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Original Article

Diagnostic efficacy of SPECT/CT MPI and CMR in children with myocarditis caused by different infection sources

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Abstract: This study aimed to analyze the diagnostic efficacy of ^{99m}Tc-methoxy isobutyl isonitrile (MIBI) single photon emission tomography (SPECT/CT) myocardial perfusion imaging (MPI) and cardiac magnetic resonance imaging (CMR) in children with myocarditis caused by different infection sources and provide an imaging reference basis for clinical diagnosis and treatment. In total, 232 children diagnosed with myocarditis were retrospectively divided into five groups according to the different infection sources: viral infection (group A), bacterial infection (group B), viral combined with bacterial infection (group C), viral combined with mycoplasma infection (group D), and bacterial combined with mycoplasma infection (group E). A chi-square test and ANOVA were used to analyze the difference between SPECT/CT MPI and CMR in the diagnosis of myocarditis in children according to their categorical infection source group, including the impact of the average daily hospital costs (a=0.05). The positive rates of SPECT/CT in groups A and D were higher than those of CMR, and the positive rates of SPECT/CT in groups C and E were lower than those of CMR, with statistically significant differences ($P < 0.05$). The SPECT/CT ischemic lesions were located in the anterior wall, or the anterior wall combined with other walls of the left ventricle in 69.5% of patients. SPECT/CT MPI had no effect on the average daily hospitalization cost ($P > 0.05$); however, the average daily hospitalization cost of CMR-negative patients in group D was higher than that of CMR-positive patients, and it was statistically significant in groups C and E ($P < 0.05$). In groups A and D, the use of ^{99m}Tc-MIBI SPECT/CT MPI was preferred for diagnosing myocarditis. The detection rate of CMR was higher in groups C and E. SPECT/CT MPI findings of ischemic segments were mostly found in the anterior wall. The results of CMR diagnosis affected the average daily hospitalization cost among patients with different infection sources; however, SPECT/CT had no such effect. These findings denote a potential targeted approach to myocarditis diagnosis in pediatric patients based on source of infection.

Keywords: SPECT/CT, pediatric myocarditis, bacterial infection, viral infection, mycomplasma infection, CMR

Introduction

Myocarditis is associated with pathological changes, such as myocardial cell degeneration, necrosis, and fibrous tissue proliferation, and can involve the pericardium [1]. These changes may result from infection or non-infection-related factors caused by pathogens (viruses, bacteria, mycoplasma, spirochetes, and protozoa), allergies, or autoimmune diseases. Patients with myocarditis may experience chest pain, fever, discomfort, palpitation, or shortness of breath, and those in the acute phase may develop chronic heart failure, dilated cardiomyopathy, and myocardial infarction; death may occur in some cases [2]. The clinical manifestations of myocarditis are not specific in children, and it is difficult for children to accurately describe their symptoms and feelings; therefore, the diagnosis of myocarditis in children remains challenging. Additionally, while endomyocardial biopsy (EMB) is the "gold standard" for the diagnosis of myocarditis, it is invasive and damaging to the body. Thus, it is usually not acceptable to the patients' families.

At present, the clinical diagnosis of myocarditis in children mainly depends on the clinical symp-

toms and comprehensive judgment of electrocardiogram (ECG), ultrasonic ECG and laboratory tests, among other aspects. The physical properties of ^{99m}Tc-methoxy isobutyl isonitrile (MIBI) make it an appropriate tracer for detecting myocardial injury in patients with myocarditis earlier; thus, it is considered the most useful drug in nuclear cardiology. ^{99m}Tc-MIBI single photon emission tomography (SPECT/CT) myocardial perfusion imaging (MPI) shows focal or regional hypoperfusion in the inflamed or necrotic myocardium [3, 4]. Cardiac magnetic resonance imaging (CMR) has the advantages of high resolution and non-invasiveness, and the capacity to perform multiple examinations, and is therefore frequently used to diagnose heart diseases in children [5]. However, the efficacy of these two imaging methods in the diagnosis of pediatric myocarditis caused by different infection sources remains unclear, with no clear theoretical basis proven at present.

