Original Article

Quality of life among pediatric and adolescent patients with migraine: A cross-sectional study

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Abstract

Introduction: Migraine can occur at any stage of childhood; however, its prevalence increases during school years, affecting various aspects of life, including daily routines and school attendance. **Objective:** To evaluate the quality of life (QOL) in children and adolescents with migraines. **Methods:** This cross-sectional study was conducted at several specialized pediatric neurology clinics between 2020 and 2023. Participants were provided with an online questionnaire. The validated Pediatric Quality of Life Inventory (PedsQL) for parental reports was applied to evaluate QOL, covering four dimensions: physical, emotional, social, and school functioning. **Results:** In total, 109 eligible patients were identified, yielding an estimated prevalence of 5.45%. The study population comprised 51% males, with a mean age of onset of 9 ± 3 years. The mean total PedsQL score across all dimensions per participant was 76 ± 17 points. Significant associations were observed for age ($P = 0.02$), adherence to dietary recommendations ($P = 0.01$), and hours spent playing video games per day ($P = 0.02$) on the total PedsQL score. **Conclusion:** Children and adolescents with migraines exhibit a reduced QOL, particularly in the emotional and school functioning domains. These findings underscore the importance of early screening and management of migraines in pediatric patients.

Keywords: Adolescents, children, emotional, migraine, quality of life, school

Introduction

Migraine affects approximately 11% of children and adolescents, making it a significant concern in pediatric health.[1] It can be classified into two types: "migraine without aura," characterized by a pulsating headache associated with photophobia, phonophobia, nausea, and vomiting, and "migraine with aura," characterized by transient visual or sensory focal neurological symptoms that arise before or accompany the headache.[2] Migraine triggers include multiple factors such as caffeine ingestion, skipping meals, higher body fat, low levels of physical activity, reduced sleep duration or lack of sleep, stress, warm climate, video games, and physical or emotional abuse.[3-5] Regarded as one of the most debilitating medical conditions globally, migraine significantly impacts the quality of life (QOL) of both children and adolescents, constraining social and physical activities, increasing school absences, and resulting in subpar academic performance. Migraine is also associated with allergies, sleep disruption, emotional and behavioral challenges, anxiety, and educational underachievement.[2,6,7] In terms of the literature, one 2012 cross-sectional study involving 5,671 children in Brazil discovered a notable association between migraines and poor academic performance.[8] Another study by Koller *et al.*[9] revealed that children with migraines exhibit

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lower QOL in terms of physical, socioeconomic, and school functioning. Similarly, a population-based study highlighted a substantial negative correlation between migraines and various aspects of QOL, including physical, social, and environmental dimensions.[10] A comprehensive 2020 review emphasized the severity of pediatric migraine as a pressing health concern, underscoring its onset during childhood and peak prevalence in adulthood. Delayed diagnosis due to parental unawareness of migraine symptoms can adversely affect children's development, academic achievement, and overall QOL.[11] Although migraines profoundly affect different aspects of a child's life, research on the specific repercussions during childhood remains lacking. Given the pivotal role of general practitioners and family medicine practitioners as primary care providers, this study offers valuable insight into the broader implications of pediatric migraines on QOL. Therefore, the principal aim of this study was to enhance our understanding of the impact of migraine on the QOL among affected children and adolescents.

Materials and Methods

Study design, sampling, participant

This cross-sectional study, approved by the Institutional Review Board (IRB) under reference number (28-23) on January 18, 2023, aimed to assess the QOL of children and adolescents diagnosed with migraines at different pediatric neurology clinics in Jeddah, Saudi Arabia. We reviewed the medical records of the eligible 3450 patients who attended pediatric neurology clinics between January 2020 and June 2023, of whom 150 were diagnosed with migraine by certified pediatric neurologists based on the International Classification of Headache Disorders. We adopted The Pediatric Quality of Life Inventory (PedsQL) version 4.0, parent reports for pediatric (ages 5–18) patients for data collection, which was sent as an electronic survey via social media.[12] Owing to the validity and reliability of this questionnaire, it can be used in different settings, including clinical trials and schools. We received 109 survey responses between 2023 and 2024, including from patients with migraines. The exclusion criteria were patients with secondary headache or those missing more than 50% of the scale items.

