#### **ORIGINAL ARTICLE**



# Reliability and validity of the glittre activities of daily living test in fully ambulatory multiple sclerosis patients

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## Abstract

**Background** Evaluation of activities of daily living (ADL) and functional exercise capacity in patients with multiple sclerosis (pwMS) is crucial in demonstrating the effectiveness of interventions.

Aims To investigate the reliability and validity of the Glittre ADL Test in pwMS.

**Methods** Twenty-five pwMS and 26 healthy adults were included in this methodological study. The Glittre ADL Test was applied. Six-Minute Walk Test (6MWT) and Nottingham Extended Activities of Daily Living Index (NEADL) were applied for concurrent validity. Expanded Disability Status Scale (EDSS), Fatigue Severity Scale (FSS), Mini Balance Evaluation Systems Test (Mini BESTest), Multiple Sclerosis Quality of Life Scale-54 (MSQoL-54), and Five Times Sit-to-Stand Test (5 STST) were applied for construct validity. The Glittre ADL Test was repeated after 3–6 days for test–retest reliability. **Results** The test–retest reliability of the Glittre ADL Test was excellent (ICC = 0.941). There was strong correlation of the Glittre ADL Test with 6MWT (rho = -0.710, p < 0.001), NEADL (rho = -0.841, p < 0.001), EDSS, (rho = 0.836,

the Glittle ADL Test with 0MW 1 (hlo = -0.710, p < 0.001), NEADL (hlo = -0.841, p < 0.001), EDSS, (hlo = 0.830, p = <0.001), Mini BESTest (rho = 0.792, p < 0.001), and 5 STST scores (rho = 0.720, p < 0.001). There was a moderate correlation between the Glittre ADL Test and the physical health sub-item score of the MSQoL-54 (rho = -0.591, p = 0.002). No correlation was found between the Glittre ADL Test and FSS (rho = 0.348, p = 0.096). There was a difference in the Glittre ADL Test results between the pwMS and the healthy adults (p = 0.001).

**Conclusions** The Glittre ADL Test has excellent reliability and strong construct and criterion validity for assessing functional exercise capacity and ADL in fully ambulatory pwMS.

Trial registration TRN: NCT04182269

Keywords Aerobic capacity · Functional exercise capacity · Glittre activities of daily living test · Multiple sclerosis

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# Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease characterized by demyelination and axonal loss in the central nervous system (CNS) [1]. Spasticity, fatigue, loss of muscle strength, tremor, balance problems, exercise intolerance, and cognitive abnormalities are some of the clinical symptoms of MS [2]. Patients' daily living activities are negatively impacted by symptoms, resulting in a decrease in their quality of life [3]. Furthermore, a decrease in MS patients' functional exercise capacity as a result of a reduction in physical activity levels is another factor that contributes to limitations in daily living activities [4–6].

To evaluate functional exercise capacity, a variety of assessment methods are used [7]. Maximal cardiopulmonary exercise tests (CPET) are considered the gold standard among these tests [8]. Furthermore, submaximal exercise tests are used to assess functional exercise capacity. As most activities of daily living (ADL) are performed at a submaximal level, submaximal tests can better determine individuals' functional levels in these activities [9]. The 6-Minute Walk Test (6MWT) is the submaximal exercise test used most commonly in patients with multiple sclerosis (pwMS). However, it only evaluates lower extremity functions. In addition to lower extremity dysfunctions, upper extremity dysfunction is also quite common in pwMS. This situation further increases the limitation in daily living activities and causes a decrease in the quality of life of the patients [10]. Therefore, there is a need for a test that considers the upper extremity.

The Glittre ADL Test was developed to measure functional exercise capacity in chronic obstructive pulmonary disease (COPD) patients by selecting tasks that are similar to the ADL that patients have the most difficulty with in their daily lives [11, 12]. Moreover, it has been established that the Glittre ADL Test is valid and reliable across a wide range of systemic and neurological illnesses [13–20].

The purpose of the present study was to investigate the test-retest reliability, criterion, and construct validity of the Glittre ADL Test in assessing functional exercise capacity and ADL in pwMS.

