Original Article

Optimal lead time for treatment of infantile epileptic spasms syndrome—a secondary data analysis

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Background: Infantile epileptic spasms syndrome (IESS) is a common epileptic syndrome in infancy. Current first-line treatments include adrenocorticotropic hormone (ACTH), corticosteroids and vigabatrin, with early control of epileptic spasms potentially benefiting long-term outcomes, such as improved psychomotor development. Early treatment, which means the prompt use of first-line treatments, is crucial for achieving an initial response in IESS. However, to date, no clear definition of the specific timeframe that constitutes early treatment has been identified. The objective of this study is to perform a secondary analysis of our previously published IESS cohort data to determine a suitable lead time.

Methods: An analysis was conducted using a cohort of 263 children with IESS who had previously received ACTH first-line treatment. This study investigated whether intervening within a certain treatment time window could potentially increase or decrease the likelihood of a short-term response.

Results: Out of the 263 children with IESS, 108 achieved a short-term response. The lead time of the response group was significantly shorter than that of the non-response group [1.50 (interquartile range, 1.00, 3.00) *vs.* 2.00 (interquartile range, 1.00, 5.00) months; P=0.003]. A restricted cubic spline graph with several adjusted variables, including time of first spasm and aetiological classification, showed a significant linear relationship between lead time and short-term response and a non-linear trend (inverted U-shaped curve), with a significant inflection point at 1.6 months. Using 1.5 months as the cutoff and dichotomising lead time, the adjusted logistic regression results showed that in children with a lead time >1.5 months, the likelihood of a short-term response decreased with increasing lead time [odds ratio (OR) =0.59, 95% confidence interval (CI): 0.33–0.92, P=0.041), whereas children with a lead time ≤1.5 months showed no significant association between lead time and short-term response (OR =1.03, 95% CI: 0.72–1.47, P=0.89).

Conclusions: For children with IESS, initiating first-line treatment within 1.5 months of the onset of spasms is recommended. For those who start first-line treatment after more than 1.5 months from the onset, the likelihood of a short-term response may significantly decrease as the lead time increases.

Keywords: Infantile epileptic spasms syndrome (IESS); initial response; lead time; early treatment

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Introduction

Infantile epileptic spasms syndrome (IESS), also known as West syndrome, is a prevalent epileptic encephalopathy in infancy, primarily characterised by unique spasmodic seizures (1,2). Unfortunately, this condition frequently results in varying degrees of cognitive developmental delays in affected children (1,3,4). Within the therapeutic paradigm for IESS, controlling spasms is deemed the pivotal endpoint for assessing treatment efficacy (1,5). The medical community widely concurs that early intervention in spasm activity is imperative for enhancing short- and long-term outcomes in these patients (4-8).

Regarding treatment modalities, substantial research and expert consensus lean towards the importance of prompt initiation of first-line pharmacotherapy for immediate disease management (4,9,10). However, given the diagnostic complexities associated with IESS, timely identification of spasms and swift commencement of first-line treatment continue to pose significant challenges in clinical practice (11-15). Although the current literature emphasises the significance of early treatment, a uniform definition of 'early' remains elusive (9,15-17). A more precise delineation of the early treatment window would be substantially beneficial for predicting short-term therapeutic responses and implementing more aggressive treatment strategies. For example, adding a second first-line agent to the treatment protocol warrants consideration, particularly in light of emerging studies indicating that combination therapy with two first-line agents, such as adrenocorticotropic hormone (ACTH) or prednisolone along with vigabatrin (VGB), may enhance short-term outcomes (18,19).

Given the diverse aetiologies of IESS and a myriad of factors identified in previous studies that may influence therapeutic success (7,20,21), research into the optimal treatment window conducted using a sizable sample cohort and well-defined aetiologies is particularly crucial. Accordingly, we conducted a thorough secondary analysis of data from 273 patients with infantile spasms who were administered first-line treatment at our institution for the first time. Our objective was to ascertain whether interventions within a specific treatment window could potentially augment or diminish the likelihood of a short-term response. Through our research, we aim to refine the treatment strategies for IESS to reach higher levels of precision and efficacy. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-334/rc).

