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Impact of COVID-19 Vaccination on Fatality and Intensive Care Unit Admission in Patients with Type 2 Diabetes Mellitus

ORIGINAL ARTICLE
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ABSTRACT

Objective: This study aims to investigate the influence of coronavirus (COVID-19) vaccination on hospital outcomes among patients with type 2 diabetes mellitus (T2DM).

Methods: A total of 324 patients hospitalized for COVID-19 were evaluated retrospectively. Type 2 diabetes mellitus patients were matched 1:1 by the propensity score matching method to individuals without diabetes for age and gender. After matching, we analyzed 70 patients with T2DM and 70 without diabetes.

Results: Individuals with T2DM exhibited a slightly higher vaccination rate than those without diabetes (67.1% vs. 54.3%, *P* = .119). Regardless of diabetes status, vaccinated participants experienced significantly lower rates of intensive care unit (ICU) admission (T2DM: 14.9% vs. 60.9%, *P* = .001; non-diabetics: 5.3% vs. 37.5%, *P* = .001) and fatality (T2DM: 2.1% vs. 60.9%, *P* = .001; non-diabetics: 0% vs. 46.9%, *P* = .001) compared to the unvaccinated group. The length of hospitalization and ICU admission rate were insignificantly higher in vaccinated individuals with T2DM than those without diabetes (9.0 days vs. 7.0 days, *P* = .154; 14.9% vs. 5.3%, *P* = .179).

Multivariate logistic regression in T2DM patients revealed that CoronaVac vaccination significantly reduced ICU admission (OR: 0.089, 95% CI 0.022-0.360, *P* = .001), while male gender increased the risk (OR: 6.59, 95% CI 1.545-28.11, *P* = .011).

Conclusion: In vaccinated individuals with T2DM, the risk of severe COVID-19 and fatality significantly decreased, similar to individuals without diabetes. This protection is not affected by vaccine type, vaccination count, or age.

Keywords: Type 2 diabetes mellitus, COVID-19, COVID-19 vaccine, hospital fatality

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been causing an unusual pandemic affecting millions worldwide since it was first identified in 2019.[1] The elderly and those with co-morbidities are usually more severely affected by the disease.[2] Patients with diabetes may have a more remarkable fatality and a higher prevalence of severe coronavirus disease 2019 (COVID-19).[3]

Despite the severity of the disease, no effective treatment has yet been discovered. However, since newly developed vaccines were released for clinical practice, hospitalizations and death rates have gradually declined.[4] Although COVID-19 vaccines have been highly effective during trials, there is still a residual risk of serious COVID-19 outcomes even after vaccination.[5]

Diabetes patients may have a reduced immune response to certain vaccines, such as hepatitis B and influenza.[6,7] Although it has been demonstrated that individuals with diabetes have similar binding-antibody responses to individuals without diabetes even after COVID-19 pneumonia,[8] another study found that poor blood glucose control was associated with decreased neutralizing antibodies and cellular immune response.[9]

It is particularly important to evaluate the efficacy of the vaccine in this vulnerable group, which has worse COVID-19 outcomes and lower immune responses. However, data on the clinical outcomes of COVID-19 in patients with type 2 diabetes mellitus (T2DM) during the post-vaccination period are limited. Our objective was to assess the impact of vaccination on COVID-19 outcomes in patients with T2DM who were hospitalized for COVID-19.

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Material and Methods

Coronavirus disease 2019 (COVID-19) patients hospitalized at a university hospital were retrospectively assessed. The diagnosis of COVID-19 was made using radiographic and PCR methods.

Using the propensity score matching (PSM) method, participants with T2DM were matched 1:1 to individuals in the non-DM group with regard to their age and gender. Additionally, participants with a propensity score in the range of 0.2 caliper width were eligible for matching.[10]

After PSM, 140 patients who met the matching criteria were evaluated, including 70 patients with diabetes and 70 patients in the group without diabetes. Figure 1 illustrates the patient recruitment plan. Patients diagnosed with type 1 diabetes mellitus, pregnant women, and those under 18 years old were excluded from the study.

