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RESEARCH ARTICLE

The Factors Affecting Mortality in Delta and Non-Delta Variant Severe COVID-19 Patients

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ABSTRACT

Objective: We aimed to evaluate the effect of delta variant, blood tests such as lymphocyte, C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), polymerase chain reaction (PCR)-cycle threshold (Ct) rates, vaccination status, and invasive mechanical ventilation (IMV) in predicting mortality in coronavirus disease-19 (COVID-19) patients.

Materials and Methods: This study is conducted as a retrospective study of all COVID-19 patients with reverse transcriptase-PCR (RT-PCR)-positive confirmation and hospitalization from the emergency room to the intensive care unit at the University of Health Sciences Istanbul Kanuni Sultan Süleyman Training and Research Hospital during the 6-month period between September 2021 and February 2022.

Results: We detected delta variant in 59 of 117 patients included in the study and 58 patients had non-delta variant SARS-CoV-2. In-hospital mortality was observed in 68 (58.1%) patients. We found that 72 (61.5%) of the patients were given IMV support and 88 (75.2%) were unvaccinated. We found that patients who received IMV support and resulted in mortality had low lymphocyte levels and high CRP and LDH values. The PCR-Ct values of the patients were 25.04±4.12 in patients with delta variant and 28.54±4.35 in patients with non-delta variant SARS-CoV-2 and we found statistically significantly higher.

Conclusion: There was no significant difference in mortality between delta variant and non-delta variant SARS-CoV-2 patients. Although patients with delta variant have low PCR-Ct values, there is no significant difference in mortality. Ferritin, lymphocyte, LDH, and CRP can be used to predict mortality in COVID-19 patients.

Keywords: COVID-19, Delta mutation, intensive care unit, mortality

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INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a contagious and severe acute respiratory syndrome disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] It first emerged in the city of Wuhan, China and spread to the whole world, causing a global pandemic. The virus, named SARS-CoV-2, has become the most serious health problem due to its rapidly increasing mortality.[2] More than 4000 variants have been identified as the global SARS-CoV-2 pandemic continues. The World Health Organization (WHO) defined five of the mutations of COVID-19 that have emerged so far as "variant of concern" and eight as "variant being monitored." The WHO warned that mutations defined as "Variant of Concern" can "increase the contagiousness and spread of the virus, change its lethality or disease symptoms, and reduce the effectiveness of prevention and control measures." While the five variants identified as "variant of concern" were named alpha, beta, gamma, delta, and omicron, those categorized as "variant being monitored" were named Epsilon, Zeta, Eta, Theta, Iota, Kappa, and Lambda.[3]

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The delta variant, in which we will also mention in our study, is a new variant of SARS-CoV-2 known as B.1.617.2, a subspecies of the lineage called "B.1.617" and was first seen in India in December 2020. The main risk of the variant is increased transmissibility. As a result of increased contagiousness, it is predicted that hospitalizations and death rates may increase in all age groups, especially in the elderly or those with comorbid diseases. The delta variant has quickly become the dominant strain worldwide due to its ability to invade the host's immune system compared to the original strain.[3] It was also found to have a higher risk of causing more serious cases than other variants. There are studies in which patients with delta mutations have a higher need for hospitalization compared to the first-onset alpha mutation.[4–6] As infection rates with the delta variant increase, increased risks for hospitalization have been demonstrated and a large Canadian study found that patients infected with the delta variant had an increased risk of intensive care unit (ICU) hospitalization and death. The same study showed that the risk of hospitalization increased by 59%, the need for intensive care increased by 105% and the risk of death increased by 61% in alpha, beta, and gamma variants as a result of the retrospective evaluation of 211,197 COVID–19 cases. It was found that there was a 120% increase in the risk of hospitalization, a 287% increase in the need for intensive care, and a 137% increase in the risk of death for the delta variant.[4] In a study conducted in Singapore, an increase of 4.9% was found in the oxygen demand, need for intensive care or risk of death for the delta variant compared to the SARS-CoV-2 alpha and beta variants.[7]

Delta variant and non-delta variant SARS-CoV-2 constitutes the mutations in the patients that we screened during our study. The primary aim of our study is to evaluate the effect of delta variant in predicting mortality in COVID-19 patients. In addition, we aimed to determine whether the patient's age, gender, comorbidities, history of vaccination, and parameters such as ferritin, lactate dehydrogenesis (LDH), C-reactive protein (CRP), and lymphocyte levels were effective in predicting mortality.

