Pediatric Rheumatology

RESEARCH ARTICLE

Open Access

Application of the Scleroderma Clinical Trials Consortium Damage Index in patients with juvenile systemic sclerosis

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Abstract

Background Juvenile systemic sclerosis (jSSc) can lead to permanent and irreversible anatomical or physiological dysfunction. The Scleroderma Clinical Trials Consortium-Damage Index (SCTC-DI), which has been employed and validated in adult patients, can quantify organ damage and predict mortality and morbidity. However, its application in paediatric patients remains unexplored.

Methods Clinical data, laboratory results, and prognostic information were collected for patients with jSSc at Peking Union Medical College Hospital (PUMCH) from January 2012 and January 2024. Differences between the SCTC-DI and the juvenile systemic sclerosis severity score (J4S) were recorded and compared. Furthermore, we compared the SCTC-DI between jSSc and adult systemic sclerosis (SSc) patients.

Results A total of 64 jSSc patients were included. Facet joint contractures, fingertip ulcers and interstitial lung disease are common manifestations. Compared with adult SSc patients, jSSc patients had a lower incidence of gastrointestinal and urinary system involvement. The baseline J4S levels were significantly correlated with SCTC-DI levels at follow-up. A higher baseline SCTC-DI score was associated with a greater progression of organ damage ($P=0.001$).

Conclusion There are differences in clinical presentations between adult SSc patients and jSSc patients. The SCTC-DI can be applied to JSSc patients, and it is recommended that JSSc patients undergo regular evaluations of the J4S as well as the SCTC-DI.

Keywords Systemic sclerosis, Children, Disease severity, Organ damage burden

Background

Juvenile systemic sclerosis (jSSc) is a chronic autoimmune disease characterized by collagen deposition in different tissues, resulting in fibrotic thickening and hardening of the skin, accompanied by fibrotic changes in internal organs such as the esophagus, intestines, heart, lungs, and kidney [1]. Currently, patients with SSc are further characterized by two main subtypes: diffuse cutaneous SSc (dcSSc), limited cutaneous SSc (lcSSc) [2]. JSSc patients are prone to multiple complications, and jSSc significantly increases patient disability and mortality. Therefore, early screening of organ involvement in SSc patients is of paramount importance.

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Currently, the Juvenile Systemic Sclerosis Severity Score (J4S) is a tool that can be used to assess the severity of jSSc and is recommended for regular evaluation in paediatric patients [3, 4]. Damage in SSc is the permanent and irreversible loss of anatomical structure or physiological function [5]. However, there is currently a dearth of assessment tools specifically tailored for evaluating organ damage in jSSc. Previous studies have shown a strong correlation between disease damage and disease severity in SSc [6]. The Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI) serves as a tool for quantifying organ damage and predicting mortality and morbidity [5]. While it has been applied and validated in adult patients [5, 7, 8], its utilization in paediatric patients has yet to be explored. Therefore, this study comprehensively summarized the clinical characteristics of Chinese jSSc patients, analyzed the application features of SCTC-DI, and compared them with other cohorts and validate the predictive efficacy of SCTC-DI in assessing disease progression.

Materials and methods

Patients

The study cohort consisted of paediatric patients diagnosed with jSSc who sought medical care at Peking Union Medical College Hospital (PUMCH) between January 2012 and January 2024. The inclusion criteria for patients were as follows: (1) age under 16 years, (2) complete data availability, and (3) fulfilled with the American College of Rheumatology/the European League Against Rheumatism (ACR/EULAR) 2013 classification criteria for SSc [9]. The exclusion criteria included patients who were lost to follow-up after the initial diagnosis, and could not be contacted through telephone follow-up with the patients themselves or their families.

Data collection

The baseline data of the paediatric patients in this study were collected within 10 years since the onset of the first SSc-related symptoms(including Raynaud's phenomenon (RP) symptoms or non-RP symptoms related to SSc), accompanied by the acquisition of detailed medical records. The follow-up data, including the J4S and the SCTC-DI, were collected at the latest available visit, minimum of 0.5 years after baseline assessment. All available clinical and laboratory data were collected from the electronic medical records system at the baseline and at the follow-up time points (up to July 2024). The SCTC-DI and the J4S were calculated for each patient, and the involvement of each system during the course of the disease was monitored (Supplementary Figure S1). The SCTC-DI data for the adult cohort were obtained from the Australian Scleroderma Cohort Study (ASCS), the Canadian Scleroderma Research Group (CSRG), the Peking University Third Hospital and Peking University People's Hospital cohort (PKUTH and PKUPH) [5, 8].

