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ORIGINAL ARTICLE

The Relationship Between Acute Phase Reactants Levels at the Time of Admission and Comorbid Conditions with Mortality in Patients Diagnosed with Covid-19

Covid-19 Tanılı Hastalarda Başvuru Anındaki Akut Faz Reaktanları Düzeyi ile Komorbid Durumlarının Mortalite ile İlişkisi

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ABSTRACT

Background/aims: The covid-19 pandemic, which is a global problem, is still one of the most important health problems today. Treatment and vaccine studies are as important in predicting prognosis and mortality as early diagnosis and prevention of the disease, which continues unabated. İn this study, it was aimed to evaluate the success of laboratory values, comorbid conditions and intensive care scoring at the time of first admission in predicting the mortality of patients admitted to intensive care with the diagnosis of Covid-19.
Methods: The study was conducted in a tertiary adult emergency deparment. The study included 106 patients who were admitted to the emergency department and subsequently admitted to intensive care, had a positive Covid-19 polymerase chain reaction(PCR) test and met the inclusion criteria.
Results: The average age of 106 patients included in the study was 71.85. Of these patients, 65.09 % were male and 24.1% were female. While 29 of the patients were survivors, 77 were deceased. İn deceased patients; procalcitonin, lactate, leukocyte, neutrophil, urea, creatine, asti crpi ferritin, d-dimer values were found higher than the other group. Lymphocyte, lymphocyte percentage and pH values were significantly low. Sequential Organ Failure Score(SOFA) and Acute Physiology and Chronic Health Evaluation(APACHE) 2 scores were higher in deceased patients.
Conclusion: Ferritin, lactate, urea and pH values, comorbid conditions, Sequantial Organ Failure Score and Acute Sphysiology and Chronic Health Assessment 2 can be used to predict mortality in covid-19 disease.

Keywords: Covid-19, CRP, d-dimer, ferritin, fibrinogen

ÖZ

Amaç: Global bir problem olan covid-19 pandemisi günümüzde hala en önemli sağlık sorunlarının başında gelmektedir. Tedavi ve aşı çalışmaları hız kesmeden devam etmekte olan hastalığın erken tanınması ve önlenmesi kadar prognozu ve mortaliteyi öngörmekte bir o kadar önemlidir. Bu çalışmada covid-19 tanısı ile yoğun bakıma yatırılan hastaların ilk başvuru anındaki laboratuvar değerlerinin, komorbid durumlarının ve yoğun bakım skorlamalarının mortaliteyi öngörme başarılarının değerlendirilmesi amaçlanmıştır.
Yöntem: Çalışma üçüncü basamak erişkin acil servisinde gerçekleştirilmiştir. Çalışmaya acil servise başvuran ve akabinde yoğun bakım yatışı verilen, covid-19 polimeraz zincir reaksiyon(pcr) testi pozitif ve dahil edilme kriterlerini karşılayan 106 hasta dahil edilmiştir.
Bulgular: Çalışmaya dahil edilen 106 hastanın yaş ortalaması 71.85 idi. Bu hastaların yüzde 65,09'unu erkek, %34,1'ini kadın cinsiyet oluşturmakta. Hastaların 29'u survival iken 77'si vefat eden hastalardan oluşmakta idi. Vefat eden hastalarda; procalsitonin, laktat, lökosit, nötrofil, üre, kreatin, ast, crp, ferritin, d-dimer değerleri diğer gruba göre yüksek saptanmıştır. Lenfosit, lenfosit yüzdesi ve ph değerleri ise anlamlı düşük olduğu tespit edilmiştir. Ardışık Organ Yetmezliği Skoru(SOFA) ve Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi(APACHE) 2 skorları vefat eden hastalarda daha yüksek tespit edilmiştir.
Sonuç: Ferritin, laktat, üre ve ph değerleri, komorbid durumlar, Ardışık Organ Yetmezliği Skoru ve Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi covid-19 hastalığında mortalite öngörmede kullanılabilir.