Data consisting of patients' age, sex, serum glucose, ALT (alanine aminotransferase), eGFR (estimated glomerular filtration rate), and Hba1c (glycosylated hemoglobin) levels were taken from hospital records. They were previously captured at the time of admission. The estimated glomerular filtration rate was calculated using the CKD-EPI formula. The fatality status, intensive care unit admission, and length of hospitalization were also obtained from hospital records.

This study received ethical approval from Çanakkale Onsekiz Mart University Clinical Research Ethical Board (approval number: 01-06, date: January 5, 2022, project number: 2011-KAEK-27/2021-21 00225067).

Coronavirus Disease 2019 Vaccination

The first batch of COVID-19 vaccinations in Türkiye started on January 14, 2021, 3 months before the first patient's admission date. At the time of the study, 2 different vaccine types were used in Türkiye, including the inactivated virus COVID-19 vaccine CoronaVac (Sinovac Life Sciences, Beijing, China) and the mRNA-based COVID-19 vaccine BNT162b2 (Pfizer–BioNTech). The vaccination status, number of vaccinations, and vaccination dates of the participants were obtained from the national health database.

Data were analyzed retrospectively and were fully anonymized to ensure patient privacy; thus, informed consent was not sought.

Statistical Analysis

The continuous variables with a normal distribution were represented by the mean and SD after evaluating the normality distribution test. Meanwhile, the non-normally distributed variables were represented by the median and interquartile range (IQR: the 25th and 75th percentiles). Numbers and percentages were used to describe categorical variables. The level of significant difference between continuous variables was determined using the Mann–Whitney *U*-test. The difference between categorical variables was also assessed using Pearson's chi-square test. Univariate and multivariate logistic regression analyses were used to evaluate the odds ratio (OR) for ICU admission among individuals with diabetes. Additionally, BNT162b2 vaccination, CoronaVac vaccination, age, and male gender were included as independent factors for multivariate regression to establish a valid model. The odds ratio was calculated with a 95% CI (95% CI) at a *statistical significance* of $P < .05$.

Kaplan-Meier survival analysis was conducted to compare the survival rates between groups for unvaccinated DM (+) vs. unvaccinated DM (–) patients. The log-rank test was used to assess the statistical significance of differences in survival curves. The statistical analyses were performed using SPSS version 19.0 (IBM SPSS Corp.; Armonk, NY, USA).

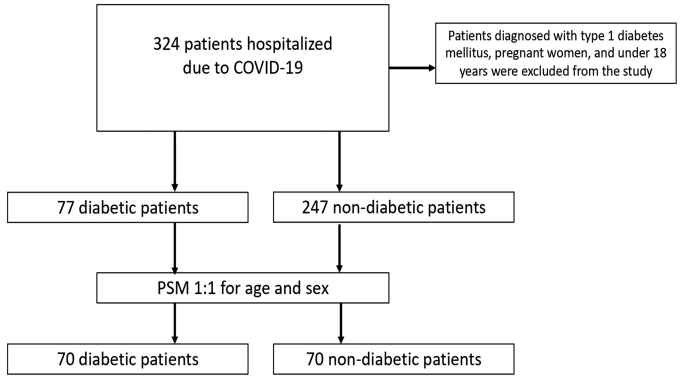

Figure 1. Patient recruitment scheme.

Results

Before Propensity Score Matching Analysis

Among the 324 patients included in the study, 23.7% (77) had diabetes. The median age of patients with diabetes was higher compared to those without diabetes (66.0 vs. 61.0, $P = .047$). However, the distribution of male gender was similar in both groups (50.6% vs. 52.5%, $P = .780$).

After Propensity Score Matching Analysis

The evaluation following PSM included 140 patients, 66 of whom (47.1%) were females with a mean age of 65.8 ± 10.5 years. There were 70 participants with diabetes and 70 in the control group. Age, gender, eGFR, and ALT distributions were similar in both groups. Nevertheless, the group with diabetes showed higher serum glucose and HbA1c values than those without diabetes.

At least 2 doses were administered to 94.1% of the vaccinated participants. Participants were admitted to the hospital for a median of 80 days following the last vaccination. All patients were admitted at least 14 days after the latest vaccine.

The vaccination rate of the patients with diabetes was higher but had no significant difference (67.1% vs. 54.3%, $P = .119$). While the number of mRNA vaccines was closely similar in both groups, the amount of CoronaVac vaccine was insignificantly higher in patients with diabetes.