Variable definitions

The term"total number of organ involvements"refers to the cumulative number of abnormal organs or systems from the disease onset to the final follow-up (July 2024) (Supplementary Table S1). The SCTC-DI data were collected and calculated according to the method developed by Nava Ferdowsi et al. [5]. Furthermore, while considering the actual conditions of Chinese children, the criterion of"low body mass index (BMI) < 18.5 kg/m^2 or > 10% weight loss in the past 12 months"was modified to"BMI < the 3rd percentile for children of the same age and gender or > 10% weight loss in the past 12 months,"based on the percentile of the CDC growth reference standards. SCTC-DI score ≥ 6, which implies a moderate to high mortality risk, was identified as a high burden of organ damage, while an SCTC-DI score < 6 was defined as a low burden [5, 8]. Organ damage progression was defined as an increase in the SCTC-DI difference (ΔSCTC-DI) between follow-up and baseline by ≥ 1 [8, 10]. As J4S serves as a method for assessing disease severity, while SCTC-DI predominantly measures permanent and irreversible loss of anatomical structure or physiological function caused by SSc, this study evaluated the correlation of those two tools in paediatric patients.

Statistical analysis

All the statistical analyses were carried out with SPSS 26.0, and Graphd Prism (V9.3.1). Continuous variables that did not conform to a normal distribution were presented as medians (interquartile ranges) [M ($Q1$, $Q3$)], and nonparametric tests were used to compare between-group differences. Categorical variables were expressed as (n, %), and chi-square tests were used for comparisons between groups. A P value < 0.05 indicated that the difference was statistically significant.

Results

Baseline characteristics of the PUMCH-JSSc cohort

A total of 64 patients with detailed information were included in this study, consisting of 29 patients (45.3%) with limited cutaneous jSSc, 35 patients (54.7%) with diffuse cutaneous jSSc. The age of onset was 11.4 (6.4, 13.9) years, with an interval of 0.9 (0.5, 2.3) years from onset to diagnosis. The male-to-female ratio was 1:1.9. Notably, among various subtypes, 33 patients (51.6%) were adolescent females aged 11–16 years. During a follow-up period of 5.5 (3.4, 10.4) years, a total of 4.0 (3.0, 5.0) systems were involved, with 12 patients lost to follow-up. Both at baseline and during follow-up,

paediatric patients with jSSc frequently exhibited abnormalities in the Raynaud's phenomenon (75.0%, 73.1%), respiratory (68.8%, 69.2%), and joint (56.3%, 57.7%) systems. Remarkably, only one patient exhibited positive urinary protein without concurrent renal dysfunction. Additionally, some patients also showed initial positivity for anti-Scl-70 antibodies (56.3%, 55.8%) and elevated C-reactive protein (CRP) levels (30.2%, 30.2%) (Table 1). During the follow-up process, three patients succumbed to infections of varying severity, all of whom had a baseline SCTC-DI ≥ 8, presenting with Raynaud's phenomenon as the onset symptom, and involving the respiratory and digestive systems simultaneously, accompanied by elevations in CRP, erythrocyte sedimentation rate (ESR), and liver enzymes (Supplementary Table S2).

Comparison of Scleroderma Clinical Trials Consortium Damage Index across different cohorts

The baseline SCTC-DI (assessed at 2.0(0.7, 5.0) years since the onset of the disease) for 64 patients with jSSc was 4.0(2.0, 7.0). During the follow-up period (2.7(1.3, 4.3) years after the baseline assessment), it increased to 6.0(2.0, 9.0) for 52 patients. Among the follow-up patients, 22 (42.3%) patients experienced progression of organ damage. The common clinical manifestations observed in the jSSc patients included small joint contractures, fingertip ulcers, and interstitial lung disease. Compared to the manifestations at baseline, the manifestations during disease progression were primarily joint, respiratory, or circulatory system abnormalities. These manifestations were specifically characterized by an increased incidence of joint contractures, impaired lung function, home oxygen therapy, pulmonary arterial hypertension, and SSc-related myocardial involvement (Table 2).

