Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:372-381
DOI: 10.4274/BMJ.galenos.2023.2023.3-14

Research

Effect of Mutational Difference on Systemic Immune Inflammation Index in Patients with a Diagnosis of COVID-19

COVİD-19 Tanılı Hastalarda Mutasyon Farklılığının Sistemik İmmün Enflamasyon İndeksi Üzerine Etkisi

Deniz Yılmaz[1], Felemez Arslan[1], Ezgi Şahin[1], Betül Erişmiş[1], Faruk Karandere[1], İnci Öztel[1], Yusuf Emre Özdemir[2], Habip Gedik[2], Mehmet Hurşitoğlu[1]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Türkiye

ABSTRACT

Objective: Mutations in coronavirus 2 [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] are a considerable issue. It could affect the infectivity and outcome of coronavirus disease-2019 (COVID-19) infection. In this prospective study, we compared the characteristics and outcomes of the main SARS-CoV-2 variants in our non-intensive care unit pandemic service inpatients.

Methods: In this study, 2,090 COVID-19 inpatients were included. The numbers of patients with alpha (group 1), delta (group 2), and omicron (group 3) variants were 701, 699, and 690, respectively.

Results: The median age of group 3 patients was significantly higher than that of the others, and the female/male ratio and presence of diabetes mellitus of group 1 patients were significantly lower than those of the others ($p<0.05$, both). Regarding the hospital stay period and outcome, group 1 patients had the highest mortality rate ($p<0.05$, Eta square =0.12). Regression analysis showed that the presence of the alpha variant, severe chest computed tomography findings and chronic kidney disease, long hospital stay, and high serum C-reactive protein and D-dimer levels at admission were risk factors for a poor outcome.

Conclusion: Early admission and/or easily obtainable clinical and laboratory determinant parameters of poor outcome could be a pathfinder for clinicians and/or researchers dealing with this challenging contagious viral disease.

Keywords: SARS-CoV-2, alpha, delta, omicron, COVID-19

ÖZ

Amaç: Koronavirüs 2'deki mutasyonlar [şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2)] önemli bir sorundur. Bulaşıcılığı ve koronavirüs hastalığı-2019 (COVİD-19) enfeksiyonunun sonucunu etkileyebilir. Bu prospektif çalışmada, yoğun bakım ünitesi dışı pandemi servislerinde yatan hastaların ana SARS-CoV-2 varyantlarının özellikleri ve sonuçları karşılaştırmaya çalışıldı.

Gereç ve Yöntem: Bu çalışmaya toplam 2.090 COVİD-19 tanısı ile yatan hasta dahil edildi. Alfa (grup 1), delta (grup 2) ve omicron (grup 3) varyant hasta sayısı sırasıyla 701, 699 ve 690 idi.

Bulgular: Grup 3 hastalarının ortanca yaşı diğerlerinden anlamlı olarak yüksekti ve grup 1 hastalarının kadın/erkek oranı ve diabetes mellitus varlığı diğerlerinden anlamlı derecede düşüktü ($p<0,05$, her ikisi de). Hastanede yatış süresi ve yatış komplikasyonu ile ilgili olarak, grup 1'deki hastalar en yüksek mortalite oranına sahipti ($p<0,05$, Eta kare =0,12). Regresyon analizi; alfa varyantı varlığının, şiddetli toraks bilgisayarlı tomografi bulgularının, kronik böbrek hastalığının, hastanede uzun yatış süresinin, başvuru sırasındaki yüksek serum C-reaktif protein ve D-dimerinin morbidite ve mortalite için risk faktörleri olduğunu gösterdi.

Sonuç: Bu erken dönemdeki yatış ve/veya komplikasyon sonucunun pratik olarak elde edilebilen klinik ve laboratuvar belirleyici parametreleri, bu tür zorlu bulaşıcı viral hastalıklarla ilgilenen klinisyen ve/veya araştırmacılar için yol gösterici olabilir.

