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# Effect of chronotype on course of treatment in patients with schizophrenia under long-acting injectable antipsychotic treatment: one-year community mental health center experience

A. ERDOĞAN KAYA[1], B. ERDOĞAN AKTÜRK[2]

[1]Department of Psychiatry, Hitit University, Çorum Erol Olçok Training and Research Hospital, Çorum, Turkey
[2]Department of Psychiatry, Mersin Tarsus State Hospital, Mersin, Turkey

**Abstract. – OBJECTIVE: A chronotype is defined as the behavioral manifestation underlying the biological clock, which is formed by the effects of physical and genetic factors. It has recently been found to be associated with many mental and physical illnesses. The aim of this study is to investigate the effects of chronotypes on the treatment course of schizophrenia.**

**PATIENTS AND METHODS: This is a clinical retrospective study. The study population was composed of subjects with schizophrenia who received long-acting, injectable antipsychotic medication. The Demographic Data Form, Morningness-Eveningness Questionnaire (MEQ), and the Pittsburgh Sleep Quality Index (PSQI) were administered to the patients. In addition, the retrospective follow-up files of the patients for the last year were investigated. The obtained data were analyzed statistically.**

**RESULTS: The chronotypes of 97 patients with schizophrenia who volunteered to participate in the study were 38.2% (n = 37) eveningness, 27.8% (n = 27) morningness, and 34% (n = 33) intermediate type. Compared to morningness and intermediate type, eveningness was associated with a higher number of acute exacerbations in patients with schizophrenia, while intermediate type and morningness did not differ significantly from each other.**

**CONCLUSIONS: Our study, as a clinical study, supports the relationship between eveningness and poor prognosis in schizophrenia. It may be helpful to consider the chronotype in the clinical follow-up of patients with schizophrenia and to be aware of individuals with the evening chronotype, which is predicted to have a higher risk of exacerbation.**

*Key Words:*
Schizophrenia, Chronotype, Antipsychotics, Prognosis.

## Introduction

Schizophrenia is a chronic mental illness accompanied by positive as well as negative and cognitive symptoms that may result in severe disability and loss of functionality[1]. It progresses with exacerbations and remissions and often significantly impairs the level of functionality in the long term[2]. Antipsychotics are mainly used in treatment; however, many patients cannot continuously comply with treatment[3]. In a mental disorder such as schizophrenia, which significantly impairs functionality, treatment irregularity is associated with a poor prognosis and frequent relapses. The loss of functionality in the social/occupational field becomes more severe[4]. In this respect, compliance with oral treatment has been considered a compelling factor in most patients with schizophrenia, and to address the need for long-acting antipsychotic agents, the production of depot drugs, which provide stable blood concentrations, has been initiated[5].

Long-acting antipsychotics have facilitated treatment compliance in patients with schizophrenia and strengthened clinicians' hand against exacerbations due to treatment interruptions[6]. However, other factors besides compliance with treatment cause relapse in schizophrenia and mental illnesses. These factors mainly include alcohol and substance use, sleep disturbances, stress, and emotional expressions from family members[7-11]. To prevent and predict exacerbations in schizophrenia, it is important to detect and eliminate factors other than treatment as much as possible. Recently, the emergence of genetic and environmental factors related to the biolog-

*Corresponding Author:* Ayşe Erdoğan Kaya, MD; e-mail: dr.ayserdogan@gmail.com

ical rhythm or the mechanism of the biological clock, as well as sleep-wake cycles, has raised the question of whether physical and mental illnesses are associated with circadian rhythm disorders[12]. Chronotype assessment as a way of revealing circadian rhythm differences has recently become a common practice[13].

The behavioral type that prefers to plan daily activities according to either morning or evening hours or the continuous form of morning and evening behavior forms is referred to as a chronotype[14]. In addition to individual factors, such as age, gender, and genetics, environmental factors, such as the region in which the individual lives, noise, air pollution, sunlight, and artificial light, also affect the chronotype[13]. Previous scholars[15] have revealed the effects of individual and environmental factors on chronotypes and circadian rhythm in addition to having effects on many other physical and mental illnesses. The relationship between chronotypes and mental illnesses, such as bipolar disorder, depression, substance and behavioral addictions, and attention deficit, has attracted considerable interest in recent years[16-18].