Highlight box

Key findings

- Patients with infantile epileptic spasms syndrome (IESS) who experience a lead time of over 1.5 months after the onset of epileptic spasm may have more difficulty achieving a short-term response.

What is known and what is new?

- Previous research has indicated that children with IESS should receive first-line treatment as early as possible, yet no specific recommendation on how short the lead time should be has been established.
- Our study suggests that 1.5 months may be an appropriate timeframe to define early treatment.

What is the implication, and what should change now?

- Based on our findings, first-line treatment should ideally commence within 1.5 months of the initial epileptic spasm onset at the latest.

Methods

Study design and population

Building on our previous findings, we reanalysed the data focusing on the effects of lead time on short-term response, and clarify within how long the lead time can probably be called "early". The retrospective study cohort comprised children diagnosed with IESS who presented to the Chinese PLA General Hospital between January 2018 and June 2023. We included patients undergoing their initial first-line treatment for IESS. Due to our previous findings that the response rate of patients seeking secondary first-line treatment is significantly lower than that in previous IESS first-line treatment studies and for patients having their first treatment in Chinese PLA General Hospital (9). Consequently, in our current study, patients who had received first-line treatment at other institutions were excluded to avoid confounding the results. According to our prior research, 273 patients came to Chinese PLA General Hospital for their first first-line treatment. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent for participation in this study was obtained from the patients' parents. Data are deidentified and protected by privacy safeguards. Ethical approval for the study was granted by the Ethics Committee of the First Medical Centre of the PLA General Hospital (No. S2020-337-01).

Inclusion criteria

The inclusion criteria were summarised as compliance with the diagnostic criteria for IESS as published by the International League Against Epilepsy (ILAE) in 2022 (1): (I) flexor, extensor or mixed epileptic spasms which often occur in clusters; (II) interictal electroencephalogram (EEG) showed with hypsarrhythmia or multifocal or focal epileptiform discharges; (III) age of epileptic spasms onset at 1–24 months. Patients had each received a comprehensive clinical examination to ascertain aetiology and were initiating first-line treatment for IESS. The detailed process of the comprehensive clinical examination followed our previously reported protocol (9). It commenced with a cranial magnetic resonance imaging (MRI) to identify any structural factors related to epilepsy, including acquired brain injuries or malformations of cortical development (MCD). If no such abnormalities were found, genetic testing was recommended. If genetic testing did not reveal significant anomalies, metabolic investigations were required. Patients who did not complete these evaluations were excluded from the study.

Aetiological classification

Patients were categorised into five distinct etiological groups as per our previous methodology (9): acquired structural abnormalities, congenital structural abnormalities with genetic/metabolic abnormalities, congenital structural abnormalities without genetic or metabolic abnormalities, congenital genetic/metabolic abnormalities without structural abnormalities, and unknown aetiology.

Influencing factors

We reanalysed previously collected data, including variables such as sex, age at first epileptic seizure, whether the initial seizure was a spasm, age at spasm onset, presence of hypsarrhythmia in EEG patterns, and developmental delays before spasm onset. An onset of seizures before 3 months was defined as seizure onset early, and spasms occurring after 12 months were considered late-onset spasms. All ages were corrected for prematurity. Some patients had taken other anti-seizure medicines during their first-line treatment, and with a usage proportion exceeding 20% in the entire cohort will be analysed.

Definition of standardized treatment, lead time and initial response

In this study, among the patients who received their first-line treatment at Chinese PLA General Hospital, only 10 initially received VGB, while the remaining 263 patients were treated with ACTH as their first-line therapy. Due to the potential differences in efficacy that various treatment modalities might present, we chose to exclude the patients treated with VGB. Standardized treatment is defined as the administration of an adequate dose of ACTH for a duration exceeding 2 weeks (5). Lead time refers to the period from the onset of epileptic spasms to the commencement of first-line treatment. Initial response was defined as the relief of spasms and the absence of spasms for at least 4 weeks after administering standardized treatment. If spasms were not relieved or persisted free for at least 4 weeks after the standardized treatments, the patient was considered unresponsive to medication (5).

