

Childhood Traumas, Attachment Styles and Related Clinical Factors in Opioid Use Disorder

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ABSTRACT

Introduction: The study aims to compare childhood traumas, attachment styles, impulsivity, and quality of life of Opioid Use Disorder (OUD) patients in remission with healthy controls and to reveal the relationships between these parameters.

Methods: The study included one hundred patients diagnosed with OUD and one hundred healthy volunteers. Sociodemographic data form, Structured Clinical Interview for DSM-5 Disorders Clinician Version, Childhood Trauma Questionnaire, Relationship Scales Questionnaire, Barratt Impulsivity Scale-11, World Health Organization Quality of Life Scale Brief Version and Substance Craving Scale were administered.

Results: Emotional abuse, physical abuse, physical neglect, and emotional neglect scores were higher in the OUD group ($p<0.001$, $p=0.004$, $p<0.001$, $p=0.005$, respectively). Attachment styles were found

to be similar in the OUD and healthy control groups. A comparison of quality of life scores revealed that general health, physical health, and social relationships subscale scores were lower in the OUD group ($p=0.001$, $p<0.001$, $p<0.001$, respectively). Unplanned impulsivity scores were higher in the OUD ($p<0.001$). Logistic regression analysis found strong associations between age, smoking, physical neglect, and unplanned impulsivity with opioid use.

Conclusion: The patients with OUD have a lower quality of life and experience more childhood trauma. Attachment styles in OUD appear similar to healthy controls. Age, smoking, physical neglect, and unplanned impulsivity have strong associations with opioid use.

Keywords: Attachment style, childhood trauma, impulsivity, opioid use disorder, quality of life.

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INTRODUCTION

According to the 2023 World Drug Report published by the United Nations Office on Drugs and Crime (UNODC), it is estimated that approximately 296 million people worldwide used drugs in 2021, and 31.5 million of the 60.3 million opioid users among these people used heroin (1). Opioid Use Disorder (OUD), which develops due to chronic use of opioids, continues to be a severe public health problem, with hundreds of thousands of deaths attributed to opioids every year worldwide (2). Therefore, effective strategies are still needed to prevent the development of addiction by identifying individuals at high risk of developing OUD.

Based on the information obtained from studies conducted to date, some individuals appear to be more prone to developing addiction than others due to various risk factors. Etiological studies investigating heterogeneous risk factors are increasingly focusing on the traumatic experiences an individual is exposed to at an early age to understand how addiction begins. Childhood traumas are known to be associated with many adverse life outcomes, including addiction, due to their both acute and long-term effects on the physical and mental health (3,4). Because traumatic experiences in childhood can affect a person's emotional regulation, leaving them unable to modulate distressing emotions healthily and adaptively, opioids may be used as an attempt to cope and alleviate these emotions, which may explain the relationship between

Highlights

- Emotional and physical abuse, physical and emotional neglect scores are higher in patients.
- Attachment styles of patients are similar to healthy controls.
- Patients have a lower quality of life, even if they are in remission.
- Unplanned impulsivity score is higher in patients with opioid use disorder.
- Smoking, physical neglect, and unplanned impulsivity are associated with opioid use

traumatic experiences and addiction (5,6). However, although many studies have shown that these experiences increase the risk of developing OUD (5,7), some studies suggest that these experiences do not correspond to stronger associations with the disease and that there may be possible

protective factors that have not yet been addressed in this population (8). Therefore, during this period, there may be an opportunity to intervene with individuals at risk to prevent the development of situations that negatively affect the individual's life, such as addiction.

