

Multisystem inflammatory syndrome in children in Singapore

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ABSTRACT

Introduction: Multisystem inflammatory syndrome in children (MIS-C) is a rare inflammatory syndrome with multisystem involvement affecting children exposed to COVID-19. This condition is rarely reported in East Asia and was not detected in Singapore until 2021. We present 12 cases of MIS-C diagnosed in KK Women's and Children's Hospital (KKH) from October 2021 to December 2021.

Method: We conducted an observational study on cases fulfilling the Singapore Ministry of Health criteria for MIS-C from January 2020 to December 2021 in KKH. Medical records were reviewed to obtain information on clinical presentation, disease course, treatment received and outcomes.

Results: In the 12 cases detected, the median age was 7.50 years (interquartile range 4.00–9.25); 8 were male. All patients had mucocutaneous symptoms similar to Kawasaki disease. Other commonly involved systems were: haematological (coagulopathy 100%, lymphopaenia 91.70% and thrombocytopenia 75.00%), gastrointestinal (75.00%) and cardiovascular (83.30%). Six patients (50.00%) had shock and were admitted to the intensive care unit. The majority of patients received treatment within 2 days of hospitalisation with intravenous immunoglobulin (IVIg) and steroids. All survived; the majority had normal echocardiograms and no long-term organ sequelae at 6 months post-discharge.

Conclusion: MIS-C emerged in Singapore as the incidence of COVID-19 in the community increased in 2021. The clinical presentation of our patients is similar to earlier reports, with some significant differences from Kawasaki disease. Multidisciplinary management, timely diagnosis, and early initiation of treatment with IVIg and steroids likely contributed to comparatively good outcomes. Our cases highlight the need for continued awareness of MIS-C among physicians, and surveillance of its incidence, short- and long-term outcomes.

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Keywords: COVID-19, children, MIS-C, inflammation, paediatrics

INTRODUCTION

While children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulting in coronavirus disease 2019 (COVID-19) have milder manifestations compared to adults,^{1,2} a rare multisystem inflammatory syndrome leading to multiorgan failure

and shock (multisystem inflammatory syndrome in children [MIS-C]) has been recognised to affect children with exposure to COVID-19. MIS-C shares similar features with Kawasaki disease (KD), another inflammatory syndrome with mucocutaneous signs such as conjunctivitis and rash, and cardiac complications.³

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CLINICAL IMPACT

What is New

- An increased number of cases of multisystem inflammatory syndrome in children (MIS-C) was observed during the Delta wave of COVID-19 in Singapore.
- In our series, patients had mucocutaneous features similar to Kawasaki disease, but also frequently presented with gastrointestinal symptoms, cardiovascular involvement, shock, coagulopathy, lymphopaenia and thrombocytopaenia. Other systems' involvement was less common.

Clinical Implications

- As COVID-19 becomes endemic in Singapore, young children could be more predisposed to MIS-C, especially unvaccinated individuals. Early diagnosis, treatment with intravenous immunoglobulin and steroids, and multidisciplinary management may result in good outcomes.

Initial reports of MIS-C largely came from the US and Europe.⁴⁻⁶ In contrast, despite the high incidence of COVID-19 in East Asia, which includes China, Japan and Korea, reports of MIS-C are rare in this region.⁷⁻¹⁰ For the first 20 months of the pandemic from January 2020 to September 2021, no cases of MIS-C were detected in Singapore.¹¹ In the year 2021, there was a sharp increase of COVID-19 infections due to the arrival of the highly transmissible Delta variant of concern (VOC),¹² and the transition of the national health policy to treat COVID-19 as an endemic disease. While Delta VOC has been shown to cause more severe presentation in adults,¹² whether it has altered the clinical pathology in children remains unknown. From October 2021 to December 2021, our hospital detected 12 cases of MIS-C. In this article, we describe their clinical presentation, disease course, treatment received and outcomes.

METHOD

This was a retrospective observational study on MIS-C cases diagnosed in KK Women's and Children's Hospital (KKH) from January 2020 to 31 December 2021. KKH is a public paediatric tertiary hospital and the national centre for management of children with COVID-19 in Singapore.

Cases were defined according to the Singapore Ministry of Health (MOH) criteria for MIS-C (Table 1), which was adopted from the World Health Organization criteria.¹³ Clinical information such as demographics, presenting symptoms, examination findings, laboratory results, treatment received, clinical course and outcomes were obtained through a review of medical records up to 6 months post-discharge. Data were analysed using descriptive statistics (median and interquartile range [IQR]) with Microsoft Excel). This study was approved by the institutional review board (CIRB No. 2020/2094). Written informed consent was waived in light of the need to inform public health outbreak control policies.

