Chron Precis Med Res 2023; 4(1): 15-21
DOI: 10.5281/zenodo.7718553

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Juvenile Localized Scleroderma from a Pediatric Rheumatology Perspective: A Single-Center Experience

Çocuk Romatoloji Perspektifinden Juvenil Lokalize Skleroderma; Tek Merkez Deneyimi

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ABSTRACT

Aim: To evaluate juvenile localized scleroderma, which is a disease with high rates of cosmetic and functional sequelae in children, from a pediatric rheumatology perspective.

Material and Method: We retrospectively investigated the data of patients who were diagnosed with juvenile localized scleroderma (JLS) in our pediatric rheumatology clinic between 2015 and 2022, were aged <18 years, and attended their follow-ups regularly. Demographic, clinical, treatment-related, and prognostic data of the patients were included.

Results: Among the 19 patients diagnosed with JLS, 12 (63.2%) were female, and 7 (36.8%) were male. The female-to-male ratio in the sample was 1.7. Eight (42.1%) patients had circumscribed JLS, 8 (42.1%) had linear JLS, 2 (10.6%) had mixed JLS, and 1 (5.3%) had generalized JLS. The patients' mean age of onset of symptoms was 8.2±5.5 years, while their mean age of diagnosis was 9.4±4.9 years. The most frequently involved anatomical regions were the extremities, whose involvement was found in 15 (78.9%) patients. The prevalence of lesions crossing joints was 57.9%, and joint damage was seen in 21.1% of the patients. The rate of cosmetic sequelae was 73.7%. There was antinuclear antibody positivity in 52.6% of the patients. Systemic involvement did not occur in any patients during their follow-ups. The most frequently used treatment agent was methotrexate. Complete remission was achieved in 2 (10.6%) patients.

Conclusion: As it can lead to high degrees of cosmetic and functional sequelae, it is necessary to diagnose juvenile localized scleroderma early and start an aggressive treatment in the early period. To avoid wasting time, it is essential, especially for pediatricians, to immediately order biopsies from suspected lesions or refer these patients to pediatric rheumatology clinics.

Keywords: Juvenile localized scleroderma, morphea, treatment

ÖZ

Amaç: Çocuklarda kozmetik ve fonksiyonel sekel oranı yüksek bir hastalık olan juvenil lokalize sklerodermayı çocuk romatoloji perspektifinden değerlendirmek.

Gereç ve Yöntem: Çocuk romatoloji kliniğimizde 2015-2022 yılları arasında juvenile lokalize skleroderma tanısı almış <18 yaş altı, takiplerine düzenli gelen hastalar retrospektif olarak incelendi. Hastalara ait demografik, klinik, tedaviye ilişkin ve prognostik veriler kaydedildi.

Bulgular: Juvenil lokalize skleroderma tanısı olan 19 hastanın 12'si (63.2%) kız, 7'si (36.8%) erkek cinsiyetteydi. Kız/erkek oranı 1,7'ydi. JLS tanısı olan hastalardan 8'i (42.1%) plak, 8'i (42.1%) lineer, 2'si (10.6%) miks ve 1'i generalize tipte idi. Şikayetlerin ortalama başlangıç yaşı 8.2±5.5 yaş, tanı yaşı ise ortalama 9.4±4.9 yaştı. En sık tutulan anatomik bölge 15 hasta (78.9%) ile ekstremitelerdi. Eklem ile ilişkili cilt lezyonu oranı 57.9% iken eklem hasarı 21.1% hastada görüldü. Kozmetik sekel oranı 73.7%'ydi. Hastaların 52.6%'sında antinükleer antikor pozitifliği vardı. Takip süresince hiçbir hastada sistemik tutulum gelişmedi. En sık kullanılan tedavi metotreksat idi. 2 hastada (10.6%) tam remisyon sağlanabildi.

Sonuç: Yüksek oranda kozmetik ve fonksiyonel sekellere yol açabileceğinden juvenil lokalize sklerodermanın erken tanınması ve erken agresif tedavisi gerekmektedir. Özellikle çocuk hekimlerinin şüphelendikleri lezyonlardan bekletmeden biyopsi yaptırması veya bu hastaları çocuk romatoloji kliniklerine yönlendirmesi zaman kaybetmemek adına önemlidir.

