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ARTICLE

Effect of Early Oral Administration of Doxycycline on Macrolide Resistance in Children with Mycoplasma Pneumoniae Pneumonia: A Retrospective Study

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Abstract

Aims/Background Mycoplasma pneumoniae pneumonia (MPP) is typically a benign and self-limiting disease. This study aimed to investigate the effect of early oral administration of doxycycline on macrolide resistance in children with MPP.

Methods This study retrospectively analyzed the clinical data of 173 MPP children treated with macrolides at the Second Affiliated Hospital of Mudanjiang Medical University from March 2020 to March 2023. Nine cases that did not meet the inclusion criteria were excluded, leaving 164 children. They were divided into Group A (early oral administration of doxycycline + macrolide treatment) (n = 85) and Group B (macrolide treatment alone) (n = 79) based on whether early oral administration of doxycycline was given. Drug sensitivity results and adverse reactions after treatment were statistically analyzed. Based on the drug sensitivity results, the MPP children were classified as having either macrolide-resistant mycoplasma pneumoniae (MRMP) or macrolide-sensitive mycoplasma pneumoniae (MSMP) infections. A stratified analysis was performed to compare the disappearance time of fever, disappearance time of shortness of breath, disappearance time of rales, and symptom improvement time on chest X-ray examination, and to further explore the clinical efficacy of early oral administration of doxycycline in different groups of children.

Results No significant differences were found in baseline data such as age, sex, and weight between the two groups ($p > 0.05$). A total of 112 out of 164 children developed macrolide resistance (68.29%), with 47 cases in Group A and 65 cases in Group B, indicating a significant difference between the two groups ($p < 0.05$). The two groups showed a significant difference in macrolide sensitivity levels after treatment ($p < 0.05$), with no significant difference in the incidence of adverse reactions ($p > 0.05$). After treatment, the time to the disappearance of febrile fever, time to disappearance time of fever, disappearance time of shortness of breath, disappearance time of rales, symptom improvement time on chest X-ray examination, and time to administration of macrolides after treatment were shorter in children with MRMP in group A than in children with MRMP in group B ($p < 0.05$). In contrast, MSMP children in both groups exhibited no significant differences in symptom disappearance time and duration of macrolides treatment ($p > 0.05$).

Conclusion Early oral administration of doxycycline is a safe and effective treatment for MPP. It helps relieve symptoms in MRMP children, shortens the duration of macrolide use, and reduces the incidence of macrolide resistance.

Key words: doxycycline; pneumonia; mycoplasma; macrolides; drug resistance; children

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Introduction

Mycoplasma pneumoniae is a major cause of community-acquired pneumonia, particularly in children and adolescents (Poddighe et al, 2022). Mycoplasma pneumoniae pneumonia (MPP), a significant public health issue affecting global pediatric health, has garnered extensive attention from both academia and clinical practice (Song et al, 2023). Three main types of drugs are used to treat MPP infection: macrolides, quinolones, and tetracyclines (Yuan et al, 2020), with quinolones being unsuitable for children. Macrolides are the first-line treatment for MPP. Recently, the prevalence of macrolide-resistant mycoplasma pneumoniae (MRMP) has increased rapidly worldwide, especially in East Asia (Yang, 2019). A survey has shown that the MRMP infection rate is rising, with significant regional differences, and that 37.0% of children are infected with MRMP (Kim et al, 2022). Since 2018, the prevalence of MRMP in Taiwan has increased dramatically (Tsai et al, 2021). Some scholars have investigated many regions of China and reported a macrolide resistance rate of 79.7%, with a rising proportion of MP with genotype II (Zhao et al, 2019).

With the marked increase in the prevalence of MRMP, treating MPP in children has become increasingly challenging (Yan et al, 2024). Therefore, timely diagnosis and the rational use of various antibiotics are crucial. Minocycline and doxycycline are tetracycline antibiotics. A study reported that early administration of minocycline can effectively reduce MRMP load (Chen et al, 2021). Furthermore, current evidence indicates that doxycycline is significantly effective in MRMP children (Chen et al, 2024; Lee et al, 2021). However, few studies have investigated the impact of early oral administration of doxycycline on macrolide resistance in MPP children. Consequently, this retrospective study was conducted to enhance the clinical evidence for antibiotic combination therapy and improve treatment efficacy in MPP children.

