During the second and third wave of the COVID-19 pandemic, the dynamics of the spread of disease in our region: A study based on hospital data

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During the second and third wave of the COVID-19 pandemic, the dynamics of the spread of disease in our region: A study based on hospital data

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ABSTRACT

Aim. The SARS-CoV-2 Omicron variant became predominant in Turkey in January 2022, coinciding with a rise in SARS-CoV-2–associated hospitalizations.

Material and Methods. Patients diagnosed with COVID-19 were collected by the infection control committee through an active surveillance program for COVID-19

throughout the pandemic. The hospitalization rate was included in the model to evaluate the relationship between each wave period and disease severity. The basic demographic data of the patients, and the potential risk factors such as comorbid diseases, and laboratory findings were included in the analysis.

Results. The rate of patients who were positive in August (26.8%) was found to be significantly lower than in February (45.9%) (p<.001). The proportion of inpatient patients treatment in August (2.3%) was found to be significantly higher than in February (1.2%) (p<.001). In addition, in the omicron variant patients' wave, the neutrophil/lymphocyte ratio was 5.31; and it was observed to be significantly higher than that of the patients (Median = 3.95) in the delta variant wave (p=.023)

Discussion. These results provide clinicians with information about the clinical course of COVID-19 patients and are very important for appropriate clinical decision-making in these patients. It is critical to continue to update COVID-19 management protocols based on the latest research.

Keywords: omicron, delta, lymphocytopenia, eosinopenia

Introduction

The Coronavirus disease-19 (COVID-19) pandemic, in the history of humanity, will forever be remembered as a bad period. Since the World Health Organization (WHO) declared COVID-19 a global epidemic in March 2020, this highly contagious disease has spread to 223 countries. It has been observed that the epidemic did not spread simultaneously and did not experience similar severity depending on the country dynamics in the world. In this process, the virus changes through mutation, which results in the emergence of a new variant, and we have experienced that this can lead to waves [1].

When defining variants, different patient clinics have shown an increase in contagiousness and disease severity, and a decrease in neutralizing antibodies produced after previous infections or vaccinations [2]. Alpha, Beta, Gamma, Delta, and Omicron variants are known to be responsible for the second and later waves of the pandemic [3].

After the rapid spread of this variant around the world, WHO recommended that this variant be classified as the variant of concern in May 2021 [2,3].

According to the daily reported data of our hospital, the second wave started at the end of July 2021, and peaked with 915 new cases per day in August 2021. In this case, the dominant variant was determined to be the delta variant [4].

After previous waves of COVID-19, Omicron was first identified on November 26, 2021, with a rapid increase in the number of COVID-19 cases in South Africa. Omicron has been shown to cause a 2.8-fold increase in infection numbers and is 10 times more contagious than the Delta variant. It has been claimed that the omicron variant has a milder course and shows a different clinical course compared to the Delta variant. It has led to different approaches in the clinical evaluation of patients and the regulation of treatment [5,6].

However, people of all ages can suffer from infection, and serious patients aged 60 and over are still at risk for the disease, as are those with underlying medical comorbidities (obesity, cardiovascular disease, chronic kidney disease, diabetes, chronic lung disease, smoking, cancer, solid organ, or hematopoietic stem cell transplant patients), who are at risk of developing more serious infections. It is also observed that the percentage of patients with comorbidities is six times higher in patients with comorbidities than in those without. (45.4% vs. 7.6%, respectively) [7].

In this study, it was aimed to analyze the patients who were infected during the period when the omicron variant was prevalent, to determine the hospitalization rate, length of hospital stay, and severity of the disease, to compare them with the patients in the wave process in which the delta variant was prevalent, and to evaluate whether the vaccination status of the hospitalized patients changed their length of stay.

Material and Methods:

In this process, there was a COVID-19 outpatient clinic in our center, which is a fourth-level university hospital. While patients with oxygen saturation above 93 were evaluated here 24/7, patients with saturation below 93 were evaluated in the emergency department.

