

# THE USE OF ACUTE-PHASE PROTEINS APACHE II AND SOFA TO PREDICT THE MORTALITY OF COVID-19 PATIENTS

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## ABSTRACT

**Objective:** Acute-phase proteins are a family of proteins synthesized by the liver. With this study, we aimed to investigate the effects of COVID-19 infection on acute phase reactants (AFR) and determine the usability of AFRs as prognostic factors in COVID-19 disease.

**Material and Method:** Serum samples taken for routine analysis of the patients admitted to the Emergency Department and diagnosed with COVID-19, were used. AFR levels of 30 patients who resulted in mortality and 30 recovered patients were evaluated. C-reactive protein (CRP), ferritin (FER), ceruloplasmin (Cp), albumin (Alb), prealbumin (Prealb), transferrin (Trf), lactate, Acute Physiology and Chronic Health Evaluation (APACHE), and Sequential Organ Failure Assessment (SOFA) assessment was performed.

**Results:** The hazard ratio and 95% confidence interval for FER, CRP, lactate, Alb, Cp, Prealb, Trf, Age, SOFA,

and APACHE were 1.001 (1.000–1.001), 1.005 (1.001–1.008), 1.141 (1.016–1.243), 1.016 (0.740–1.399), 1.016 (0.740–1.399), 1.056 (1.017–1.100), 0.978 (0.917–1.035), 1.000 (0.995–1.006), 1.032 (1.004–1.064), 1.104 (0.971–1.247), and 1.012 (0.974–1.051), respectively, in univariable model. Only CRP, lactate, and FER found significant in multivariable model. In addition, patients in the nonsurvivors group had significantly higher FER, CRP, lactate, APACHE, age, and SOFA. Nonsurvivors also had lower Alb, Prealb, and serum Trf level compared to survivors.

**Conclusion:** CRP, lactate, and FER, which we have shown to be significantly higher in severe COVID-19 patients, will be valuable parameters that will contribute to clinical improvement if they are used in the follow-up of patients due to their easy measurement and predictive values.

**Keywords:** Acute-phase proteins, survival, COVID-19, mortality, APACHE, SOFA.

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## COVID-19 HASTALARI MORTALİTESİNİ TAHMİN ETMEK İÇİN AKUT FAZ PROTEİNLERİ, APACHE II VE SOFA KULLANIMI

### ÖZET

**Amaç:** Akut faz proteinleri, karaciğer tarafından sentezlenen bir protein ailesidir. Bu çalışma ile COVID-19 enfeksiyonunun akut faz reaktanları (AFR) üzerindeki etkilerini araştırmayı ve AFR'lerinin COVID-19 hastalığında prognostik faktör olarak kullanılabilirliğini belirlemeyi amaçladık.

**Materyal ve Metot:** Acil Servise başvuran ve COVID-19 tanısı konulan hastalardan rutin analiz için alınan serum örnekleri kullanıldı. Mortalite ile sonuçlanan 30 ve iyileşen 30 hastanın AFR düzeyleri değerlendirilmiştir. C-reaktif protein (CRP), ferritin (FER), seruloplazmin (Cp), albümin (Alb), prealbumin (Prealb), transferrin (Trf), laktat, Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi (APACHE) ve Sıralı Organ Yetmezliği Değerlendirmesi (SOFA) yapıldı.

**Bulgular:** FER, CRP, laktat, Alb, Cp, Prealb, Trf, Age, SOFA ve APACHE için tek değişkenli modelde hazard ratio ve %95 güven aralığı sırasıyla 1,001 (1,000–1,001), 1,005 (1,001–1,008), 1,141 (1,016–1,243), 1,243, 1,016 (0,740–1,399), 1,016 (0,740–1,399), 1,056 (1,017–1,100), 0,978 (0,917–1,035), 1,000 (0,995–1,006), 1,032 (1,004–1,064), 1,104 (0,971–1,247) ve 1,012 (0,974–1,051) idi. Çok değişkenli modelde yalnızca CRP, laktat ve FER anlamlı bulundu. Ek olarak, nonsurvivor gruptaki hastalarda FER, CRP, laktat, APACHE, yaş ve SOFA anlamlı olarak daha yüksekti. Nonsurvivor grup, survivor gruba kıyasla daha düşük Alb, Prealb ve serum Trf seviyelerine sahipti.

