higher neutrophil and lower lymphocyte counts compared to non-serious cases. In addition, the NLR (neutrophil/lymphocyte ratio) level has also been accepted as an inflammatory and prognostic factor in severe COVID-19[36]. Varim et al[11] developed a simple index by dividing the neutrophil count by albumin and found that NAR showed 71.1% sensitivity and 71.7% specificity in predicting the mortality of patients with COVID-19 (AUC 0.736, 95% CI, 0.641-0.832, $p<0.001$). In addition, they emphasized that this simple index could be used instead of the NLR, platelet/lymphocyte ratio, fibrinogen/albumin ratio and the lymphocyte/CRP ratio. In our study, the neutrophil and NAR levels of the deceased patient group were found to be higher than those who survived ($p<0.001$). At the same time, the AUC of NAR was the highest of all other parameters evaluated in the study (0.825, $p<0.001$). When the NAR cut-off value was >0.29, it had 74.3% sensitivity, 74.3% specificity, $p<0.001$. Therefore, it can be stated that NAR is an independent and strong risk factor associated with the prognosis in severe COVID-19 patients.

Limitations

Firstly, this study was a single-center, retrospective study with a small number of patients. Therefore, it should be confirmed by multi-center, prospective studies with a larger number of patients. Secondly, only the complete blood count and serum biochemistry values of the patients at the time of admission were examined. The dynamic changes in laboratory values of hospitalized patients could not be analyzed. Thirdly, since this was a retrospective study, the duration of symptoms or the body mass index of patients was unknown. Fourthly, we cannot completely exclude the existence of possible unmeasured factors affecting in-hospital mortality and the effect of selection bias, despite the cascade of patients.

Conclusions

Based on our study results, low serum albumin levels can be used as an additional tool for severity and risk stratification in severe COVID-19 patients. Moreover, the NAR, BAR, and the CAR levels were found to be more valuable than albumin levels in predicting prognosis in these patients. Since obtaining these parameters is fast and since they are inexpensive, reproducible, and easily accessible, they provide the advantage of being used simply in pandemic conditions, especially in emergency unit settings. These findings need to be confirmed by more extensive and prospective studies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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This study did not receive any funding or support.

Ethics Approval

The study was approved by the Necmettin Erbakan University Faculty of Medicine Local Ethics Committee [date: 03/09/2021 and number: 2021/3396 (6808)]. The study was conducted according to the principles of the Helsinki Declaration.

Informed Consent

Because the retrospective data retrieval would not affect patients' clinical management, informed consent was not sought for the present study. The identity information of the patients was kept confidential.

Availability of Data and Materials

Primary data used in this research article will be available on request.

Authors' Contributions

Concept: B.E, Design: B.E, T.A, Data Collection or Processing: B.E, T.A, Analysis or Interpretation: B.E, T.A, Writing: B.E.

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References

1) Violi F, Cangemi R, Romiti GF, Ceccarelli G, Oliva A, Alessandri F, Pirro M, Pignatelli P, Lichtner M, Carraro A, Cipollone F, D'ardes D, Pugliese F, Mastroianni CM. Is Albumin Predictor of Mortality in COVID-19? Antioxid Redox Signal 2021; 35: 139-142.
2) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao

Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.

3) Li H, Wang YM, Xu JY, Cao B. Potential antiviral therapeutics for 2019 novel coronavirus. Zhonghua Jie He He Hu Xi Za Zhi 2020; 43: E002.

4) Kim H, Jo S, Lee JB, Jin Y, Jeong T, Yoon J, Lee JM, Park B. Diagnostic performance of initial serum albumin level for predicting in-hospital mortality among aspiration pneumonia patients. Am J Emerg Med 2018; 36: 5-11.

5) Huang J, Cheng A, Kumar R, Fang Y, Chen G, Zhu Y, Lin S. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol 2020; 92: 2152-2158.