Data on hospital admissions of patients diagnosed with COVID-19 were collected by the infection control committee through an active surveillance program for COVID-19 throughout the pandemic. First of all, it was determined that the Delta variant was active during July and August 2021, and the Omicron variant was active between January and February 2022. As a result of this determination, it was determined that the highest number of patients was in August for the delta variant and in February for the Omicron variant. In order to compare these two periods, the data of patients with positive SARS-CoV-2 tests, who were also hospitalized, were entered into the database, retrospectively. The hospitalization rate was included in the model to evaluate the relationship between each wave period and disease severity. The basic demographic data of the patients, potential risk factors such as comorbid diseases, laboratory findings, length of hospital stay, and hospitalization results (discharge, intensive care, and death) were included in the analysis.

Statistical analysis

The normality assumptions of the variables were examined with the Kolmogorov-Smirnov test. The median, minimum, and maximum values were given in the descriptive statistics of continuous variables. Frequency (n) and percentage (%) values were given for the definition of categorical variables. The Mann-Whitney U test was used to compare the continuous variables between the two groups, and the Chi-square analysis was used for the relationships between categorical variables. IBM SPSS.25 software was used in all analyses, and the $p< 0.05$ value was accepted as the level of significance.

Results

In July 2021, 5380 patients applied to the COVID-19 outpatient clinic, 717 were found to be positive, and 104 were hospitalized and treated. In August 2021, 12665 people applied, 3394 were found to be positive, and 79 patients were hospitalized and treated. Similarly, in January 2022, 13948 people applied to the outpatient clinic, 4317 patients were found to be positive, and 109 patients were hospitalized and treated. In February, the number of applicants reached 16431, and 7538 patients were found positive, 90 patients were hospitalized and treated.

With the available data, the peak periods of the disease in our region were determined to be August 2021 for delta and February 2022 for omicron, respectively. A total of 169 patients were included in the study, with 90 having the Delt variant, and 79 having the Omicron variant during the peak period. Table 1 shows the positive rates and hospitalization rates by month.

As shown in Table 1, 12665 patients applied in August and 16431 in February. A chi-square analysis was performed to determine whether there is a significant

relationship between the month and positivity. The rate of patients who were positive in August (26.8%) was found to be significantly lower than in February (45.9%) (p<.001).

In August, 90 patients out of 3394 positive patients and 79 patients out of 7538 positive patients in February received inpatient treatment. A chi-square analysis was performed to determine whether there was a significant relationship between the month and the status of receiving inpatient treatment. The proportion of patients who received inpatient treatment in August (2.3%) was found to be significantly higher than in February (1.2%) (p<.001).

Table 1. Comparison of positivity status and hospitalization by months

	Delta (August)		Omicron (February)		Total		χ2	p
	n	%	n	%	n	%		
Positivity status							1109.88	<.001
Negative	9271	73.2	8893	54.1	18164	62.4		
Positive	3394	26.8	7538	45.9	10932	37.6		
Total	12665	100	16431	100	29096	100		
Hospitalization							19.762	<.001

No	3315	97.7	7448	98.8	10763	98.5
Yes	79	2.3	90	1.2	169	1.5
(Delta or omicron)						
Total	3394	100	7538	100	10932	100

Comparison of patient characteristics by month

As shown in Table 2, 52.2% of the patients diagnosed in February, which was considered the omicron variant, were female, whereas 41.8% of the patients diagnosed in August, which was considered the delta variant, were female, and this difference was not found to be statistically significant (p=0.175).

Table 2. Comparison of gender, vaccination status, co-mortality, and outcome by variants

	Delta (August)		Omicron (February)		χ2	P
	n	%	N	%		
Gender					1.843	.175
Woman	33	41.8	47	52.2		
Male	46	58.2	43	47.8		
Vaccination status*					-	-
None	29	36.7	25	27.8		

One	6	7.6	3	3.3		
Two	21	26.6	25	27.8		
Tree and more	23	29.1	37	41.1		
comorbid*					-	-
Diabetes	2	4.3	6	7.9		
Hypertension	7	14.9	24	31.6		
Diabetes + Hypertension	13	27.7	18	23.7		
Other	25	53.2	28	36.8		
Conclusion					-	-
Ex	1	1.3	2	2.2		
Discharge	63	80.8	76	85.4		
Medical rejection	9	11.5	6	6.7		
Intensive care	5	6.4	5	5.6		

* Since the assumption of chi-square analysis was not met, p values were not given, only frequency and percent values are given.

