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Cytokine and Whole-Genome Sequence Analysis in Korean Patients With Multisystem Inflammatory Syndrome in Children

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ABSTRACT

Background: Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious complication after coronavirus disease 2019. In South Korea, the Korea Disease Control and Prevention Agency has conducted national surveillance of MIS-C from May 2020 to March 2023. This project was carried out during the second phase of the surveillance, which included enhancements to the reporting system starting in August 2022. In addition to monitoring the epidemiological and clinical characteristics, we analyzed cytokine changes and genetic factors.
Methods: A user-friendly web-based reporting system using an electronic case report form (e-CRF) was established to provide clinicians in the field with easy access to reports. Cases collected from August 2022 to March 2023 were evaluated to confirm diagnoses, and unclassified cases from the prior research period were also reviewed. For patients who provided consent, serum cytokine measurements and whole-genome sequence analyses were conducted.
Results: In this study, 55 cases were confirmed as MIS-C. Of the 32 cases reported via e-CRF in the second period, 28 were confirmed as MIS-C. Among 31 cases reported but unclassified in the first period, 27 were subsequently confirmed as MIS-C. The median patient age was 7.8 years (range: 2 months to 16 years), with 54.5% (30/55) male. Clinically, 15 patients (27%) had abnormal echocardiography findings, and 5 (9.1%) required intensive care unit care. Steroids were administered to 45 patients (81.8%) and intravenous immunoglobulin to 46 (83.6%). No mortality occurred. In two patients, 17 serum cytokines were measured pre- and

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post-treatment, with interleukin (IL)-6, IL-17/IL-17A, IL-1ra/IL-1F3, IL-10, and CXC motif chemokine ligand 10 (CXCL10)/inducible protein 10 kDa (IP-10) peaking before treatment and decreasing afterward. Whole-genome sequencing in 6 patients revealed no previously reported MIS-C-associated genetic variants.
Conclusion: Continuous monitoring of MIS-C cases is essential, as some may develop serious complications. Clinicians should remain vigilant in diagnosing MIS-C, and further research is needed to elucidate its pathogenesis.

Keywords: Pediatric Multisystem Inflammatory Disease, COVID-19 Related; Cytokines; Whole Genome Sequencing; COVID-19

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is a severe hyperinflammatory condition associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] In May 2020, European and U.S. physicians reported children exhibiting Kawasaki disease (KD)-like symptoms,[2-4] including fever, variable rash, conjunctivitis, peripheral edema, and significant gastrointestinal symptoms accompanied by hyperinflammatory shock. Most had a recent SARS-CoV-2 infection or an epidemiological link to it. In response, the World Health Organization and the U.S. Centers for Disease Control and Prevention (CDC) each issued preliminary case definitions and case report forms for MIS-C in May 2020.[5,6]

In South Korea, the Korea Disease Control and Prevention Agency (KDCA) initiated national MIS-C surveillance and investigation in May 2020.[7] During the first surveillance period from June 2020 to April 2022, 91 cases were reported, most occurring during the Omicron wave. MIS-C cases during the Omicron wave exhibited less severe clinical manifestations compared to cases from the pre-Delta or Delta wave,[8] consistent with trends in other countries.[9]

Studies have reported elevated inflammatory cytokines and an expansion of T-cell clonotypes expressing the T-cell receptor *TRBV11-2* gene in MIS-C.[10,11] In addition, associations between MIS-C and genetic susceptibilities, such as autosomal recessive deficiencies of *OAS1*, *OAS2*, and *RNASEL* or defects in *SOCS1*, *XIAP*, or *CYBB,* have also been reported.[12-14] However, immunopathological studies on MIS-C remain rare in Asian countries.

In this study, we examined the epidemiological and clinical characteristics of MIS-C in South Korea during the second surveillance period, from August 2022 to April 2023. Additionally, cytokine kinetics and genetic analyses were conducted in patients who provided consent.

METHODS

Case collection

MIS-C surveillance, sponsored by the KDCA, initially took place from June 2020 to April 2022 and was extended for a second period from August 2022 to March 2023. To improve the collection of clinical, laboratory, and epidemiological data, a user-friendly web reporting system with an electronic case report form (e-CRF) was introduced.[15] This system allowed clinicians easier access to report MIS-C cases across Korea. Cases collected were reviewed

and evaluated according to the MIS-C definition,[8] and previously unclassified cases from the first period were also reassessed for MIS-C confirmation.

