# INCIDENCE AND RISK FACTORS OF MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) AMONG PEDIATRIC PATIENTS RE-CEIVING CARE IN A TERTIARY HOSPITAL IN CENTRAL THAILAND

Nutthaporn Narknok<sup>1,2</sup>, Boonsub Sakboonyarat<sup>3</sup>

<sup>1</sup> Department of Pediatric Cardiology, Ananda Mahidol Hospital, Lopburi 15000, Thailand

<sup>2</sup> Department of Pediatrics, Phramongkutklao College of Medicine, Bangkok 10400, Thailand

<sup>3</sup> Department of Military and Community Medicine, Phramongkutklao College of Medicine, Bangkok 10400, Thailand

### Abstract

**Background:** Multisystem Inflammatory Syndrome in Children (MIS-C) involves severe complications after contracting SARS-CoV-2. Nevertheless, limited evidence is available of MIS-C incidence in Thailand. Therefore, the present study aimed to determine MIS-C incidence and its risk factors among Thai children.

**Methods:** A retrospective cohort study was conducted between 2020 and 2021. The data were obtained from medical records of pediatric patients under 15 years receiving a diagnosis of SARS-CoV-2 and obtaining treatment at Ananda Mahidol Hospital, Lopburi Province, central Thailand. The World Health Organization defined MIS-C incidence as occurring within eight weeks after contracting SARS-CoV-2. A multivariable Cox proportional hazard regression model was used for estimating the adjusted hazard ratio (AHR) and 95% confidence interval (CI) for factors associated with MIS-C.

**Results**: Three thousand pediatric patients with a history of SARS-CoV-2 were included in the present study. The majority (51%) were males. The median time of follow-up was 56 days. Twenty-five patients (0.83%) developed MIS-C, representing an incidence rate of 14.95 (95% CI: 9.67–22.07) per 100,000 person-days. The incidence rates among males and females were 18.77 (95% CI: 10.73–30.49) and 10.97 (95% CI: 5.02–20.83) per 100,000 person-days, respectively (*p*-value = 0.192). After adjusting for potential confounders, independent risk factors for MIS-C included a history of asthma (AHR: 7.65; 95% CI: 1.69–34.67), history of allergic rhinitis (AHR: 15.71; 95% CI: 5.73–43.05), history of nephrotic syndrome (AHR: 49.6; 95% CI: 5.89–417.06), every 10 mg/dL increase of C-reactive protein (AHR: 1.71; 95% CI: 1.28–2.29) and having COVID-19-related symptoms involving at least two systems (AHR: 9.36; 95%CI: 2.2–39.78) compared with those involving less than two systems.

**Conclusion:** A modest incidence of MIS-C was estimated among Thai children, while a higher incidence of MIS-C among male patients was observed. Factors associated with MIS-C included underlying diseases and elevated C-reactive protein levels in SARS-CoV-2.

Keywords: MIS-C, SARS-CoV-2, C-Reactive Protein, Thailand

J Southeast Asian Med Res 2023: 7:e182 https://doi.org/10.55374/jseamed.v7.182

Correspondence to:

Narknok N, Department of Pediatric Cardiology, Ananda Mahidol Hospital, Lopburi 15000, Thailand and Department of Pediatrics, Phramongkutklao College of Medicine, Bangkok 10400, Thailand E-mail: guide18cardioped@gmail.com

Received: 21 June 2023 Revised: 13 September 2023 Accepted: 19 September 2023

# Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory communicable disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).<sup>(1)</sup> It can occur at any age and often involves severe symptoms among the elderly and people with congenital diseases from a widespread worldwide outbreak, resulting in many hospitalized patients and deaths(1). Among pediatric patients, COVID-19 is often asymptomatic, alternatively producing mild symptoms compared with adults. After the first widespread outbreak in 2020, reports of MIS emerged, similar to Kawasaki disease in a severe form following SARS-CoV-2.<sup>(2)</sup>