As shown in Table 3, the age of patients infected with the omicron variant (Median: 69.50, min-max: 24.00 - 89.00) was significantly higher than that of patients infected with the delta variant (Median = 55.00) (p<0.001). In addition, the lymphocyte value of the patients in the omicron variant wave (Median = 1.01 min-max:) was found to be significantly lower than that of the patients in the delta variant wave (Median = 1.10) (p=0.038). In addition, patients' neutrophil/lymphocyte values (Median = 5.31) in the omicron variant wave were significantly higher than those of the patients (Median = 3.95) in the delta variant wave (p=.023). On the other hand, there was no

significant difference between the patients in February and August in terms of length of stay, ferritin, d-dimer, and C-reactive protein (CRP) values (p>0.05).

Median values were used because the variables were not regularly distributed.

As shown in Table 3, the median age of patients infected with the omicron variant was 69.50 (min-max:). This result is significantly higher than patients infected with the delta variant (Median = 55.00) (p<0.001). In addition, the lymphocyte value of the patients in the omicron variant wave (Median = 1.01 min-max☺ was found to be significantly lower than that of the patients in the delta variant wave (Median = 1.10) (p=0.038). In addition, in the omicron variant wave, the neutrophil/lymphocyte ratio was 5.31, and it was observed to be significantly higher than that of the patients (Median = 3.95) in the delta variant wave (p=.023). On the other hand, there was no significant difference between patients in February and August in terms of length of stay, ferritin, d-dimer, and C-reactive protein (CRP) values (p>0.05).

Table 3. Comparison of patients' hospitalization age, length of stay, ferritin, d-dimer, CRP, and lymphocyte values by variants

Parameters	Delta	Omicron		
Ha	Median (Min. - Max.)	Median (Min. - Max.)	U	P
Age	55.00 (24.00 - 98.00)	69.50 (24.00 - 89.00)	2441.50	<0.001
Length of stay	5.00 (1.00 - 47.00)	5.00 (1.00 - 41.00)	3355.00	0.527
Ferritin	355.00 (17.00 - 1500.00)	271.50 (10.00 - 1500.00)	1954.50	0.405
D-dimer	0.82 (0.04 - 17.50)	0.94 (0.00 - 20.20)	2204.00	0.638
CRP	52.00 (1.53 - 306.00)	37.50 (1.60 - 437.00)	2873.00	0.233
Lymphocyte	1.10 (0.20 - 3.60)	1.01 (0.10 - 5.80)	2747.50	0.038

Eosinophil	.02 (.00 – .03)	01 (.00 – .06)	3520.50	.911
Neutrophil	5.01 (3.22 – 7.28)	6.00 (3.62 – 7.47)	3285.50	.396
Neutrophil / Lymphocyte	3.95 (2.42– 6.76)	5.31 (3.10 – 10.59)	2685.00	.023

Discussion

Since the onset of the COVID-19 pandemic, it has been observed worldwide that SARS-CoV-2 creates waves with different clinical features by revealing variants. Two different waves of COVID-19 epidemics were experienced in our region, and each of them was formed by different variants. It has been shown in many studies that the clinical manifestations of COVID-19 are different during the Delta and Omicron dominant periods. This study was planned to investigate the differences between the clinical features of patients infected with Delta and Omicron variants of COVID-19 hospitalized during the waves.

The British cohort indicates that the confirmed omicron cases had a 44% lower risk of hospitalization than the confirmed delta cases [8]. Similarly, in the ZOE COVID study conducted in the United Kingdom; the rate of hospitalization (1.9%) during the prevalence of omicron was found to be significantly lower than the rate of hospitalization during the prevalence of delta (2.6%) [9]. In the study from Israel, the population of patients with autoimmune rheumatic disease, who purchased any immunosuppressive drug within six months and who applied to the hospital

associated with COVID-19, was investigated. In this group of immunocompromised patients, compared to the Delta group, the Omicron group was found to have a lower rate of COVID-19-related hospitalizations (3.9% vs. 1.3% for Delta and Omicron, respectively, p <0.001) [10]. In parallel with these studies, our results showed that the positivity rate of Omicron cases was 45.9%, the rate of hospitalization was (1.2%), and the rate of positivity (26.8%) in Delta cases was 2.3%. There was a statistically significant difference in terms of hospitalization. (p<.001)

Delta dominance was observed to decrease with the spread of the omicron, and it was determined that the profiles of the affected patients began to change.

