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ORIGINAL ARTICLE

Observational Study

Efficacy of β2-adrenergic receptor agonist combined with corticosteroid in the treatment of children with cough variant asthma

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Abstract

BACKGROUND

Cough variant asthma (CVA) is one of the most common respiratory diseases in children, which has a serious impact on the quality of life and daily activities of children. For severe CVA, immunomodulatory drugs are needed.

AIM

To evaluate the efficacy of salmeterol combined with budesonide in the treatment of pediatric CVA.

METHODS

130 children with CVA from January 2020 to December 2022 were prospectively selected and randomly divided into an observation group (salmeterol combined with budesonide) and a control group (budesonide combined with a placebo). Compare the clinical efficacy of two groups before and after intervention. The evaluation parameters include cough frequency score, nocturnal cough arousal, and lung function indicators. Serum inflammatory markers, immune function markers and airway anatomical indicators were also measured.

RESULTS

After the intervention, the total effective rate of the observation group was significantly higher than that of the control group, and the cough frequency score and the night cough wake rate of the observation group were lower than that of the control group, with a statistically significant difference. In addition, the changes of lung function indicators, serum markers and immune function markers in the observation group were better than those in the control group.

CONCLUSION
The clinical efficacy of salmeterol combined with Budesonide in the treatment of CVA is better than that of Budesonide alone.

Key Words: Salmeterol; Budesonide; Cough variant asthma; Pediatrics; Efficacy analysis

Core Tip: Cough variant asthma (CVA) seriously affects children's daily activities and physical health. For severe CVA, immunomodulatory drugs are needed. The purpose of this study is to evaluate the efficacy of salmeterol combined with budesonide in the treatment of CVA in children. The results showed that after the intervention, the clinical symptoms of patients in the observation group were lighter and the level of immune markers was higher. The results of this study show that the combined treatment of the two drugs is better than budesonide alone.

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INTRODUCTION

Cough variant asthma (CVA) is one of the most common airway diseases in children and is characterized by cough as the main symptom while other typical asthma symptoms may not be obvious[1,2]. The prevalence of CVA in children is increasing year by year, which has a serious impact on the quality of life and daily activities of children[3,4]. Currently, drugs used to treat CVA include inhaled corticosteroids (ICS), bronchodilators, leukotriene receptor antagonists, long-acting anticholinergics, and immunomodulators[5-9]. ICS drugs such as beclomethasone propionate, fluticasone and budesonide are used to relieve coughs and asthma attacks by reducing airway inflammation and controlling symptoms. Bronchodilators relieve airway spasms and dilate the airway by relaxing the smooth muscle of the airway to relieve coughing and breathing difficulties, and the main bronchodilators include short-acting beta2-agonists such as salbutamol and long-acting β2 receptor agonist (LABA) such as salmeterol. Leukotriene receptor antagonists block leukotriene receptors, reduce airway inflammation and relieve asthma symptoms. Long-acting anticholinergic drugs relieve airway spasm and improve lung function by blocking cholinergic receptors. For severe CVA, immunomodulatory drugs may need to be considered to regulate the immune system's overresponse and reduce airway inflammation[10,11].

As a common medical treatment, ICS are commonly used in the treatment of asthma to reduce airway inflammation and control symptoms[12,13]. However, some ICS have limited efficacy in children with CVA and may need to be combined with other medications to achieve better control[14]. In recent studies, ICS in combination with LABA such as salmeterol can provide a more effective treatment strategy[15,16]. Salmeterol acts as a LABA to relieve airway spasms by dilating airway smooth muscle[17]. Budesonide is a potent ICS that reduces airway inflammation and controls asthma symptoms[18]. However, comprehensive studies and evaluations on the efficacy of salmeterol combined with budesonide in children with cough-variant asthma are lacking. The aim of this study was to systematically evaluate the efficacy of the salmeterol, a LABA, combined with budesonide, an ICS, in the treatment of children with CVA, and to explore its effect on clinical efficacy and recovery indicators of childhood asthma control.