6) Cheng A, Hu L, Wang Y, Huang L, Zhao L, Zhang C, Liu X, Xu R, Liu F, Li J, Ye D, Wang T, Lv Y, Liu Q. Diagnostic performance of initial blood urea nitrogen combined with D-dimer levels for predicting in-hospital mortality in COVID-19 patients. Int J Antimicrob Agents 2020; 56: 106110.

7) Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, Luo M, Chen L, Zhao Y. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect 2020; 81: e6-e12.

8) Küçükceran K, Ayrancı MK, Girişgin AS, Koçak S, Dündar ZD. The role of the BUN/albumin ratio in predicting mortality in COVID-19 patients in the emergency department. Am J Emerg Med 2021; 48: 33-37.

9) Küçükceran K, Ayranci MK, Girişgin AS, Koçak S. Predictive value of D-dimer/albumin ratio and fibrinogen/albumin ratio for in-hospital mortality in patients with COVID-19. Int J Clin Pract 2021; 75: e14263.

10) Karakoyun I, Colak A, Turken M, Altin Z, Arslan FD, Iyilikci V, Yilmaz N, Kose S. Diagnostic utility of C-reactive protein to albumin ratio as an early warning sign in hospitalized severe COVID-19 patients. Int Immunopharmacol 2021; 91: 107285.

11) Varim C, Yaylaci S, Demirci T, Kaya T, Nalbant A, Dheir H, Senocak D, Kurt R, Cengiz H, Karacaer C. Neutrophil count to albumin ratio as a new predictor of mortality in patients with COVID-19 ınfection. Rev Assoc Med Bras 2020; 66 Suppl 2: 77-81.

12) WHO. Clinical management of severe acute respiratory infection when Novel coronavirus (nCoV) infection is suspected: interim guidance. Available at: https://www.who.int/internal-publications-detail/clinical-managementof-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. (Accessed March 10, 2020).

13) Ministry of Health, Republic of Turkey. Guidance to COVID-19(SARSCov2 infection). Available at: https://hsgm.saglik.gov.tr/depo/birimler/gocsagligi/covid19/rehber/COVID-19 Rehberi20200414 eng v4 002 14.05.2020.pdf

14) Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the Clinical Characteristics of Coronavirus Disease 2019 (COVID-19). J Gen Intern Med 2020; 35: 1545-1549.

15) Gemcioglu E, Davutoglu M, Catalbas R, Karabuga B, Kaptan E, Aypak A, Kalem A.K, Ozdemir M, Yesilova N.Y, Kalkan E.A, Civak Musa, Küçüksahin Orhan, Erden Abdulsamet, Ates Ihsan. Predictive values of biochemical markers as early indicators for severe COVID-19 cases in admission. Future Virol 2021; 16: 353-367.

16) Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian DS. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020; 71: 762-768.

17) Acharya R, Poudel D, Bowers R, Patel A, Schultz E, Bourgeois M, Paswan R, Stockholm S, Batten M, Kafle S, Lonial K, Locklear I. Low Serum Albumin Predicts Severe Outcomes in COVID-19 Infection: A Single-Center Retrospective Case-Control Study. J Clin Med Res 2021; 13: 258-267.

18) Feketea GM, Vlacha V. The Diagnostic Significance of Usual Biochemical Parameters in Coronavirus Disease 19 (COVID-19): Albumin to Globulin Ratio and CRP to Albumin Ratio. Front Med 2020; 7: 566591.

19) Akman C, Bakırdöğen S. The role of serum inflammatory markers, albumin, and hemoglobin in predicting the diagnosis in patients admitted to the emergency department with a pre-diagnosis of COVID-19. Rev Assoc Med Bras 2021; 67 Suppl 1: 91-96.

20) Uyar E, Merdin A, Yamanyar S, Ezgü MC, Artuk C, Taşkın G, Arslan Y, Ceritli S. Could serum albumin value and thrombocyte/lymphocyte ratio be an important prognostic factor in determining the severity of COVID 19? Turk J Med Sci 2021; 51: 939-946.