Anahtar Kelimeler: Juvenil lokalize skleroderma, morfea, tedavi

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Başvuru Tarihi/Received: 03.02.2023
Kabul Tarihi/Accepted: 15.02.2023

INTRODUCTION

Juvenile scleroderma is a rarely encountered chronic autoimmune disease characterized by excessive collagen accumulation in connective tissue and fibrosis (1,2). It has two subtypes: juvenile localized scleroderma (JLS) and juvenile systemic scleroderma (3-5). JLS, also known as morphea, is the most frequently seen form of scleroderma in childhood that predominantly affects the skin and subcutaneous tissue and can reach the fascia and muscles below the skin (1,2). Extracutaneous symptoms, including neurological, musculoskeletal, and eye complications, can be seen in 22% of patients (6). The term localized scleroderma is a general term, and it includes various subtypes with different clinical presentations and disease severities. The latest classification, which was made by the Pediatric Rheumatology European Society (PReS), divides the disease into five subtypes. These subtypes are as follows: (1) circumscribed morphea, (2) linear scleroderma, (3) generalized morphea, (4) pansclerotic morphea, and (5) mixed morphea (7).

While the etiopathogenetic mechanisms that cause localized scleroderma are not entirely known, it is thought that several factors, such as infections, drugs, hormones, and autoimmune mechanisms, are influential in the onset of the disease (8,9).

The treatment of the disease varies depending on the subtype of the disease, the size of the lesion, the number of lesions, and the existing damage. Initially, treatments such as phototherapy, imiquimod and topical steroids are used in localized morphea. Systemic steroids, immunosuppressive drugs such as methotrexate and mycophenolate mofetil are preferred when morphea progresses despite topical treatments and in linear, generalized, mixed and pansclerotic scleroderma subtypes (10,11). Mortality in JLS cases is rare, but patients suffer high rates of cosmetic problems, disfigurement, dysfunctions, and neurological issues.

There are a limited number of studies conducted in Turkey on this disease, which is seen in children ten times as prevalently as systemic sclerosis and can create severe cosmetic and functional problems. Existing studies are usually those conducted by dermatologists (12-14). This study aims to investigate the demographic, clinical, and laboratory characteristics and treatment methods of JLS patients from a pediatric rheumatology perspective.

MATERIAL AND METHOD

This retrospective observational study included patients diagnosed with JLS in our pediatric rheumatology clinic between 2015 and 2022, were aged <18 years and attended their follow-ups regularly. Patients with JLS who had not been followed up for at least six months and patients with a diagnosis of juvenile systemic sclerosis were excluded.

For the patients, data on the age of diagnosis, the age of onset of complaints, sex, JLS subtype, disease duration, anatomical region of involvement, accompanying systemic symptoms, the presence of triggering factors, family history of rheumatic disease, laboratory data [hemogram, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), infection screenings, antinuclear antibody (ANA), rheumatoid factor (RF), anti-extractable nuclear antibody (ENA)], the presence of comorbidities, treatments used, treatment response status, and follow-up duration were retrospectively collected from their electronic records. The sequelae of the patients causing morbidity were recorded by dividing them into cosmetic, functional (e.g., contracture, joint deformity, extremity shortening), and neurological categories.

Disease subtypes were classified as circumscribed, generalized, linear, pansclerotic, or mixed. One or more oval or round plaques localized in at most two anatomical regions (head and neck, each extremity, posterior and anterior trunk) were classified as limited morphea; four or more infiltrating plaques, each larger than 3 cm, involving at least two anatomical regions were categorized as generalized morphea. Sclerotic lesions showing linear bands [en coup de sabre (ECDS) affecting the extremities and head, Parry-Romberg variants] were classified as linear morphea; those with a combination of 2 or more types were classified as mixed; and those involving deep layers of skin and connective tissue (e.g., adipose tissue, fascia, muscle tissue, bone tissue) were classified as pansklerotic morphea (7).