Table 1. Singapore Ministry of Health (MOH) case definition of multisystem inflammatory syndrome in children (MIS-C) (from MOH Circular 171/2021, 11 November 2021, reproduced with permission from MOH, Singapore).

Criteria for case definition of MIS-C (all 6 criteria must be met)

1. Age 0–19 years
2. Persistent high fever ($>38.5^{\circ}\text{C}$) for ≥ 3 days
3. Signs of multisystem involvement (at least 2 systems below):
 - a. Cardiovascular (e.g. raised cardiac biomarkers, pericarditis, coronary abnormalities and ECG abnormalities)
 - b. Hypotension or shock
 - c. Gastrointestinal (e.g. diarrhoea, vomiting and abdominal pain)
 - d. Mucocutaneous features (e.g. rash, conjunctivitis, mucositis, and swollen hands or feet)
 - e. Neurological manifestations (e.g. headache, altered mental state and seizures)
 - f. Haematological (e.g. lymphopaenia, thrombocytopaenia and coagulopathy)
 - g. Respiratory (e.g. shortness of breath and tachypnoea)
 - h. Renal (e.g. markers of acute renal injury)
4. Elevated markers of inflammation (e.g. C-reactive protein, ferritin, procalcitonin and fibrinogen)
5. Other bacterial/viral causes are excluded
6. Evidence of current or recent COVID-19 infection (e.g. PCR-positive, serology-positive or -)

ECG: electrocardiogram; PCR: polymerase chain reaction

RESULTS

We identified 12 cases of MIS-C. The summary of findings of their clinical characteristics, disease course, treatment received and outcomes are presented in online Supplementary Materials, Supplementary Table S1, while the details of each case are in online Supplementary Table S2. The majority of the patients were male ($n=8$, 66.67%). The median age was 7.50 years (IQR 4.00–9.25). Five patients were of Malay ethnicity, 4 were Chinese and 3 were Indians. Four patients (33.30%) had underlying chronic conditions—one with a history of cholesteatoma and recurrent middle

ear infections, one with epilepsy, one with recurrent wheezing and one with well-controlled asthma.

All patients had evidence of prior COVID-19 infection with a positive anti-N SARS-CoV-2 immunoglobulin G antibody (online Supplementary Table S1). Ten patients had history of confirmed COVID-19 infection with positive antigen rapid test or SARS-CoV-2 polymerase chain reaction (PCR). Two cases were close household contacts, but did not test positive during the acute infection—one had acute respiratory symptoms while the other was asymptomatic. Majority ($n=11$, 91.67%) had mild or asymptomatic infection. Two cases were hospitalised—one due to young age and one due to mild asthma exacerbation. The median interval between COVID-19 infection or exposure and the onset of MIS-C was 25.00 days (IQR 22.00–29.50).

All patients had involvement of at least 3 systems (online Supplementary Tables S1 and S2). Mucocutaneous features of conjunctivitis and haematological abnormality with coagulopathy (raised D-dimer or prolonged clotting time) were present in all patients. Lymphopaenia was found in 11 cases (91.7%) with a median absolute lymphocyte count of 0.63×10^9 cells/L (IQR 0.49–0.83). Thrombocytopenia was present in 9 cases (75.00%), with a median platelet of 101.50×10^9 cells/L (IQR 90.50–143.25).

Cardiovascular involvement was the next most common ($n=10$, 83.30%) with abnormalities in echocardiogram or raised N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. The following abnormalities were seen in 8 out of 11 patients (72.70%) with inpatient echocardiograms: coronary artery abnormalities ($n=3$), dilated ventricles ($n=3$) and reduced cardiac function ($n=4$) (online Supplementary Tables S1 and S2). NT-proBNP level $>500\text{pg/mL}$ was seen in 8 out of 10 patients (median 2558.50pg/mL , IQR 1118.25–10779.50). Six patients (50%) had shock and were admitted to the intensive care unit (ICU). All received fluid boluses and 4 required inotropic support. Case #2 had the most severe presentation, requiring triple inotropic support for 5 days.

