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The comparison of fatigue, sleep quality, physical activity, quality of life, and psychological status in multiple sclerosis patients with or without COVID-19

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ABSTRACT

Purpose: The study was purposed to investigate the effect of COVID-19 disease on fatigue, sleep quality, physical activity, quality of life, and psychological status in people with MS.
Methods: A total of 104 people with MS, including 46 of them with COVID-19 disease history, were enrolled in the study. All patients were evaluated with the Expanded Disability Status Scale (EDSS), Fatigue Severity Scale (FSS), Pittsburgh Sleep Quality Index (PSQI), International Physical Activity Questionnaire Short Form (IPAQ-SF), the EuroQoL Instrument (EQ-5D-3L), the Fear of COVID-19 Scale (FCV-19S) and the Coronavirus Anxiety Scale (CAS).
Results: People with MS in the COVID-19 positive group had a significantly lower IPAQ-Total score ($p = 0.014$). Besides, the FCV-19S scores of COVID-19 positive patients were significantly higher ($p = 0.006$). EQ-5D-3L Index and EQ-5D-3L VAS scores were higher in the group with COVID-19 ($p_1 = 0.021$, $p_2 = 0.014$, respectively). FCV-19S had a moderate correlation with EDSS ($r = -0.362$). IPAQ-Total was moderately associated with MS duration, EDSS and FSS ($r_1 = -0.471$, $r_2 = -0.389$, $r_3 = -0.388$, respectively). The EQ-5D-3L Index was moderately correlated with FSS ($r_1 = -0.404$). There was a weakly significant relationship between EQ-5D-3L Index and BMI, MS duration, PSQI and CAS ($r_1 = -0.471$, $r_2 = -0.389$, $r_3 = -0.388$, $r_4 = -0.326$, respectively). On the other hand, EQ-5D-3L was moderately associated with VAS and EDSS and PSQI ($r_1 = -0.393$, $r_2 = -0.357$, respectively).
Conclusion: COVID-19 negatively affected the people with MS's physical activity and coronavirus related fear parameters. However, the causality of this influence should be investigated in detail.

1. Introduction

The world met the new coronavirus (COVID-19) with the increase in pneumonia cases in China at the end of 2019 (Verstrepen et al., 2020; World Health, 2020). In a study conducted with 214 patients in China at the beginning of the pandemic, the rate of neurological symptoms was 36.4%, while this rate was 45.5% in severe infections (Mao et al., 2020). The neurological complications of the novel COVID-19 are thought to be a result of the systemic response to the infection and the direct effects of the virus. In addition to causing neurological complications in healthy individuals, COVID-19 infection also affected the treatment approach, physical and psychological conditions of individuals with chronic neurological diseases. Immunomodulatory and immunosuppressant drugs are currently used to treat Multiple Sclerosis (MS), which are notable effective but require careful risk management in terms of infections. During the pandemic process, close monitoring of disease activity and the physical and psychological status of people with MS under treatment, especially those with COVID-19 infection, has gained particular importance (Möhn et al., 2020).

Although it is known that all infections can worsen MS symptoms, the relationship between COVID-19 infection and MS is still unclear. In a study conducted with 232 people with MS with COVID-19 from Italy at the beginning of the pandemic, it was reported that 96% of the patients survived the infection mildly without developing pneumonia (Sormani, 2020). In another study investigating the mental effects of the pandemic process in people with MS, it was revealed that 70% of people with MS

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have a more severe infection than the average population due to their diseases and medications (Costabile et al., 2020). In a multicenter study brought to the literature from Turkey, COVID-19 positive people with MS were evaluated. It was revealed that mild infection was associated with younger age and less comorbidity. Severe disease was associated with advanced age, progressive type MS, and the high Expanded Disability Status Scale (EDSS) (Sen et al., 2021).

