ORIGINAL ARTICLE

Cutaneous Manifestations of Pediatric COVID-19 and Multisystem Inflammatory Syndrome in Children (MIS-C)

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Background: Characteristics of dermatological manifestations are frequently encountered in pediatric COVID-19, similar to the presentation in multisystem inflammatory syndrome in children (MIS-C), which typically emerges following COVID-19 infection. The rash exhibits considerable diversity and lacks specificity. However, investigations into the dermatological features of COVID-19 in children and MIS-C remain limited.

Objective: To investigate cutaneous manifestations in both COVID-19 and MIS-C in children.

Materials and Methods: Cross-sectional study between February and August 2022 in hospitalized children with COVID-19 who had cutaneous lesions and all hospitalized children with MIS-C.

Results: Forty-six cases of COVID-19 patients with dermatological manifestations were identified among 1,602 COVID-19 patients, constituting 2.9%. Additionally, 35 cases of MIS-C were diagnosed. The majority of COVID-19 patients in the present study exhibited mild symptoms, accounting for 42 cases (91.3%). The median age of COVID-19 patients was 1.8 years, which was significantly lower than that of the MIS-C group, which was 4.3 years, with a statistically significant difference (p=0.024). The most common rash types observed in both groups were urticaria, maculopapular rash, and macular erythema. Other rash types noted in COVID-19 included erythema nodosum, Stevens-Johnson syndrome, erythema multiforme-like, vesicles, and livedo reticularis. Among MIS-C patients, 31 cases (88.6%) presented with mucocutaneous manifestations, with 26 cases (74.3%) exhibiting concurrent mucocutaneous involvement. There was no significant difference in the occurrence of cardiac symptoms between the group with mucocutaneous manifestations and/or dermatological symptoms, which was 81.8%, compared to the group without mucocutaneous or dermatological symptoms, which was 100% (p=0.102).

Conclusion: The cutaneous manifestations in pediatric COVID-19 and those with MIS-C vary widely and are non-specific. In patients presenting with fever and rash during a COVID-19 outbreak, recognizing these cutaneous symptoms is crucial for prompt diagnosis and treatment especially those who are asymptomatic. Further studies involving COVID-19 patients, both with and without rash, may provide correlation between disease progression and skin manifestation.

Keywords: COVID-19; Pediatric dermatology; Multisystem inflammatory syndrome; SARS-CoV-2

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COVID-19 in previously healthy children is usually a mild or asymptomatic disease, without associated mortality[1]. Fever and respiratory symptoms were the most frequent manifestations in early pediatric series from China and Italy[2,3]. In comparison to adults, infections in children tend to exhibit milder respiratory symptoms and are often asymptomatic or exhibit only mild, non-specific symptoms[4]. Factors that may contribute to this phenomenon include a lesser predisposition to factors associated with severe disease, such as comorbidities or endothelial damage in the lungs. Additionally, it has been observed that the antibody response to SARS-CoV-2 infection is more robust in children, characterized by higher levels of cytokines, increased interferon production, elevated CD4+/CD8+ levels, and superior CD8+ antigen response. However, the implications of these immunological mechanisms may manifest in other systemic symptoms, such as dermatological manifestations[5].

While the mortality rate of pediatric COVID-19 patients is low, reports have identified severe complications, even in previously healthy children. These complications include multisystem

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inflammatory syndrome in children (MIS-C), which has been a leading cause of hospitalization due to COVID-19-related illness, accounting for up to 40% of hospitalizations with respiratory symptoms from COVID-19 and frequently necessitating admission to intensive care units (ICU)[6,7].

Due to the often-elusive nature of COVID-19 symptoms in children, clinicians may need to rely on observation of non-specific manifestations, such as cutaneous symptoms, to aid in diagnosis. Cutaneous symptoms, being extrapulmonary manifestations, rank seventh among the common signs of COVID-19 in children as morbilliform, chilblain-like, urticarial, macular erythema, vesicle, papulosquamous, and retiform purpura. Other cutaneous manifestations that may be encountered include erythema multiforme-like lesions, thrombocytopenic purpura, dengue-like exanthem, leukocytoclastic vasculitis, erythema elevatum diutinum-like, and photo-distributed rashes[8].

Furthermore, the most serious condition associated with SARSCoV-2 infection in the pediatric population, MIS-C is well documented in literature[9,10]. In the MIS-C group, cutaneous and/or mucosal symptoms such as conjunctival injection and oral mucosal changes may be observed. Studies have found cutaneous and/or mucosal symptoms to be the most common manifestations following fever.