Anahtar Kelimeler: Covid-19, CRP, d-dimer, ferritin, fibrinojen

Introduction

In December 2019, pneumonia cases of unknown etiology were detected in Wuhan, China's Hubei province. In its early stages, respiratory tract infection symptoms with acute respiratory distress syndrome (ARDS), acute respiratory failure and other serious complications occurred (1). On January 7, a new coronavirus was detected in throat swab samples taken from patients by the Chinese Center for Disease Control and Prevention (CDC). Since the pathogen was phylogenetically similar to SARS-CoV and its effects on the human body were similar, it was identified as a new enveloped beta coronavirus and named SARS-CoV-2 (2). On March 11, 2020, Covid-19 disease was declared a pandemic at the world press conference held by WHO Director General Tedros Adhanom Ghebreyesus (3). In April, approximately 1 year after the acceptance, the total number of cases worldwide reached 140,327,309 and the total number of deaths reached 3,006,828.

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Comorbid conditions are as important as demographic and genetic characteristics in terms of the incidence and severity of Covid-19 disease. There are extensive studies conducted on this subject. In a meta-analysis study based in the People's Republic of China, 1558 patients were recorded. As a result of this meta-analysis, while there was no correlation between liver disease, malignancy or kidney diseases and Covid-19, hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease and cerebrovascular disease were stated as serious risk factors (4).

In the diagnosis of Covid-19, many molecular, serological, biochemical tests and radiological imaging are used. The basis for identifying the disease is virus isolation and detection of nucleic acid. Antibody and antigen tests also play an important role in diagnosis and follow-up. Scoring such as Acute Physiology and Health Evaluation Score (APACHE) and Sequential Organ Failure Assessment Score (SOFA) are used to predict mortality in intensive care units.

In this study, it was aimed to evaluate the success of age, gender, comorbidities, venous blood gas, hemogram, acute phase reactants and biochemical parameters and APACHE 2 and SOFA scores in predicting mortality in patients diagnosed with Covid-19 in the emergency department and admitted to the intensive care unit.

Material and Methods

This research was designed as a retrospective cohort study. Patients with a definitive diagnosis of Covid-19 in the adult emergency department of a tertiary healthcare institution between 01.08.2020 and 31.10.2020, in line with the Covid-19 diagnostic guide of the Ministry of Health, were accepted into the study. This study was approved by the T.R. KTO Karatay University Clinical Research Local Ethics Committee decision number 2020/026. The inclusion criteria for the study were determined as having a definitive diagnosis of Covid-19 and being over 18 years of age, and patients whose data could not be fully accessed were excluded from the study.

In our study, 156 patients were scanned and 106 patients whose data were available were included in the study. Fibrinogen, procalcitonin, ferritin, lactate dehydrogenase, troponin I, sodium, potassium, chlorine, pH, pCO2, pO2, base deficit (be), lactate, bicarbonate, ck-mb, d-dimer, c-reactive protein (crp), platelet count (plt), leukocyte count, aspartate aminotransferase (ast) and alanine aminotransferase (alt) values, lymphocyte count, lymphocyte percentage and albumin values were examined. APACHE 2 and SOFA scores were calculated. Demographic characteristics of the patients were obtained using Structured Query Language (SQL) queries.

Kurtosis and skewness coefficients, Kolmogorov Smirnov and Shapiro-Wilk tests results, histogram and Q and Q graph analysis methods were used to examine the distribution of the data. Independent Sample t test was used for comparisons between two groups with normal distribution, and Mann Whitney U test was used for comparisons between two groups with non-normal distribution. Pearson Chi-Square test was applied to examine the difference between categorical data. ROC (Receiver Operating Characteristic) curve was used to determine the predictive values of laboratory parameters. Sensitivity and specificity values were obtained as a result of the ROC analysis and accuracy values were calculated using prevalence; accuracy was obtained using the formula = (TN + TP)/(TN + TP + FN + FP). Backward LR model and Cox Proportional Hazard Regression analysis were applied to evaluate the risks of laboratory parameters thought to have an impact on survival. Descriptive statistics of the data are described as mean±standard deviation for numerical variables with normal distribution, as Median (IQR) for numerical variables with non-normal distribution, and as frequency (percentage) for categorical variables. All statistical analyzes were analyzed and reported in IBM SPSS Statistics 22.0 program at a=0.05 significance level and 95% confidence level.