Statistical analysis

We first compared whether there were significant differences in the above-collected data between the two groups (response *vs.* non response). Then, we conducted a collinearity analysis using a logistic regression model, in which factors with a variance inflation factor (VIF) <5 were considered for subsequent analysis. To determine the nonlinear relationship between lead-time and short-term response, we employed the restricted cubic splines (RCS) method, testing 3–7 knots for each factor that passed collinearity analysis, and selecting the model with the lowest Akaike information criterion (AIC) value for RCS testing.

When interpreting RCS analysis results, an inflection point signified a transition or boundary in differing association patterns between the predictor variable and the outcome. If the RCS analysis revealed a U-shaped, inverted U-shaped, or L-shaped curve with a clearly identifiable inflection point, the data were divided into two segments based on this point. This segmented logistic regression facilitated a more nuanced understanding of the relationship between the predictor variable and outcome in each segment by accounting for distinct association patterns in different curve regions. All statistical analyses in our study were performed using R software (version 4.2.2).

Results

Among the 263 patients enrolled, 148 were male. The median age at the first epileptic seizure was 5.5 months [interquartile range (IQR), 3.3, 8.0 months], with 43 children (16.3%) experiencing early onset epilepsy, defined as having their first seizure before the age of 3 months. The median age at the onset of spasms was 6.0 months (IQR, 4.0, 8.3 months), and the median age at the initiation of first-line treatment was 8.0 months (IQR, 6.0, 12.0 months). The median lead time was 2.00 months (IQR, 1.00, 4.00 months). Of the children, 57 (21.7%) presented with non-spasm seizures as their first seizure type, 36 (13.7%) had additional types of seizure during the spasms, 30 (11.4%) experienced spasms onset at an age greater than 12 months, 146 (55.5%) exhibited a hypsarrhythmia in EEG patterns, and 112 (43.1%) showed significant psychomotor developmental delays before spasm onset. According to the previously defined aetiological classification, patients were categorised as follows: 62 (23.6%) with acquired structural abnormalities, 30 (11.4%) with congenital structural abnormalities with genetic/metabolic abnormalities, 84 (31.9%) with congenital structural abnormalities without genetic or metabolic abnormalities, 29 (11.0%) with congenital genetic/metabolic abnormalities without structural abnormalities, and 58 (22.1%) with unknown aetiology (*Table 1*).

An initial response was achieved in 108 (41.1%) of the patients. Significant differences were observed between the responsive and non-responsive groups regarding lead time [1.50 (IQR, 1.00, 3.00) *vs.* 2.00 (IQR, 1.00, 5.00) months; P=0.003] and seizure onset early (10/108, 9.3% *vs.* 33/155, 21.3%; P=0.009). No significant differences were found in terms of gender, first seizure type, late-onset spasms, other types of seizures during spasms, hypsarrhythmia, developmental delay before spasms onset, IESS classification, age of spasm onset, combined with topiramate or combined with valproic acid (P>0.05, *Table 1*).

When all factors were included in a logistic regression model, significant collinearity was observed between age at spasms onset, age at treatment initiation, and lead time. Consequently, factors such as age at spasm onset and age at treatment initiation were excluded from the RCS analysis, with detailed VIF values presented in *Figure 1*. The RCS analysis with four knots yielded the lowest AIC value of 352.5. Thus, a four-knot RCS was employed, which revealed a significant inverted U-shaped relationship between lead time and initial response (P=0.005, *Figure 2*), with a trend towards nonlinearity (P-nonlinear =0.15, *Figure 2*). The apex of the curve was located at a lead time of 1.608 months. Because the minimum unit of time we calculated was 1 week (close to 0.25 months), we chose 1.5 months as the cutoff value. Subsequent regression analysis stratified at this inflection point indicated that for children with IESS and a lead time of fewer than 1.5 months, an increase in lead time did not significantly affect the likelihood of short-term response (OR =1.03, 95% CI: 0.72–1.47, P=0.89, *Table 2*). However, for those with a lead time of 1.5 months or more, an increased lead time was associated with a significantly reduced probability of short-term response (OR =0.59, 95% CI: 0.33–0.92, P=0.041, *Table 2*).