The median of SCTC-DI at baseline for jSSc patients from the PUMCH cohort was lower than that of adult SSc patients in the ASCS and CSRG cohorts, aligning with the SCTC-DI observed in the Chinese adult PKUTH and PKUPH cohorts (Supplementary Table S3). Notably, compared with those in the adult cohort, the proportions

Table 1 Baseline characteristics of patients with juvenile systemic sclerosis

Characteristics	Baseline($n=64$)	Baseline for patients with follow-up ($n=52$)
Male: Female (n)	22:42	16:36
Age of onset (years-old)	11.4(6.4,13.9)	11.8(6.0,14.0)
Time from onset to diagnosis (years)	0.9(0.5,2.3)	0.8(0.5,2.3)
Number of organs involved in the course of the disease		
mRSS	12.0(8.0,17.0)	12.0(8.0,16.0)
Raynaud's phenomenon	48/64(75.0%)	38/52(73.1%)
Respiratory system	44/64(68.8%)	36/52(69.2%)
Joint system	36/64(56.3%)	30/52(57.7%)
Digestive system	23/64(35.9%)	20/52(38.5%)
Haematological system	18/63(28.6%)	15/52(28.8%)
Musculoskeletal System	13/64(20.3%)	10/52(19.2%)
Cardiovascular System	11/63(17.5%)	11/51(21.6%)
Nervous System	5/64(7.8%)	4/52(7.7%)
Urinary System	1/64(1.6%)	1/52(1.9%)
Laboratory tests at baseline		
Elevated CRP	16/53(30.2%)	13/43(30.2%)
Elevated ESR	16/59(27.1%)	13/48(27.1%)
Anaemia	6/62(9.7%)	5/51(9.8%)
Abnormal liver function	16/62(25.8%)	14/51(27.5%)
Hypoalbuminaemia	12/53(22.6%)	9/45(20.0%)
Hypocomplementemia	14/57(24.6%)	12/46(26.1%)
Positive anti-Scl-70 antibodies	36/64(56.3%)	29/52(55.8%)
Presence of ≥ 2 autoantibodies	46/64(71.9%)	38/52(73.1%)

Continuous variables with a non-normal distribution are represented as *M* (*Q*1, *Q*3) (median with interquartile range), while categorical variables are expressed as the number of positive cases/numbers of evaluated cases (proportion).

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate

Table 2 Frequency of Scleroderma Clinical Trials Consortium Damage Index items for juvenile systemic sclerosis patients in the Peking Union Medical College Hospital cohort

Items	All patients($n=64$)	Patients with follow-up ($n=52$)	
	Baseline	Baseline ($n=52$)	Follow-up ($n=52$)
Musculoskeletal and skin			
Joint contracture (small joints)	26(40.6)	22(42.3)	28(53.8)
Joint contracture (large joints)	14(21.9)	11(21.2)	16(30.8)
Sicca symptoms	5(7.8)	3(5.8)	5(9.6)
Proximal muscle weakness	7(10.9)	5(9.6)	1(1.9)
Calcinosis complicated by infection or requiring surgery	2(3.1)	4(7.7)	4(7.7)
Vascular			
Digital ulceration	22(34.4)	18(34.6)	24(46.2)
Digital amputation required	4(6.3)	3(5.8)	3(5.8)
Gastrointestinal			
Esophageal dysmotility	4(6.3)	4(7.7)	4(7.7)
Esophageal stricture	0	0	1(1.9)
Refractory gastro-esophageal reflux disease	3(4.7)	3(5.8)	4(7.7)
GAVE	0	0	0
Pseudo-obstruction	1(1.6)	0	1(1.9)
BMI < 3rd percentile for children of same-age and sex or weight loss of > 10% in past 12 months	4(6.3)	2(3.8)	2(3.8)
Respiratory			
ILD > 20% extent on HRCT	23(35.9)	19(36.5)	25(48.1)
FVC < 70%	10(15.6)	8(15.4)	13(25.0)
Dependence on home oxygen	1(1.6)	0	4(7.7)
Cardiovascular			
PAH	4(6.3)	4(7.7)	6(11.5)
Moderate to severe right ventricular dysfunction	2(3.1)	2(3.8)	2(3.8)
Myocardial disease	2(3.1)	2(3.8)	3(5.8)
Moderate to large pericardial effusion	0	0	0
Renal			
History of SRC	0	0	0
eGFR < 45 mL/min/1.73 m^2	0	0	0
CKD stage 5 and need for renal replacement therapy	0	0	0
SCTC-DI (score)	4.0 (2.0, 7.0)	4.0 (2.0, 7.8)	6.0(2.0, 9.0)