21) Richter B, Sulzgruber P, Koller L, Steininger M, El-Hamid F, Rothgerber DJ, Forster S, Goliasch G, Silbert BI, Meyer EL, Hengstenberg C, Wojta J, Niessner A. Blood urea nitrogen has additive value beyond estimated glomerular filtration rate for prediction of long-term mortality in patients with acute myocardial infarction. Eur J Intern Med 2019; 59: 84-90.

22) Tatlisu MA, Kaya A, Keskin M, Avsar S, Bozbay M, Tatlisu K, Eren M. The association of blood urea nitrogen levels with mortality in acute pulmonary embolism. J Crit Care 2017; 39: 248-253.

23) Milas GP, Issaris V, Papavasileiou V. Blood urea nitrogen to albumin ratio as a predictive factor for pneumonia: A meta-analysis. Respir Med Res 2022; 81: 100886.

24) Dundar ZD, Kucukceran K, Ayranci MK. Blood urea nitrogen to albumin ratio is a predictor of in-hospital mortality in older emergency department patients. Am J Emerg Med 2021; 46: 349-354.

25) Zhang B, Zhou X, Qiu Y, Song Y, Feng F, Feng J, Song Q, Jia Q, Wang J. Clinical characteristics of 82 cases of death from COVID-19. PLoS One 2020; 15: e0235458.

26) Ge YL, Liu CH, Wang N, Xu J, Zhu XY, Su CS, Li HL, Zhang HF, Li ZZ, Li HL, Zhang X, Chen H, Yu HL, Fu AS, Wang HY. Elevated plasma D-dimer in adult community-acquired pneumonia patients is associated with an increased inflammatory reaction and lower survival. Clin Lab 2019: 65.

27) Gao Y, Li T, Han M, Li X, Wu D, Xu Y, Zhu Y, Liu Y, Wang X, Wang L. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol 2020; 92: 791-796.

28) Dix C, Zeller J, Stevens H, Eisenhardt SU, Shing KSCT, Nero TL, Morton CJ, Parker MW, Peter K, McFadyen JD. C-reactive protein, immunothrombosis and venous thromboembolism. Front Immunol 2022; 13: 1002652.

29) Vasileva D, Badawi A. C-reactive protein as a biomarker of severe H1N1 influenza. Inflamm Res 2019; 68: 39-46.

30) Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, Jiang X, Li X. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol 2020; 92: 856-862.

31) Fan Z, Fan K, Gong Y, Huang Q, Yang C, Cheng H, Jin K, Ni Q, Yu X, Luo G, Liu C. The CRP/albumin ratio predicts survival and monitors chemotherapeutic effectiveness in patients with advanced pancreatic cancer. Cancer Manag Res 2019; 11: 8781-8788.

32) Yu Y, Wu W, Dong Y, Li J. C-Reactive Protein-to-Albumin Ratio Predicts Sepsis and Prognosis in Patients with Severe Burn Injury. Mediators Inflamm 2021; 2021: 6621101.

33) Oh TK, Song IA, Lee JH. Clinical usefulness of C-reactive protein to albumin ratio in predicting 30-day mortality in critically ill patients: A retrospective analysis. Sci Rep 2018; 8: 14977.

34) Wang X, Xu Y, Huang H, Jiang D, Zhou C, Liao H, Chen X. An increased pretreatment C-reactive protein-to albumin ratio predicts severe novel corona virus infected pneumonia. Research Square 2020, https://doi.org/10.21203/rs.3.rs-31723/v1.

35) Wang X, Li X, Shang Y, Wang J, Zhang X, Su D, Zhao S, Wang Q, Liu L, Li Y, Chen H. Ratios of neutrophil-to-lymphocyte and platelet-to-lymphocyte predict all-cause mortality in inpatients with coronavirus disease 2019 (COVID-19). Epidemiol Infect 2020; 148: e211.

36) Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, Deng Y, Wang H, Chen R, Yu Z, Li Y, Shang J, Zeng L, Zhao J, Guan C, Liu Q, Chen H, Gong W, Huang X, Zhang YJ, Liu J, Dong X, Zheng W, Nie S, Li D. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: a retrospective cross-sectional study. J Med Virol 2020; 92: 2573-2581.