Original article / *Araştırma*

Is there a relationship between basophil, platelet-related parameters and developmental stuttering?

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ABSTRACT

Objective: *Studies show that developmental stuttering (DS) may be associated with inflammatory processes. Complete blood count (CBC) values have been used as indicators of a systemic inflammatory response. We aimed to evaluate the relationship between CBC values particularly basophil, platelet, and lymphocyte-related parameters and DS.* ***Method:*** *In this retrospective case-control study, the CBC values of 54 patients who were diagnosed with DS were compared with the data of 54 healthy subjects.* ***Results:*** *Basophil count, percentage of basophil, and platelet count were significantly higher (p=0.001, r=0.35; p=0.044, r=0.19; p=0.045, r=0.11; respectively); mean platelet volume was significantly lower in the patient group (p=0.000, r=-0.54). The areas under the ROC curve of basophil count, percentage of basophil, and platelet count for patient group were 0.708, 0.611, and 0.636. A significant correlation was found between basophil count and platelet count (r=0.276, p=0.048), basophil count and mean platelet volume (r=-0.420, p=0.002), basophil count and percentage of basophil (r=0.685, p=0.000). Basophil count correlated with disease duration (r=-0.296, p=0.035). According to the Binary logistic regression analysis, low mean platelet volume predicts DS.* ***Discussion:*** *Inflammation might play a role in the etiopathogenesis of DS. Basophil and platelet-related parameters may be potential markers for DS.* ***(Anatolian Journal of Psychiatry 2020; 21(2):187-194)***

Keywords: *basophil, complete blood count, mean platelet volume, developmental stuttering, immune*

Bazofil ve trombosit ile ilgili parametreler ile gelişimsel kekemelik arasında bir ilişki var mı?

ÖZ

Amaç: *Çalışmalar gelişimsel kekemeliğin (GK) inflamatuar süreçlerle ilişkili olabileceğini göstermektedir. Tam kan sayımı (TKS) değerleri sistemik inflamatuar yanıtın göstergesi olarak kullanılmaktadır. Amacımız, özellikle bazofil, trombosit ve lenfositle ilişkili parametreler olmak üzere TKS ile GK arasındaki ilişkiyi değerlendirmektir.* ***Yöntem:*** *Bu geriye dönük olgu-kontrol çalışmasında, GK tanısı konmuş 54 hastanın TKS değerleri, 54 sağlıklı bireyin verileriyle karşılaştırıldı.* ***Bulgular:*** *Hasta grubunda, bazofil sayısı, bazofil yüzdesi ve trombosit sayısı anlamlı olarak daha yüksekti (p=0.001, r=0.35; p=0.044, r=0.19; p=0.045, r=0.11; sırasıyla) ve ortalama trombosit hacmi anlamlı olarak daha düşüktü (p=0.000, r=-0.54). Hasta grubunun bazofil sayısı, bazofil oranı ve trombosit sayısı düzeylerine ait ROC eğrisi altında kalan alanlar 0.708, 0.611 ve 0.636 idi. Bazofil sayısı ve trombosit sayısı (r=0.276, p=0.048), bazofil sayısı ve ortalama trombosit hacmi (r=-0.420, p=0.002), bazofil sayısı ve bazofil oranı (r=0.685, p=0.000) arasında anlamlı bir ilişki bulundu. Bazofil sayısı ile hastalık süresi arasında korelasyon vardı (r=-0.296, p=0.035). Binary lojistik regresyon analizine göre, düşük ortalama trombosit hacmi GK'yi öngörmektedir.* ***Tartışma:*** *GK'nin*

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etiyopatogenezinde inflamasyon rol oynayabilir. Bazofil ve trombosit ile ilişkili parametreler GK için potansiyel inflamasyon belirteçleri olabilir. ***(Anadolu Psikiyatri Derg 2020; 21(2):187-194)***

Anahtar sözcükler: *Bazofil, tam kan sayımı, ortalama trombosit hacmi, gelişimsel kekemelik, bağışıklık*