**Sonuç:** Ağır COVID-19 hastalarında anlamlı olarak yüksek olduğunu gösterdiğimiz CRP, laktat ve FER parametreleri kolay ölçümü ve prediktif değeri nedeniyle hastaların takibinde kullanılmalrı durumunda klinik iyileşmeye katkı sağlayacak değerli parametreler olacaktır.

**Anahtar kelimeler:** Akut faz proteinleri, survival, COVID-19, mortalite, APACHE, SOFA.

### INTRODUCTION

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China, with clinical presentations greatly resembling viral pneumonia. Coronavirus disease 2019 (COVID-19) is highly infectious and contagious. The World Health Organization was declared the epidemic a public health emergency of international concern on January 30, 2020. The clinical manifestations change rapidly, and severe cases can lead to hypoxia, multiple organ dysfunction, and death.<sup>1</sup> An exaggerated inflammatory response induced by the virus represents one of the most important negative prognostic factors.<sup>2</sup>

Many classes of inflammation markers have been identified and one of them, Acute-phase proteins (APPs), is a family of proteins synthesized by the liver. In response to injury, levels of some APPs, such as C-reactive protein (CRP), ferritin (FER) and ceruloplasmin (Cp), increase. In contrast, levels of others, such as albumin (Alb), prealbumin (Prealb) and transferrin (Trf), fall.<sup>3</sup>

FER is a cytosolic protein that stores excess iron and a non-specific acute phase reactant (APR).<sup>4</sup> Infection or inflammation generate anemia and important changes in iron metabolism, and FER increases with infections.<sup>5</sup> Microbes have an essential need for iron, which is

required for many microbial metabolic processes and for microbial pathogenicity.<sup>6</sup> FER levels could be used to differentiate between fever of unknown origin caused by infectious and noninfectious diseases.<sup>7</sup> These changes are important considerations for FER status assessments.

Cp is a serum ferroxidase that contains greater than 95% of the copper found in plasma.<sup>8</sup> It has demonstrated that Cp is an essential protein in the body with multiple functions such as regulating the homeostasis of copper and iron ions, ferroxidase activity, oxidizing organic amines, and preventing the formation of free radicals.<sup>9</sup>

Alb and Prealb are both indicators of protein nutrition status. Because Prealb has a shorter half-life than Alb, Prealb is more sensitive than Alb to changes in protein-energy state. Like albumin, prealbumin is also a negative acute-phase reactant reducing stress, and both of them could be used as predictors for prognosis of some diseases.<sup>10</sup>

CRP is a hallmark of the acute inflammatory response, and an extensively studied systemic marker of inflammation resulting from immune-stimulating conditions such as infection, tissue damage, and cancer.<sup>11</sup> Among all these markers, the techniques currently available for CRP is easy to perform and present low cost and high analytical sensitivity.<sup>12</sup>

The APRs correlate with the degree of inflammation phase and could be used as independent predictors. However, the use of markers of infection can show test results normal in sepsis, especially in patients with a depressed immune response. The prognostic indices can be used for the analysis of a cohort or to a group of specific diseases and can guide health strategies or allocation of resources. Among them, acute physiology and chronic health evaluation (APACHE) system includes a 12-point acute physiology score, age point, and chronic health evaluation, which are readily available in most emergency departments. Further, the calculation of the score is robust and uncomplicated.<sup>13</sup> And another, the sequential assessment of organ failure (SOFA), is also widely used to predict outcomes in critically ill patients.<sup>14</sup> These scores are more extensive, because of the use of multiple physiological variables from different organic systems. In addition, the use of prognostic indices can be used not only to predict which patients are likely to develop sepsis but also to predict which patient can survive or not sepsis. The early recognition of patients at risk of developing sepsis allows for an appropriate approach that would be started in intensive care unit (ICU) admission, and this may improve outcomes.<sup>15</sup>

In this study, serum CRP, Trf, Cp, FER, Alb and Prealb levels were evaluated in COVID-19 patients admitted to the Emergency Department (ED) to compare different predictive values of some prognostic indices and biomarkers.