A retrospective study from France announced that patients infected with Omicron were younger when compared to the Delta variant. (54 years [IQR, 33 to 75 years] and 62 years [IQR, 45 to 75 years]; difference, 8.0 years [95% CI, 4.6 to 11.4 years]). [11] In another study, when the median age was compared between both vaccinated and unvaccinated subjects (Omicron = 54 years; Delta = 62 years; p<0.01), it was seen that omicron affected the younger population [12]. When the ages of the hospitalized patients were inspected, it was observed that the average age of the hospitalized patients in the Omicron wave was younger than the previous waves in different studies [13]. According to the results of the study conducted in South Africa; the patients hospitalized during the omicron wave were also younger (median age 59 years maximum in delta wave versus 36 years in Omicron wave; P < .001) [14].

Unlike these studies, Stupica et al. compared the periods of delta and omicron variants. The median age of 529 patients hospitalized for the delta variant was 65 years; The median age of 407 patients hospitalized during the Omicron period was 75.15 years [15]. In the results we obtained, younger patients were hospitalized due

to the Delta variant, and the Omicron variant appeared to result in the hospitalization of older patients. These results can be explained by the increase in clinical experience during this period, the decrease in hospitalization rates in the period when the Omicron variant was dominant, and also due to the higher vaccination rate at that time.

Several studies have recently been published evaluating disease severity, mortality, and biomarkers in coronavirus patients. These markers are important in evaluating the prognosis of patients and guiding treatment strategies. In particular, well-known inflammatory markers such as CRP have been identified as early markers indicating the severity of a COVID-19 infection [16].

In our study, in the evaluation of the Delta variant and Omicron variant, it was determined that the median values of ferritin and CRP of delta variant patients were higher than the omicron values, and the median D-dimer values were lower than the omicron values, but these differences were not considered statistically significant.

When evaluated in terms of the relationship between high D-dimer levels and survival rates, D-dimer is expected to be lower in cases where inflammation is not severe, and it may be associated with a milder course of the omicron variant in our study [17].

It highlights the importance of detecting D-dimer levels in patients with COVID-19.

Lymphopenia indicates an impaired cellular immune response, and lymphocyte levels are often used to detect infection. Although T cells may be normal or high at the onset of the disease, a tendency to generally have low lymphocyte counts has been observed [18].

Between 67% and 90% of COVID-19 patients have lymphopenia [19]. Recent studies have shown that approximately 85% of severe COVID-19 patients have lymphopenia.

The lymphocyte count was found to be below 1000 /µL in %63 [20].

In another study, while the median value was 1500/µL in asymptomatic patients, values as low as 700 in severe patients were observed [21]. Recent studies have shown that lymphopenia is associated with disease severity and a poor prognosis [22,23]. In another study, it was observed that lymphocytopenia was associated with PCR positivity on the 7th day, and the lymphocytes of patients with prolonged PCR positivity remained low [24]. When 169 COVID patients with only the omicron variant were examined, more strikingly, the lymphocyte count was found to be below 1100/µL on average, and this value was observed in 89% of the patients [25]. In our study, the median value was 1,100 /µL in the delta variant and 1.010 /µL in the omicron variant. When we compared the two values, it was found to be significant (p=0.038). The ratio of neutrophil count to lymphocyte count (NLR) is also known as an inflammatory marker in inflammatory diseases [26].

When evaluating COVID-19 patients, instead of evaluating the lymphocyte count alone, the ratio of Neutrophil count to Lymphocyte count (NLR) was taken into consideration, and it was suggested that a high NLR was significantly associated with the severity of the disease and was an independent biomarker for poor clinical outcomes [27].