INTRODUCTION

Childhood-onset fluency disorder, also known as stuttering or stammering is a common disorder that is defined as interruptions in normal fluency and time patterning of speech (unsuitable for the individual's age) in Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5).[1] A lifetime incidence of 5% is the most consistently reported statistic and stuttering can be developmental or acquired.[2,3] Stuttering is a neurodevelopmental disorder associated with significant psychological burden and social stigma.[4] A growing body of genetic, neurologic, and theoretical research has provided insight into the pathophysiology of stuttering, but there is no consensus to date.[5]

It has been shown that, contrary to previous beli efs, the central nervous system (CNS) is not im mune-privileged. The nervous and immune systems are interconnected in a complex way and there are two-way interactions in both health and disease.[6] Immune mediators are normally expressed in healthy brain and not only crucial for brain development including neurogenesis, migration, differentiation, synapse formation and plasticity but also essential in normal brain functioning.[7] Given these critical regulatory roles in normal development and brain functioning, immune dysregulation may cause abnormal brain development structurally and/or functionally and may result in neurodevelopmental disorders such as autism,[8] attention deficit hyperactivity disorder (ADHD)[9] and intellectual disability.[10]

To the best of our knowledge, no previous studies have evaluated the inflammatory markers in Developmental Stuttering (DS). However, there are important findings in the literature that inflammation may be related to DS. Firstly, both clinical and epidemiological studies suggest that comorbidity is very common among all neurodevelopmental disorders and the co-occurrence is much higher than expected by chance alone.[11-14] These data and the findings of genetic, imaging, and environmental epidemiological studies suggest that rather than being considered as distinct entities, neurodevelopmental disorders could be considered as different patterns of impairment on a common underlying neurodevelopmental continuum.[15,16] Secondly, Strom and Silverberg stated that allergic conditions such as pediatric eczema, childhood asthma, hay fever and food allergy are associated with increased risk of speech disorders. It has been claimed that this increase may be related to chronic inflammatory processes.[17,18] Thirdly, Celik et al.[19] reported an association between seroprevalence of infection with *Toxoplasma gondii* and stuttering. It may be associated with inflammation due to latent parasitic infection. The current study is conducted in light of the hypothesis that the inflammatory processes might play a role in the etiopathogenesis of DS.

Some inflammatory markers can be examined with the conventional and inexpensive method of complete blood count (CBC). Blood cell counting can provide data on the composition of cells, such as red blood cells, monocytes, neutrophils, lymphocytes, basophils, blood platelets, and cell ratios, such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio, lymphocyte-monocyte ratio (LMR), which can be used as indicators of systemic inflammatory responses.[20] That cell counts and their ratios obtained from CBC may provide information about these different immunological processes.

The study aimed to investigate whether parameters that could point to the immunological mechanisms involved in the etiopathogenesis of DS exist.

METHODS

Participants

In this case-control study, CBC especially in terms of white blood cell (WBC), red blood cell (RBC), hemoglobin (HGB), hematocrit (HTC), platelet count (PLT), and mean platelet volume (MPV), neutrophil (NEU), lymphocyte (LYM), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), eosinophil to lymphocyte ratio (ELR), basophil to lymphocyte ratio (BLR) of 54 (44 males and 10 females) patients without any psychiatric treatment history who admitted to the psychiatry outpatient clinic of our University Training and Research Hospital and diagnosed with DS were compared with the data of 54 healthy (44 males and 10 females) subjects who were similarly distributed in regard to age. The diagnosis of DS was made according to DSM-5[1] by an experienced child and adolescent

psychiatrist and a speech-language pathologist.

Patients and controls with incomplete data were not included in the study. Subjects with organic disease or those with the potential to affect the measured parameters (drug use, hypertension, diabetes mellitus, coronary artery disease, cancer, hyperlipidemia, infectious diseases, pregnancy, rheumatologic diseases, acute and chronic inflammatory diseases) were excluded. Patients with other psychiatric comorbidities including substance use disorder, depression, anxiety, and psychosis spectrum were not included in the study even though their primary diagnosis was DS. This study was approved by the ethics committee of our University Training and Research Hospital (Date: 20/03/2018, Protocol Number: 2018/2-16).

Hematological analysis

Venous blood samples were obtained from the antecubital vein of both patient and control group between 8 and 10 a.m. after at least 8 h of starving. The samples were centrifuged within 30 minutes and in the same day, centrifugation was followed in the 'CELL-DYN 3700 SL Analyzer (Abbott Diagnostics, Chicago, U.S.A.)' device at our University Training and Research Hospital biochemistry laboratory.