MATERIALS and METHODS

Our study was planned as a single-center and retrospective. After the approval of the Ethics Committee, all COVID-19 patients were included in this study who had positive confirmation of reverse transcriptase-polymerase chain reaction (RT-PCR) and were hospitalized in ICU in the Health Sciences University Istanbul Kanuni Sultan Suleyman Training and Research Hospital in a 6-month period between September 2021 and February. RT-PCR positive samples without variant analysis were excluded from the study. All data (clinical symptoms, findings, demographic data, laboratory results, RT-PCR and variant analyses, PCR-Ct (PCR cycle threshold, Ct), vaccination status, invasive mechanical ventilation (IMV) needs, hospital stay of the patients included in the study and clinical follow-ups) were obtained by scanning the hospital information management system. The vaccination status of the patients was obtained from the vaccination history of the patients and their relatives and recorded in the study form. In the study, Diagnovital Diagno 5plex NS SARS-COV-2 Real Time PCR kit (RTA, Turkey) was used in nasopharyngeal swab samples collected from patients in our hospital's COVID-19 test center. This is a real-time and one-step RT-PCR test kit that targets SARS-CoV-2 specific ORF 1 a/b and N gene regions, S L452R mutation for delta variant detection, E484K mutation for beta and gamma, and B.1.1.7 mutation for alpha. If only the ORF 1 a/b and N gene regions specific to SARS-CoV-2 were detected in the test results, SARS-CoV-2 was reported as positive.

Those who were found to be SARS-CoV-2 positive, one of the variants containing L452R mutation positive, alpha variant (B.1.1.7), and E484K-including variants negative were considered as delta variant. Other than that, only the ORF 1a/b and N gene regions specific to SARS-CoV-2 were detected and the SL452R mutation, E484K mutation for beta and gamma variant detection and B.1.1.7 mutation for alpha variant detection were not detected, while SARS-CoV-2 were evaluated as positive.

While our study was continuing, after a new variant called Omicron was reported by the WHO on November 26, 2021, according to the results of the mutation detection with the Diagnovital Diagno 5plex NS SARS-COV-2 RT-PCR kit in the test samples of the patients, Bio-Speedy SARS-CoV-2 + Omicron RT -Qpcr (Bioeksen, Turkey) kit was studied and all samples were found to be omicron variant negative.

In the analysis of the vaccination data of the patients, while information about the vaccine could not be reached in 41.9% (n=49), it was found that 25.6% (n=30) were unvaccinated. Again, it was determined that 6% (n=7) of the patients who were considered as insufficient vaccination had 2 Sinovac (China) vaccines and 1.7% (n=2) had 1 dose of Biontech (Germany) vaccine. These patients were included in the unvaccinated group. Our patients who had two doses of Biontech (n=6, 5.1%), two doses of Sinovac + 1 dose of Biontech (n=8, 6.8%), three doses of Sinovac (n=14, 12%), and three doses of Sinovac + 1 dose of Biontech. dose Biontech (n=1, 0.9%) were included in the vaccinated group.

Table 1. Descriptive features

	n	%
Female	60	51.3
Male	57	48.7
Delta variant (+)	59	50.4
Non-delta variant SARS-CoV-2 (+)	58	49.6
Mortality	68	58.1
Those who were given IMV support	72	61.5
Those with comorbid disease	91	77.8
HT	45	38.5
DM	28	23.9
Asthma+COPD	23	19.7

HT: Hypertension; DM: diabetes mellitus; COPD: Chronic obstructive pulmonary disease

The obtained data were analyzed in the Statistical Package for the Social Sciences Statistics 24.0 (IBM Inc., New York, USA). While mean, standard deviation, and median (IQR) values were used to represent continuous variables, categorical variables were represented as numbers (percentage). Pearson Chi-square test was used in the analysis of categorical data. Normality test of continuous variables was done with Kolmogorov–Smirnov and Shapiro-Wilk tests. Independent sample t-test was used in the two-group analysis of normally distributed continuous variables and the Mann–Whitney U-test was used in pairwise comparison of non-normally distributed continuous variables. Statistical analyses were performed at a 95% confidence interval and P value of <0.05 was considered as statistically significant.