Most studies conducted have been in adults, with limited research in this demographic and a lack of data in the Thai population, thus warranting the necessity of the present study.

Materials and Methods

A retrospective review of pediatrics patients aged less than 15 years old admitted with COVID-19 confirmed by either antigen test kit (ATK) or reverse transcriptase-polymerase chain reaction test (RT-PCRT) positive for SAR-CoV-2, with dermatological symptoms, between February and August 2022, was done. Furthermore, children that met the World Health Organization (WHO) preliminary case definition for MIS-C as a framework for identifying children between February and August 2022 at Queen Sirikit National Institute of Child Health were also included. The authors reviewed demographic including age, gender, cutaneous symptoms, duration, and clinical characteristics associated with each morphology. Comparative analysis of categorical data entailed the utilization of either the chi-square test or Fisher's exact test. Data were analyzed with IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA) with the p-value at a significant level of 0.05.

Table 1. Demographic data of patients with COVID-19 and MIS-C

Data	COVID-19 (n=46)	MIS-C (n=35)	p-value
Age (years); median (IQR)	1.8 (0.6, 3.8)	4.3 (1.2, 8.5)	0.024
Male:female ratio	1.7:1	1.8:1	0.820
High fever*; n (%)	45 (97.8)	35 (100)*	0.380
Mucocutaneous involvement	46 (100)	31 (88.6)	0.052
Upper respiratory symptoms	36 (78.3)	8 (22.9)	<0.001
GI symptoms	25 (54.3)	25 (71.4)	0.117
Seizure	2 (4.3)	3 (8.6)	0.434
Respiratory distress	4 (8.7)	10 (28.5)	0.028
Testicular pain	0 (0.0)	1 (2.9)	0.249
Cardiac symptoms	0 (0.0)	22 (62.9)	<0.001
• Myocarditis	0 (0.0)	15 (42.9)	<0.001
• Coronary artery abnormalities	0 (0.0)	9 (25.7)	<0.001
• Pericardial effusion	0 (0.0)	1 (2.9)	0.249
• Cardiogenic shock	0 (0.0)	11 (31.4)	<0.001

MIS-C=multisystem inflammatory syndrome in children; IQR=interquartile range

* High fever T >38.5°C

The present study was approved by the Research Ethics Review Committee of the Queen Sirikit National Institute of Child Health, QSNICH IRB, approval REC.044/2565.

Results

During the present study period, the authors collected inpatient data on pediatric COVID-19 patients treated at the Queen Sirikit National Institute of Child Health, totaling 1,602 cases. Among these, 46 cases presented with cutaneous manifestations of COVID-19, while 35 cases were classified under the MIS-C group.

The median age of COVID-19 patients with cutaneous manifestations was 1.8 years (interquartile range [IQR] 0.6, 3.8), whereas in the MIS-C group, it was 4.3 years (IQR 1.2, 8.5), with a statistically significant difference (p=0.024). The male-to-female ratio was 1.7 to 1.8:1 in both groups, showing no significant difference (Table 1).

The majority of COVID-19 patients were in the age group of 1 to 4 years, comprising 19 cases (41.3%), while in the MIS-C group, the majority were also in the 1 to 4 years and 5 to 9 years age groups, with an equal number of 10 cases each (28.6%).

The most common symptoms of COVID-19 were fever in 45 cases (97.8%), upper respiratory tract symptoms in 36 cases (78.3%), and gastrointestinal symptoms in 25 cases (54.3%). Additionally, four cases (8.7%) presented with respiratory distress due

