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Renal artery branch stenosis induced hypertension in children: a case series



Hongwei Zhang¹, Yao Lin¹, Yang Liu¹, Mingming Zhang¹, Yanjun Deng¹, Gang Shen² and Lin Shi^{1*}

Abstract

Purpose Renal artery branch stenosis induced hypertension (HTN) in children is rare and facing a great challenge in diagnosis and treatment. This study aimed to summarize the clinical features and experience in diagnosis and treatment of these children.

Methods Four children diagnosed with renal artery branch stenosis induced HTN in the Cardiovascular Department of Children's Hospital, Capital Institute of Pediatrics were retrospectively summarized with the clinical data, the process of diagnosis and treatment, and the prognosis.

Results All patients were male with the age of 8~9 years. All were diagnosed with stage 2 HTN and most had significant symptoms. Routine examinations showed no abnormalities. A slight perfusion defect in the kidney was observed on abdominal contrast-enhanced computed tomography (CECT) in all cases. Renal artery branch stenosis was clearly detected by selective renal artery angiography. One had stenosis in the interlobular artery of the kidney, and the remaining had secondary branches stenosis. In terms of treatment, two children underwent selective renal artery embolization (SRAE), one underwent dilation by microcatheter, and the other one did not undergo interventional therapy due to arterial segmental narrowing. More than one year after SRAE, the number of antihypertensive medications was cut down with the blood pressure (BP) level reduced to normal.

Conclusion Renal artery branch stenosis should be considered in younger children with early onset of HTN and significantly elevated BP. Selective renal artery angiography is the gold standard for diagnosis. However, the treatment is challenging, and SRAE may be a better choice in some cases.

Keywords Hypertension, Renal artery branch stenosis, Renovascular hypertension, Children

Lin Shi shilin9789@126.com ¹Department of Cardiology, Children's hospital, Capital Institute of Pediatrics, Beijing 100020, China ²Department of Intervention and Hemangioma, Children's hospital, Capital Institute of Pediatrics, Beijing 100020, China HTN is considered a leading risk factor for cardiovascular disease and premature death worldwide [1]. Studies have shown that elevated BP in childhood increases the risk for adult HTN and metabolic syndrome [2–3]. Since the publication of "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" in 2004, pediatric HTN has attracted increasing attention. Epidemic investigations have indicated that there has been an increase in the prevalence of childhood high BP, including both HTN and elevated BP with the actual prevalence of $\sim 3.5\%$ [4]. The etiology of HTN is classified as primary HTN and secondary



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HTN. Primary HTN is now the predominant diagnosis for hypertensive children and adolescents [4]. The secondary causes of HTN in children including renal disease and renovascular disease, cardiac or endocrine causes, and medication related HTN, etc.

Renovascular hypertension (RVH) is caused by renal artery stenosis (RAS), including stenosis of the main renal artery and its branches, which leads to a reduction in renal blood flow, activation of the renin-angiotensin-aldosterone system (RAAS), and subsequently an increase in BP. RVH is a common cause of secondary hypertension in children, accounting for 5-25% of cases [5]. Children with RVH usually have relatively high BP and clinical symptoms, and BP is difficult to control by a single anti-hypertensive drug. For these patients, renal vascular ultrasound or computed tomography can establish a definitive diagnosis, but it is only capable of detecting primary branch stenosis, while identifying narrowing in secondary branches and beyond may be challenging. Therefore, diagnosis of RVH induced by artery branch stenosis is difficult. Furthermore, reported cases were limited in children, and there is no consensus on the treatment regimen for this kind of HTN. Recently renal artery intervention therapy was widely applied and could provide immediate improvement of kidney function and BP for those with renal artery abnormality. However, balloon dilation and stent implantation were not suitable for children with renal branch artery stenosis, especially those with interlobular artery stenosis, therefore, the treatment for those patients is facing great challenge.

This article analyzes the clinical characteristics, diagnosis, and treatment strategies of four children with HTN induced by renal artery branch stenosis, with the aim of providing clinical guidance for diagnosis and patent therapeutic regimen.