Treatment response was categorized as complete remission, partial remission, or treatment resistance. Complete remission was accepted as the absence of new lesions for at least a year despite the termination of drug treatment and the inactivation of existing lesions. Partial remission was obtained to alleviate initial symptoms (fading of color, reduced hardness, shrinking size) for at least three months. Treatment resistance was defined as the persistence of active disease despite full-dose treatment. Finally, relapse was considered the activation of the disease during the tapering of the treatment or after the completion of the treatment (15, 16).

The local ethics committee approved the study (approval no: E2-23-3179).

Statistical Analysis

The statistical analyses were conducted using the SPSS Version 20 (SPSS Inc., Chicago IL, USA) software. The qualitative variables are expressed as percentages, and the quantitative variables are presented with a mean (± standard deviation) values if they were normally distributed and median (minimum-maximum) values

if they were non-normally distributed. The categorical data were compared using $\chi 2$ tests, and the numeric data were compared using Student's t-test.

RESULTS

In the study period, the number of patients diagnosed with rheumatic diseases in our pediatric rheumatology clinic and regularly followed up was 3870. Nineteen (0.5%) of these patients were diagnosed with JLS. Among the JLS patients, 12 (63.2%) were female, and 7 (36.8%) were male. The female-to-male patient ratio was 1.7. Eight (42.1%) patients had circumscribed JLS, 8 (42.1%) had linear JLS, 2 (10.6%) had mixed JLS, and 1 (5.3%) had generalized JLS. There was no statistically significant difference between the sexes regarding their localized scleroderma subtypes (p=0.782). Among the patients with linear localized scleroderma, 2 (10.5%) patients had ECDS. The patients' mean age of onset of symptoms was 8.2±5.5 years, while their mean age of diagnosis was 9.4±4.9 years. While the mean age of onset of symptoms in the female patients was 7.3±5.7 years, the mean age of onset of symptoms in the male patients was 9.9±4.7 years, and there was no significant difference between the female and male patients (p=0.332). The mean ages of onset of symptoms among the patients also did not vary significantly based on their disease subtypes (p=0.303). The median delay in diagnosis was five months (minimum: 1 month - maximum: 5.1 years). Five (26.2%) patients had comorbidities. Among these five patients, 1 had asthma, 1 had hydronephrosis, 1 had immune thrombocytopenic purpura, 1 had idiopathic facial paralysis, and 1 had pangastritis. Three (15.8%) patients had a family history of rheumatoid arthritis, an autoimmune disease, in their first-degree relatives. Two (10.6%) patients had a family history of Behçet's disease.

Factors that could potentially trigger localized scleroderma were present in 4 (21.1%) patients (**Table 1**). The initial symptoms of the disease were skin hardening in 5 (26.3%) patients, skin redness-bruising in 5 (26.3%), brown spots on the skin in 4 (21.1%), white patches on the skin in 2 (10.6%), skin swelling in 1 (5.3%), skin thinning in 1 (5.3%), and hair loss in 1 (5.3%). The most frequently involved anatomical regions are the extremities, whose involvement was encountered in 15 (78.9%) patients, followed by trunk involvement in 5 (26.3%) patients, and head-neck region involvement in 4 (21%) patients (**Table 1**). The lesions of 11 (57.9%) patients crossed joints, whereas those of 8 (42.1%) patients were unrelated to joints. The lesions crossed ankle joints in 5 (26.3%) patients, knee joints in 3 (15.8%), hip joints in 2 (10.5%), and elbow joints in 1 (5.3%). Four (21.1%) patients had joint involvement. Two (10.6%) patients had Raynaud syndrome.

ANA positivity was found in 10 (52.6%) patients. This positivity was at 1/100 titers in 6 (31.5%) patients, 1/320 titers in 3 (15.7%), and 1/1000 titers in 1 (5.2%). ENA positivity was detected in 2 (10.5%) patients, one of these cases showed DFS-70 positivity, and the other showed SS-A positivity. ANA positivity was not significantly related to systemic treatment requirement, prognosis, or sequelae (p=0.162, p=0.468, p=0.620). RF positivity was found in only 1 (5.3%) patient. All patients had negative viral panel results. Borrelia IgG was examined in 8 patients, whose results were all negative. CRP positivity was seen in only 1 (5.3%) patient, and ESR positivity was present in 4 (21.2%) patients. The median CRP value was 0.5 mg/L (0-10 mg/L), while the median ESR value was 6 mm/h (2-15 mm/h). While 6 (31.5%) patients had vitamin D deficiency, one had iron deficiency, and no patients had vitamin B12 deficiency. Biopsies were performed on all patients except for two patients with ECDS and 1 with a facial lesion. Fourteen patients who underwent biopsies had typical localized scleroderma symptoms (epidermis thinning, dermis collagen fiber increase, atrophy in subcutaneous adipose tissue, and fibrosis), and two patients showed nonspecific symptoms.