Anahtar Kelimeler: SARS-CoV-2, alpha, delta, omicron, COVİD-19

Address for Correspondence: Felemez Arslan, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
Phone: +90 543 835 57 97 E-mail: feloarslan@gmail.com ORCID ID: orcid.org/0000-0001-8318-1860

Cite as: Yılmaz D, Arslan F, Şahin E, Erişmiş B, Karandere F, Öztel İ, Özdemir YE, Gedik H, Hurşitoğlu M. Effect of Mutational Difference on Systemic Immune Inflammation Index in Patients with a Diagnosis of COVID-19. Med J Bakirkoy 2023;19:372-381

Received: 25.03.2023
Accepted: 25.06.2023

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a highly contagious viral infection (1). Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) demonstrates a somewhat lower mutational rate than other RNA viruses, approximately 12,800 mutations have been identified (2). The well-known variants are alpha B.1.1.7 (known as 20I/501Y.V1, VOC 202012/01), beta B.1.351 (known as 501Y.V2), and gamma P.1 (known as alpha, delta, and omicron) are the main determining responsible variants for COVID-19 infection in Türkiye World Health Organization (3). The last VOC of the SARS-CoV-2 virus is the omicron (4). Alpha, delta, and omicron are the main determining variants responsible for COVID-19 infection in Türkiye (5). As mentioned in a study by Loucera et al. (6), combining genomic data with patients' clinical data will help us better understand the effect of mutations on the outcome of this challenging infection. To the best of our knowledge (at least in Türkiye), there are no studies assessing patients' early admission clinical, laboratory, and radiological characteristics according to the variants of SARS-CoV-2 viruses. In this retrospective study, we attempted to study these issues in our hospital's non-critical alpha, delta, and omicron variants infected by COVID-19 in-patients.

METHODS

This retrospective study was approved by University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital's Clinical Research Ethics Committee (decision no: 2022-12-18, date: 20.06.2022). Data of the above-mentioned hospital's medical pandemic services for COVID-19 patients were collected. According to the dates of predominance of alpha (01 April-30 June 2021), delta (01 August-30 November 2021), and omicron (01 January-30 April 2022) variants, COVID-19 patients were divided into group 1 (alpha), group 2 (delta), and group 3 (omicron), respectively.

Inclusion criteria;

1. Age >18 years old,

2. Positivity of the COVID-19 real-time reverse transcriptase polymerase chain reaction test at admission,

3. Presence of first-day admission laboratory records.

Exclusion criteria;

1. Those who were discharged at their request before completing their treatment and follow-up,

2. Taking medications that could affect routine laboratory measures (such as steroids, chemotherapy, radiotherapy, etc.) (within one month of the diagnosis of COVID-19 infection).

Behind demographic, clinical characteristics, and the outcome of the patients, their early admission laboratory and radiology investigations were recorded. In addition, comorbidities [such as hypertension (HT), diabetes mellitus (DM), ischemic heart disease, etc.] were recorded. Chronic kidney disease (CKD) stage ≥2 was also included in the analysis (7).

Chest computed tomography (CT) scoring system;

The semiquantitative CT severity scoring system was used (8). The scoring system was as follows: 0= no involvement, 1= less than 5% involvement, 2=5-25% involvement, 3=26-50% involvement, 4=51-75% involvement, and 5 more than 75% involvement. The sum of these yields a total score ranging from 0 to 25 points. A score of 0-8 is accepted as mild, 9-16 as moderate, and ≥17 as severe lung involvement.

Systemic immune-inflammation index;

This blood parameter was calculated using the formula: neutrophil × platelet (PLT)/lymphocyte (9).

Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 statistical package for Windows. Our study parameters data showed a non-normal distribution. Therefore, the description of data was expressed by median and interquartile range. For categorical measures, ratios and/or percentages were used. For the comparison of the 2 groups, the Mann-Whitney U test was used. Otherwise, the Kruskal-Wallis test was used for the comparison of ≥3 groups parameters. The Games Howell test was used as a post-hoc test of the Kruskal-Wallis test. The effect size (ES) was determined using Eta square ($\eta 2$) or epsilon square ($\epsilon 2$) tests, as appropriate. The values of these tests range between 0 (no association) and 1 (complete association) (1). A comparison of frequencies was performed by the chi-square test. For the degree of association, a Cramer's V value was determined (between 0.0-1.0). A Cramer's V value close to 0.00 indicates no association. A value >0.15 indicates a strong association, and >0.25 indicates a strong association (10). Spearman tests were also used to evaluate the correlation between quantitative variables. Regression analysis was performed by putting the presence or absence of the nominal. Also by putting laboratory parameters (median value) into 2 different logistic regression models (Model: Forward LR) (adjusting od ratio at 95% confidence interval). A p-value <0.05 was accepted as significant for all others.