Statistical analysis

SPSS for Windows statistical package version 22 (SPSS Inc., Chicago, IL, United States) was used for all statistical analyses. The numerical data were expressed as means and standard deviations, and the categorical data were expressed as frequencies and percentages. Normal distribution suitability was assessed using the Kolmogorov-Smirnov test. Mann-Whitney U Test was used for those with no normal distribution. Independent-samples t-test was used to make comparisons between two groups to determine significant differences between groups. Linear variables of hematological parameters of the DS and control group were compared with student's t-test. ROC curve analysis was used to measure the diagnostic value of WBC, PLT, BASO, and BASO ratio. Pearson correlation analysis was performed in the DS group. Binary logistic regression analysis was used in disease prediction. Cohen's d, R^2, and r were calculated as the effect size. A value of less than 0.05 (p-value) was considered statistically significant.

RESULTS

The mean age was 6.33±2.87 (range: 3-15 years old) in the DS group and 6.72±2.69 (range: 3-13 years old) in the control group. The ratio of males was 81.40% in both patient and control group and there was no significant difference in terms of age between the two groups (p=0.470). The mean duration of DS was 24.98±29.06 months (range: 0.25-120 months).

According to the comparison of CBC values, WBC, PLT, BASO, and BASO ratio were significantly higher (r=0.19, p=0.037; r=0.11, p=0.045; r=0.35, p=0.001; r=0.19, p=0.044, respectively); MPV was significantly lower in the DS group (r=-0.54, p<0.001). Other variables showed no significant differences. A comparison of sociodemographic variables and CBC values of the DS and control groups are given in Table 1. There was no significant difference in CBC parameters between females and males in the DS group.

According to the Pearson correlation analysis, a significant negative correlation was found between BASO ratio and WBC (r=-0.367, p=0.008), BASO ratio and MPV (r=-0.391, p=0.004), BASO and MPV (r=-0.420, p=0.002). A significant positive correlation was found between BASO and WBC (r=0.276, p=0.048), BASO and PLT (r=0.276, p=0.048). BASO was negatively correlated with duration of disorder (r=-0.296, p=0.035). The results of Pearson's correlation analysis of DS group are given in Table 2.

Binary logistic regression analysis was applied to examine the factors affecting being in the DS group (Table 3). Low MPV was found to be a predictor of DS (Nagelkerke R^2=0.483, OR=2.71). The predictors included in a logistic regression model to determine important risk factors for stuttering were WBC, PLT, BASO, BASO% and MPV. The model explained 48% of the variance on being stutterer.

Receiver operating characteristic (ROC) curve analysis performed to assess the diagnostic value of WBC, PLT, BASO, and BASO ratio is shown in Figure 1. The area under the ROC curve of WBC value for DS was 0.623, PLT value for DS group was 0.636, BASO value for DS was 0.708, and BASO ratio value for DS was 0.611. The optimal cut-off value for WBC was 7.75, and its sensitivity and specificity for the diagnosis of DS were 61.5% and 63.6%, respectively. The optimal cut-off value for PLT was 299.850, and its sensitivity and specificity for the diagnosis of DS were 67.3% and 57.1%, respectively. The optimal cut-off value for BASO was 0.085, and its sensitivity and specificity for the diagnosis of

Table 1. Comparison of sociodemographic variables and complete blood count values of patients with developmental stuttering and healthy controls