Gastrointestinal symptoms comprising abdominal pain, vomiting and/or diarrhoea were present in 9 patients (75.00%). None were suspected of having appendicitis. Case #2 was referred to the surgeons as his abdominal ultrasound showed small bowel thickening and suspicion of intramural air. He was treated for enterocolitis, with bowel rest and antibiotics. Case #4 was diagnosed with mild pancreatitis, with mildly elevated amylase (maximum 216 U/L , normal $28\text{--}112\text{ U/L}$). Among 5 patients who had abdominal ultrasonography, 3 had gallbladder wall thickening and 1 had hydrops.

Other systems' involvement was seen less frequently. Neurological involvement was seen in 5 patients (41.70%): 3 patients had headache, 1 patient with a background of epilepsy had breakthrough seizures occurring immediately prior to onset of fever, and 1 patient had aseptic meningitis. Four patients (33.30%) had respiratory involvement, with 1 patient (case #2), requiring mechanical ventilation. His chest radiograph showed bilateral pleural effusions and consolidation, and no infection was detected to cause such presentation. Four patients (33.30%) had acute kidney injury with mild elevation of creatinine.

All patients had elevated C-reactive protein (CRP) and procalcitonin, with a median of 136.00mg/L (IQR $94.25\text{--}185.70$) and $2.74\mu\text{g/L}$ (IQR $0.88\text{--}19.14$), respectively. Ferritin and lactate dehydrogenase were significantly elevated in some patients (online Supplementary Tables S1 and S2).

All patients received intravenous (IV) antibiotics and were worked up for infectious causes. Case #5's blood culture grew *Staphylococcus aureus*—while this was deemed likely a contaminant, IV antibiotics were continued for 1 week as he was on high-dose steroids. One patient was positive for rhinovirus/enterovirus; 2 patients were positive for SARS-CoV-2 but were likely shedding their previous COVID-19 infection. Tests for Group A *Streptococcus* infection with anti-streptolysin O titer, typhoid and dengue fever were also done with no significant positive results.

Both diagnosis of MIS-C and administration of treatment were done within a median of 2.00 days from admission (IQR $2.00\text{--}3.00$) (online Supplementary Table S1). All patients received one dose of 2g/kg of intravenous immunoglobulin (IVIg). Eleven patients (91.70%) received steroids in the form of IV methylprednisolone with subsequent conversion to oral prednisolone (online Supplementary Tables S1 and S2). Case #3 was not given steroids as the initial diagnosis was KD, and there was rapid improvement of fever and symptoms with IVIg alone. The initial dose of methylprednisolone varied from around 1.25mg/kg/day (low dose) to 30mg/kg/day (high dose). High-dose steroids were given for 3–5 days to all patients with shock, except for Case #6 as her haemodynamic status had rapidly stabilised after receiving low-dose steroids. Case #11 also received high-dose steroids due to persistently severe periorbital erythema and swelling despite low-dose steroids. Case #2 received subcutaneous anakinra, an interleukin-1 inhibitor, as he was still hypotensive and febrile with rising CRP despite IVIg and high-dose steroids. All patients received aspirin as an antiplatelet medication. Two

patients received clopidogrel instead of aspirin when their liver transaminases were elevated. Six patients (50%) received enoxaparin as antithrombotic prophylaxis (online Supplementary Tables S1 and S2).

Once treatment was initiated, there was rapid response in terms of fever, with a median time of 2.00 days (IQR 2.00–2.00) to defervescence (temperature $<38^{\circ}\text{C}$ for at least 24 hours). For patients admitted to ICU, their median stay was 3.00 days (IQR 3.00–3.00). In the case of Case #2, he weaned off inotropes and extubated after 3 days since the addition of anakinra.

All patients survived and were discharged after a median hospital stay of 6.00 days (IQR 5.00–7.50). They were followed up by various subspecialties and are at least 6 months post-discharge at the time of writing. Case #11 was lost to follow-up after 16 days post-discharge. None were readmitted for recurrence of MIS-C. The median time to documented normalisation of CRP was 16.50 days (IQR 14.00–18.00) from onset of MIS-C and 12.50 days (IQR 10.75–14.25) from admission. Oral steroid was weaned once CRP normalised. The median total duration of steroids (including IV) was 42.00 days (IQR 26.00–49.50). Antiplatelet was continued for at least 6–8 weeks, or until echocardiograms were normal, whichever was later. The median duration of antiplatelet treatment is 52.50 days (IQR 48.50–60.00) as of writing, with case #5 still on aspirin as of 8 months post-discharge for his coronary artery dilation. Antithrombotic prophylaxis with enoxaparin was continued until D-dimer levels normalised or at <5 times the upper normal limit. The median duration of enoxaparin was 17 days (IQR 8.50–20.25). Case #8, who had elevated D-dimer levels as his prothrombotic risk factor and was on enoxaparin, was readmitted 1 day after discharge for haematochezia. His anti-factor Xa level was within prophylactic range and he had no other risk factors for bleeding. Enoxaparin was stopped as his D-dimers had normalised.

