

Original Article

Central nervous system malformations and contributing disorders

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Abstract: Purpose: Neurologic disorders may be seen in patients with cerebral malformations. The aim of this study is determining epilepsy and the other contributing disorders in the patients with cerebral malformations using Gross Motor Function Classification Scale (GMFCS) and Bimanual Fine Motor Function Scale (BFMFS) are used to determine motor function. Methods: The clinical and neuroradiologic features of 76 patients with cerebral malformations admitted between the dates December 2011 and May 2012 were evaluated and motor prognosis is determined. Result: The most common associated disorders were mental retardation, epilepsy, language and speech disorders, malnutrition, Cerebral Palsy. Epilepsy was seen at half of the patients, and it was most common in cerebral cortex malformations ($P<0.05$). GMFCS level 5 was most common associated with cerebral cortex malformations. Most of the patients with cerebral palsy had GMFCS level 5. Oromotor dysfunction was most common in cerebral cortex malformations. Patients' developmental state and oromotor function got worse with increasing GMFCS level. Epileptic patients had higher GMFCS and BFMFS levels than others. Conclusion: Central nervous system malformations are frequently associated with epilepsy and mental retardation, there were severe neurologic findings in these patients. We concluded that GMFCS and BFMFS may be beneficial to determine the motor prognosis in these patients.

Keywords: BFMFS, GMFCS, cerebral malformations

Introduction

Central nervous system malformation constitutes about 8.8-13.3% of all congenital malformations [1-3]. Aetiology of the majority is not well known, but chromosome abnormalities, monogenic disorders, environmental factors (maternal infections, maternal diabetes, radiation, thalidomide, valproic acid, A hypervitaminosis) are thought to play a role [2].

Severe neurological complications may be seen with central nervous system malformations, and clinical findings may change according to the developmental stage, type of malformation, affected part of the brain [1-3]. New neurological findings may emerge during the maturation of central nervous system according to the week of the fetus, so it is hard to estimate the motor prognosis [1-3]. The determination of the motor prognosis in the early period is difficult.

The fear of the parents is whether their child will be able to resume a normal life in the future and be able to walk. Initially, Palisiano et al. [4] developed a scale to determine the motor prognosis of patients with cerebral palsy. The Gross Motor Function Classification Scale (GMFCS) consists of measuring the sitting and walking ability in children with CP [4]. The motor prognosis can be a guide for possible additional disorders and for planning the treatment [5, 6]. The aim of this study was to evaluate the contributing disorders including epilepsy and the others, to determine their relationship with cerebral malformation by GMFCS, BFMFS. Rosenbaum had reported that these scales may be used to determine motor prognosis with diseases other than cerebral palsy [7].

Central nervous system malformations are frequently associated with epilepsy and mental retardation, and severe neurologic findings are

detected in these cases. We decided that GMFCS and BFMFS might be beneficial to determine motor prognosis in these patients.

Material and methods

This study was performed between December 2011 and May 2012 in Pediatric Neurology Department, with a total of 76 patients diagnosed with central nervous system malformation. The ethics committee approval number is PR-11-12-09-04.

Epilepsy and other contributing disorders were evaluated in these patients. Gross motor function classification scale (GMFCS) was used to measure the motor function. Bimanual fine motor function scale (BFMFS) was used to measure upper extremity fine motor function. These scales give more reliable results after 2 years of age, so patients under the age of 2 were not included the study. Cerebral palsy was classified clinically according to the recommendations of the workshop held in Bethesda and the European Cerebral Palsy Surveillance Group [8]. The nutritional habits of the patients were evaluated. Each patient was ophthalmologically evaluated, and Visual Evoked Potentials were studied. All patients were examined by an otolaryngologist and Otoacoustic Emission (OAE) was performed. Patients who failed the OAE were evaluated with electrophysiological audiometry. The seizure history was assessed in detail. All patients underwent electroencephalography (EEG). The electroencephalography records were performed using the Nihon Kohden Neurofax 7310 F EEG device. The patients who had 2 or more seizures in the absence of any stimulating factor and with no repeated seizures on the same day were accepted as epileptic.

For children over 6 years of age, the WISC-R intelligence test, and for children under 6, the Ankara developmental screening inventory test was performed. All patients routinely underwent urine-blood amino acid analysis.