	Developmental stuttering (n=54)	Control (n=54)	p
Age (years)	6.33±2.87	6.72±2.69	0.470
Gender			
Male (n=88)	44 (81.40%)	44 (81.40%)	
Female (n=20)	10 (18.60%)	10 (18.60%)	
White blood cell (10^3/uL)	8.98±2.55	7.98±2.41	**0.037**
Red blood cell (10^6/uL)	4.95±0.37	5.04±0.47	0.258
Hemoglobin (g/dL)	12.94±0.94	13.10±1.39	0.485
Hematocrit (%)	39.25±2.71	39.30±3.92	0.928
Platelet (10^3/uL)	328.74±91.41	306.86±99.36	**0.045**
Mean platelet volume (fL)	6.82±1.15	8.45±1.38	**<0.001**
Neutrophil (10^6/uL)	4.00±1.57	3.44±1.50	0.071
Lymphocyte (10^3/uL)	3.73±1.33	3.38±1.11	0.136
Monocyte (10^3/uL)	0.70±0.24	0.64±0.25	0.241
Basophil (10^3/uL)	0.10±0.05	0.07±0.03	**0.001**
Eosinophil (10^3/uL)	0.33±0.25	0.29±0.30	0.462
Neutrophil %	44.73±9.95	42.90±9.74	0.353
Lymphocyte %	41.85±10.11	43.60±10.61	0.383
Monocyte %	8.05±1.92	8.57±2.79	0.273
Basophile %	1.36±0.94	1.07±0.36	**0.044**
Eosinophil %	3.79±2.71	3.90±3.77	0.858
Neutrophil to lymphocyte ratio	1.25±0.88	1.12±0.57	0.416
Platelet to lymphocyte ratio	107.29±112.16	94.82±29.19	0.431
Eosinophil to lymphocyte ratio	0.09±0.08	0.10±0.10	0.969
Basophil to lymphocyte ratio	0.03±0.08	0.02±0.00	0.254

Table 2. Pearson's correlation analysis of developmental stuttering group

		Duration of disorder	White blood cell	Platelet	Mean platelet volume	Percentage of basophil	Basophil count
Duration of disorder	Pearson's correlation	1	-0.132	-0.069	0.204	-0.196	-0.296*
	Sig. (2-tailed)		0.348	0.624	0.143	0.169	0.035
White blood cell	Pearson's correlation	-0.132	1	0.187	0.087	-0.367**	0.276*
	Sig. (2-tailed)		0.348	0.176	0.532	0.008	0.048
Platelet	Pearson's correlation	-0.069	0.187	1	-0.105	0.116	0.276*
	Sig. (2-tailed)		0.624	0.176	0.451	0.411	0.048
Mean platelet volume	Pearson's correlation	0.204	0.087	-0.105	1	-0.391**	-0.420**
	Sig. (2-tailed)		0.143	0.532	0.451	0.004	0.002
Percentage of basophil	Pearson's correlation	-0.196	-0.367**	0.116	-0.391**	1	0.685**
	Sig. (2-tailed)		0.169	0.008	0.411	0.004	<0.001
Basophil count	Pearson's correlation	-0.296*	0.276*	0.276*	-0.420**	0.685**	1
	Sig. (2-tailed)		0.035	0.048	0.048	0.002	<0.001

**: Correlation is significant at the 0.05 level (2-tailed); **: Correlation is significant at the 0.01 level (2-tailed)*

DS were 69.2% and 63.3%, respectively. The optimal cut-off value for BASO% was 1.00, and its sensitivity and specificity for the diagnosis of DS were 67.3% and 49.0%, respectively (Figure 1).

Cohen's d, r, R^2 values were calculated for PLT, MPV, BASO, and BASO ratio (Table 4).

DISCUSSION

To the best of our knowledge, this is the first study in the literature to examine the inflamma-

Table 3. Binary logistic regression analysis of developmental stuttering group

	Binary	p	Expectation (B)	95% CI Lower	Upper
White blood cell	-0.363	0.342	0.696	0.329	1.471
Mean platelet volume	0.997	**<0.001**	2.711	1.743	4.217
Percentage of basophil	-1.828	0.483	0.161	**0.001**	26.482
Basophil count	1.434	0.964	4.195	**<0.001**	26E+27
Platelet	0.005	0.095	1.005	0.999	1.012

Nagelkerke R^2=0.483, OR=2.71

Table 4. The values of effect size

	Cohen's d	r	R^2
Platelet	0.23	0.11	0.01
Mean platelet volume	-1.28	-0.54	0.29
Basophil count	0.75	0.35	0.12
Percentage of basophil	0.40	0.19	0.03

