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Health-related quality of life and parental depression in children with pulmonary arterial hypertension

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Abstract

Background: Impaired health-related quality of life (HRQoL) is a common problem in pulmonary arterial hypertension (PAH), but there is limited data on HRQoL in children with PAH. We aimed to investigate the QoL, determine the potential risk factors for poor HRQoL in children with PAH, and assess the depression and anxiety of their families.

Methods: We performed a prospective cross-sectional study of children with PAH, healthy peers, and their parents. HRQoL was measured by the self-reported and age-adapted KINDL questionnaire. Beck Depression Inventory (BDI) and hospital anxiety and depression scale (HADS) were used to assess the depression and anxiety of parents.

Results: Children with PAH had statistically lower total HRQoL scores than healthy peers ($p < 0.001$). There was no correlation between HRQoL and duration of disease, World Health Organization functional class, pro-B-type natriuretic peptide, 6-min walk test, and combined or single treatment. BDI and HADS scores were significantly higher in the parents of patients ($p < 0.001$, $p = 0.023$, $p < 0.001$, respectively). There was a negative correlation between HRQoL and BDI in patients ($p = 0.016$), while there was no significant correlation between HRQoL and HADS ($p > 0.05$).

Conclusion: We demonstrated impairment of HRQoL of children with PAH. In addition, there was a correlation between the depression of the families and the QoL of the children.

KEYWORDS

children, depression, KINDL-R, pulmonary arterial hypertension, quality of life

1 | INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronic and progressive disease characterized by increased pulmonary artery pressure and pulmonary vascular resistance. It can be seen in any age with different etiologies.[1,2] Regardless of the etiology, common symptoms, such as dyspnea, fatigue, dizziness, chest pain, and palpitations restrict patients' physical activities and daily life. These restrictions may negatively affect the emotional state of patients.[3,4]

Although recent advances in early diagnosis and treatment have improved the prognosis of PAH,[5] the long-term use and adverse effects of the drugs (nausea, vomiting, diarrhea, chest pain, peripheral edema, headache, joint and muscle pain, etc.), chronic and progressive course of the disease even with treatment adversely affect the health-related quality of life (HRQoL) of patients.[6] Frequent hospitalizations, limitations in daily activities, interruption of school life, and decrease in social interaction affect all aspects of patients' lives negatively (e.g., emotional, physical, social).[6] All these difficult

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processes can cause social isolation by negatively affecting the relationships of children with their families and friends. Furthermore, psychological problems are faced not only by the patients but also by the families. Long and tiring follow-up and treatment processes, the progression of the disease, financial problems can be challenging for families. Parents who focus on the treatment of their children may not be aware of their own emotional problems. While the physical consequences of the disease are closely monitored by clinicians, the psychological consequences are often overlooked.

With the treatments developed in recent years, the majority of pediatric patients with PAH can reach adulthood.[5,7] After demonstrating the relationship between QoL and survival, the QoL has become important for clinicians as well as patients.[8,9]

While there are many adult studies on QoL in PAH,[10,11] limited data exist regarding QoL in children with PAH.[12,13]

The current study mainly aimed to investigate the QoL and determine the potential risk factors for poor HRQoL in children with PAH. Second, we aimed to assess the relationship between families' depression and anxiety and children's QoL.

2 | MATERIALS AND METHODS

This study employed a prospective cross-sectional design. We enrolled patients under 18 years followed up with PAH between March 2019 and March 2020. PAH was defined as mean pulmonary artery pressure ≥ 25 mmHg, pulmonary capillary wedge pressure ≤ 15 mmHg, and pulmonary vascular resistance index ≥ 3 WU·m^2, measured by right heart catheterization.[14] Only patients who underwent right heart cardiac catheterization were enrolled as patients.

Exclusion criteria were defined as patients who had diseases that cause developmental delay or cognitive impairment, such as Down syndrome, patients under 4 years old, patients who did not complete the questionnaire, and patients who did not provide consent.