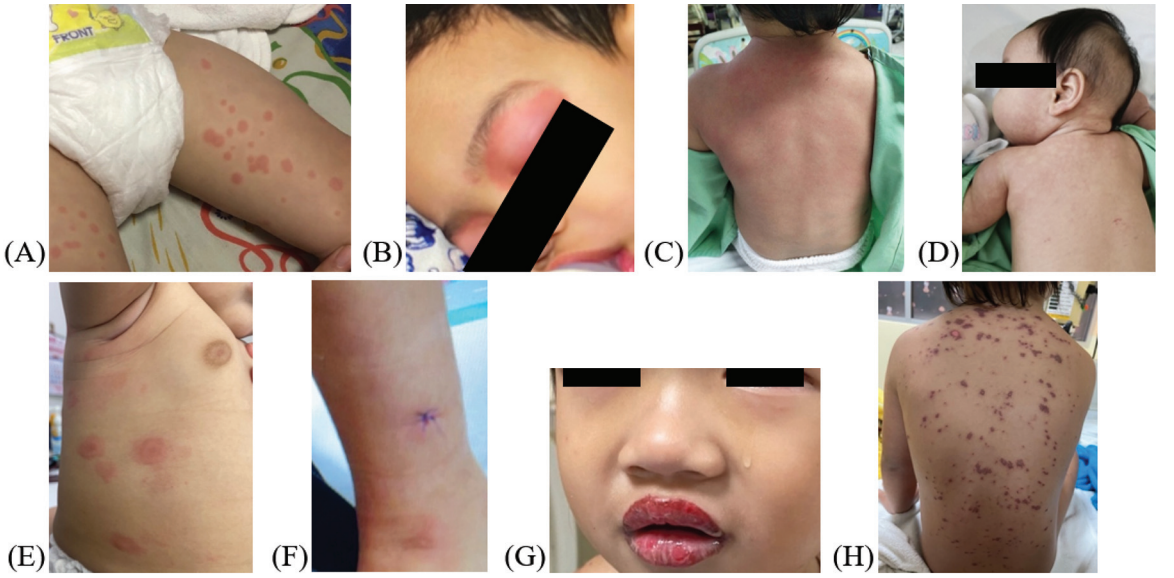

Figure 1. Cutaneous manifestation in COVID-19. (A) Urticaria; (B) Macular erythema periorbital area; (C) Macular erythema on the back; (D) Livedo reticularis on face, neck, and back; (E) Erythema multiforme-like rash on trunk; F) Erythema nodosum (biopsy confirmed); (G, H) Steven-Johnson syndrome.

to pneumonia. The median duration of COVID-19 symptoms was 5.2 days (IQR 3.8, 10.0) and none of COVID-19 patients had any cardiac symptoms as in MIS-C patients ($p<0.001$).

In the MIS-C group, all patients presented with high fever (Table 1). The most commonly encountered symptom, aside from high fever, was cutaneous and/or mucosal involvement, observed in 31 cases (88.6%). Other notable symptoms included gastrointestinal manifestations in 25 cases (71.4%), myocarditis in 15 cases (42.9%), cardiogenic shock in 11 cases (31%), and coronary artery abnormalities in nine cases (25.7%).

When comparing patients from both groups, the upper respiratory tract symptoms were significantly more prevalent in the COVID-19 group compared to the MIS-C group, at 78.3% versus 22.9% ($p=0.000$). Additionally, respiratory distress was significantly more common in the MIS-C group compared to the COVID-19 group at 28.5% versus 8.7% ($p=0.028$), and cardiac symptoms were exclusively found in the MIS-C group at 62.9% versus 0% (($p<0.001$) (Table 1).

The most frequently encountered types of rashes in COVID-19 were urticaria, observed in 17 cases (36.9%), followed by maculopapular (MP) rash in 12 cases (26.1%), and macular erythema in 11 cases (23.9%). Other rash types included erythema multiforme-like rash in one case, erythema nodosum, with skin biopsy confirmed, in one case, vesicular rash in one case, Stevens-Johnson syndrome in one case, and livedo reticularis in two cases, totaling six cases (13.1%) (Figure 1).

In the MIS-C group, skin manifestations included MP rash in 19 cases (54.2%), macular erythema in seven cases (20%), urticaria in four cases (11.4%), and erythema multiforme-like rash in one case (2.8%) (Figure 2).

Urticaria and MP rash were found in COVID-19 group significantly more than in MIS-C group ($p<0.05$). The most commonly reported symptom associated with rashes in COVID-19 was pruritus, observed in 35 cases (76.1%), while in the MIS-C group, pruritus was present only in six cases (17.1%), with a statistically significant difference ($p<0.001$). The onset of rash typically occurred after the onset of illness in both groups and did not differ significantly. The median duration of rash in COVID-19 was three days (IQR 2, 7), and in MIS-C, was 4.5 days (IQR 1.3, 7.8), showing no significant difference. Mucosal involvement was observed in 26 cases (74.3%) in the MIS-C group encompassing both ocular and oral mucosa, which was significantly higher compared to the COVID-19 group, where it was observed in only one case (2.2%) ($p<0.001$) (Table 2).