However, most of the abovementioned studies are cross-sectional, but long-term studies are still required to investigate whether other factors affect the treatment course of mental disorders. Very few studies have been conducted on chronotypes in patients with schizophrenia. Moreover, the data on the effects of chronotypes on the course of the illness are insufficient.

The aim of this clinical study is to investigate the relationship between treatment courses and chronotypes in schizophrenia. We hypothesize that a chronotype affects the prognosis of schizophrenia, as in other mental and physical illnesses.

## Patients and Methods

The Clinical Research Ethics Committee of Hitit University approved this study (Date-Decision #2023/29). In addition, in human studies, all procedures were performed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

### Methods of Data Collection and Sampling

Patients with schizophrenia who were seen at a Community Mental Health Center (CMHC) in the last year were included in this study. The inclusion criteria for the patients were as follows: meeting the DSM-V diagnostic criteria for schizophrenia, being between the ages of 18-65, being literate, being willing to participate in the study, and being under long-acting injectable antipsychotic treatment.

The psychiatric exclusion criteria were depression or bipolar disorder, anxiety disorder, cognitive impairment, and mental retardation. Other exclusion criteria were medical conditions that can affect mental status and sleep quality, such as neurological illnesses, endocrine dysfunction, chronic kidney or liver diseases, oncological diseases, chronic pulmonary diseases, sleep apnea syndrome, heart failure, and alcohol and substance use disorders. The sample selection procedures and the study population are shown in Figure 1.

The patients were called for follow-up, and data including age, gender, disease duration, marital status, Pittsburg Sleep Quality Index (PTSQI) scores, and Morning-Evening Questionnaire (MEQ) scores of those meeting the inclusion criteria were recorded. The clinical data and the number of exacerbations of the patients were evaluated retrospectively by examining the follow-up files. The patients were divided into two groups: those with two or more psychotic exacerbations in the last year (with hospitalization or recommended hospitalization) with relatively worse prognoses and those with better prognoses. The relationship between chronotypes and prognoses was evaluated statistically.

### Chronotype Assessment

The individuals' chronotypes were determined using the MEQ. The test was conducted on a Likert scale with 19 questions, which was developed by Horne and Östberg as shown by Miguel et al[19]. The Turkish validity and reliability study was conducted by Punduk et al[20]. The participants received points for each question according to their responses: 1-4 points for questions 3-9 and 13-16; 1-5 points for questions 2, 10, 17, and 18; 0-6 points for questions 11 and 19; and 0-5 points for question 12. Based on the total score, three circadian types were determined: morningness (59-86 points), eveningness (16-41 points), and intermediate type (42-58 points).

### Sleep Quality Assessment

The PSQI is a self-report questionnaire with 19 items that assess the quality and quantity of sleep; it was developed by Monk et al[21]. The Turkish validity and reliability study was conducted by Agargün et al[22]. The PSQI is composed of