The World Health Organization (WHO)<sup>(1)</sup> defined MIS as a multisystem inflammatory condition among children and adolescents temporally related to COVID-19.(2) The US Centers for Disease Control and Prevention (CDC) defined it as MIS-C<sup>(3)</sup>, and the UK Royal College of Pediatrics and Child Health named it Pediatric MIS associated with Coronavirus Disease 2019 (PIMS-TS or PIMS)(4). MIS-C involves severe complications after contracting SARS-CoV-2, starting when recovering from the disease or two to six weeks after contracting. The condition is primarily found among pediatric patients with a history of mild or showing no symptoms of COVID-19. The average age of children experiencing the condition was 9.7 years, and was found among boys more than among girls.<sup>(5)</sup> Signs and symptoms include fever, inflammation, systemic deterioration or shock. Like Kawasaki disease, fever, rash, red eyes, swollen hands and feet, dried cracked lips and enlarged lymph nodes are also included. Other signs include nervous system symptoms, blood circulation failure, impaired cardiac function, cytokine storm, macrophage activation syndrome, thrombosis and pulmonary embolism.<sup>(6)</sup>

More symptoms include myocarditis, which is more likely to develop as a shock and more severe signs include rapidly deteriorating gastrointestinal symptoms, acute renal failure and subsequent death.<sup>(6)</sup> Therefore, MIS-C among pediatric patients involves severe signs and symptoms that may cause disability and death.

In the US, MIS incidence among patients under 21 years and previously tested positive for SARS-CoV-2 was approximately 1 in 3,000 to 4,000 (5.1 cases per 1,000,000 monthly cases of that age group).<sup>(3, 7)</sup> MIS-C incidence was higher among Hispanics, Blacks, and Asians or Pacific Islanders compared with Whites. Furthermore, younger individuals revealed higher MIS-C incidence than older individuals.<sup>(7)</sup>

In Thailand since 2020, COVID-19 has also been a significant public health problem affecting the Thai population at every age.<sup>(8)</sup> However, epidemiologic information on MIS-C remains scarce, especially among pediatric patients. Therefore, the present study aimed to estimate the MIS-C incidence among Thai pediatric patients with a history of SARS-CoV-2 and determine factors associated with MIS-C incidence in this population.

### Methods

### Ethics Considerations

The study was reviewed and approved by the Institutional Review Board, Royal Thai Army Medical Department (IRBRTA), Bangkok, Thailand (approval number S039h/65), in compliance with international guidelines such as the Declaration of Helsinki, the Belmont Report, CIOMS Guidelines and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice (ICH—GCP) (approval number S040h/65). Regarding the secondary data used, the IRBRTA granted a waiver of informed consent.

### Study Design and Subjects

A retrospective cohort study was conducted at Ananda Mahidol Hospital, a tertiary hospital in Lopburi Province, central Thailand. The criteria of eligible participants comprised pediatric patients under 15 years receiving a diagnosis of SAR-CoV-2 at Ananda Mahidol Hospital between January 1, 2020, and December 31, 2021. SAR-CoV-2 confirmation included (1) a positive result of SARS-CoV-2 Real-Time Polymerase Chain Reaction, (2) a positive result of SARS-CoV-2 serology test, or (3) a positive result of SARS-CoV-2 antigen test.

### Data Collection

In the current study, 3,000 pediatric patients with a history of SARS-CoV-2 were enrolled. Patient information was reviewed and retrieved by a pediatrician. A standard case report form was used to collect baseline data of individuals from medical records including demographic characteristics, comorbidity, clinical symptoms and laboratory testing at the date of diagnosis of SARS-CoV-2. The recommendation of the CDC and WHO diagnosis guidelines defined the MIS-C diagnosis.