According to the national viral genomic surveillance,[16] periods were defined based on dominant Omicron subvariants: the BA.2 period (February 28, 2022–June 20, 2022), the BA.5 period (June 21, 2022–December 19, 2022), and the BA.2.75 period (December 20, 2022–March 28, 2023). We analyzed MIS-C patient characteristics by subvariant period, including clinical features (mucocutaneous symptoms, hypotension, respiratory difficulty, gastrointestinal and neurologic symptoms, abnormal echocardiography), past medical history, laboratory findings (complete blood count, chemistry, C-reactive protein, erythrocyte sedimentation rate), treatment, and clinical outcomes (intensive care unit [ICU] admission, survival status). The reference range for lymphocyte counts was defined based on age (0–1 year, 3,000–9,300 cells/μL; 1–2 years, 3,000–8,900 cells/μL; 2–7 years, 1,800–6,000 cells/μL; 7–12 years, 1,500–4,100 cells/μL; ≥ 12 years, 1,400–3,500 cells/μL).[17] Clinical comparisons across subvariant periods and comparison of clinical severity based on vaccination status or lymphocyte counts were performed using R (v.4.3.3; R Foundation for Statistical Computing, Vienna, Austria) with the moonBook package (v.0.3.1). For categorical variables, the χ^2 test or Fisher's exact test was employed, while the analysis of variance or Kruskal-Wallis test was used for continuous variables.

In selected centers, additional research on serum cytokine changes and whole-genome sequence (WGS) analyses was performed among MIS-C patients who provided consent.

Cytokine analysis

Cytokine analysis was conducted at pre-treatment, post-treatment day 1, day 3 (± 1), day 7 (± 1), and day 14 (± 3) using residual serum from routine clinical procedures. Th1, Th2, and Th17 cytokines and chemokines were measured and they included: tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), chemokine (C-C motif) ligand 3 (CCL3)/macrophage inflammatory protein (MIP)-1α, CXC motif chemokine ligand (CXCL) 10/IFN-γ inducible protein 10kDa (IP-10), CXCL11/interferon-inducible T-cell alpha chemoattractant (I-TAC), interleukin (IL)-4, IL-5, IL-13, IL-6, IL-17/IL-17A, CCL20/MIP-3α, CXCL1, interleukin-1 receptor antagonist (IL-1ra)/IL-1F3, IL-18/IL-1F4, MIP-3β/CCL19, MCP-1/CCL2, and IL-10. Cytokine and chemokine levels were assessed using multiplex enzyme-linked immunosorbent assay kits (Koma Biotechnology, Seoul, Korea) in accordance with the manufacturer's instructions.

Whole genome sequence analysis

Genome sequencing, analysis, and interpretation were performed using the RareVision system (Inocras, San Diego, CA, USA). Peripheral blood samples were obtained from MIS-C patients, and genomic DNA was extracted using Allprep DNA/RNA kits (Qiagen, Venlo, Netherlands). For whole-exome sequencing, exon regions were captured with the xGen Exome Research Panel v2 (Integrated NDA Technologies, Coralville, IA, USA). DNA libraries were prepared using TruSeq DNA PCR-Free Library Prep Kits (Illumina, San Diego, CA, USA) and sequenced on an Illumina NovaSeq6000 (Illumina) platform (30× mean depth of coverage). Genome sequences were aligned to the human reference genome (GRCh38/hg38) using the BWA-MEM algorithm.[18] PCR duplicates were removed with SAMBLASTER,[19] and initial mutation calling for base substitutions and short indels was conducted using HaplotypeCaller2[20] and Strelka2.[21] Structural variations were identified with Delly.[22] Variants were filtered, assessed for Mendelian inheritance, and analyzed for *de novo* mutations and

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mutational impact. Variants were then classified based on guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[23] To enhance pathogenicity prediction accuracy, we utilized an in-house software that organizes and incorporates updated database information.

Ethics statement

The present study on cytokine and WGS analyses was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB Nos: 2022-10-137 and 2020-08-020) with informed consent obtained from patients and/or their parents.

RESULTS

Epidemiologic and clinical characteristics

During this study period, a total of 55 cases were reported.[15] Among the 32 cases reported via the e-CRF during the second period, 28 were confirmed as MIS-C. Additionally, of the 31 previously reported unclassified cases from the first period, 27 were confirmed as MIS-C. Among the eight patients who were ruled out the MIS-C, the reasons for exclusion included an insufficient number of clinical manifestations to meet the diagnostic criteria for MIS-C (n = 3), the presence of an alternative pathogen or diagnosis (n = 2), a recent coronavirus disease 2019 (COVID-19) infection within less than two weeks, with the condition considered a severe manifestation of COVID-19 (n = 2), and an interval of more than 60 days between COVID-19 diagnosis and the onset of MIS-C symptoms (n = 1). The number of weekly MIS-C cases and pediatric coronavirus disease 2019 (COVID-19) cases is illustrated in **Fig. 1**. The median age of patients was 7.8 years (range: 2 months to 16 years), with males comprising 54.5% (30/55) of the cases. The median interval between confirmed COVID-19 infection and MIS-C admission was 38 days (interquartile range: 27–52 days). In terms of clinical presentation, most patients exhibited mucocutaneous manifestations (89%) and gastrointestinal symptoms (78%). Hypotension was observed in 25% of the MIS-C