Informed consent was obtained from each subject before the study. We are committed to protecting patient privacy and complying with the Declaration of Helsinki.

RESULTS

The final analysis was performed with 2,090 patients. The female/male ratio and median (minimum-maximum) age of them were 938 (44.90%)/1152 (55.10%), and 63.00 (18.00-97.00) years old, respectively. The numbers of alpha, delta, and omicron variants were 701, 699, and 690, respectively. A comparison of the study parameters between alpha (group 1), delta (group 2), and omicron (group 3) mutant patients is shown in Table 1. As seen in this table, the median age of group 3 patients was significantly higher than that of the other 2 groups ($p<0.05$, both, and ES =0.53). On the other hand, the female/male ratio and presence of DM in group 1 patients were significantly lower than those in groups 2 and 3 ($p<0.05$, all, and ES was 0.10, and 0.36, respectively). In addition, group 2 patients had a significantly lower rate of HT and cardiovascular disease (CVD) than the other 2 groups ($p<0.05$, all, and ES was 0.10, and 0.09, respectively). The CKD rate of group patients was higher than that of the other two groups ($p<0.05$, and ES =0.11). Although the rate of patients with no comorbidities was lowest in group 1, the rate of patients with 1, 2, and ≥3 comorbidities was significantly lower in group 2 ($p<0.05$, all, and ES =0.35). Regarding the hospital stay period and outcome, group 1 patients had the longest hospital stay and highest mortality rate than the other two groups ($p<0.05$, both, and ES was 0.81, and 0.12, respectively).

A comparison of the study parameters of our study of COVID-19 patients (n=2,090) according to the outcome of survival (n=1,704) or death (n=386) is shown in Table 2. Table 2 presents a comparison of the study parameters for our study of COVID-19 patients. The total number of patients in the study was 2,090, out of which 1,704 survived and 386 unfortunately passed away. Those who died were significantly older than those who survived this infection ($p<0.05$, ES =1.99). The ratio of the F/M ratio of the dead patients was lower than that of the survived patients (154/232 versus 784/920, respectively, $p<0.05$ and EF =0.047). Regarding the comorbidities, the presence rates of HT, CKD, and CVD in the dead group were higher than those in the survived group ($p<0.05$, all, and ES was 0.056, 0.069, and 0.074, respectively). On the other hand, the rate of the presence of DM was higher in the surviving group but not reached a statistical significance ($p>0.05$). Comparison according to the number of comorbidities showed a non-significant difference between the surviving and dead patient groups ($p>0.05$). The presence of severe chest CT findings at admission and hospital stay period of the dead patients was higher than the survived patients, while the early admission $\%SO_2$ levels showed an opposite pattern ($p<0.05$, all, and ES was 0.233 and 0383, 0.389, respectively). Regarding the early admission laboratory blood tests measure, the median Hgb level eosinophils, lymphocytes, and PLT counts were significantly higher in the survived, and the median remaining blood test levels were significantly higher in the dead patients' group (for the details see Table 2). Table 2 provides detailed information about the study parameters in relation to the outcome of survival or death among COVID-19 patients. The results indicate that the presence of severe chest CT findings upon admission and the duration of hospital stay were more frequent in patients who did not survive compared with those who survived ($p<0.05$). Conversely, the levels of early admission $\%SO_2$ (oxygen saturation) showed the opposite trend, being higher in the survival group ($p<0.05$). The ES for these associations were 0.233 and 0.38. Regarding the early admission laboratory blood tests, the median levels of hemoglobin (Hgb), eosinophils, lymphocytes, and PLT counts were significantly higher in the group of patients who survived, whereas the median levels of the remaining blood tests were significantly higher in the group of patients who died. Further details can be found in Table 2.