Materials and methods

This is a retrospective observational study. Four children with HTN caused by renal artery branch stenosis were recruited and analyzed retrospectively from June 2021 to March 2023. Hypertension is diagnosed when SBP and/or DBP \geq 95th percentile for sex, age, and height on all three occasions. Childhood hypertension can be categorized into two stages: stage 1 hypertension is defined as SBP and/or DBP ranging from 95th to 99th + 5 mmHg; stage 2 hypertension is defined as SBP and/or DBP and/or BP and/or DBP and/or DBP and/or DBP and/or DBP and/or DBP and/

The clinical data of these children were collected, including general information, BP, renal function, serum electrolytes, urine-related examinations, echocardiography, vascular ultrasound, abdominal CECT, selective renal artery angiography, and other examinations related to the secondary causes of HTN.

Results

All four children were male, with the age of $8 \sim 9$ years at the time of diagnosis, and the duration from onset to diagnosis of $17 \sim 300$ days. Three children had obvious clinical symptoms. No Café-au-lait-Spots(CAML) could be seen on them. Only one of the four children was slim. Shown in Table 1. The rest of the physical examination did not reveal any significant abnormalities. Liver and kidney function, serum electrolytes, thyroid function, cortisol rhythm, circulating catecholamines and their metabolites, and vascular ultrasound were all normal in the four cases. No retinal changes were observed by oph-thalmic examination. There were no other signs of vascular involvement.

Case 1 is an 8-year-old obese boy presented with stage 2 HTN, evidenced by a maximal BP of 170/80 mmHg, but without clinical symptoms. HTN was discovered by incidence (school medical examination). The prolonged duration from onset to diagnosis (300 days) likely contributed to the development of target organ damage, including microalbuminuria, increased left ventricular mass index(LVMI), and left atrial dilatation. Renin level of 195 uIU/ml was significantly elevated. Liver and kidney function, serum electrolytes, thyroid function, cortisol rhythm, circulating catecholamines and their metabolites, and vascular ultrasound were all normal. No retinal changes were observed by ophthalmic examination. Renal ultrasound revealed the volume of the right kidney is slightly smaller. Abdominal CECT showed a slightly poor enhancement in the affected part of the right kidney. Renal artery angiography was performed, which revealed a single interlobar artery stenosis of the superior right kidney (Figs. 1a). However, it was too thin for balloon dilation. Two sessions of SRAE, including coil and microsphere embolization, with an interval of eight months were carried out after fully assessment of renal function and Multidisciplinary Team Consultation, including members from Department of Nephrology, Intervention and Hemangioma, General Surgery and Cardiology (Figs. 2). After the first procedure, his BP dropped briefly, but then gradually increased, and selective renal artery angiography showed residual blood flow in the embolization artery, so the second procedure was performed eight months later. Preoperative medications included Captopril, Metoprolol succinate, and Reserpine. During the following 18 months, the medication regimen was adjusted to Captopril and Metoprolol succinate, and the patient's BP was decreased to normal, below 120/70mmHg.