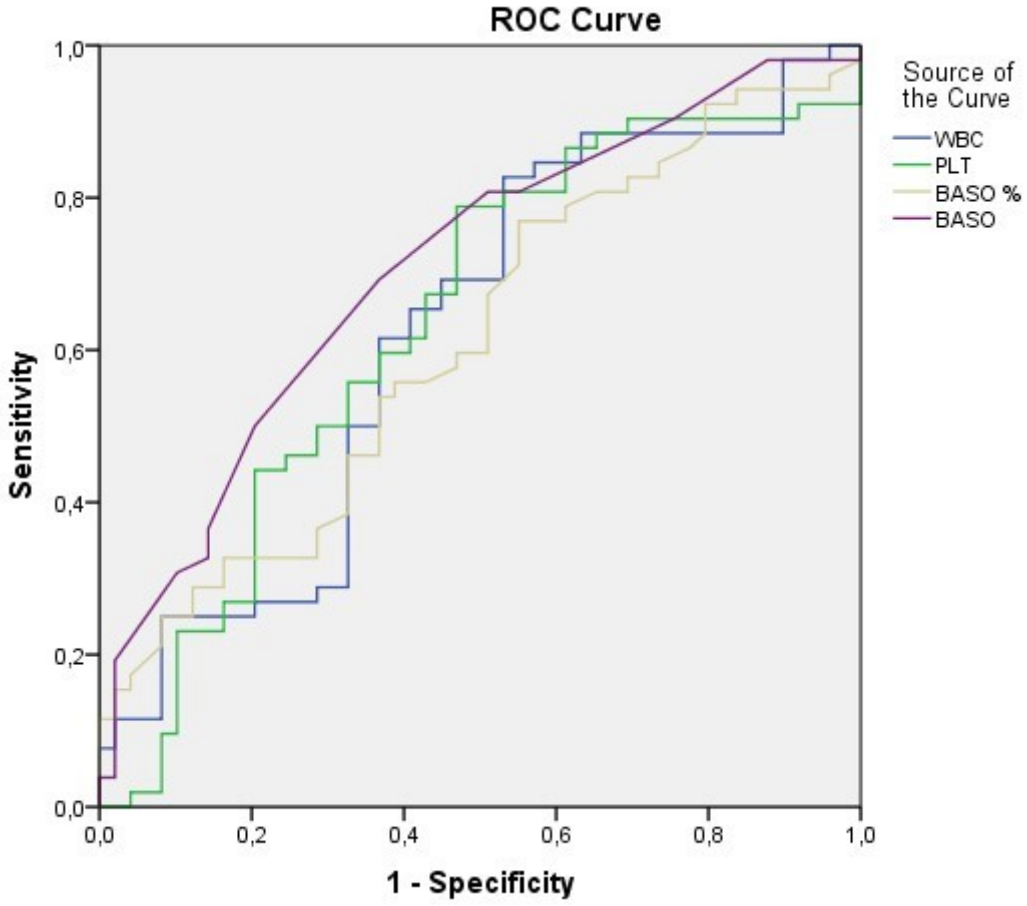

Figure 1. ROC curve analysis performed to assess the diagnostic value of WBC, PLT, BASO ratio, and BASO

tion status in DS. The inflammation status of children with DS was evaluated by comparing the complete blood cell parameters in DS patients and a healthy control group. Recent studies have shown that complete blood cell parameters can be used as an indicator of inflammation.[20]

The first significant finding in the study was that the WBC count was significantly higher in the stuttering group. WBC count can indicate disorders such as an infection or inflammation. But taken alone, the WBC count may have little value unless correlated with the patient's clinical condition and analyzed with different types of WBC.[21] Neutrophil, monocyte, lymphocyte counts and NLR, PLR, MLR did not differ between the groups. Hesapcioglu et al.[22] reported high monocyte level and high MLR, Kutlu et al.[23] found increased NLR in Autism Spectrum Disorder. Avcil[24] reported NLR, PLR, MLR and neutrophil count of the ADHD group were significantly higher than healthy group. The results of these studies were interpreted in favor of the inflammation processes in autism and ADHD. In our study, these inflammation parameters were not significant.