The control group consisted of healthy children who applied to the outpatient clinic with an innocent murmur, did not have any chronic disease, did not take any medications, and had normal physical examinations and echocardiogram. Nineteen patients and healthy peers, and one of their parents were included in the study.

We reviewed the medical records to obtain demographic characteristics, cardiac hemodynamic measurements, and treatments received. World Health Organization functional class (WHO-FC) (WHO-FC I, no symptoms of PAH (dyspnea, fatigue, chest pain, syncope, etc.) with exercise or at rest; WHO-FC II, no symptoms at rest but a slight limitation of physical activity; WHO-FC III, may not have symptoms at rest but a marked limitation of physical activity; WHO-FC IV, symptoms at rest and severe symptoms with any activity),[15] 6-minute walk test (6MWT), pro-B-type natriuretic peptide (proBNP), vitamin D, hemoglobin, and echocardiographic findings were evaluated when patients filled out the questionnaire at the follow-up visits.

This study was approved by the local Ethics Committee. Informed consent was obtained from all participants.

2.1 | Health-related quality of life

HRQoL was evaluated with KINDL-R which was originally designed in German and translated into several languages. In the current study, the Turkish version of the KINDL-R was used.[16] Questionnaire (KINDL-R) assesses QoL in six different domains: physical and emotional well-being, self-esteem, family, friends, and everyday functioning each of them including four items. Each item in the test is 5-point Likert-scaled (positively worded items: never scores 1 and always scores 5; negatively worded items: never scores 5 and always scores 1). From the item scores, the total Kid-KINDL score and each dimension score can be calculated and transformed into a 0–100 result where a higher score represents better QoL.[17]

There are three versions of the KINDL based on self-report used according to the determined age groups. Additionally, each version of the questionnaire can be completed both by children and adolescents and also by their parents.

In this study, self-report all versions are used: KiddyKINDL for children aged 4–6 years, KidKINDL for aged 7–13 years, and KiddoKINDL for aged 14–17 years.[16]

2.2 | Anxiety and depression score

The Beck Depression Inventory (BDI) and hospital anxiety and depression scale (HADS) questionnaires were administered to one of the family members of the participants to evaluate the depression and anxiety of the parents.

BDI was used for assessing the presence and severity of parents' depression. BDI includes 21 items, each including four alternative statements ranging in order of severity from 0 to 3. The statements express feelings common in depression (e.g., guilty, punishment feelings, self-dislike, changes in the sleeping pattern). Higher scores indicate greater symptom severity. BDI scores ranging from 0 to 13 indicate normal—minimal depressive levels; scores ranging from 14 to 18 indicate mild—moderate depressive levels; scores ranging from 19 to 29 indicate moderate—severe depressive levels; scores ranging from 30 to 63 indicate extremely severe depressive levels. Scores below 12 are not considered clinically significant.[18]

HADS was used to assessing the anxiety and depression of parents.[19] It is divided into two scales including seven items each for the screening of depression and anxiety. The total scores for depression and anxiety range between 0 and 21. Scores ≥8 represent symptoms of depression while ≥10 for anxiety. Higher scores indicate greater depression and/or anxiety.[20,21]

2.3 | Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) Version 15.0 (SPSS Inc). Continuous data were presented as means with standard deviation or medians with minimum and maximum values. Categorical data were presented as

frequencies and percentages. Continuous variables were tested for normal distribution using the Shapiro–Wilk test. Two dependent groups were compared using the independent sample *t*-test for normal distributions and Mann–Whitney U-test for nonnormal distributions. Correlation coefficients (*r*) were calculated using the Pearson correlation test or Spearman's rank test. A two-sided $p < 0.05$ was considered statistically significant for all analyses.

3 | RESULTS

There were 26 patients with pulmonary hypertension of which seven were excluded, due to having Down syndrome ($n = 3$) and being under 4 years old ($n = 4$). There were 19 children with PAH enrolled, 11 were female, the mean age was 11.4 ± 3.7 years, median disease duration was 72 (6–144) months. There was no significant difference between the patients and the control group in terms of distribution of age, sex, and ethnicity. The demographic and clinical characteristics of the study population are shown in Table 1.