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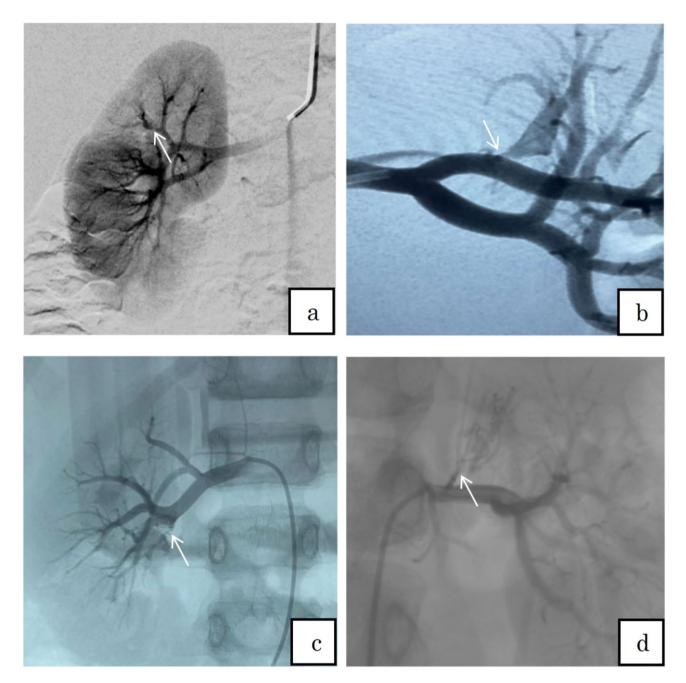
Case number	1	2	3	4
Gender	male	male	male	male
Age(year)	8.83	9.16	8.25	8.58
Days from onset to diagnosis(day)	300	17	17	240
Maximal blood pressure(mmHg)	170/80	180/140	150/116	220/150
Clinical symptoms	None	Dizziness Abdominal pain Vomiting	Dizziness Headache Vomiting	Headache Vomiting Loss of consciousness
BMI (kg/m²)	22.3	23.9	14.0	20.3
Renin (3.1-41.2ulU/ml)	195.0	126.9	595.2	None
Target organ damage	Microalbuminuria LVH left atrial dilatation	None	LVH	Cerebral hemorrhage
Renal ultrasound	Left: 9.3*4.5*3.7 cm right: 8.4*3.6*3.7 cm	Left: 8.7*4.6*4.7 cm right: 8.9*4.3*4.6 cm	Left: 8.6*4.0*3.1 cm right: 7.9*4.0*3.4 cm	None
Invasive procedure	Selective renal artery angiography selective renal artery embolization	Selective renal artery angiography microcatheter dilation	Selective renal artery angiography	Selective renal artery angiography selective renal artery embolization
Preoperative medicate	Captopril 25 mg Tid, Metoprolol succinate 47.5 mg Qd, Reserpine 0.25 mg Tid	Amlodipine 7.5 mg Qd, Captopril 25 mg Q8h, Prazosin 0.75 mg Q12h	Nifedipine 7.5 mg Tid, Captopril 12.5 mg Tid	Amlodipine 10 mg Qd, Captopril 25 mg Tid
Postoperative medication Captopril 50 mg Tid, Metoprolol succinate 47.5 mg Qd		Amlodipine 5 mg Qd, Captopril 25 mg Q8h	Amlodipine 5 mg Qd, Captopril 12.5 mg Tid	Amlodipine 10 mg Qd
Postoperative blood pressure	Normal	Stage 1	Stage 2	Normal

BMI: body mass index; LVH: left ventricular hypertrophy

Case 2 is a 9-year-old boy presented with severe HTN (maximal BP of 180/140 mmHg) and obvious clinical symptoms, including dizziness, abdominal pain, and vomiting. Elevated renin level was found with the value of 126.9 uIU/ml. Other routine examinations showed no abnormalities. No target organ damage was observed. Renal ultrasound indicated normal kidney sizes. Abdominal CECT showed a wedge-shaped poor enhancement in the superior left kidney (Figs. 3). Left superior branch stenosis was confirmed in selective renal artery angiography (Figs. 1b). Due to the stenotic vessel was extremely narrow and delicate, only the 2.2 F microcatheter could be sent into the stenosis site to achieve slight dilation. Subsequently, after the 2.7 F microcatheter dilation and repeated angiographies, it was observed that the stenotic segment of the left upper renal artery had widened compared to previous assessments (Figs. 4). No complications such as fever, hemolysis, or infection were observed after the procedure. The patient received dual antiplatelet therapy with Aspirin for 3 months and Clopidogrel for 1 month after the procedure. Preoperative medications included Amlodipine, Captopril, and Prazosin. Postoperatively, the medication regimen was adjusted with Amlodipine and Losartan, resulting from a reduction of BP to Stage 1 levels (below 130/80 mmHg) with no discomfort during the following 22 months.

Case 3 is an 8-year-old slim boy presented with severe hypertension (maximal BP of 150/116 mmHg) and significant symptoms of dizziness, headache, and vomiting. The renin level was significantly elevated at 595.2 uIU/ml. Increased LVMI was detected. Renal ultrasound revealed that the right kidney was slightly smaller than the left one. Abdominal CECT showed a slightly poor enhancement in the right kidney. Other routine examinations showed no abnormalities. The patient was highly suspected as renal artery branch stenosis and then underwent selective renal artery angiography. Right inferior branch stenosis was confirmed in the procedure (Figs. 1c). This patient had extremely narrow and tortuous branch vessels and did not undergo further interventional treatment. Preoperative medications included Nifedipine and Captopril, although the drugs were changed to Amlodipine and Captopril and the drug dosages were increased after the procedure, the BP of this boy remained at Stage 2 level, fluctuating between 130-140/80-90 mmHg, during the 21-month follow-up.

