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Attention Deficit Hyperactivity Disorder as a Risk Factor for Fractures

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ABSTRACT

Objectives: It has been reported that attention-deficit/hyperactivity disorder (ADHD) is related to an increased risk of fracture. However, relevant data have been provided from either population with fractures or population-based cohort studies. In this study, we aimed to determine the fracture risk in children with ADHD.

Methods: The children with ADHD between the ages of 6 and 16 who were admitted between April 2019 and July 2020 and healthy children matching in age and gender were included in this study. A semi-constructed diagnosis interview, Conners' Parent Rating Scale-Revised-Short Form, and Strengths and Difficulties Questionnaire were administered to both groups.

Results: Two hundred and twelve children with ADHD and 215 healthy children were included in this study. One-time fracture was found in 76 (35.8%) children in the ADHD group and 39 (18.1%) children in the healthy group (p<0.001). While there were recurrent fractures in 27 (12.7%) patients in the ADHD group, this rate was 13 (6.0%) for healthy controls (p=0.018). Also, 45 (59.2%) of the children with fractures and 57 (41.9%) of the children without fractures had comorbid diseases (p=0.016).

Conclusion: ADHD poses a significant risk for fractures and is related to an increased risk of fracture. It would be advisable to screen children with bone fractures concerning ADHD and referring them to a child and adolescent psychiatrist if there is a suspicion of ADHD.

Keywords: Attention deficit-hyperactivity disorder, bone fractures, children

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is defined as attention deficit, hyperactivity, and behavioral and impulse control problems that are inappropriate for age and developmental level. According to the symptom types, ADHD has three sub-presentations: "predominantly inattentive presentation", "predominantly hyperactive/impulsive presentation" and "combined presentation" with the characteristics of the two presentations.[1] ADHD is 2-5 times more common in boys than girls and in the clinical manifestation, hyperactivity and impulsivity are prominent in boys and attention deficit symptoms are prominent in girls.[1, 2]

Bone fractures are one of the most common reasons for hospitalization and operations in children. In the etiology of pediatric fractures, accidental and non-accidental traumas, and pathological conditions have been defined as the main causes. Falls (running or from a height), fighting, pedestrian injuries, and cycling or playground activities include causes of accidental trauma.[3-7] In the previous studies, ADHD has been shown to pose a risk for accidental injuries, and the risk of injury increases 1.5 fold with ADHD and behavioral disorders.[8-

[11] It has also been emphasized that children with diagnosis of ADHD are at a higher risk of fracture in comparison with children without ADHD.[7-15]

Children treated for fractures exhibited more excessively hyperactive behaviors and impulsivity than children treated for non-traumatic orthopedic reasons, and the rate of ADHD was higher.[11, 16, 17] Also, it was found that children with ADHD are significantly highly probable to experience severe and severe trauma compared to normal children and at a higher risk of repeated trauma due to their tendency to act faster and carelessly.[7-10]

Although the relationship between ADHD and childhood bone fracture risk seems clear in the literature since the majority of available studies have been conducted in non-clinical or community samples, data on the effect of ADHD on fracture risk and related factors are still limited. On the other hand, reproducing evidence on factors associated with fractures in children with a diagnosis of ADHD may facilitate the development of special interventions to reduce the occurrence of injuries and fractures in these children. In addition, since the treatment of fractures will incur additional socioeconomic costs, minimizing the risk of fractures in these children will result in significant health benefits. Besides, family physicians are more likely to face these children compared to other specialists, even if not directly. Therefore, they should also be aware of the clinical features of this disorder and the relationship between bone fractures and ADHD to be able to reduce the risk of fractures in these children, hence social and economic detriments. This study was aimed to assess the incidence of fractures and related factors in children with ADHD.

METHOD

The present study included 212 consecutive children and adolescents aged 6-16 years who were diagnosed with ADHD for the first time between April 2019 and July 2020 or who had been diagnosed previously but never received any treatment and 215 healthy children matched for age, gender, socio-cultural characteristics, and educational status. ADHD diagnoses of the participants were made in the Child-Adolescent Mental Health and Diseases clinic, depending on Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria.[1] The control group was randomly recruited from healthy children who presented to the pediatrics clinic of the hospital, who did not have a diagnosed psychiatric disorder or any chronic medical disorder requiring treatment. Children with a history of head trauma with loss of consciousness, those who were suspected to be exposed to child abuse, and those with diseases such as osteogenesis imperfecta were excluded from this study. Other exclusion criteria included the presence of intellectual disability, autistic spectrum disorders, epilepsy, alcohol-substance use, mania or psychotic disorder during the interview. Children with uncorrected auditory or visual problems that can lead to cause injury and hence fractures were excluded from the study to keep the effects of the confounding factors to a minimum.