Non-normally distributed variables are expressed as medians (interquartile ranges) [*M* (*Q*1, *Q*3)], and categorical variables are expressed as (n, %)

GAVE gastric antral vascular ectasia, *BMI* body mass index, *ILD* interstitial lung disease, *HRCT* high-resolution CT, *PAH* pulmonary arterial hypertension, *SRC* scleroderma renal crisis, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease

of jSSc patients with features such as sicca syndrome, refractory gastroesophageal reflux disease, and low BMI were significantly lower ($P< 0.001$). Moreover, none of the jSSc patients in our cohort showed evidence of esophageal stricture, gastric antral vascular ectasia, or renal dysfunction. The prevalence of digital ulcers was higher in jSSc patients compared to the PKUTH and PKUPH cohorts *(*$P= 0.010$) and the CSRG cohort ($P< 0.001$)). JSSc patients exhibited a higher proportion of ILD extent > 20% on HRCT ($P< 0.001$, $P= 0.012$) and forced vital capacity < 70% ($P< 0.001$, $P< 0.001$) than adult patients in the ASCS and CSRG cohorts, yet comparable to those in the PKUTH and PKUPH cohorts ($P= 0.563$, 0.414, respectively) (Supplementary Table S3).

Correlation analysis of Scleroderma Clinical Trials Consortium Damage Index and juvenile systemic sclerosis severity score

There were correlations between J4S and SCTC-DI at baseline and follow-up time points (Supplementary Figure S2). Due to the fact that the J4S is primarily used to assess the severity of SSc, while the SCTC-DI is designed to evaluate permanent anatomical or physiological losses caused by SSc, we evaluated 52 patients with jSSc who

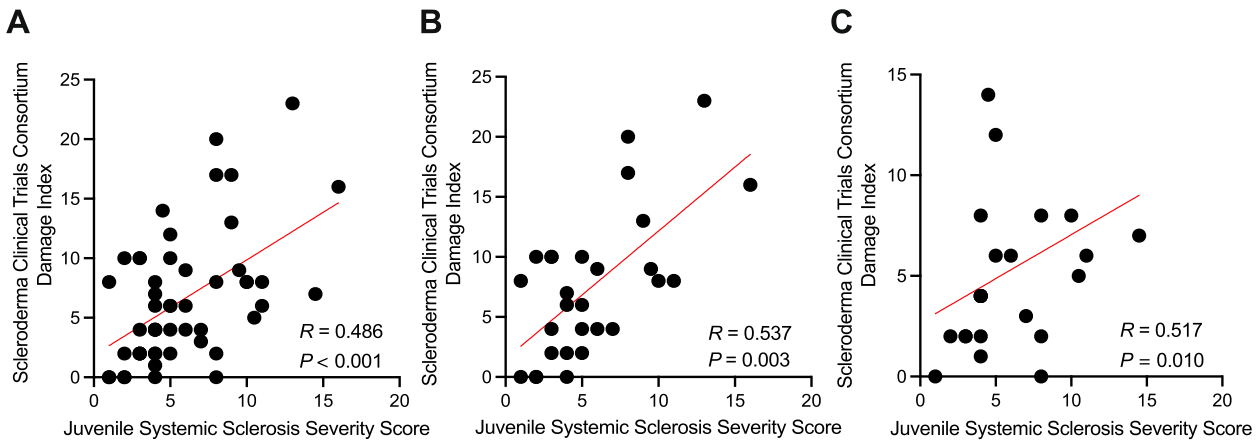

Fig. 1 Correlations between juvenile systemic sclerosis severity score (J4S) and Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI) in patients with juvenile systemic sclerosis (jSSc). **A** Correlations between baseline J4S of jSSc patients and the SCTC-DI at follow-up; **B** Correlations between baseline J4S and follow-up SCTC-DI in patients with diffuse cutaneous jSSc; **C** Correlations between baseline J4S and follow-up SCTC-DI in patients with limited cutaneous jSSc

completed follow-up to analyze the correlation between baseline J4S and SCTC-DI at follow-up. The baseline J4S [5.0(3.3, 8.0)] of jSSc patients were found to correlate with the SCTC-DI at follow-up [6.0(2.0, 9.0)] ($R = 0.486$, $P < 0.001$) (Fig. 1A). Subtype analysis demonstrated the strongest correlation between J4S and SCTC-DI among dcSSc patients (5.0(3.0, 8.0) *vs.*7.5(2.5, 10.0), $R = 0.537$, $P = 0.003$) (Fig. 1B), followed by lcSSc patients (4.8(4.0, 8.0) *vs.*4.00(2.0, 7.8), $R = 0.517$, $P = 0.010$) (Fig. 1C).