Currently, it is known that MS or MS immunotherapies do not increase the incidence of infection or the severity of infection with the increase of experience on this subject (Berger et al., 2020; Giovannoni et al., 2020; Sen et al., 2021). A study comparing the depression, anxiety, fatigue, and sleep quality parameters of people with MS with healthy controls during the pandemic process showed that the MS group had a higher burden of depressive symptoms, increased fatigue levels, and had worse sleep quality (Motolese et al., 2020). Since inflammatory changes, intrinsic predisposing factors, and disability in MS cause more mood disorders and fatigue in individuals with MS than in the healthy population (Induruwa et al., 2012; Patten et al., 2003), it is not surprising that people with MS are more affected by a stressor such as the pandemic process. Although the effects of the pandemic and the course of the infection in people with MS have been investigated many times in the literature, no other studies demonstrated the effect of the coronavirus on clinical and neuropsychiatric symptoms. The aim of the study was to investigate the effect of COVID-19 disease on fatigue, sleep quality, physical activity, quality of life, and psychological status in multiple sclerosis patients.

2. Materials and methods

2.1. Study design and participants

A prospective case-control study was carried out in Ege University Neurology Department with a total of 104 people with MS, including 46 of them with COVID-19 disease history. A neurologist conducted the diagnosis of the MS according to the revised McDonald criteria (Polman et al., 2011). The inclusion criteria of the study were; patients with no MS relapse in the last one month and individuals whose EDSS score $\leq$ 6.5. In addition, people with MS who had COVID-19 history only in the last six months were included in the study. Patients who had an MS relapse and/or COVID-19 infection in the last month were excluded from the study. In this way, it was purposed to eliminate acute COVID-19 infection related-symptoms and persistent post-COVID symptoms (Fernández-de-Las-Peñas et al., 2021).

2.2. Procedure

The individuals were recruited in the study with a online survey based assessment. The neurologist of the clinic invited people with MS to the study with a telephone call. The individuals were reached the tests via message link and completed the surveys in Google Forms. The COVID-19 symptoms were questioned with checklist-based survey. The EDSS data of all people with MS were at most 1 month before the study evaluation time. The study was carried out in accordance with the ethical principles and the Helsinki Declaration. Informed consent of the patients was obtained. The study protocol was approved by the ethics committee of Ege University (No: 21-6T/8).

2.3. Study outcomes

Demographic and clinical characteristics (MS duration, EDSS score, relapse count after COVID-19 era, other chronic diseases) of all people with MS included in the study were recorded (Table 1). All patients were evaluated with the Expanded Disability Status Scale (EDSS), Fatigue Severity Scale (FSS), Pittsburgh Sleep Quality Index (PSQI), International Physical Activity Questionnaire Short Form (IPAQ-SF), the EuroQoL Instrument (EQ-5D-3L), the Fear of COVID-19 Scale (FCV-19S) and the Coronavirus Anxiety Scale (CAS).

Table 1
The baseline physical and clinical characteristics of the participants.

	COVID-19 positive people with MS (n = 46)	COVID-19 negative people with MS (n = 58)	p
Age (years, mean±SD)	36.5 ± 11.2	39.7 ± 9.9	0.149[a]
Gender (women/men,%)	76/24	63.7/36.3	0.177[b]
Weight (kg, mean±SD)	69.6 ± 12.9	69.7.2 ± 16.6	0.793[a]
Height (m, mean±SD)	1.67 ± 0.09	1.66 ± 0.10	0.803[a]
BMI (kg/m^2, mean±SD)	25.0 ± 4.8	24.8 ± 4.6	0.819[a]
MS duration (years, mean±SD)	8.0 ± 5.8	9.2 ± 5.7	0.214[a]
EDSS (score, mean±SD)	1.44 ± 1.63	1.75 ± 1.40	0.072[a]
Relapse after COVID-19 era (yes/no,%)	13/33	79.4/20.6	0.306[b]
Relapse count after COVID-19 era (count, mean±SD)	0.13 ± 0.3	0.46 ± 1.44	0.233[a]
Other chronic diseases (yes/no,%)	30.4/69.6	27.5/72.5	0.750[b]

SD: standard deviation, **n:** number of patients, **BMI:** Body Mass Index, **MS:** Multiple Sclerosis, **EDSS:** Expanded Disability Status Scale, **a:** Mann–Whitney U test, **b:** Pearson Chi Square test.

2.4. Expanded Disability Status Scale (EDSS)

The EDSS evaluates the functional status of the patients. EDSS represents MS progress in and assesses treatments' effect. EDSS is considered the gold-standard measure of disability in patients with MS (Kurtzke, 1983).