In this study, the results of SPECT/CT MPI were compared with those of CMR, and the distribution characteristics of the ischemic lesions in each ventricular wall in patients with positive SPECT/CT MPI were analyzed. In addition, the diagnostic efficacy of ^{99m}Tc-MIBI SPECT/CT MPI and CMR imaging in diagnosing myocarditis in children caused by different infectious sources and the influence of the average daily hospitalization expenses were explored to provide a theoretical basis for clinical selection of the best examination method.

Materials and methods

Data

Two hundred and thirty seven children diagnosed with infectious myocarditis at the Department of Pediatrics of our hospital who underwent ^{99m}Tc-MIBI SPECT/CT MPI and CMR imaging concurrently between January 2018 and December 2022 were retrospectively selected. According to the hematological examination results, they were divided into five groups: viral infection (group A), bacterial infection (group B), viral combined with bacterial infection (group C), viral combined with mycoplasma infection (group D), and bacterial combined with mycoplasma infection (group E). The results of SPECT/CT MPI and CMR imaging in each group were analyzed, and the results were classified as negative and positive according to whether the results were related to myocarditis. The ischemic segments in patients with positive SPECT/CT MPI and the average daily hospitalization costs of each child were recorded.

Inclusion criteria

The criteria for inclusion were as follows: Children aged 0-16 years who have been diagnosed with myocarditis and whose source of infection (viral, bacterial, or mycoplasma) has been identified by laboratory testing. SPECT/CT MPI and CMR imaging were performed during the same period of hospitalization.

Myocarditis in children can be clinically diagnosed if it meets three primary main clinical diagnostic criteria, or 2 primary main clinical diagnostic criteria and 3 secondary clinical diagnostic criteria, except for other diseases [5]. Main clinical diagnostic basis included: 1) cardiac insufficiency, cardiogenic shock or cardio-brain syndrome; 2) enlarged heart; 3) creatinekinase (MB, CK-MB) or cardiac troponin T or I (cTnI or cTnT) increased with dynamic changes; 4) significant ECG changes (ECG or 24 h holter electrocardiogram); and 5) CMR presents typical manifestations of myocardial inflammation. Secondary clinical diagnosis basis included: 1) history of preemptive infection, such as upper respiratory tract 1-3 weeks before onset or a history of gastrointestinal virus infection; 2) chest tightness, chest pain, palpitation, fatigue, dizziness, pale face having gray color, abdominal pain and other symptoms (at least 2), small infants with breast rejection, cyanosis, cold limbs, etc; 3) increased lactate dehydrogenase (LDH), a-hydroxybutyric dehydrogenase (A-HBDH), or aspartate transferase (AST); and 4) the ECG is mildly abnormal and 5) positive anti-myocardial antibody.

Exclusion criteria

The exclusion criteria were as follows: 1) patients older than 16 years of age; 2) an interval exceeding 7 days between SPECT/CT MPI and CMR examinations; 3) children with other serious diseases (the main diagnosis was not infectious myocarditis); and 4) patients in whom SPECT/CT MPI and CMR enhanced imaging could not be performed according to the specifications (unless there are clear contrain-

dications). Five cases were excluded from the study.

Imaging method SPECT/CT myocardial perfusion imaging

^{99m}Tc04-was provided by Beijing Atomic Hi-Tech Co., Ltd., and the MIBI medicine kit was provided by the Jiangsu Provincial Institute of Atomic Energy Medicine.

Resting/loaded drug preparation: A fixed amount of $^{99m}TcO_4$-eluent was added to the MIBI bottle, mixed, boiled in water for 15 min, and cooled to room temperature. The radiochemical purity was detected as greater than 95% before intravenous injection. Each child was administered an injection of 5-10 mCi (minimum dose of 1 mCi) per body weight. Fat-rich meal or high-fat milk was given half an hour after the injection, and imaging was performed 1.5 hours later.

Resting/load image acquisition: The Siemens Symbian T16 SPECT/CT instrument (all quality control parameters passed the test by a third party) was used. NM/CT tomographic fusion acquisition was selected, with a matrix of 128*128 and zoom of 1.32. Thirty-two frames were acquired, and each frame was acquired for 10-15 s.