Clinical application of the Scleroderma Clinical Trials Consortium Damage Index

A total of 52 patients underwent long-term follow-up, and 66.7% (18/27) of the patients in the high-burden of organ damage (SCTC-DI ≥6) group experienced progression of organ damage (ΔSCTC-DI ≥1). In contrast, among patients with SCTC-DI <6 at baseline, and 16.0% (4/25) of the patients experienced organ damage progression. This finding indicated that a higher baseline SCTC-DI score was associated with a greater progression of organ damage (ΔSCTC-DI ≥1) ($P = 0.001$). Furthermore, a non-significant, higher rate of organ damage progression was identified for the dcSSc compared to the lcSSc subtype in their jSSc cohort ($P = 0.08$) (Fig. 2).

Discussion

Previous studies have shown that the mortality rate of SSc patients increases with increasing SCTC-DI score [7]. Pulmonary interstitial disease and heart failure were the primary causes of death in both adult and paediatric SSc patients [11]. Infections and malignant tumours were the major contributors to non-SSc-related mortality in SSc patients [12, 13]. Fingertip ulcers and heart disease in SSc patients are associated with an elevated risk of severe infections. Therefore, heightened vigilance is necessary for patients with concurrent heart disease and fingertip ulcers to monitor and promptly address the occurrence of infections [14]. Three jSSc patients in this cohort displayed a high organ damage at baseline and eventually died of different degrees of infection. Consequently, upon suspicion of jSSc, a comprehensive systemic assessment should be promptly conducted, and paediatric rheumatologists should be alert to the occurrence of infection in jSSc patients.

Assessing disease severity and long-term prognosis in patients with SSc is challenging due to the heterogeneous and multisystem clinical manifestations, individual

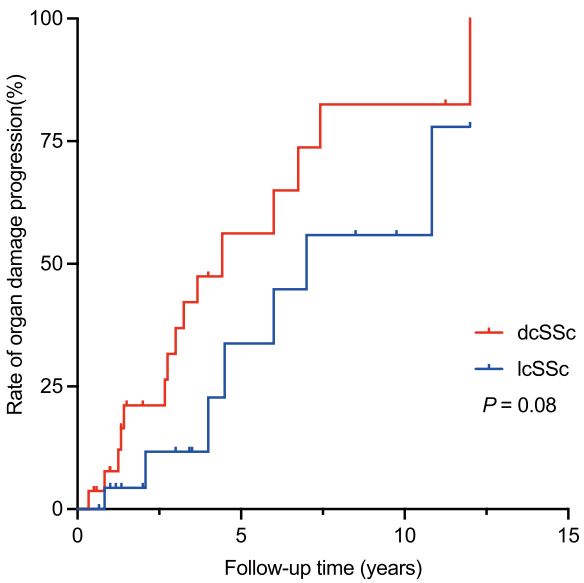

Fig. 2 Cumulative incidence rate of organ damage progression

differences, and varying rates of disease progression. J4S, a well-recognized effective tool for assessing the severity of jSSc, exhibits reversible changes and thus requires regular assessment [3, 15]. Currently, the SCTC-DI has been developed to evaluate irreversible organ damage in adults [5]. This study marked the first application of the SCTC-DI in paediatric patients and demonstrated a correlation between the J4S and the SCTC-DI (Fig. 1), which suggests that paediatric clinicians should pay attention to the assessment of SCTC-DI in clinical practice to predict the organ damage.

Previous studies have shown that clinical manifestations vary among different subtypes of SSc, with diffuse cutaneous jSSc exhibiting more severe impairment compared to limited cutaneous jSSc. Notable disparities exist in mRSS and pulmonary and cardiac involvement between patients with diffuse cutaneous jSSc and limited cutaneous jSSc [16, 17]. Furthermore, the SCTC-DI in adult SSc patients progressively increases over time, with dcSSc patients consistently showing higher SCTC-DI scores compared to lcSSc at each evaluated time point [18]. The progression of organ injury in the two subtypes of jSSc at our centre is inconsistent (Fig. 2), emphasizing the need for a larger sample size and longer-term follow-up.