Although trauma can predispose the individual to a wide variety of psychopathologies, addiction does not develop in every individual who has a negative experience in childhood. Both psychosocial and cultural factors may potentially provide key protective and risk characteristics that need to be assessed and intervened to prevent the development of OUD (9). Attachment theory may provide a helpful framework in this case, and insecure attachment may be an essential mediator between traumatic experiences in childhood and psychopathology in adulthood. According to Bowlby's attachment theory, a close attachment bond is formed through the interaction between the infant and caregivers, and then child internalizes this bond (10). This situation affects the individual's attachment styles, determines their relationships in adulthood, and is related to mental well-being. Nurturing relationships and robust social support systems may serve as protective factors of adverse health outcomes such as traumatic childhood experiences and substance use. On the other hand, those who experienced traumatic experiences in childhood have an insecure attachment style, which may predispose them to opioid use in adulthood (11). Although insecure attachment certainly does not predict the development of psychopathology, it can create vulnerability in the individual because it can create maladaptive strategies to interpret and interact with the world. In addition, people may turn to substance use to find a connection and fill the gap in their lives (11,12). Therefore, since attachment styles and childhood traumatic experiences can be among the critical factors explaining both vulnerability and resilience in response to mental distress (12,13), it is essential to analyze their roles in the development of OUD. Although previous studies have provided valuable information on how childhood traumatic exposure and attachment styles are individually associated with addiction, it is still unclear how these are associated with opioid use when multiple individual-level variables are considered together.

Impulsivity is critical to understand the initiation, maintenance, and relapse of substance use (14). While some researchers view impulsivity as an independent risk factor for psychiatric symptomatology, other researchers think that impulsivity may contribute to psychopathology when it interacts with some risk factors (14,15). Therefore, another critical aspect of this study is investigating the relationships between impulsivity and other variables, which negatively affect interpersonal relationships by disrupting a person's quality of life and functionality.

Given the severe clinical course in OUD patients, it is essential to examine how various risk factors may be related to treatment outcome, defined as relapse. Both traumatic experiences, attachment characteristics, and impulsivity may affect the individual's decisions and increase the likelihood of leaving treatment early (16). Our study also aimed to investigate the effects of various risk factors on treatment compliance and relapse.

Although these factors have been examined separately in the literature, to our knowledge, only a few studies evaluate these factors collectively in the same patient group. The primary purpose of this study is to investigate whether the childhood traumas, attachment styles, impulsivity levels, and quality of life of OUD patients in remission differ from healthy controls and to reveal the relationships between these parameters. H1 hypothesis of the study: Childhood traumas, impulsivity, fearful attachment and preoccupied attachment style are more common in OUD patients. Moreover, these parameters are interrelated and predict OUD.

MATERIAL AND METHODS

Study Sample and Procedure

The study enrolled patients who applied to Akdeniz University Alcohol and Substance Addiction Research and Application Center Outpatient Clinic between September 2021 and March 2022 who were diagnosed with OUD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria and who were in remission for at least one month. Remission was confirmed by urinalysis in all patients in the study. In our clinic, all OUD patients are subjected to a urinalysis at every outpatient clinic visit. Patients with any substance detected in urinalysis were not included in the study. Inclusion criteria for the OUD group; being between the ages of 18–65, and being at least a primary school graduate. Exclusion criteria for the OUD group; using a substance other than opioids, presence of a psychiatric comorbidity other than OUD in the psychiatric history (psychotic disorder, mood disorders, etc.), presence of alcohol use disorder, presence of organic disease (liver disease, kidney disease, asthma, cardiovascular disease, cancer, etc.), having a history of neurological disease (e.g., head trauma, epilepsy, central nervous system disease, etc.), pregnancy for female patients, mental retardation, using medication other than buprenorphine-naloxone (antidepressant, antipsychotic, mood stabilizer, etc.). Criteria for inclusion in the control group; being between the ages of 18–65 and being at least a primary school graduate. Exclusion criteria for the control group; Having a history of substance use, having a history of alcohol use disorder, having a psychiatric disease, having an organic disease. In addition, the control group was selected from people similar to the OUD group in terms of age and sex. The control group was randomly selected. A face-to-face interview was also held with the control group. Those who met the inclusion and exclusion criteria were included in the study. Some of them were hospital employees. Some of them were randomly selected individuals living in Antalya province by the researcher. The researchers conducted all interviews with the patient and control group participants face-to-face. This study was conducted according to the latest version of the Declaration of Helsinki and approved by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (18.08.2021 - Decision No: 595).