Methods

Research Design

This study retrospectively analyzed the clinical data of 173 MPP children treated with macrolides at the Second Affiliated Hospital of Mudanjiang Medical University from March 2020 to March 2023. The inclusion criteria were as follows: (1) patients aged 8–14 years; (2) patients who had not received other drug treatments before admission and who presented with fever, shortness of breath, and rales; (3) drug sensitivity results within 48 hours of admission showing macrolide-sensitive mycoplasma pneumoniae (MSMP); (4) and patients with complete clinical data. The exclusion criteria included: (1) patients with other infections; (2) patients with immune deficiencies; (3) patients with bronchopulmonary dysplasia, tuberculosis, or other diseases; and (4) patients who did not undergo a drug sensitivity test for macrolides. Based on these criteria, 4 children with incomplete clinical data, 3 children with MRMP before medication, and 2 children with mixed infections were excluded. Ultimately, 164 cases were included in the study. This study, adhering to the principles of the Declaration of Helsinki (World Medical Association, 2013),

was approved by the ethical committee of the Second Affiliated Hospital of Mudanjiang Medical University (approval No.: 20200104). The guardians of children who were aware of the purpose and significance signed an informed consent.

Based on whether early oral administration of doxycycline (manufacturer: Jiangsu Lianhuan Pharmaceutical Co., Ltd.; origin: Yangzhou, China; approval No.: H32021266; specification: 0.1 g ($C_{22}H_{24}N_2O_8$)) was given after the diagnosis of MPP infection and before the drug sensitivity results of macrolides were available, the 164 MPP children were divided into Group A (early oral administration of doxycycline + macrolide treatment) and Group B (macrolide treatment alone). The drug sensitivity results and adverse reactions after treatment were analyzed, and the duration of fever, shortness of breath, and rales were compared. The flow chart of the study is shown in Fig. 1.

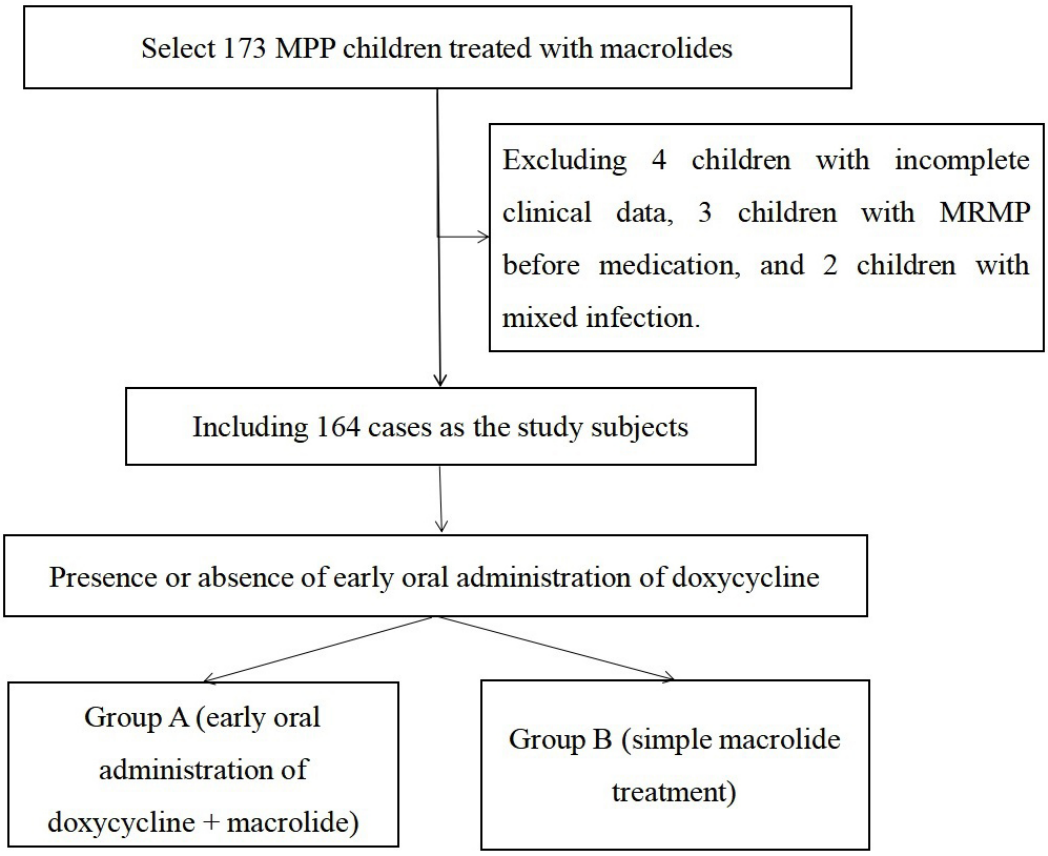

Fig. 1. Flow chart of the study. Notes: MPP, mycoplasma pneumoniae pneumonia; MRMP, macrolide-resistant mycoplasma pneumoniae.