The regression analysis of parameters that could affect the outcome is shown in Table 3. The mortality risk is 1.94 times higher in patients with alpha variants. There is a 1.25-fold mortality risk in the delta, but it was not significant ($p>0.05$); 1.70 times in those with severe chest CT finding, 2.70 times in the presence of CKD, 1.02 times in mortality risk with one unit increase in length of stay, 0.92 times in mortality when income saturation increases by one unit, lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer increases by n units mortality risk increases by 1,002, 1,006, 1.04, respectively. Table 3 displays the results of the regression analysis conducted to examine the parameters that could impact the outcome. The findings reveal that individuals with alpha variants of COVID-19 have a 1.94 times higher risk of mortality. Similarly, there was a 1.25-fold mortality risk associated with the delta variant, although this finding did not reach statistical significance ($p>0.05$). Moreover, the presence of severe chest CT findings was linked to a 1.70-fold higher mortality risk. Patients with CKD face a significantly elevated mortality risk of 2.70 times. Additionally, for every unit increase in the length of hospital stay, there is a 1.02 times higher mortality risk. Conversely, a one-unit increase in oxygen saturation levels leads to a mortality risk of 0.92 times. Furthermore, the mortality risk

Table 1. Comparison of study parameters according to mutations

	Mutation				
Parameter	**Alpha1 n=701**	**Delta2 n=699**	**Omicron3 n=690**	**p-value**	**Effect size**
Gender				**<0.001**	0.10[a]
Female	261 (37.2%)	330 (47.2%)	347 (50.3%)		
Male	440 (62.8%)	369 (52.8%)	343 (49.7%)		
Post-hoc		1-2, 1-3			
Age (years)				**<0.001**	0.053[b]
Median	62.50	63.00	70.00		
IQR	16.00	28.00	22.00		
Q1-Q3	53.00-70.00	48.00-76.00	59.00-81.00		
Range	18.00-97.00	18.00-95.00	20.00-97.00		
Post-hoc		1-3, 2-3			
Hypertension				**<0.001**	
Absent	330 (47.1%)	394 (56.4%)	309 (44.8%)		0.10[a]
Present	371 (52.9%)	305 (43.6%)	381 (55.2%)		
Post-hoc		2-1, 2-3			
Diabetes mellitus				**<0.001**	
Absent	226 (32.2%)	506 (72.4%)	473 (68.7%)		0.36[a]
Present	475 (67.8%)	193 (27.6%)	216 (31.3%)		
Post-hoc		1-2, 1-3			
Chronic kidney disease				**<0.001**	0.11[a]
Absent	658 (93.9%)	651 (93.1%)	601 (87.1%)		
Present	43 (6.1%)	48 (6.9%)	89 (12.9%)		
Post-hoc		3-1, 3-2			
Cardiovascular disease				**<0.001**	0.09[a]
Absent	539 (76.9%)	581 (83.1%)	512 (74.2%)		
Present	162 (23.1%)	118 (16.9%)	178 (25.8%)		
Post-hoc		2-1, 2-3			
Numbers of comorbidities				**<0.001**	0.35[a]
0	119 (17.0%)	307 (43.9%)	172 (24.9%)		
1	217 (31.0%)	146 (20.9%)	163 (23.6%)		
2	200 (28.5%)	138 (19.7%)	196 (28.5%)		
≥3	165 (23.5%)	108 (15.5%)	159 (23.0%)		
Post-hoc		1-2, 1-3, 2-3			
Chest CT findings				**<0.001**	0.32[a]
Not severe	457 (65.3%)	590 (89.5%)	596 (92.7%)		
Severe	243 (34.7%)	69 (10.5%)	47 (7.3%)		
Mortality				**<0.001**	0.12[a]
Survived	526 (75.0%)	583 (83.4%)	595 (86.2%)		

Table 1. Continued					
Died	175 (25.0%)	116 (16.6%)	95 (13.8%)		
Post-hoc		1-2, 1-3			
Duration of hospital stay (days)				**<0.001**	0.081[b]
Median	14.00	9.00	9.00		
IQR	11.00	8.00	9.00		
Q1-Q3	14.00-20.75	6.00-14.00	6.00-15.00		
Range	0.00-104.00	4.00-85.00	1.00-128.00		
Post-hoc		1-2, 1-3			
SII (x10^9 cells/L)				**<0.001**	0.013[b]
Median	957.00	1043.80	1368.99		
IQR	1553.36	1545.16	2202.98		
Q1-Q3	513.95-2067.30	539,91-2085,07	676.91-2879.89		
Range	4.33-720438.09	25.76-17818.18	0.00-22016.94		
Post-hoc	2-3				
Platelet count (x10^9 cells/L)				**<0.001**	0.014[b]
Median	199.00	192.00	218.50		
IQR	101.50	101.00	117.25		
Q1-Q3	154.00-255.50	152.00-253.00	166.00-283.25		
Range	9.00-954.00	26.00-803.00	8.00-1147.00		
Post-hoc	3-1, 3-2				
Lymphocyte count (x10^9 cells/L)				**<0.001**	0.008[b]
Median	1060.00	930.00	1040.00		
IQR	830.00	750.00	950.00		
Q1-Q3	710.00-1540.00	600.00-1350.00	660.00-1610.00		
Range	2.10-1175.00	70.00-18340.00	40.00-144810.00		
Post-hoc	1-2				
Neutrophil count (x10^9 cells/L)				**<0.001**	0.021[b]
Median	5150.00	5200.00	6670.00		
IQR	4200.00	4230.00	5562.50		
Q1-Q3	3700.00-7900.00			3520.00-7750.00	4152.50-9715.00
Range	40.00-18700.00	126.00-19720.00	0.00-30620.00		
Post-hoc	3-1, 3-2				