Magnetic resonance imaging (MRI) was performed by 1.5 T MRI scanner (Siemens, VisionPlus, Germany) equipped with the head coil. MRI performed by a 1.5 Tesla device is clearly demonstrate the some extensive brain abnormalities, but it is equally clearly missing many others, including focal polymicrogyria, focal pa-

chygyria, gray matter heterotopias in white matter, and focal cortical dysplasias. The reliability of this assessment of structural abnormalities to correlate with clinical deficits, signs and symptoms is limited because of technical inadequacy.

The motor functions were measured with gross motor function classification scale (GMFCS) and bimanual fine motor function scale (BFMFS) [4, 9, 10].

Patients with cerebral malformations including medulla spinalis anomalies, isolated mega cisterna magna anomalies, isolated arachnoidal cysts were excluded.

Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows 16.0 (SPSS Inc. Chicago, IL) statistical pocket program was used to evaluate the data. The frequency distribution was expressed as %, and the age was expressed as "years", and given as the average values $\pm$ standard deviation. The Student t-test was used for comparison of 2 average values, and the chi-square test used for comparison of the percentages. The Spearman correlation analysis was used for the correlation analysis. A *P* value of <0.05 was accepted as a statistically significant level.

Results

The mean age of the total of 76 patients was 6.4 ± 3.5 (2-15 years), and the female/male ratio was 2.1. Twenty patients did not have any risk factor. Twenty-one of the patients had more than one risk factor. Prenatal risk factors were seen in 45.5%, natal risk factors were seen in 22.7%, postnatal risk factors were seen in 31.8% of cases. The most frequently seen risk factor was bleeding during the prenatal period. Meconium aspiration was most commonly observed during the natal period, and asphyxia, hyperbilirubinemia were the most frequently seen during the postnatal period.

Head control was not acquired in 15 (19.7%) patients, 24 patients (31.5%) could not sit without support, 30 patients (39.4%) had spasticity, 17 (22.4%) patients had axial hypotonia, 33 patients (43.4%) could not walk, 21 patients (27.6%) walked ataxic, hemiplegic, diplegic; 35 patients (46%) could not speak. Most frequent

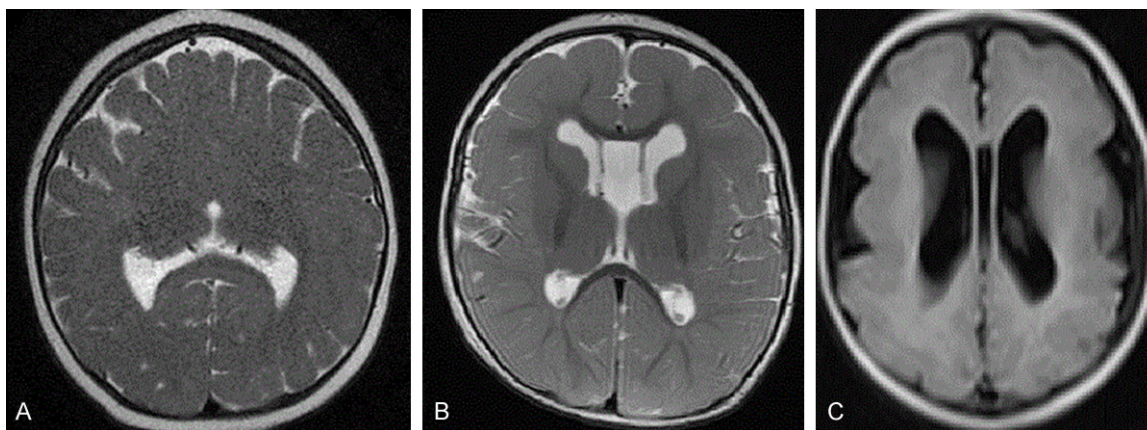


Figure 1. MRI of some patients. A. Holoprosencephaly; B. Pachygyria, Cavum septum pellicidum et vargea; C. Lysencephaly and pachygyria.