Survey

Data collection was performed via a survey that comprised of a written consent statement, followed by four questionnaire sections: demographics, migraine features, migraine-triggering factors, and PedsQL, as outlined: 1) Demographics: sex, nationality, known cases of other medical diseases. 2) Migraine features: age at first migraine headache attack, age at migraine diagnosis, use of prophylactic or analgesic medication, and number of hospital visits per month. 3) Migraine-triggering factors: family history of migraine headaches, restricted diet, hours spent playing video games, and school exams. 4) PedsQL 4.0: a brief 23-item measure that evaluates QOL across four areas of functioning: physical functioning (eight items), emotional functioning (five items), social functioning (five items), and school functioning (five items). PedsQL 4.0 Generic Core Scales (Pediatric Quality of Life Inventory TM) assesses patients divided into three age ranges: young children (5–7 years), children (8–12 years), and adolescents (13–18 years). This questionnaire asks respondents to indicate the extent of a problem each item has experienced in the past month. The parent report forms Respondents use a five-point Likert scale to rate item severity (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). The questionnaire yielded a total QOL and summary scores for each domain. To obtain scores, items are reverse-scored and transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0); averaged total scores near 0 indicate lower QOL, while scores approaching 100 indicate higher QOL.

Data analysis

To analyze the data, we used industry-standard applications, such as Microsoft Excel version 16.0 (Microsoft Corp., Redmond, WA, USA), to collect and organize data. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY). Frequencies and percentages were used to describe categorical variables, whereas the means and standard deviations were used to describe continuous variables. Data were compared using the Chi-square and Fisher's exact tests. Statistical significance was set at $P < 0.05$. Missing data from the files was obtained by directly contacting the parents or legal guardian of patients.

Results

Demographic characteristics

A descriptive summary of the participants' characteristics is presented in Table 1. The questionnaire was sent to 150 patients with migraine, of whom 109 agreed to participate in this study. Of these, approximately 39% were aged 13–18, 46% were aged 8–12, and 16% were aged 5–7. The average age at onset was approximately 9 ± 3 years. Of the participants, approximately 51% were male, while 49% were females. The sex distribution across different age groups is shown in Figure 1. Notably, there was a higher proportion of males than females in the 5–7 and

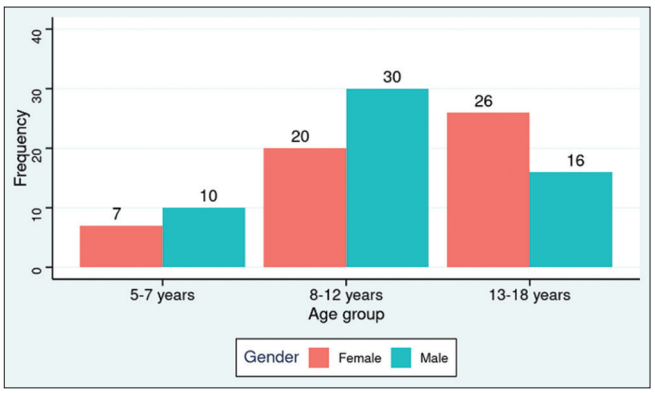

Figure 1: Distribution of gender by age group

Table 1: Descriptive data of the participants

Characteristic	Descriptive statistic (*n*=109)
Age group *n* (%)	
5–7 years	17 (15.60)
8–12 years	50 (45.87)
13–18 years	42 (38.53)
Age of onset mean (SD)	8.99 (3.31)
Gender *n* (%)	
Female	53 (48.62)
Male	56 (51.38)
Nationality *n* (%)	
Saudi	94 (86.24)
Non-Saudi	15 (13.76)
Migraine family history *n* (%)	
No	30 (27.52)
Yes	79 (72.48)
Migraine medication use *n* (%)	
No	70 (64.22)
Yes	39 (35.78)
Hospital visits per month for migraine *n* (%)	
Less than one time	77 (70.64)
One to two times	28 (25.69)
Two to three times	3 (2.75)
More than three times	1 (0.92)
Diet to alleviate migraine *n* (%)	
No	97 (88.99)
Yes	12 (11.01)
Hours spend playing video games *n* (%)	
Less than 1 h	14 (12.84)
1–2 h	24 (22.02)
2–3 h	30 (27.52)
More than 3 h	41 (37.61)
Comorbid conditions *n* (%)	
No comorbidity	37 (24.18)
ADHD	1 (0.65)
Allergic Rhinitis	34 (22.22)
Asthma	11 (7.19)
Depression or Anxiety	13 (8.50)
Epilepsy	7 (4.58)
Heart complications	1 (0.65)
Obesity	19 (12.42)
Migraine triggers *n* (%)	
No triggers	13 (4.38)
Dehydration	45 (15.15)
Irregular meals	25 (8.42)
Sensory stimuli	52 (17.51)
Sleep disturbances	59 (19.87)
Stress	47 (15.82)
Weather changes	42 (14.14)
Other	14 (4.71)
Do migraine attacks increase during exam period? *n* (%)	
No	63 (57.80)
Yes	46 (42.20)
Has your child's grades been affected by migraine? *n* (%)	
No	83 (76.15)
Yes	26 (23.85)
Difficulty understanding your child's condition by others *n* (%)	
No	72 (66.06)
Family	14 (12.84)
Friends	6 (5.50)
Teachers at school	4 (3.67)
Colleagues at school	13 (11.93)