Guidelines for diagnosing MIS-C, as recommended by the CDC and WHO, include patients with fever  $\geq 38^{\circ}$ C for 24 hours with at least two or more systemic symptoms:

1) rash, red eyes or inflammation of the mucous membranes; 2) low blood pressure or shock; 3) symptoms of the cardiovascular system; 4) bleeding easily due to abnormal blood clotting; 5) gastrointestinal symptoms; 6) respiratory symptoms; 7) neurological symptoms and 8) sudden renal failure. Additionally, a blood test was used showing inflammation in at least one of the following criteria: 1) C-reactive protein (CRP) > 5 mg/dl, 2) D-dimer > 2 mg/l, 3) erythrocyte sedimentation rate (ESR) >40 mm/hr, 4) fibrinogen >400 mg/dl, 5) ferritin >500 micrograms/ml, 6) hypoalbuminemia (<3 g/dl), 7) IL-6 >1.8 pg/ ml, 8) lymphopenia (ALC <1000 cells/m<sup>3</sup>), 9) LDH >280 U/L, 10) neutrophilia (ANC >7,700 cells/m<sup>3</sup>) and 11) procalcitonin >0.05 ng/ml. Moreover, no other cause indicated similar symptoms including toxic shock syndrome or staphylococcal scalded skin syndrome.

### Statistical Analysis

All analyses were conducted using Stata Corp., 2021, *Stata Statistical Software: Release 17*, College Station, TX, USA: Stata Corp. LLC. Baseline characteristics were analyzed using descriptive statistics. Continuous data were presented as mean and standard deviation (SD), while categorical data were presented as percentages. The person-time of observation was calculated for each participant as the duration between the participant's baseline data and the day MIS-C occurred. Those remaining patients without MIS-C were right-censored on the 56th day after the date of SAR-CoV-2 diagnosis. The incidence rates of MIS-C were calculated with 95% confidence intervals (CI) per 100,000 person-days of observation. The Kaplan-Meier estimator was used to compute survival patterns. The log-rank test was used to compare survival between males and females, while Cox proportional regression analysis was used to determine factors associated with MIS-C. Multivariable analysis was performed to estimate adjusted hazard ratios (AHR) and presented with a 95% CI. A two-sided p-value less than 0.05 was considered statistically significant.

### Results

#### Baseline Characteristics

Table 1 presents the baseline demographic and clinical characteristics of 3,000 pediatric patients with a history of SAR-CoV-2 included in the study. Of all participants, the majority (51%) were males. The average age of the study participants was 7.4±4.2 years. Fifty-one individuals (1.7%) presented a history of asthma, while 52 individuals (1.7%) possessed a history of allergic rhinitis. The most prevalent clinical presentation of SAR-CoV-2 was respiratory symptoms and fever, accounting for 70.1 and 59.6%, respectively. 90.1% of patients received care as outpatient treatment. Regarding laboratory testing at baseline, the average CRP was 51.0±20.3 mg/dl, while the average ESR was  $57.3\pm12.2$ . The average aminotransferase level was 47.0±8.8 U/L and 29.7±9.7 U/L for aspartate and alanine transaminase, respectively. Incidence of MIS-C among Patients with SARS-CoV-2

The median time of follow-up was three months. **Table 2** presents the incidence rate of MIS-C among patients with SARS-CoV-2. Twenty-five patients (0.83%) developed MIS-C, representing an incidence rate of 15.0 (95% CI: 9.7 to 22.1) per 100,000 person-days. **Figure 1** illustrates the Kaplan–Meier graph of MIS-C. Among patients developing MIS-C, the median age was 7.1 years, and 64% were males. The MIS-C incident rate was 18.8 (95% CI: 10.7 to 30.5) per 100,000 person-days among males, whereas 11.0 (95% CI: 5.0 to 20.8) per 100,000

person-days among females. Figure 2 illustrates the Kaplan–Meier graph of MIS-C by sex (p = 0.192).

Characteristics	n (%)
Sex	
Female	1469 (49.0)
Male	1531 (51.0)
Age (years)	
<6	1060 (35.3)
6 to 10	1041 (34.7)
11 to 15	899 (30.0)
mean $\pm$ SD	7.4 ±4.2
median (Q1-Q3)	7.1 (3.8-11.0)
Underlying diseases	
G-6PD	8 (0.3)
Asthma	51 (1.7)
Allergic Rhinitis	52 (1.7)
Congenital Heart disease	7 (0.2)
Thalassemia	15 (0.5)
Autistic	5 (0.2)
Nephrotic syndrome	7 (0.2)
Sinusitis	3 (0.1)
History of hospital admission due to COVID-19	
No	2702 (90.1)
Admit	298 (9.9)
Contact	
Family	2990 (99.7)
School	10 (0.2)
Clinical symptoms at baseline	
Fever	1788 (59.6)
Skin	18 (0.6)
Cardiovascular system	0 (0)
Hematology	0 (0)
Gastrointestinal system	192 (6.4)
Respiratory system	2103 (70.1)
Neurological system	147 (4.9)
Overall No. of symptoms at baseline	
<2	1425 (47.5)
≥2	1575 (52.5)
Laboratory test results at baseline	