Drug Sensitivity Test Methods

Before and after treatment, throat swab specimens collected from patients were isolated and cultured using Hayflick Medium (manufacturer: Shanghai Kanglang Biological Technology Co., Ltd.; origin: Shanghai, China). The drug sensitivity results were determined according to the standards of the Clinical and Laboratory Standards Institute (CLSI) (Waites et al, 2011), with sensitivity levels categorized

as susceptible, intermediate, or resistant. The detailed criteria were as follows: (1) Susceptible: when the recommended dose was used at the infection sites, the isolated strains were generally inhibited by the antimicrobial agents at achievable concentration levels. (2) Intermediate: the minimum inhibitory concentration of antimicrobial agents was close to the concentration reached in blood and tissues, with the response rate of isolated strains potentially lower than that of sensitive strains. (3) Resistant: the isolated strains were not inhibited by the antimicrobial agents at achievable concentration levels and/or showed a minimum inhibitory concentration that indicated resistance.

Data Collection

The demographic characteristics and clinical data of the children were collected from the medical record system. These included age, sex, weight, residence, history of macrolide use, laboratory examination data, imaging examination data, symptom disappearance time (fever, shortness of breath, rales), adverse reactions, symptom improvement time on chest X-ray examination, hospitalization duration, and fever rate within 48 hours. Fever duration refers to the number of days during which the child's temperature was $\geq$38 °C and the interval between each fever episode was $<$24 hours. The duration of fever is defined as a temperature decrease to less than 37.5 °C for more than 48 hours. Symptom improvement time on chest X-ray examination is defined as a reduction of more than 30% in consolidation and infiltration areas after treatment compared to before treatment.

Statistical analysis

The categorical variables were expressed as (n (%)) and analyzed using the following tests. (1) Fourfold table test: (i) The Pearson chi-square test was employed when all theoretical numbers (T) were $\geq$5 and the total sample size (n) was $\geq$40. (ii) Continuity correction was utilized when $1 \leq T < 5$ and $n \geq 40$. (iii) Fisher's exact test was used when $T < 1$ or $n < 40$. (2) $R \times C$ table test: The Pearson chi-square test was used when cells with theoretical numbers less than 5 comprised less than 20% of the cells, or when $T \geq 1$. Conversely, Fisher's exact test was used when cells with theoretical numbers less than 5 comprised more than 20% of the cells, or when $T < 1$. The Shapiro-Wilk method was used to assess the normal distribution of continuous variables. Non-normally distributed data were tested using the Mann-Whitney U test and expressed as (M (P_{25}, P_{75})). A significance level of ($p < 0.05$) was considered statistically significant. Data were processed using SPSS 27.0 (IBM Corp., Armonk, NY, USA). Symptom disappearance time, symptom improvement time, and duration of macrolides use after treatment were compared using stratified analysis. Figs. 1,2 were created using Microsoft Office Word 2006 (Microsoft Corporation, Redmond, WA, USA).

Results

Comparison of Baseline Data in Both Groups

No significant difference existed in baseline data such as age, sex and weight between the two groups ($p > 0.05$), as shown in Table 1.

Table 1. Comparison of baseline data in both groups.