Topical treatments were given to 9 (47.3%) patients (**Table 1**). While 2 (10.6%) patients received only topical treatments, 17 (89.4%) received systemic therapies. There was no significant difference among the subtypes of localized scleroderma in terms of systemic treatment requirement (p=0.451). The most frequently used systemic treatment was methotrexate, which 15 (78.9%) patients used. This was followed by systemic corticosteroids in 11 (57.9%) patients, colchicine in 1 (5.3%), hydroxychloroquine in 1 (5.3%), and mycophenolate mofetil in 1 (5.3%). The combination of systemic corticosteroids and methotrexate was the most frequently observed treatment modality, which 9 (47.3%) patients used. The median follow-up duration of the patients was 2.5 years (minimum: 6 months - maximum: 9 years). The treatment responses of the patients are shown in **Table 1**. There was no significant difference among the subtypes of localized scleroderma in terms of prognosis (p=0.893). Cosmetic sequelae were found in 14 (73.7%) patients, cosmetic and functional sequelae were found in 4 (21.1%) patients, and 1 (5.3%) patient did not have any sequelae. The functional sequelae were in the form of joint movement restriction in 3 (15.8%) patients, whereas 1 (5.3%) patient had contracture. The demographic, clinical, and treatment-related characteristics of the patients are presented in **Table 1.**

Table 1: Demographic, clinical and treatment-related data of patients with juvenile localized scleroderma

Patient No	Gender	Age at diagnosis*	Time to diagnosis*	Disease duration*	JLS subtype	Anatomical localization	Trigger Factor	Treatment	Prognosis	Sequelae
1	M	14	2	3,9	Linear scleroderma	Head	-	CS+MTX	Partial remission	Cosmetic
2	F	5	4,5	3	Linear scleroderma	Lower extremity	-	MTX+ topical tacrolimus	No response	Cosmetic
3	M	2,7	0,5	8	Linear scleroderma	Upper&lower extremity	Pneumonia	CS+MTX	Partial remission	Cosmetic, fonctionel
4	F	13,1	0,5	6	Generalize scleroderma	Head, trunk &lower extremity	-	HQ	No response	Cosmetic
5	F	7,6	5,1	1,7	Linear scleroderma	Head	COVID-19	MTX+ Colchicine	Partial remission	Cosmetic
6	F	17,3	0,3	0,8	Circumscribed scleroderma	Upper extremity	-	Topical steroid	Partial remission	Cosmetic
7	F	4	1	2	Linear scleroderma	Upper extremity	-	CS+MTX	Partial remission	Cosmetic, Fonctionel
8	M	15	0,4	1,5	Circumscribed scleroderma	Trunk	-	Topical calcipotriol & betamethasone	Partial remission	Cosmetic
9	F	17,8	2	0,8	Circumscribed scleroderma	Lower extremity	Upper respiratory tract infection	CS+MMF	No response	Cosmetic, Fonctionel
10	F	11,3	0,2	1,2	Circumscribed scleroderma	Lower extremity	-	CS+MTX+ Centaury oil	Complete remission	Cosmetic
11	M	7,7	0,2	6	Mix scleroderma	Trunk& Lower extremity	-	CS+MTX	Partial remission	Cosmetic
12	F	9	0,7	6	Circumscribed scleroderma	Lower extremity	-	CS+Topical tacrolimus	Partial remission	No sequel
13	F	2,5	1,9	4	Circumscribed scleroderma	Trunk& Lower extremity	-	MTX+ Topical steroid	No response	Cosmetic
14	M	13,6	0,6	3	Linear scleroderma	Upper extremity	-	CS+ MTX	Partial remission	Cosmetic, Fonctionel
15	M	6,1	0,1	9	Circumscribed scleroderma	Lower extremity	-	MTX+ Topical tacrolimus	Complete remission	Cosmetic
16	F	4	1,8	1,6	Mix scleroderma	Lower extremity	-	CS+ MTX+ Topical calcipotriol& betamethasone	Partial remission	Cosmetic
17	F	7,6	0,4	1,1	Linear scleroderma	Upper& Lower extremity	-	CS+ MTX	No response	Cosmetic
18	M	14,5	0,3	0,3	Circumscribed scleroderma	Head	COVID-19	CS+ MTX	Partial remission	Cosmetic
19	F	6	0,6	2,5	Linear scleroderma	Lower extremity	-	MTX+Topical steroid+ Centaury oil	Partial remission	Cosmetic