Table 1. Baseline characteristics of study participants (Cont.)

Characteristics	n (%)
CRP (mg/dl)	
mean $\pm$ SD	51.0±20.3
median (Q1-Q3)	53.0 (36.5-68.0)
ESR (mm/hr)	
mean $\pm$ SD	57.3±12.2
median (Q1-Q3)	57.0 (47.0-67.0)
LDH (U/L)	
mean $\pm$ SD	69.9±7.1
median (Q1-Q3)	70.0 (64.0-76.0)
White Blood Cell (x10 <sup>3</sup> cell/m <sup>3</sup> )	
mean $\pm$ SD	6.1±1.7
median (Q1-Q3)	6.0 (4.5-7.5)
Absolute neutrophil count (cell/m <sup>3</sup> )	
mean $\pm$ SD	2482.7±1061.9
median (Q1-Q3)	2366.1 (1822.1-3040.6)
Absolute lymphocyte (cell/m <sup>3</sup> )	
mean $\pm$ SD	2012.9±862.3
median (Q1-Q3)	1856.3 (1420.0-2506.2)
Hematocrit (volume%)	
mean $\pm$ SD	34.9±4.2
median (Q1-Q3)	35.7 (32.0-38.0)
Hemoglobin (g/dl)	
mean $\pm$ SD	11.8±1.2
median (Q1-Q3)	12.0 (11.0-13.0)
Platelet (x 10 <sup>3</sup> cell/m <sup>3</sup> )	
mean $\pm$ SD	308.7±512.8
median (Q1-Q3)	303.8 (270.4-346.7)
Albumin (g/dl)	
mean $\pm$ SD	3.3±0.9
median (Q1-Q3)	3.0 (2.0-4.0)
AST (U/L)	
mean $\pm$ SD	47.0±8.8
median (Q1-Q3)	47.0 (42.0-54.0)
ALT (U/L)	
mean $\pm$ SD	29.7±9.7
median (Q1-Q3)	30.0 (23.0-37.0)

G-6PD: Glucose-6-phosphate dehydrogenase deficiency, COVID-19: Coronavirus 19 disease, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.



Figure 1. Kaplan–Meier Survival Graph of Multisystem Inflammatory Syndrome in Children



Figure 2. Kaplan-Meier survival graph of Multisystem Inflammatory Syndrome in Children by sex

Characteristics	Total	Number of MIS-C	Person-days of	Incidence rate per 100,000
	Number	(70)	observation	person-days (95% CI)
Overall	3000	25 (0.83)	167227	14.95 (9.67-22.07)
Sex				
Female	1469	9 (0.61)	82007	10.97 (5.02-20.83)
Male	1531	16 (1.05)	85220	18.77 (10.73-30.49)
Age (years)				
<6	1060	9 (0.85)	59085	15.23 (6.97-28.92)
6 to 10	1041	11 (1.06)	57938	18.99 (9.48-33.97)
11 to 15	899	5 (0.56)	50204	9.96 (3.23-23.24)
History of Admiss	ion due to	COVID-19 infection		
No	2702	24 (0.89)	150583	15.94 (10.21-23.71)
Yes	298	1 (0.34)	16644	6.01 (0.15-33.48)