MATERIALS AND METHODS

Participants

This study used a prospective approach to select 130 children with CVA who were diagnosed and treated at our hospital between January 2020 and December 2022. The patients were randomly assigned (1:1) to observation group and control group using random number table method. The observation group received salmeterol combined with budesonide, while the control group received the budesonide combined with placebo. The baseline characteristics were balanced between the 2 groups. The comparison of basic data between the two groups before intervention showed that the difference was not statistically significant and was comparable (Table 1). This study protocol was approved by the Ethics Committee of the first People's Hospital of Jiangxia District, Wuhan, and all the children's families have voluntarily participated in the study and have signed informed consent forms.

Inclusion and exclusion criteria

All the children met the diagnostic criteria of pediatric CVA[1]. The main eligibility criteria included: (1) Cough: Persistent or periodic cough, lasting at least 4 wk, and frequent attacks; (2) Variability: Cough changes significantly in

Table 1 Comparison of basic data between the two groups, *n* (%) (mean ± SD)

Group	Number of cases	Age (yr)	Man	Woman	Weight (kg)	Course of disease (mo)	Vitamin D consumption D (ng/mL)	Spring (*n*)	Summer (*n*)	Autumn (*n*)	Winter (*n*)
Observation group	65	7.86 ± 1.56	35 (53.85)	30 (46.15)	25.3 ± 3.18	7.6 ± 2.5	27.5 ± 5.87	15	8	14	28
Control group	65	8.36 ± 1.28	36 (55.38)	29 (44.62)	26.7 ± 3.89	6.9 ± 3.2	26.8 ± 6.21	21	10	11	23
χ^2	/	1.893	0.895	0.968	0.987	0.798	1.562	2.784			
P value	/	0.562	0.256	0.527	0.332	0.189	0.636	0.546			

response to different triggers, such as exercise, cold air, viral infection, or allergies; (3) Wheezing sounds: Wheezing sounds can be heard during an asthma attack or when airflow is blocked; (4) Doctors make a comprehensive assessment based on the child's medical history, symptoms and signs; and (5) Voluntarily participate in this study and cooperate with relevant examinations.

The main exclusion criteria were: (1) Complicated with serious heart, liver, kidney and other dysfunction; (2) Persistent cough caused by other causes, such as respiratory infections, chronic bronchitis, *etc.*; (3) Chronic cough induced by mycoplasma infection; (4) Half-treatment withdrawal or late follow-up lost contact; and (5) Allergic to the drug in this study.

Therapeutic method

On the basis of conventional treatment, children in the observation group were treated with Budesonide (Shanghai Xinyi Pharmaceutical Co., LTD., China, SFDA Approval No. H20010552) combined with Salmeterol aerosol (Glaxo Wellcome Production, French, Registration No. H20140382) for atomization inhalation. And the children in the control group were treated with atomized inhalation of Budesonide combined placebo. In the course of atomizing inhalation therapy, In the course of treatment, both drugs are used 1 press at a time, the oxygen flow rate is 6-8 L/min and the treatment is performed twice a day for 2 mo. During the treatment period, all children received anti-asthmatic, anti-infection and other conventional symptomatic treatment.

Observation indicators

Clinical efficacy: According to the Clinical practice guidelines for the diagnosis and management of children with cough in China (version 2021) diagnostic criteria[19], the clinical efficacy of the two groups was evaluated, including the following aspects: (1) The number of daytime symptoms; (2) The number of emergency relievers used; (3) Number of awakenings caused by nighttime asthma symptoms; and (4) Exercise restriction due to asthma. The evaluation criteria are as follows: Obvious effect: Children's cough, wheezing and other symptoms disappeared, and lung function was significantly improved; Effective: The clinical symptoms were relieved and the lung function was improved. Ineffective: The symptoms and signs of the child were basically unchanged. The formula for calculating the total effective rate is: (Obvious cases + effective cases)/total number of cases × 100%.

Cough score: According to the Guidelines for the Diagnosis and Treatment of Cough (2021)[19], the cough symptoms of the two groups of children were evaluated, 0 points: No cough during the day or night; 1 point: Intermittent coughing during the day or waking up coughing once during the night.; 2 points: Cough intermittently or singly during the day or waking up coughing twice during the night; 3 points: Paroxysmal coughing during the day or waking up coughing more than three times during the night. A higher score referred to more serious cough.