## Methods

#### Participants

This study was conducted at Hacettepe University, Faculty of Physical Therapy. Twenty-five pwMS and age-/sexmatched 26 healthy volunteers were included present study. All participants signed the written informed consent form before the study. The study was carried out in accordance with the Declaration of Helsinki's Ethical Rules, and the local ethics committee granted approval (GO 18/856-24). The eligibility criteria were as follows: (1) being between the ages of 18 and 65, (2) having relapsing-remitting multiple sclerosis (RRMS) type MS, (3) having a maximum score of 4 from the Expanded Disability Status Scale (EDSS), (4) not changing medication in the last 6 months, (5) not having an attack in the last 3 months, (6) getting more than 24 points from the Standardized Mini Mental Status Test. The exclusion criteria were as follows: (1) using a walking aid or orthosis, (2) having a neurological disease other than MS, (3) having orthopedic or rheumatologic problems that will affect function, (4) having a peripheral vestibular problem, (5) having a cardiovascular or pulmonary disease. The inclusion criterion for healthy participants was the absence of any known disease and the agreement to participate in the study voluntarily.

#### **Outcome measurements**

To avoid fatigue, the participants' evaluations were conducted on two different days at similar intensities. With the supervision of a physical therapist, the participants completed performancebased and self-report evaluations. The evaluations included the Glittre ADL Test [11], 6MWT [9], Nottingham Extended Activity of Daily Living Index (NEADL) [21], Fatigue Severity Scale (FSS) [22], Mini Balance Evaluation Systems Test (Mini BESTest) [23, 24], Multiple Sclerosis Quality of Life Scale-54 (MSQoL-54) [25], and Five Times Sit-to-Stand Test (5 STST) [26]. Furthermore, the Glittre ADL Test was administered twice on the same day with a half-hour interval to determine whether there was a learning effect. The results of the second Glittre ADL Test from these two assessments were used in the analysis of validity and reliability, as well as in the analysis of construct validity. For reliability analysis, the Glittre ADL Test was repeated 3-6 days later.

#### Glittre activities of daily living test

The Glittre ADL Test was used to evaluate functional exercise capacity. This test, as described by Skumlien et al. [11], consists of the following tasks: walking over a flat surface, stair ascending and descending, transferring objects from one shelf to another (as well as placing them on the floor and back on the shelves), and rising from and sitting in a chair. The female participants carried a 2.5-kg backpack, whereas the male participants carried a 5.0-kg backpack. The participants' dyspnea, heart rate, blood pressure, and oxygen saturation were measured before the test, and as soon as the test was over the time taken to complete it was recorded [11]. The reference equation developed by Reis et al. [27] was used to calculate the normal values of the Glittre ADL Test in healthy individuals.

#### Six-minute walk test (6MWT)

The 6MWT was used as a criterion measure to assess functional exercise capacity. Following resting measures, the 6MWT was performed according to the standards of the American Thoracic Society [9]. Blood pressure, heart rate, oxygen saturation, dyspnea, and perception of fatigue were all measured before and after the test, and the total distance walked was recorded. The reference equation developed by Gibbons et al. [28] was used to calculate the expected 6MWT distance.

#### Nottingham extended activity of daily living index (NEADL)

The NEADL was used as a criterion measure to assess activities of daily living. The scale consists of 22 questions. The participants answered questions by choosing from the following options: "on your own" (3 points), "on your own with difficulty" (2 points), "with help" (1 point), and "not at all" (0 points). The highest score is 66. Low points indicate an increased limitation in ADL [21, 29].

#### Fatigue severity scale (FSS)

The FSS consists of 9 items and each item is scored between 1 and 7 (1 indicates "strongly disagree," 7 indicates "strongly agree"). The FSS score was calculated by adding all points from items and averaging. A high score indicates increased severity of fatigue [22, 30].

#### Mini balance evaluation systems test (Mini BESTest)

The Mini BESTest consists of 4 subscales, namely preparatory movement, reactive postural control, sensory orientation, and dynamic walking, and a total of 14 items. Each tested condition is given 1 to 3 points (0, severe; 1, moderate; and 2, normal) according to the patients' performance in the tested situation. The highest score that can be obtained from the test is 28. A decrease in the score obtained from the test indicates a worsening in physical condition [23].

#### Multiple sclerosis quality of life scale-54 (MSQoL-54)

This scale consists of 14 subscales and 54 items. Subscales that give information about the physical and mental states are grouped and two separate point totals are obtained as physical and mental health composite scores. While 100 points represent the best condition, 0 points represent the worst [25]. Only the physical health sub-item score of the MSQoL-54 scale was used in the analyses since functional exercise capacity assessment is our primary measurement.