8–12 age brackets, while the 13–18 age group exhibited a female predominance. However, a more in-depth exploration of the association between sex and age groups using the Chi-square test indicated a non-significant relationship (X2 = 4.83, $P = 0.09$).

Epidemiology of participants' migraine

The prevalence of pediatric migraine within this pooled sample from multiple pediatric neurology clinics between January 2020 and June 2023 was 5.45%, while the total number of patients attending the pediatric neurology clinic in the center during this period was 2750.

Most participants (72%) reported a family history of migraines, while a majority (64%) also reported not using any medication for migraine. In terms of migraine-related hospital visits per month, most participants (71%) reported a frequency of less than one visit per month, while approximately a quarter (26%) reported one to two visits per month. Most participants (90%) did not consistently follow any specific diet aimed at alleviating their migraines. In terms of hours spent playing video games per day, 38% reported playing more than 3 h hours per day, approximately 28% spent 2–3 h, 22% spent 1–2 h, and only 13% spent less than 1 h playing video games per day.

Approximately, 24% of participants reported no comorbidities. The most common comorbidities were allergic rhinitis (22%) and sleep disturbance (20%). The most frequently reported migraine triggers were sleep disturbances (20%), sensory stimuli such as bright lights and loud sounds (18%), stress (16%), dehydration (15%), and weather changes (14%). The proportionate distribution of migraine triggers among participants is presented in Figure 2. For most participants, migraine attacks did not increase during examination periods (58%), nor did they affect their children's grades (76%). Most participants (66%) reported that they did not face difficulties from others in understanding their children's migraine conditions. Approximately, 13% reported difficulties in understanding from their families, 12% from school colleagues, 6% from friends, and 4% from teachers at school.

PedsQL 4.0 scores

The descriptive statistics for the PedsQL scores are summarized in Table 2. The mean functioning scores for the physical, emotional, social, and school domains were 79 ± 19.04, 67 ± 25,

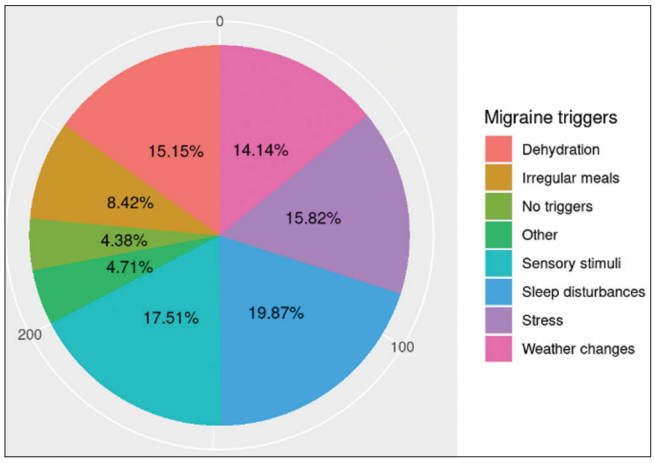

Figure 2: Pie chart of migraine triggers

84 ± 18, and 73 ± 20 points, respectively. The mean total score across all dimensions per participant was 76 ± 17 points.