Items	Sum	Group A (n = 85)	Group B (n = 79)	Z/χ^2	*p*-value
Age (years, M (P_{25}, P_{75}))	164	11.00 (9.00, 13.00)	11.00 (9.00, 13.00)	–0.340	0.734
Sex (n (%))				0.010	0.921
Male	65	34 (40.00)	31 (39.24)		
Female	99	51 (60.00)	48 (60.76)		
Weight (kg, M (P_{25}, P_{75}))	164	40.40 (31.80, 47.65)	41.80 (33.00, 49.80)	–0.393	0.694
Residence (n (%))				0.463	0.496
Urban areas	91	45 (52.94)	46 (58.23)		
Rural areas	73	40 (47.06)	33 (41.77)		
History of macrolides (n (%))				2.225	0.136
Yes	109	61 (71.76)	48 (60.76)		
No	55	24 (28.24)	31 (39.24)		
Macrolides (n (%))				4.998	0.172
Erythromycin	62	38 (44.71)	24 (30.38)		
Azithromycin	50	24 (28.24)	26 (32.91)		
Clarithromycin	38	15 (17.65)	23 (29.11)		
Others	14	8 (9.41)	6 (7.59)		
Drug sensitivity results within 48 h after admission (n (%))				0.198	0.656
Susceptible	39	19 (22.35)	20 (25.32)		
Intermediate	125	66 (77.65)	59 (74.68)		
Resistant	0	0	0		
White blood cell count ($\times 10^9$/L, M (P_{25}, P_{75}))	164	9.40 (7.40, 12.65)	9.80 (8.00, 12.30)	–0.403	0.687
Neutrophilic granulocyte (%, M (P_{25}, P_{75}))	164	78.00 (71.00, 82.00)	78.00 (71.00, 83.00)	–0.066	0.947
C-reactive protein (mg/L, M (P_{25}, P_{75}))	164	17.70 (11.55, 24.40)	16.80 (10.80, 26.80)	–0.005	0.996
Perihilar infiltration (n (%))				0.033	0.855
Yes	30	16 (18.82)	14 (17.72)		
No	134	69 (81.18)	65 (82.28)		
Pulmonary consolidation (n (%))				0.064	0.801
Yes	66	35 (41.18)	31 (39.24)		
No	98	50 (58.82)	48 (60.76)		
Flaky consolidation (n (%))				0.034	0.854
Yes	22	11 (12.94)	11 (13.92)		
No	142	74 (87.06)	68 (86.08)		
Pleural effusion (n (%))				0.171	0.679
Yes	19	9 (10.59)	10 (12.66)		
No	145	76 (89.41)	69 (87.34)		

Group A (early oral administration of doxycycline + macrolide treatment); Group B (macrolide treatment alone).

Table 2. Comparison of macrolide sensitivity levels in both groups after treatment.

Groups	n	Susceptible	Intermediate	Resistant
		n (%)	n (%)	n (%)
Group A	85	15 (17.65)	23 (27.06)	47 (55.29)
Group B	79	3 (3.80)	11 (13.92)	65 (82.28)
χ^2			14.929	
p-value			0.001	

Comparison of Drug Sensitivity Results in Both Groups after Treatment

After the corresponding drug treatment, a total of 112 out of 164 children developed macrolide resistance, resulting in an incidence of 68.29%. The proportion of macrolide sensitivity levels in both groups changed significantly ($p < 0.001$). After treatment, 47 cases in Group A and 65 cases in Group B were identified with MRMP, showing a significant difference between the two groups ($p < 0.05$), as detailed in Table 2 and Fig. 2.