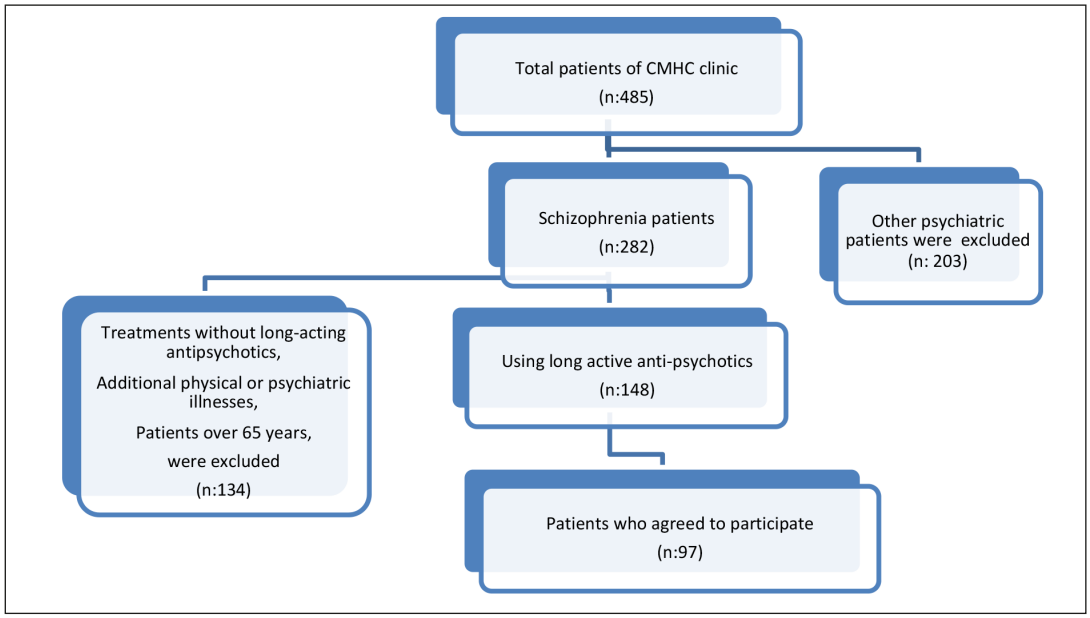


**Figure 1.** The sample selection flow chart.

seven components: subjective sleep quality, sleep efficiency, sleep disturbance, sleep latency, sleep duration, use of sleeping medication, and daytime dysfunction. The points assigned to the items range from 0 to 3, with a maximum score of 21. An increase in the score is associated with worse sleep quality. A total score of ≤5 is considered normal, and that of >5 is considered poor sleep quality.

### *Statistical Analysis*

The research data were analyzed using IBM SPSS 22.0 for Windows (IBM Corp., Armonk, NY, USA). The Kolmogrov-Smirnov and Shapiro-Wilk tests were used to assess normal distribution. An independent sample *t*-test and one-way ANOVA were used for groups with normal distribution according to their mean scores. The Kruskal-Wallis' test and Mann-Whitney U test

**Table I.** Correlation analysis of BMI with tested markers.

| | Morningness (n: 27) | İntermediate (n: 33) | Eveningness (n: 37) | *p*-value |
|---|---|---|---|---|
| Age | 47.78 ± 9.39 | 44.33 ± 11.87 | 46.95 ± 10.83 | 0.426* |
| Gender | | | | |
| Male | 15 (%55.6) | 19 (%57.6) | 20 (%54.1) | |
| Female | 12 (%44.4) | 14 (%42.4) | 17 (%45.9) | 0.957** |
| Marital status | | | | |
| Single | 12 (%44.4) | 22 (%66.7) | 15 (%40.5) | 0.237** |
| Married | 13 (%48.2) | 10 (%30.3) | 20 (%54.1) | |
| Divorced | 2 (%7.4) | 1 (%3.0) | 2 (%5.4) | |
| Duration of illness | 15.48 ± 6.24 | 14.48 ± 8.25 | 16.05 ± 5.82 | 0.631* |
| Medication | | | | |
| Paliperidone | 14 (%51.9) | 24 (%72.7) | 24 (%64.9) | 0.243** |
| Aripiprazole | 13 (%48.1) | 9 (%27.3) | 13 (%35.1) | |
| Sleep quality | 4.0 (2.0-6.0) | 4.0 (2.0-10.0) | 4.0 (2.0-5.0) | 0.662*** |
| Exacerbation | 1.0 (0-1.0) | 1.0 (0-1.0) | 2.0 (1.0-3.0) | 0.001*** |
| Prognosis | | | | |
| Better | 21 (%77.8) | 27 (%81.8) | 15 (%40.5) | **<0.001**** |
| Worse | 6 (%22.2) | 6 (%18.2) | 22 (%59.5) | **<0.001** |

*One-Way ANOVA test. **Pearson Chi-Square test. ***Kruskal-Wallis test.

were used for groups without normal distribution. Pearson's chi-square test and Fisher's exact test were used for categorical variables. Binary logistic regression was used for regression analysis; significance was accepted as $p < 0.05$ and the confidence interval was accepted as 95%.

## Results

The study was conducted with 97 volunteers among 148 patients with schizophrenia who were seen in a CMHC. Demographic data of these patients, prognostic data of the last year, and cross-sectional PSQI and MEQ scores were analyzed. Of the patients, 55.7(54) were male, 44.3% (43) were female, 50.5% (49) were single, 44.3% (43) were married, and 5.2% (5) were divorced. The mean age was 46.29 years, and the mean illness duration was 15.3 years, with an average of 16.5 years for women and 14.4 years for men.