2.5. Fatigue Severity Scale (FSS)

The FSS assesses the effect of fatigue on functionality rather than the severity of fatigue-related symptoms. Individuals are asked to consider their last week while answering the questions. The scale includes a total of 9 questions. High scores indicate an increased degree of fatigue. Armutlu et al. adapted the Turkish version of the FSS The FSS assesses the effect of fatigue on functionality rather than the severity of fatigue-related symptoms (Armutlu et al., 2007).

2.6. Pittsburgh Sleep Quality Index (PSQI)

PSQI is a safe and standardized sleep questionnaire containing 19 items that evaluate the sleep quality, presence and severity of sleep disorders in the last month. The Turkish version was administered by Ağargün et al. (Ağargün et al., 1996).

2.7. International Physical Activity Questionnaire Short Form (IPAQ-SF)

Turkish validity-reliability study in Turkey was conducted by Sağlam et al. It gives information about the time spent by individuals in light, moderate and vigorous activities and the sitting time (Saglam et al., 2010).

2.8. EuroQoL instrument (EQ-5D-3L)

EQ-5D-3L consists of an index and Visual Analog Scale (VAS) scores. The scale score is calculated from five dimensions. It is scored between 0.59 and 1. 1 point means "perfect health" (Janssen et al., 2013).

2.9. The fear of COVID-19 scale (FCV-19S)

Ahorsu et al. developed the FCV-19S (Ahorsu et al., 2020). A Turkish psychometric study was conducted by Satici et al. FCV-19S consist seven-questionnaire. It includes 5 answers for each item with a Likert

scale (Satici et al., 2020).

2.10. The coronavirus anxiety scale (CAS)

CAS is a 5-item questionnaire with a high reliability (Cronbach's alpha = 0.93) and validity (Lee, 2020). The CAS was adapted in Turkish by Evren et al. (Evren et al., 2020).

2.11. Sample size

The power analysis of the research was carried out with the G-Power 3 computer application (Erdfelder et al., 1996). Since reference values of a similar study were not available, Cohen's d was used to determine the effect size value (Gignac and Szodorai, 2016). Assuming the medium effect size value of 0.50, a total of 46 patients were estimated to be sufficient with 80% power and 95% confidence level for each group.

2.12. Statistical analysis

SPSS software (Statistical Package for Social Sciences) for Windows v25.0 was used to analyze the datasets (SPSS Inc, IBM Corp, Armonk, New York). Mean ± standard deviation (SD) and percent (%) were presented for the variables. The statistical significance level was preferred as 0.05. "One-sample Kolmogorov–Smirnov test" and "Histogram" was used to show the normality of the variables. "Mann-Whitney U test" was used to compare case group differences, as all variables were not conformed to normality. Furthermore, "Pearson's chi-square" analysis was used to check the differences between the categorical variables.

3. Results

A total of 104 people with MS (38.3 ± 10.6 years, 72 women, 32 men) were enrolled in the study. The mean age of the COVID-19 positive and negative people with MS was 36.5 ± 11.2 and 39.7 ± 9.9, respectively. The physical and clinical characteristics of the individuals are presented in Table 1. There was no significant difference in the characteristics between the COVID-19 positive and negative people with MS ($p > 0.05$). In other words, cases with or without COVID-19 were significantly similar in terms of age, gender, weight, height, BMI, MS duration, EDSS, presence/number of relapses after the baseline of the COVID-19 era, also another chronic disease history. In this respect, the physical and clinical features of our two case groups were comparable.

COVID-19 related symptoms were; exercise intolerance, musculoskeletal pain, headache, pulmonary findings (e.g., dyspnea), loss of sense of smell, and attention-concentration dysfunction. People with MS in the COVID-19 positive group had a significantly lower IPAQ-Total score (Metabolic Equivalent of Task (MET) minutes per week) ($p = 0.014$). However, there was no significant difference between COVID-19 positive and negative patients in sitting physical activity (PA), walking PA, moderate PA, and vigorous PA subscores of the IPAQ. Besides, the FCV-19S scores of COVID-19 positive patients were significantly higher ($p = 0.006$). On the other hand, EQ-5D-3L Index and EQ-5D-3L VAS scores were higher in the group with COVID-19 ($p_1 = 0.021$, $p_2 = 0.014$, respectively). There was no significant difference between patients with and without COVID-19 in terms of FSS, PSQI and CAS scores ($p > 0.05$) (Table 2).