Furthermore, patients with specific type of rash including erythema nodosum, vesicles, Stevens-Johnson syndrome, and livedo reticularis, would have less respiratory symptoms compared to other non-specific rash type ($p<0.001$) (Table 3).

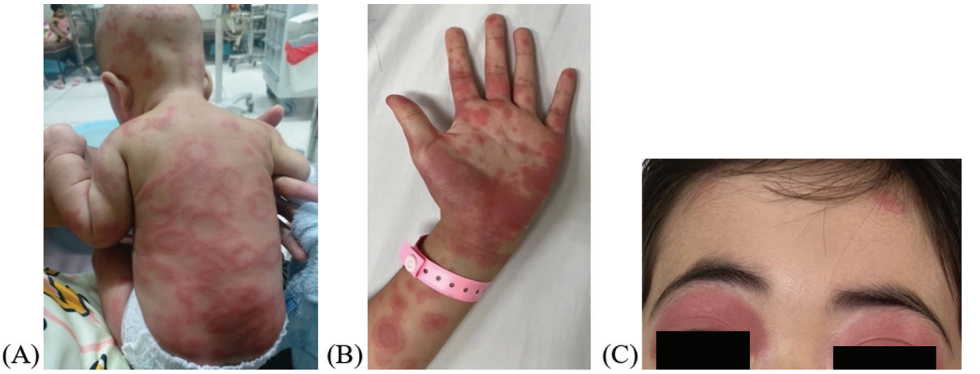

Figure 2. Cutaneous manifestation in MIS-C. (A) Generalized urticaria, (B) Erythema multiforme-like rash, (C) Macular erythema on periorbital area.

Table 2. Cutaneous manifestation in COVID-19 and MIS-C

Data	COVID-19 (n=46)	MIS-C (n=35)	p-value
Cutaneous manifestations; n (%)			
Morbilliform/Maculopapular rash	12 (26.1)	19 (54.2)	0.003
Macular erythema	11 (23.9)	7 (20.0)	0.581
Urticaria	17 (36.9)	4 (11.4)	0.001
Erythema multiforme-like rash	1 (2.1)	1 (2.8)	0.330
Vesicular rash	1 (2.1)	0 (0.0)	0.155
Reticulate erythema	2 (4.3)	0 (0.0)	0.617
Erythema nodosum	1 (2.1)	0 (0.0)	0.155
Steven-Johnson syndrome	1 (2.1)	0 (0.0)	0.155
Cutaneous symptoms; n (%)			0.001
Pruritus	35 (76.1)	6 (17.1)	
Pain	1 (2.2)	2 (5.7)	
Relationship to non-cutaneous symptoms; n (%)			0.438
Before	4 (8.7)	4 (11.4)	
Concurrent	27 (58.7)	16 (45.7)	
After	10 (21.7)	3 (8.6)	
Duration of cutaneous manifestation (day); median (IQR)	3.0 (2.0, 7.0)	4.5 (1.3, 7.8)	0.927
Mucosal involvement; n (%)	1 (2.2)	26 (74.3)	0.001

MIS-C=multisystem inflammatory syndrome in children; IQR=interquartile range

When stratifying rash types in COVID-19 by age groups, it was observed that MP rash was most frequently encountered in children younger than one year with eight cases (43.8%). Urticaria rash was more prevalent in certain age groups, specifically in the 1 to 4 years with eight cases (42.1%), the 5 to 9 years with three cases (60%), and the 10 to 15 years with four cases (66.7%) (Figure 3).

Among MIS-C group, there was no significant statistical difference found in the occurrence of cardiac symptoms between those with mucosal and/or cutaneous manifestations and those without (Table 4).

Discussion

The global pandemic of SARS-CoV-2 virus has led to the emergence of coronavirus of 756,581,850 confirmed cases worldwide. In Thailand, there have been 4,727,628 confirmed cases reported, with a notably high percentage of infections occurred among children and adolescents, aged 0 to 14 years, accounting for up to 20% of the cases as of February 17, 2026[11,12]. The first wave of COVID-19 outbreak in Thailand was identified in March 2020, with the latest wave, the fifth wave, commencing in mid-January 2024, attributed to the Omicron variant lineage[13].