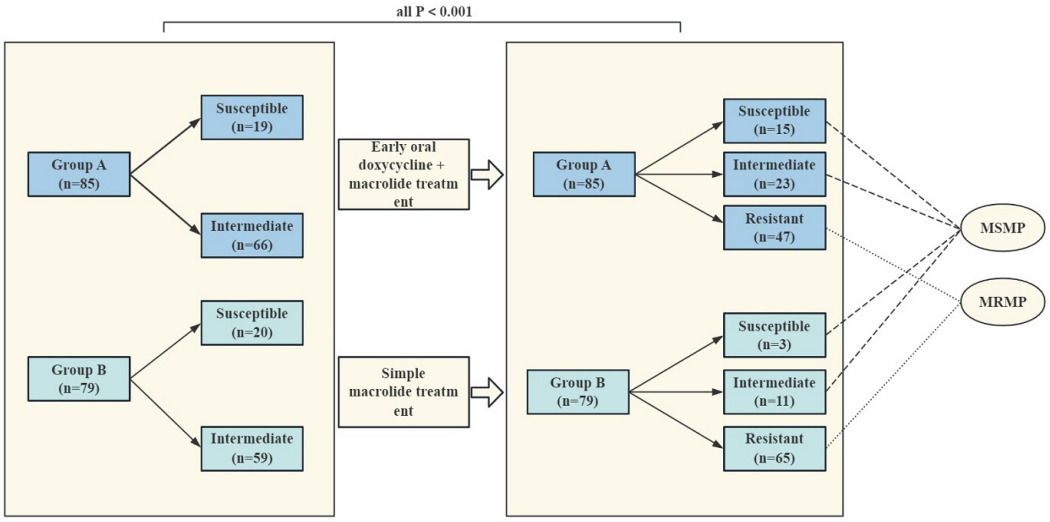

Fig. 2. Comparison of macrolide sensitivity levels in both groups before and after treatment. Notes: MRMP, macrolide-resistant mycoplasma pneumoniae; MSMP, macrolide-sensitive mycoplasma pneumoniae.

Group A showed a significant difference in macrolide sensitivity levels before and after treatment, with $\chi^2 = 68.246$ and $p < 0.001$. Group B also demonstrated a significant difference in macrolide sensitivity levels before and after treatment, with $\chi^2 = 110.480$ and $p < 0.001$.

Comparison of Adverse Reactions in Both Groups after Treatment

Group A had 1 case of nausea and vomiting and 1 case of yellowing of the teeth during treatment, resulting in an adverse reaction incidence of 2.35% (2/85). Group B had 1 case of diarrhea and abdominal pain, with an adverse reaction incidence of 1.27% (1/79). There was no significant difference between the two groups ($p > 0.05$), as shown in Table 3.

Table 3. Comparison of adverse reactions in both groups after treatment.

Groups	n	Nausea and vomiting	Yellowing teeth	Diarrhea and abdominal pain	Total incidence of adverse reactions
		n (%)	n (%)	n (%)	n (%)
Group A	85	1 (1.18)	1 (1.18)	0 (0.00)	2 (2.35)
Group B	79	0 (0.00)	0 (0.00)	1 (1.27)	1 (1.27)
χ^2					0.000
p-value					1.000

Comparison of Symptom Disappearance Time and Time of Imaging Performance Improvement in Both Groups after Treatment

The MRMP children in Group A showed a shorter disappearance time for fever, shortness of breath, and rales compared to MRMP children in Group B ($p < 0.001$). There was no significant difference in the disappearance time of symptoms between the two groups of MSMP children after treatment ($p > 0.05$), as shown in Table 4.

Comparison of Medication Time of Macrolides in Both Groups

The medication time for macrolides in MRMP children was 10.00 (8.00, 12.00) days in Group A and 12.00 (10.00, 14.50) days in Group B, showing a significant difference between the two groups ($Z = -3.337$, $p = 0.001$). In contrast, the medication time for macrolides in MSMP children was 10.00 (7.75, 12.00) days in Group A and 11.50 (8.00, 12.00) days in Group B, with no significant difference between the two groups ($Z = -0.491$, $p = 0.623$).

Discussion

MP can cause not only severe upper and lower respiratory tract symptoms but also other extrapulmonary diseases and post-infection complications (Hu et al, 2022). Macrolides, as the first-line treatment for MP, are widely used in outpatient settings due to their high oral bioavailability and once-daily dosing. However, over the past decade, MRMP has emerged globally (Chen et al, 2020). Patients infected with MRMP are challenging to treat, often experiencing prolonged infection durations and high morbidity. A study analyzing 247 clinical specimens with positive MP DNA found more diverse genotypes and a higher incidence of macrolide resistance-related mutations in pediatric specimens (Yan et al, 2020). In this study, a total of 112 MPP children developed macrolide resistance after treatment, resulting in an incidence of 68.29%. This indicated that children are at a higher risk of developing MRMP infections. Therefore, clinical attention must be given to the management of MPP in children to minimize the occurrence of macrolide resistance. However, the results of this study may not fully represent the changes in macrolide resistance rates among Chinese children, due to significant variations in survey results, study periods, and measurement standards across different regions.

Table 4. Comparison of symptom disappearance time and symptom improvement time on chest X-ray examination.