Measurement and Assessment Tools

All participants completed the Sociodemographic Data Form prepared by the researchers. We used the Structured Clinical Interview for DSM-5 Disorders Clinician Version (SCID-5/CV) form to determine participants' current psychopathology (17) and confirmed the diagnosis of OUD. To question participants' childhood traumatic experiences, we used the Childhood Trauma Questionnaire (CTQ) (18), which includes questions that retrospectively evaluate emotional, physical, and sexual abuse and neglect experienced before the age of 20. In addition, we administered the Relationship Scales Questionnaire (RSQ) (19), which evaluates people's attachment styles in 4 subscales (secure, fearful, preoccupied, dismissive), and the Barratt Impulsivity Scale (BIS-11) (20), which determines impulsivity levels, to the participants. The World Health Organization Quality of Life Scale Brief Version (WHOQOL-BREF) (21) was used to evaluate the quality of life of the individuals. In addition, the Substance Craving Scale (SCS) (22) was used to determine the level of substance use craving in the study's patient group.

Statistical Analyses

We performed statistical analysis using the data of 200 patients in the patient and control groups and terminated the study. As a result of the post hoc power analysis performed on the last data collected, we calculated the power of the study to be approximately 92%. We performed the power analysis with the G*Power 3.1.9.7 for the Windows package program. We gave descriptive statistics for continuous (numerical) variables as mean \pm standard deviation or median, minimum, and maximum, depending on the distribution. We summarized categorical variables as numbers and percentages. We checked the normality of numerical variables

with Shapiro-Wilk and Kolmogorov-Smirnov tests. In comparing two independent groups, We used the Independent Samples T-Test in cases where numerical variables were normally distributed and the Whitney U test in cases where numerical variables were not normally distributed. In non-parametric tests, we evaluated the differences between groups with the Dwass-Steel-Critchlow-Fligner test. In examining the relationships between numerical variables, we used Spearman's Rho correlation coefficient in cases where the variables were not normally distributed. We applied multiple logistic regression analysis to identify factors that may predict OUD risk. We performed statistical analyses with IBM Statistical Package for Social Sciences (SPSS) program version 26.0 (IBM Corporation, Armonk, NY, USA). We accepted the statistical significance level as $p < 0.05$.

RESULTS

Descriptive statistics of the sociodemographic data of the study participants are summarized in Table 1. Clinical data of the patient group are summarized in Table 2. Comparisons between the patient and control groups for CTQ, RSQ, BIS-11, and WHOQOL-BREF scores are summarized in Table 3.

We made some sub-comparisons on sociodemographic data. We found statistically significantly higher SCS scores in patients with OUD, those with low-income family relationships, and those who attempted suicide ($p=0.018$ and $p=0.029$, respectively). Considering the CTQ scores, sexual abuse scores were higher in women than in men, and emotional abuse and neglect scores were higher in individuals living in families where there was no parental cohabitation ($p < 0.001$ for each). Patients with low-income family relationships had higher fearful attachment scores ($p=0.025$). In contrast, male patients who did not have other substance use individuals in their families and who did not smoke had higher secure attachment scores ($p=0.032$, $p=0.014$, respectively). Patients with suicide attempts had significantly higher unplanned impulsivity scores than patients without suicide attempts ($p=0.044$). Patients who smoked had lower physical and psychological health scores ($p=0.003$ and $p < 0.001$, respectively). Patients with poor family relationships had lower psychological and social relationship scores ($p=0.005$ and $p < 0.001$, respectively). The social relations scale scores of OUD patients who had a family member who used substances were significantly lower ($p=0.038$).

Inter-scale correlations were analyzed. In the patient group, negative correlations were found between SCS and WHOQOL-BREF subscale

Table 1. Comparison of sociodemographic data of opioid use disorder (OUD) and healthy control group

	OUD (n=100) n (%)	Healthy control (n=100) n (%)	p
Age (years) (mean ± SD)	30.8±7.3	30.7±7.3	0.961
Sex			
Female	13 (13.0)	10 (10.0)	0.658
Male	87 (87.0)	90 (90.0)	
Marital status			
Single	62 (62.0)	83 (83.0)	<0.001***
Married	28 (28.0)	17 (17.0)	
Divorced	10 (10.0)	0 (0.0)	
Parent status			
Together	66 (66.0)	84 (84.0)	0.012*
Divorced	21 (21.0)	11 (11.0)	
One or both dead	13 (13.0)	5 (5.0)	
Education status			
Primary education	44 (44.0)	4 (4.0)	<0.001***
High school	48 (48.0)	92 (92.0)	
University	8 (8.0)	4 (4.0)	
Work status			
Employed	59 (59.0)	45 (45.0)	<0.001***
Unemployed	41 (41.0)	28 (28.0)	
Student	0 (0.0)	27 (27.0)	
Smoker	96 (96.0)	35 (35.0)	<0.001***
Smoking duration (median) [min-max]	10.0 [2.0–40.0]	5.0 [2.0–10.0]	<0.001***
Family relations			
Good, always in touch	61 (61.0)	100 (100.0)	<0.001***
Moderate, occasionally in contact	32 (32.0)	0 (0.0)	
Bad, almost no contact	7 (7.0)	0 (0.0)	