Analysis of variance of PedsQL score

The analysis of variance (ANOVA) results are summarized in Table 3. Overall, we found a significant main effect of age (F (2,100), P = 0.02), commitment to diet (F (1,100), P = 0.01), and hours spent playing video games per day (F (3,100), P = 0.02) on the total PedsQL score. The post-hoc pairwise analyses using Tukey's HSD test are summarized in Table 4. Tukey's HSD comparisons indicated that participants within the 5–7 years age group on average scored 11.05 points higher on the PedsQL compared to participants aged 13–18 years (95% confidence interval (CI) [0.73, 21.38]). Contrary to what one might expect, participants committed to a diet scored on average 11.28 points lower on the PedsQL compared to participants who were not committed to a diet (95% CI [-20.45, -2.11]). Furthermore, participants who spent 2–3 h per day playing video games scored on average 13.85 points higher on the PedsQL than participants who played for less than 1 h per day (95% CI [1.09, 26.62]).

Discussion

Migraine is frequent in Saudi Arabia, exerting a substantial impact on a significant segment of the pediatric and adolescent population.[13] Existing literature has extensively explored the characteristics, triggering factors, and repercussions of migraines on various aspects of life in these age groups. This study thus aimed to comprehensively assess the impact of the disease on the QOL of children aged 5–18 years.[13] A systematic review encompassing 48 studies estimated a global migraine prevalence of 11% among patients aged 8–18 years.[1] In Arab countries, the prevalence ranged from 7.10% to 13.7% in patients aged 6–18 years.[14] In our study, the prevalence was 5.45% among patients aged 5–18 years. This variance could be attributed to differences in sample sizes and study designs. In our study, 46% of the participants fell within the 8–12 years age group, with a male predominance (30 out of 50), while the 13–18 years age group had a higher proportion of females (26 out of 42). A previous prospective study of 1.2 million children and adolescents indicated a disease prevalence of approximately 1% for both sexes around the age of 10 years, increasing to 3.49% for females and 1.72% for males by the age of 19 years.[15] Sex hormones, notably estrogen, and menstruation, are believed to trigger migraines, which may be the reason for disparity in prevalence between the sexes during adolescence.[16] Among our participants, 72% had a family history of migraine, with prevalent triggers including sleep disturbances, sensory stimuli, stress, dehydration, and weather changes. These findings are consistent with those of various studies that have identified

Table 2: Descriptive statistics of the PedsQL 4.0 scores

	Descriptive Statistic	
	Mean	**SD**
Physical Functioning	78.93	19.04
Emotional Functioning	67.48	24.71
Social Functioning	84.17	18.05
School Functioning	72.98	19.63
Total Score	76.29	16.74

SD=Standard deviation

Table 3: Analysis of variance of total PedsQL score across participants' characteristics

Variable	Df	Sum Sq	Mean Sq	*F*	*P*
Age	2	1934.59	967.29	4.24	0.02*
Gender	1	65.02	65.02	0.29	0.59
Migraine Medication	1	173.83	173.83	0.76	0.38
Diet	1	1466.21	1466.21	6.43	0.01*
Hours spent playing video games	3	2301.37	767.12	3.36	0.02*
Residuals	100	22797.18	227.97		

Df=Degrees of freedom; Sum Sq=Sums of square; Mean Sq=Mean sums of Square. Note: Significant P<0.05 are followed by an asterisk (*)

Table 4: *Post-hoc* Tukey's HSD Pairwise Comparisons

Pairwise contrasts	Tukey's HSD	
	Est (95% CI)	***P* adj**
Age		
5–7 years to 13–18 years	11.05 (0.73, 21.38)	0.03*
8–12 years to 13–18 years	7.29 (-0.23, 14.81)	0.06
8–12 years to 5–7 years	-3.76 (-13.85, 6.32)	0.65
Gender		
Male-Female	1.51 (-4.23, 7.25)	0.60
Migraine medication		
Yes-No	-2.48 (-8.47, 3.50)	0.41
Diet		
Yes-No	-11.28 (-20.45, -2.11)	0.02*
Hours spent playing video games		
>3 h-< 1 h	7.94 (-4.28, 20.15)	0.33
1–2 h-< 1 h	13.02 (-0.24, 26.29)	0.05
2–3 h-< 1 h	13.85 (1.09, 26.62)	0.03*
1–2 h-> 3 h	5.09 (-5.05, 15.23)	0.56
2–3 h-> 3 h	5.92 (-3.56, 15.40)	0.37
2–3 h-1–2 h	0.83 (-9.97, 11.63)	0.99