Case 4 is an 8-year-old boy presented with extremely high BP (220/150 mmHg) and severe symptoms, including headache, vomiting, and loss of consciousness. The delayed diagnosis (240 days from onset) contributed to the development of a cerebral hemorrhage. Other routine

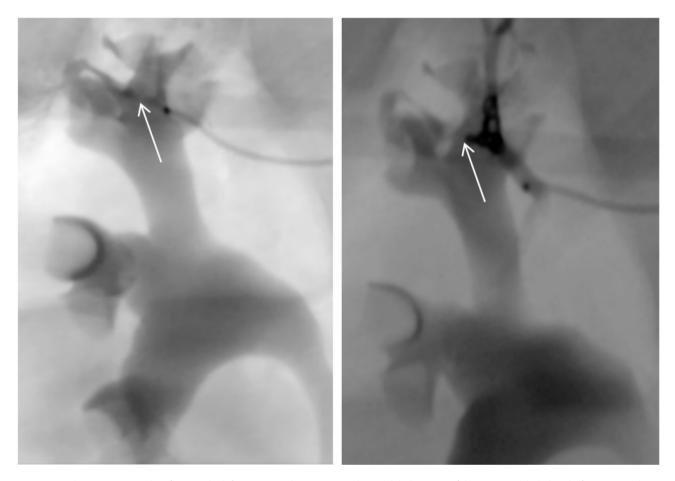


Figs. 1 Selective Renal Artery Angiography: a reveals a stenosis in the interlobular artery of the superior right kidney in case 1; b and d show left superior branch stenosis in case 2 and 4; c reveals right inferior branch stenosis in case 3 (as indicated by the arrow)

examinations showed no abnormalities similarly. Abdominal CECT showed a wedge-shaped poor enhancement in the superior left kidney. Left superior branch stenosis was confirmed in selective renal artery angiography (Figs. 1d). Microsphere embolization was performed with no complications which successfully reduced the BP to Stage 1 levels. After the embolization, the medication regimen was adjusted with monotherapy of Amlodipine. During the 17-month follow-up, his BP was gradually reduced to normal, below 120/80mmHg.

Discussion

RVH is one of the common causes of HTN in children, which is often misdiagnosed but can be controlled or even cured [5]. However, there is no large-scale epidemiological research or statistical data on pediatric HTN induced by renal artery branch stenosis currently, and most are case reports, which may usually be misdiagnosed. Compared with primary HTN in children, the four cases of HTN induced by renal artery branch stenosis in this study had an earlier onset age. Although

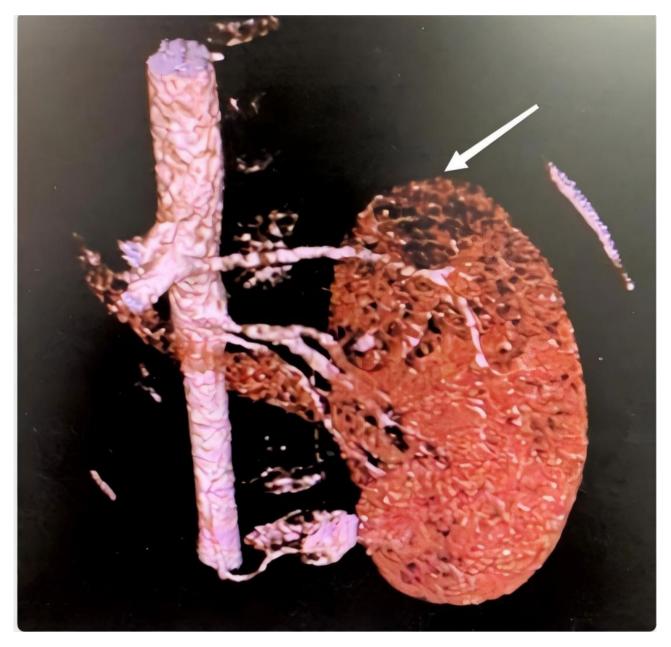


Figs. 2 Renal artery angiography of case 1. The left image reveals a stenosis in the interlobular artery of the superior right kidney before SRAE (coil embolization), and the right image shows no vascular visualization after SRAE (as indicated by the arrow)