RESULTS

A total of 117 patients, 60 (51.3%) female and 57 (48.7%) male, were included in the study. While delta variant was detected in 59 (50.4%) patients, non-delta variant was detected in 58 (49.6%) of them. Mortality was observed in 68 (58.1%) patients and IMV support was given to 72 (61.5%) patients. When we group the vaccination status of the patients as vaccinated and unvaccinated, it was determined that 88 (75.2%) were unvaccinated. Comorbid disease was found in 91 (77.8%) of the patients. When the distribution of these diseases is evaluated, the most common comorbidity is hypertension with 38.5% (n=45), followed by diabetes mellitus and asthma+chronic obstructive pulmonary disease (COPD), respectively. (23.9% [n=28] and 19.7% [n=23], respectively.) The descriptive features of the patients are shown in Table 1.

When we compared the PCR-Ct values of the patients, the values of patients with delta variant were 25.04±4.12, while the values of patients with non-delta variant SARS CoV-2 were 28.54±4.35, which was statistically significantly higher (p<0.01). No statistically significant difference was found in the analysis of PCR-Ct values according to gender, vaccination status, hospital outcome, IMV support, and comorbid disease status of the patients (Table 2).

Table 2. Analysis of PCR-Ct values

	n	Mean	SD	p
Clinical outcome				
Discharged	42	26.62	4.14	0.929
Mortality	57	26.70	4.88	
Variant				
Delta variant	53	25.04	4.12	<0.01
Non-delta variant SARS-CoV-2	46	28.54	4.35	
Vaccination status				
Unvaccinated	77	26.48	4.68	0.450
Vaccinated	22	27.32	4.14	
IMV support				
No	40	26.60	4.25	0.905
Yes	59	26.71	4.80	
Gender				
Female	51	26.37	4.60	0.511
Male	48	26.98	4.55	
Comorbidity				
No	22	28.32	4.24	0.054
Yes	77	26.19	4.57	

SD: Standard deviation; IMV: Invasive mechanical ventilation

Independent sample t test and PCR-Ct values of 99 patients were studied.

Ferritin values of male patients were found to be statistically significantly higher than the ferritin values of female patients (p<0.01). Again, although the CRP values of male patients were significantly higher than female patients, there was no statistically significant difference (p=0.052).

When we grouped the patients according to the presence of comorbidity, it was found that the ferritin value was statistically significantly higher in patients who had comorbidity than in patients who did not have (p=0.023). In addition, although LDH values were significantly higher in the group without comorbidity, there was no statistically significant difference (p=0.058).

It was determined that the patients who were given IMV support had statistically significantly lower lymphocyte levels than the patients who did not (p<0.01). CRP and LDH values

Table 3. Comparisons of laboratory parameters and length of stay

	IMV		Variant		Clinical outcome	
	No (45)	**Yes (72)**	**Delta (59)**	**Non-delta variant SARS-CoV-2 (58)**	**Discharged (49)**	**Mortality (68)**
Lymphocyte (10^3/µL)	1 (1.10)	0.60 (0.48)	0.70 (0.80)	0.70 (0.80)	0.90 (0.85)	0.60 (0.50)
p	**<0.01**		0.704		**<0.01**	
D-dimer (µg/mL FEU)	1.58 (4.29)	1.88 (4.85)	1.56 (3.87)	2.44 (5.20)	1.57 (3.87)	2.02 (5.44)
p	0.436		0.193		0.190	
CRP (mg/L)	95 (86.50)	154.5 (145.50)	121 (113)	115.50 (154.50)	102 (113)	147.50 (136.50)
p	**<0.01**		0.560		**0.029**	
Ferritin (µg/L)	328 (828)	578.5 (1007.25)	461 (732)	558.50 (1134.75)	328 (780)	627.50 (1003.75)
p	**0.022**		0.311		**<0.01**	
LDH (U/L)	395 (270)	474 (302)	453 (288)	419.50 (382.25)	392 (283)	497.50 (295)
p	**<0.01**		0.166		**<0.01**	
Number of hospitalized days	9 (10)	8 (9.75)	8 (10)	8 (10)	9 (11)	8 (7.75)
p	0.822		0.959		0.416	
Clinical outcome						
Discharged	41	8	24	25		
Mortality	4	64	35	33		
p	**<0.01****		0.790**			
Variant						
Delta	20	39	24	35		
Non-Delta Variant SARS-CoV-2	25	33	25	33		
p	0.306**		0.790**			