Table 2. Incidence of Multisystem Inflammatory Syndrome among Children

MIS-C: Multisystem Inflammatory Syndrome in Children, CI: Confidence interval

Risk Factors of MIS-C among Patients with SARS-CoV-2

Univariable Cox regression analysis for risk factors of MIS-C was performed and is presented in **Table 3**. The independent risk factors for MIS-C among patients with SARS-CoV-2 are shown in **Table 4**. After adjusting for confounders, the risk factors of MIS-C included a history of

asthma (AHR: 7.7; 95% CI: 1.7 to 34.7), a history of allergic rhinitis (AHR: 15.7; 95% CI: 5.7 to 43.1), a history of nephrotic syndrome (AHR: 49.6; 95% CI: 5.9 to 417.1), every 10 mg/dL increase of CRP (AHR: 1.7; 95% CI: 1.3 to 2.3) and having COVID-19 related symptoms in at least two systems (AHR: 9.4; 95% CI: 2.2 to 39.8) compared with those in less than two systems.

**Table 3.** Univariable Cox regression analysis for risk factors of Multisystem Inflammatory Syndrome among Children

Factors	No MIS-C	MIS-C	Univariable analysis		
	n (%)	n (%)	Unadjusted HR	95% CI	<i>p</i> -value
Sex					
Female	1460 (99.4)	9 (0.6)	1		
Male	1515 (99.0)	16 (1.1)	1.71	0.76-3.87	0.197
Age (years)					
mean $\pm$ SD	$7.4\pm4.3$	$6.8\pm3.7$	0.97	0.89-1.07	0.539
<6	1051 (99.2)	9 (0.85)	1		
6 to 10	1030 (98.9)	11 (1.1)	1.25	0.52-3.01	0.625
11 to 15	894 (99.4)	5 (0.6)	0.65	0.22-1.95	0.446
History of Admission					
Outpatients	2678 (99.1)	24 (0.9)	1		
Admitted	297 (99.7)	1 (0.3)	0.38	0.05-2.79	0.34
Asthma					
No	2926 (99.2)	23 (0.8)	1		
Yes	49 (96.1)	2 (3.9)	5.17	1.22-21.91	0.026

Factors	No MIS-C	MIS-C	Univariable analysis		
	n (%)	n (%)	Unadjusted HR	95% CI	<i>p</i> -value
Allergic Rhinitis					
No	2928 (99.3)	20 (0.7)	1		
Yes	47 (90.4)	5 (9.6)	14.78	5.55-39.38	< 0.001
Nephrotic syndrome					
No	2969 (99.2)	24 (0.8)	1		
Yes	6 (85.7)	1 (14.3)	20.31	2.75-150.14	0.003
No. of symptoms at baselin	e				
<2	1423 (99.9)	2 (0.14)			
≥2	91552 (98.5)	23 (1.5)	10.46	2.47-44.36	0.001
CRP (mg/dl)					
mean $\pm$ SD	$50.9\pm20.3$	$67.0\pm10.2$	1.05	1.02-1.08	< 0.0001
ESR (mm/hr)					
mean $\pm$ SD	$57.3 \pm 12.2$	$59.8 \pm 13.1$	1.02	0.98-1.05	0.311
LDH (U/L)					
mean $\pm$ SD	$69.9\pm7.12$	$70.0\pm7.4$	1.00	0.95-1.06	0.957
White Blood cell					
mean $\pm$ SD (x10 <sup>3</sup> cell/m <sup>3</sup> )	$6.1\pm1.8$	$6.8\pm1.8$	1.0002	1.0001-1.0004	0.047
Absolute neutrophil count					
mean $\pm$ SD	$3.0\pm1.1$	$2.7\pm0.9$	1.0001	0.99-1.0004	0.343
$(x10^3 \text{ cell/m}^3)$					
Absolute lymphocyte coun	t				
mean $\pm$ SD	$2.0\pm0.9$	$2.2\pm1.1$	1.0002	0.99-1.001	0.359
$(x10^3 \text{ cell/m}^3)$					
Hemoglobin (g/dl)					
mean $\pm$ SD	$11.8\pm1.2$	$12.0\pm1.0$	1.14	0.82-1.60	0.437
Hematocrit (volume%)					
mean $\pm$ SD	$34.9\pm4.2$	$34.9\pm4.1$	0.99	0.91-1.10	0.978
Platelet					
mean $\pm$ SD	$308.6\pm51.3$	$311.9\pm48.3$	1.00	0.99-1.00	0.755
$(x10^3 \text{ cell/m}^3)$					
Albumin (g/dl)					
mean $\pm$ SD	$3.3\pm0.9$	$3.5\pm0.8$	1.30	0.83-2.03	0.240
AST (U/L)					
mean $\pm$ SD	$47.0\pm8.8$	$49.8\pm7.4$	1.04	0.98-1.09	0.121
ALT (U/L)					
mean $\pm$ SD	$29.7 \pm 9.7$	$32.4 \pm 6.0$	1.03	0.98-1.07	0.173