IQR: Interquartile range, CT: Computed tomography, SII: Systemic immune-inflammation index
Kruskal-Wallis test, Post-hoc: Games Howell test, statistically significant p<0.05.
[a]Eta square [(**η**2), [b]Epsilon sqare (**ϵ**2) (degree of freedom =2)].

increased by 1,002, 1,006, and 1.04 times with each unit increase in LDH, CRP, and D-dimer levels, respectively. These results provide important insights into the various factors that can influence mortality outcomes.

DISCUSSION

In our study, the ratio of female/male in Alpha variant-infected COVID-19 inpatients was significantly lower than the ratio of the other two variant-infected patient groups. On the other hand, the median age of the omicron variant

Table 2. Comparison of study parameters according to outcomes

	Outcome				
Parameters	**Survived (n=1704)**	**Died (n=386)**	**df**	**p**	**Effect size**
Age (years)			**1**	**<0.001**	0.199
Median	64.00	70.00			
IQR	23.00	19.00			
Range	18.00-96.00	25.00-97.00			
Gender			**1**	**0.029**	0.047[a]
Female/male	784/920	154/232			
Hypertension			**1**	**0.010**	0.056
Absent/present	865/839	168/218			
Diabetes mellitus			**1**	NS	0.038
Absent/present	967/736	238/148			
Chronic kidney disease			**1**	**0.002**	0.069
Absent/present	1573/131	337/49			
Cardiovascular disease			**1**	**<0.001**	0.074
Absent/present	1573/129	336/50			
Severe chest CT findings			**1**	**<0.001**	0.233
Absent/present	1426/229	217/130			
Comorbidities			**3**	NS	0.054
0	497 (23.8%)	101 (28.6%)			
1	429 (49.1%)	97 (53.8%)			
2	443 (75.0%)	91 (79.3%)			
≥3	335 (95.4%)	97 (100.0%)			
Variants			**2**	**<0.001**	0.123[a]
Alpha	526	175			
Delta	583	116			
Omicron	595	95			
Duration of hospital stay (days)			**2074**	**<0.001**	0.384
Median	10.00	16.00			
IQR	8.00	11.00			
Range	0.00-104.00	1.00-128.00			
SII			**2088**	**<0.001**	0.199
Median	1014.00	1567.00			
IQR	1595.00	2597.00			
Range	0.00-720438.00	3.91-302.91			
SO_2 (%)			**2084**	**<0.001**	0.389
Median	94.00	91.00			
IQR	4.00	8.00			
Range	55.00-99.00	46.00-99.00			