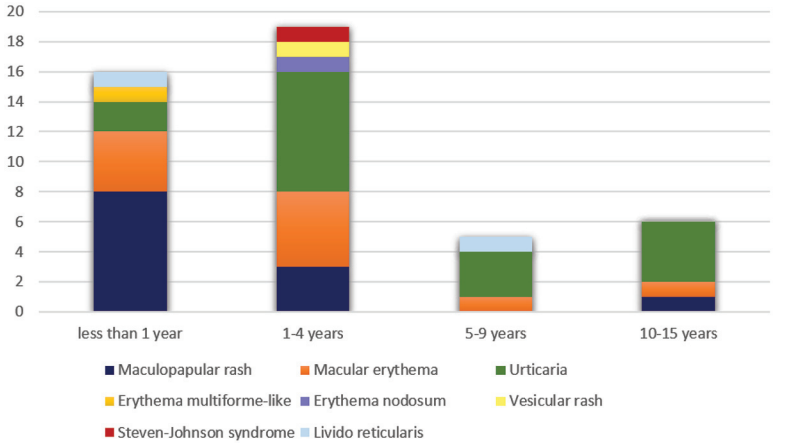

Figure 3. Specific type of cutaneous manifestations in COVID-19 according to age group.

Table 3. COVID-19 symptoms related to specific type of rash (n=46)

Data	Morbilliform/maculopapular rash (n=12)	Macular erythema (n=11)	Urticaria (n=17)	Other types* (n=6)	p-value
COVID-19 symptoms; n (%)					
Fever	12 (100)	11 (100)	17 (100)	5 (83.3)	0.120
Upper respiratory symptoms	11 (91.7)	11 (100)	13 (76.5)	1 (16.7)*	<0.001
Respiratory distress	1 (8.7)	1 (9.1)	2 (11.8)	0 (0.0)	0.670
GI symptoms	8 (66.7)	9 (81.8)	6 (35.3)	2 (33.3)	0.050
Seizure	0 (0.0)	0 (0.0)	2 (11.8)	0 (0.0)	0.310

GI=gastrointestinal

* Other skin types including erythema multiforme-like 1 case, erythema nodosum 1 case, vesicle 1 case, Stevens-Johnson syndrome 1 case, and livedo reticularis 2 case

Table 4. Cardiac involvement in MIS-C patients

Data	Cardiac involvement (n=22); n (%)	No cardiac involvement (n=13); n (%)	p-value
Sex			0.689
Male	15 (68.2)	8 (61.5)	
Female	7 (31.8)	5 (38.5)	
COVID-19 pneumonia	1 (4.5)	2 (15.4)	0.121
Cutaneous/mucosal involvement	18 (81.8)	13 (100)	0.102

During the present study period between February and August 2022, the authors collected data on pediatric COVID-19 patients treated inpatient department at the Queen Sirikit National Institute of Child Health, totaling 1,602 cases. Among these, 46 cases presented with cutaneous manifestations of COVID-19, while 35 cases were classified under the MIS-C group. The prevalence of 2.9% was observed among hospitalized patients with cutaneous manifestations, closely aligned with the findings reported by Parri et al. at 3%[3] and Pousa et al. at 3.4%[14].

The cohort examined within the scope of COVID-19 and MIS-C exhibited a significantly lower median age compared to prior studies in both groups[15,16]. Upon comparison, the median age of patients with COVID-19 and MIS-C in the present study was found to be statistically significantly younger for patients with COVID-19.

Cutaneous reactions to COVID-19 are polymorphic, and more than one type of rash can appear in an individual patient[17-19]. Other viral infections, medication reactions, and connective tissue disorders produce similar non-specific rashes to SARS-CoV-2[17,18]. In the present series, the most common cutaneous reaction was urticaria, MP rash, and macular erythema. These three types of rashes were observable in hospitalized patients with mild

symptoms, as in prior pediatric studies[15,16,20].

Acute urticarial lesions have been discussed in COVID-19 studies[18,21-25]. Prevalence of these lesions among other skin manifestations has varied from 7% to 40% in smaller case series. These lesions typically present as an erythematous slightly raised papular rash followed by intense pruritic sensations[26]. Although considered one of COVID-19's most frequent cutaneous manifestations, urticarial lesions have been a common dermatological condition even before the pandemic. Many other viruses produce non-specific urticarial reactions, and most children infected with SARS-CoV-2 are symptom-free. Hence, the diagnosis of SARS-Co-2 infection is challenging based on the presence of urticaria alone. However, urticarial rash in combination with pyrexia raise the possibilities of the early phase of COVID-19 disease.