#### Five times sit-to-stand test (5 STST)

This test is used to evaluate the lower extremity's general muscle strength. It was carried out using the protocol specified by Moller et al. [26]. The participants, who were sitting on a chair without arm support with their arms crossed on their chest, were asked to stand up and sit down 5 times and to do the test as fast as they could. A manually controlled electronic stopwatch was used to record the time it took to complete the test.

## Statistical analysis

Statistical analysis of the data was performed with SPSS (IBM SPSS Statistics 23). Normality tests were performed. As descriptive statistics, mean and standard deviation were given if the numerical variables met the normal distribution conditions, while median and minimum–maximum values were given if they did not, and frequency and percentage

values were given for the qualitative variables. For the statistical analysis of the data obtained from the study, the level of significance was set at 0.05.

*Test–retest reliability:* test–retest reliability was evaluated with the intraclass correlation coefficient (ICC).

## **Criterion validity**

- Concurrent validity: the relationship between the time to complete the Glittre ADL Test and the total distance covered in the 6MWT and NEADL was determined by Spearman's correlation analysis.
- 2 Predictive validity: the performance of the Glittre ADL Test in differentiating different subgroups of MS [(mild: EDSS ≤ 2) and (moderate: EDSS 2.5–4)] was examined. For this purpose, receiver operating characteristic (ROC) analysis was performed. The area under the ROC curve was calculated [(area under the curve (AUC)]. An AUC of 0.50 indicated non-sensitivity, while an AUC of 1.00 indicated perfect sensitivity and specificity [31].

**Construct validity** construct validity was investigated with hypothesis tests. The relationships between the time to complete the Glittre ADL Test and the EDSS, FSS, Mini BESTest, physical health sub-item of the MSQoL-54, and 5 STST assessment scores were analyzed by Spearman's correlation analysis. The classification described by Dancey and Reidy was used to interpret the strength of the correlations  $(0.1-0.3 = \text{weak correlation}, 0.4-0.6 = \text{moderate correlation}, \geq 0.7 = \text{strong correlation} [32].$ 

Known group validity the difference between the completion times of the Glittre ADL Test of the patient and healthy control groups was compared using the Mann–Whitney U Test.

## Results

The study was completed with 51 participants, 25 pwMS with a maximum EDSS score of 4 (MS group), and 26 healthy individuals (HC group). There was no difference in baseline characteristics between the groups (p > 0.05) (Table 1). It was determined that the study was completed with 97% power according to the post hoc power analysis.

## Learning effect

When the first and second Glittre ADL Test results obtained on the same day were compared, it was found that the second test  $(2.96 \pm 0.72)$  took less time to perform than the first  $(3.28 \pm 0.82)$  (p < 0.001). This result showed that a learning effect occurred with the second application of the Glittre ADL Test. The results of the second test were used in all statistics.

	MS group $(n=25)$		HC group $(n=26)$		р
	$\overline{\overline{X}}\pm S$	$\widetilde{X}(\min-\max)$	$\overline{\overline{X}}\pm S$	$\widetilde{X}(\min-\max)$	
Age (years)	$33.36 \pm 8.50$	34 (22–54)	$33.46 \pm 8.47$	33.5 (22–50)	0.966 <sup>a</sup>
Height (cm)	$170.24 \pm 11.52$	168 (152–190)	$166.46 \pm 8.65$	166 (151–190)	0.190 <sup>a</sup>
Body weight (kg)	$66.54 \pm 10.84$	65 (50–92)	$68.42 \pm 11.40$	68 (50-90)	0.549 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	$23.02 \pm 3.54$	22.71 (17.99-32.04)	$24.67 \pm 3.47$	24.94 (16.91-32.03)	0.098 <sup>a</sup>
Disease duration (years)	$5.75 \pm 5.39$	4 (0.17–21)			
EDSS (0-10)	$2.28 \pm 1.09$	2 (1-4)			

Table 1 Characteristics and anthropometric profile of the participants

 $\overline{X}\pm S$ , Mean  $\pm$  Standard Deviation,  $\widetilde{X}$  (min–max), Median (minimum–maximum), p, Statistical Significance Level <sup>a</sup>Independent Samples t Test, *BMI* Body Mass Index, *EDSS*, Expanded Disability Status Scale

# **Test-retest reliability**

Reliability was excellent between the second measurement of the Glittre ADL Test and the third measurement repeated 3-6 days apart (ICC = 0.941, p < 0.001) (Table 2).