Children with PAH had statistically lower total HRQoL scores than healthy peers ($p < 0.001$). In addition, subscales score of physical well-being, emotional well-being, self-esteem, family, friends, and everyday functioning were lower ($p = 0.001$, $p < 0.001$, $p = 0.032$, $p < 0.001$, $p < 0.001$, $p < 0.001$, respectively) (Table 2).

There was no correlation between total HRQoL scores and duration of disease, WHO-FC, 6MWT, proBNP, vitamin D, PVR, and combined or single treatment. There was no correlation between the duration of disease and the total HRQoL score; however, a correlation was found between the duration of disease and the family functioning ($r = -0.755$, $p < 0.001$). Correlation between HRQoL domains and invasive and noninvasive parameters are shown in Table 3.

HADS scores were significantly higher in the parents of patients compared to the healthy group ($p = 0.023$, $p < 0.001$, respectively).

The mean BDI score was 16.6 ± 8.5. It was significantly higher in the parents of patients compared to the healthy group ($p < 0.001$) (Table 4). Depression symptoms were minimal in 13.5%, moderate in 31%, and severe in 15% of the parents of patients.

There was a negative correlation between total HRQoL score, emotional and self-esteem functioning, and BDI in patient group ($r = -0.546$, $p = 0.016$; $r = -0.619$, $p = 0.005$; and $r = -0.489$, $p = 0.034$) respectively) (Figure 1), while there was no significant correlation with HADS ($p = 0.226$, $p = 0.317$) (Table 3).

TABLE 1 Demographic and clinical characteristics of the study population

Characteristics	Patients (*n*:19)	Controls (*n*:19)
Age (years)	11.4 ± 3.7	11.5 ± 3.7
Gender, *n* (%)		
Male	8 (42.1%)	8 (%42.1)
Female	11 (57.9%)	11 (%57.9)
Ethnicity		
Turks	11 (57.9%)	12 (%63.1)
Kurds	7 (36.8%)	6 (%31.6)
Laz	1 (5.3%)	1 (%5.3)
PAH etiology, *n* (%)		
PAH-CHD	14 (73.7%)	
IPAH	5 (26.3%)	
Disease duration, months[a]	72 (6–144)	
WHO-FC, *n* (%)		
I	1 (5.3%)	
II	14 (73.7%)	
III	4 (21.0%)	
6MWT, m	480.0 ± 91.2	
proBNP pg/ml[a]	195 (24–2892)	
Vitamin D ng/ml	13.4 ± 4.9	
Hb, g/dl	14.0 ± 2.3	
mPAP, mmHg[a]	53 (30–98)	
PVR, WU·m^2	11.0 ± 5.9	
TAPSE, cm	2.1 ± 0.7	2.2 ± 0.4
EF %	73.0 ± 6.0	75.0 ± 5.0
FS %	40.0 ± 5.0	42.0 ± 6.0
Treatment, *n* (%)		
Single	9 (47.4%)	
Combined	10 (52.6%)	

Abbreviations: 6MWT, 6-min walk test; EF, ejection fraction; FS; fractional shortening; Hb, hemoglobin; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension due to congenital heart disease; proBNP, pro-B-type natriuretic peptide; PVR, pulmonary vascular resistance; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization functional class.

[a]Data were presented as median (minimum–maximum).

4 | DISCUSSION

The chronic course of PAH and the uncertainty of its progression put patients and their families under a heavy burden. While the physical symptoms of the disease and the treatment process were closely monitored by the clinicians, the effects of the disease on daily life and the social conditions of the patients could be ignored. However, with the improvements in treatment and surveillance in recent years, clinicians begin to pay attention to QoL as well as quantity of life.

Many studies demonstrated that the QoL is impaired in adults with PAH, while studies in children with PAH are limited.[12,13] Our patient group was more homogeneous compared to other studies.

74% of the patients were PAH-CHD, and 26% were IPAH. And we evaluated Turkish children; our study is the first and only evaluation performed in non-US children.