A semi-structured psychiatric interview (Affective Disorders and Schizophrenia Interview Schedule for School-Age Children, Present and Lifetime Form, DSM-5-Turkish Version) was performed on all participants in this study to determine the presence of any current and past psychopathology.[18, 19] This semi-structured psychiatric interview is a detailed interview applied by the child psychiatrist to the children and parents. Also, a detailed history was taken to determine whether the trauma occurred accidentally or due to other reasons or pathologies, and the study included only accidental trauma cases.

Personal data form was prepared by the researchers by reviewing the literature for the purpose of this study. It was an interview form that included questions about the sociodemographic data of the patients (such as gender, age, place of residence and monthly income), characteristics of ADHD (such as presentation), and characteristics of fractures (cause and localization of the fracture, treatment type, hospitalization requirement). The parameters in the form were evaluated and filled in by the researchers during the interview.

Conner's Parent Rating Scale-Revised Short Form (CPRS-R-S) is applied to the parents to evaluate the ADHD symptoms of children.[20] The scale consists of 27 items under three subscales (Oppositional, Cognitive Problems-Inattention, and Hyperactivity) and an auxiliary scale (ADHD Index-ADHD). The questions are answered on a 4-point Likert scale and each item is scored between 0 and 3 points (0=not true at all (never, seldom); 1=partially true (occasionally); 2=quite true (often, quite a bit); 3=true at all (very often, very frequently). High scores indicate severe problematic behaviors. Kaner et al. performed Turkish validity and reliability study.[21]

The Strengths and Difficulties Questionnaire (SDQ) is used to assess psychiatric problems in children and adolescents between the ages of 4 and 17 years (parent form), and a self-report form for 11-17-year-old adolescents is also available. The questionnaire is formed of 25 items and five subscales: emotional symptoms, behavioral problems, inattention-hyperactivity disorder, peer problems, and prosocial behavior.[22] Each item is scored between 0 and 2 points (0=not true, 1=partially true, 2=absolutely true). The "Total

Difficulty Score" is derived from the sum of all items in the first four subscales, and the "Strengths Score" is reflected by the prosocial behavior subscale. In this study, we used the parent and adolescent versions of the scale and evaluated the total difficulty score, behavioral problems score and inattention-hyperactivity score. The scale was adapted into Turkish by Güvenir et al.[23]

Statistical data were analyzed using SPSS 22.0 software (IBM Corporation, Armonk, NY, USA). Normality was tested using the Shapiro-Wilk test. Numerical and categorical data were presented by frequency, percentage, mean, standard deviation, median, minimum and maximum. Student t-test was used for normally distributed continuous variables, and Mann Whitney U was used for abnormally distributed continuous variables. Besides, Chi-square test was used for categorical variables. Statistical significance was considered as $p<0.05$.

RESULTS

In this study, 427 children, 212 children with ADHD and 215 healthy controls were included. The mean age was 10.3±2.8 years in the ADHD group and 10.2±2.8 years in the control group (p=0.822). With regard to family history of ADHD, positive family history was found in 117 (55.2%) subjects in the study group and in 43 (20.0%) in the controls (p<0.001). The sociodemographic variables are shown in Table 1.

In the study group the mean age at diagnosis was calculated as 7.4±1.9 years. Of the children with ADHD, 59 (27.8%) had predominantly inattentive presentation, 34 (16.0%) had predominantly hyperactive/impulsive presentation, and 119 (56.1%) had combined presentation. At least, one psychiatric comorbid diagnosis was present in 102 (48.1%) of the children with ADHD. However, comorbidities were not classified separately.