Results

The average age of 106 patients included in the study was 71.85±13,085 years. The patients included in the study were evaluated in two main groups: survival and non-survival. 65.09% (69) of the patients were male and 34.1% (37) were female. The median value of the patients' average length of hospital stay was 5 days and the interquartile range value was 7 days. When the distribution of mortality by gender was examined, it was seen that 47 (68.1%) of the male patients did not survive while 22 (31.9%) survived. In female patients, this situation was determined as non-survival 30 (81.1%) and survival 7 (18.9%). Comorbid diseases of the patients included in the study are shown in Table 1.

Table 1. *Gender and Accomanying Disease Distribution of Patients*

Variables		Non-survival (n=77)	Survival (n=29)	Test results	P-value
Age		75 (16)	69 (18)	Z=-2.336	0.019
Gender	Male	47 (%68.1)	22 (%31.9)	X^2=2.037	0.153
	Female	30 (%81.1)	7 (%18.9)		
Hospitalization (day)		4 (9)	5 (5)	Z=-0.164	0.870
Comorbidity					
	Yes	61 (%79.2)	17 (%58.6)	X^2=4.599	0.032
	No	16 (%20.8)	12 (%41.4)		
Comorbidities					
Hypertension		50 (%64.9)	14 (48.3)		
Diabetes Mellitus		35 (%45.5)	8 (%27.6)		
Cerebrovascular disease		8 (%10.4)	2 (%6.9)		
Coronary artery disease		32 (41.6)	8 (%27.6)		
Pulmonary artery disease		15 (%19.5)	4 (%13.8)		
Asthma/COPD		16 (%20.8)	3 (10.3)		
Acute/Chronic Kidney Failure		9 (%11.7)	3 (%10.3)		

COPD: Chronic Obstructive Pulmonary Disease

Any of the patients' comorbid conditions were not found significant in predicting mortality. Laboratory values thought to be related to COVID-19 in the patients included in the study and statistical analysis results between survival and non-survival patient groups are shown in Table 2.

Table 2. *Comparison of Laboratory Parameters Between Survival and Non-Survival Patients*