The relationship of significant scores with other parameters in people with MS with COVID-19 was presented in Table 3. FCV-19S, which had a statistically significant difference between the two case groups, had a moderate correlation with EDSS ($r = -0.362$). On the other hand, FCV-19S was weakly correlated with BMI and PSQI ($r_1 = -0.314$, $r_2 = 0.218$, respectively). IPAQ-Total was moderately associated with MS duration, EDSS and FSS ($r_1 = -0.471$, $r_2 = -0.389$, $r_3 = -0.388$, respectively).

Moreover, the EQ-5D-3L Index was moderately correlated with FSS ($r_1 = -0.404$). There was a weakly significant relationship between EQ-5D-3L Index and BMI, MS duration, PSQI and CAS ($r_1 = -0.471$, $r_2 = -0.389$, $r_3 = -0.388$, $r_4 = -0.326$, respectively). On the other hand, EQ-5D-3L was moderately associated with VAS and EDSS and PSQI ($r_1 = -0.393$, $r = -0.357$, respectively). Finally, there was a weak correlation between EQ-5D-3L VAS and BMI, MS duration and FSS ($r_1 = -0.304$, $r_2 = -0.329$, $r_3 = -0.316$, respectively).

Table 2
The comparison of the scores between the groups.

	COVID-19 positive people with MS ($n = 46$) Mean ± SD	COVID-19 negative people with MS ($n = 58$) Mean ± SD	p
IPAQ - Total (MET min week−1)	1140.8 ± 1428.2	2331.3 ± 3811.9	0.014[a]
Sitting PA (MET min week−1)	355.6 ± 429.4	381.5 ± 369.4	0.156[a]
Walking PA (MET min week−1)	475.3 ± 525.0	912.0 ± 1134.4	0.069[a]
Moderate PA (MET min week−1)	27.1 ± 59.9	21.1 ± 43.1	0.481[a]
Vigorous PA (MET min week−1)	302.6 ± 926.6	1016.5 ± 3014.9	0.310[a]
EQ-5D-3L Index	0.81 ± 0.19	0.74 ± 0.18	0.021[a]
EQ-5D-3L VAS	80.5 ± 20.1	68.8 ± 21.3	0.014[a]
FSS	4.18 ± s1.3	4.6 ± 1.7	0.138[a]
PSQI	12.4 ± 2.2	12.6 ± 2.4	0.447[a]
FCV-19S	98.0 ± 20.4	85.8 ± 19.7	0.006[a]
CAS	0.93 ± 2.3	1.39 ± 3.0	0.775[a]

SD: standard deviation, **n:** number of patients, **IPAQ:** International Physical Activity Questionnaire-Short Form, **MET:** Metabolic equivalent, **PA:** Physical activity, **EQ-5D-3L index:** Index score of the EQ-5D-3L, **EQ-5D VAS:** Visual Analog Scale of the EQ-5D-3L, **FSS:** Fatigue Severity Scale, **PSQI:** Pittsburgh Sleep Quality Index, **FCV-19S:** Fear of COVID-19 Scale, **CAS:** Coronavirus Anxiety Scale, **a:** Mann–Whitney U test.

Table 3
The relationship of significant scores with other parameters in people with MS with COVID-19.

n: 46	FCV-19S	EQ-5D-3L Index	EQ-5D-3L VAS	IPAQ - Total
Age	-0.257	-0.156	-0.226	-0.245
BMI	-0.314*	-0.342*	-0.304*	-0.271
MS duration	-0.249	-0.292*	-0.329*	-0.471**
Relapse count	-0.207	-0.162	-0.199	0.088
EDSS	-0.362*	-0.245	-0.393**	-0.389**
FSS	-0.140	-0.404**	-0.316*	-0.388**
PSQI	-0.218*	-0.349*	-0.357**	-0.170
CAS	-0.097	-0.326*	-0.238	-0.144

SD: standard deviation, **n:** number of patients, **MS:** Multiple Sclerosis, **IPAQ:** International Physical Activity Questionnaire-Short Form, **EQ-5D-3L index:** Index score of the EQ-5D-3L, **EQ-5D VAS:** Visual Analog Scale of the EQ-5D-3L, **FSS:** Fatigue Severity Scale, **PSQI:** Pittsburgh Sleep Quality Index, **FCV-19S:** Fear of COVID-19 Scale, **CAS:** Coronavirus Anxiety Scale, **r:** Spearman correlation coefficient, *: $p < 0.05$, **:$p < 0.001$.

