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Research Article

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Gastrointestinal Manifestations and Disease Severity in Children with Multisystem Inflammatory Syndrome: A Retrospective Cohort Study

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ABSTRACT

Background: Multisystem inflammatory syndrome in children (MIS-C) is a post-infectious hyperinflammatory complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Gastrointestinal manifestations are common, but their relationship with disease severity remains uncertain.

Objective: To evaluate the association between gastrointestinal manifestations and MIS-C severity and to characterize clinical and laboratory features associated with severe disease.

Methods: This retrospective cohort study included 122 consecutive patients aged 0–17 years who were diagnosed with MIS-C at a tertiary pediatric referral center in Tbilisi, Georgia, between 2020 and 2023. Patients were classified as having moderate (n=82) or severe (n=40) disease. Categorical variables were compared using Pearson's chi-square test, and continuous variables were analyzed using the independent-samples t test or Mann–Whitney U test, as appropriate. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for clinical manifestations.

Results: Gastrointestinal manifestations were present in 84 patients (68.9%) and were more frequent in moderate than severe MIS-C (76.8% vs 52.5%; p=0.006). Gastrointestinal involvement was associated with lower crude odds of severe disease (OR 0.33, 95% CI 0.15–0.75). Severe MIS-C was associated with neurocognitive manifestations (OR 5.10, 95% CI 1.43–18.16), respiratory involvement (OR 6.33, 95% CI 2.51–15.97), shock (OR 32.73, 95% CI 7.05–151.93), and Kawasaki-like manifestations (OR 12.68, 95% CI 3.36–47.90). Severe disease was also associated with higher body temperature, erythrocyte sedimentation rate, neutrophilia, and C-reactive protein. Thrombocytopenia and D-dimer did not differ significantly between groups.

Conclusions: Gastrointestinal manifestations were common but occurred more frequently in moderate MIS-C, suggesting that they may represent an early or clinically prominent inflammatory phenotype rather than an isolated marker of advanced disease. Severe MIS-C was characterized primarily by hemodynamic instability, respiratory and neurocognitive involvement, Kawasaki-like features, and greater inflammatory activity. Prospective multicenter studies are needed to determine the independent prognostic value of specific gastrointestinal manifestations.

Keywords: Multisystem Inflammatory Syndrome in Children, Mis-C, Sars-Cov-2, Gastrointestinal Manifestations, Abdominal Pain, Vomiting, Diarrhea, Disease Severity, Inflammatory Biomarkers

Introduction

Multisystem inflammatory syndrome in children (MIS-C) emerged in 2020 as a rare but potentially life-threatening complication of SARS-CoV-2 infection. Initial reports from the United Kingdom, continental Europe, and the United States described children presenting with persistent fever, hyperinflammation, gastrointestinal symptoms, mucocutaneous findings, myocardial dysfunction, and shock several weeks after community peaks of coronavirus disease 2019 (COVID-19) [1-6]. Although acute SARS-CoV-2 infection is generally milder in children than in adults, MIS-C can progress rapidly and frequently requires intensive monitoring, vasoactive support, and immunomodulatory treatment [7-10].

MIS-C is considered a delayed immune-mediated disorder rather than a manifestation of uncontrolled viral replication. Most

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affected patients have serological evidence of previous SARS-CoV-2 infection, whereas molecular testing may be negative at presentation. Proposed mechanisms include dysregulated innate and adaptive immunity, expansion of activated T-cell and B-cell populations, cytokine release, complement activation, endothelial injury, and microvascular inflammation [11-16]. These processes contribute to myocardial dysfunction, vasoplegia, coagulopathy, gastrointestinal inflammation, neurologic abnormalities, and other forms of multisystem injury.