Intensive care unit admission rates were comparable across patients with and without diabetes (30.0% vs. 20.0%, $P = .172$), similar to

MAIN POINTS

- COVID-19 vaccination significantly reduces severe outcomes in patients with type 2 diabetes.
- Vaccinated patients with type 2 diabetes show lower ICU admission and fatality compared to the unvaccinated.
- The type of vaccine, vaccination count, and patient age do not impact the observed protection.
- Male gender remains a risk factor for ICU admission in patients with type 2 diabetes.

Table 1. General Characteristics of Participants after Propensity Score Matching

	DM (+) N = 70	DM (−) N = 70	*P*
Male gender, n (%)	36 (51.4%)	38 (54.3%)	.735
Age, year	65.8 ± 10.6	65.8 ± 10.6	.962
Glucose, mg/dL*	193.5 (138-312.0)	117.5 (104.8-144.0)	.0001
Hba1c, %, mmol/mol	7.9 (63)	6.0 (42)	.0001
eGFR, mL/min/1.73 m²*	68.0 (39.0-88.8)	74.5 (53.2-95.0)	.129
ALT, U/L*	18.0 (11.0-26.0)	20.0 (12.8-33.0)	.117
COVID-19 Vaccination 1 dose ≥2 doses	67.1% 2.9% 64.3%	54.3% 4.3% 50%	.119
CoronaVac, n (%)	38, 54.2%	27, 38.6%	.062
BNT162b2 n (%)	20, 28.6%	19, 27.1%	.850
Number of days from last vaccination*	80 (32-110)	83.5 (43.8-114.3.0)	.704
Length of hospitalization, day*	9.5 (5.0-14.0)	7.5 (5.0-13.3)	.130
ICU admission, N (%)	21 (30.0%)	14 (20.0%)	.172
Fatality, N (%)	15 (21.4%)	15, (21.4%)	.999

ALT, alanine aminotransferase; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; ICU, intensive care unit.
*Median (IQR).

in-hospital fatality (21.4% vs. 21.4%, *P* = 1). Table 1 lists the general characteristics of participants after PSM.

Results According to Vaccination Status

The distributions of age, gender, eGFR, ALT, serum glucose, and HbA1c were similar between the vaccinated and unvaccinated individuals with diabetes. Although the length of hospitalization was lower in vaccinated individuals with diabetes and those without diabetes, there was no statistical difference between the 2 groups. Intensive care unit admissions and fatality were significantly lower in vaccinated individuals with diabetes and those without diabetes (Table 2). One death was recorded among vaccinated patients. Observably, it was an elderly female patient with diabetes who had received 3 doses of CoronaVac.

In the vaccinated group, the length of hospital stay and ICU admission were also higher in individuals with diabetes than those without; however, the difference was not statistically significant (Table 3).

Also, in the unvaccinated group, the intensive care unit admission rate and fatality were relatively higher in individuals with diabetes compared to those without diabetes, but there was no statistical difference (respectively; 60.9% vs. 37.5%, *P* = .087; 60.9% vs. 45.5%, *P* = .186) (Table 3). According to their diabetes status, the fatality of unvaccinated patients was shown by Kaplan–Meier analysis (log rank *P* = .351) (Figure 2).

Univariate and Multivariate Logistic Regression Analysis for Intensive Care Unit Admission Among Individuals with Diabetes

In univariate logistic regression analysis, the BNT162b2 vaccine was not a significant factor in reducing ICU admissions (beta: −0.723, OR: 0.485, 95% CI: 0.140-1.681, *P* = .254). The number of days after the vaccination was also not a significant factor in reducing ICU admission (beta: −0.002, OR: 0.998, 95% CI: 0.985-1.012, *P* = .823). However, the CoronaVac vaccine (beta: −1.887, OR: 0.152, 95% CI: 0.047-0.487, *P* = .002) and the total number of vaccinations (beta: −0.660, OR: 0.517, 95% CI: 0.332-0.803, *P* = .003) were significant factors in reducing ICU admissions.