## MATERIAL AND METHOD

### Study Design and Population

This study was conducted on COVID-19 patients who were admitted to the ED of Konya Training and Research Hospital between July 2020 and August 2020. The inclusion criteria were: 1) being diagnosed of COVID-19, 2) age of >18 years. The exclusion criteria were: 1) reverse transcription polymerase chain reaction was not studied, 2) the patient's prediagnosis was changed and COVID-19 was excluded, 3) laboratory data could not be accessed. The study protocol was approved by the Ethics Committee of Necmettin Erbakan University, Meram Faculty of Medicine, Turkey (No. 2020/2028, July 3, 2020). Patients who met the definitive case definition of COVID-19 and agreed to participate in the study were included. APR levels at first admission to the ED were evaluated in patients. Patients participating in the study were divided into two groups as survivors (n=30) and nonsurvivors (n=30).

### Data Collection

The baseline data, including age, gender, comorbidities, intra-hospital outcome at discharge and mortality, duration of hospital stay, APACHE and SOFA score upon admission were extracted from the medical records of the patients.

### Serum Biomarkers

Analysis of the markers were performed on samples obtained by centrifugation at 1500 g for 10 minutes of samples taken into serum separating tubes. Samples with clotted, hemolyzed, and lipemic were rejected. Plasma samples were stored at -80 °C until analysis. All of the APRs were evaluated on a clinical chemistry analyzer. CRP, Trf, Cp, Alb, FER, and Prealb were analyzed with Abbott Kits (Abbott Laboratories, Illinois, USA), manufactured for use with Architect c8000 Auto-Analyzer. Trf, Cp, CRP and Prealb plasma levels underwent immunoturbidimetric analysis; Alb was analyzed by bromocresol green method and FER by chemiluminescence process.

### Statistical Analysis

Numerical variables were given as mean, standard deviation, or median (Q1-Q3). Categorical variables are shown with frequency and percentage. In the analysis of numerical variables Cox regression, Mann-Whitney U test, Shapiro-Wilk test and Independent samples t test were used. Chi-square test was used for the categorical variable. In addition, logistic regression analysis was applied to CRP, FER, Cp, Alb, Prealb, Trf, Lactate and APACHE. Analyzes were done with SAS University Edition 9.4.  $p < 0.05$  was considered significant.

## RESULTS

Sixty patients admitted to the ED and diagnosed with COVID-19 were prospectively studied. Of the patients participating in the study, 33 were men, and 27 were women. Demographic data, hospital length of stay, APACHE, SOFA, and APR results by comparison of groups of patients designated survivors (n=30; 56.6% males, age of 40 [31–51] years) and nonsurvivors (n=30; 53.3% males, age of 73.23 [65–82] years) are reported in Table 1. The length of stay in the hospital for survivors and non-survivors was 5 [4-7] and 9.5 [6-17], respectively.

According to the results of the multivariate model, FER (hazard ratio (HR)= 1.001, 95% confidence interval (CI)=1.000–1.001,  $p < 0.004$ ), CRP (HR=1.005, 95%

Table 1. Characteristics of nonsurvivor and survivor COVID-19 patients.			
Patients [n= 60]	Nonsurvivors [n= 30]	Survivors [n=30]	p value
Gender M [%]/F	16 [53.3]/14	17 [56.67]/13	0.80
Age, year**	73.2 [11]	41.2 [15.2]	<0.01
Hospital length of stay, day*	9.5 [6-17]	5 [4-7]	0.36
Albumin**	2.09 [1.05]	4.17 [0.39]	<0.01
Ceruloplasmin*	34 [26-37.5]	28 [25-30]	<0.01
Prealbumin*	6.5 [4-9.5]	19.5 [16-22]	<0.01
Transferrin**	114 [52]	239 [39]	<0.01
Ferritin*	568.89 [213.18-956.78]	80.26 [25.61-145.41]	<0.01
CRP*	131 [91.1-193]	3.45 [3.11-5.89]	<0.01
SOFA*	5.5 [4-7.5]	1 [1-1]	<0.01
APACHE**	19.8 [8.7]	3.43 [1.33]	<0.01
Lactate*	2.53 [1.89-3.17]	0.88 [0.74-0.96]	<0.01

APACHE: Acute physiology and chronic health evaluation. CRP: C-reactive protein, SOFA: sequential organ failure assessment. Values expressed as median [interquartile range] or mean±standard deviation.  
\* Mann-Whitney U test was used \*\*Independent Samples-T test was used