Laboratory Parameters	Non-survival (n=77) mean(±SD)	Survival (n=29) mean(±SD)	Test Results	P-value
PH	7.32 (0.17)	7.37 (0.10)	Z=-2.266	0.023
PC02	38.0 (15.50)	39.0 (14.70)	Z=-0.854	0.393
P02	39.0 (22.20)	37.0 (22.60)	Z=-0.510	0.610
HCO3	19.16 (±5.12)	22.64 (±6.94)	t=-2.815	0.006
BE	6.4 (6.95)	2.3 (4.60)	Z=-3.101	0.002
Lactate	3.06 (1.82)	2.19 (1.03)	Z=-4.632	0.000
Leukocyte	11.16 (7.73)	8.26 (7.07)	Z=-2.381	0.017
Hemoglobin	12.22 (±2.38)	13.03 (±2.34)	t=-1.559	0.122
PLT	223.0 (110.50)	214.0 (133.00)	Z=-0.252	0.801
LYM	0.79 (0.90)	0.88 (0.89)	Z=-0.170	0.865
Neutrophil	9.70 (7.99)	7.95 (6.40)	Z=-2.293	0.022
LYM %	7.50 (6.40)	9.80 (12.75)	Z=-1.233	0.217
Neutrophil %	88.40 (8.60)	86.20 (18.75)	Z=-1.173	0.241
Glucose	151.00 (90.50)	123.00 (82.00)	Z=-1.308	0.191
Urea	86.0 (78.00)	44.0 (39.50)	Z=-4.093	0.000
Creatine	1.52 (1.56)	1.10 (0.62)	Z=-2.892	0.004
AST	46.0 (47.00)	31.0 (24.00)	Z=-2.800	0.005
ALT	22.0 (21.50)	25.0 (35.00)	Z=-0.702	0.483
Na	133.22 (±7.29)	135.21 (±4.01)	t=2.70	0.008
K	4.66 (0.92)	4.56 (1.11)	Z=-0.315	0.752
Cl	103.40 (±7.61)	99.93 (±5.99)	t=2.21	0.029
CK MB	2.60 (4.07)	2.37 (4.34)	Z=-0.046	0.963
Troponin	48.20 (253.14)	13.99 (30.21)	Z=-3.561	0.000
CRP	154.0 (134.5)	66.2 (126.4)	Z=-2.959	0.003
Ferritin	624.0 (1005.8)	308.0 (582.5)	Z=-2.945	0.003
Procalsitonin*	0.65 (1.77)	0.33 (0.35)	Z=-3.580	0.000
Fibrinojen**	684.0 (559.0)	587.0 (489.0)	Z=-1.099	0.272
D Dimer	2.45 (6.35)	1.20 (3.10)	Z=-1.957	0.050
Apache	23.01 (±4.75)	17.90 (±3.98)	t=5.156	0.000
Sofa	11.61 (±1.20)	5.97 (±1.09)	t=22.074	0.000

*n1=68, n2=28 ** n1=71, n2=28, mean(±SD), SD; standard deviation

APACHE: Physiology and Chronic Health Assessment, AST: Aspartate Aminotransferase, ALT: alanin aminotransferase, BE: Base Deficit, CRP: C-Reactive Protein, CK: Creatine Kinase, LYM: lymphocyte, SOFA: Sequential Organ Failure Assessment

As stated in Table:1; In the patients included in the study, a significant difference was observed in terms of age and comorbidity in the variables examined in two groups: survival and non-survival. It was determined that the average age of patients who died and the number of patients with any disease were higher than those who survived.

As a result of the analysis; There was a significant difference in pH, bicarbonate, lactate, leukocyte, neutrophil, urea, creatine, ast, troponin, crp, ferritin, procalcitonin, d-dimer values and SOFA-APACHE 2 scores between two groups examined.

The results of the ROC (Receiver Operating Characteristic) analysis performed to determine the estimated values of laboratory parameters that were significant as a result of univariate statistical analysis are displayed in Table 3.

Proportional Hazard Backward LR and Cox Proportional Hazard Regression analysis were performed to evaluate the risk status of the parameters examined in the study, which were found significant as a result of univariate analysis for COVID-19 disease. The results obtained from this analysis are shown in Table:4.

According to the examination, pH is a protective factor, lactate, urea and ferritin values are risk factors, all of which have an effect on survival. A 1 unit increase in lactate, urea and ferritin levels increases mortality by 1.014, 1.007 and 1.0004 times, respectively.