The odds ratio for ICU admission in the group with diabetes was evaluated using multivariate logistic regression. BNT162b2 vaccination, CoronaVac vaccination, age, and male gender were included as independent factors to establish a valid model. However, BNT162b2 vaccination (beta: −1.016, OR: 0.362, 95% CI: 0.080-1.636, *P* = .187) and age (beta: 0.065, OR: 1.067, 95% CI: 0.996-1.143, *P* = .063) were not significant factors in reducing ICU admissions. Although CoronaVac vaccination (beta: −2.424, OR: 0.089, 95% CI: 0.022-0.360, *P* = .001) reduced ICU admission, the male gender was a risk factor for ICU admission (beta: 1.886, OR: 6.59, 95% CI: 1.545-28.11, *P* = .011) (Table 4).

Discussion

Our study revealed significantly lower rates of ICU admissions and fatalities among both vaccinated individuals with diabetes and those without diabetes. The length of hospitalization after vaccination was also lower in both groups than in those not vaccinated, although there was no significant difference.

Table 2. In-hospital Outcomes According to Diabetes and Vaccination Status after Propensity Score Matching

	DM (+) N = 70			DM (−) N = 70		
	Vaccination (+) N = 47	Vaccination (−) N = 23	*P*	Vaccination (+) N = 38	Vaccination (−) N = 32	*P*
Length of hospitalization, day*	9.0 (5.0-13.0)	12.0 (6.0-17.0)	.234	7.0 (5.0-10.0)	11.5 (4.0-17.8)	.086
ICU admission, N (%)	7 (14.9%)	14 (60.9)	<.001	2 (5.3%)	12 (37.5%)	.001
Fatality, N(%)	1 (2.1)	14 (60.9%)	<.001	0	15 (46.9%)	<.001
Male gender (%)	53.2%	47.8%	.673	55.3%	53.1%	.858
Age, year	65.3 ± 10.2	66.7 ± 11.4	.491	64.6 ± 9.8	67.1 ± 11.4	.255
eGFR, mL/min/1.73 m²*	70.0 (42.0-92.0)	56.0 (30.8-84.0)	.263	79.5 (66.3-95.0)	65.5 (42.0-95.8)	.216
ALT, U/L*	18.0 (11.0-26.0)	10.0 (10.7-31.2)	.652	20.0 (12.0-33.5)	21.5 (13.5-32.0)	.697
Glucose, mg/dL*	206.0 (138-324.0)	170.0 (139.0289.0)	.630	115.5 (101.8-141.5)	118 (107.5-143.0)	.447
Hba1c, %, mmol/mol	8.4 (68)	7.2 (55)	.133			

ALT, alanine aminotransferase; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; ICU, intensive care unit.
*Median (IQR).

Table 3. In-hospital Outcomes According to Vaccination Status after Propensity Score Matching

	Vaccination (+)			Vaccination (−)		
	DM (+) N = 47	DM (−) N = 38	*P*	DM (+) N = 23	DM (−) N = 32	*P*
Length of hospitalization (days)*	9.0 (5.0-13.0)	7.0 (5.0-10.0)	.154	12.0 (6.0-17.0)	11.5 (4.0-17.8)	.844
ICU admission, N (%)	7 (14.9%)	2 (5.3%)	.179	14 (60.9%)	12 (37.5%)	.087
Fatality, N (%)	1 (2.1%)	0 (0%)	1.0	14 (60.9%)	15 (45.5%)	.186

DM, diabetes mellitus; ICU, intensive care unit.
*Median (IQR).

Additionally, there was no significant difference between patients with and without diabetes regarding fatality after vaccination. Only 1 patient with diabetes died in the vaccinated group. The rate of ICU admission and length of hospital stay were numerically higher in vaccinated patients with diabetes than in vaccinated patients without diabetes. However, these data had no statistical significance. The reduction in fatality is unchanged by blood sugar regulation, the total number of vaccines, the type of vaccine, and the number of days after the last vaccination.