Discussion

Early identification and treatment of IESS are crucial for improving the prognosis of affected children. Unfortunately, the process from spasm onset to diagnosis and subsequent timely and effective first-line treatment often requires a considerable time, and this situation does not appear to have significantly improved globally (12,14,16). For example, Raga *et al.* revealed that among 175 children with spasms, the lead time was within 1 month for fewer than half (86 patients) (15). This finding shows no improvement compared to the median time of 24.5 days reported by Hussain *et al.* in 2017 and remains suboptimal (12). The situation appears even more daunting in Asia. Surana *et al.* reported a median time from spasms to treatment of 60 days (16), and a review of seven studies from India and Pakistan reported a median lead time of 2.4 months (16). In our study, the median lead time for all children with IESS was 2 months, clearly indicating that timely identification and first-line treatment of IESS also remain a significant challenge in China.

Although existing research emphasises the importance of early treatment, no clear consensus on what constitutes 'early' in this context currently exists. Knupp *et al.* observed no significant differences in short-term response when the treatment interval was set at 4 weeks (22). However, Surana *et al.* found significant differences in the treatment interval between the response and non-response groups (16). Specifically, the median treatment lead time for the response group was 30 days (range, 0 days–43 months), compared to 90 days (range, 14 days–66 months) for the non-response group, with a statistically significant difference (P=0.002). Furthermore, our previous research indicated that a

Table 1 Patient demographics and baseline characteristics

Characteristics	Treatment effect			Statistic value	P value
	Overall (n=263)	Non response (n=155)	Response (n=108)		
Gender				0.49	0.48†
Female	115 (43.7)	65 (41.9)	50 (46.3)		
Male	148 (56.3)	90 (58.1)	58 (53.7)		
Age of seizure onset (months)	5.5 (3.3, 8.0)	5.0 (3.0, 8.0)	5.5 (4.4, 7.6)	7,411.50	0.11‡
First seizure type				1.07	0.30†
Non spasm	57 (21.7)	37 (23.9)	20 (18.5)		
Spasm	206 (78.3)	118 (76.1)	88 (81.5)		
Age of spasm onset (months)	6.0 (4.0, 8.3)	6.0 (4.0, 8.5)	6.0 (4.9, 8.0)	7,895.00	0.43‡
Seizure onset early				6.74	0.009†*
>3 months	220 (83.7)	122 (78.7)	98 (90.7)		
≤3 months	43 (16.3)	33 (21.3)	10 (9.3)		
Late-onset spasm				0.84	0.36†
>12 and ≤24 months	30 (11.4)	20 (12.9)	10 (9.3)		
≤12 months	233 (88.6)	135 (87.1)	98 (90.7)		
Other type during spasm				0.01	0.94†
With other seizure type	36 (13.7)	21 (13.5)	15 (13.9)		
Without other seizure type	227 (86.3)	134 (86.5)	93 (86.1)		
Hypsarrhythmia				0.07	0.79†
No	117 (44.5)	70 (45.2)	47 (43.5)		
Yes	146 (55.5)	85 (54.8)	61 (56.5)		
Development delay prior to spasms onset				0.62	0.43†
No	148 (56.9)	84 (54.9)	64 (59.8)		
Yes	112 (43.1)	69 (45.1)	43 (40.2)		
Treatment age (months)	8.0 (6.0, 12.0)	9.0 (6.0, 14.0)	8.0 (6.5, 10.0)	9,056.50	0.26‡
Lead time (months)	2.00 (1.00, 4.00)	2.00 (1.00, 5.00)	1.50 (1.00, 3.00)	10,135.50	0.003‡*
IESS classification				7.50	0.11†
Unknown	58 (22.1)	32 (20.6)	26 (24.1)		
Congenital structural abnormalities without positive genetic finding	84 (31.9)	48 (31.0)	36 (33.3)		
Acquired structural abnormalities	62 (23.6)	32 (20.6)	30 (27.8)		
Normal structure with positive genetic finding	29 (11.0)	20 (12.9)	9 (8.3)		
Congenital structural abnormalities with positive genetic finding	30 (11.4)	23 (14.8)	7 (6.5)		
Combined with topiramate				1.36	0.24†
Yes	75 (28.5)	40 (25.8)	35 (32.4)		
No	188 (71.5)	115 (74.2)	73 (67.6)		
Combined with valproic acid				1.31	0.25†
Yes	157 (59.7)	97 (62.6)	60 (55.6)		
No	106 (40.3)	58 (37.4)	48 (44.4)		