4. Discussion

The present research was aimed to demonstrate the effect of COVID-19 disease on fatigue, sleep quality, physical activity, quality of life, and psychological status in multiple sclerosis patients. Besides, our study examined the relationship between the significant parameters with other relevant clinical assessments in people with MS with COVID-19. To the best of our knowledge, no other studies examined the impact of COVID-19 disease-related fatigue, sleep quality, physical activity and other neuropsychiatric conditions in patients with MS. Some symptoms of people with MS that occur due to their disease are similar to the symptoms of the COVID-19 virus (Islam et al., 2020; Mazza et al., 2020). In this respect, it is unique to reveal how patients' clinical conditions are

affected by their symptoms and possible lifestyle changes. It will provide the current information on COVID-19 disease in people with MS. Our results showed that the level of physical activity decreased, and the level of fear associated with coronavirus increased in COVID-19 positive patients. However, compared with the COVID-19 negative case group, the quality of life was significantly higher in the positive cases. On the other hand, COVID-19 disease did not affect the sleep quality, fatigue and anxiety levels of the people with MS.

The most observed COVID-19 symptoms in current case reports and other comprehensive descriptive studies were neuropsychiatric and clinical symptoms such as sleep disturbance, decreased quality of life, reduced fatigue and fear or anxiety (Amdal et al., 2021; Vanichkachorn et al., 2021). On the other hand, we questioned the level of physical activity that both the quarantine and the cardiopulmonary symptoms related to the COVID-19 disease may have mainly affected.

Our results reported that patients with COVID-19 were less physically active than the negative case group. It is estimated that physical activity decreased in both groups during the quarantine period (Woods et al., 2020). However, the decrease was higher in COVID-19 positive people with MS was higher presumably due to the cardiopulmonary symptoms and neuropsychiatric changes. Besides, we assumed that a virus-induced fatigue effect might be related to physical activity based on correlation analysis.

Kalron et al. investigated the physical activity behaviors of people with MS during the COVID-19 period. Noting that MS or disease-modifying therapies do not adversely affect the morbidity of COVID-19, the researchers focused on the possibility of sedentary behaviors. The authors stated that 33.3% of the patients had decreased physical activity (Kalron et al., 2021). In our study, COVID-19 positive people with MS were compared with negative cases. The result of our study showed that the effects of the COVID-19 disease further reduce physical activity. Reguera-García, on the other hand, found the total score calculated by IPAQ in the patients in their sample 2614.7 ± 2472.40 Metabolic Equivalent of Task (MET) minutes per week. This mean value was found to be 2331.3 ± 3811.9 MET minutes per week in our sample. On the other hand, COVID-19 positive cases were reported to be 1140.8 ± 1428.2 min per week which is almost half the value of negative cases (Reguera-García et al., 2020). These numerical values reveal how much the physical activity levels of COVID-19 positive individuals are highly affected.

Considering the neuropsychiatric changes, COVID-19 positive cases had fears related to coronavirus. However, this situation was not at the level of anxiety. Although the FVC-19S and CAS are similar to each other, these questionnaires contain different questions. In the Coronavirus Anxiety Scale, it is examined whether the situation has reached the grade of anxiety beyond fear, terms such as feeling "paralyzed", "faint", "nauseous" related to COVID-19. Besides, correlational analysis revealed that fears of the patients might have also affected the sleep quality of the patients. Ramezani et al. emphasized that the COVID-19 pandemic causes depression in people with MS with a history of neuropsychiatric disorders, and elderly people with MS are more prone to anxiety. It was emphasized that anxiety was not present, especially in young and educated individuals (Ramezani et al., 2021). The fact that individuals with COVID-19 disease have more fears and similar anxiety in our study can be attributed to the fact that the cases are young and have high academic backgrounds. However, Yunier et al. reported that patients with positive MS had more fear and anxiety associated with COVID-19. It was indicated that the factors causing this situation might have been caused by the subjective experiences of the patients and the limitations of access to medical care (Yunier et al., 2021). Since our cases were followed up with comprehensive telemedicine during the pandemic period, we interpreted that their fears may not have reached the level of anxiety.