The chronotypes of the patients were 38.2% (n = 37) eveningness, 27.8% (n = 27) morningness, and 34% (n = 33) intermediate type. There was no significant difference among the chronotype subgroups in terms of age, gender, marital status, antipsychotic medication used, illness duration, and sleep quality. According to the data of the last year, worse prognosis (2 or more exacerbations) was higher in the evening chronotype group compared to the other groups ($p < 0.001$), and the mean number of exacerbations was significantly higher ($p = 0.001$). Demographic data according to the chronotype subgroups are shown in Table I.

The long-acting injectable antipsychotics used by the patients were 63.9% (n = 62) paliperidone palmitate and 36.1% (n = 35) aripiprazole. The long-acting drugs used did not show a significant advantage over each other in terms of the number of acute exacerbations ($p = 0.627$). Likewise, the sleep quality scores of the patients did not significantly correlate with the number of acute exacerbations ($r = 0.159$, $p = 0.120$).

The number of exacerbations according to the patients' chronotypes did not show a normal distribution according to the Shapiro-Wilk test. The Kruskal-Wallis test was performed to evaluate whether there was a statistically significant difference in the frequency of exacerbations based on the chronotype. There was a significant difference between the number of exacerbations according to the chronotype ($p = 0.001$). The Mann-Whitney U test was used to determine which chronotype was prominent in terms of acute exacerbation. Evening chronotype was found to be associated with exacerbation significantly more than morningness ($p = 0.002$) and intermediate type ($p = 0.002$), while intermediate type and morningness did not differ significantly in terms of exacerbation ($p = 0.943$).

In terms of the number of acute exacerbations, 37.1% (n = 36) of the patients had never experienced an acute exacerbation, 27.8% (n = 27) had experienced it one time, 17.5% (n = 17) two times, 14.5% (n = 14) three times, and 3.1% (n = 3) four times. According to the number of exacerbations, patients with two or more exacerbations were defined as the worse prognosis group, and those with less than two exacerbations as the group with better prognosis; the data of the groups are summarized in Table II.

The regression analyses of worse prognoses based on age, duration of illness, gender, chronotype, sleep, and medication are explained in Table III. The logistic regression model was also statistically significant: $\chi^2 = 20.006$ ($p = 0.003$). The model explained 25.7% (Nagelkerke R square = 0.257) of variance in prognosis and correctly classified 74.2% of the cases. The eveningness chronotype was found to be significantly related to a worse prognosis (OR = 7.337, $p < 0.001$).

## Discussion

Schizophrenia is a chronic mental illness that progresses with exacerbations and remissions and is affected by many factors during the course of treatment[23]. These factors are mainly compelling life events, nonadherence to treatment, stress, and alcohol and substance use. Recently, the relationship of chronotypes with mental illnesses and their prognoses has begun to be discussed in clinical studies[24-27].

In our study, the effects of age, gender, illness duration, sleep quality, drug use, and chronotype on the prognostic process were investigated in patients with schizophrenia receiving long-acting antipsychotic drug-injectable treatment. The higher proportion of male and single patients may be related to the higher incidence of schizophrenia in these groups[28]. Age, type of antipsychotic drug used, duration of illness, gender, and sleep quality did not significantly affect prognosis in patients, which partially eliminated the effects of confounding factors. We did not find any significant relationship between gender and prognosis. Even though the male gender is associated with

**Table II.** Comparison of the prognosis subgroups in terms of descriptives, sleep quality, medication and chronotype.

| | Better prognosis (n: 63) | Worse prognosis (n: 34) | *p*-value |
|---|---|---|---|
| Age | 47.00 ± 10.16 | 44.97 ± 11.98 | 0.394* |
| Gender | | | |
| Male | 36 (57.1%) | 18 (52.9%) | 0.723*** |
| Female | 27 (42.9%) | 16 (47.1%) | |
| Marital status | | | |
| Single | 32 (50.8%) | 17 (50.0%) | 0.972** |
| Married | 28 (44.4%) | 15 (44.1%) | |
| Divorced | 3 (4.8%) | 2 (5.9%) | |
| Duration of illness | 15.83 ± 6.86 | 14.50 ± 6.75 | 0.425** |
| Sleep Quality | 3.0 (1.0-5.5) | 4.5 (3.0-8.0) | 0.108** |
| Chronotype | | | |
| Morningness | 21 (33.3%) | 6 (17.7%) | |
| Eveningness | 15 (23.8%) | 22 (64.6%) | <0.001*** |
| Intermediate | 27 (42.9%) | 6 (17.7%) | |
| Medication | | | |
| Paliperidone | 40 (63.5%) | 22 (64.7%) | |
| Aripiprazole | 23 (36.5%) | 12 (%35.3) | 0.905*** |