Tukey's HSD='Tukey's Honestly Significance Difference test; Est=Estimated difference in means; CI=Confidence Interval; *P* adj=adjusted *P*. Note. Significant P<0.05 are followed by an asterisk (*)

similar triggers.[14] For example, one systematic review involving 200 participants reported stress; noise; and hot, humid weather as the primary triggers.[17] Given Jeddah's warm climate and high humidity levels, managing these triggers is crucial to enhance QOL. While behavioral triggers can be mitigated, factors such as a family history of migraine and a persistent hot climate pose challenges to avoidance strategies. Consistent with previous research, our study found that allergic rhinitis was the most prevalent comorbidity of migraines, affecting 22% of the sample. This finding indicates a robust comorbidity between migraines and allergic rhinitis among adolescents. Additionally, sleep disturbances were a significant comorbidity, with an incidence of 20% in our sample. Addressing sleep-related challenges is essential for managing adolescent migraines and improving the overall well-being of afflicted individuals. Our study aimed to quantify the impact of migraines on QOL across the social, school, physical, and emotional functioning domains. Participants exhibited lower scores on school and emotional functioning. Prior research has indicated that severe migraine attacks correlate with lower academic performance and increased absenteeism. Although 76.15% of the patients reported that their grades were unaffected by migraines, children with migraines generally experienced higher rates of school absence than their peers without migraines. Regarding social functioning, previous studies have indicated that children with migraines face more difficulties in social disengagement and participation in activities.[18] However, our study did not reflect on these issues, possibly because of its reliance on parental reports, which may not fully capture children's social experiences. More than one-third of the parents in our study reported that their children had difficulty performing physical activity, highlighting the significant impact of migraines on daily physical activity and routines. However, data in the existing literature are insufficient to comprehensively compare the influence of migraine on physical activity in children.[19] Prior research has indicated that children with migraines exhibit a higher tendency towards anxiety, loneliness, depression, and other emotional challenges.[20] The lower emotional domain scores in our study highlight the need for emotional support to enhance the QOL in these patients. In our study, the total PedsQL 4.0 score was significantly higher in the 5–7 age group, likely due to the milder form of the disease and lower degree of stress, a major trigger identified in this study. Dietary triggers were also found to be significant in our study, with participants following a specific diet reporting lower PedsQL scores; the stress of adhering to a diet may have contributed to this finding. Additionally, participants who spent 2–3 h per day playing video games had higher PedsQL scores than those who played less than 1 h per day. This finding contrasts with existing literature suggesting that excessive screen time may trigger migraines. However, in regards to this unexpected outcome, it is crucial to consider the various contributing factors. For example, age could influence these results, as well as whether participants who spent less than 1 h had a family history of migraine. Additionally, investigating screen time patterns, such as whether those spending 2–3 h took frequent breaks, could provide insights into the observed differences. As such, a comprehensive analysis of these factors is required to better understand the relationship between video game use and migraine attacks. This study has some limitations, which should be mentioned, including its small sample size and reliance on parental reports. Future research should therefore incorporate larger sample sizes and include children's perspectives to provide a more comprehensive understanding of the impact of migraines on QOL.

Conclusion

Migraine exerts a discernible impact on the pediatric population in Saudi Arabia, as evidenced by its demonstrable negative repercussions on school and emotional functioning, as shown in the present study. Discerning and mitigating migraine triggers has paramount significance within pediatric and adolescent cohorts, thereby offering a potential avenue to optimize QOL in this demographic. The prevalence of comorbidities, notably allergic rhinitis and sleep disturbances, among adolescents with migraines underscores the need for comprehensive therapeutic strategies. The deployment of a meticulously validated questionnaire in this study further served to fortify the internal validity of our findings, thereby accentuating the methodological rigor applied. Furthermore, this study conscientiously underscores the need to incorporate the perspectives of afflicted children, despite their inherent reliance on parental perspectives. Notwithstanding these strengths, the exigency for further research is unabated, with further studies indispensable to corroborate extant findings and unravel the intricacies of the underlying mechanistic pathways. This imperative stems from the recognition that validation using broader and more diverse samples will be pivotal to enhance the generalizability and scientific robustness of our conclusions.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Onofri A, Pensato U, Rosignoli C, Wells-Gatnik W, Stanyer E, Ornello R, *et al.* Primary headache epidemiology in children and adolescents: A systematic review and me-ta-analysis. J Headache Pain 2023;24:8.
2. Szperka C. Headache in Children and Adolescents. Continuum (Minneap Minn). 2021;27(3):703-731. Available from: https://pubmed.ncbi.nlm.nih.gov/34048400/.
3. Yamanaka G, Morichi S, Suzuki S, Go S, Takeshita M, Kanou K, *et al.* A review on the triggers of pediatric migraine with the aim of improving headache education. J Clin Med 2020;9:3717.
4. Waldie KE, Thompson J, Mia Y, Murphy R, Wall C, Mitchell EA. Risk factors for migraine and tension-type headache in 11 year old children. J Headache Pain 2014;15:1-9.
5. Straube A, Heinen F, Ebinger F, von Kries R. Headache in school children: Prevalence and risk factors. Deutsch