Resting/load reconstruction method: Iterative reconstruction (subset, 24; four iterations) was performed with horizontal long axis, vertical long axis, and short axis.

Load method: The vasodilator drug ATP was used. The total dose of the drug was calculated as 0.80 mg/kg/5 min. ^{99m}Tc-MIBI was injected at 3 min.

Image evaluation: Two experienced nuclear medicine physicians independently analyzed the images. They were not aware of the infection source during image analysis. If the results of the image analysis were inconsistent, the disagreements were resolved through consultation. For statistical convenience, the nine segments were combined into five segments, namely, the anterior wall, apex, inferior wall, septal wall, and lateral wall. In the presence of decreased or absent perfusion, decreased ejection fraction, abnormal wall motion, and abnormal chamber size in the resting or load image part of the segments, the result was considered positive (**Figure 1**).

Cardiac MRI imaging

CMR studies were performed with a Siemens Aera 1.5-T scanner with a 16-element coil (Siemens, Erlangen, Germany). The imaging protocol for all patients included cine steady-state free precession (SSFP) sequences acquired on the short axis (SAX) from the base to the apex and long axis cardiac planes: FOV, 400×310 mm^2; slice thickness, 7 mm; echo/repetition time (TE/TR), 1.1/40 ms; Late gadolinium enhancement (LGE) imaging was performed using a phase-sensitive inversion recovery (PSIR) T1-weighted gradient echo pulse sequence acquired along the same planes as previously described, 10 min after the intravenous administration of the contrast agent (gadoterate meglumine-DOTAREM, Roissy, Guerbet, France) at 0.2 mmol/kg [FOV, 400×290 mm^2; repetition time, 747 ms; echo time, 3 ms; fip angle, 25°; and inversion time (TI), 280-400 ms]. CMR at baseline was performed for the analysis of the cardiac ejection fraction and to identify acute edema, inflammatory damage, and/or myocardial necrosis and rule out cardiac fibrosis at the follow-up. CMR was considered positive for focal myocarditis if at least one value was modified (**Figure 2**).

Statistical analysis

The chi-square test among multiple independent samples was used to analyze the diagnostic efficacy of the two imaging methods among the patients in the five groups. The paired data (four-grid) of the McNemar test was used to analyze the diagnostic efficacy of the two imaging modalities for patients in each group. The differences in the average daily hospitalization costs of the patients among the groups, between the two imaging methods, and between the negative and positive groups were analyzed using analysis of variance and two-sample *t*-test. Statistical analysis was performed using SPSS 26 software (IBM, Armonk, NY, USA), with a=0.05.

Results

Demographic analysis

The chi-square test showed no significant difference in sex among the infection groups ($P > 0.05$). The average age was 8.55±3.682 years, the minimum age was 6 months, and the maximum age was 15 years old, with no difference among the groups ($P > 0.05$) (**Table 1**).