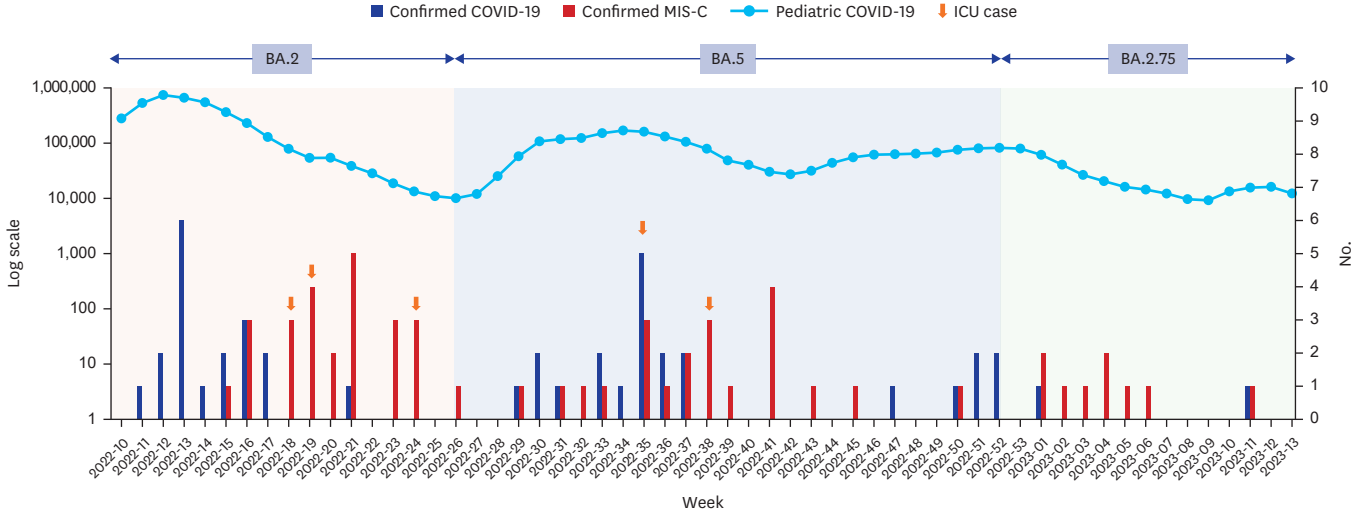


Fig. 1. Weekly severe acute respiratory syndrome coronavirus 2 exposures in MIS-C cases and their MIS-C occurrence (right axis), cases of ICU admission (arrow), and total number of pediatric COVID-19 cases (left axis, in log-scale) in South Korea. Periods by dominant Omicron variants: BA.2, Feb 28, 2022 to Jun 20, 2022; BA.5, Jun 20, 2022 to Dec 19, 2022; BA.2.75, Dec 19, 2023 to Mar 28, 2023.
COVID-19 = coronavirus disease 2019, MIS-C = multisystem inflammatory syndrome in children, ICU = intensive care unit.

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patients, and 15 patients (27%) had abnormal echocardiographic findings. Five patients (9.1%) required hospitalization in the ICU. Among the MIS-C patients, 38 patients (69%) had lymphopenia, while 17 patients (31%) had lymphocyte counts within the normal range. Of the five patients admitted to the ICU, four had an absolute lymphocyte count (ALC) of less than 1,500/μL, and three had an ALC below 1,000/μL. ICU admissions were more frequent in patients with lymphopenia (4/38, 10.5%) than in those with normal lymphocyte counts (1/17, 5.9%), although the difference was not statistically significant ($P = 0.963$). Echocardiographic findings did not differ significantly between the two groups (abnormal findings: 26.3% [10/38] in the lymphopenia group vs. 29.4% [5/17] in the non-lymphopenia group; $P > 0.999$).

White blood cell (WBC) count, absolute neutrophil count, ALC, and platelet count showed statistically significant variation across the dominant Omicron variant periods, with the lowest levels observed during the BA.2 period (**Table 1**). Steroids were administered to 45 patients (81.8%), while intravenous immunoglobulin (IVIG) was given to 46 patients (83.6%). Among the 55 patients, only two patients received vaccination had less severe clinical manifestations. None of the vaccinated patients exhibited abnormal echocardiographic findings (vaccination group vs. non-vaccination group, 0% vs. 28.3%), and none required ICU admission (vaccination group vs. non-vaccination group, 0% vs. 9.4%).