Ärztebl Int 2013;110:811.

6. Arruda MA, Bigal ME. Behavioral and emotional symptoms and primary headaches in children: A population-based study. Cephalalgia 2012;32:1093-100.
7. Natalucci G, Faedda N, Calderoni D, Cerutti R, Verdecchia P, Guidetti V. Headache and alexithymia in children and adolescents: What is the connection?. Front Psychol 2018;9:48.
8. Arruda MA, Bigal ME. Migraine and migraine subtypes in preadolescent children: Association with school performance. Neurology 2012;79:1881-8.
9. Koller LS, Diesner SC, Voitl P. Quality of life in children and adolescents with migraine: An Austrian monocentric, cross-sectional questionnaire study. BMC Pediatr 2019;19:1-9.
10. Abdollahpour I, Salimi Y, Shushtari ZJ. Migraine and quality of life in high school students: A population-based study in Boukan, Iran. J Child Neurol 2015;30:187-92.
11. Langdon R, DiSabella M, Strelzik J, Fletcher A. Pediatric migraine and academics. Curr Pain Headache Rep 2020;24:1-8.
12. Varni JW, Seid M, Kurtin PS. PedsQL™ 4.0: Reliability and validity of the pediatric quality of life inventory™ version 4.0 generic core scales in healthy and patient populations. Med Care 2001;39:800-12.
13. Al Ghadeer HA, AlSalman SA, Albaqshi FM, Alsuliman SR, Alsowailem FA, Albusror HA, *et al.* Quality of life and disability among migraine patients: A sin-gle-center study in Alahsa, Saudi Arabia. Cureus 2021;13:e19210.
14. El-Metwally A, Toivola P, AlAhmary K, Bahkali S, AlKhathaami A, Al Ammar SA, *et al.* The epidemiology of migraine headache in Arab countries: A systematic review. ScientificWorldJournal 2020;2020:4790254.
15. Albers L, Kries RV, Straube A, Heinen F, Landgraf MN, Obermeier V, *et al.* Age-and sex-specific first health care use for migraine in 2016 in children and adolescents from prospectively collected health insurance data in Germany. Cephalalgia 2019;39:1156-63.
16. Ge R, Chang J, Cao Y. Headache disorders and relevant sex and socioeconomic patterns in adolescents and young adults across 204 countries and territories: An updated global analysis. J Headache Pain 2023;24:1-4.
17. Chakravarty A, Mukherjee A, Roy D. Trigger factors in childhood migraine: A clinic-based study from eastern India. J Headache Pain 2009;10:375-80.
18. Kashikar-Zuck S, Zafar M, Barnett KA, Aylward BS, Strotman D, Slater SK, *et al.* Quality of life and emotional functioning in youth with chronic migraine and juvenile fibromyalgia. Clin J Pain 2013;29:1066-72.
19. Denche-Zamorano Á, Paredes-Mateos V, Pastor-Cisneros R, Carlos-Vivas J, Contreras-Barraza N, Iturra-Gonzalez JA, *et al.* Physical activity level, depression, anxiety, and self-perceived health in Spanish adults with migraine: A cross-sectional study. Int J Environ Res Public Health 2022;19:13882.
20. Falla K, Kuziek J, Mahnaz SR, Noel M, Ronksley PE, Orr SL. Anxiety and depressive symptoms and disorders in children and adolescents with migraine: A systematic review and meta-analysis. JAMA Pediatr 2022;176:1176-87.