# **Criterion validity**

# **Concurrent validity**

There was a strong negative correlation between the time the patients took to complete the Glittre ADL Test and the total distance covered in the 6MWT (rho = -0.710, p < 0.001). Strong correlations were found between the Glittre ADL Test and NEADL (rho = -0.841, p < 0.001).

## **Predictive validity**

In the ROC analysis performed according to the completion times of the Glittre ADL Test in pwMS, the AUC value was 0.961 and statistically significant (p < 0.001). With this result, it was determined that the Glittre ADL Test had a high discrimination level for mild and moderate pwMS according to the level of neurological impairment. As a result of this analysis, the recommended cutoff value was

chosen as 2.79 min, with 92% sensitivity and 90% specificity, according to the Youden Index [33] (Fig. 1).

# **Construct validity**

Strong correlations were found between the Glittre ADL Test and the EDSS (rho=0.836, p < 0.001), Mini BESTest (rho=0.792, p < 0.001), and 5 STST (rho=0.720, p < 0.001) and a moderate correlation between it and the physical health sub-item of the MSQoL-54 (rho=-0.591, p=0.002). No correlation was found between the Glittre ADL Test and the FSS (rho=0.348, p=0.096). Of the 5 hypotheses we established, 4 were confirmed (80%). Construct validity of the test was confirmed as more than 75% of the results were consistent with our hypotheses [34] (Table 3).

# **Known group validity**

According to the results for the Glittre ADL Test completion times, a difference was found between the MS and HC groups (p = 0.001). Accordingly, the time to complete the Glittre ADL Test was shorter in healthy participants than in pwMS.

Table 2Reliability analysisof the Glittre ADL Test in themultiple sclerosis group andhealthy control group

	MS group		HC group		
	$\overline{X} \pm S$	$\widetilde{X}(\min-\max)$	$\overline{\overline{X}} \pm S$	$\widetilde{X}(\min-\max)$	
Glittre ADL Test 2 (min)	$2.96 \pm 0.72$	2.55 (2.25-4.39)	$2.36 \pm 0.29$	2.34 (1.58-3.10)	
Glittre ADL Test 3 (min)	$2.84 \pm 0.64$	2.50 (2.22-4.04)	$2.38 \pm 0.39$	2.35 (1.55-3.15)	
р		< 0.001 <sup>a</sup>		< 0.001 <sup>a</sup>	
rho		0.918		0.941	
ICC	0.941		0.843		

 $\overline{X}\pm$ S, Mean $\pm$ standard Deviation,  $\widetilde{X}$  (min–max), Median (minimum–maximum), *HC* Healthy Control, *Glittre ADL Test* Glittre Activities of Daily Living Test, *min* Minute, *p* Statistical Significance Level, *r* Correlation Coefficient, *ICC* Intraclass Correlation Coefficient

<sup>a</sup>Spearman's correlation analysis

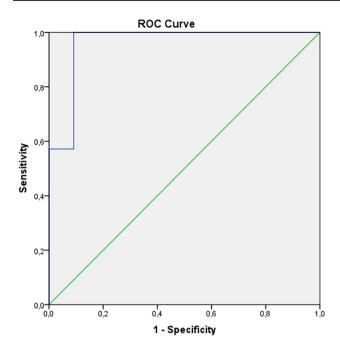


Fig. 1 ROC curves for predicting mild to moderate disability level

The time to complete the Glittre ADL Test in the MS group was longer than the expected values calculated according to the age and BMI of healthy individuals [27]. In the control group, the results were closer to the expected values. In addition, there was a statistically significant difference between the percentages of the groups reaching the 6MWT expected values [28] (p < 0.05) (Table 4).