Table 2. Continued					
Hemoglobin (g/dL)			**1881**	**<0.001**	0.177
Median	12.50	11.90			
IQR	2.73	2.85			
Range	5.00-135.00	5.80-17.00			
Hematocrit (%)			**2071**	**0.007**	0.089
Median	37.9	38.1			
IQR	7.70	300.00			
Range	11.50-509.00	18.00-506.00			
White blood cell count (x10^6 cells/L)			**2088**	**<0.001**	0.119
Median	7120.00	8030.00			
IQR	4930.00	6065.00			
Range	1.38-96000.00	2.35-151220.00			
Lymphocyte count (x10^9 cells/L)			**2088**	**<0.001**	0.278
Median	1060.00	770.00			
IQR	850.00	618.00			
Range	2.10-88270.00	100.00-144810.00			
Neutrophil count (x10^9 cells/L)			**2088**	**<0.001**	0.188
Median	5390.00	6985.00			
IQR	4480.00	5405.00			
Range	0.00-29180.00	550.00-30620.00			
Eozinophil count (x10^9 cells/L)			**2088**	**<0.001**	0.207
Median	0.20	0.00			
IQR	30.00	10.00			
Range	0.00-2420.00	0.00-610.00			
Platelet count (x10^3 cells/L)			**2088**	**<0.001**	0.163
Median	206.00	192.00			
IQR	111.00	91.00			
Range	11.00-1147.00	22.00-954.00			
Glucose (mg/dL)			**1989**	**<0.001**	0.165
Median	144.00	152.00			
IQR	99.58	109.00			
Range	48.00-3801.00	14.00-4123.00			
Creatinin (mg/dL)			**2000**	**<0.001**	0.432
Median	0.94	1.73			
IQR	0.53	2.25			
Range	0.10-231.00	0.32-96.00			
Lactate dehydrogenase (U/L)			**2073**	**<0.001**	0.453
Median	309.50	459.00			
IQR	168.25	328.00			

Table 2. Continued					
Range	44.00-5080.00	0.00-5200.00			
Procalcitonin (ng/mL)			**2042**	**<0.001**	0.651
Median	0.14	2.00			
IQR	0.30	10.72			
Range	0.01-33872.00	0.03-22682.00			
C-reactive protein (mg/L)			**2058**	**<0.001**	0.221
Median	88.00	178.00			
IQR	113.00	205.00			
Range	0.00-526.00	1.00-451.67			
D-dimer (µg/mL FEU)			**1989**	**<0.001**	0.487
Median	0.74	2.86			
IQR	1.19	4.83			
Range	0.00-99.00	0.01-89.00			
Fibrinogen (mg/dL)			**1902**	**<0.001**	0.172
Median	570.00	645.00			
IQR	198.00	242.00			
Range	152.00-1200.00	114.00-120.00			

df: Degree of freedom, SO_2: Early admission oxygen saturation, IQR: Interquartile range, CT: Computed tomography, SII: Systemic immune-inflammation index
[a]Chi-square test

Table 3. Regression analysis results of study parameters according to outcome

Independent variables	**B**	**S.E.**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% CI for EXP(B)**	
Variants			9,074	2	0.011			
Alpha variant	0.664	0.221	9,008	1	0.003	1,943	1,259	2,998
Delta variant	0.23	0.202	1,296	1	0.255	1,259	0.847	1.87
Presence of severe chest CT findings (+)	0.532	0.186	8,223	1	0.004	1,703	1,184	2.45
CKD (+)	0.996	0.232	18,451	1	p<0.001	2,708	1,719	4,266
Duration of hospital stay (days)	0.02	0.007	8.65	1	0.003	1.02	1,007	1,033
Age (years)	0.05	0.006	62,553	1	p<0.001	1,052	1,039	1,065
Admission SO_2 (%)	-0.079	0.015	25,739	1	p<0.001	0.924	0.897	0.953
LDH (U/L)	0.002	0	37,668	1	p<0.001	1,002	1,002	1,003
CRP (mg/L)	0.006	0.001	46,542	1	p<0.001	1,006	1,004	1,008
D-dimer (µg/mL FEU)	0.039	0.005	52,892	1	p<0.001	1.04	1,029	1,051
Constant	-0.759	1.57	0.234	1	0.629	0.468		

S.E.: Standard error, df: Degree of freedom, SO_2: Early admission oxygen saturation, CI: Confidence interval, CT: Computed tomography, CKD: Chronic kidney disease, LDH: Lactate dehydrogenase, CRP: C-reactive protein

group was significantly higher than that of the other two groups (p<0.05, both). Previous studies also showed a higher rate of alpha infections in males than in females (11), but the emergence of new mutant variants and/or vaccines somewhat affected these issues (12). We should mention that the rate of known comorbidities (HT, DM, CKD, and CVD) that could affect the course and outcome of this disease was also different between the study groups. This should also be considered [the presence of severe chest CT findings and mortality rate, and duration of hospital stay

were significantly higher in alpha variant group patients (in comparison to the other 2 groups) ($p<0.05$, all, and ES were 0.32, 0.12, and 0.08, respectively)] (12,13). Regarding the laboratory parameters, although most of them were significantly different between the groups, their ES was not significantly different (Table 1).