Pulmonary function assay: Before and after treatment, forced vital capacity (FVC), forced expiratory volume in one second (FEV1), peak expiratory flow (PEF) and maximal voluntary ventilation (MVV) of the two groups were measured by a pulmonary function tester (Zhejiang Yiliankang Medical Equipment Co., LTD, China, size: PF286), and the ratio of FEV1 to FVC was calculated.

Immunofunction assay: Before and after treatment, 5 mL fasting blood samples were taken from the peripheral veins of all patients. Serum was obtained from the samples after centrifugation, and CD^{3+}, CD^{4+} and CD^{8+} cells were analyzed during the detection by flow cytometry of CytoFocus421 of Beijing Zhizhen Biotechnology Co., LTD.

Immunoglobulin assay: The blood samples were centrifuged by an automatic centrifuge (Microfuge 20/20R) with a centrifuge parameter set at 3000 RPM, a centrifuge radius of 10 cm, and a centrifuge time of 15 min. After centrifugation, the supernatant is taken and stored at -80 ℃. Subsequently, serum expression concentrations of immunoglobulin A (IgA) and immunoglobulin M (IgM) were measured using the Beckman Coulter AU5800 biochemical analyzer. The kit used is from Shanghai Huzhen Industrial Co., LTD.

Serum inflammatory indexes were measured: The venous blood collection method was the same as described above. After the blood samples were collected, the serum interleukin-6 (IL-6), interleukin-4 (IL-4) and tumor necrosis factor-α (TNF-α) concentrations were detected by enzyme-linked immunosorbent assay.

Airway anatomical index: Lung scans were performed using GE Lightspeed spiral computed tomography (CT) and Barc displays, ranging from the autonomic arterial arch to the bottom layer of the lung. The scanned images were saved and analyzed. To ensure the accuracy of the results, two experienced radiologists took independent measurements using

blind methods and averaged them. In the process of measurement, the window width of 1500 Hu and window position of -450 Hu were used to select 5 CT levels at the end of inspiratory breath of children with asthma. The image was enlarged on the display and lumen diameters were measured on segmental, subsegmental bronchus and transsectional images. At the same time, the outer diameter and inner diameter of the airway cavity were measured. Finally, the airway wall thickness and airway wall area are calculated automatically by a calculation program.

Statistical analysis

SPSS 20.0 statistical software was used to analyze the data. The counting data were expressed as [example (%)], and (2 test or Fisher exact probability method. The measurement data conforming to the normal distribution were expressed as (mean ± SD), and the comparison between the two groups was performed by *t*-test, and $P < 0.05$ was considered statistically significant.

RESULTS

Clinical data

Basic data of children in observation group and control group were collected, including age, sex, weight, course of disease, vitamin D consumption and season of onset. The observation group consisted of 35 males and 30 females. The average age of the patients was (7.86 ± 1.56) years, and the average course of disease was (7.6 ± 2.5) mo. In the control group, there were 36 males and 29 females. The average age of the patients was (8.36 ± 1.28) years, and the average course of disease was (6.9 ± 3.2) mo. There was no significant difference in the general data between the two groups ($P > 0.05$) (Table 1).

Comparison of clinical efficacy

The total effective efficacy rate in the observation group (96.92%) was higher than the control group (90.77%), with statistical difference ($P < 0.05$), as shown in Table 2. Indicating that the efficacy of Salmeterol combined with Budesonide in the treatment of children with CVA was higher than that of Budesonide alone.

Comparison of clinical cough score

After treatment, the score of cough frequency and the number of cough wake times in the two groups were decreased, and the difference was statistically significant ($P < 0.05$). At the same time, the reduction rate of salmeterol combined with budesonide was significantly higher than that of budesonide alone, and the difference was statistically significant ($P < 0.05$) (Table 3).

Comparison of pulmonary function

The post-treatment MVV, PEF, FEV1 and FEV1/FVC were higher than those pretreatment in both groups ($P < 0.05$). Moreover, the post-treatment MVV, PEF, FEV1 and FEV1/FVC in the observation group were higher than those in the control group ($P < 0.05$) (Table 4). The results showed that salmeterol combined with budesonide improved lung function better than budesonide alone.