Quality of life was another parameter that showed differences in the two case groups. The group of patients with COVID-19 had an unexpectedly higher quality of life. We presumed that one of the biggest reasons for this significance might be that the patients behaved more carefully in their nutrition and daily care activities. Besides, COVID-19 progressed with milder symptoms in this age group with an average of 39 and may not have affected the quality of life in the short term. On the other hand, potential occupational reasons should not be ignored. The study was conducted in a large city, and most cases were young and active working adults. We emphasized that the impact of the work-life, transportation in the big city, and the emotional, cognitive and physical burden brought by business life on the quality of life may be more than the impact of the coronavirus on the quality of life. Because in our country, COVID-19 positive cases remained in quarantine for at least 14 days. During this period, positive cases stayed away from occupational-based physical and mental stress. The latest study revealed the negative effect on the quality of life in patients with MS during the pandemic period. In another prospective cohort study, it was stated that quality of life was not affected in patients with MS during the era. However, we could not compare our results with other case-control studies, as our study compared positive and negative cases for the first time in terms of relevant parameters. On the other hand, it should be kept in mind that the quality of life is a parameter that cannot be affected in a short time.

There was no difference between the two groups in terms of fatigue and sleep quality. It has been revealed that COVID-19 disease causes fatigue and sleep disorders (Barzegar et al., 2021). However, in our relatively young MS sample, the results of these two parameters did not differ with the negative case group. A current regression model should be established to more precisely consider sleep quality and fatigue that may affect COVID-19 positive people with MS. Caravaca et al. showed that quarantine of COVID-19 worsened the sleep quality of people with MS (Andreu-Caravaca et al., 2021). Another research determined that the COVID-19 pandemic in patients with relapsing-remitting multiple sclerosis was associated with reduced sleep quality and fatigue (Motolese et al., 2020). In our study design, we interpreted that the COVID-19 disease may not have a direct effect since negative-positive patients were compared. In other words, by looking at the other two studies, these parameters might have decreased in both groups only due to quarantine.

In correlational relationships, it was determined that physical activity was associated with MS duration, EDSS and fatigue. In other words, as the chronicity and severity of MS disease and fatigue in patients increased, the physical activity levels of individuals decreased. We reported that physical activity, which was observed to be lower in the group with COVID-19, may have been more affected in patients with a worse MS prognosis. On the other hand, quality of life was associated with BMI, MS duration, MS severity, fatigue, and sleep quality. COVID-19-related fear was associated with BMI, EDSS, and sleep quality. Although the relationship between these parameters was expected, we could not analyze the relationship with COVID-19 in detail since we did not perform a causality analysis.

4.1. Limitations

Some limitations of the study must be acknowledged. First, patients' COVID-19 related clinical examination could not be comprehensively demonstrated, as there was no standardized tool to show the severity of COVID-19. Suppose to have such a numerical or categorical variable, evaluating the current evaluation parameters with regression analysis within the scope of causality could make a more significant contribution to clinical practice. Secondly, it could create a regression model between existing parameters related to COVID-19 and other parameters predicted to be in a causal relationship. Moreover, we considered that the regression analysis of the current sample (COVID-19 positive = 46) did not have a sufficient sample size and that the regression model might not provide satisfactory results. Therefore, future studies can create a comprehensive regression model with a larger sample. Finally, evaluating patients at two separate times with a longitudinal evaluation model, and addressing their results more comprehensively, may provide

a longer-term symptom follow-up.

5. Conclusions

In conclusion, COVID-19 negatively affected the MS patient's physical activity and coronavirus related fear parameters. However, the causality of this influence should be investigated, and the long-term consequences of neuropsychiatric connections and physical inactivity should be focused on.

Ethical approval

The study was carried out in accordance with the ethical principles and the Helsinki Declaration. Informed consent of the patients was obtained. The study protocol was approved by the ethics committee of Ege University (No:21-6T/8).

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CRediT authorship contribution statement

Mehmet Özkeskin: Conceptualization, Investigation, Methodology, Writing – original draft. **Fatih Özden:** Conceptualization, Methodology, Writing – original draft. **Bedriye Karaman:** Investigation, Writing – review & editing. **Özgül Ekmekçi:** Investigation, Writing – review & editing. **Nur Yüceyar:** Investigation, Writing – review & editing.

Declaration of competing interest

The authors report no conflicts of interest and certify that no funding has been received for this study and/or preparation of this manuscript.

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