Continuous variables are shown as median (IQR) and frequency data in Chi-square table, Mann–Whitney U-test, **: Pearson Chi-square. IQR: Interquartile range; CRP: C-reactive protein; LDH: Lactate dehydrogenesis

were found to be statistically significantly higher in patients who were given IMV support than in patients who were not (p<0.01 and p<0.01, respectively).

When we grouped the patients according to vaccination status and variant type, we did not find a statistically significant difference between the groups in terms of laboratory parameters and length of stay.

When we grouped the patients according to their clinical outcomes, it was found that the patients with mortality had statistically significantly lower lymphocyte levels compared to the discharged patients (p<0.01). At the same time, patients with mortality were found to have statistically significantly higher CRP, ferritin, and LDH values compared to discharged patients (p=0.029, <0.01, and <0.01, respectively) (Table 3).

DISCUSSION

COVID-19 is a viral infection that has a serious public health threat and currently results in high mortality. Countries around the world are experiencing serious problems related to the pandemic in terms of the burden on both the economy and health systems. New findings about the disease are constantly updated every day.

In the study of Twohig et al.[6] in England, it was reported that patients infected with the delta variant and unvaccinated required more need for hospitalization than those infected with the alpha variant. In a study conducted in the USA, it was found that the risk of admission to intensive care and death was increased in patients infected with the delta variant.[5] Again, in a large Canadian study, patients infected with the delta variant were found to have an increased risk of ICU admission and death. For the delta variant, there was a 120% increase in the risk of hospitalization, a 287% increase in the need for intensive care, and a 137% increase in the risk of death.[4] In our study, there was no statistically significant difference in mortality in patients with delta variant and non-delta variant SARS-CoV-2, although the number of patients with delta variant and exitus was higher.

There are many studies in the literature reporting that low lymphocyte levels affect prognosis.[8,9] In a study conducted in China, in which hospitalized patients with COVID-19 positive pneumonia were examined and it was reported that patients who died had lower lymphocyte levels.[9] In the study conducted by Deng et al.,[8] in which they examined patients with recovery and death in COVID-19 patients, lower lymphocyte levels were observed in mortality patients. In accordance with the literature, it was found that patients who died during ICU follow-up had lower lymphocyte levels in laboratory tests. We can say that the abnormality in blood parameters specific to the disease increases in direct proportion to the severity of the disease and mortality.

In a study by Bağ Soytaş et al.,[10] in which they examined the factors affecting mortality in geriatric patients hospitalized with COVID-19, it was found that there was an increase in mortality in patients with high CRP, ferritin, and LDH levels. In a study, in which COVID-19 patients from China who recovered and those who died were examined, it was found that the CRP levels were increased in the patients who ended up with exitus.[8] In our study, it was determined that the patients who resulted in mortality had high CRP levels. Consistent with the literature, we also found that the most effective parameters are ferritin, LDH, CRP, and lymphocyte levels in predicting mortality in COVID-19 patients. We believe that close monitoring of these parameters and early intervention in possible changes have vital importance.