In our study, the prevalence of diabetes was observed to be 55.3% among 85 vaccinated participants. In another study from Israel, the prevalence of diabetes was reported to be 48% among 152 vaccinated cases hospitalized for COVID-19.[11] However, compared to large case series on hospitalized unvaccinated patients, diabetes was more prevalent in patients with vaccination breakthrough infection (48%-55.3% vs. 27.9%-34.7%).[12-14]

Although the exact cause of higher morbidity and fatality from COVID-19 in patients with diabetes is unknown, many factors have been associated with the observed increments. For instance, some factors, such as predisposition to coagulation, increased ACE2 expression, and changes in the immune system, are believed to accompany the observed co-morbidities.[15,16]

Immunologic response to SARS-CoV-2 may also be affected in patients with diabetes. However, the studies on this subject are based on antibody response, and the results are contradictory. In a small study evaluating immune response after COVID-19 infection, patients with T2DM were more likely to have non-detectable anti-SARS-CoV-2 antibodies than patients without diabetes.[17] Another prospective observational study of 509 COVID-19 patients found that patients with diabetes exhibited a humoral response similar to those without diabetes and were unaffected by glucose levels.[18] In other studies, including 150 patients, type 2 diabetes and hyperglycemia do not affect the kinetics and durability of the neutralizing antibody response to SARS-CoV-2.[8]

There have been critical improvements in COVID-19 outcomes following the development of vaccines. However, it has been suggested that T2DM immune dysregulation also hampers the immune responses after vaccination against SARS-CoV-2, as seen in some other vaccines.[6,7] Glycemic control may play a crucial role in the immune response to mRNA COVID-19 vaccines. Hyperglycemia at the time of vaccination impairs the immune response, as evidenced by reduced SARS-CoV-2-neutralizing antibodies and CD4+ T cell activity. Conversely, proper glycemic management post-vaccination can enhance immune function.[9,19]

However, our study's retrospective design and the absence of direct measurement of immune response markers (such as antibody titers) limit our ability to fully elucidate the underlying immunological mechanisms. Nevertheless, the COVID-19 vaccines used in this study appear sufficient to counteract the potential negative effects of moderate hyperglycemia on the immune response, demonstrating

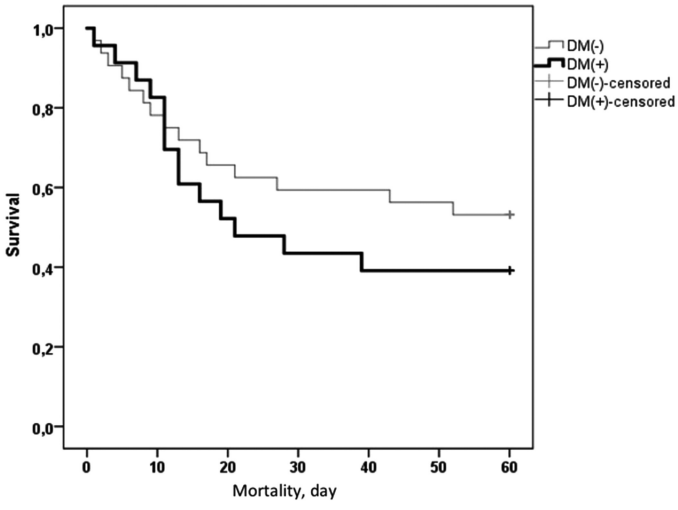

Figure 2. Kaplan–Meier plot showing the risk of fatality in groups for unvaccinated DM (+) vs. unvaccinated DM (−) patients (log rank *P* = .351).

Table 4. Univariate and Multivariate Logistic Regression Analysis for Intensive Care Unit Admission among Individuals with Diabetes

Variables	*B*	SE of *B*	Exp*B*	95% CI of Exp*B*	*P*
Univariate Logistic Regression Analysis					
BNT162b2 vaccine	−0.723	0.634	0.485	0.140-1.681	.254
CoronaVac vaccine	−1.887	0.596	0.152	0.047-0.487	.002
Number of days after vaccination	−0.002	0.007	0.998	0.985-1.012	.823
Total number of vaccinations	−0.660	0.225	0.517	0.332-0.803	.003
Multivariate Logistic Regression Analysis					
BNT162b2 vaccination	−1.016	0.770	0.362	0.080-1.636	.187
CoronaVac vaccination	−2.424	0.716	0.089	0.022-0.360	.001
Age	0.065	0.035	1.067	0.996-1.143	.063
Male gender	1.886	0.740	6.590	1.545-28.11	.011
Constant	−8.323	2.747	0.001		.002

R^2: 0.411.*B*, beta coefficient, CI, confidence interval; Exp*B*, odds ratio; *P*, significance; SE, standard error.

significant benefits in reducing adverse clinical outcomes in vaccinated individuals with T2DM.