Cytokine analysis

In two patients, 17 types of serum cytokines were measured before and after treatment (**Fig. 2A-D**). Cytokine measurements were conducted using serial specimens obtained from the two patients (P1 and P2). P1, a 2-month-old girl, presented to the hospital with a fever that began one day prior to admission. She developed a skin rash, bilateral conjunctival injection, lip erythema, edema of the hands and feet, diarrhea, vomiting, and a cough. The patient had a SARS-CoV-2 infection at 3 weeks of age, and no pathogens were identified at the time of hospitalization. Before treatment, P1 exhibited a leukocytosis with a neutrophil-dominant pattern (**Fig. 2E**). After receiving intravenous steroids and immunoglobulin on the third day of admission, she made a full recovery. Additionally, by day 6 of treatment, leukocytosis with lymphocytosis was observed (**Fig. 2E**). P2, a 12-month-old boy, had a history of COVID-19 infection one month before admission. He presented with a fever lasting five days, accompanied by bilateral conjunctival injection, lip erythema, and edema of the hands and feet. At admission, leukocytosis with a neutrophil-dominant pattern (**Fig. 2E**). The patient showed clinical improvement following intravenous steroid treatment. By day 6, leukocyte count had decreased to normal range (**Fig. 2E**). Neither patient required intensive care or experienced cardiac complications.

In both patients, IL-6, IL-17/IL-17A, IL-1ra/IL-1F3, IL-10, and CXCL10/IP-10 exhibited a pattern of peaking before treatment initiation and subsequently decreasing after treatment (**Fig. 2A**). Additionally, in one patient, IFN-γ, TNF-α, IL-18/IL-1F4, CCL20/MIP-3α, CCL19/MIP-3β, and CXCL11/I-TAC also peaked before treatment and decreasing afterward in one of the two patients (**Fig. 2B**). CCL3/MIP-1α and MCP-1/CCL2 levels remained above the reference value following treatment (**Fig. 2C**). IL-4, IL-5, IL-13, and CXCL1 either increased to a peak after treatment or were measured below the reference value (**Fig. 2D**).

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Table 1. Demographics and clinical characteristics of patients with multisystem inflammatory syndrome in children by dominant variants of severe acute respiratory syndrome coronavirus 2

Variables	Period by variants[a]			*P* value
	BA.2 (n = 25)	BA.5 (n = 21)	BA.2.75 (n = 9)	
Sex (Male)	19 (76.0)	8 (38.1)	3 (33.3)	0.014
Age, yr	7.3 (0.2–17)	8.3 (0.2–14.4)	5.5 (0.3–12.8)	0.419
Vaccination	1 (4.0)	1 (4.8)	0 (0)	0.155
Past medical history[b]	1 (6.7)	3 (15.8)	0 (0)	0.369
Confirmed COVID-19				0.626
By PCR	22 (88.0)	19 (90.5)	7 (77.8)	
By epidemiological link or antibody test	3 (12.0)	2 (9.5)	2 (22.2)	
Interval between confirmed COVID-19 and MIS-C admission, days	46.5 (25.0–83.0)	36.5 (7.0–58.0)	29.0 (25.0–48.0)	0.053
Clinical manifestations				
Mucocutaneous	23 (92.0)	17 (81.0)	9 (100)	0.253
Hypotension	4 (17.4)	9 (42.9)	1 (11.1)	0.083
Respiratory difficulty	6 (24.0)	9 (42.9)	0 (0)	0.048
GI symptoms	21 (84.0)	17 (81.0)	5 (55.6)	0.193
Neurologic symptoms	5 (23.8)	8 (40.0)	0 (0)	0.072
Abnormal echocardiography	7 (28.0)	6 (28.6)	2 (22.2)	0.932
Intensive care unit	3 (12.0)	2 (9.5)	0 (0)	0.56
Laboratory findings				
WBC (10^3/mL)	8.5 ± 4.3	9.1 ± 4.6	14.9 ± 4.7	0.002
ANC (10^3/mL)	6.0 ± 3.7	6.7 ± 3.8	10.5 ± 3.9	0.011
ALC (10^3/mL)	1.2 ± 1.2	1.7 ± 1.3	3.3 ± 2.8	0.005
Hemoglobin (g/dL)	12.0 ± 1.1	11.6 ± 1.4	11.1 ± 1.8	0.205
Platelet (10^3/mL)	178.2 ± 103.1	181.5 ± 143.0	296.1 ± 109.9	0.038
Procalcitonin (ng/mL)	2.6 ± 2.2	1.7 ± 2.1	2.6 ± 5.7	0.629
CRP (mg/dL)	9.2 ± 6.8	10.4 ± 8.1	13.0 ± 6.1	0.420
ESR (mm/hr)	28.6 ± 14.7	33.1 ± 29.5	54.4 ± 36.3	0.054
Total bilirubin (mg/dL)	1.2 ± 1.7	0.7 ± 0.6	0.5 ± 0.3	0.216
AST (IU/L)	87.7 ± 118.3	59.6 ± 60.6	28.9 ± 12.1	0.216
ALT (IU/L)	81.6 ± 76.0	55.2 ± 63.7	25.0 ± 15.1	0.078
BUN (mg/dL)	9.8 ± 4.8	11.6 ± 8.5	9.7 ± 6.2	0.628
Creatinine (mg/dL)	0.5 ± 0.2	0.5 ± 0.3	0.5 ± 0.6	0.977
Albumin (g/dL)	3.3 ± 0.7	3.5 ± 0.7	3.2 ± 0.7	0.674
LDH (IU/L)	399.3 ± 154.6	407.8 ± 223.6	310.9 ± 77.7	0.383
Treatment				
Steroid	18 (72.0)	19 (90.5)	8 (88.9)	0.225
IVIG	23 (92.0)	18 (85.7)	5 (55.6)	0.038
Aspirin	18 (72.0)	12 (57.1)	7 (77.8)	0.431
Inotrophics	2 (8.0)	5 (23.8)	0 (0)	0.126