**Table 3.** Univariable Cox regression analysis for risk factors of Multisystem Inflammatory Syndrome among Children (Cont.)

MIS-C: Multisystem Inflammatory Syndrome in Children, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HR: Hazard ratio, CI: Confidence interval

Factors	Adjusted HR	95% CI	<i>p</i> -value
Sex			
Female	1		
Male	1.65	0.70-3.92	0.255
Age (years)	0.94	0.85-1.05	0.266
Asthma			
No	1		
Yes	7.65	1.69-34.67	0.008
Allergic Rhinitis			
No	1		
Yes	15.71	5.73-43.05	< 0.001
Nephrotic syndrome			
No	1		
Yes	49.55	5.89-417.06	< 0.001
No. of COVID-19 symptoms at baseline			
Less than two symptoms	1		
At least two symptoms	9.36	2.20-39.78	0.002
CRP (every 10 mg/dL increase)	1.71	1.28-2.29	< 0.001
AST (every 10 unit/L increase)	1.25	0.77-2.03	0.371

**Table 4.** Multivariable cox regression analysis for risk factors of Multisystem Inflammatory Syndrome among Children

\*Adjusted for sex, age, asthma, allergic rhinitis, nephrotic syndrome, number of clinical symptoms at baseline, CRP, and AST, COVID-19: Coronavirus 19 disease, CRP: C-reactive protein, AST: Aspartate aminotransferase, HR: Hazard ratio, CI: Confidence interval

#### Discussion

The present study provides essential evidence concerning MIS-C incidence and related risk factors among Thai pediatric patients. A higher incidence of MIS-C was observed among male patients. The corresponding risk factors for MIS-C included a history of asthma, allergic rhinitis, nephrotic syndrome, more elevated CRP and COVID-19-related symptoms in two or more systems.

Patients with MIS-C in the current study exhibited similar characteristics to those reported in the US and Europe. The median age at onset was 7.3 to 10 years, and 59% were males.<sup>(9)</sup> We found that the overall incidence rate of MIS-C among Thai pediatric patients was 15.0 per 100,000 person-days, approximately 0.8%. This rate is relatively high compared with related studies in other countries. For instance, it approximated 0.002% of US children under 21 years<sup>(7)</sup>, 0.003% among children under 18 years in Italy<sup>(10)</sup> and 0.01% among children under 19 years in Sweden.<sup>(11)</sup> Our study included pediatric patients under 15 years. Thus, this may explain our finding, which is supported by the evidence of a higher incidence of MIS-C among younger children under 15 years compared with that of those over 15 years.<sup>(11)</sup>

Regarding sex, we found that the incidence of MIS-C among males was higher than that among females, consistent with related reports in the US<sup>(7)</sup> and Sweden.<sup>(11)</sup> This finding may be explained by the biological differences (genetic and epigenetic) between males and females, which may impact the immune response to SARS-CoV-2.<sup>(12)</sup> We also found a lower MIS-C incidence among patients older than 11 years compared with younger patients. These findings are compatible with the related studies, reporting that higher-aged individuals exhibit a lower incidence of MIS-C.<sup>(7, 11)</sup>

We demonstrated that MIS-C incidence among patients with asthma was 7.5 times that of those without asthma. However, the estimated AHR could have been more precise. This finding agrees with that of the related study in Sweden, demonstrating the association between asthma and MIS-C among children.<sup>(11)</sup> Asthma results in dysregulation in the immune system, making fighting viral infections harder.<sup>(13, 14)</sup> Furthermore, the related study indicated that the rate of COVID-19 hospital admission was higher among children with asthma than those without asthma.<sup>(15)</sup>