the onset was relatively insidious, the patients' BP level had reached the stage 2 with specific symptoms at diagnosis. Clinical symptoms such as dizziness, headache, and vomiting were more prominent. No obvious positive signs were found in physical examination. The target organ damages of HTN mainly involved the heart or kidney. Although some renal ultrasounds showed a slight decrease in the diameter of the affected kidney compared to the healthy one, it couldn't confirm the stenosis of renal artery branch. Only a slight decrease in the enhancement density of the affected part of the kidney was observed in abdominal CECT. However, the stenosis of renal artery branch was further confirmed by the selective renal artery angiography. Two cases of renal artery branch stenosis which had the same clinical characteristics were documented by Zarah Andersson et al. [7]. This suggested the stenosis of renal artery branch should be considered in those young children with stage 2 HTN but without other positive findings, and the abdominal CECT may be an initial choice for screening. It is reported that high-quality CECT plays an important role in the screening for RVH in children [8]. In a study by Orman et al. Published in 2021, CECT had sensitivity of 90.0% and specificity of 89.7% for the diagnosis of RAS, but two third-order lesions were not detected with CECT [9]. Once branch stenosis was suspected, the selective renal artery angiography should be considered which is the gold standard for diagnosis [5].

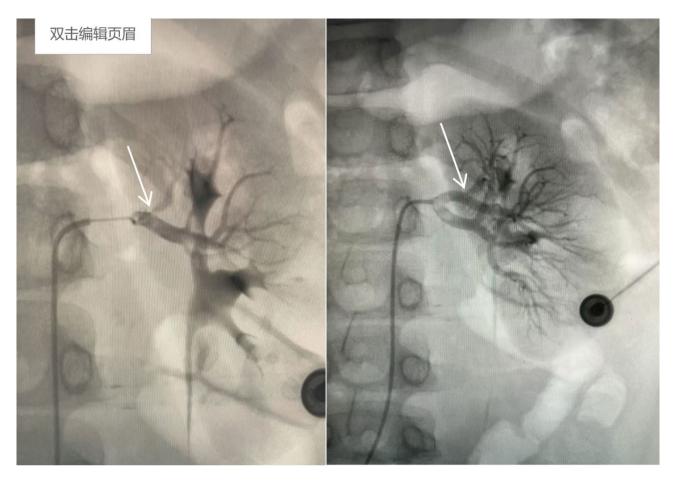
The most common cause of RAS is atherosclerotic lesions, accounting for about 90%, followed by fibromuscular dysplasia (FMD), which accounts for 10%, and less than 1% is vasculitis [10]. However, for pediatric patients, FMD, Williams syndrome, type 1 neurofibromatosis, and vasculitis are more common [5]. FMD is the commonest, with lesions usually located in the middle of the blood vessels, and the most common form is fibrous proliferation on the inner side of the blood vessels, forming a characteristic "beaded" appearance [11]. Unfortunately, no clear cause was found in any of these four cases. Genetic examination was also not performed due to parental concerns.

Over the last few decades, the progress in radiology and cardiology, antihypertensive drugs, and vascular intervention techniques and instruments have deeply influenced the treatment of RAS [12]. The treatment of RVH mainly includes drug therapy, renal artery intervention,



Figs. 3 Abdominal CECT in case 2: a wedge-shaped poor enhancement in the superior left kidney (as indicated by the arrow)

and surgical treatment [13, 14]. In this study, all patients were treated with 2 or 3 antihypertensive drugs, mainly including calcium channel blockers, angiotensin-converting enzyme inhibitors, and α -blockers, etc., but the antihypertensive effects were not satisfactory. Renal artery intervention therapy includes percutaneous balloon angioplasty and percutaneous intravascular stent implantation, which has become the preferred treatment for pediatric RAS, with small trauma, safety and effectiveness, and good clinical benefits, which not only controls BP well but also protects the renal function of the affected side. However, these are all results of interventional treatment for renal artery main trunk stenosis. For children with renal artery branch stenosis, they are not suitable apparently. Clinically, renal artery branch stenosis is often in the secondary or more distal branches in children and can not be performed balloon dilatation or stent implantation. Therefore, it's a great challenge in treatment for these patients. SRAE began to be used in this condition. It refers to the occlusion of the renal artery, or some of its branches, by injection of an embolic agent through an endovascular catheter [15]. Since 1970s, SRAE has become a useful minimally invasive therapeutic option for various clinical situations, including renal trauma, complications following renal surgery or biopsy, kidney tumors, renal artery aneurysm, arteriovenous