Values are presented as number (%), mean ± standard deviation, or median (range).
COVID-19 = coronavirus disease 2019, PCR = polymerase chain reaction, MIS-C = multisystem inflammatory syndrome in children, GI = gastrointestinal, WBC = white blood cell, ANC = absolute neutrophil count, ALC = absolute lymphocyte count, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, AST = aspartate transaminase, ALT = alanine transaminase, BUN = blood urea nitrogen, LDH = lactate dehydrogenase, IVIG = intravenous immunoglobulin.
[a]Period by dominant Omicron variants: BA.2, Feb 28, 2022 to Jun 20, 2022; BA.5, Jun 20, 2022 to Dec 19, 2022; BA.2.75, Dec 19, 2023 to Mar 28, 2023. [b]History of prematurity (n = 1), history of leukemia (n = 1), congenital heart disease (n = 1), and history of meningitis without complication (n = 1).

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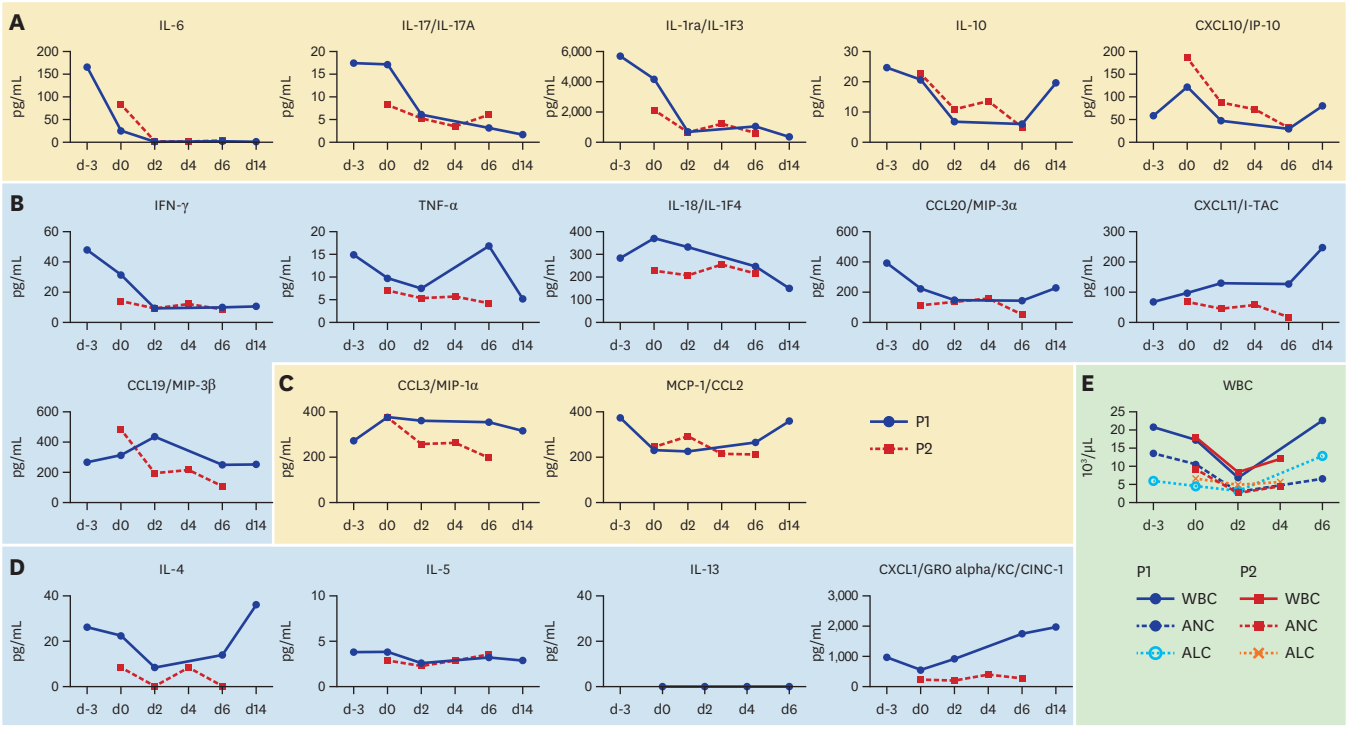