Additionally, we also demonstrated that allergic rhinitis was associated with MIS-C incidence. Although pathophysiology-linked allergic rhinitis and MIS-C incidence were unclear, one recent report showed that children diagnosed with MIS-C had a history of allergic rhinitis.<sup>(16)</sup> The mechanism of allergic rhinitis involves the emergence of anti-IgE antibody and specific antibodies to cytokines correlating to allergic inflammation.<sup>(17)</sup> Therefore, this may link to MIS-C through the inflammatory pathway.

We explored that pediatric patients with nephrotic syndrome tended to have a higher incidence of MIS-C than those without. Although the estimated AHR for the association between those was imprecise, this finding may be explained by the fact that patients with nephrotic syndrome are prone to acute kidney injuries linked to MIS-C.<sup>(3, 18)</sup> Furthermore, we reported that MIS-C incidence among patients with two or more clinical symptoms of COVID-19 tended to be higher than those with less than two clinical symptoms of COVID-19. Therefore, our findings suggest that pediatric patients with comorbidities having SAR-CoV-2 and presenting more clinical symptoms of COVID-19 should be closely monitored for MIS-C at least within eight weeks after the onset of COVID-19.

Patients with MIS-C in the present study exhibited increased inflammatory markers, especially CRP, which was also reported in other MIS-C cohorts in other countries.<sup>(19–23)</sup> After adjusting for potential confounders, we found that every 10 mg/dL increase of CRP tended to increase the risk for MIS-C by 71%. Moreover, our estimated AHR for the association between CRP and MIS-C was relatively precise (95% CI: 1.28–2.29). High CRP level associated with MIS-C, like the proinflammatory effect of SARS-CoV-2 infection, has been reported among adults with severe COVID-19, with whom MIS-C shares some characteristics including dysregulated innate immune response and cytokine storm.<sup>(22, 23)</sup> This issue may be a key point for monitoring MIS-C among patients with COVID-19 with high CRP values.

The present study encountered several limitations. First, the study included only pediatric patients with SAR-CoV-2 receiving care in one tertiary hospital in central Thailand; therefore, the generalizability is limited. Second, we included participants under 15 years; thus, we did not have the opportunity to assess the MIS-C incidence among children and adolescents of older age. Third, regarding the power of the study, the estimated AHR for the risk factors for MIS-C may not have been relatively precise. However, the present study constituted an early study providing epidemiologic data on MIS-C among pediatric patients in Thailand. Understanding SARS-CoV-2 transmission among children and its short term consequences is essential. Reinforcing the need for long term multidisciplinary follow-up is crucial because whether these patients will experience a chronic impairment or other sequelae remains unknown.

# Conclusion

A modest incidence of MIS-C was estimated among Thai children, while a higher incidence of MIS-C among male patients was observed. Factors associated with MIS-C were underlying diseases including a history of asthma, allergic rhinitis, nephrotic syndrome, COVID-19-related symptoms in two or more systems and high C-reactive protein levels in SARS-CoV-2.

### Availability of data and materials

The datasets generated or analyzed during the current study are not publicly available because they contain sensitive identifying information. Because ethics restrictions have been placed, the datasets are available from the author on reasonable request (contact Nutthaporn Narknok via guide18cardioped@gmail.com)

# **Competing interests**

The authors declare they have no competing interests.

### Acknowledgments

The authors thank the Director and staff of Ananda Mahidol Hospital, Lopburi Province, for their support in completing this study.

# Authors' contributions

NN and BS developed the concept for the study.

NN collected the data. BS analyzed the data. NN and BS wrote the first draft; the authors contributed and approved the final version.