Regarding the history of fractures until the date of this study, it was determined that 76 (35.8%) of the cases in the study group had a history of at least one positive fracture, while this rate was 39 (18.1%) in the control group; accordingly, the two groups statistically differed (p<0.001). In addition, in the study group, 27 (12.7%) of the patients had at least two fractures, while in the control group, this rate was 13 (6.0%) and this difference was statistically significant (p=0.018). The data regarding the characteristics and treatment approaches of the fractures are given in Table 2.

When the patients with and without only one fracture were evaluated according to their diagnostic status, the diagnosis of ADHD was statistically significantly higher in the patients with fracture compared to the group without fracture. On the other hand, the two groups with and without fractures were similar in age, gender, family income level and place of residence. Factors associated with fractures are shown in Table 3.

With regard to the association between clinical variables of

Table 1. Sociodemographic characteristics of the participants

	ADHD group (n=212)	Control group (n=215)	p
Gender			
Female	145 (68.4)	139 (64.7)	0.412
Male	67 (31.6)	76 (35.3)	
Age groups			
6-10 years	119 (56.2)	123 (57.2)	0.822
11-13 years	62 (29.2)	65 (30.2)	
14 years and above	31 (14.6)	27 (12.6)	
Income level of family			
The minimum wage/less than minimum wage	87 (41.0)	92 (42.8)	0.714
Above the minimum wage	125 (59.0)	123 (58.2)	
Place of residence			
Province	136 (64.2)	141 (65.6)	0.765
County	38 (17.9)	33 (15.3)	
Village/township	38 (17.9)	41 (19.1)	
Family history of ADHD	117 (55.2)	43 (20.0)	<0.001

Chi-square test.
Data were given as n (%).
ADHD: Attention Deficit Hyperactivity Disorder.

Table 2. Characteristics of the fractures

	ADHD group (n=76)	Control group (n=39)	p
History of only one fracture	76 (35.8)	39 (18.1)	<0.001
Localization of fracture			
Upper extremity	35 (46.1)	26 (66.7)	0.037
Lower extremity	34 (44.7)	8 (20.5)	
Skull, neck or body	7 (9.2)	5 (12.8)	
The activity that caused fracture			
Fall	27 (35.5)	21 (53.8)	0.403
Fight	11 (14.5)	3 (7.7)	
Pedestrian injury	10 (13.2)	3 (7.7)	
Sports/playing injuries	18 (23.6)	8 (20.5)	
Bicycle accident	10 (13.2)	4 (10.3)	
Treatment method			
Outpatient	61 (80.3)	37 (94.9)	0.034
Inpatient	15 (19.7)	2 (5.1)	

Chi square test.
Data were given as n (%).
ADHD: Attention deficit hyperactivity disorder.

Table 3. Factors related with the fractures

	Group with fracture (n=115)	Group without fracture (n=312)	p
Groups			
ADHD	76 (66.1)	136 (43.6)	<0.001
Control	39 (33.9)	176 (56.4)	
Gender			
Male	80 (69.6)	204 (65.4)	0.412
Female	35 (30.4)	108 (34.6)	
Age groups			
6-10 years	67 (58.2)	175 (56.1)	0.724
11-13 years	31 (27.0)	96 (30.8)	
14 years and above	17 (14.8)	41 (13.1)	
Income level of family			
The minimum wage/less than minimum wage	44 (38.3)	135 (43.3)	0.352
Above the minimum wage	71 (61.7)	177 (56.7)	
Place of residence			
Province	72 (62.6)	205 (65.7)	0.339
County	24 (20.9)	47 (15.1)	
Village/Township	19 (16.5)	60 (19.2)	
Family history of ADHD	60 (52.2)	100 (32.1)	<0.001

Chi-square test.
Data were given as n (%).
ADHD: Attention Deficit Hyperactivity Disorder.

Table 4. Comparison of clinical variables in ADHD children with and without fracture

	Group with fracture (n=76)	Group without fracture (n=136)	p
Comorbidity	45 (59.2)	57 (41.9)	0.016*
Age (years)	10.0 (6.0-16.0)	10.0 (6.0-16.0)	0.578†
Age at diagnosis (years)	7.0 (5.0-13.0)	7.5 (5.0-12.0)	0.040†
ADHD presentations			
Predominantly inattentive	15 (19.7)	44 (32.4)	0.089*
Predominantly hyperactive-impulsive	16 (21.1)	18 (13.2)	
Combined	45 (59.2)	74 (54.4)	

*Chi-square test, †Mann–Whitney U.
Data were given as n (%) and median (min-max).
ADHD: Attention Deficit Hyperactivity Disorder.