In addition to urticarial lesions, MP rash was found as the second most common cutaneous reaction in the present series along with macular erythema. These types of reactions have also been listed in COVID-19 case series[17,27]. A MP rash is a non-specific term utilized to describe cutaneous reaction patterns with macules and papules and occurs in almost 50% of adults with COVID-19[16,18,20]. MP rash was noted in 47% of Spanish COVID-19 patients, more than half of them reported pruritus. A sizable international registry lists macular erythema in 13% of patients.

From the present series, it was noted that cutaneous reactions such as erythema multiforme-like, erythema nodosum, vesicles, Stevens-Johnson syndrome, and livedo reticularis in COVID-19 often did not present with upper respiratory tract symptoms, distinguishing them from other types of rashes such as urticaria, MP, and macular erythema, with statistical significance. This observation aligns with previous reports where patients lacked or minimally presented with upper respiratory symptoms in certain types of rashes[28].

Although there have been only three reported cases of Stevens-Johnson syndrome associated with COVID-19[29], upon investigating the etiology in the patients identified in the present series, including infection with *Mycoplasma pneumoniae*, Herpes simplex virus-1 and -2, human herpes virus-6, -7, and -8, hepatitis B virus, Epstein-Barr virus, varicella-zoster virus, coxsackie virus, adenovirus, human parvovirus B19, or medication usage, no causative agents were identified. Therefore, the authors hypothesized COVID-19 as a potential trigger for Stevens-Johnson syndrome.

However, chilblain-like, papulosquamous, and retiform purpura rashes were not observed in the study of Dinulos et al[8]. This absence may be attributed to the mild symptoms of patients in the study, with only 8.7% experiencing pneumonia and receiving non-invasive respiratory support, with only one case requiring ICU admission. Consequently, the retiform purpura rash, typically associated with severe infection leading to acute respiratory distress syndrome (ARDS) and found in adults, as well as papulosquamous rash, also found in adult studies, were not encountered[30]. Similarly, the chilblain-like rash, though not evident in this study, has been documented in patients with mild symptoms who were hospitalized, influenced by warmer climatic conditions compared to the previous studies. There also report of skin disease aggravation or new onset of skin disease for example psoriasis and alopecia areata in adult, of which we have to follow up in our cases of COVID-19 infection[30].

In the MIS-C group, the most frequently observed symptoms following the universally present high fever were mucocutaneous manifestations, detected in up to 88.6% of the cases, consistent with findings from Andina-Martinez et al. at 86%[6] and Baykal et al. at 93%[31]. The mucocutaneous manifestations in this study exhibited considerable diversity, with commonly encountered presentations including MP rash, macular erythema, and urticaria, as in previous investigations. However, the frequency of specific rash types varied across studies[6,31-33].

In the present series, the authors did not identify any differences in MIS-C patients with or without mucocutaneous manifestations regarding cardiac symptoms, as in the findings from Rao et al.[33], which similarly found no such distinctions. However, given that only four cases lacked mucocutaneous manifestations, it is plausible that the limited number of such cases may have contributed to the absence of discernible differences in symptoms or disease severity. Further investigations are warranted to elucidate these observations. There were also no differences observed in the necessity for intravenous immunoglobulin therapy among patients with or without mucocutaneous manifestations, including those with severe MIS-C. Specifically, among patients with non-severe MIS-C and mucocutaneous involvement, there were 18 cases (69.2%), compared to eight cases (30.8%) with both mucocutaneous involvement and severe MIS-C (p=0.213). This contrasts with a previous study that identified mucocutaneous involvement as a protective factor

against the development of severe MIS-C29.

What is already known on this topic?

Characteristics of dermatological manifestations are frequently encountered in pediatric COVID-19, similar to the presentation in MIS-C, which typically emerges following COVID-19 infection. The rash exhibits considerable diversity and lacks specificity.

What this study adds?

In COVID-19, there are other rash types, apart from MP rash, urticaria, and papular erythema including erythema nodosum, Stevens-Johnson syndrome, erythema multiforme-like, vesicles, and livedo reticularis. Respiratory symptoms tend to be less or absent in these types of rashes. Among MIS-C patients, there was no significant difference in the occurrence of cardiac symptoms between the group with mucocutaneous manifestations and/or dermatological symptoms compared to the group without mucocutaneous or dermatological symptoms.

Conflicts of interest

The authors declare no conflict of interest.

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