Groups		n	Disappearance time of fever (d, M (P_{25}, P_{75}))	Disappearance time of shortness of breath (d, M (P_{25}, P_{75}))	Disappearance time of rales (d, M (P_{25}, P_{75}))	Symptom improvement time on chest X-ray examination (d, M (P_{25}, P_{75}))
MRMP	Group A	47	2.00 (1.00, 3.00)	2.00 (2.00, 3.00)	4.00 (3.00, 5.00)	4.00 (4.00, 5.00)
	Group B	65	4.00 (3.00, 5.00)	4.00 (3.00, 5.00)	5.00 (4.00, 6.00)	7.00 (5.00, 9.00)
	Z		–6.213	–4.663	–4.632	–6.190
	p-value		<0.001	<0.001	<0.001	<0.001
MSMP	Group A	38	2.00 (1.75, 2.00)	3.00 (2.00, 4.00)	3.00 (3.00, 4.00)	4.00 (3.00, 4.00)
	Group B	14	2.00 (2.00, 3.00)	3.50 (2.75, 4.00)	4.00 (3.00, 5.00)	3.00 (3.50, 5.00)
	Z		–1.463	–0.414	–0.855	–0.235
	p-value		0.143	0.679	0.393	0.814

Notes. MRMP, macrolide-resistant mycoplasma pneumoniae; MSMP, macrolide-sensitive mycoplasma pneumoniae.

Macrolide resistance can lead to clinical issues such as prolonged duration of fever, cough, and extended hospital stays. Therefore, alternative antibiotics, including tetracyclines like doxycycline and minocycline, are recommended for use within 7–14 days (Pereyre et al, 2016). Oishi and Ouchi (2022) found no cross-resistance between macrolides and other classes of antibiotics such as tetracyclines and quinolones. Thus, rational selection and early application of different types of antibiotics can be meaningful for improving efficacy in the early stages of MPP treatment. This retrospective study found that administering doxycycline before performing or obtaining drug sensitivity test results can reduce the occurrence of macrolide resistance, control disease progression, alleviate symptoms such as fever, shortness of breath, and rales, and shorten hospitalization time.

Macrolide resistance is increasing, and the hydrophobic nature of macrolides is thought to contribute to intrinsic resistance to most antibiotics, exerting synergistic effects when combined with other antibiotics (Heidary et al, 2022). Doxycycline, a broad-spectrum synthetic derivative of tetracycline, has good lung tissue penetration, potential antiviral and immunomodulatory effects, and is considered safe for the heart. Its mechanism of action involves blocking the binding of aminoacyl-tRNA to mRNA by specifically binding to the bacterial ribosomal 30S subunit at the A site. This action inhibits the addition of new amino acids to the growing peptide chain, thereby disrupting the translation process and inhibiting protein synthesis (Ali et al, 2021; Bidell et al, 2020). Differences in the mechanisms of action between tetracyclines and macrolides (Ohe et al, 2021) may explain why early oral administration of doxycycline can reduce the occurrence of macrolide resistance and accelerate disease improvement in MPP children. From any perspective, early oral administration of doxycycline combined with macrolides appears to be a reliable treatment for MPP in children.

This study has several limitations. Due to its retrospective nature and limited research funds, the study was conducted at a single hospital, which may affect the reliability of the conclusions. Additionally, there may be selection and confounding biases that could impact the results. Future studies should improve experimental design, increase the sample size, and conduct multi-center prospective research to further confirm the clinical value of early oral administration of doxycycline and provide high-quality references for clinical practice.

Conclusion

Compared with macrolide treatment alone, early oral administration of doxycycline can alleviate symptoms in MRMP children and reduce the incidence of macrolide resistance, demonstrating better clinical efficacy.

Key Points

- Mycoplasma pneumoniae pneumonia (MPP) children have a high risk of developing macrolide-resistant mycoplasma pneumoniae (MRMP) infections.
- Early oral administration of doxycycline can alleviate symptoms in MRMP children and shorten the duration of macrolide medication.
- Early oral administration of doxycycline can reduce macrolide resistance.
- Early oral administration of doxycycline is an effective and safe treatment for MPP, without increasing the incidence of adverse reactions.

Availability of Data and Materials

The datasets used and/or analysed during the current study were available from the corresponding author on reasonable request.

Author Contributions

XZ designed the study. BC, LY, XL and XZ conducted the study. LY and XL collected and analyzed the data. BC drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors gave final approval of the version to be published. All authors participated fully in the work, took public responsibility for appropriate portions of the content, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or completeness of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This study has been approved by the ethical committee of the Second Affiliated Hospital of Mudanjiang Medical University (approval No.: 20200104). The guardians of children who were aware of the purpose and significance signed an informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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