Outpatient echocardiograms were performed for all patients between day 16 and day 286 post-MIS-C onset. Eleven patients had inpatient echocardiograms available for comparison—8 were abnormal with 7 subsequently having a normal outpatient scan, while the other 3 had normal findings during acute illness and on follow-up. Case #3 only had an outpatient echocardiogram, which was found to be normal. Among the 8 patients with inpatient abnormal scans, all but 1 (case #5) had a subsequent normal scan by 6 months post-discharge, with a median time of 16.50 days (IQR 14.00–44.50) for the resolution of any echocardiogram

abnormality from MIS-C onset (online Supplementary Tables S1 and S2). Median time to resolution from MIS-C onset for the 4 cases with reduced cardiac function and 3 cases with coronary artery abnormalities detected inpatient was 14 days (IQR 13.00–14.75) and 42 days (IQR 28–72), respectively. In 2 patients (cases #5 and #8), new coronary arterial dilation was detected in outpatient scans (on day 50 and day 22 of illness, respectively). This finding resolved by day 52 for case #8 while it was still detected in case #5 on day 218 (online Supplementary Table S2).

For other systems, by the last outpatient review at 16–286 days post-onset of MIS-C, most patients reported no significant residual abnormalities during their outpatient visits. One patient was readmitted 4 months later for chronic fatigue, body aches and low mood, and was diagnosed to have adjustment disorder on a background of social issues.

DISCUSSION

Since 2020, KKH implemented a surrogate surveillance of MIS-C through the monitoring of KD incidence during the pandemic. We found no increase in KD incidence and admissions to the ICU due to KD in 2020 compared to the years before the COVID-19 pandemic.^{14,15} The earlier absence of MIS-C in Singapore was possibly due to the lower COVID-19 incidence in children in 2020, with much fewer children infected compared to the rest of the population.¹⁶ For the whole of 2020, only 265 children (aged 0–18 years) were infected (unpublished data from MOH, cited with permission from MOH, Singapore). In stark contrast to the earlier absence of MIS-C, the 12 cases in this report were diagnosed in a span of 9 weeks after October 2021, following the peak of the Delta wave, which saw more than 20,000 children (aged 0–18 years) infected with COVID-19 from September to December 2021 alone (unpublished data from MOH, cited with permission from MOH, Singapore). Leow et al. published one case of MIS-C diagnosed in the National University Hospital, Singapore in 2021.¹¹ On 6 November 2021, MIS-C was reported to have occurred in 4 out of the over 8,000 paediatric COVID-19 patients in Singapore since the start of the pandemic;¹⁷ in the US, the reported incidence was 31.6 per 100,000 COVID-19 cases for persons <21 years.¹⁸ As the incidence of MIS-C reflects the level of COVID-19 transmission in the community, the arrival of the highly transmissible Omicron variant¹⁹ in Singapore, and the move towards treating COVID-19 as an endemic virus may lead to a rise in MIS-C incidence.

In terms of clinical presentation, our results highlight the similarities and differences between MIS-C and KD described in prior reviews. The median age of our patients at 7.5 years is on the lower end of the reported range (7.3–10.8 years old) for MIS-C,^{20,23} but older compared to the reported range for KD, which predominantly affects children aged <5 years.³ The male predominance (66.67%) noted in our series has also been previously reported.^{20,22,23} Race may be a risk factor as high incidence of MIS-C has been observed to occur in children of African, Hispanic or South Asian origin.^{20,22,23} Racial proportion of COVID-19 infection rates alone could not account for the racial disparities observed in MIS-C incidence, suggesting a role for biological as well as social determinants in increasing inflammation and risk of more severe outcomes.²⁴ Our patients belonged to the 3 most common races in Singapore.²⁵ However, our sample size is not large enough to draw conclusions on any racial predisposition.