## Discussion

In our study, the Glittre ADL Test had excellent reliability and strong validity for assessing functional exercise capacity and ADL in pwMS. 2383

 Table 4
 Comparison of percentages of Glittre ADL Test and 6MWT

 relative to predicted values between groups

	MS group ( $n = 25$ )		HC group $(n=26)$		р
	$\overline{X} \pm S$	$\widetilde{X}(\min - \max)$	$\overline{X} \pm S$	$\widetilde{X}(\min - \max)$	
Glittre ADL Test (% of pre- dicted)	118±28	107 (84–168	)93±11	93 (63–118)	<0.001 <sup>a</sup>
6MWT (% of pre- dicted)	74±10	76 (46–89)	83±9	82 (70–105)	0.001 <sup>b</sup>

 $\overline{X}\pm$ S, Mean  $\pm$  Standard Deviation,  $\widetilde{X}$  (min–max), Median (minimum– maximum), *HC* Healthy Control, *Glittre ADL Test*, Glittre Activities of Daily Living Test, *6MWL* 6-Minute Walk Test, *p* Statistical Significance Level

<sup>a</sup>Mann–Whitney U Test

<sup>b</sup>independent samples *t* test

In different patient groups in which the validity and reliability of the Glittre ADL Test were investigated, it is recommended that the test should be performed twice for a reliable measurement since the test has a learning effect [16, 19]. Similar to the aforementioned studies, in the present study, it was determined that the test had a learning effect because the completion times of the Glittre ADL Test that was performed for the second time were better than the first application times, and it was more appropriate to perform the Glittre ADL Test twice in pwMS for a more reliable evaluation.

In the literature, it is reported that the Glittre ADL Test performances of patients with scleroderma [35], Parkinson's disease [20], leprosy [17], COPD [36], and cystic fibrosis [13] are worse than those of healthy individuals. Similar to previous studies, in our study, the pwMS took longer to complete the Glittre ADL Test compared to the healthy controls. In addition, it was determined in the present study that the Glittre ADL Test can distinguish pwMS

Table 3Correlations of theGlittre ADL Test and 6MWTwith the EDSS, NEADL, FSS,Mini BESTest, MSQoL-54, and5TSTS

		EDSS	NEADL	FSS	Mini BESTest	MSQoL-54 Physical Health	5 STST
Glittre	rho	0.836**	-0.841**	0.348	-0.792**	-0.591*	0.720**
ADL Test	p	< 0.001	< 0.001	0.096	< 0.001	0.002	< 0.001
6MWT	rho	-0.811**	0.632*	-0.368	0.694**	0.531*	-0.722**
	р	< 0.001	0.001	0.077	< 0.001	0.008	< 0.001

*Glittre ADL Test*, Glittre Activities of Daily Living Test, *6MWL* 6-Minute Walk Test, *EDSS* Expanded Disability Status Scale, *NEADL* Nottingham Activities of Daily Living Index, *FSS* Fatigue Severity Scale, *Mini BESTest* Mini Balance Evaluation Test, *MSQoL-54* Multiple Sclerosis Quality of Life Scale-54, *5 STST* Five Times Sit-to-Stand Test

\*Spearman's correlation is significant (p < 0.05)

\*\*Spearman's correlation is significant (p < 0.001)

as mildly and moderately impaired according to the level of neurological impairment. Patients with severe impairment according to the EDSS score were not included in our study. For this reason, the ability of the Glittre ADL Test to distinguish severe impairment from low and moderate impairment can be investigated in future studies. In addition, only RRMS-type pwMS were included in our study. The predictive value of the test in progressive MS forms is unknown. Likewise, Goldman et al. [37] determined that 6MWT can categorize pwMS as mild, moderate, and severe according to the level of neurological impairment. In RRMS-type pwMS with an EDSS score of 4 or below, the test was conducted safely and without any modifications to its administration.

In addition to these results, in our study, the Glittre ADL Test reflected the performance of pwMS in ADL, as in heart failure patients [38] and COPD [12]. Moreover, the Glittre ADL Test could better reflect the performance in ADL than the 6MWT. Since our study was the first in the literature to use the Glittre ADL test in pwMS, this result could not be compared with other studies in pwMS. However, similarly, Driehuis et al. [39] determined that there was a relationship between aerobic capacity and the level of independence in daily living activities inside and outside the home in pwMS with fatigue complaints. In another study, Savc1 et al. [40] reported that the limitation in ADL in pwMS is related to functional exercise capacity and that the 6MWT can provide better information than maximum oxygen consumption about the performance of pwMS in their daily activities. Solway et al. [41] also examined functional walking tests and found that among tests such as the 6MWT, 12MWT, 2MWT, and Shuttle walking test, the test that best reflects performance in ADL is the 6MWT. Hena et al. [42] stated that the Glittre ADL Test could provide a more appropriate assessment than the 6MWT in the evaluation of functional capacity and ADL in patients with bronchiectasis. This result reported by Hena et al. [42] was similar to ours. The advantage of the 6MWT is that it requires less material compared to the Glittre ADL Test. However, The Glittre ADL Test can provide more information about daily living activities because it includes many daily life activities such as sitting, standing, going up and down stairs, reaching, and object manipulation, as well as walking.