Table 2. Univariable and multivariable analysis results.						
Factors	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p value	HR	95% CI	p value
Ferritin	1.001	1.000-1.001	0.001	1.001	1.000-1.001	0.004
CRP	1.005	1.001-1.008	0.005	1.005	1.001-1.009	0.02
Lactate	1.141	1.016-1.243	0.009	1.153	0.988-1.288	0.02
Albumin	1.016	0.740-1.399	0.922			
Ceruloplasmin	1.056	1.017-1.100	0.006			
Prealbumin	0.978	0.917-1.035	0.469			
Transferrin	1.000	0.995-1.006	0.897			
Age	1.032	1.004-1.064	0.033			
SOFA	1.104	0.971-1.247	0.123			
APACHE	1.012	0.974-1.051	0.5267			

HR: Hazard Ratio. 95% CI: 95 % Confidence Interval. APACHE: Acute physiology and chronic health evaluation. CRP: C-reactive protein, SOFA: Sequential organ failure assessment.

Table 3. Comparison of survivor and nonsurvivor groups by t-test.			
	Nonsurvivors	Survivors	p value
Albumin	2.09 ± 1.04	4.17 ± 0.38	p<0.001
Ceruloplasmin	26.86 ± 12.31	27.8 ± 3.55	p=0.691
Prealbumin	6.73 ± 6.1	19.36 ± 4.46	p<0.001
Transferrin	100.5 ± 6.15	239.1 ± 39.06	p<0.001
Ferritin	694.1 ± 582	123.2 ± 133.2	p<0.001
C-reactive protein	154.9 ± 83.93	5.12 ± 3.28	p<0.001
Lactate	2.91 ± 2.75	0.86 ± 0.16	p<0.001
APACHE	19.8 ± 8.7	3.43 ± 1.33	p<0.001
Age	73.23 ± 11.03	41.16 ± 15.15	p<0.001
SOFA	5.9 ± 2.57	1.03 ± 0.41	p<0.001

APACHE: Acute physiology and chronic health evaluation. CRP: C-reactive protein, SOFA: Sequential organ failure assessment.

CI=1.001–1.009,  $p<0.02$ ) and, Lactate (HR=1.153, CI=0.988-1.288,  $p<0.02$ ) were found significant. In addition, a univariable survival analysis was performed for each variable. The univariate logistic regression showed the following results: FER (HR=1.001, 95% CI=1.000–1.001,  $p=0.0004$ ), CRP (HR=1.005, 95% CI=1.001–1.008,  $p<0.005$ ), Lactate (HR=1.141, CI=1.016-1.243,  $p=0.009$ ), Alb (HR=1.016, CI=0.74-1.399,  $p=0.922$ ), Cer (HR=1.056, CI=1.017-1.100,  $p=0.006$ ), Prealb (HR=0.978, CI=0.917-1.035,  $p=0.469$ ), Trf (HR=1, CI=0.995-1.006,  $p=0.897$ ), Age (HR=1.032, CI=1.004-1.064,  $p=0.033$ ), SOFA (HR=1.104, CI=0.971-1.247,  $p=0.123$ ), APACHE (HR=1.012, CI=0.974-1.051,  $p=0.5267$ ). Table 2 presents the results of the multivariate and univariate Cox regression hazard analysis.

When the Non-survivors and Survivors groups were compared, there was a significant difference ( $p<0.0001$ ) for Alb, Prealb, Trf, FER, CRP, Lactate, APACHE, Age and SOFA, but no significant difference was found between the two groups only for Cp ( $p=0.691$ ). The comparison of survivors and non-survivors groups by t-test is shown in Table 3.

Logistic regression analysis was applied to some clinically important variables. CRP, FER, Cp, Alb, Prealb, Trf, Lactate and APACHE parameters were included in the analysis and the results are given in Table 4. Among the evaluated variables, Alb, Prealb, Trf, FER and APACHE were found to be independent predictors of survival.

## DISCUSSION

Detection of prognostic factors is very important for COVID-19 patients newly admitted to the ED and may shed light on clinical treatment. We planned our study thinking that certain inflammatory markers and scores could help clinicians monitor the severity and prognosis of COVID-19.

APRs are a class of proteins whose plasma concentrations increase (positive acute-phase proteins) or decrease (negative acute-phase proteins) in response to inflammation. The expression APP is often used synonymously for APR, although some APRs are polypeptides rather than proteins.<sup>16</sup>

In our study, while the levels of Alb, Prealb, and Trf, which are negative APRs, were significantly lower in the non-survivors group than in the Survivors group, the positive APRs, FER and CRP, were significantly higher. There was no significant increase in Cp values in both patient groups.