Data are presented as n (%) or median (IQR). †, Pearson's Chi-squared test; ‡, Wilcoxon rank sum test; *, statistical difference. IESS, infantile epileptic spasms syndrome; IQR, interquartile range.

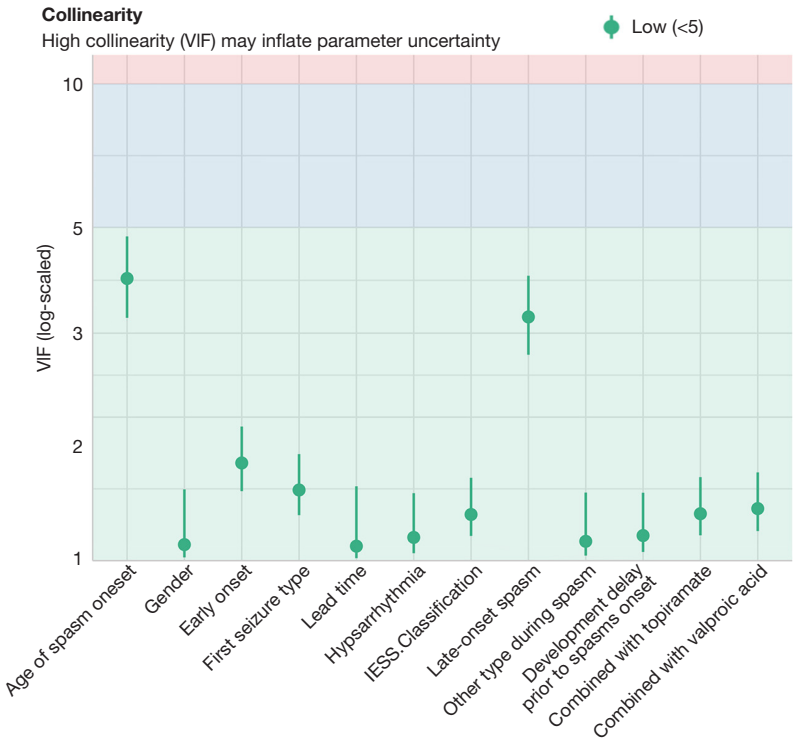

Figure 1 VIF and tolerance of factors in the logistic models (VIF <5). IESS, infantile epileptic spasms syndrome; VIF, variance inflation factor.