Fig. 2. Cytokine kinetics and WBC changes of two patients with multisystem inflammatory syndrome in children by treatment. (**A**) Cytokines with peak levels before treatment that decreased after treatment in both patients. (**B**) Cytokines with peak levels before treatment that decreased after treatment in one of the two patients. (**C**) Cytokines remaining above the reference value after treatment. (**D**) Cytokines increasing to a peak after treatment or measured below the reference value. (**E**) Temporal changes in WBC, ANC, and ALC during the treatment period.
d = day of treatment, d0 = the day of treatment initiation, WBC = white blood cell, ANC = absolute neutrophil count, ALC = absolute lymphocyte count.

Table 2. Genetic variants associated with multisystem inflammatory syndrome in children based on a literature review

Genetic variants	No.	Ethnicity	Study population	References
OAS1 deficiency (AR)	1	1 Filipino	558 MIS-C patients originating from Europe, Africa, Asia, and America	Lee et al.[12]
OAS2 deficiency (AR)	3	1 Spanish 2 Turkish		
RNase L deficiency (AR)	1	1 French Canadian		
SOCS1	1	NA	1 case only	Lee et al.,[13] Chou et al.[14]
XIAP	1	NA	13 Hispanic (5 white, 1 black, 7 others), 5 non-Hispanic (2 white, 1 black, 1 Asian, 1 other)	Chou et al.[14]
CYBB	1	NA		
HLA-A*02, B*35, C*04	5	5 European	6 European, 2 African	Sacco et al.[10]
PRF1	1	1 Guyanese	39 MIS-C patients including Hispanic, African American, Caucasian, Greek, and Southeast Asian	Vagrecha et al.[24]
LYST	2	1 African American, 1 Hispanic		
AP3B1	1	1 African American		
DOCK8	4	2 African American, 2 Hispanic		
UNC13D	1	1 Guyanese		
STXBP2	1	1 African American		
STX11	1	1 North Indian	1 case only	Vagrecha et al.[25]

AR = autosomal recessive, MIS-C = multisystem inflammatory syndrome in children, NA = not applicable.

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Table 3. Summary of clinical characteristics and outcomes of the multisystem inflammatory syndrome in children patients who underwent cytokine and/or genetic analyses

Patients	Sex/age	Cytokine analysis	WGS	Underlying disease	Clinical manifestations					ICU care	Outcome
					Mucocutaneous	GI	Hypotension	Neurology	Respiratory		
P1	F/2 mon	Done	NA	None	Y	Y	N	N	Y	N	Survived
P2	M/12 mon	Done	Undetected	None	Y	N	N	N	N	N	Survived
P3	F/11 yr	NA	Undetected	None	Y	N	Y	N	N	Y	Survived
P4	M/12 yr	NA	Undetected	None	Y	N	Y	N	N	Y	Survived
P5	M/3 yr	NA	Undetected	None	Y	Y	N	N	N	N	Survived
P6	M/7 yr	NA	Undetected	None	Y	Y	N	N	Y	Y	Survived
P7	M/5 yr	NA	Undetected	None	Y	N	N	N	N	N	Survived

WGS = whole genome sequencing, GI = gastrointestinal, ICU = intensive care unit, NA = not applicable, Y = yes, N = no.

Whole genome sequence analysis

In six patients (P2–P7), whole genome sequence analyses were performed, and previously reported genetic variants associated with MIS-C were not observed (**Table 2**). Half of these patients required intensive care due to hypotension, ascites, or pleural effusion. Their clinical characteristics are summarized in **Table 3**. Notably, there were no fatal cases.

DISCUSSION

This study represents the first immunological investigation of cytokine kinetics and genetic analysis in MIS-C patients during the Omicron wave in South Korea. Patients with MIS-C during this period exhibited relatively lower severity. The levels of serum cytokines, including IL-6, IL-17/IL-17A, IL-1ra/IL-1F3, IL-10, and CXCL10/IP-10, increased at presentation and decreased after treatment, with no genetic variants identified.

In a study conducted in the U.S., 61% of MIS-C patients were admitted to the ICU, and 25% required inotropics during the pre-Delta wave.[26] McCrindle et al.[27] reported that MIS-C patients during the Omicron wave experienced a less severe clinical course, with clinical features more often resembling those of KD than in earlier periods. According to the first surveillance period, the clinical manifestations of MIS-C during the Omicron wave were generally less severe than those during the pre-Delta and Delta dominant waves in South Korea.[8] This study focused on the Omicron wave, where most patients developed mild clinical manifestations. Additionally, while the number of ICU hospitalizations and patients requiring inotropics decreased toward the BA2.75 period in our study, this decline was not statistically significant. A recent study suggested that lymphopenia could be a predictor of disease severity in MIS-C.[28] Although statistical significance was not observed in our study, most of the ICU patients demonstrated lymphopenia.

