Procalcitonin/Albumin Ratio as a Novel Biomarker for Predicting Mortality in COVID-19

Hasan Ergenç[1], Zeynep Ergenç[1], Cemal Koray Öztürk[2], Hasan Tahsin Gozdas[3], Özlem Karaca Ocak[4], Özgür İnce[5]

[1]*Department of Internal Medicine, Ayancık State Hospital, Sinop, Turkey*
[2]*Department of Anesthesiology, Yenikent State Hospital, Sakarya, Turkey*
[3]*Department of Infectious Diseases and Clinical Microbiology, Abant İzzet Baysal University, Faculty of Medicine, Bolu, Turkey*
[4]*Department of General Surgery, Medicana International Hospital, Samsun, Turkey*
[5]*Department of Pulmonology, Medicana International Hospital, Samsun, Turkey*

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) first appeared in China in December 2019, and has become a global pandemic. Because the clinical progression of the disease is highly variable, better prediction of prognosis and mortality is important. In the present study, we investigated the role of procalcitonin/albumin ratio (PAR) as a new biomarker in predicting mortality in patients with COVID-19 infection.

Methods: In this study, patients with COVID-19 diagnosis were enrolled from Sakarya Yenikent State Hospital and Ayancık State Hospital between 09.11.2020 and 04.05.2021. The demographic characteristics, biochemical and hematological parameters such as age, gender, length of hospital stay, and comorbidities of the patients were collected retrospectively from medical records.

Results: Of the 105 patients, 51 were mild and 54 were critically ill. Between mild and critical cases, age, lymphocyte count, red cell distribution width, neutrophile count, mean corpuscular volume (MCV), monocyte count, albumin, C-reactive protein, ferritin, procalcitonin, D-dimer, and PAR were statistically different ($p<0.001$ for all). All patients in the critical group and only 2% of the mild group died. PAR showed the largest area under the curve (0.949) for the prediction of mortality ($p<0.001$).

Conclusion: We report that PAR, a simple, cheap, and easily accessible biomarker, can be used to predict the prognosis in patients with COVID-19 infection.

Keywords: COVID-19; Procalcitonin/Albumin Ratio; Mortality; Prognosis

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Correspondence to: Dr Hasan Ergenç

Address: Department of Internal Medicine, Ayancık State Hospital, Sinop, Turkey

E-mail: dr.hasanergenc@hotmail.com

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INTRODUCTION

SARS-CoV-2, which emerged in the city of Hubei in China in December 2019, is a RNA virus and is responsible for the coronavirus disease 2019 (COVID-19) which has become a global pandemic within a short time **[1,2]**. The clinical progression may vary from mild to fatal critical illness. The COVID-19 infection is severe and mortality rates are high especially in those with chronic diseases **[3,4]**. The main symptoms are fever, cough, shortness of breath, gastrointestinal disturbances, and diarrhea. Acute respiratory distress syndrome develops in severe cases, which may lead to the death of patients **[5,6]**.

It is important to predict the severity of clinical illness of COVID-19 patients and determine mortality and prognosis. Therefore, the identification of a reliable biomarker that can be used to evaluate the clinical prognosis at the time of admission is important. Hematological, biochemical, and hormonal parameters are widely used, relatively inexpensive, easily accessible, and may provide information about the prognosis **[6]**.

Albumin is the main protein in the blood and is synthesized by the liver. It is a negative acute phase reactant with antioxidant features. It was also shown to provide the down-regulation of angiotensin-converting enzyme 2 (ACE2) receptors, which have roles in the entry of SARS-CoV-2 into the cell **[7]**. It was shown in previous studies that hypoalbuminemia is prevalent in

COVID-19 patients admitted to the emergency department and that hypoalbuminemia is associated with increased mortality **[8]**.
Procalcitonin/albumin ratio (PAR) can be used to show the prognosis and mortality in the early period. Few studies have examined the role of PAR in predicting the COVID-19 clinical course and additional studies are needed to validate these findings. In this study, we investigated the use of PAR in predicting mortality in COVID-19 patients.

METHODS

The study was a two-center retrospective study enrolling patients with COVID-19 infection between 09.11.2020 and 04.05.2021. The diagnosis of COVID-19 was made according to the World Health Organization (WHO) interim guide and confirmed with the nucleic acid test positivity. Patients who presented with mild symptoms and did not require admission to the intensive care unit (ICU) due to limited pulmonary involvement were classified as mild COVID-19 cases (MCC), while those requiring ICU admission or required 60% or higher inspired oxygen concentration were classified as critical COVID-19 cases (CCC).
The demographic characteristics including age, gender, length of hospital stay, hemogram, and biochemical parameters of the patients who were included in the study were determined by a retrospective review of electronic health records. The study was conducted by the ethical rules with the approval of Medicana International Samsun Hospital clinical research ethics committee (decision no: 7158, date: 09.12.2021).