*Independent Sample *t*-test. **Mann-Whitney U test. ***Pearson Chi-Square test.

poor prognosis, in a meta-analysis[29] examining the predictors of schizophrenia prognosis, no definitive evidence was found for a gender-prognosis relationship.

Although early-onset illness and long illness duration are expected to be associated with poor prognoses, untreated illness duration is also an important factor in this regard. In our study sample, patients with a short illness duration were actually diagnosed late and had a long untreated period before diagnosis due to low socioeconomic status and local cultural reasons. This may have caused the inability to detect a relationship between illness duration and prognosis.

Previous research[30] investigating the relationship between psychiatric disorders and sleep has found that sleep problems are common in patients with positive symptoms and that they decrease with improvement in sleep problems. In our study, sleep quality averages in schizophrenia were close to normal levels and had no significant effect on prognosis; this is attributable to the fact that the patients were under treatment and the sleep quality was evaluated only during the remission period.

The higher number of patients subject to paliperidone palmitate treatment in our study may be related to the stronger dopaminergic antagonism

**Table III.** Regression table predicted likelihood of worse prognosis based on age, duration of illness, gender, chronotype, sleep and medication.

| | | | | | | | 95% C.I. for Odds Ratio | |
|---|---|---|---|---|---|---|---|---|
| | B | S.E. | Wald | df | Sig. | Odds Ratio | Lower | Upper |
| Age | -.014 | .033 | .167 | 1 | .682 | .987 | .924 | 1.053 |
| Duration | -.028 | .054 | .267 | 1 | .606 | .973 | .876 | 1.081 |
| Gender (1) | -.271 | .494 | .301 | 1 | .583 | .763 | .289 | 2.010 |
| Chronotype* (1) | 1.993 | .500 | 15.883 | 1 | <.001 | 7.337 | 2.753 | 19.553 |
| Sleep | .070 | .049 | 2.004 | 1 | .157 | 1.072 | .974 | 1.181 |
| Medication (1) | .044 | .505 | .008 | 1 | .930 | 1.045 | .389 | 2.811 |
| Constant | -.692 | 1.362 | .258 | 1 | .612 | .501 | | |

The dependent variable; Prognosis (worse: 1, better: 0) and independent categorical variables; Gender (male:1, female:0), Medication (paliperidone: 1, aripiprazole: 0), Choronotype (eveningness: 1, other: 0) were coded into the model. *According to this model, categorical variables were classified into two category: Eveningness chronotype group was accepted one category, morningness plus intermediate group were accepted other category.

of paliperidone compared to aripiprazole[31], as well as local physician preferences. Moreover, the fact that long-acting injectable paliperidone palmitate was approved and used before long-acting injectable aripiprazole in Turkey may be one of the reasons for this situation. There was no significant difference in terms of exacerbation between the use of aripiprazole and paliperidone palmitate, which is consistent with the literature data[32]. This situation allowed us to evaluate the effects of chronotypes on prognoses and the number of attacks more accurately in our study.

According to the literature[33], the most common chronotype in the general population is the intermediate type. In clinical studies investigating the chronotype in psychiatric patients, the evening chronotype is more dominant in general[34]. The fact that the most frequently detected chronotype in our study was the evening chronotype supports previous studies[33-35]. Morningness is more common than the intermediate type because of the mechanisms related to schizophrenia, genetic factors, or the drugs used. In our study, the evening chronotype was found to be associated with a significantly worse prognosis than the intermediate and morning chronotypes. This finding is similar to those previously obtained regarding the relationship between evening type and poor prognosis in the treatment of mental illnesses such as substance use disorder and bipolar disorder[24,35-37]. In 2020, an 18-month follow-up study conducted by Melo et al[24], which included 80 bipolar disorders, found that eveningness was associated with a poor illness prognosis. In Menculini et al's[38] study, which included 178 bipolar disorder patients, the evening chronotype was found to be associated with poor prognoses, severe mood attacks, accompanying irritability, anxiety, and impulsivity. The fact that the evening chronotype is more common in mental illnesses and is associated with poor prognoses in mental disorders suggests that it is a condition that affects the common pathways in the pathogenesis of these illnesses. Endogenous diurnal changes (hormone secretion, body temperature, sleep-wake pattern, and socialization) controlled by the circadian clock are effective in the course of psychiatric illnesses, such as bipolar disorder, substance use disorder, anxiety disorder, and eating disorder[39]. These changes in the evening chronotype may negatively affect mental disorders through unhealthy behavioral patterns, poor eating habits, and metabolic reflections. However, it is not clear whether the evening chronotype is a cause that plays a role in the etiopathogenesis of mental disorders or a result that occurs in the course of the illness.