Comparison of inflammatory response

The serum levels of IL-4, IL-6 and TNF-α were compared between the two groups before and after treatment, and there was no statistical difference between the observation group and the control group before treatment ($P > 0.05$). The post-treatment IL-6, IL-4 and TNF-α levels were lower than those pre-treatment in both groups ($P < 0.05$), and post-treatment IL-6, IL-4 and TNF-α levels in the observation group were lower than those in the control group ($P < 0.05$) (Table 5). These results indicated that Salmeterol combined with Budesonide was more effective in improving inflammatory response than Budesonide alone.

Comparison of T lymphocyte count

Before treatment, the levels of CD^{3+}, CD^{4+} and CD^{8+} cells count between the observation group and the control group has no statistical difference ($P > 0.05$). After treatment, the CD^{3+} and CD^{4+} cells count in both groups were higher than before treatment ($P < 0.05$), while the CD^{8+} cells count were lower than before treatment ($P < 0.05$). Also, the post-treatment CD^{3+} and CD^{4+} cells count in observation group was higher, while CD^{8+} cells count was lower in the observation group than those in the control group ($P < 0.05$) (Table 6).

Comparison of immunoglobulin degree

The post-treatment serum IgA and IgM levels were higher than those before treatment in both groups ($P < 0.05$), and the post-treatment levels in the observation group were higher than those in the control group ($P < 0.05$) (Table 7).

Comparison of airway anatomical index

Airway wall thickness and total airway wall area were compared between the two groups before and after treatment, and there was no significant difference between the two group before treatment ($P > 0.05$). After treatment, airway wall thickness and total area decreased in both groups ($P < 0.05$), and the above parameters in the observation group were lower than those in the control group ($P < 0.05$) (Table 8).

Table 2 Comparison of efficacy between the two groups, *n* (%)

Group	Number of cases	Obvious effect	Effective	Ineffective	Total effective efficacy rate
Control group	65	30 (46.15)	29 (44.62)	6 (9.23)	59 (90.77)
Control group	65	38 (58.46)	25 (38.46)	2 (3.08)	63 (96.92)[a]
χ^2					9.562
P value					0.001

[a]*P* < 0.05 *vs* control group.

Table 3 Comparison of clinical cough score between the two groups

Clinical cough score	Pre-treatment		*t*	*P* value	Post-treatment		*t*	*P* value
	Observation group (*n* = 65)	Control group (*n* = 65)			Observation group (*n* = 65)	Control group (*n* = 65)		
Cough score	2.06 ± 1.22	2.26 ± 1.63	1.067	0.287	0.56 ± 0.54[a]	0.97 ± 0.47	3.785	0.001
Nighttime coughs	3.16 ± 2.01	3.28 ± 1.06	1.892	0.092	1.03 ± 0.25[a]	2.89 ± 0.98	7.894	0.012

[a]*P* < 0.05 *vs* before treatment.

Table 4 Comparison of pulmonary function between the two groups

Pulmonary unction index	Pre-treatment		*t*	*P* value	Post-treatment		*t*	*P* value
	Observation group (*n* = 65)	Control group (*n* = 65)			Observation group (*n* = 65)	Control group (*n* = 65)		
MVV (L/min)	4.26 ± 0.22	4.32 ± 0.63	1.956	0.643	7.36 ± 1.54[a]	5.97 ± 1.47	4.278	0.003
FEV1 (L)	1.16 ± 0.21	1.28 ± 0.66	1.537	0.291	3.43 ± 1.25[a]	1.89 ± 0.98	2.089	0.014
FEV1/FVC (%)	64.6 ± 5.34	65.4 ± 4.65	0.958	0.452	79.8 ± 5.56[a]	73.8 ± 5.06	2.563	0.013
PEF (L/s)	2.23 ± 0.56	2.08 ± 0.58	1.071	0.749	3.56 ± 0.78[a]	3.05 ± 0.54	2.417	0.021

[a]*P* < 0.05 *vs* before and after intervention in the same group.
MVV: Maximal voluntary ventilation; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; PEF: Peak expiratory flow.