Statistical Analysis: The data were analyzed with the IBM SPSS V23 (Statistical Package for Social Science, Armonk, NY). The conformity to normal distribution was evaluated with the Kolmogorov-Smirnov test. The chi-square test was used to compare categorical variables. The independent two-sample ***t***-test was used to compare the normally distributed data, and the Mann-Whitney U test was used to compare the non-normally distributed data. The univariable logistic regression analysis was used to examine the risk factors that affected mortality. The ROC analysis was used to determine the cut-off point for the PAR to predict mortality. Analysis results were presented as mean ± standard deviation and median (range) for quantitative data, and frequency (percent) for categorical data. The significance level was taken as $p<0.05$.

RESULTS

Of the 105 patients, 51 were MCC and 54 were CCC. There were more males in the CCC vs. MCC group (33 vs. 20; P=0.025). Similarly, CCC had older patients than the MCC group (69.2 vs. 54.0 years; $p<0.001$) and a longer length of stay (7 vs. 17 days; $p<0.001$). Mortality was significantly higher in the CCC group than MCC group (1 vs. 54; $P<0.001$). The median WBC count, RDW, neutrophil count, mean corpuscular volume (MCV), fasting glucose, urea, LDH, AST, CRP, ferritin, procalcitonin, and PAR were significantly higher in CCC than in MCC ($p<0.001$ for all; Table 1). Similarly, the median lymphocyte count, mean platelet volume (MPV), platelet-crit, monocyte count, albumin, and D-dimer were significantly higher in CCC than in MCC. No statistically significant differences were noted between the groups in terms of other variables.
The result of the risk factors that affected mortality with univariable logistic regression analysis is given in Table 2. When the cut-off value for PAR was taken as 0.0023, the area under the curve (AUC) was found to be 0.949 (Figure 1). This value was statistically significant ($p<0.001$). The sensitivity and specificity were 87.3% and 91.3%, respectively.

DISCUSSION

The present study showed that COVID-19 increases the risk of mortality in the elderly and men. We validated prior literature that the risk of mortality was higher in patients with high WBC count, RDW, granulocyte count, MCV, fasting glucose, urea, LDH, AST, CRP, and ferritin, and was lower in patients with high MPV and platelet-crit values **[9,10]**. We further found that low serum albumin and higher procalcitonin (PCT) increased the risk of mortality and that PAR can be used to predict disease severity and outcomes. PCT is a glycoprotein that is secreted from thyroid parafollicular cells. In the presence of infection, PCT levels are significantly elevated after being released by all parenchymal cells. The PCT value is below 0.05ng/mL in blood under normal conditions. It is already known that it increases rapidly in the blood in 2 to 6 hours with the development of infection **[11]**. Studies conducted in the early period of COVID-19 infection showed that the PCT value is associated with the severity of the disease **[12]**. In patients admitted to the emergency department with fever and respiratory distress complaints during the

Table 1. Distribution of mild and critical cases of COVID-19 patients according to hospitalization and laboratory parameters