In our study, there was a relationship between the Glittre ADL Test and 6MWT and balance and the increase in balance disorders of the patients negatively affected their functional exercise capacity. There are many studies in the literature showing the relationship between walking performance and balance in pwMS [43–45]. These studies support our results. Moreover, in our study, the correlation between the Mini BESTest and Glittre ADL Test was higher than the correlation with 6MWT. This difference may be explained by the fact that the Glittre ADL Test includes more activities that affect balance such as climbing down stairs, crouching, sitting, and standing up. In this respect, it can be considered that the Glittre ADL Test may reflect additional problems related to balance, apart from gait disorders.

According to research, MS patients' quality of life is lower than that of healthy individuals [46]. However, it is critical to identify the factors associated with a decrease in quality of life. Studies have reported that there is a relationship between HRQoL and depression, fatigue, psychological distress, and cognitive disorders [46, 47]. Numerous other disease-related factors, such as the severity of the disability or the type of MS, as well as personal factors like education and age, can have an impact on HRQoL [46]. There was a moderate correlation between both the Glittre ADL Test and 6MWT with a physical health sub-item score of MSQoL-54 in our study. In addition to the psychological factors that affect the quality of life, in our study, the relationship between quality of life with aerobic capacity was investigated using only the physical health sub-item of the MSQoL-54. The beneficial impact of exercise approaches on quality of life can be used to support the relationship that we identified [48].

In our study, there was also a correlation between the time to complete the Glittre ADL Test and the time to complete 5 STST in our pwMS. The functional evaluation of both tests, their dependence on speed, the fact that the Glittre ADL Test includes sitting and standing activities of the patient, and different activities that require lower extremity muscle strength can explain this relationship. In addition, there was a correlation between the total distance covered in the 6MWT and the completion time of 5 STST. The fact that walking performance is also related to lower extremity muscle strength can explain the relationship between the two tests. Similar to the findings in our study, other studies have also determined that there is a relationship between lower extremity muscle strength and walking performance, and functional capacity of the lower extremity in pwMS [44, 49].

There are some limitations to our study. One of these is that there was only one evaluator in our study and therefore inter-rater reliability could not be evaluated. In addition, since the Glittre ADL Test includes upper extremity functions, another limitation is that the relationship between test performance and upper extremity functions was not examined. In addition, it should be noted that our study was conducted only in RRMS-type and in pwMS who scored 4 or less according to the EDSS. Our results should not be generalized to all pwMS.

# Conclusion

The Glittre ADL Test is a valid and reliable method for the evaluation of the functional exercise capacities and ADL of pwMS. Glittre ADL Test is a submaximal exercise test that does not require expensive materials, is easy to apply, and can be completed in a short time. The advantage of the Glittre ADL Test is that it includes activities that require the use of both the upper and lower extremities. The Glittre ADL Test provides a compherensive evaluation of patients since pwMS can have impairments in both their upper and lower extremities. Another favor of the Glittre ADL Test is that it includes several activities that are similar to daily living activities, in comparison to other functional exercise tests. However, due to the learning effect, it would be more appropriate to perform the Glittre ADL Test twice for an appropriate assessment of pwMS.

Author contribution Conceptualization: Gözde Kaya, Nezire Köse, Yeliz Salcı; methodology: Gözde Kaya, Nezire Köse, Yeliz Salcı, Aslı Tuncer, Rana Karabudak; formal analysis and investigation: Gözde Kaya, Nezire Köse, Yeliz Salcı, Jale Karakaya; writing—original draft preparation: Gözde Kaya, Nezire Köse, Yeliz Salcı; writing review and editing: Gözde Kaya, Nezire Köse, Yeliz Salcı; resources: Aslı Tuncer, Rana Karabudak; supervision: Nezire Köse, Yeliz Salcı, Kadriye Armutlu.

**Data Availability** The data that support the findings of this study are available from the corresponding author, [G.K.], upon reasonable request.

## Declarations

Conflict of interest The authors declare no competing interests.

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