Table 5 Comparison of inflammatory response between the two groups before and after treatment (mean ± SD)

Inflammatory response index	Pre-treatment		*t*	*P* value	Post-treatment		*t*	*P* value
	Observation group (*n* = 65)	Control group (*n* = 65)			Observation group (*n* = 65)	Control group (*n* = 65)		
IL-6 (ng/L)	25.78 ± 5.18	25.32 ± 4.63	2.132	0.097	20.36 ± 4.54[b]	21.9 ± 5.47	1.891	0.012
IL-4 (ng/L)	24.6 ± 4.34	23.4 ± 3.65	1.267	0.258	20.8 ± 5.56[b]	22.8 ± 5.06	1.673	0.018
TNF-α (μg/L)	1.27 ± 0.32	1.28 ± 0.63	1.879	0.784	0.43 ± 0.25[b]	0.89 ± 0.48	2.693	0.014

[b]*P* < 0.05 *vs* compare before and after intervention in the same group
IL-6: Interleukin-6; IL-4: Interleukin-4; TNF-α: Tumor necrosis factor-α.

DISCUSSION

CVA is a common type of childhood asthma characterized by a chronic cough with symptoms that fluctuate wildly across time and environment[6]. Salmeterol, a long-acting beta-2 adrenergic receptor agonist, is a commonly used asthma medication that reduces airway spasms by dilating bronchial smooth muscles, thereby relieving breathing difficulties and

Table 6 Comparison of T-lymphocytes count between the two groups before and after treatment (mean ± SD)

Group	CD^{3+} (%)				CD^{4+} (%)				CD^{8+} (%)			
	Pre-treatment Post-treatment	Post-treatment Post-treatment	*t*	*P* value	Pre-treatment Post-treatment	Post-treatment Post-treatment	*t*	*P* value	Pre-treatment Post-treatment	Post-treatment Post-treatment	*t*	*P* value
Observation group (*n* = 65)	44.6 ± 6.34	67.4 ± 4.65	-8.25	0.008	29.8 ± 5.56	42.8 ± 5.06	-9.78	0.011	33.2 ± 5.21	25.6 ± 4.89	10.6	0.012
Control group (*n* = 65)	44.7 ± 7.32	58.8 ± 5.63	-2.67	0.004	28.3 ± 5.25	38.9 ± 7.48	-8.96	0.012	32.7 ± 6.18	28.5 ± 5.12	9.78	0.023
t	1.785	2.165			0.895	2.418			0.794	0.947		
P value	0.562	0.024			0.732	0.002			0.001	0.003		

Table 7 Comparison of immunoglobulin levels between the two groups before and after treatment (mean ± SD)

Group	IgA (g/L)		*t*	*P* value	IgM (g/L)		*t*	*P* value
	Pre-treatment Post-treatment	Post-treatment Post-treatment			Pre-treatment Post-treatment	Post-treatment Post-treatment		
Observation group (*n* = 65)	1.26 ± 0.34	1.84 ± 0.65	-7.23	0.012	9.08 ± 1.56	11.8 ± 1.06	-6.98	0.021
Control group (*n* = 65)	1.27 ± 0.32	1.48 ± 0.63	-9.67	0.007	9.03 ± 1.25	10.9 ± 1.48	-9.56	0.032
t	0.765	6.165			0.655	2.418		
P value	0.724	0.014			0.751	0.012		

IgA: Immunoglobulin A; IgM: Immunoglobulin M.

Table 8 Comparison of airway anatomical index between the two groups before and after treatment (mean ± SD)

Group	Airway wall thickness(mm^2)		*t*	*P* value	Total airway wall area(mm^2)		*t*	*P* value
	Pre-treatment Post-treatment	Post-treatment Post-treatment			Pre-treatment Post-treatment	Post-treatment Post-treatment		
Observation group (*n* = 65)	2.16 ± 0.46	0.84 ± 0.65	8.26	0.014	7.08 ± 0.56	3.28 ± 1.26	10.98	0.011
Control group (*n* = 65)	2.27 ± 0.22	1.98 ± 0.43	7.64	0.005	7.03 ± 0.25	4.39 ± 1.68	11.56	0.006
t	1.762	8.135			0.398	4.468		
P value	0.425	0.016			0.216	0.016		