In adult studies, Cambridge pulmonary hypertension outcome review (CAMPHOR), which is a PAH-specific scale, was used for HRQoL measurements.[22–24] We used KINDL since there was no specific scale for children with PAH. Similar to other children's study,[12,13] our study demonstrated that children with PAH had statistically lower total HRQoL scores than healthy peers. In addition, subscales scores of physical well-being, emotional well-being, self-esteem, family, friends, and everyday functioning were lower. It has been shown that HRQoL is a prognostic marker in PAH and is associated with survival.[8,9,25] In the current study, we could not evaluate the effect of HRQoL on survival due to the small number of patients, but we examined the relationship of HRQoL with predictors of prognosis (e.g., WHO-FC, 6MWT, proBNP).[7]

TABLE 2 KINDL-R scores of patients and control groups

KINDL-R	PAH (*n*:19) Mean (SD)	Control (*n*:19) Mean (SD)	*p*
Physical well-being	46.4 (14.0)	88.2 (11.2)	<0.001
Emotional well-being	66.8 (10.6)	81.6 (15.4)	0.001
Self-esteem	51.0 (18.8)	73.7 (12.9)	<0.001
Family	73.4 (16.3)	83.9 (12.6)	0.032
Friends	67.4 (15.7)	85.9 (11.6)	<0.001
School	44.1 (14.6)	67.0 (13.2)	<0.001
Total score	57.3 (9.5)	79.0 (10.0)	<0.001

Abbreviations: PAH, pulmonary arterial hypertension; SD, standard deviation.

Studies have shown associations between WHO-FC and total scores and domains of the HRQoL.[12,13] Contrary to expectations, there was no correlation between HRQoL and WHO-FC in our study. We considered this result may be related to the absence of patients in WHO-FC IV and most of our patients (79%) were in WHO-FC I–II.

Although the correlation between 6MWT and QoL was not statistically significant, the coefficients of correlations were clinically remarkable in our study. Similarly, Handler et al.[13] indicated the correlation between 6MWT and QoL was not significant in pediatric patients with PAH.

There are many studies showing a correlation between QoL and 6MWT in adults[8,11,25] but the reason we could not show this correlation may be that the number of patients was insufficient because we could not test under 7 years of age.

As demonstrated in previous studies,[8,9] we did not find any relationship between hemodynamic parameters and HRQoL. This may be related to the degree of clinical reflection of hemodynamic parameters and the timing of assessment of hemodynamic parameters not being synchronous with HRQoL.

Vitamin D deficiency is frequently seen in patients with PAH. Vitamin D is thought to affect smooth muscle cell proliferation and endothelial function, which play a role in the pathogenesis of PAH.[26] It has been shown that vitamin D replacement therapy in patients with PAH results in significant improvement of right ventricular (RV) size and 6MWT.[26] Additionally, vitamin D supplementation in PAH rats improved survival via ameliorating pathological RV hypertrophy in Tanaka et al.[27] studies. Vitamin D levels were also low in our patients. In light of these data, we evaluated the effect of vitamin D on QoL in patients with PAH. However, we could not find a correlation between vitamin D and QoL, which may be due to the small number of our subjects. To the best of our knowledge, our study is the first study about the relationship between vitamin D and quality of life in children with PAH.

TABLE 3 Correlation between HRQoL and parameters, BDI, and HADS

	Disease duration	WHO-FC	6MWT	proBNP	Vitamin D	PVR	Therapy (*n*)	BDI	HADS-A	HADS-D
Physical well-being	−0.048	−0.159	0.233	−0.174	0.151	−0.245	0.279	−0.198	−0.216	−0.337
Emotional well-being	−0.236	0.104	−0.228	0.143	−0.165	0.218	0.392	−0.619**	−0.100	−0.376
Self-esteem	0.083	0.193	0.150	0.037	0.254	0.202	0.228	−0.489*	−0.224	−0.265
Family	−0.755**	0.245	0.026	0.452	−0.136	0.186	0.193	0.197	0.393	0.266
Friends	0.040	0.139	0.322	0.035	0.190	0.029	0.264	−0.269	−0.177	0.021
School	0.050	−0.042	0.294	−0.355	−0.194	0.061	0.073	−0.147	−0.259	−0.226
Total score	−0.121	0.031	0.246	−0.161	−0.051	0.038	0.038	−0.546*	−0.291	−0.243

Note: Data were presented as *r* values.