ADHD and fractures, we found that the presence of comorbidity was associated with fractures, and in children with fractures had a higher frequency of comorbidity compared to the group without fractures. The comparison of clinical variables of children with ADHD with and without fractures is presented in Table 4.

In regard to the relationship between the CPRS-R-S scores used to evaluate ADHD symptoms, and fractures, it was found that the hyperactivity scores, the inattention scores, conduct disorder scores, and the ADHD index score were statistically significantly higher in the group with fractures. SDQ subscores regarding behavioral problems and ADHD scores and total difficulty subscale scores were significantly higher both the parent form and the adolescent form scores of children with fractures than those children without fractures. Comparison of CPRS-R-S and SDQ children with and without fracture are given in Table 5.

DISCUSSION

In this study, it was analyzed the prevalence of fractures in children with ADHD, associated clinical factors, and the relationship between some features of fractures and ADHD. Remarkably, children with ADHD had a significantly higher frequency of both one-time and recurring fractures compared to the control group. Regarding the characteristics of fractures, the causes of the fractures were similar between the two groups, while the localization and the treatment type of the fractures differed significantly between the two groups. The results of the present study showed that chil-

Table 5. Comparison of CPRS-R-S and SDQ children with and without fracture

	Group with fracture (n=115)	Group without fracture (n=312)	p
CPRS-R-S-Hyperactivity-impulsivity scores	9.0 (3.0-22.0)	7.0 (2.0-18.0)	<0.001
CPRS-R-S-Cognitive problems-inattention scores	17.0 (5.0-29.0)	14.0 (4.0-30.0)	<0.001
CPRS-R-S-Oppositional scores	6.0 (0.0-15.0)	4.0 (0.0-16.0)	<0.001
CPRS-R-S-ADHD index scores	27.0 (12.0-42.0)	21.0 (7.0-46.0)	<0.001
SDQ-Parent-total difficulties scores	16.0 (5.0-30.0)	12.0 (2.0-30.0)	<0.001
SDQ-Parent-conduct problems score	4.0 (0.0-10.0)	2.0 (0.0-10.0)	<0.001
SDQ-Parent-inattention-hyperactivity scores	7.0 (2.0-10.0)	6.0 (1.0-10.0)	<0.001
SDQ-Adolescent-total difficulties scores	14.0 (5.0-20.0)	10.0 (3.0-24.0)	<0.001
SDQ-Adolescent-conduct problems score	2.0 (0.0-7.0)	1.0 (0.0-7.0)	0.012
SDQ-Adolescent-inattention-hyperactivity scores	8.0 (2.0-10.0)	6.0 (1.0-10.0)	0.003

Mann–Whitney U.

Data were given as median (min-max).

ADHD: Attention Deficit Hyperactivity Disorder; CPRS-R-S: Conner's Parent Rating Scale-Revised Short Form; SDQ: Strengths and Difficulties Questionnaire.

dren in the ADHD group have a significantly higher proportion of lower extremity fractures and fractures requiring hospitalization compared to controls. Another important finding is that the family history for ADHD is significantly positively related to fractures. Regarding the association between fractures and clinical variables of ADHD, it was determined that the existence of comorbidity is considerably positively associated with fractures and the mean age at diagnosis was earlier in those with fractures. However, we could not find a relationship between the types of ADHD presentation and fractures.

The literature shows that few studies analyzed the effects of ADHD on fracture risk and the relationship between fractures and clinical variables of ADHD.[7, 9, 10, 12, 13, 15-17] Our results are compatible with previous studies reporting that ADHD is related to fractures, and children with ADHD have an increased risk of fracture than children without ADHD.[7, 9, 10, 12, 13, 15] Previous studies have reported that ADHD and other behavioral disorders increase the risk of injury significantly, and children with fractures show more hyperactive-impulsive behaviors and behavioral disorders.[8, 9] In a recent study, it has been indicated that ADHD is linked to a 1.3-fold higher risk of fracture in a cohort of 18.200 patients.[12] Moreover, it has been found that children with ADHD have a higher risk of experiencing severe trauma and repeated traumas due to their problems of risk-taking behavior and attention and hyperactivity disorders.[6, 10, 24] Likewise, it has been reported that excessively reckless physical activity, which is a common feature of children with ADHD, significantly contributes to repeated fractures.[24, 25] For this reason, it is emphasized that children who are impulsive and hyperactive are more vulnerable to repeated fractures before the recovery is completed due to their reckless behavior.[16] In this study, children in the ADHD group had a meaningful higher recurrent fracture rate than that of the control group, which is consistent with the literature.