We used the Independent Samples T-test for the age variable, the Mann-Whitney U test for the smoking duration variable, and the Pearson Chi-Square, Fisher's Exact, or Fisher Freeman Halton test for other variables.

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

Table 2. Clinical characteristics of patients with opioid use disorder (OUD)

	OUD (n=100) n (%)
Opiate use	
Inhalation	76 (76.0)
Intravenous	24 (24.0)
Infectious disease	
Hepatitis C Virus	22 (22.0)
Human Immunodeficiency Virus	1 (1.0)
Self-mutilation	32 (32.0)
Attempted suicide	18 (18.0)
Number of suicide attempts (median) [min-max]	1 [1.0–2.0]
Patient with a history of forensic events	47 (47.0)
Patient with a family history of substance use disorder	9 (9.0)
Duration of treatment (months) (median) [min-max]	23.0 [2.0–109.0]
Buprenorphine-naloxone dose (mg) (median) [min-max]	8.0 [2.0–20.0]
Duration of opiate use (year) (median) [min-max]	6.0 [1.5–18.0]

Table 3. Comparison of scale scores of opioid use disorder (OUD) and control group

	OUD (n=100)	Control (n=100)	p
Substance craving scale §	0.0 [0.0–23.0]	--	--
Substance craving scale †	3.8±5.7		
WHO Quality of Life – Brief Version			
Physical health §	57.1 [17.9–92.9]	82.1 [53.6–100.0]	<0.001***
Psychological §	66.7 [8.3–100.0]	66.7 [29.2–100.0]	0.942
Social relationships §	58.3 [0.0–100.0]	75.0 [8.3–100.0]	<0.001***
Environment §	62.5 [6.2–96.9]	67.2 [40.6–100.0]	0.109
Barratt Impulsivity Scale-11			
Attentional impulsivity §	17.0 [9.0–24.0]	17.0 [10.0–26.0]	0.417
Motor impulsivity §	21.0 [12.0–35.0]	20.0 [13.0–64.0]	0.047*
Unplanned impulsivity §	26.0 [16.0–38.0]	24.0 [14.0–31.0]	<0.001***
Relationship Scales Questionnaire			
Secure attachment §	4.0 [2.2–7.0]	4.0 [2.8–7.0]	0.252
Fearful attachment §	4.0 [1.0–6.5]	4.0 [1.5–6.0]	0.786
Preoccupied attachment §	3.9 [1.0–6.8]	4.0 [2.2–6.5]	0.085
Dismissive attachment §	4.1 [1.6–7.0]	4.4 [3.0–6.0]	0.049*
Childhood Trauma Questionnaire §	41.0 [25.0–83.0]	34.0 [25.0–62.0]	<0.001***
Emotional abuse §	7.0 [5.0–25.0]	6.0 [5.0–13.0]	<0.001***
Physical abuse §	5.0 [5.0–25.0]	5.0 [5.0–15.0]	0.004**
Physical neglect §	9.0 [5.0–18.0]	7.0 [5.0–13.0]	<0.001***
Emotional neglect §	12.0 [5.0–25.0]	11.0 [5.0–17.0]	0.005**
Sexual abuse †	6.11±3.15	5.54±1.91	0.125

†: Mean ± Standard deviation; §: Median [min-max].