Table 1. Distribution of brain malformations in cases with or without epilepsy

Brain malformation	Total	Epilepsy		Total
	N (%)	No n (%)	Yes n (%)	N (%)
VIM	26 (34.2)	11 (61.2)	7 (38.8)	18 (100)
CCM	18 (23.6)	7 (26.9)	19 (73.1)	26 (100)
PFM	12 (15.8)	12 (100)	-	12 (100)
VIM+CCM	13 (17.2)	3 (23.1)	10 (76.9)	13 (100)
VIM+PFM	2 (2.7)	2 (100)	-	2 (100)
CCM+PFM	4 (5.2)	3 (75)	1 (25)	4 (100)
VIM+CCM+PFM	1 (1.3)	-	1 (100)	1 (100)
Total	76 (100)	38 (50)	38 (50)	76 (100)

complaints were neurodevelopmental delay (31.6%), convulsion (30.3%), and microcephaly (13.2%).

Cerebral malformations were classified as ventral induction malformations (VIM), cerebral cortex malformations (CCM), posterior fossa malformations (PFM).

Distribution of patients was as following; 18 patients with VIM (23.6%), 26 patients with CCM (34.2%), 12 patients with PFM (15.8%), 13 patients with VIM+CCM (17.2%), 2 patients with VIM+PFM (2.7%), 4 patients with CCM+PFM (5.2%), 1 patient with VIM+CCM+PFM. MRI images of some patients are shown in **Figure 1**.

The other contributing disorders were, in particular, neurodevelopmental delay/mental retardation (86.8%), language and speech problems (86.8%), epilepsy (50%), ophthalmological problems (46%) and, oromotor dysfunction

(43.4%), followed by malnutrition (39.4%), cerebral palsy (27.6%), orthopedic problems (11.8%), hearing loss (10.5%), endocrine problems (7.8%).

Epilepsy is most commonly found at CCM. Thirty eight patients had epilepsy, 19 of epileptic patients had CCM (50%), 10 of the epileptic patients had VIM+CCM (26.4%), 7 of the epileptic patients had VIM (18.4%).

Cerebral cortical malformation was seen in 73.1% and VIM+CCM was observed in 76.9% of the epileptic patient group. The most commonly seen malformation was CCM ($P<0.05$), (**Table 1**).

Thirty-one of epileptics had cerebral cortex malformation; 11 (68.8%) had unilateral cortical involvement, 9 (60%) had bilateral cortical involvement, 11 (84.6%) had diffuse cortical involvement. Epilepsy was more frequent in cases with diffuse cortical involvement than the others ($P<0.05$) (**Table 1**).

Epilepsy was the most common in cases with GMFCS level 5 ($P<0.05$), 14 of the patients with GMFCS level 5 had cerebral palsy ($P<0.05$), 11 of them had a retardation based on Ankara developmental screening inventory test (ADS-IT) ($P<0.05$), 10 patients had retardation on WISC-R. Speechless 19 patients (54.3%) had GMFCS level 5. Seventeen of patients who had speech disorder were at GMFCS level 1, 11 of them was at GMFCS level 2, 2 of them was at GMFCS level 5 ($P<0.05$). Malnutrition was seen

Table 2. Distribution of clinical features based on GMFCS levels

	GMFCS					Total N (%)
	Level 1 N (%)	Level 2 N (%)	Level 3 N (%)	Level 4 N (%)	Level 5 N (%)	
Epilepsy						
No	18 (47.4)	10 (26.3)	2 (5.3)	4 (10.5)	4 (10.5)	38 (100)
Yes	11 (28.9)	7 (18.4)	2 (5.3)	1 (2.7)	17 (44.7)	38 (100)
CP						
No	29 (52.7)	12 (21.8)	3 (5.5)	4 (7.3)	7 (12.7)	55 (100)
Yes	-	5 (23.7)	1 (4.8)	1 (4.8)	14 (66.7)	21 (100)
ADSIT						
Normal	6 (100)	-	-	-	-	6 (100)
Retarded	10 (30.3)	5 (15.2)	3 (9.1)	4 (12.1)	11 (33.3)	33 (100)
WISC-R						
Normal	4 (100)	-	-	-	-	4 (100)
Retarded	9 (27.2)	12 (36.3)	1 (3.1)	1 (3.1)	10 (30.3)	33 (100)
Speech						
Speechless	3 (8.6)	5 (14.3)	3 (8.6)	5 (14.3)	19 (54.2)	35 (100)
Disturbance	17 (56.7)	11 (36.7)	-	-	2 (6.6)	30 (100)
Malnutrition						
No	21 (45.7)	12 (26.1)	3 (6.5)	1 (2.2)	9 (19.5)	46 (100)
Yes	8 (26.7)	5 (16.7)	1 (3.3)	4 (13.3)	12 (40)	30 (100)
Oromotor dysfunction						
No	25 (58.1)	12 (27.9)	2 (4.7)	3 (7)	1 (2.3)	43 (100)
Yes	4 (12)	5 (15.2)	2 (6.1)	2 (6.1)	20 (60.6)	33 (100)
Ophthalmologic Problems						
No	19 (46.3)	9 (22)	1 (2.4)	2 (4.9)	10 (24.4)	41 (100)
Yes	10 (28.6)	8 (22.8)	3 (8.6)	3 (8.6)	11 (31.4)	35 (100)