MIS-C presents various phenotypes, making differential diagnosis essential when suspecting this condition in patients. According to the Kaneta et al.,[29] 54% of patients who were concerned for MIS-C at the time of presentation were ultimately ruled out and categorized as “MIS-C mimickers,” including infectious diseases (79%), rheumatologic disorders (5%), and cardiac diagnoses (4%). The spread of various respiratory viruses after pandemic and the relatively milder manifestations of MIS-C have made it challenging to distinguish MIS-C from other diseases. However, in our study, through surveillance via e-CRF with logical screening processes, we ensured that cases not meeting the diagnostic criteria for MIS-C were not reported. Additionally, we conducted expert consultations on ambiguous cases despite screening through e-CRF surveillance. Through this process, we believe that

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the confirmed MIS-C cases in our study are highly reliable, resulting in the exclusion of eight patients. Nevertheless, diagnosing MIS-C remains challenging in clinical practice. Therefore, further studies are needed to define precise diagnostic criteria and identify reliable biomarkers for MIS-C.

Overexpression of certain innate immunological pathways may contribute to severe manifestations and complications in MIS-C patients.[30-32] Certain signaling pathways, such as the NLRP3 inflammasome and NF-κB signaling activated by viral recognition within infected cells, can lead to the excessive production of pro-inflammatory cytokines and chemokines.[31,33] The adaptive immune system also contributes to COVID-related hyperinflammatory syndromes.[33] Previous reports have demonstrated that cytokines and chemokines, including IL-6,[26,32,34-38] IL-17/IL-17A,[36-38] IL-1ra/IL-1F3,[34] IL-10,[10,26,34,36,38,39] CXCL10/IP-10,[10,37,38] IFN-γ,[10,36,38-40] TNF-α, [36,39] CCL20/MIP-3α,[38] CXCL11/I-TAC,[38] MCP-1/CCL2,[38] and CCL3/MIP-1α[38] are elevated in MIS-C patients. In this study, we observed that IL-6, IL-17/IL-17A, IL-1ra/IL-1F3, IL-10, and CXCL10/IP-10 levels were significantly higher in the pre-treatment samples compared to the post-treatment samples.

In several studies measuring serial cytokine levels in MIS-C patients, a rapid decrease in multiple cytokines was observed following treatment with steroids and/or IVIG.[34,35,41] In particular, Takasago et al.[35] highlighted the dynamics of 71 cytokines in MIS-C patients, while Butters et al.[34] reported a distinct elevation in serum levels of IL-1ra, IL-10, IL-6, MCP-1, and TNF-α at presentation. Following treatment with IVIG and/or methylprednisolone, these cytokines demonstrated a rapid decrease. Among the cytokines measured in our study, we also noted that IFN-γ, TNF-α, IL-6, IL-17/IL-17A, IL-10, IL-18/IL-1F4, IL-1ra/IL-1F3, CXCL10/IP-10, CXCL11/I-TAC, CCL20, and MIP-3β/CCL19 exhibited similar trends peaking at presentation and rapidly decreasing after treatment.

Among the 17 cytokines measured in this study, those that showed a peak pattern before treatment and a decrease after therapy in both patients included IL-6, IL-17/IL-17A, IL-10, IL-1ra/IL-1F3, and CXCL10/IP-10. Due to its pleiotropic properties, IL-6 plays a pivotal role in the pathogenesis of inflammatory diseases or cytokine storms.[42] In addition, IL-17 is a potent pro-inflammatory cytokine known to increase in production under the combined influence of IL-6 and transforming growth factor-β.[43] IL-1ra is a cytokine that belongs to the IL-1 superfamily. In patients with MIS-C, autoantibodies against IL-1ra have been reported, which impair its bioactivity and lead to excessive IL-1 signaling, suggesting that the impairment of IL-1ra bioactivity may be associated with excessive IL-1 signaling in MIS-C.[44] These cytokines are thought to play an essential role in the pathophysiology of MIS-C. However, IL-6 levels may also increase in conditions such as KD,[37,45] critical COVID-19[38,46] and other critical conditions, including septic shock and toxic shock syndrome.[47] Furthermore, an increase in IL-1ra may indicate activation of the innate immune response via the IL-1 pathway, which resembles the mechanisms observed in macrophage activation syndrome, toxic shock syndrome, and KD.[32] Elevations in IL-6, IL-17, IL-1ra, and IL-10 have been reported in both MIS-C and KD.[30]