Characteristics	Mild COVID-19 cases (MCC)		Critical COVID-19 cases (CCC)		*p* value
	Mean±SD	Median (min.-max)	Mean±SD	Median (min-max)	
Age	53.98±19.82	56.00 (17.00 - 86.00)	69.19±11.12	70.00(42.00-89.00)	<0.001*
Hospitalization Duration	6.79±3.27	6.00 (1.00 - 16.00)	17.31±9.29	17.50(2.00 - 61.00)	<0.001**
WBC	5.95±3.19	5.20 (2.50 - 23.00)	10.59±15.12	7.77(2.73 - 115.00)	<0.001**
HGB	12.66±1.55	12.40 (9.90 - 15.80)	12.68±2.04	12.80 (8.00 - 18.00)	0.962
Plt	207.75±88.03	184.00 (88.00 - 502.00)	191.20±67.73	177.00(70.00 - 420.00)	0.570
RDW	13.25±1.35	13.00(11.10 - 17.10)	16.91±2.94	16.00(13.40 - 26.90)	<0.001**
Lymphocyte	1. 32±0.57	1.20 (0.40 - 3.10)	3.04±14.48	0.66(0.22 - 107.00)	<0.001**
Neutrophil	4.09±2.91	3.45 (1.30 - 19.90)	7.08±3.90	6.27(1.68 - 20.00)	<0.001**
MCV	82.20±8.42	82.60(33.00 - 94.00)	88.52±7.18	90.10(65.00 - 102.00)	<0.001**
MPV	10.58±1.23	10.50 (8.80 - 13.90)	8.46±1.29	8.45(5.60 - 11.50)	<0.001*
Plateletcrit	0.22±0.08	0.20 (0.10 - 0.53)	0.17±0.09	0.16 (0.07 - 0.74)	<0.001**
Monocyt	0.49±0.26	0.40 (0.10 - 1.50)	0.45±0.69	0.33 (0.04 - 5.10)	0.012**
Fasting Glucose	122.29±62.08	103.00 (67.00 - 389.00)	158.65±46.71	151.50(95.00 - 323.00)	<0.001**
Urea	34.91±24.80	27.50 (8.60 - 147.20)	50.87±28.39	44.00(10.00 - 163.00)	<0.001**
Creatinine	0.95±0.56	0.80 (0.40 - 4.40)	0.90±0.31	0.85 (0.28 - 1.59)	0.630
LDH	266.02±120.21	243.00 (111.00 - 667.00)	473.65±167.25	447.50(192.00 - 947.00)	<0.001**
AST	31.84±16.89	28.00 (11.00 - 86.00)	51.44±30.78	41.00(19.00 - 153.00)	<0.001**
ALT	27.69±25.42	19.00 (9.00 - 141.00)	32.93±23.19	26.50 (7.00 - 129.00)	0.055
Albumin	43.81±4.06	44.00 (33.00 - 51.00)	33.01±4.28	33.00(24.60 - 43.80)	<0.001**
CRP	43.94±56.16	26.20 (2.00 - 304.50)	114.88±65.32	113.90(4.20 - 296.00)	<0.001**
Ferritin	152.25±143.09	121.20 (6.70 - 643.80)	54 3.64 ± 467.93	422.00(11.46 - 1896.00)	<0.001**
Procalcitonin	0.07±0.08	0.05 (0.01 - 0.49)	0.55 ± 1.11	0.25(0.04 - 7.97)	<0.001**
D-Dimer	14.75±23.61	1.64 (0.19 - 84.00)	1.51±2.10	0.69 (0.22 - 11.10)	0.002**
Procalcitonin/Albumin	0.0015±0.0017	0011 (<0.0012 - 0.0120)	0.0165±0.0315	0.0079 (0.0014 - 0.2220)	<0.001**

Mean: Mean, **SD:** Standard Deviation, **Min:** Minimum value, **Max:** Maximum value *Independent paired-samples *t*-test statistics, **Mann-Whitney U Test statistics

pandemic, COVID-19 infection remains at the top of differential diagnosis **[13]**. In a study of 213 patients presenting to the emergency department with fever and shortness of breath, patients with high PCT levels at admission had higher rates of hospitalization in the ICU and mortality **[14]**. In a systematic review that 51 studies, patients who had higher PCT levels had more severe disease **[15]**. Our study findings validate these earlier results by findings higher mortality. Albumin is synthesized in the liver, and its half-life in plasma is 21 days **[16]**.