in 12 patients with GMFCS level 5 ($P>0.05$). Oromotor dysfunction was seen 33 of the patients, 20 (60.6%) of them had GMFCS level 5 ($P<0.05$) (**Table 2**).

Twenty-one patients had cerebral palsy, 16 of them (42.1%) had epilepsy; epilepsy was the most frequent contributing disorder in patients with cerebral palsy ($P<0.05$).

Microcephaly was seen most commonly in CCM group (29.7%). The most common malformation seen in cerebral palsy was VIM+CCM ($P<0.05$). Language and speech problems were seen in sixty-five patients and CCM was the most commonly seen malformation (30.7%). The neurodevelopmental delay was detected in 66 of the patients, CCM was seen in 34.2%, VIM was seen in 23.7%, PFM was observed in 15.7% of them.

Lower extremity motor functions were scored with GMFCS, according to this scale, 29 pati-

ents had level 1, 21 patients had level 5, 17 patients had level 2 GMFCS. Cerebral cortex malformation was the most frequent in patients with level 1 and 5 GMFCS (**Table 3**).

Upper extremity motor functions were scored with BFMFS. According to this scale, 31 patients had level 1 BFMFS, the most commonly seen malformation was CCM in level 1 and CCM+VIM in level 5 cases.

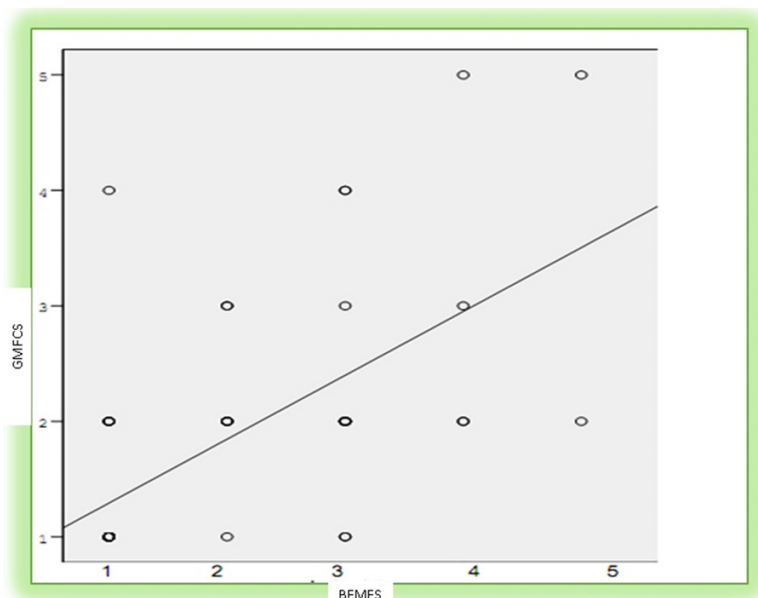
Positive correlation was detected between GMFCS and BFMFS, BFMFS levels increased with increasing the GMFCS level ($r=0.90$), ($P<0.05$), (**Figure 2**).

Conclusion

Central nervous system malformations are seen in 3% of newborns, in 75% of fetal deaths, in 40% of the children dead within the first year of life [3].