JLS: Juvenile localized scleroderma, F: Female, M: Male, CS: Cortikosteroid, MTX: Methotrexate, HQ: Hydroxychloroquine, MMF: Mycophenolate mofetil, *year

DISCUSSION

Juvenile localized scleroderma is a rarely encountered chronic pediatric disease characterized by skin and subcutaneous tissue fibrosis. Among these patients, who are usually followed up in dermatology clinics, only those requiring systemic treatment are followed up in pediatric rheumatology outpatient clinics. The rate of these patients among all patients with rheumatic diseases who are regularly followed up in our clinic is approximately 0.5%. Our study found the ratio of female JLS patients to male JLS patients as 1.7. In our study, the ratio of female JLS patients to male JLS patients was found as 1.7. Circumscribed scleroderma and linear scleroderma were the most frequently diagnosed types of JLS. Although there was no statistically significant difference between the female and male patients, it was seen that the complaints of the female patients started at earlier ages. It was observed that in this rare disease, despite systemic and aggressive treatment, the rate of complete remission was very low.

The incidence of JLS varies in the range of 0.4-1 in 100,000, and various studies have reported female/male patient ratios differing from 1.2/1 to 2.4/1 (17,18,19). In the multi-center study that was conducted with 489 patients diagnosed with JLS by the Juvenile Scleroderma Working Group of the Pediatric Rheumatology European Society (PReS), it was reported that the mean age of disease onset was 7.3 years, and this did not significantly change based on the subtypes of the disease (20,21,22). In a study in Taiwan, the mean age of disease onset in JLS was reported as 6.7 years (23). The mean age of disease onset was determined to be 8.2 years in our study, and like in other studies, there was no significant difference in this value based on sex or disease subtypes. To understand whether there are regional differences in the age of disease onset in JLS, nationwide multi-center studies are needed.

While the most frequently diagnosed form of localized scleroderma in adulthood is circumscribed morphea, linear scleroderma is the most prevalent JLS subtype in childhood, usually seen in the first two decades of life (24). In our study, the circumscribed and linear localized scleroderma rates were equal, and both were 42.1%. The rate of extracutaneous involvement in linear scleroderma is high, and it can lead to various sequelae, especially in the extremities of patients (12,25,26). Moreover, in ECDS, another form of linear scleroderma, the forehead and scalp are involved, cutaneous, subcutaneous, bone, and even brain tissue can be affected, and the disease can lead to various neurological symptoms (27,28). ECDS was detected in 10.5% of the patients in our study. In the study by the Juvenile Scleroderma Working Group, has the broadest series of patients so far, 22.4% of the 489 pediatric patients had non-skin involvement. Among these non-skin involvement cases, 47.2% were articular, 17.1% were neurological, 9.3% were vascular, 8.3% were ocular, 6.2% were gastrointestinal, 2.6% were respiratory, 1% were cardiac, and 1% were renal involvement cases (7). Among our patients, other than joint involvement, only 2 (10.6%) patients had Raynaud syndrome. While most of our patients had lesions crossing their joints, joint involvement was present in 21.1%. Three of these patients had restricted joint motion, and one had developed contracture. The rate of restricted joint movement and contracture has been reported in the range of 18-21% in the literature (7,27,29,30). The rate of arthritis has been reported as 5-20%, whereas none of our patients had arthritis. The rate of restricted joint movement and contracture in our study was similar to those reported in other studies in the literature.