Abbreviations: 6MWT, 6-min walk test; BDI, Beck Depression Inventory; HADS-A, hospital anxiety and depression scale-anxiety; HADS-D, hospital anxiety and depression scale-depression; HRQoL, health-related quality of life; proBNP, pro-B-type natriuretic peptide; PVR, pulmonary vascular resistance; WHO-FC, World Health Organization functional class.

*$p < 0.05$.; **$p < 0.001$.

It was indicated that parental distress is related to lower HRQoL in children with chronic diseases.[28,29] In the study of Handler et al.,[13] depression and anxiety states of families were not evaluated. They used only the PedsQL parent report. We evaluated the depression and anxiety states of families with BDI and HADS and their effects on QoL. The results of our study indicate that HADS and BDI scores were significantly higher in patients' parents, and 46% of patients' parents had moderate-severe depression symptoms. It was observed that, as the depression symptoms of the families increased, the QoL of the patients decreased. The well-being of one of the family members affects the other individuals as well.[30] During the illness, families provide emotional, social, and physical support to their children. Increased stress in parents can make it difficult for their children to recognize their needs[31] and provide adequate support[32] and accordingly, impairment in HRQoL of children may be observed.[33] We consider parental distress should be taken into account as well as clinical and hemodynamic parameters when the disease aggravates, and the QoL deteriorates in children with PAH.

TABLE 4 BDI and HADS scores of patients' and controls' parents

	Patients' parents Mean (SD)	Controls' parents Mean (SD)	*p*
BDI	16.6 ± 8.5	7.2 ± 5.6	<0.001
HADS-A	8.7 ± 4.5	5.8 ± 2.7	0.023
HADS-D	8.7 ± 5.0	3.6 ± 1.7	<0.001

Abbreviations: BDI, Beck Depression Inventory; HADS-A, hospital anxiety and depression scale-anxiety; HADS-D, hospital anxiety and depression scale-depression; SD, standard deviation.