There was a significant difference in the study parameters of patients who survived or died from COVID-19 infection. Behind the statistical significance, most of these showed a somewhat high ES (Table 2). Regression analysis of all parameters that may affect the outcome of patients. As shown in Table 3, the presence of the Alpha variant infection was one of the important determinants of mortality. This variant increased the risk of mortality by 1.25 times. Previous studies also showed a high risk of hospitalization and death in patients with alpha variant COVID-19 infections. Significant differences were observed in the study parameters between COVID-19 patients who survived and those who succumbed to the infection. These differences were not only statistically significant but also demonstrated relatively high ES, as indicated in Table 2. To further explore the factors influencing patient outcomes, a regression analysis was conducted, considering all potential parameters. The results presented in Table 3 highlight the significance of alpha variant infection as a crucial determinant of mortality. Patients infected with the alpha variant faced a 1.25-fold higher risk of mortality. This finding aligns with previous studies that have also reported a heightened risk of hospitalization and death associated with the alpha variant of COVID-19. In a commentary by Cevik and Mishra (14). The severity of this variant-related COVID-19 infection is increased with ages more than 30 years. Additionally, this severity of infection is more pronounced in patients older than 65 years. In our patient data set, age was also a predictor of outcome. The median age of those patients who died was significantly higher than that of those who survived this infection in our study patients (70 versus 64 years old, $p<0.05$) (Table 2). This finding is also consistent with other published studies (14,15). Lung involvement is a predictor of the severity and outcome of this viral disease (16). Our study findings also showed increased mortality with increased severity of lung involvement as detected by chest CT (Table 2 and 3) (8). Previous studies from Türkiye and other countries have shown a poor outcome of COVID-19 in CKD patients (15,17,18). Our study results also support these findings. The presence of CKD in our study patients (regardless of the type of COVID-19 variant) increased the mortality risk by 1,719 times (Table 3). Although other predictors of mortality were determined in our study, the determination of the effect of CKD on the mortality of COVID-19 is of paramount importance that could help in planning the management and/or in planning similar studies in this field.

One of the important limitations of this study is that it was retrospective. Therefore, we could not assess the effect of the type of therapy on the outcome. The management of the disease was performed according to the Turkish Ministry of Health's guidelines applicable at the related periods and/or peaks of COVID-19 infection. The other limiting factor is not including intensive care unit (ICU) patients in this study. To decrease bias and incorrect data, we used data from our non-ICU pandemic services. This study has a notable limitation as it is retrospective in nature, which means that we were unable to evaluate the impact of different therapies on patient outcomes. The management of the disease followed the guidelines provided by the Turkish Ministry of Health during the relevant periods and peaks of COVID-19 infection. Another limitation is that the study did not include patients from the ICU. To mitigate potential biases and ensure accurate data, we relied on data obtained from non-ICU pandemic services.

CONCLUSION

Our study results determined unique useful early admission predictors of COVID-19 infection that could be used in different stages and variants of SARS-CoV-2 viral infection. These findings could be a pathfinder for clinicians and/or researchers dealing with this challenging contagious viral disease. The findings of our study have identified valuable predictors for early admission in COVID-19 infection, which can be applied across various stages and variants of SARS-CoV-2 viral infection. These results provide valuable guidance for clinicians and researchers involved in the management of this complex and highly contagious viral disease. They serve as a valuable resource for navigating the challenges posed by COVID-19.

ETHICS

Ethics Committee Approval: This retrospective study was approved by University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital's Clinical Research Ethics Committee (decision no: 2022-12-18, date: 20.06.2022).

Informed Consent: Informed consent was obtained from each subject before the study.