There are studies in the literature showing an increased in-hospital mortality in patients given IMV support. In a meta-analysis published by Elsayed et al.,[11] mortality for COVID-19 patients requiring IMV was higher than most common medical conditions (severe COPD) requiring admission to the ICU. In our study, mortality was found to be higher in patients who were given IMV support, in line with the literature. In a study conducted in Italy at the beginning of the pandemic, it was reported that mortality is less common in patients given IMV support. They thought that the reason for this was that young patients were preferred instead of providing IMV support to elderly patients due to the low number of mechanical ventilators and the large number of patients at the beginning of the pandemic.[12]

There are studies in the literature indicating that patients with a higher SARS-CoV-2 viral load have higher mortality and lower PCR-Ct levels. Magleby et al.[13] stated that there is an increased risk of intubation and death in patients with higher viral load and low PCR-Ct values. In the same study, it was shown that comorbid diseases were more common in patients with low PCR-Ct and high viral load. Although the PCR-Ct value was found to be significantly lower in patients with delta variants compared to non-delta variant SARS-CoV-2 in our study, we did not find a significant difference between the presence of comorbid disease, the need for IMV, and mortality. The reason for this may be that the presence of comorbid diseases in patients with a diagnosis of COVID-19 is a factor that increases intubation and mortality. In addition, the reason also may be that we evaluated the PCR-Ct value of a single nasopharyngeal swab sample collected at ICU admission in our patients and we could not evaluate the PCR-Ct dynamics over time and the PCR-Ct value at the beginning of the infection.

When we grouped patients with delta variant and non-delta variant according to vaccination status, no statistically significant difference was found between the groups in terms of laboratory parameters and length of stay. When we look at the literature, studies investigating the protection of two different mRNA vaccines against the delta variant; while the development of COVID-19 could be prevented by 33% after the first dose, the protection after the second dose was 60% with the Oxford/AstraZeneca vaccine (UK) and has been determined that it can reach 88% with the Pfizer/BioNTech (Germany) vaccine. While the distribution of delta variants is slow in regions where two-dose vaccination is applied, the number of cases increases rapidly in regions where single-dose vaccination is applied. For this reason, the opinion that the administration of two doses of mRNA vaccine against the delta variant will gain importance in preventing the new wave.[14] In addition, while initial PCR-Ct values were similar in vaccinated and unvaccinated delta variant patients, viral load decreased more rapidly in vaccinated patients than in unvaccinated.[15] In a study investigating the efficacy of the vaccine on COVID-19-related symptoms, hospital admissions, and mortality in patients aged 70 years and older in the UK, a single dose of BioNTech was found to be approximately 80% effective in preventing

hospital admissions for COVID-19 and 85% in preventing death with COVID-19.[16] Our study is retrospective and this is the most important limitation. Vaccination status of the patients was obtained from the vaccination history of the patient and their relatives. If the medical records of patients who died could not be accessed, if they were not questioned and noted in the history, or if they were unknown, the vaccination status of these patients was considered unknown. Since the information about how many days before the vaccination was made is not clear in many patients, those who were vaccinated were considered vaccinated regardless of how long after the vaccination they became ill. Another limitation is that ferritin, LDH, CRP, and PCR-Ct values were recorded only at ICU admission, and the changes in these values during patient follow-up were not examined. RT-PCR samples of some of the patients hospitalized in the ICU with positive RT-PCR were taken in state hospitals and were excluded from the study, because variant analysis could not be performed. This has resulted in a decrease in the number of our patients.

CONCLUSION

There was no significant difference in mortality between delta variant and non-delta variant SARS-CoV-2 patients. Although patients with delta variants have low PCR-Ct values, there is no significant difference in their mortality. Ferritin, lymphocyte, LDH, and CRP can be used to predict mortality in patients diagnosed with COVID-19.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (No: 320, Date: 08/12/2021).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

Authorship Contributions: Concept: B.G.Y., S.Z.M.K., E.K., U.M.K., S.D., A.S.Ş.; Design: B.G.Y., S.Z.M.K., E.K., U.M.K., S.D., A.S.Ş.; Supervision: B.G.Y., S.Z.M.K., E.K., U.M.K., S.D., A.S.Ş.; Funding: S.D., E.K., B.G.Y., S.Z.M.K.; Materials: E.K., B.G.Y., S.Z.M.K.; Data Collection or Processing: B.G.Y., E.K., S.Z.M.K.; Analysis or Interpretation: U.M.K., B.G.Y.; Literature Search: B.G.Y., S.D., A.S.Ş.; Writing: B.G.Y., S.Z.M.K., U.M.K., S.D.; Critical review: B.G.Y., S.Z.M.K., E.K., U.M.K., S.D., A.S.Ş.

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