The World Health Organization (WHO), the US Centers for Disease Control and Prevention (CDC), and professional societies developed clinical and surveillance definitions based on fever, systemic inflammation, multisystem involvement, evidence of SARS-CoV-2 infection or exposure, and exclusion of alternative diagnoses [17-20]. Definitions evolved during the pandemic, but gastrointestinal involvement has remained a central component of the recognized clinical spectrum.
Gastrointestinal symptoms are reported in approximately 60%–90% of children with MIS-C and commonly include abdominal pain, vomiting, and diarrhea [5,8,21-25]. In some patients, severe abdominal pain and imaging abnormalities mimic appendicitis, terminal ileitis, mesenteric adenitis, pancreatitis, or other surgical conditions [26–30]. The high expression of angiotensin-converting enzyme 2 in intestinal epithelial cells initially raised the possibility of direct viral gastrointestinal injury. However, the delayed timing of MIS-C, the low frequency of persistent viral detection, and evidence of systemic endothelial and immune activation support a predominantly post-infectious inflammatory mechanism [31-34].

The prognostic significance of gastrointestinal involvement remains uncertain. Some studies have associated severe gastrointestinal disease with hospitalization, intensive care, inflammatory abnormalities, or surgical complications [26,27]. Other multicenter analyses found that gastrointestinal involvement was not independently associated with critical illness, length of stay, or mortality after adjustment for relevant covariates [25]. Differences in symptom definitions, disease stage, referral patterns, and the distinction between common gastrointestinal symptoms and organ-specific complications may explain these inconsistent findings.

Most published MIS-C cohorts originate from North America and Western Europe, whereas data from Eastern Europe and the South Caucasus remain limited. Regional evidence is important because healthcare access, referral pathways, population characteristics, circulating variants, and treatment practices may influence presentation and measured outcomes. We therefore evaluated the association between gastrointestinal manifestations and clinical severity in children with MIS-C treated at a tertiary pediatric center in Georgia. We also compared major clinical manifestations and inflammatory laboratory variables between moderate and severe disease groups.

Materials and Methods

Study Design and Setting

This retrospective, single-center cohort study was conducted at Iashvili Children Central Hospital, a tertiary pediatric referral center in Tbilisi, Georgia. Consecutive children and adolescents diagnosed with MIS-C between January 2020 and December 2023 were evaluated. Reporting was guided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [35].

Participants and Diagnostic Criteria

The study included 122 hospitalized patients aged 0–17 years with a clinical diagnosis of MIS-C and evidence of previous SARS-CoV-2 infection or epidemiologic exposure. Diagnosis required persistent fever, laboratory evidence of systemic inflammation, involvement of at least two organ systems, and exclusion of a more plausible alternative diagnosis, in accordance with WHO and CDC definitions applicable during the study period [17-19]. Patients with insufficient clinical documentation, an alternative diagnosis explaining the inflammatory syndrome, or inadequate information for severity classification were excluded.

Severity Classification

Patients were categorized as having moderate (n=82) or severe (n=40) MIS-C according to the clinical condition documented at admission or during the early hospitalization period. Severe disease was characterized by major organ dysfunction, including hemodynamic instability or shock, clinically significant respiratory compromise, severe neurologic involvement, myocardial dysfunction, the need for vasoactive or advanced supportive treatment, or management in a pediatric intensive care setting. Because shock and advanced respiratory compromise contributed to severity classification, their associations with severe disease are descriptive and should not be interpreted as independent prognostic effects.

Data Collection and Variable Definitions

Demographic, clinical, and laboratory data were extracted from medical records and entered into a structured database. Variables included age, sex, disease severity, body temperature, gastrointestinal, neurocognitive and respiratory manifestations, shock, Kawasaki-like features, erythrocyte sedimentation rate (ESR), lymphocyte-, neutrophil-, platelet- and anemia-related variables, C-reactive protein (CRP), and D-dimer.

Gastrointestinal involvement was defined as documented abdominal pain, vomiting, or diarrhea and was analyzed as a composite binary variable. Neurocognitive involvement included altered mental status, confusion, somnolence, irritability, headache, behavioral change, or another documented neurologic or cognitive abnormality. Respiratory involvement included tachypnea, respiratory distress, hypoxemia, or requirement for oxygen or advanced respiratory support. Shock was defined according to documented hypotension, impaired tissue perfusion, or need for vasoactive or inotropic support. Kawasaki-like manifestations included conjunctival injection, rash, oral mucosal changes, extremity changes, or cervical lymphadenopathy.