Table 3. GMFCS distribution in cases with or without cerebral malformation

GMFCS	Cerebral malformation							Total
	VIM	CCM	PFM	VIM+CCM	VIM+PFM	CCM+PFM	VIM+CCM+PFM	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Level 1	6 (20.7)	11 (37.9)	7 (24.3)	3 (10.5)	1 (3.3)	1 (3.3)	-	29 (100)
Level 2	3 (17.6)	5 (29.4)	3 (17.6)	2 (11.8)	-	3 (17.6)	1 (5.9)	17 (100)
Level 3	3 (75)	1 (25)	-	-	-	-	-	4 (100)
Level 4	1 (20)	1 (20)	2 (40)	1 (20)	-	-	-	5 (100)
Level 5	5 (23.8)	8 (38.1)	-	7 (33.3)	1 (4.8)	-	-	21 (100)

**Figure 2.** Distribution of GMFCS vs BFMFS.

Clinical, EEG, neuroimaging features of 76 patients with central nervous system malformations were evaluated in the present study; GMFCS and BFMFS were used to determine motor prognosis. The female/male ratio was 2.1. Some cerebral malformations such as subcortical band heterotopia, anencephaly, Aicardi syndrome have been reported more frequently in girls [2]. A study of cases with congenital CMV infection revealed that brain malformations which seen more frequently in girls were due to inadequate immune response [11].

Cerebral malformations occur due to abnormal development during neuronal proliferation, migration, myelination and lead to developmental delay, microcephaly, hemiparesis, intractable epilepsy [12]. The type of the malformation, involved brain region, and patients' age may cause different symptoms and motor

disturbances. Associated genetic syndromes also cause additional symptoms [13, 14].

In the present study, CCM (isolated or together with other anomalies) was seen in 44 patients. The most frequent complaint at admission was convulsion. Pachygyria was the most frequently seen in the CCM group. The neurological findings were mostly seen with CCM. GMFCS level was more severe in CCM. Microcephaly, mental retardation, language problems and oromotor dysfunction were more frequently observed with CCM.

Dysmorphic findings may be related to ventral induction malformations. Different neu-

rological findings may be observed with associated cerebral malformations. Isolated corpus callosum agenesis may be asymptomatic or may cause attention deficit, CP, speech disturbances. Corpus callosum malformations mostly associated with the other malformations and it is incidentally seen by neuroimaging [13-15]. Ventral induction malformation was the second most commonly seen in our study. Corpus callosum anomalies were most common in the group of ventral induction anomalies. Cerebral palsy was frequent in association with VIM+CCM. Microcephaly, language and speech disorders, ophthalmologic problems, walking problems, epilepsy, mental retardation and developmental delay were seen in similar rates both in VIM and CCM.

Hahn et al. [16] reported intractable epilepsy association with holoprosencephaly in the

presence of cortical malformation. In the present study, holoprosencephaly was detected in four patients (2 semilobar, 1 lobar, 1 interhemispheric variant). These patients had varying degrees of infantile spasms, dysmorphic findings, mental retardation, microcephaly, language and speech problems, diabetes insipidus, hypothyroidism.

Neurological findings may change by malformation type in cerebellar disturbances. Cerebellar hypoplasia may be associated with ataxia, motor deficit, hyperpnea, abnormal eye movements, increased intracranial pressure, autism, mutism, learning problems, language problems [17, 18]. Patients with cerebellar malformation had language and speech problems, microcephaly, ophthalmologic problems and cerebellar hypoplasia and, Dandy-Walker malformation was the most common one in the present study.

Epilepsy was the most common disorder associated with cerebral malformations. Hypo/hyperexcitation of cortical neurons in the dysplastic cerebral tissue is thought to be the mechanism for epilepsy [19]. CCM has been detected in intractable epilepsy cases during the childhood [20, 21]. Epilepsy frequency and clinical spectrum vary with malformation type [19, 22]. In the present study, half of the patients had epilepsy. Lysencephaly-pachygyria-agyria was detected in 64.5% of the epileptic patients. Status epilepticus developed in 18.4% of epileptic patients.

Visual problems may emerge due to disruption of cerebral cortex and cerebral malformation [23]. In this study, the most common visual disturbance was visual impairment and mostly seen in corpus callosum malformation.

Sullivan et al. [24] established oromotor dysfunction including drooling, vomiting, speech disturbances in the children with chronic neuromuscular disorders. In the present study 2.6% of the patients had gastrostomy, 30.2% had oromotor dysfunction and 39.4% had malnutrition. Our findings support that cerebral malformations may cause oromotor dysfunction and malnutrition.