A high NLR has been reported to be associated with the severity of COVID-19. [28,29] In our study, the neutrophil/lymphocyte ratio (Median = 5.31) of the patients in the omicron variant wave was found to be significantly higher than that of the patients in the delta variant wave (Median = 3.95) (p=.023).

Eosinophils were first described by Paul Ehrlich in 1879. These myeloid cells are called eosinophils because of the bright red staining of the eosin granules on them. Research

on eosinophil biology has revealed several interesting contributions of eosinophils to health and disease [30]. The level of eosinophils drew attention in studies conducted during the COVID-19 pandemic. It has been determined that a low eosinophil percentage may be associated with COVID-19, and even [31] showed that eosinophil counts decreased significantly to abnormal values both during the initial diagnosis and during the re-positivity episode [32]. In the study conducted in India in June 2020, eosinopenia was detected in 79.25% of COVID-19 patients at the time of admission, while eosinopenia was not detected in any of the COVID-19-negative patients in the same period. As an early diagnostic marker, eosinopenia ($<0.05 \times 10^9$ /L) has been shown to have an accuracy of 85.24%, a sensitivity of 80.68%, and a specificity of 100% [33]. In the study of Roca et al. in Italy, eosinophil counts were observed to be 0.01 10^9/L (mean 0.028, SD ± 0.04) [34]. Our data similarly supported low eosinophil counts at admission; In the delta variant of COVID-19 disease, 0.02 (0.00 – 0.03) x 10^9/L was detected, and in the omicron variant, it was 0.01 (0 – 0.06) 10^9/L.

In the COVID-19 pandemic, the vaccine has emerged as the most effective method in the fight to control the epidemic and reduce the risk of mortality and morbidity. As a result of rapid studies, it has been shown that vaccines reduce the infection mortality rate and that they are effective [35].

Since the Omicron variant was first identified, studies have reported that this variant is more contagious, suggesting that omicron can inhibit natural innate and vaccine-induced immunity, resulting in lower vaccine efficacy [36-38]. Reinfection has been shown to be higher than expected following Omicron variant infection in a study in Iceland [39] and suggests that re-infections are becoming more common [40].

When we looked closely at the vaccination status of our patients, the rate of those

who were never vaccinated was 36.7% during the delta variant, while the rate of patients who were never vaccinated during the omicron variant was 27.8%. Patients with three or more vaccines were detected in %41 during the omicron variant wave of the coronavirus disease 2019 pandemic; while it was %29 during the delta variant wave. This is a result in-line with the view that the Omicron variant has significantly increased immune escape abilities compared to other variants, but this difference between the two variants was not found to be statistically significant.

Vaccine- or infection-induced immunity is shown to be less effective against the Omicron variant than the Delta variant. However, in other studies, it was observed that a sufficient level of neutralizing-antibody titers was achieved with booster doses even if the antibody titer was lower, and the importance of additional doses was emphasized [41,42].

There were some limitations regarding vaccine data in our study. We recorded only the number of vaccinations administered to the patients. Since it was a retrospective study, we could not question the interval between vaccination and whether there was a booster dose. Therefore, some patients may have a full vaccination schedule with a booster dose (i.e., 1 dose after previous COVID-19 disease followed by a booster dose), but only 2 vaccines have been recorded.

Consequently, adult patients who were hospitalized during the SARS-CoV-2 pandemic during the Omicron variant predominance and the Delta variant predominance were examined. It was observed that the positivity rate of the Omicron variant was significantly higher, and the hospitalization rate was significantly lower. Inpatients who were infected with the Omicron variant were older. However, during the COVID-19 pandemic period, different clinical features and different laboratory features were

observed in patients hospitalized with the Omicron variant predominance and the Delta variant predominance. The differences in commonly used biomarkers have been demonstrated. During both variants, it was observed that patients had significantly lower eosinophils and lymphocytes. These results provide clinicians with information about the clinical course of COVID-19 patients and are very important for appropriate clinical decision-making for the necessary treatment. It is critical to continue to update the COVID-19 management protocols based on the latest research.

For guiding public health planning and response, compared to previous SARS-CoV-2 variants, further and prospective studies are needed on the clinical severity of the omicron variant and the newly identified variants.

Conflict of Interest: The authors have no conflicts of interest to declare.

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