Common clinical features of MIS-C seen in our patients were mucocutaneous signs similar to KD, gastrointestinal involvement and shock. The latter 2 are known to be less frequent in KD.^{20,23} Coagulopathy also has been frequently reported in MIS-C,²⁶ and thrombocytopenia and lymphopenia are more common in MIS-C^{22,23} compared to KD.³ Involvement of other systems such as neurological or respiratory system is less frequently reported in MIS-C.^{20,23} Our case series also confirms the high morbidity of MIS-C with a high proportion requiring ICU care,^{22,23,27,28} although mortality is low ($\leq 2\%$).^{22,23,28,29}

Our findings support the continued concern for MIS-C highlighted by MOH in its Circular No. 171/2021 to doctors (cited with permission from MOH, Singapore), with advice to suspect MIS-C in children with possible KD and consistent features of MIS-C, both within 2–8 weeks of confirmed COVID-19 infection. All our cases provided a history of diagnosed COVID-19 infection, and MIS-C occurred within a median of 25 days from the infection. However, as COVID-19 becomes endemic in Singapore, prior COVID-19 infection may not be readily apparent from history alone, which makes performing serology important to uncover previously undiagnosed COVID-19 infection.

The management of MIS-C in our institution involves multidisciplinary care according to guidelines jointly formulated by the paediatric intensive care units of KKH and National University Hospital, Singapore (Fig. 1). Prompt treatment of MIS-C with both IVIg

and steroids are our first-line therapy, with high-dose steroids given to those with shock or end-organ disease. This is in contrast to KD where steroids are used only in recalcitrant cases.³ As such, the proportion of our steroid use (91.7%) is higher compared to previous reviews (range 49–63%).^{20,23,27} The American College of Rheumatology (ACR) recommends a stepwise approach in the immunomodulatory treatment of MIS-C, with IVIg and low-to-moderate-dose of steroids to be used in hospitalised patients.³⁰ Observational studies have shown that initial treatment with IVIg plus steroids was associated with a more favourable fever course and less risk of cardiac dysfunction compared to IVIg alone,^{31,32} while timely administration of anti-inflammatories may prevent progression and need for admission to ICU.³³ The use of anakinra is recommended by ACR in cases with refractory MIS-C despite IVIg and steroids.³⁰ Such cases are less common^{21–23,27} with only 1 case in our series requiring this. Variations in treatment highlight the ongoing uncertainty about the ideal treatment strategy for MIS-C given the spectrum of severity. Randomised clinical trials are currently underway.³⁴

Antiplatelet and antithrombotic prophylaxis are also part of our management as MIS-C causes a prothrombotic state.³⁵ For the management of antiplatelet prophylaxis, aspirin is recommended by ACR to be given to hospitalised MIS-C patients³⁰ and prior reviews report its common use.^{21–23} For the management of antithrombotic prophylaxis, patients were first assessed for prothrombotic risk factors, such as age >12 years, immobility, high body mass index, mechanical ventilation, and D-dimer levels ≥ 5 times the upper limit of normal, prior to initiation of enoxaparin.³⁶ While bleeding due to antithrombotic prophylaxis in MIS-C is not common,^{35,37} this was seen in one of our patients and is an adverse outcome that needs to be monitored.

With the current management strategy, the outcomes in our series have been favourable with a lower ICU admission rate (50% versus reported range of 60–79%)^{22,23,28} and a comparable hospitalisation duration (median 6 days vs reported range 7–11 days),^{22,27,29} compared to those reported. Our patients also had good cardiac outcomes, with all cases of reduced cardiac function subsequently normalised. Long-term cardiac sequelae seen in echocardiograms were also uncommon, as observed in only 1 patient, in keeping with previous reports.^{27,29} Early diagnosis and administration of treatment likely contributed to the positive outcomes of our patients.