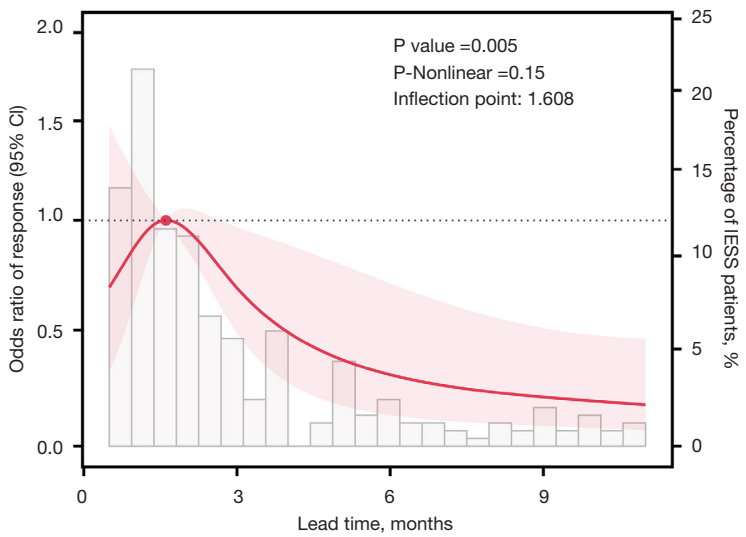

Figure 2 Association between lead time and treatment effect with the RCS function. The four-knot model is located at the 5th, 35th, 65th, and 95th percentiles. The X-axis represents the specific time of the lead time. The Y-axis on the left represents the OR to present treatment effect for any value of lead time compared to individuals with reference value (50th percentile) of lead time. The Y-axis on the right represents the proportion of patients with different lead times in the entire cohort. The logistic regression was adjusted for gender, first seizure type, early onset, late onset, other type during spasm, hypsarrhythmia, development delay prior to spasms onset, IESS classification, age of spasm onset, combined with topiramate, and combined with valproic acid. IESS, infantile epileptic spasms syndrome; OR, odds ratio; CI, confidence interval; RCS, restricted cubic splines.

Table 2 Effect of standardised lead time level on treatment effect: adjusted odds ratios from segmented logistic regression analysis

Characteristics	OR per SD	95% CI	P value
Lead time (≤1.5 months) (n=121, 46.0%)	1.03	0.72, 1.47	0.89
Lead time (>1.5 months) (n=142, 54.0%)	0.59	0.33, 0.92	0.041

ORs were adjusted for gender, first seizure type, seizure onset early, late-onset spasm, other type during spasm, hypsarrhythmia, development delay prior to spasms onset, IESS classification, age of spasm onset, combined with topiramate, and combined with valproic acid. OR, odds ratio; SD, standard deviation; CI, confidence interval.

shorter interval between treatment initiation appears more favourable for short-term prognosis (9). In this study, we found that if children received first-line treatment within 1.5 months after spasm onset, the treatment interval was not significantly associated with short-term response. However, as the treatment interval exceeded 1.5 months, the likelihood of short-term response progressively decreased. Hence, we suggest defining the early treatment window as within 1.5 months of spasm onset.

When considering factors that influence short-term response, aetiology emerges as a significant determinant. Studies suggest that acquired structural abnormalities may yield better outcomes (20,23), and that children with later-onset spasms and no preceding seizure types tend to respond more favorably (24). In our previous research, we identified lead time and occurrence of epileptic seizures within 3 months as key factors affecting efficacy (9). Our logistic regression analysis, controlling for these variables, still indicates that initiating treatment after 1.5 months reduces the chances of a short-term response, reinforcing the importance of this early treatment window.

Limitations

There are limitations in this study. First, as a secondary analysis of previously published data, this study is inevitably subject to the inherent selection biases of retrospective data analysis. Second, the determination of the timing of spasms relies on caregivers' reports, and as we have previously noted, spasms can be challenging to recognise, which may lead to shorter calculated lead times than the actual situation. Additionally, due to the potential difficulty parents may face in recalling the exact date of their child's spasm onset, we have used 1 week (equivalent to 0.25 months) as the minimum unit for calculating lead time in our study. However, given real-world constraints, requiring frequent EEG monitoring for all children with IESS before the onset of spasms seems impractical. Third, although our results showed a clear U-shaped curve, it was not statistically significant, which is consistent with our previous findings. Nevertheless, our subsequent analysis confirmed that children treated within 1.5 months did not exhibit a time-dependent effect related to lead time, leading us to propose a 1.5-month window for early treatment. It is important to acknowledge that following a subgroup analysis, we observed that the subgroup of children who received timely first-line treatment within 1.5 months of spasm onset was relatively small. This limitation may impact the reliability of our findings. Therefore, any conclusions drawn from this data should be approached with caution.

Conclusions

In summary, the short-term response group had a shorter lead time compared to the non-response group. Rapid identification, diagnosis, and treatment of IESS in children remain challenging. Initiating first-line treatment as early as possible remains a significant influencing factor for achieving a short-term response. We recommend that first-line treatment should be initiated within 1.5 months following spasm onset; otherwise, the likelihood of a short-term response diminishes over time.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://

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Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-334/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-334/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent for participation in this study was obtained from the patients' parents. Data are deidentified and protected by privacy safeguards. Ethical approval for the study was granted by the Ethics Committee of the First Medical Centre of the PLA General Hospital (No. S2020-337-01).

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