It has been stated that autoantibody positivity accompanies JLS, and the prevalence of ANA positivity varies in the range of 32-76% (21, 22, 24, 31). Regarding other autoantibodies, various studies have demonstrated that the prevalence of anti-Scl-70 positivity is 2-3%, and the prevalence of anti-cardiolipin positivity is 0-12% (7,24,32). Our study found ANA positivity in 52.6% of the patients. One patient had SS-A positivity, and another had DFS-70 positivity, but the positivity of these autoantibodies was not associated with the clinical statuses of these patients. It has been stated in the literature that in case autoantibodies are detected in localized scleroderma, it is necessary to carefully monitor these patients in terms of systemic symptoms that can develop later, and these patients can have systemic involvement later in life (32-34). However, the Juvenile Scleroderma Working group did not find a significant difference between patients with and those without ANA positivity in terms of prognosis, treatment, or sequelae. On the other hand, in the same study, a significant correlation was identified between RF positivity and arthritis (7). Our study did not find any relationship between ANA positivity and systemic treatment requirement, sequelae, or prognosis. During their follow-ups, no patients included in our study developed systemic symptoms. While one patient in our study showed RF positivity, no patient had arthritis.

In circumscribed morphea cases, various topical treatments are usually recommended for patients (35-37). These patients usually undergo these topical treatments as a result of their examination by dermatology clinics before rheumatology clinics. Patients who do not respond to topical treatment and require systemic treatment are referred to rheumatology clinics for the examination of systemic symptoms and recommendations for treatment modalities. While 84.2% of the JLS patients being followed up in our clinic received systemic treatments, 47.3% received topical treatments. The most frequently used systemic therapy was methotrexate, which was used in 78.9% of the patients. Studies conducted with large samples of JLS patients have also reported methotrexate as the most prevalently used systemic treatment (7,15). According to the EULAR treatment guidelines, mycophenolate mofetil treatment is recommended for patients who are intolerant to methotrexate or do not respond to treatment with methotrexate (16). Studies performed by dermatology clinics in Turkey have reported the usage of colchicine treatment and its effective outcomes (38). The treatment decision for JLS patients should be made based on joint monitoring by dermatology and pediatric rheumatology clinics.

In JLS cases, especially in circumscribed morphea, complete remission was reported to occur at the end of the first five years. While it was observed that juvenile linear localized scleroderma could have a much more aggressive course, and remission was not seen in 10-year follow-up (15). Long-term morbidity is highly prevalent in JLS cases, and the most frequently encountered sequelae cosmetic and musculoskeletal damage (39). The rate of complete remission in our study was very low. Complete remission could be achieved by aggressive treatment in only 2 (10.6%) patients, who had circumscribed morphea. During their follow-ups, cosmetic sequelae were seen in 73.1% of our patients, whereas 21.1% had joint damage. In a study carried out with 133 patients in Italy, subcutaneous adipose tissue loss and cosmetic sequelae in the early period were reported in 2/3 of the patients (15). The reason for the low remission rate in our study, even with the inclusion of the circumscribed morphea cases, maybe that most patients who do not respond to various topical treatments and have a more aggressive course of the disease are followed up in pediatric rheumatology clinics, and the follow-up durations of our patients were short.

This study had some limitations. The most important limit was the low number of patients. Because it was

a retrospective study, accessing detailed clinical data and investigating long-term outcomes was impossible. Nonetheless, our study is valuable in the scientific sense because the number of studies in Turkey investigating JLS cases from a pediatric rheumatology perspective is insufficient.

CONCLUSION

Consequently, although JLS is a pediatric disease that is rarely encountered, it constitutes a significant group of conditions because it has high rates of cosmetic and functional sequelae. In this sense, it will be an appropriate approach for clinicians to not refrain from ordering biopsies for lesions that they consider suspicious and refer such patients to pediatric rheumatology clinics in the early period. Considering the high sequela rates of the disease, it is clear that there is a need for multi-center studies in Turkey that will allow us to understand JLS better.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 18.01.2023, Decision No: E2-2023-3179).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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