In our study, the model obtained as a result of regression analysis, which included chronotype, illness duration, gender, sleep quality, and the antipsychotic drugs used, had high prognostic predictive power in the course of treatment. The statistical results indicated that chronotype is a novel predictive factor that should be considered in the follow-up and treatment of schizophrenia.

While schizophrenia has been extensively studied, there is a need for stronger evidence of new prognostic factors that can be used in follow-up and treatment due to the difficulties experienced in the treatment course. The power of the evening chronotype in predicting poor prognosis in schizophrenia in our results was similar to that observed in previous clinical studies[24,40] that highlighted the importance of chronotypes in the course of bipolar disorders. These studies may provide clinicians with a new perspective on the biological internal clock in patients with severe psychiatric disorders[24,40]. However, it is not entirely clear how prognostic factors such as stress, traumatic life events, and alcohol and substance use disorders affect the progression of schizophrenia and other psychopathologies. These factors might worsen illnesses by interfering with chronobiological mechanisms.

Although chronotypes have been extensively investigated in physical and mental illnesses, most of these studies did not go beyond cross-sectional evaluations[15,17]. The number of clinical studies conducted on the long-term treatment course of chronotypes and mental disorders is quite insufficient. It is crucial to identify a factor that affects the course of treatment, particularly in psychopathologies like schizophrenia, where follow-up and treatment compliance are highly challenging. Our study deserves attention, as it is one of the rare studies examining the effect of chronotype on prognosis in patients with schizophrenia under treatment.

Based on the data we obtained, we suggest that interventions on chronobiological mechanisms in psychiatric patients with evening chronotypes can contribute to the course of the illness. For example, bright light therapy, sleep deprivation, interpersonal relations and social rhythm therapy, cognitive behavioral therapy techniques, and transitioning patients to morningness or intermediate type can contribute to the course of the illness and the treatment process.

### Limitations

Due to the study's retrospective nature, it included few patients, did not examine other factors affecting prognosis (family expression, social support, etc.), and did not include patients who received only oral medication. We plan to conduct further research on a larger sample with a prospective design, including therapeutic interventions on chronotypes.

## Conclusions

A chronotype may be associated with certain physical and mental illnesses, as well as their prognosis. Our study, as a clinical study, supports the relationship between eveningness and poor prognosis in schizophrenia. Being especially careful in the patient group at high risk of exacerbation predicted by the evening chronotype may be beneficial in terms of follow-up and treatment. Therapeutic interventions on chronotypes in psychotic patient groups with evening chronotypes may benefit the prognosis of the illness, and further studies evaluating this issue can guide clinicians.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### Ethics Approval

This study was conducted according to the Declaration of Helsinki and was approved by the Ethical Committee for Clinical Research of Hitit University (Date and Decision #2023/29).

### Informed Consent

Informed consent was obtained from all subjects involved in the study.

### Data Availability

The authors confirm that the data supporting the findings of this study are available from the corresponding author on reasonable request.

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This research received no external funding.

### Authors' Contributions

Ayşe Erdoğan Kaya: design of the study, acquisition of data, analysis and interpretation of data, drafting the article, making critical revision, supervision. Beyza Erdoğan Aktürk: analysis and interpretation of data, drafting the article, making critical revision. All authors have read and agreed to the version of the article to be published.

### ORCID ID

Ayşe Erdoğan Kaya: 0000-0002-6780-9301
Beyza Erdoğan Aktürk: 0000-0002-5072-9241.

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