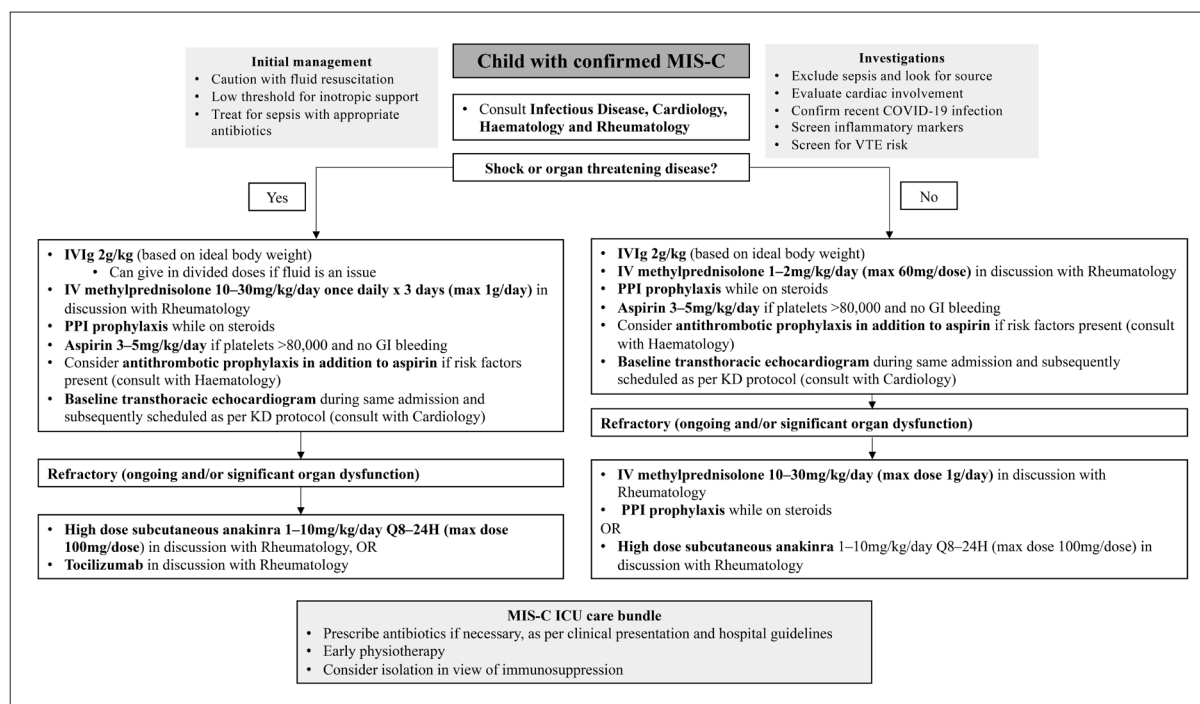


Fig. 1. Paediatric intensive care unit guidelines for multisystem inflammatory syndrome in children (MIS-C) of KK Women's and Children's Hospital (KKH) and National University Hospital (NUH), Singapore (published with permission from KKH and NUH).

GI: gastrointestinal; ICU: intensive care unit; IVIg: intravenous immunoglobulin; KD: Kawasaki disease; PPI: proton pump inhibitor; VTE: venous thromboembolic

More commonly reported long-term sequelae of MIS-C are symptoms of muscular fatigue, neurological sequelae, anxiety and emotional lability.²⁷ While this was seen in one of our patients, there may be underdiagnosis as we relied on self-reporting for such symptoms.

An important strategy to mitigate the risk of MIS-C is vaccination against COVID-19, which has been shown to be associated with a lower incidence of MIS-C in adolescents.³⁸ In the US, as of 31 October 2022, 46.2% and 25.2% out of 9,073 MIS-C cases reported to the Centers for Disease Control and Prevention occurred in children 5–11 years old and <1–4 years old, respectively,³⁹ underlining the importance of vaccinating these age groups as well. At the time of their infection, none of our patients were age-eligible for vaccination—11 would have been eligible based on current MOH recommendations, with the recent inclusion for children aged 6 months to 4 years.⁴⁰ Unvaccinated children remain at a higher risk for COVID-19 and consequent risk for MIS-C.

Our study is limited in that it is a retrospective, single-centre study with a small sample size. Nonetheless, KKH is the largest tertiary paediatric hospital in Singapore and would have likely received the majority of MIS-C cases. Timings for evaluation of

inflammatory markers and echocardiograms were not standardised, and it is possible that values and scans normalised earlier than detected. We also did not actively survey for other system outcomes, such as neurological and respiratory symptoms. Despite these limitations, to our knowledge, our study is the first series on MIS-C in Singapore and East Asia, with outcome data up to 6 months post-discharge.

CONCLUSION

Our study shows that children in Singapore are vulnerable to developing MIS-C especially during widespread community transmission of COVID-19, which may intensify with the arrival of new VOCs and relaxation of pandemic restrictions. Physicians should suspect MIS-C in febrile children with features of KD, and in children with recent COVID-19 infection together with gastrointestinal symptoms, shock, and haematologic abnormalities of coagulopathy, lymphopaenia and thrombocytopenia to diagnose MIS-C early and initiate prompt treatment with IVIg and steroids. The impact of the current Omicron surge on MIS-C incidence, and short- and long-term outcomes including side effects of treatment and non-cardiac sequelae, warrants continued surveillance and future studies.

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