# References

- 1. Velavan TP, Meyer CG. The COVID-19 epidemic. Trop Med Int Health 2020; 25: 278-80.
- Organization WH. Multisystem inflammatory syndrome in children and adolescents with COVID-19: scientific brief, May 15 2020. World Health Organization; 2020. Available from:https://www.who.int/news-room/commentaries/detail/multisysteminflammatorysyndrome-in-children-and-adolescents-withcovid-19.
- 3. Prevention C for DC and Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). CDC Health Alert Network. 2020. Available from: https://www.cdc.gov/ mis/mis-c.html.
- 4. RCoPaC H. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Royal College of Paediatrics and Child Health London 2020. Available from:https://www.rcpch.ac.uk/resources/ paediatric-multisystem-inflammatorysyndrome-temporally-associated-covid-19pims-guidance.
- 5. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, et al. Overcoming COVID-19 Investigators. Characteristics and outcomes of US children and adolescents with multisystem inflammatory

syndrome in children (MIS-C) Compared With Severe Acute COVID-19. JAMA 2021; 325: 1074-87.

- 6. Evans C, Davies P. SARS-CoV-2 paediatric inflammatory syndrome. Paediatr Child Health (Oxford) 2021; 31: 110-5.
- Payne AB, Gilani Z, Godfred-Cato S, Belay ED, Feldstein LR, Patel MM, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. JAMA Netw Open 2021; 4: e2116420.
- Yorsaeng R, Suntronwong N, Thongpan I, Chuchaona W, Lestari FB, Pasittungkul S, et al. The impact of COVID-19 and control measures on public health in Thailand, 2020. Peer J 2022; 10: e12960.
- 9. Abrams JY, Godfred-Cato SE, Oster ME, Chow EJ, Koumans EH, Bryant B, et al.Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2: A systematic review. J Pediatr 2020; 226: 45-54.
- La Torre F, Elicio MP, Monno VA, Chironna M, Moramarco F, Campanozzi A, et al. Incidence and prevalence of multisystem inflammatory syndrome in children (MIS-C) in southern Italy. Children (Basel) 2023; 10: 766.
- 11. Rhedin S, Lundholm C, Horne A, Smew AI, Osvald EC, Haddadi A, et al. Swedish Pediatric MIS-C Consortium; Brew BH, Almqvist C. Risk factors for multisystem inflammatory syndrome in children - A population-based cohort study of over 2 million children. Lancet Reg Health Eur 2022; 19: 100443.
- Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol 2020; 20: 442-7.
- Papi A, Johnston SL. Rhinovirus infection induces expression of its own receptor intercellular adhesion molecule 1 (ICAM-1) via increased NF-kappaB-mediated transcription. J Biol Chem 1999; 274: 9707-20.
- 14. Yeh SY, Schwartzstein R. Asthma: Pathophysiology and diagnosis. Asthma, Health and Society: A Public Health Perspective 2010; 19–42.

- 15. Shi T, Pan J, Katikireddi SV, McCowan C, Kerr S, Agrawal U, et al. Public Health Scotland and the EAVE II collaborators. Risk of COVID-19 hospital admission among children aged 5-17 years with asthma in Scotland: a national incident cohort study. Lancet Respir Med 2022; 10: 191-8.
- 16. Cirks BT, Rowe SJ, Jiang SY, Brooks RM, Mulreany MP, Hoffner W, et al. Sixteen weeks later: expanding the risk period for multisystem inflammatory syndrome in children. J Pediatric Infect Dis Soc 2021; 10:686-90.
- 17. Min YG. The pathophysiology, diagnosis and treatment of allergic rhinitis. Allergy Asthma Immunol Res 2010; 2: 65-76.
- 18. Menon S. Acute Kidney Injury in Nephrotic Syndrome. Front Pediatr 2019; 6: 428.
- Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al. California MIS-C response team. COVID-19-associated multisystem inflammatory syndrome in children - United States, March-July 2020.

MMWR Morb Mortal Wkly Rep 2020; 69: 1074-80.

- 20. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasakilike multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020; 369: m2094.
- 21. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020; 395: 1771-8.
- 22. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020; 395: 1607-8.
- 23. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF et al. Overcoming COVID-19 investigators; CDC COVID-19 response team. multisystem inflammatory syndrome in US children and adolescents. N Engl J Med 2020; 383: 334-46.