In other studies evaluating the features of fractures, in the reverse direction, it has been found that children who have experienced fractures have remarkably higher impulsivity/

hyperactivity scores than the rate predicted in the normal population, and the diagnosis of ADHD was significantly more frequent in these children compared to children without fractures.[7, 8, 11, 16, 17] In a study, 21% of 42 children with proximal humerus fractures were diagnosed with ADHD.[7] Another study showed that 39.1% of children with fractures had higher scores of the impulsivity/hyperactivity subscale of the Conners Parents Rating Scale than the cut-off score.[16] In our study, it was determined that those with bone fractures scored markedly higher not only in impulsivity/hyperactivity but also in inattention and behavioral problems than those without the fracture. The dissimilar results may be due to methodological differences. However, the exact cause of fractures in children with ADHD and the mechanisms of the relationship between bone fracture and ADHD have not been known clearly. The nature of the essential symptoms of ADHD, especially hyperactivity and impulsivity, were suggested to be the main factors that make these children more susceptible to accidents and bone fractures.[6, 10, 24, 25] It has been reported that injuries and fractures in these children can be caused by clumsiness, careless and reckless behavior, disobedience to the rules during activities and games, disregarding taking safety measures, and difficulties in peer relations. At the same time, it was found that children diagnosed with ADHD are insufficient in predicting the possible severe consequences of risky behaviors and in taking precautions against injuries compared to their normal peers. Thus, they are more susceptible to accidents.[5, 7, 8, 26] In addition, it has been suggested that the risk perception, which regulates risk-taking behaviors, is impaired in children with ADHD; therefore, they experience more injuries.[6, 24, 27] Other risk factors for bone fractures in children with ADHD are that they have slower and longer reaction times in experimental situations, motor coordination deficits, and defective protective reactions.[12, 28-31]

In the normal pediatric population, the areas at the highest risk for fractures are the upper extremities.[4-7] In this study, although a similar tendency was identified for the upper extremity to be the most common fracture site in both ADHD and control groups, it was determined that lower extremity fractures are significantly higher in the study group. Results of this study is in line with the study of Uslu et al., indicating that children who are experienced lower extremity fractures have higher scores of mean impulsivity/hyperactivity than children with upper extremity fractures.[16] Another study, supporting our results found that the lower extremity was the anatomical region with the highest risk of fracture in children affected by ADHD.[13] Indirect reasons for lower extremity fractures in children with ADHD to be more common than the control group include motor coordination deficits, insufficient defense reactions, defective protective reactions, and slower reaction times.[16, 28-30] This may be because in normal conditions, trying to prevent a more severe injury by extending the arm reflexively is a common cause of upper extremity fractures, and in the presence of ADHD, there are deficits in this protective mechanism.[32] However, since fractures in different anatomical regions may be due to different injury mechanisms, further research between specific fractures and correlation factors is required for possible explanations. In addition, a more detailed examination of the relationship between the mechanisms of lower extremity fractures and ADHD's behavioral patterns may guide the creation of a coping strategy to protect children with ADHD from fractures.

Accidental trauma and fractures usually occur as a result of falls (running or from height), playground activities, fighting, cycling, and traffic accidents.[3-7] In our study, children with ADHD did not differ from controls concerning the type of activity that caused the fracture. However, some studies have revealed that the rate of fractures due to falls and traffic accidents is higher than the rate of fractures caused by sports injuries, fights, and game entertainments.[8, 16] Controversial results may be due to methodological differences, such as heterogeneity of sampling and cultural differences in study populations. Nevertheless, these relationships need to be explored further.