CRP is the most widely used infection biomarker in intensive care patients, which is measured as a direct indicator of the acute phase reaction and provides quick information about the situation due to its kinetics. Its relationship with cytokines also contributes to its clinical value as a parameter of inflammatory activity.<sup>17,18</sup>

Zeng *et al.* stated that inflammatory markers, especially CRP, procalcitonin, interleukin-6 and erythrocyte sedimentation rate, were positively correlated with the severity of COVID-19.<sup>19</sup>

In the study of Chen *et al.* investigating COVID-19 pneumonia, there was no statistically significant difference in CRP levels between the non-severe and severe groups, the mean CRP level was higher in the severe group.<sup>20</sup> All other studies have revealed a positive correlation between the severity of COVID-19 and the level of CRP. Our study showed the predictive value of some APRs, such as CRP in patients with COVID-19.

We also revealed that high lactate and FER levels of COVID-19 patients in the non-survivor group have predictive value in indicating the severity of the disease. FER is a cytosolic iron storage and detoxification protein that is increased in inflammation, liver disease, and malignancy. In the clinical setting, serum FER assessment is most commonly used to estimate body iron stores as low ferritin, while high serum FER has been associated with inflammation in the body for patients with normal body iron stores.<sup>21,22</sup>

Lactate, a product of anaerobic glucose metabolism, is a widely used cellular hypoxia-related marker for disease severity in intensive care unit (ICU) patients. It is a good indicator of the severity of metabolic acidosis secondary to tissue hypoperfusion.<sup>23</sup>

Since lactate is often used in therapy monitoring, little is known about lactate levels in the clinical state of the disease, which raises the question of whether it can be used in clinical decision making. Our study showed that lactate levels were significantly higher in the non-survival patient group.

The value of monitoring lactate levels in critically ill patients has been evaluated by numerous studies. When lactate levels were high for longer in ICU patients, there was an increased risk of multiple organ failure or death.<sup>23,24</sup>

As in all these studies, we think that lactate, whose prognostic value we have shown, is a valuable parameter in the follow-up of severe COVID patients.

Table 4. Logistic regression analysis results.		
Parameters	OR (%95 CI)	p value
Albumin	432.167 (9.398->999)	0.001
Ceruloplasmin	1.012 (0.956-1.071)	0.686
Prealbumin	1.437 (1.216-1.697)	<0.001
Transferrin	1.110 (1.033-1.192)	0.004
Ferritin	0.993 (0.989-0.997)	0.0005
C-reactive protein	0.774 (0.533-1.124)	0.178
Lactate	<0.001 (<0.001-1.736)	0.056
APACHE	0.15 (0.026-0.867)	0.034

\*APACHE: Acute Physiology and Chronic Health Assessment, CI: Confidence interval, OR: Odds ratio

The APACHE and SOFA scores will theoretically be more useful than one variable alone, as they contain many physiological parameters in the prognosis prediction of intensive care patients. However, some other biomarkers (CRP, albumin, and lactate) play a role as important factors predicting independent mortality in critically ill patients.<sup>25</sup> We revealed that although APACHE and SOFA scores were statistically different between survivors and non-survivors, they had no predictive value in COVID-19 patients.

For these reasons, Hackler *et al.* determined Copper (Cu) and Cp in relation to biomarkers of selenium (Se) status in the serum of COVID-19 patients and tested their predictive value for survival and suggested that serum Cu and SELENOP levels contribute to a good prediction of survival.<sup>26</sup>

Cp is a glycoprotein of the serum, mainly produced by the liver.<sup>27</sup> Physiological properties of Cp include being the body's main copper carrier; having ferroxidase, ascorbate oxidase and antioxidant activity; being an acute phase reactant.<sup>9</sup> In our study, it was found that there was no significant difference in Cp serum levels between the two groups with survivors and non-survivors COVID-19 groups.

## CONCLUSION

The data presented in this study indicated good performance of some inflammation markers in predicting critically ill patients with COVID-19 presenting to the ED. APRs such as CRP, lactate, and FER, which we show predictive value in COVID-19 patients, will be valuable parameters that will contribute to clinical improvement if they are used in the follow-up of patients due to their easy measurement and clinical value.

\*The authors declare that there are no conflicts of interest.



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