CXCLs regulate inflammation and immune responses by guiding the migration of leukocytes, including neutrophils, monocytes, and macrophages.[48] In a study assessing cytokine profiles based on the presence or absence of cardiovascular involvement, CXCL1 and CXCL2 levels decreased following treatment in MIS-C patients with cardiovascular abnormalities.[41] Additionally, a study conducted in Japan measured cytokine kinetics in a single MIS-C patient with reduced cardiac function, revealing peaks in CXCL1 and CXCL2

during the early stages of the disease. This suggests that CXCL1 and CXCL2 may indicate neutrophil activation's role in the pathogenesis of MIS-C.[35] In our study, CXCL1, MCP-1/CCL2, and CXCL11/I-TAC levels increased significantly in the later stages of the disease. Notably, our patients exhibited no abnormal findings on echocardiography, indicating that this milder disease course may be associated with a lack of robust chemokine responses.

In MIS-C, elevated levels of cytokines and chemokines contribute to a hyperinflammatory state characterized by extensive immune cell recruitment, activation, and tissue damage. Cytokines such as IL-6, IL-17, IFN-γ, and TNF-α drive the pro-inflammatory response, while IL-10 and IL-1ra represent the body's attempts to mitigate this inflammation. Chemokines like CXCL10, CCL20, CXCL11, MCP-1/CCL2, and CCL3 facilitate the recruitment of various immune cells, perpetuating the inflammatory cycle and contributing to the multisystem involvement seen in MIS-C. Understanding these dynamics is crucial for developing targeted therapies to manage the condition effectively; however, this study did not identify any specific cytokines associated with MIS-C. Further research is needed to discover biomarkers unique to this condition.

It has been reported that cytokines such as IL-1β, IL-6, IFN-α, granulocyte macrophage-colony stimulating factor, and high-mobility group box 1 exhibit significant upregulation, particularly in severe MIS-C cases compared to mild MIS-C or mild COVID-19.[49] Studies of COVID-19 in adults have indicated that excessive cytokine production correlates with disease severity.[50] Due to the mild symptoms observed in the patients whose cytokine responses were analyzed, the cytokine profile in this study also did not reflect a robust response.

Depending on the cohort, the reported prevalence of genetic defects associated with MIS-C ranges from 0.9% to 25%.[12,14,25] Genetic mutations linked to immune dysregulation, such as *SOCS1, XIAP,* and *CYBB*[13,14] as well as those related to familial hemophagocytic lymphohistiocytosis or cytokine storm syndrome (including *PRF1, UNC13D, STX11, STXBP2, LYST, AP3B1,* and *STX11*),[24,25] and certain HLA allele combinations (HLA-A*02, HLA-B*35, and HLA-C*04)[10,51] have been identified in MIS-C patients. However, none of the six patients analyzed in this study exhibited genetic defects associated with MIS-C. KD which presents clinical manifestations similar to MIS-C, occurs in Northeast Asia, particularly in Japan and Korea, and is rare in Western populations.[52] In contrast, MIS-C has predominantly been reported in Hispanic and non-Hispanic Black children.[53,54] Lee et al.[26] suggested that MIS-C and KD may have distinct genetic predispositions. We were only able to perform genetic testing in six patients due to limited research funding, and none of them were found to have pathogenic variants. In a previous large multicenter study involving 558 patients, only five individuals were found to carry genetic variants.[13] Given this low prevalence, it is not unexpected that no variants were identified in our small cohort. Moreover, there is a lack of studies focusing on East Asian populations, as most research on genetic variants associated with MIS-C has been conducted in Western populations.[10,12-14,24] In a large multicenter study, fewer than ten East Asian MIS-C patients were included—none of whom live in Korean—and no rare *OAS1*, *OAS2* or *RNASEL* variants were identified among them (as confirmed through direct correspondence with the author).[12] These findings underscore the need for further research specifically targeting East Asian populations to better understand potential genetic susceptibilities.

This study has several limitations. First, there was no control group to compare cytokine responses. Second, only a small number of children with MIS-C were investigated for

genetic variants, and cytokine analysis was conducted on only two MIS-C patients with mild manifestations. Further analysis with a larger cohort is necessary to identify additional genetic associations and understand the immunopathogenesis of MIS-C within the Asian population. Third, although the CDC updated the case definition for MIS-C in January 2023, this study adhered to the previous definition to maintain consistency in surveillance. Finally, as the pandemic progressed, non-pharmaceutical interventions such as social distancing and mask-wearing were relaxed, leading to a decrease in COVID-19 testing. This shift resulted in an increase in infections from other respiratory viruses and a decline in reported MIS-C cases, complicating the differential diagnosis with other diseases like KD.

Although the national surveillance system has been discontinued, sporadic cases of COVID-19 continue to occur, and severe complications can still develop. Clinicians should remain vigilant in diagnosing MIS-C, and additional research is essential to elucidate the pathogenesis of this condition in the future.

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