***p<0.001; **p<0.01; *p<0.05

Table 4. Multiple logistic regression analysis to identify factors that increase the risk of opioid use disorder

	B	SE	Exp (B)	%95 GA	p
Age	0.071	0.034	1.074	1.005–1.147	0.035*
Smoking (ref=none)	3.411	0.576	30.307	9.803–93.703	<0.001***
Physical abuse	0.131	0.083	1.140	0.970–1.341	0.112
Physical neglect	0.174	0.078	1.190	1.022–1.385	0.025*
Unplanned impulsivity	0.147	0.055	1.158	1.039–1.291	0.008**

***p<0.001; **p<0.01; *p<0.05

Omnibus Test of Model Coefficient <0.001

Hosmer Lemeshow Test=0.552

Nagelkerke R square=0.564

scores (respectively: $r=-0.362$, $p<0.001$; $r=-0.355$, $p<0.001$; $r=-0.362$, $p<0.001$; $r=-0.359$, $p<0.001$; $r=-0.375$, $p<0.001$). There was also a significant positive correlation between the emotional abuse scores of the patients and their preoccupied and dismissive attachment scores ($r=0.207$, $p=0.038$; $r=0.260$, $p=0.009$). There were significant negative correlations between emotional neglect scores and WHOQOL-BREF subscores (respectively: $r=-0.354$, $p<0.001$; $r=-0.310$, $p=0.002$; $r=-0.371$, $p<0.001$; $r=-0.362$, $p<0.001$; $r=-0.512$, $p<0.001$). There were significant positive correlations between sexual abuse scores and attentional impulsivity and unplanned impulsivity scores (respectively: $r=0.363$, $p<0.001$; $r=0.395$, $p<0.001$), whereas negative correlations were found between WHOQOL-BREF general health and environment sub-scores (respectively: $r=0.316$, $p=0.001$; $r=0.400$, $p<0.001$).

The results of the multivariate multiple logistic regression analysis conducted by including the variables of age, smoking and alcohol use, emotional abuse and neglect, physical abuse and neglect, and unplanned impulsivity, which were significant in the univariate model according to the univariate logistic regression analysis conducted to determine the risk factors for OUD, are shown in Table 4. Age, smoking, physical neglect, and unplanned impulsivity remained significant factors in the model.

DISCUSSION

Identifying the mechanisms underlying OUD and individual variables in this process is critical to developing more effective therapeutic and preventive interventions. In this regard, our study examined the relationship between childhood trauma, attachment styles, and OUD and whether various sociodemographic or clinical characteristics mediate this relationship. In our study, CTQ total score, emotional abuse, physical abuse, physical neglect and emotional neglect scores were found to be higher in the OUD group. Attachment styles are similar in both groups. When WHOQL-BREF scores were compared, general health, physical health and social relations subscale scores were found to be lower in the OUD group. BIS-11 unplanned impulsivity subscale scores were found to be higher in the OUD group than in healthy controls. Age, smoking, physical neglect and unplanned impulsivity significantly predicted OUD.

In the present study, childhood traumatic experience scores in the patient group were significantly higher than in healthy controls. So, foremost, the results of this study support the literature that traumatic experiences in childhood are associated with OUD in adulthood (8,23). Our finding showing that physical neglect, one of these experiences, has a stronger relationship with OUD than other traumatic experiences stands out among other studies in the literature. Considering that not every person with a traumatic childhood experience develops OUD, we also examined other variables that may predict individual differences in this relationship. Indeed, some individuals may be at greater risk for OUD due to sociocultural stressors, negative behaviors of the caregiver, poor upbringing, or lack of social support (9). Studies in the literature show that there are differences between genders in the rates of exposure to and being affected by trauma (24). In the OUD patients in our study, sexual abuse scores were significantly higher in women than in men. We think that women with OUD may have been exposed to more sexual abuse during childhood than men. In this respect, we believe that studies with very large samples should be conducted, especially evaluating women with OUD.

In addition, the study represents an investigation of attachment styles in a sample of OUD patients. An individual's attachment style develops in infancy and affects adulthood. As attachment is replaced by individual freedom during adolescence, adolescents are more likely to engage in risky behavior. Relationships between attachment style and addictions have been reported in the literature. In a study conducted in our country, significant relationships were found between substance use