Outcomes

The primary outcome was the association between gastrointestinal manifestations and MIS-C severity. Secondary outcomes included between-group differences in neurocognitive and respiratory manifestations, shock, Kawasaki-like features, body temperature, ESR, lymphocytopenia, neutrophilia, thrombocytopenia, anemia, CRP, and D-dimer.

Statistical Analysis

Analyses were performed using IBM SPSS Statistics, version 27. Categorical variables are presented as frequencies and percentages and were compared using Pearson's chi-square test. Continuous variables are presented as mean ± standard deviation when the available analysis supported parametric reporting. The independent-samples t test was used for ESR, whereas non-normally distributed or ordinal variables were compared using the Mann–Whitney U test. Crude ORs and 95% CIs were calculated from 2×2 tables for clinical manifestations. All tests were two-sided, and $p<0.05$ was considered statistically significant. The analysis was exploratory, no formal adjustment for multiple comparisons was applied.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Iashvili Children Central Hospital (approval number: [insert approval number]). Because of the retrospective design and use of anonymized routinely collected data, the requirement for individual informed consent was waived in accordance with institutional regulations.

Results

Study Population

A total of 122 patients were included. Seventy-two (59.0%) were male and 50 (41.0%) were female. Age ranged from birth to 17 years, with a mean of 7.33±4.72 years. Eighty-two patients (67.2%) had moderate MIS-C and 40 (32.8%) had severe disease (Table 1).

Table 1: Demographic and General Characteristics of the Study Cohort

Characteristic	Total cohort (N=122)
Age, mean ± SD, years	7.33 ± 4.72
Age range, years	0–17
Male sex, n (%)	72 (59.0)
Female sex, n (%)	50 (41.0)
Moderate MIS-C, n (%)	82 (67.2)
Severe MIS-C, n (%)	40 (32.8)
Study period	2020–2023

Clinical Manifestations and Severity

Table 2: Clinical Manifestations According to MIS-C Severity

Manifestation	Moderate n=82, n (%)	Severe n=40, n (%)	χ^2	p value	Crude OR*	95% CI
Gastrointestinal manifestations	63 (76.8)	21 (52.5)	7.42	0.006	0.33	0.15–0.75
Neurocognitive manifestations	58 (70.7)	37 (92.5)	7.39	0.007	5.10	1.43–18.16
Respiratory manifestations	35 (42.7)	33 (82.5)	17.28	<0.001	6.33	2.51–15.97
Shock	2 (2.4)	18 (45.0)	36.17	<0.001	32.73	7.05–151.93
Kawasaki-like manifestations	3 (3.7)	13 (32.5)	19.63	<0.001	12.68	3.36–47.90

*Crude odds of severe disease among patients with versus without the specified manifestation. CI, confidence interval, OR, odds ratio.

Gastrointestinal manifestations were documented in 84 patients (68.9%). They were significantly more frequent in moderate than severe disease (76.8% vs 52.5%, $\chi^2=7.42$, $p=0.006$). The crude odds of severe MIS-C were lower among patients with gastrointestinal manifestations (OR 0.33, 95% CI 0.15–0.75).

Neurocognitive manifestations occurred in 70.7% of moderate and 92.5% of severe cases and were associated with increased crude odds of severe disease (OR 5.10, 95% CI 1.43–18.16). Respiratory involvement was present in 42.7% and 82.5%, respectively (OR 6.33, 95% CI 2.51–15.97). Shock was recorded in 2.4% of moderate and 45.0% of severe cases (OR 32.73, 95% CI 7.05–151.93). Kawasaki-like manifestations were documented in 3.7% and 32.5%, respectively (OR 12.68, 95% CI 3.36–47.90).