coughing symptoms[20]. The use of salmeterol has been widely discussed in children with CVA. Studies have shown that salmeterol is effective in reducing cough frequency and duration and improving respiratory symptoms in children. On the other hand, the corticosteroid budesonide is widely used as an anti-inflammatory drug in the treatment of asthma [21]. It can inhibit airway inflammation, reduce airway edema and excessive mucus, and thus improve airway patency. The use of budesonide has also been extensively studied in children with cough-variant asthma. Studies have shown that budesonide can significantly improve lung function and reduce inflammatory response in children[22,23]. In addition, budesonide improves immune function by increasing CD^{4+} cell count and immunoglobulin levels[18].

In this study, we observed the efficacy of the β2-receptor agonist salmeterol in combination with the corticosteroid budesonide in the treatment of children with cough-variant asthma. In terms of clinical efficacy, we found that the combination regimen significantly reduced cough frequency and duration, improved the overall response rate of treatment, and improved the life quality of children. In terms of lung function, the children's PEF and FEV1 were significantly improved. In addition, the serum inflammatory indicators IL-6, TNF-α, IL-4 were significantly reduced, and the improvement of immune function included the increase of the number of CD^{4+}, CD^{3+} cells and the levels of immunoglobulin IgA and IgM.

CONCLUSION

In summary, the β2-receptor agonist salmeterol combined with the corticosteroid budesonide is an effective regimen for the treatment of children with cough-variant asthma. The combination therapy can significantly improve clinical symptoms, increase lung function, reduce inflammation levels, and improve immune function.

These findings have important clinical implications for clinicians in the treatment of children with cough-variant asthma, but this study has some limitations, such as a small sample size and a short study period. Therefore, future studies can further expand the sample size and extend the observation time to further validate our findings.

ARTICLE HIGHLIGHTS

Research background

The combination of inhaled corticosteroids (ICS) and long-acting β2 receptor agonist (LABA), such as salmeterol, can provide a more effective treatment strategy, but there is a lack of comprehensive research and evaluation on the efficacy of salmeterol combined with budesonide in the treatment of cough variant asthma (CVA) in children.

Research motivation

To systematically explore the efficacy of LABA salmeterol combined with ICS budesonide in the treatment of CVA in children, and to provide some clinical treatment suggestions for the treatment and clinical recovery of CVA in children.

Research objectives

The purpose of this study is to systematically evaluate the efficacy of LABA salmeterol combined with ICS budesonide in the treatment of CVA in children, and to explore the influence of the combination of the two drugs on the clinical efficacy and recovery index of asthma control in children.

Research methods

Children with CVA were selected prospectively and randomly divided into observation group (salmeterol combined with budesonide) and control group (budesonide combined with placebo). The clinical efficacy and immune function markers of the two groups were compared.

Research results

After treatment, the effect and efficiency of the two groups were improved to some extent. The symptoms of CVA in the treatment group were relieved, and the lung function index and immune marker level were also better than those in the control group.

Research conclusions

Both salmeterol combined with budesonide and budesonide alone can treat CVA to a certain extent, but the therapeutic effect of the former is significantly higher than that of the latter in symptom improvement, immune marker level and lung function level.

Research perspectives

Salmeterol combined with budesonide is an effective method to treat CVA disease, which is worth popularizing in clinic.

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FOOTNOTES

Co-first authors: Jun-Yi Cao and Ying-Chun Wang.

Author contributions: Cao JY, and Wang YC designed the research; Deng XX performed the research; Deng XX contributed new reagents/analytic tools; Cao JY, Wang YC, and Deng XX analyzed the data; Cao JY, and Wang YC wrote the paper. Cao JY and Ying-Chun Wang contributed equally to this work as co-first authors equally to this work. The reasons for designating Cao JY and Wang YC as co-first authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-first authors authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-first authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Cao JY and Wang YC contributed efforts of equal substance throughout the research process. The choice of these researchers as

co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Cao JY and Wang YC as co-first authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

Institutional review board statement: The study was reviewed and approved by the first People's Hospital of Jiangxia District.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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