Figs. 4 Renal artery angiography of case 2: the left image shows selective renal angiography before the microcatheter dilation, while the right image illustrates the left upper renal artery had widened after dilation (as indicated by the arrow)

malformations, and medical kidney disease. It may be used as an adjunct or as an alternative to surgery, and has the potential to improve patient management and reduce hospital stay. SRAE may become another interventional treatment option for renal artery branch stenosis. Zhao Xin et al. reported that interventional treatment is a safe and effective treatment for pediatric RVH [16]. In the 1970s, there was a case report of a 15-year-old patient with intractable HTN who underwent selective renal angiography for the second time, only to find the stenosis of the interlobular artery of the superior left kidney. Two selective renal artery embolization surgeries were performed, and the patient had fever, elevated white blood cells, and transient intestinal obstruction after the operation. He soon recovered, and his BP was well-controlled without antihypertensive medication one year after the embolization [17]. In the 1980s, LiPuma JP et al. reported a case of an 11-year-old HTN boy who underwent selective renal angiography, which showed occlusion of the right renal artery and its branches, and treated with selective renal artery embolization. The patient developed severe right renal area pain and moderate hematuria after the operation, but both fully recovered, and his BP returned to normal after a one-year follow-up without antihypertensive medication [18]. In addition, William WC et al. reported a case of a 3.5 years old girl with intractable HTN who underwent her second time vascular imaging at age 5, which revealed stenosis of the right anterior branch, and accepted embolization. The patient had mild adverse reactions after the operation, but her BP was well-controlled [19]. In the early 21st century, there were also case reports of children undergoing renal artery branch stenosis embolization, and only taking one antihypertensive drug to control BP to normal levels [20-21]. The two embolization cases in this study and the above case reports suggested that SRAE can got a relative better blood pressure control with single or dual antihypertensive drugs therapy, and may be a safe and effective therapy without severe complications. As a result, SRAE may become another interventional treatment option, although it is rarely used clinically in children at present, and long-term follow-up of changes in the patient's condition is still needed to observe the efficacy of the intervention plan. Therefore, RAE may be a better option, and the success of the two embolization cases also provides a certain reference significance for the future treatment

of such patients. Of course, in addition to interventional treatment, surgical intervention can also be performed, such as arterial reconstruction surgery, nephrectomy or renal autotransplantations [22–26]. Obviously, the choice of treatment for pediatric renal artery branch stenosis needs to be based on the individual characteristics of the patient, risk and benefit estimates, weighing the pros and cons, and respecting the wishes of the patient and guardian, ultimately deciding on an individualized treatment plan.

In a summary, RAS can lead to various systemic complications, including RVH, chronic kidney disease, cardiovascular events, and metabolic disorders [27]. Early diagnosis and timely intervention are crucial for slowing disease progression. Renal artery branch stenosis induced hypertension in children is rare and difficult to diagnose by routine examinations, which may usually be misdiagnosed. The abdominal CECT and vascular reconstruction may provide valuable clues, and selective renal angiography is the golden standard for diagnosis. Currently, there is no unified standard for the treatment of pediatric renal artery branch stenosis. Combined with the vascular characteristics of children, SRAE may be a better choice for some cases. Further clinical practice is needed to clarify its effectiveness.

Abbreviations

BMI	Body mass index				
BP	Blood pressure				
CAML	Café-au-lait-Spots				
CECT	Contrast-enhanced computed tomography				
FMD	Fibromuscular dysplasia				
HTN	Hypertension				
LVH	Left ventricular hypertrophy				
LVMI	Left ventricular mass index				
RAAS	Renin-angiotensin-aldosterone system				
RAS	Renal artery stenosis				
RVH	Renovascular hypertension				
SRAE	Selective renal artery embolization				

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Author contributions

HWZ: data collection and analysis, statistical analysis, and drafting of the article. YL: data interpretation and analysis, statistical analysis, guidance of the article drafting, and critical review and revision. YL, MMZ, GS: drafting of the article, and supporting contribution. YJD: data analysis and supporting contribution. LS: guidance of the article drafting, and critical review and revision. All authors contributed to the article and approved the submitted version.

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Data availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Children's Hospital, Capital Institute of Pediatrics, and all methods were conducted in accordance with the ethical standards expressed in the Declaration of Helsinki (1964, revised in 2000).

Consent for publication

Informed written consents to publish the cases have been obtained from the patients' parents.

Competing interests

The authors declare no competing interests.

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