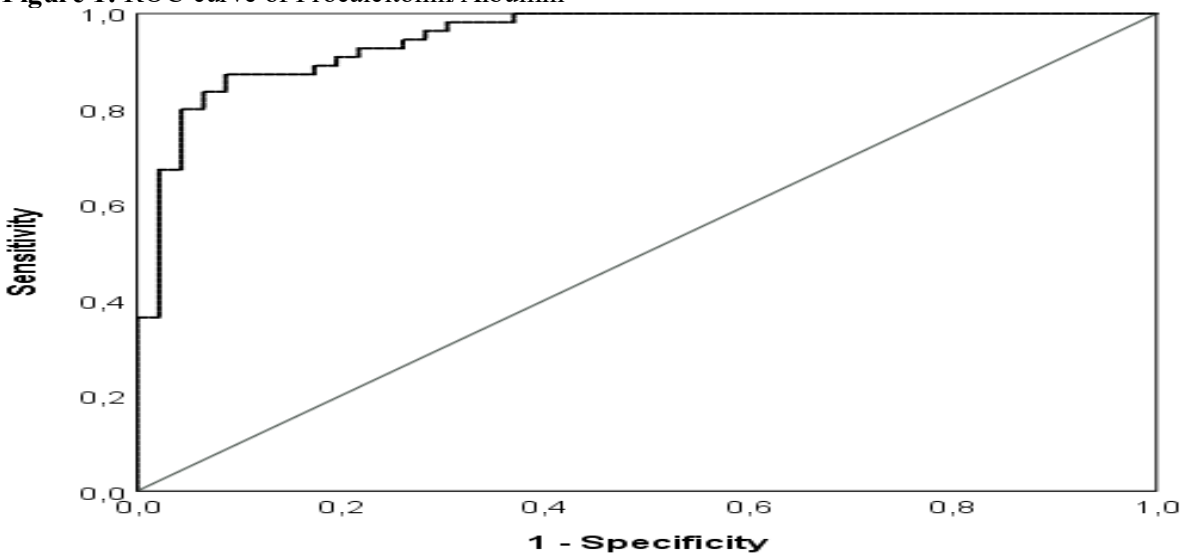
Low albumin levels increase the risk of mortality, especially in hospitalized patients, including patients with COVID-19 **[17-20]**. The present study validates earlier findings that low albumin levels are associated with poor prognosis and increased mortality in COVID-19. PAR has not been studied in COVID-19 patients to determine prognosis before our study. Our findings have important implications for clinical care and future research. Both tests, PCT and albumin, are commonly performed in the clinical care of COVID-19 patients at the time of

Table 2. Examination of risk factors that affect mortality with univariable logistic regression analysis

	OR (95% CI)	p	ACR
Gender (Female)	2.25 (1.03 - 4.91)	0.042	60
Age	1.06 (1.03 - 1.10)	<0.001	70.5
WBC	1.23 (1.07 - 1.42)	0.003	69.5
Hemoglobin	1.01 (0.81 - 1.25)	0.908	52.4
Platelet	0.997 (0.992 - 1.002)	0.235	55.2
RDW	3.45 (2.18 - 5.45)	<0.001	86.7
Lymphocyte	1.02 (0.95 - 1.1)	0.515	52.4
Neutrophil	1.35 (1.14 - 1.59)	<0.001	71.2
MCV	1.15 (1.07 - 1.24)	<0.001	73.3
MPV	0.28 (0.17 - 0.46)	<0.001	78.1
Plateletcrit	0.0004 (0.000 - 0.18)	0.012	65.7
Monocyte	0.87 (0.41 - 1.85)	0.729	52.9
Fasting Glucose	1.01 (1.00 - 1.02)	0.003	67.6
Urea	1.02 (1.00 - 1.04)	0.005	61.9
Creatinine	0.74 (0.29 - 1.83)	0.519	50.5
LDH	1.012 (1.007 - 1.016)	<0.001	81.9
AST	1.04 (1.02 - 1.07)	0.001	66.7
ALT	1.00 (0.99 - 1.02)	0.318	57.1
Albumin	0.52 (0.40 - 0.69)	<0.001	88.1
CRP	1.02 (1.01 - 1.03)	<0.001	74.3
Ferritin	1.007 (1.004 - 1.01)	<0.001	78.7
Procalcitonin	4.10 (1.96 – 8.56)	<0.001	82.9
D-Dimer	0.91 (0.85 - 0.98)	0.016	63.7
Hospitalization Duration	1.35 (1.19 - 1.54)	<0.001	79.2

ACR: Accurate Classification Ratio, (reference category)

Figure 1: ROC curve of Procalcitonin/Albumin



admission. Because the information is already available, the calculation of the PAR is straightforward, and information on clinical prognosis can be readily made available. Future research on the role of these two biomarkers in the clinical course of COVID-19 needs to be explored further.

The major limitation of this study is its retrospective design and relatively small sample size. The study was conducted in two local hospitals and only the initial measurement of laboratory results was evaluated.

CONCLUSION

High admission PAR is a predictor of critical illness and mortality in COVID-19 patients. If validated in other clinical studies, this can be easily included in regular clinical care to determine the prognosis of patients with COVID-19.