and dismissive and preoccupied attachment styles (25). Likewise, in a study conducted in our country, the average avoidant attachment score of individuals with alcohol use disorder was found to be higher (26). However, in our study, attachment styles in OUD patients were found to be similar to healthy controls. Although only the dismissive attachment score was slightly higher in the control group in our study, the p value of 0.049 makes its significance extremely insignificant. In other words, we can say that attachment styles are similar in both groups. This situation seems incompatible with the existing literature (27). This can be explained by the fact that many psychosocial and cultural variables can affect attachment styles in a complex way (9,27). The emphasis on family ties in various cultures can serve as a robust support system and thus be a protective factor against adverse health outcomes such as substance use (28). On the other hand, the same situation can also be a risk factor for increased substance use by contributing to mood dysregulation among individuals who have problematic relationships with their parents (29). The fact that there was no difference between the attachment styles of the groups in our study may be related to the strong family ties in our country. The fact that parents in both sample groups were sensitive to their children's needs and established an ideal and safe relationship with them and that similar child-rearing styles were common in society may have affected this situation. Again, regression analyses in our study did not reveal a strong relationship between attachment styles and OUD. On the other hand, in our study, it is seen that there are strong relationships between individuals who experienced emotional neglect and abuse in childhood and fearful attachment styles in adulthood. In other words, attachment style alone may not be a risk factor for substance use.

Another important aspect of this study is that it investigates the relationship between impulsivity and other variables. There are relatively few studies that have comprehensively and simultaneously examined the relationship between impulsivity and such a variety of variables (14,15). Therefore, the data of this study may develop some approaches to prevent impulsive behaviors, which are among the diagnostic criteria of many psychopathologies. Our study found that motor and unplanned impulsivity scores were higher in the patient group than in the control group. Although there is a difference between groups in terms of motor impulsivity, the p value of 0.047 may indicate that the significance is low. The result should be evaluated from this perspective. Regression analyses also support this, showing that there is a strong relationship between unplanned impulsivity and OUD. Our study also found that motor impulsivity scores were significantly higher in men than women. Accordingly, it can be said that men have more difficulty in suppressing emotional, cognitive, and behavioral reactions than women and that they take action without thinking about the consequences. Perhaps this may be one of the reasons why OUD is more common in men. In addition, our research findings suggest that emotional and sexual abuse from traumatic experiences in childhood may be associated with motor and attentional impulsivity, and sexual abuse may be associated with unplanned impulsivity. We also found that patients with suicide attempts had higher unplanned impulsivity scores than those without suicide attempts.

Our study also investigated the relationship between various sociodemographic and clinical variables and quality of life by examining patterns of impairment in different quality-of-life domains between OUD patients in remission and healthy controls. Consistent with previous research, our study supports the idea that OUD patients have a lower quality of life than healthy controls (30). In our study, relationships were found between individuals' quality of life and smoking, the presence of another member of the family who uses substances, loss of a parent, and the level of craving. Again, the correlation analysis detected negative significant relationships between childhood traumas and impulsivity and quality of life.

Craving, a diagnostic criterion and treatment target for OUD, is considered by some researchers to be predictive of future relapse (31). As a result of the correlation analyses we conducted in our study, we could not detect a significant relationship between craving scale scores and other variables, which suggests that craving is a complex structure and that more studies focusing on craving may be needed.

To the best of our knowledge, our study is one of the few studies that evaluate such a variety of sociodemographic and clinical characteristics in patients with OUD. However, readers should also consider some limitations when evaluating the results of this study. Firstly, a limitation of this study is that we evaluated the variables using self-report scales, and the patients answered the questions asked on some scales with retrospective recall. Additionally, since the sample was selected from a single center, the study has limitations regarding representing all OUD patients in Türkiye. While the early remission criterion for DSM-5 is at least 3 months, another limitation is that patients who were in remission for at least 1 month were included in our study.

As a result of our research, we can say that OUD patients have more childhood trauma and these patients are more impulsive. We can say that the attachment styles of OUD patients are similar to healthy controls, and their quality of life is worse in some areas. Correlations have been shown between patients' emotional abuse scores and their preoccupied and dismissive attachment scores. We can say that there is no relationship between attachment style and OUD. We can also say that age, smoking, physical neglect and unplanned impulsivity independently increase the risk of OUD. We can say that childhood traumas and impulsivity are important risk factors for OUD that should be considered together. Prospective studies with larger samples are needed on this subject in the future.

Ethics Committee Approval: This study was conducted according to the latest version of the Declaration of Helsinki and approved by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (18.08.2021 - Decision No: 595).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

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