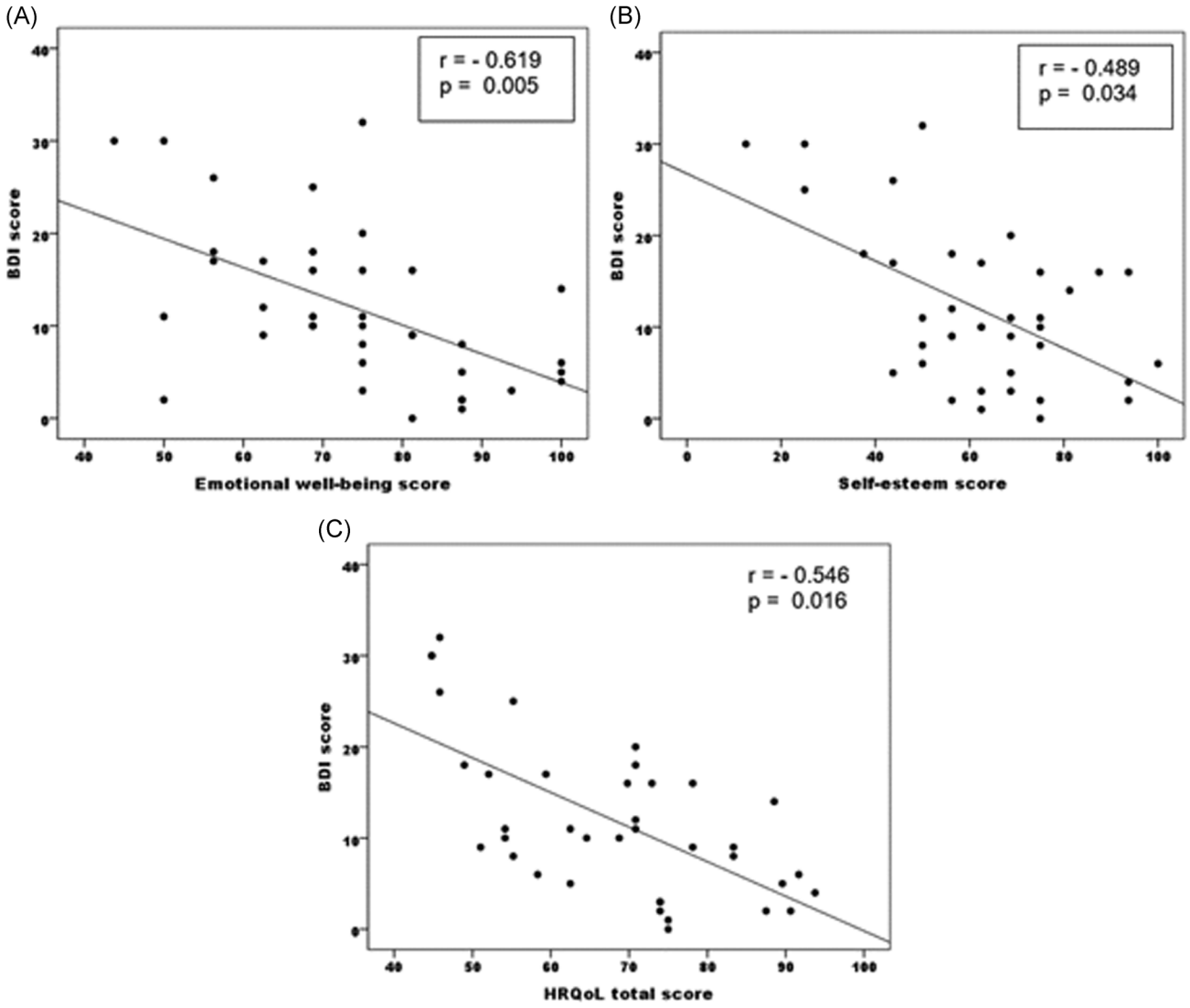


FIGURE 1 (A) Correlation between BDI scores of the patient's parents and patients' emotional well-being scores. (B) Correlation between BDI scores of the patients' parents and patients'self-esteem scores. (C) Correlation between BDI scores of the patients' parents and total HRQoL scores of the patients. BDI, Beck Depression Inventory; HRQoL, health-related quality of life

There are several limitations in this study. First, KINDL is a generic scale for HRQoL and the measurements may not be sensitive enough since it is not PAH specific like CAMPHOR. However, KINDL was used in our study because there is no specific questionnaire for children with PAH. Developing a PAH-specific scale for children can provide a better assessment of the HRQoL of patients. Second, parents filled BDI and HADS questionnaires to evaluate their psychological states. However, socioeconomic characteristics and additional diseases that may affect their depression and anxiety were not evaluated.

Finally, the relationship between QoL and surveillance could not be evaluated due to the small sample size, and we believe that the reason might be the small number of patients for the lack of correlation between HRQoL and prognostic parameters.

5 | CONCLUSION

In the current study, we found that the HRQoL of children with PAH is lower than the normal population, and their families have higher depression and anxiety. In addition, we demonstrated that there was a negative correlation between HRQoL of children and the depression of their families. Consequently, we suggest that to improve the HRQoL of children with PAH, the distress of their families should be evaluated and supported in clinical practice.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Fatma H. Canbeyli: Conceptualization (equal); investigation (equal); supervision (equal); writing – original draft (equal); and writing – review and editing (equal). **Vildan Atasayan**: Data curation (equal); investigation (equal); and resources (equal). **Fatma S. Tunaoglu**: Formal analysis (equal); investigation (equal); and writing – original draft (equal). **Ayse D. Oguz**: Formal analysis (equal); investigation (equal); methodology (equal); and writing – review and editing (equal). **Bulent Celik**: Formal analysis (equal); investigation (equal); methodology (equal); and resources (equal). **Serdar Kula**: Conceptualization (equal); investigation (equal); supervision (equal); writing – original draft (equal); and writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

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