Temperature and Inflammatory Variables

Table 3: Body temperature and ESR According to Disease Severity. ESR, Erythrocyte Sedimentation Rate, Sd, Standard Deviation

Variable	Moderate MIS-C	Severe MIS-C	Test statistic	p value
Body temperature, mean ± SD, °C	40.01 ± 0.71	40.55 ± 0.50	U=978.0, Z=−3.942	<0.001
ESR, mean ± SD	42.27 ± 14.24	48.03 ± 16.17	t(120)=−2.004	0.047

Body temperature was significantly higher in severe MIS-C (40.55±0.50°C) than in moderate disease (40.01±0.71°C, U=978.0, Z=−3.942, $p<0.001$). ESR was also higher in severe disease (48.03±16.17 vs 42.27±14.24, t[120]=−2.004, $p=0.047$).

Other Laboratory Variables

Table 4: Mann–Whitney U Test Results for Laboratory Variables

Laboratory variable	Moderate mean rank	Severe mean rank	Mann–Whitney U	Z	p value
Lymphocytopenia	70.78	42.48	879.00	−4.160	<0.001
Neutrophilia	55.20	72.75	1150.00	−2.596	0.009

Thrombocytopenia	65.84	52.61	1284.50	−1.939	0.053
Anemia	67.71	48.76	1130.50	−2.780	0.005
C-reactive protein	55.30	74.21	1131.50	−2.776	0.005
D-dimer	45.31	45.94	838.50	−0.106	0.916

The direction of lymphocytopenia, thrombocytopenia, and anemia findings should be confirmed from the original coding and absolute laboratory values before submission.

Neutrophilia and CRP ranks were significantly higher in severe disease. Thrombocytopenia and D-dimer did not differ significantly between groups. The statistically significant rank differences for lymphocytopenia and anemia cannot be interpreted conclusively without confirmation of variable coding and reporting of absolute values.

Discussion

This study evaluated gastrointestinal manifestations and disease severity in 122 children with MIS-C treated at a tertiary pediatric center in Georgia. Gastrointestinal symptoms were present in approximately two-thirds of patients but were significantly more frequent in moderate than severe disease. In contrast, severe MIS-C was characterized by respiratory and neurocognitive involvement, shock, Kawasaki-like manifestations, higher fever, and greater inflammatory activity. These findings suggest that common gastrointestinal symptoms may identify a clinically prominent or earlier inflammatory phenotype, whereas severe disease is defined primarily by progressive multisystem dysfunction.

The prevalence of gastrointestinal involvement in this cohort (68.9%) is consistent with systematic reviews and multicenter studies reporting rates of approximately 60%–90% [21-25]. Abdominal pain, vomiting, and diarrhea are often among the earliest manifestations and may lead to evaluation in emergency or surgical settings. Severe gastrointestinal complications, including appendicitis-like presentations, ileitis, abdominal fluid collections, pancreatitis, and intussusception, have also been described [26–30]. Importantly, the composite exposure used in the present study captured common symptoms rather than radiologically or surgically defined severe gastrointestinal disease.

The inverse crude association between gastrointestinal manifestations and severe disease should not be interpreted as protective. Several mechanisms may explain this pattern. Prominent abdominal symptoms may prompt earlier medical evaluation and treatment before cardiovascular deterioration. Gastrointestinal complaints may also be underdocumented in critically ill children when shock, encephalopathy, or respiratory failure dominates clinical assessment. Finally, common gastrointestinal symptoms and severe organ-specific gastrointestinal injury may represent biologically and prognostically distinct phenotypes.

Our findings are compatible with the VIRUS registry analysis, in which gastrointestinal involvement was common but was not independently associated with critical illness, hospital length of stay, or mortality among patients with acute COVID-19 or MIS-C [25]. Conversely, the Italian multicenter cohort by Lo Vecchio and colleagues found that severe gastrointestinal diagnoses were associated with hospitalization, intensive care, lymphopenia, and MIS-C [26]. The apparent difference reinforces the importance of distinguishing symptom-based composites from severe gastrointestinal pathology.