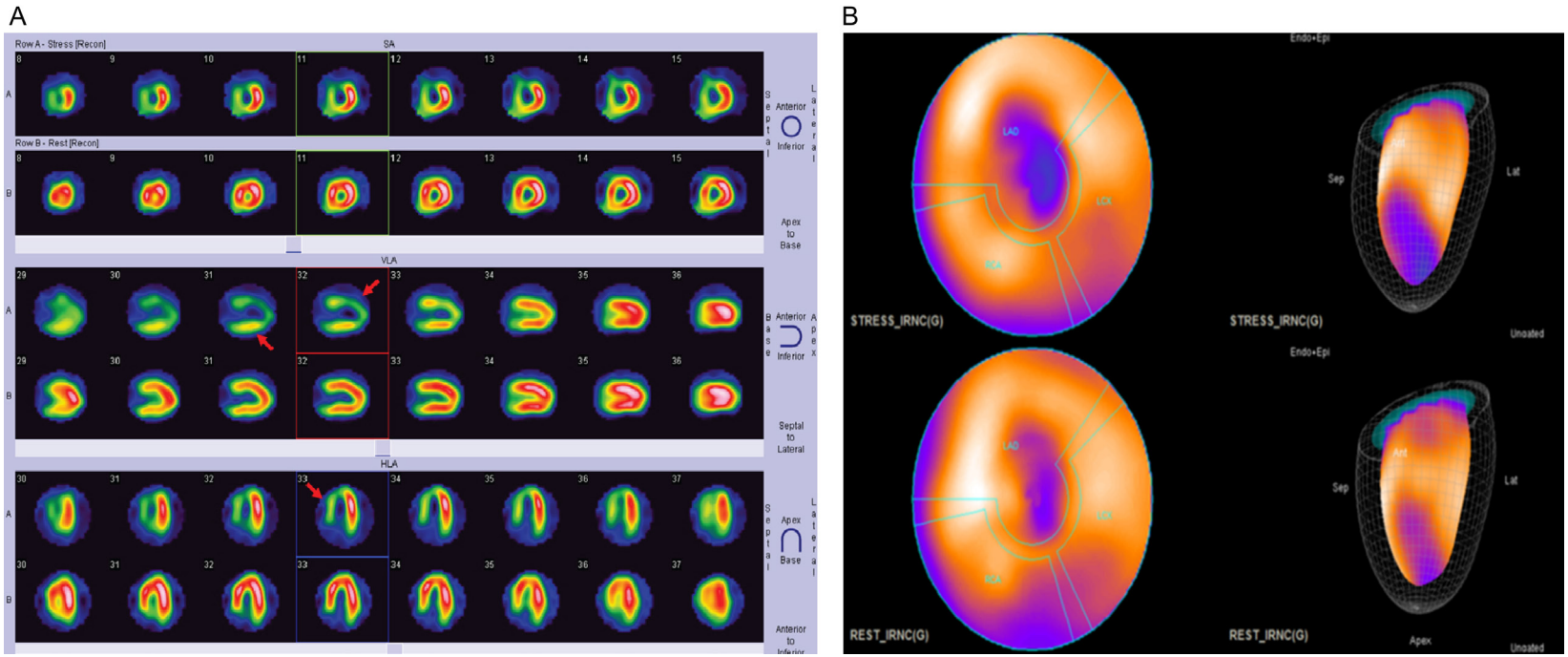

Figure 1. A. SPECT MPI in a 5-year-old child showed reversible ischemia in the anterior, inferior wall, and interwall of the left ventricle. B. A bull's-eye map of myocardial perfusion load imaging in a 6-year-old child showed significantly reduced apical radioactivity distribution.

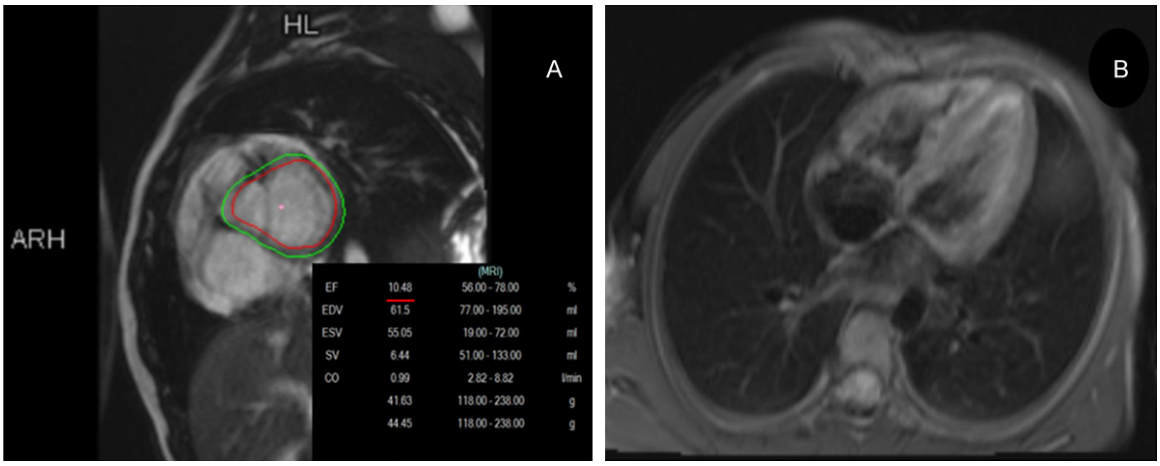

Figure 2. A. This 6-year-old child had a CMR left ventricular ejection fraction of 10%. B. Tirm sequences in 8-year-old children showed increased myocardial signals in anterior, interwall and lateralwall, which were considered myocardial edema.