In our study, 2 different vaccines were administered to the subjects. The first is an inactivated whole-virus SARS-CoV-2 vaccine (CoronaVac by Sinovac), which was first approved in Türkiye. The second vaccine employed is a messenger RNA (mRNA) vaccine known as the BNT162b2 vaccine. It was produced by Pfizer–BioNTech.

Reportedly, in one of the largest clinical studies, BNT162b2 was 95 percent effective in preventing COVID-19 (95% CI, 90.3-97.6). Vaccine effectiveness was similar (usually 90%-100%) across hypertension and obese subgroups. However, this study did not provide information about the diabetes subgroup.[20] In a study testing the CoronaVac vaccine, IgG seropositivity was significantly lower in men and individuals with diabetes or chronic illnesses.[21] Additionally, our study observed that COVID-19 vaccination effectively reduces the risk of fatality, notwithstanding the vaccine type, diabetes status, blood sugar regulation, or gender.

People with T2DM who received the CoronaVac vaccination had a considerably decreased risk of ICU admission. However, patients with diabetes who received the BNT162b2 vaccine did not have a statistically significant reduction in the risk of ICU admission. This discrepancy may be disregarded, considering the outstanding benefit of both vaccines in reducing the risk of fatality. The presence of both unvaccinated individuals and those who received the CoronaVac vaccine in the comparison group may have led to an underestimation of the impact of the BNT162b2 vaccine on ICU admissions. Meanwhile, more extensive population studies may be more accurate in interpreting the specific effect of each vaccine on clinical outcomes.

Marfella et al (2022)[9] investigated the effect of hyperglycemia on neutralizing antibody levels and cellular immune response in patients with diabetes after receiving the BNT162b2 vaccination. While neutralizing antibodies and antigen-specific CD4 cell response were shown to be lower in patients with diabetes with poor glycemic control, they were found to be similar in patients with diabetes with good glycemic control and healthy participants. This discrepancy with our findings is most likely because our data is based on clinical outcome data, in contrast to Marfella's investigation, which was based solely on laboratory parameters of the immune response.

In a study that included 73 patients with diabetes who required hospitalization after 2 doses of BNT162b2 vaccination, diabetes was not a risk factor for poor COVID-19 outcomes.[10] Additionally, a large population-based study conducted in the United Kingdom showed that T2DM increased hospital admissions by 1.28-1.76-fold and the risk of fatality by 1.26-1.43-fold after COVID-19 vaccination. However, the number of hospital admissions and fatalities of COVID-19 following the 2-dose vaccination was very low. The data analyzed in this study were mainly based on following 1 vaccination dose. Patients who received 2 vaccinations accounted for 3.7% (71) of 1939 hospital admissions and 4% (81) of 2031 mortality evaluated in the study.[22]

The main limitation of our study is that it is centered on retrospective observational data from one center. Due to our study's retrospective nature, we could not assess comorbidities other than diabetes, such as cardiovascular disease, hypertension, and smoking status. The study included a limited number of cases. However, recruiting more patients for post-vaccine analysis is challenging, even in large multicenter studies. Other limitations include not assessing antibody levels, cellular immune responses, or SARS-CoV-2 variants. Although vulnerability to COVID-19 was not evaluated in our study, the clinical results of the hospitalized patients significantly contribute to the post-vaccine efficacy data. Furthermore, the process of PSM effectively balanced the age and gender distributions between the group with diabetes and the group without diabetes and enabled us to assess vaccination efficacy independently of these factors, which are known to influence the severity of COVID-19 outcomes significantly.

Conclusion

The results of the study show that vaccination against COVID-19, with or without T2DM, has a positive effect on the duration of hospital stay, admission to the ICU, and fatality. Diabetes status, vaccine type, blood sugar regulation, and gender did not significantly impact fatality reduction.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study was approved by Çanakkale Onsekiz Mart University Clinical Research Ethical Board (approval number: 01-06, date: January 5, 2022, project number: 2011-KAEK-27/2021-2100225067).

Informed Consent: Data were analyzed retrospectively and were fully anonymized to ensure patient privacy; thus, informed consent was not sought.

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