Some risk factors may play a role in cerebral palsy damaging upper motor neurons during the prenatal period. High frequency of central nervous system malformation in cerebral palsy

suggests the idea that there is an etiologic and pathogenic relationship between cerebral malformations and cerebral palsy [25-27]. In the present study, brain malformations were seen in 27.6% of cases with cerebral palsy. The relationship between cerebral malformation and cerebral palsy was statistically significant ($P < 0.05$). In accordance with some studies, patients with cerebral palsy and also cerebral malformation had mental retardation, visual disturbances, epilepsy with higher rates than the others [27].

It is difficult to comment that neurological functions and motor prognosis result from the developing central nervous system. Damages especially during the prenatal period in the premotor cortex, supplementary motor area, primary and secondary motor somatosensory cortex cause spasticity, difficulty of perception, apraxia, agnosia, visual and hearing problems [26-28]. Estimation of motor prognosis is hard due to severity and extensiveness of brain malformation during the early childhood period. GMFCS and BFMFS are used to estimate motor prognosis in patients with cerebral palsy. Pathophysiological and neurological mechanisms in cerebral palsy serve as a model for cerebral malformation and cause similar neurological problems.

Gross motor function classification scale becomes a commonly used method for evaluating the motor prognosis [29, 30]. GMFCS gives useful prognostic results to doctors and patient's family [9].

In the present study, there was a non-significant relationship between influenced brain region, extensiveness, patients symptoms but diffuse and bilateral cortical involvement correlate with increased levels of GMFCS. In the present study, GMFCS level 5 was seen most commonly in CCM followed by VIM. More than one malformation did not cause an increase in GMFCS levels. Comorbidities such as mental retardation, hearing loss, visual disturbances, epilepsy correlate with increased GMFCS levels [31, 32].

More severe associated disorders correlate with more severe GMFCS levels. In other studies, the half of cerebral palsy patients were detected at GMFCS level 4 and level 5, most of the patients with high level had quadriparetic-

type cerebral palsy [5, 33]. In our study, 66.7% of patients with cerebral palsy had level 5 GMFCS. More severe cerebral palsy type was associated with more severe GMFCS levels. In this study, 52.7% of the 55 patients other than cerebral palsy had GMFCS levels 1 and 12.7% of the 55 patients other than cerebral palsy had GMFCS levels 5. Both GMFCS and BFMFS were higher in patients with epilepsy. Neurodevelopmental status and oromotor function worsened with increased levels of GMFCS. Speechless patients and patients with language disorders were most common in a group had GMFCS level 5 ($P<0.005$).

Learning disabilities, epilepsy, visual disturbance are closely related to increased GMFCS and BFMFS levels. Especially, GMFCS shows the motor prognosis. GMFCS is the most common related factor in educational difficulties and social behavior. A correlation between GMFCS and BFMFS were reported by Beckung and Hagberg [34] as the first time. Their study showed that great motor function of the patient more severely influenced than fine motor functions [34]. In our study, BFMFS levels increased with increasing GMFCS levels.

In the present study, 76 patients with central nervous system malformation were evaluated. The most common malformation was CCM including lissencephaly, pachygyria, schizencephaly and cortical dysplasia. Epilepsy and mental retardation were the most common associated disorder. More severe and diffuse cerebral malformations correspond to more severe neurological findings and higher GMFCS levels. The patients with epilepsy and mental retardation had higher GMFCS and BFMFS levels.

Conclusion

During the prenatal period in which brain development fastly occurs, the central nervous system malformation may initially impair neurological functions, and then the permanent motor and cognitive disturbances occur. We have decided that GMFCS and BFMFS are useful for determining the motor prognosis in children older than 2 years. These scales can be used as a warning method and help to guide the clinician for the treatment plan for patients who had motor deficits.

Disclosure of conflict of interest

None.

Authors' contribution

Sevgi Yimenicioğlu carried out the concept, study design, data collection, Ayten Yakut carried out the literature overview Arzu Ekici participated in the design of the study. Coskun Yazar conceived of the study, and Kursat Bora Carman participated in its design and coordination and Ozan Kocak helped to draft the manuscript, Didem Arslantaş performed the statistical analysis. All authors read and approved the final manuscript.

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