Table 1. Patient characteristics

Groups	Male/female ratio	Age (years)
Group 1	34/39	8.14±3.72
Group 2	18/13	8.84±4.32
Group 3	20/11	7.97±3.86
Group 4	30/34	9.14±3.48
Group 5	18/15	8.61±3.12
Total	120/112	8.55±3.68
	x^2=4.013	F=0.883
P	P=0.404	P=0.475

Comparison of the positive rate of SPECT/CT MPI and CMR

McNemar's chi-square test was performed to assess the positive rate of SPECT/CT MPI and CMR in the different infection source groups. The positive rates of SPECT/CT MPI in groups A and D were higher than that of CMR, and the positive rates of SPECT/CT MPI in groups C and E were lower than that of CMR. The differences were statistically significant ($P < 0.05$). There was no significant difference in the positive rate of SPECT/CT MPI and CMR in group B ($P > 0.05$).

The positive rates of SPECT/CT MPI and CMR among the different infection groups were found using a multi-group chi-square test. The positive rate of SPECT/CT MPI was different among the groups ($P < 0.05$): group D was the highest (75.4%), followed by group A (68.5%), group B (54.8%), group E (36.4%), and group C (25.8%). There were significant differences between groups D and C and groups D and E ($P < 0.01$). There was no difference in the positive rate of CMR diagnosis among all groups ($P > 0.05$) (**Table 2**).

Distribution characteristics of myocardial ischemic lesions in SPECT/CT MPI

In total, 134 patients were diagnosed with myocardial ischemia by SPECT/CT MPI. Only one ischemic segment was observed in 72.4% of the patients, two in 20.9% of the patients, and three in 6.7% of the patients. The number of patients with only one ischemic segment in group D was smaller than that in the other groups, while the number of patients with two and three ischemic segments was higher than that in the other groups; the number of ischemic segments in the other groups was similar.

The analysis of all the ischemic segments (164) in 134 patients showed that 69.5% of the ischemic segments were in the anterior wall of the left ventricle or the anterior wall combined with other walls, followed by 10.4% in the interwall, 9.8% in the apex, 7.3% in the inferior wall, 3.0% in the lateral wall. The distribution of each group was consistent. In group A, 75.0% of the ischemic segments were in the anterior wall, and the number of ischemic segments in the lateral wall was 0. In group B, 63.6% of the ischemic segments were in the anterior wall, and the number of ischemic segments in the apex was 0. The number of ischemic segments in the lower wall and lateral wall in group E was 0 (**Table 3**).

Table 2. Comparison between the positive rates of the two imaging methods

Groups	Number of cases (N)	SPECT/CT (%)	CMR (%)	P
Group A	73	50 (68.5%)	35 (47.9%)	P=0.050
Group B	31	17 (54.8%)	17 (54.8%)	P=0.100
Group C	31	8 (25.8%)#	19 (61.3%)	P=0.027
Group D	64	47 (75.4%)*	36 (56.8%)	P=0.050
Group E	33	12 (36.4%)#	24 (72.7%)	P=0.017
Total	232	134 (57.8%)	131 (56.5%)	
x^2		22.542	5.844	
P		0.000	0.211	

Note: * and # show a significant difference.