Results of this study showed that the two groups notable differ from the point of treatment modality. We found that those in the ADHD group have a considerably higher rate of hospitalization, which can be considered as an indicator of a more severe injury. One plausible explanation for this result can be that children with ADHD are more likely to be exposed to severe trauma than normal children and to sustain severe trauma due to their symptoms. These results agree with the previous studies that provide data that those with ADHD are susceptible to more severe types of injury and consequent fractures that require hospitalization.[7, 8, 16] In a previous study, higher impulsivity/hyperactivity scores were found in children treated with open reduction and fixation.[16] Another study has found that those with ADHD noteworthy differ from those with non-ADHD concerning operation rates, with substantially higher rates (55% vs. 15%).[7] In addition, it has been emphasized that the conservative treatment of fractures of those with ADHD is more difficult and complex compared to their healthy peers due to the nature of ADHD symptoms.[7]

In this study, the existence of comorbidity was strongly connected with fractures, which can be explained by the more severe ADHD symptoms, and it is not surprising that fractures may increase in the case of comorbidity. In addi-

tion, results of this study indicated that the mean age at diagnosis of ADHD was earlier in the group with a fracture. The most logical explanation for this may be that ADHD symptoms are more prominent in children with fractures and these symptoms may be noted and diagnosed at younger ages.

The majority of previous studies shown that the risk of fracture is higher in males than females in the normal population.[3, 4, 9, 33] In the normal population, it has been shown that the risk of fracture increases in children in both sexes up to the age of 11 or 12 years and then decreases in girls but increases even more in boys. After 13 or 14 years of age, the risk is twice as high for boys than for girls.[4, 33] As for ADHD, male dominance is observed in patients with ADHD with fracture, probably because ADHD is more common in males and males are more impulsive and hyperactive and have more risk-taking behavior.[8] Another study also confirmed a male-dominant trend in pediatric fractures in the normal control cohort. However, interestingly, it was reported that the risk of fracture was higher for females compared to males with ADHD.[13] Controversial results can be attributed to the methodological and cultural differences of the studies.

This study has some limitations. The effects of medication and adherence to treatment on fractures were not analyzed. Also, we did not examine the consequences of fractures (such as healing time or morbidity). We examined children with ADHD in a cross-sectional design at a single institution. These weaknesses prevent our results from being generalized. Despite these limitations, a strength of our study is that the data are not based solely on scale information, but also a psychiatric evaluation has been performed by a child psychiatrist, as well as the information obtained from parents. Other strengths of this study are that patients have been selected from the clinical sample and the sample size was relatively large, comorbid conditions other than conduct disorders were excluded, and patients were drug-free. Bearing these limitations in mind, future longitudinal studies with a large sample size, including multiple centers, will be remarkably fruitful. In future studies, the relationship between the state of treatment and comorbidities in children with ADHD and fractures should also be investigated. Also, the causal factors between ADHD and an increased risk of bone fractures also require further investigation. Despite the limitations of this study, our results provide important information about the association between ADHD and bone fracture. Consequently, this study provides additional findings to previous studies and extends the outcomes of prior studies on fractures in those with ADHD.

CONCLUSION

This study is one of the few studies investigating the frequency and clinical correlations of bone fractures in children with ADHD in a clinical sample. Results of this study confirmed studies that ADHD is a disorder associated with an increased incidence of first-time and recurrent bone fractures. Also, our results suggest that bone fractures may also be an indicator of ADHD in children. Therefore, screening for ADHD symptoms by some questions regarding inattention, hyperactivity, restlessness, acting without thinking in children who admit to the emergency and/or orthopedic clinics for fractures, and if suspected for ADHD, referring these children to a child and adolescent psychiatrist it would be appropriate. This can also limit the rate of future fractures and associated mortality and morbidity in children with ADHD. As a result, ADHD should be considered among risk factors for fractures in children.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Ethics Committee Approval: Local Ethics Committee of Sivas Cumhuriyet University approved the study protocols and informed consent forms (Approval Date: 20 Mar 2019, Approval Number: 2019-03/06). After a full verbal explanation of the aim and procedure of this study, parents and children gave written and verbal informed consent.

Authorship Contributions: Concept – A.U.C., S.A.S., I.U.; Design – A.U.C., S.A.S.; Supervision – A.U.C.; Materials – S.A.S.; Data collection &/or processing – A.U.C., S.A.S.; Analysis and/or interpretation –A.U.C., I.U.; Literature search – I.U.; Writing –I.U., S.A.S.; Critical review –A.U.C.

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