The second significant finding was increased basophil count and basophil percentage in DS group. This increase may indicate that chronic inflammation plays a role in the etiology of DS. Basophils are circulating blood granulocytes that comprise roughly 0.1-0.3% of all circulating WBCs. Basophils have an excess of immunoglobulin E (IgE) receptors and histamine and are mainly involved in allergic reactions, including hypersensitivity reactions and anaphylaxis. Such reactions involve the release of histamine and major proinflammatory cytokines, including IL-6, on activation.[25] Furthermore, basophils share a hematopoietic heritage with tissue-residing mast cells, which also play an important role in the inflammatory reaction.[26] Interestingly, the mast cell is known to play a major role in the central nervous system (CNS) neuroinflammation.[27] While we need to address more detailed mechanisms by which basophils and mast cells exercise their functions, it is now clear that basophils and mast cells play crucial and non-redundant roles in allergy, parasitic infection protection and other types of immune disorders.[28] Interestingly enough, allergic diseases, such as eczema, food allergy, hay fever and asthma, are known to be associated with language disorders.[17,18] Asthma and hay fever are associated with immunologic aberrancy secondary to basophilic activity including IgE hypersecretion and Th2 cytokine profile.[29,30] These inflammatory cytokines may cross the blood-brain barrier and affect behavioral, executive, and emotional neurocircuitry.[31] Indeed, a previous functional magnetic resonance imaging study of individuals undergoing asthma episodes found increased activation of the anterior cingulate cortex (ACC),[18,32] a portion of the brain active during normal speech.[18,33] Abnormal activation of the ACC has also been demonstrated during silent reading and speech tasks in individuals who stutter.[4] It is possible that repeated inflammatory insults to neurocircuitry relevant to speech and language increase the risk of speech disorders in children with chronic inflammation. Celik et al.[19] reported the association between seroprevalence of *T. gondii* and stuttering may be due to hyperdopaminergic state in brains of patients infected with *T. gondii* and this association may explain the increased prevalence of toxoplasmosis in stuttering children. This finding supports the hypothesis of dopamine excess about DS.[34] Increased dopamine may be due to an inflammatory reaction initiated by basophils. It ıs well documented that peripheral cytokines may indirectly affect central nervous system structures through the activation of vagal afferent fibers.[35] Cytokines have been reported to play a pivotal role in tryptophan metabolism and dopaminergic pathways in the brain.[9] There is not much additional data on the relationship between psychiatric disorders and basophil level. In one study, basophil levels were reported to be related to inflammation in anxious depression,[36] whereas in another study, basophil levels were significantly higher in the panic disorder group according to controls.[37]

The third significant finding was an increased platelet account with lower MPV in DS according to controls. The involvement of blood platelets in inflammatory response is related to the release of cytokines and chemokines that attract leukocytes and promote endothelial adhesion at the site of damage. During the inflammatory process, blood platelets may interact with leukocytes by forming platelet-leukocyte aggregates.[38,39] It has been demonstrated that in inflammatory conditions, also IL-6, IL-1, and TNF-α can stimulate precursor cells of blood platelets.[38,40] The function of IL-6 through the membranous receptor IL-6R is associated with enhanced Th production in the liver and its direct effect on megakaryocytes. This means that blood platelet count may increase markedly in an inflammatory condition. When platelets rapidly migrate to the site of inflammation where they undergo activation and wear.[38,41] This seems to

explain the drop in MPV in patients with ongoing inflammation.[38,42] Decreased MPV was noted in exacerbation of inflammatory diseases such as rheumatoid arthritis,[43] ulcerative colitis[44] and different neoplastic diseases.[45] Consistent with the literature, lower MPV and high platelet count appears to be associated with ongoing inflammation.[46-49] Additionally, low MPV was found to be a predictor of DS.

In conclusion, our study indicates that the lymphocyte-related ratios are not significantly different in the DS group when compared to the control group; while the BASO, BASO ratio, PLT, and MPV have a significant difference between the groups. This is the first study to explore the relationship between DS and inflammatory processes. Although cross-sectional design prevents results from being made on causality; WBC, Basophil, Platelet count and MPV values indicate that developmental stuttering may be associated with inflammatory processes. Further longitudinal studies with larger sample size may clarify the inflammatory involvement in DS.

Our study has several limitations. The most important of all is the retrospective nature of the study. Another one is the small sample size. The lifestyle and nutritional characteristics of the individual are also other confounding factors in our study. Adding that, our hypothesis is not supported by the change of other inflammatory markers.

Authors' contributions: M.Z.K.: concept, literature search, analysis and/or interpretation, writing; M.H.O.: concept, design, literature search, data collection and/or processing, analysis and/or interpretation, writing; E.S.: design, analysis and/or interpretation.

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