Table 3. Distribution characteristics of SPECT/CT lesions segments

Group (N)		Group A (50)	Group B (17)	Group C (8)	Group D (47)	Group E (12)	Total (134)
Number of ischemic segments	One	39 (78.0%)	13 (76.5%)	6 (75.0%)	30 (63.8%)	9 (75.0%)	97 (72.4%)
	Two	8 (16.0%)	3 (17.7%)	2 (25.0%)	12 (25.5%)	3 (25.0%)	28 (20.9%)
	Three	3 (6.0%)	1 (5.9%)	0 (0.0%)	5 (10.6%)	0 (0.0%)	9 (6.7%)
Chamber wall	Anterior wall	45 (75.0%)	14 (63.6%)	11 (73.3%)	34 (64.2%)	10 (71.4%)	114 (69.5)
	Apex	5 (8.3%)	0 (0.0%)	2 (13.3%)	7 (13.2%)	2 (14.3%)	16 (9.8%)
	Inferior wall	6 (10.0%)	3 (13.6%)	1 (6.7%)	2 (3.8%)	0 (0.0%)	12 (7.3%)
	Inter wall	4 (6.7%)	4 (18.2%)	1 (6.7%)	6 (11.3%)	2 (14.3%)	17 (10.4%)
	Lateral wall	0 (0.0%)	1 (4.5%)	0 (0.0%)	4 (7.5%)	0 (0.0%)	5 (3.0%)
	Total	60 (100.0%)	22 (100.0%)	15 (100.0%)	53 (100.0%)	14 (100.0%)	164 (100.0%)

Table 4. Analysis of the average daily hospitalization cost of SPECT/CT MPI

Groups	Negative (N) (CNY)	Positive (N) (CNY)	F	P
A	23 (1411.12±710.91)	50 (1243.22±549.93)	1.236	0.270
B	14 (1412.45±628.25)	17 (1346.09±736.01)	0.021	0.885
C	23 (1682.80±532.61)	8 (1549.91±542.19)	0.442	0.151
D	17 (1429.27±410.10)	47 (1438.80±517.45)	0.043	0.836
E	21 (1438.80±401.66)	12 (1223.98±741.11)	2.490	0.125
F	0.441	1.050		
P	0.778	0.484		

Note: CNY, Chinese Yuan.

Effect of SPECT/CT and CMR on the average daily hospitalization cost

The average daily hospitalization cost of children with negative and positive SPECT/CT MPI and CMR results in the same infection group was analyzed using the two-sample *t*-test, and the average daily hospitalization cost of children with negative and positive SPECT/CT MPI and CMR results among the different infection groups was analyzed using ANOVA. There was no difference in the average daily hospitalization cost between the patients with negative and positive SPECT/CT MPI results in the same infection group (P=0.270 > 0.05), and there was no difference between the average daily hospitalization cost of SPECT/CT MPI patients in different infection groups (P=0.125 > 0.05) (**Table 4**). The average daily hospitalization cost of CMR-positive patients in group D was lower than that of the CMR-negative patients (P < 0.05). The average daily hospitalization cost of CMR-negative patients in group E was lower than that of those in groups D and C (P < 0.05) (**Table 5**).

Discussion

Previously reported cases have shown that myocarditis can potentially cause perfusion defects that can be easily identified on ^{201}Tl or ^{99m}Tc-MIBI myocardial perfusion imaging. Al-

Table 5. Analysis of the average daily hospitalization cost of CMR

Groups	Negative (N) (CNY)	Positive (N) (CNY)	F	P
A	37 (1311.05±511.12)	35 (1362.33±711.28)	1.057	0.308
B	14 (1200.23±523.02)	17 (1427.20±600.10)	1.311	0.262
C	15 (1606.55±492.72)#	16 (1510.22±629.21)	1.562	0.221
D	28 (1521.31±643.22)#	36 (1219.11±327.21)	6.901	0.011
E	9 (1059.36±430.27)*	24 (1518.90±620.11)	0.493	0.488
F	2.297	1.446		
P	0.030	0.223		

Note: * and # show a significant difference, CNY, Chinese Yuan.