Table 3. *ROC (Receiver Operating Characteristic) Analysis Results*

Variable	Cut-Off value	Sensitivity %	Specificity %	AUC (Area Under the Curve)	%95 Confidence Interval(CI)		P-value	Accuracy %
Age	>74.5	54.55	75.86	0.659	0.531	0.787	0.016	62.3
Saturation	<85.5	89.61	48.28	0.686	0.559	0.812	0.003	78.3
Respiratory Rate	>18.5	89.61	37.93	0.649	0.528	0.770	0.018	75.5
PH	<7.315	82.76	49.35	0.643	0.532	0.754	0.024	59.5
HCO_3	<22.95	58.62	81.82	0.686	0.565	0.807	0.003	75.5
Be	>6.1	55.95	82.76	0.696	0.580	0.811	0.002	60.4
Lactate	>2.68	66.23	86.21	0.793	0.699	0.886	0.000	71.7
Neutrophil	>11.02	42.86	82.76	0.645	0.526	0.763	0.022	53.8
Urea	>59.5	75.32	72.41	0.759	0.655	0.863	0.000	74.5
Creatine	>1.185	75.32	58.62	0.683	0.567	0.798	0.004	70.8
AST	>36.5	64.94	68.97	0.677	0.557	0.796	0.005	66.0
Na	>139.5	33.77	89.66	0.629	0.519	0.739	0.041	49.1
Cl	>104.5	42.86	86.21	0.658	0.545	0.771	0.013	54.7
Troponin	>35.395	63.64	75.86	0.725	0.612	0.838	0.000	67.0
CRP	>29.65	93.51	41.38	0.687	0.567	0.807	0.003	79.2
Ferritin	>138.5	90.91	37.93	0.686	0.567	0.805	0.003	76.4
Procalsitonin	>0.465	67.65	75.00	0.733	0.619	0.848	0.000	63.2
APACHE	>23.5	55.84	93.10	0.793	0.701	0.885	0.000	56.6
SOFA	>8.5	100.0	100.0	1.000	1.000	1.000	0.000	100.0

APACHE: Physiology and Chronic Health Assessment, AST: Aspartate Aminotransferase, BE: Base Deficit, CRP: C-Reactive Protein, SOFA: Consecutive Organ Failure Evaluation Score

Table 4. *Cox proportional Hazard Regression Model for Laboratory Parameters*

Variable	β	Standard Error	Wald	Hazard Ratio (HR)	%95 Confidence Interval(CI)		P-value
PH	-2.399	1.089	4.853	0.091	0.011	0.768	0.028
Lactate	0.167	0.078	4.594	1.182	1.014	1.377	0.032
Urea	0.007	0.002	12.390	1.007	1.003	1.011	0.000
Ferritin	0.000	0.000	4.076	1.0004	1.00001	1.00007	0.043

* Backward LR model was applied, p value for model significance p<0.001

Discussion

Considering that there is currently no definitive treatment for Covid-19 disease, where vaccine and vaccination studies continue unabated, reliable and rapid biomarkers are needed for early recognition and prediction of mortality. Making appropriate and timely decisions in choosing a therapeutic approach will only be possible thanks to this foresight.

Although hyperuricemia is often associated with respiratory diseases, studies showed that hypouricemia occured in severe Covid-19 disease (5). Urea level is used in clinical practice as an indirect indicator of dehydration and kidney functions. In our research, contrary to the literature, urea levels were higher in non-survival patients than in surviving patients. While the median urea value was 86 in non-survival patients, this value was calculated as 44 in surviving patients. Values above the cut-off value were determined as a risk factor and were associated with mortality.

To determine the acid-base balance and evaluate the breathing pattern, pH, bicarbonate, partial oxygen and carbon dioxide (paO2, paCO2), saturation, base deficit and lactate values were checked in blood samples taken from the arterial or venous system. In our research, it was determined that the pH value was lower in non-survival patients compared to surviving patients. Values above the cut-off value were considered as a protective factor and were associated with mortality (HR: 0.091). There are no sufficient studies in the literature on blood gases in the mortality analysis of Covid-19 disease. In the study conducted by Morne C. Bezuidenhout et al. (6), the relationship between blood gases, taken during the admission of 56 intensive care patients to the intensive care unit, and mortality was investigated. Increased pH and lower partial oxygen pressure were significantly associated with survival. In the study of Maria Viviana Carlino et al. (7), 28 patients were examined and lactate level was accepted as a predictor of admission to intensive care.

Lactate value is used as an indirect indicator of tissue perfusion. There are also studies showing that it modulates the inflammatory response in macrophages (8). In our research, lactate value was found higher in non-survival patients compared to surviving patients. Values above the cut-off value were determined as a risk factor. Its increase is associated with mortality. A one-unit increase in lactate value increases mortality by 1.182 times (HR: 1.182).