REFERENCES

1. Bernard Stoecklin S, Rolland P, Silue Y, Mailles A, Campese C, Simondon A, Mechain M, Meurice L, Nguyen M, Bassi C, Yamani E, Behillil S, Ismael S, Nguyen D, Malvy D, Lescure FX, Georges S, Lazarus C, Tabaï A, Stempfelet M, Enouf V, Coignard B, Levy-Bruhl D; Investigation Team. First cases of coronavirus disease 2019 (COVID-19) in France: surveillance, investigations and control measures, January 2020. *Euro Surveill.* 2020;25(6):2000094
2. Abrishami A, Khalili N, Dalili N, Khaleghnejad Tabari R, Farjad R, Samavat S, et al. Clinical and radiologic characteristics of COVID-19 in patients with CKD. *Iran J Kidney Dis.* 2020;14(4):267-77
3. Carey IM, Critchley JA, DeWilde S, Harris T, Hosking FJ, Cook DG. Risk of Infection in Type 1 and Type 2 Diabetes Compared With the General Population: A Matched Cohort Study. *Diabetes Care.* 2018;41(3):513–21
4. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA.* 2020;323(20):2052
5. Gallo Marin B, Aghagoli G, Lavine K, Yang L, Siff EJ, Chiang SS, Salazar-Mather TP, Dumenco L, Savaria MC, Aung SN, Flanigan T, Michelow IC. Predictors of COVID-19 severity: A literature review. *Rev Med Virol.* 2021;31(1):1-10
6. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, Zhang P, Liu X, Gao G, Liu F, Jiang Y, Cheng X, Zhu C, Xia Y. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerg Microbes Infect.* 2020;9(1):1123-1130
7. Xu P, Sriramula S, Lazartigues E. ACE2/ANG-(1-7)/Mas pathway in the brain: the axis of good. *Am J Physiol Regul Integr Comp Physiol.* 2011;300(4):R804-17
8. Cheng MP, Papenburg J, Desjardins M, Kanjilal S, Quach C, Libman M, et al. Diagnostic Testing for Severe Acute Respiratory Syndrome–Related Coronavirus 2. *Ann Intern Med.* 2020;172(11):726–34
9. García de Guadiana-Romualdo L, Morell-García D, Morales-Indiano C, Bauça JM, Alcaide Martín MJ, Esparza Del Valle C, et al. Characteristics and laboratory findings on admission to the emergency department among 2873 hospitalized patients with COVID-19: the impact of adjusted laboratory tests in multicenter studies. A multicenter study in Spain (BIOCOVID-Spain study). *Scand J Clin Lab Invest.* 2021;81(3):187-93
10. Pourbagheri-Sigaroodi A, Bashash D, Fateh F, Abolghasemi H. Laboratory findings in COVID-19 diagnosis and prognosis. *Clin Chim Acta.* 2020;510:475–82
11. Ahmed S, Siddiqui I, Jafri L, Hashmi M, Khan AH, Ghani F. Prospective evaluation of serum procalcitonin in critically ill patients with suspected sepsis - experience from a tertiary care hospital in Pakistan. *Ann Med Surg (Lond).* 2018;35:180–4
12. Ke C, Wang Y, Zeng X, Yang C, Hu Z. 2019 Novel coronavirus disease (COVID-19) in hemodialysis patients: a report of two cases. *Clin Biochem.* 2020;81:9–12
13. Carpenter RC, Mudd AP, West CP, Wilber E, Wilber ST. Diagnosing COVID-19 in the emergency department: a scoping review of clinical examinations, laboratory tests, imaging accuracy, and biases. *Acad Emerg Med.* 2020;27(8):653-70
14. Nazerian P, Gagliano M, Fanelli A, Grifoni S. Prognostic Role of Procalcitonin in Patients with Fever and Respiratory Complains During the COVID-19 Pandemic. *SN Compr Clin Med.* 2021;3(5):1074-1075
15. Ahmed S, Jafri L, Hoodbhoy Z, Siddiqui I. Prognostic Value of Serum Procalcitonin in COVID-19 Patients: A Systematic Review. *Indian J Crit Care Med.* 2021;25(1):77-84
16. Rothschild MA, Oratz M, Schreiber SS. Serum albumin. *Hepatology.* 1988;8(2):385–401
17. Akirov A, Masri-Iraqi H, Atamna A, Shimon I. Low albumin levels are associated with mortality risk in hospitalized patients. *Am J Med.* 2017;130(12):1465.e11-1465.e19
18. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: Pathogenesis and Clinical Significance. *JPEN J Parenter Enteral Nutr.* 2019;43(2):181-193
19. Huang J, Cheng A, Kumar R, Fang Y, Chen G, Zhu Y, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. *J Med Virol.* 2020;92(10):2152-8
20. Shao S, Zhao Z, Wang F, et al. Risk factors associated with disease aggravation among 126 hospitalized patients with COVID-19 in different places in China: A retrospective observational study. *Medicine (Baltimore).* 2020;99(45):e22971