Authorship Contributions

Surgical and Medical Practices: D.Y., F.A., İ.Ö., M.H., Concept: D.Y., F.A., B.E., M.H., Design: D.Y., F.A., B.E., M.H., Data Collection or Processing: F.K., İ.Ö., Analysis or

Interpretation: F.A., B.E., F.K., M.H., Literature Search: F.A., E.Ş., F.K., İ.Ö., Y.E.Ö., H.G., M.H., Writing: F.A., E.Ş., Y.E.Ö., H.G., M.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. Hursitoglu M, Isıksacan N, Erismis B, Karandere F, Kural A, Kumbasar AB, et al. In-vitro cytokine production and nasopharyngeal microbiota composition in the early stage of COVID-19 infection. Cytokine 2022;149:155757.
2. Papanikolaou V, Chrysovergis A, Ragos V, Tsiambas E, Katsinis S, Manoli A, et al. From delta to Omicron: S1-RBD/S2 mutation/deletion equilibrium in SARS-CoV-2 defined variants. Gene 2022;814:146134.
3. Tian D, Sun Y, Zhou J, Ye Q. The global epidemic of SARS-CoV-2 variants and their mutational immune escape. J Med Virol 2022;94:847-57.
4. Fan Y, Li X, Zhang L, Wan S, Zhang L, Zhou F. SARS-CoV-2 Omicron variant: recent progress and future perspectives. Signal Transduct Target Ther 2022;7:141.
5. Özüdoğru O, Bahçe YG, Acer Ö. SARS CoV-2 reinfection rate is higher in the Omicron variant than in the Alpha and Delta variants. Ir J Med Sci 2023;192:751-6.
6. Loucera C, Perez-Florido J, Casimiro-Soriguer CS, Ortuño FM, Carmona R, Bostelmann G, et al. Assessing the Impact of SARS-CoV-2 Lineages and Mutations on Patient Survival. Viruses 2022;14:1893.
7. The National Kidney Federation. CHRONIC KIDNEY DISEASE. 2022. Dr Oshini Shivakumar. https://www.kidney.org.uk/chronic-kidneydisease?gclid=Cj0KCQjw48OaBhDWARIsAMd966BxitxaUCdCjgeWjdhOAwPWStD41P9bPBZ74Ff6Nw-_vrGArG1LnjwaArUgEALw_wcB.
8. Yaltırık Bilgin E, Bilgin E, Fidan H, Çelenk Y, Tok T. Correlation of Clinical Course with Computed Tomography Findings and Biochemical Parameters at the Time of Admission in COVID-19 Patients. Turk J Anaesthesiol Reanim 2022;50:274-81.
9. Feng JF, Chen S, Yang X. Systemic immune-inflammation index (SII) is a useful prognostic indicator for patients with squamous cell carcinoma of the esophagus. Medicine (Baltimore) 2017;96:e5886
10. Erismis B, Karabela SN, Eksi F, Karandere F, Dogan B, Okay F, et al. Annual influenza vaccination effect on the susceptibility to COVID-19 infection. Cent Eur J Public Health 2021;29:14-7.
11. Agrawal H, Das N, Nathani S, Saha S, Saini S, Kakar SS, et al. An Assessment on Impact of COVID-19 Infection in a Gender Specific Manner. Stem Cell Rev Rep 2021;17:94-112.
12. Kahn F, Bonander C, Moghaddassi M, Rasmussen M, Malmqvist U, Inghammar M, et al. Risk of severe COVID-19 from the Delta and Omicron variants in relation to vaccination status, sex, age and comorbidities - surveillance results from southern Sweden, July 2021 to January 2022. Euro Surveill 2022;27:2200121.
13. Wilk-Sledziewska K, Sielatycki PJ, Uscinska N, Bujno E, Rosolowski M, Kakareko K, et al. The Impact of Cardiovascular Risk Factors on the Course of COVID-19. J Clin Med 2022;11:2250.
14. Cevik M, Mishra S. SARS-CoV-2 variants and considerations of inferring causality on disease severity. Lancet Infect Dis 2021;21:1472-4.
15. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med 2020;180:1345-55.
16. Kanne JP, Bai H, Bernheim A, Chung M, Haramati LB, Kallmes DF, et al. COVID-19 Imaging: What We Know Now and What Remains Unknown. Radiology 2021;299:E262-79.
17. Ozturk S, Turgutalp K, Arici M, Odabas AR, Altiparmak MR, Aydin Z, et al. Mortality analysis of COVID-19 infection in chronic kidney disease, haemodialysis and renal transplant patients compared with patients without kidney disease: a nationwide analysis from Turkey. Nephrol Dial Transplant 2020;35:2083-95.
18. Pecly IMD, Azevedo RB, Muxfeldt ES, Botelho BG, Albuquerque GG, Diniz PHP, et al. COVID-19 and chronic kidney disease: a comprehensive review. J Bras Nefrol 2021;43:383-99.