It was determined that the lymphocyte count and percentage were lower in non-survival patients than in surviving patients. There are studies in the literature showing that among all laboratory parameters, the lymphocyte percentage value can be used as the most significant and consistent parameter in predicting the progression of the disease and being used as a guide (9). However, as a result of the analyzes we made in our study, no significant difference was found in terms of mortality. In a meta-analysis, it was determined that patients with a confirmed diagnosis of Covid-19 had a tendency to have low lymphocyte counts and high neutrophil counts (10). Our results were similar to those of this meta-analysis. It was calculated that the neutrophil values in non-surviving patients were higher than the neutrophil values in surviving patients, and this is significant in terms of mortality. In another study conducted on the mortality prediction of neutrophil values, it was observed that neutrophil values in fatal cases gradually increased during the course of the disease. This increase in neutrophil values may indicate the involvement of a bacterial superinfection in Covid-19 disease and can be used as an indicator for the progression of the disease (11).

Crp value was determined higher in non-survival patients than in surviving patients. While the median CRP value was 154 in non-survival patients, this value was calculated as 66 in surviving patients and was considered significant in terms of mortality. In a meta-analysis, it was determined that high serum CRP, procalcitonin, d-dimer and ferritin levels were associated with poor prognosis and mortality in 25 studies and 5350 patients examined (12). Similar results were obtained in a study including 140 patients originating from China, and high CRP was evaluated as a poor prognosis criterion (13).

Procalcitonin value was found higher in non-surviving patients than in surviving patients. While the median procalcitonin value was 0.65 in non-survival patients, this value was calculated as 0.33 in surviving patients and was significant in terms of mortality. In studies, procalcitonin, like CRP and other acute phase reactants, was evaluated as a poor prognosis criterion and was associated with mortality (13,14). It is anticipated that it may be more useful to use it with serial measurements such as the Crp parameter.

In our study, no significant difference was detected between non-survival and surviving patients for fibrinogen value. On the other hand, d-dimer level was higher and significant in non-survival patients compared to surviving patients. Studies have predicted that d-dimer and fibrinogen values gradually increase in serial measurements in patient groups with a poor prognosis and may be an indicator of poor prognosis (15,16).

For troponin value, it was higher and more significant in non-survival patients compared to survival patients. Our study is compatible with the literature. Troponin I value, which is used as an indicator of cardiac involvement in many studies, suggests that it can be used as an indicator of poor prognosis (17-19).

In our study, ferritin value was determined higher in non-survival patients compared to surviving patients. While the median value was 624 in non-survival patients, it was calculated as 308 in survival patients and was significant. As a result of the analysis, the increase in the ferritin value, whose cut-off value was calculated as 138.5, was evaluated as a risk factor for the disease (HR: 1.004). Our study is compatible with the literature. In many studies, it has been revealed that high ferritin value is a guide in terms of deterioration in the course

of the disease and resulting in death (19,20).

In our research, APACHE II and SOFA scores, which are among the intensive care scoring systems, were higher in non-survival patients than in surviving patients. As a result of the analysis, the cut-off value was 23.5 for APACHE II and 8.5 for SOFA. The results were found significant for both scoring systems. In particular, the SOFA score has been determined to be the most effective parameter in predicting mortality with 100% sensitivity, specificity and accuracy. These values are compatible with the literature.

Conclusion

As a result, ferritin, lactate, urea and pH values, comorbid conditions, APACHE 2 and SOFA scoring systems during intensive care admission, which are the tests taken at the time of first admission to the health institution, can be used to predict mortality in Covid-19 disease.

With rapid evaluation at the first application, patients will be able to start treatment more quickly.

Ethical Aspects of the Research: This study was approved by the T.R. KTO Karatay University Clinical Research Local Ethics Committee decision number 2020/026.

Conflict of interest: no

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