though neither the sensitivity nor specificity of this technique is sufficient for a reliable diagnosis of myocarditis, it must be noted that myocarditis is one of the many causes of perfusion defects in ^{201}Tl or ^{99m}Tc-MIBI [6]. In this study, the positive rate of myocarditis with simple viral infection and viral combined with mycoplasma infection in SPECT/CT MPI was 68.5% and 75.4%, respectively, and the positive rate showed a statistically significant difference from that of CMR. Several studies, mainly in murine models, have found that viral myocarditis is associated with the spasm of the coronary microvasculature, focal myocytolytic necrosis, and interstitial fibrosis. Immunohistochemical techniques show that patients with lymphocytic myocardial infiltrates often have an increased expression of intercellular and vascular adhesion molecules in the vascular endothelium of the intramural coronary arteries, indicating low-grade inflammation. These findings suggest that the inflammatory process associated with myocarditis may cause a reduction in coronary perfusion reserve [7]. Similar to the higher SPECT/CT positive rate in the viral infection group in this study, the positive rates of SPECT/CT MPI in children with simple bacterial infection (such as streptococcus), bacterial combined viral infection, and bacterial combined with mycoplasma infection were 54.8%, 25.8%, and 36.4%, respectively. The positive rates of the latter two infections were considerably lower than those of CMR, and the differences were statistically significant. The mechanism of how bacterial infection causes myocarditis coronary artery ischemia has not been elucidated, and this study cannot explain this phenomenon. We aim to continue to explore this phenomenon in our subsequent study.

^{99m}Tc-MIBI was previously considered a suitable tracer for detecting myocardial injury in patients with myocarditis [8]. Recently, Sun et al. conducted research on viral myocarditis and reported that a decrease in perfusion by different degrees is a sign of myocarditis, which is closely related to ST-T segment changes and myocardial enzyme levels [9]. The present study confirmed this and found that most of the areas with reduced SPECT/CT perfusion in children with myocarditis were distributed in the anterior wall of the left ventricle and one segment of the anterior wall; moreover, ischemia was found to occur rarely in the inferior and lateral walls. Very few children had more than two segments of ischemia, and the abovementioned distribution characteristics were consistent among the infection groups. Moreover, conducting a literature review did not provide sufficient evidence regarding a relevant mechanism for this phenomenon. This study speculated that it may be related to the easy accumulation of infectious bacteria in the myocardium of the left ventricular anterior wall in children; however, the possibility of physiological anterior wall ischemia in children cannot be ruled out. We aim to investigate this in future studies.

The use of CMR in children with myocarditis has increased over the past 15 years as CMR does not produce ionizing radiation. The use of CMR results in higher hospital costs and longer length of stay; however, in severely ill children, the use of CMR can improve the clinical outcomes at a lower cost [10]. In this study, the average daily hospitalization cost of CMR-positive patients was lower than that of CMR-negative patients in the viral combined with mycoplasma infection group, whereas the other groups had the same cost. In the viral combined with mycoplasma infection, it was possible to provide more accurate clinical treatment earlier to the patients who were CMR-positive. In contrast, CMR-negative patients may need to use other means to find the cause, which

increases the costs. The average daily hospitalization cost of CMR-negative children with myocarditis caused by bacterial combined with mycoplasma infection was the lowest, indicating that the treatment and diagnostic means that would incur more costs were excluded when CMR was negative in this infection group. We found that SPECT/CT MPI had no effect on the average daily hospital cost of children with myocarditis in the different infection groups, and different SPECT/CT diagnosis results did not increase the average daily hospital cost of children with myocarditis. ^{99m}Tc-MIBI labeled drug has a certain amount of radioactivity, which leads to radiation exposure in children. CMR does not produce ionizing radiation; therefore, some families choose CMR examination over SPECT/CT examination. However, the poor cooperation of children during CMR examination coupled with the use of contrast media makes it unsuitable for use in some children. The estimated absorbed radiation doses to the whole body and myocardium are 0.0045 MGy/MBq and 0.0046 MGy/MBq, respectively, which are far lesser than the permitted radiation dose for children and will not cause radiation damage in children [11].

Conclusions

The reasonable selection of ^{99m}Tc-MIBI SPECT/CT MPI is beneficial for the diagnosis and treatment of children with infective myocarditis. Therefore, the selection of ^{99m}Tc-MIBI SPECT/CT MPI and CMR imaging is conducive to the diagnosis and treatment of pediatric infective myocarditis.

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Disclosure of conflict of interest

None.

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