In comparison to adults, jSSc patients typically exhibit systemic involvement in the vascular and musculoskeletal systems (Supplementary Table S3), consistent with the findings of previous literature reports [11, 19]. The proportion of patients with fingertip ulcers and decreased pulmonary ventilation function was greater in this study than in the ASCS and CSRG cohorts but comparable to that in the PKUTH and PKUPH cohorts. In both adult and paediatric SSc patients, renal involvement was relatively rare [11], and there was no history of scleroderma-related renal crisis in jSSc patients in this study. A key limitation of this study is the retrospective nature of the chart review, which may have impacted the comprehensive capture of symptoms and organ manifestations. While our clinical practice includes a thorough review of patient symptoms, some assessments, such as esophageal manometry for dysmotility, require invasive testing that may be less frequently performed, particularly in children. As a result, the reported frequency of esophageal dysmotility may be underestimated, highlighting the potential for underreporting in other similar outcomes. The SCTC-DI in jSSc patients was lower than that in adult patients, with specific scoring items exhibiting variations compared to both domestic and international adult cohorts. The organ damage progression in jSSc patients mainly manifested as abnormalities in the circulatory and respiratory systems, as detected by follow-up with the SCTC-DI (Table 2). The incidence of severe organ damage was lower in jSSc patients than in adult SSc patients [20]. Due to the lower degree of visceral organ involvement and lower specificity of the autoantibody spectrum in children, patients with jSSc have a better prognosis and long-term outcome than adults [7, 21]. When applying the SCTC-DI to jSSc patients in this study, adjustments to the definition of BMI were necessary. Therefore, further optimization of the SCTC-DI to make it more suitable for children represents a direction for future research.

Conclusion

The SCTC-DI scores in jSSc patients were comparable to those in Chinese adult SSc patients but lower than those observed in international adult SSc cohorts. Common systemic involvements in jSSc patients include the vascular and musculoskeletal systems, while involvement of the digestive and urinary systems is relatively less common. The baseline J4S levels were significantly correlated with SCTC-DI levels at follow-up among different jSSc subtypes. The higher baseline SCTC-DI scores, the faster the progression of organ damage. However, the incidence of organ damage progression varied among patients with different subtypes.

Abbreviations

ASCS	Australian Scleroderma Cohort Study
BMI	Body mass index
CRP	C-reactive protein
CSRG	Canadian Scleroderma Research Group
dcSSc	Diffuse cutaneous SSc
ESR	Erythrocyte sedimentation rate
JSSc	Juvenile systemic sclerosis
J4S	Juvenile systemic sclerosis severity score
lcSSc	Limited cutaneous SSc
PKUTH	Peking University Third Hospital
PKUPH	Peking University People's Hospital cohort
PUMCH	Peking Union Medical College Hospital
SCTC-DI	Scleroderma Clinical Trials Consortium Damage Index
SSc	Systemic sclerosis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12969-025-01110-6.

Supplementary Material 1.

Acknowledgements

We thank the support, cooperation, and trust of patients and their families.

Authors' contributions

All authors contributed to the study conception and design. CHZ collected, analysed the clinical data, performed literature review and wrote the manuscript. CYW collected and analysed the clinical data. SHG analysed the clinical data and revised the manuscript. MSM diagnosed the patients and recorded clinical data. WW performed some patients' gene detections as well as bioinformatics analysis. TYZ analysed the clinical data. YZ, XYT, HZJ, ZFZ participated in clinical care and recorded clinical data. HMS diagnosed the patients,

designed and supervised the project, wrote and revised the manuscript. All authors read and approved the final manuscript.

Funding
This work was supported by National Key Research and Development Program of China (2021YFC2702001) and National High Level Hospital Clinical Research Funding (2022-PUMCH-B-079).

Data availability
The datasets are available from the authors upon reasonable request and with permission of the Institutional Review Board of Peking Union Medical College Hospital.

Declarations

Ethics approval and consent to participate
This study complied with the Declaration of Helsinki, and was approved by the Institutional Review Board of Peking Union Medical College Hospital (JS-3362D). Informed consent forms were obtained from all patients and their legal guardians.

Consent for publication
All authors agreed on submitting and publishing this manuscript. This article is the authors' original work, and has neither been received for publication, nor under consideration for publication elsewhere.

Competing interests
The authors have no financial competing interests to be disclosed.

Received: 5 September 2024 Accepted: 8 May 2025
Published online: 14 May 2025

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