Respiratory involvement was strongly associated with severe disease. Respiratory abnormalities in MIS-C may result from primary pulmonary inflammation, pleural effusion, cardiogenic pulmonary edema, capillary leak, fluid overload, shock, or metabolic stress. Thus, respiratory compromise often reflects the cumulative burden of cardiovascular and systemic dysfunction rather than isolated viral pneumonia [5,8,36].

Neurocognitive manifestations were also substantially more frequent in severe MIS-C. Neurologic findings in MIS-C range from headache and irritability to encephalopathy, seizures, ataxia, and peripheral neurologic complications [37-39]. Proposed mechanisms include cytokine-mediated neuroinflammation, endothelial dysfunction, blood–brain barrier disruption, metabolic derangement, and cerebral hypoperfusion. The broad definition used in this study does not distinguish mild symptoms from major neurologic dysfunction, but the high frequency in severe disease supports careful neurologic assessment.

Shock showed the largest crude association with severe MIS-C. This is consistent with the central role of myocardial dysfunction, vasoplegia, and circulatory failure in critical disease [3–8,40]. However, shock contributed to the severity definition, creating partial circularity, the OR therefore describes the cohort rather than establishing independent predictive value. Kawasaki-like manifestations were also more frequent in severe disease. Although MIS-C and Kawasaki disease share mucocutaneous and coronary features, MIS-C typically affects older children and is more often accompanied by gastrointestinal symptoms, shock, myocardial dysfunction, lymphopenia, thrombocytopenia, and marked inflammation [41-44].

Severe disease was associated with higher temperature, ESR, neutrophilia, and CRP. CRP and neutrophilia are consistently elevated in MIS-C and have been associated with intensive care requirements, cardiovascular involvement, and severe outcomes in multiple cohorts [45–48]. Neutrophil activation, endothelial interaction, and neutrophil extracellular trap formation may contribute to microvascular injury and thrombosis. The ESR difference was modest and should be interpreted cautiously because the p value was close to 0.05 and multiple comparisons were performed.

D-dimer did not differ between severity groups. This does not indicate that values were normal, rather, coagulation activation may have been substantial across the entire clinical spectrum. Published studies have reported heterogeneous associations

between D-dimer and severity, partly because of differences in assay units, sampling time, and outcome definitions [45-49]. Absolute concentrations and assay-specific reference limits would improve interpretation.

The findings have practical implications. Persistent fever with abdominal pain, vomiting, or diarrhea after SARS-CoV-2 exposure should prompt evaluation for MIS-C, including a complete blood count, inflammatory markers, coagulation studies, cardiac biomarkers, electrocardiography, and echocardiography when clinically indicated [18-20,50]. Gastrointestinal symptoms alone should not determine risk classification. Escalating fever, respiratory compromise, altered mental status, hemodynamic instability, cardiac abnormalities, and increasing inflammatory markers should raise concern for severe disease and support early multidisciplinary management.

Immunomodulatory treatment evolved during the study period. Observational comparative studies support IVIG, glucocorticoids, or their combination, with several analyses demonstrating improved short-term cardiovascular outcomes or reduced treatment escalation with combined initial therapy [51-55]. Treatment was not analyzed in the present study, and therapeutic associations cannot be inferred from these data.

This study has several strengths. It includes consecutive patients treated within a single tertiary institution, reducing inter-center variation in documentation and clinical pathways. It contributes data from an underrepresented region and evaluates clinical manifestations alongside inflammatory laboratory variables. Reporting crude ORs and 95% CIs improves interpretation of the magnitude and precision of categorical associations.

Limitations include the retrospective single-center design, potential referral and documentation bias, composite symptom definitions, and the absence of multivariable analysis. Severity was assessed using clinical criteria that overlapped with some analyzed manifestations. The dataset did not consistently include symptom-specific gastrointestinal detail, imaging findings, cardiac biomarkers, echocardiographic measurements, treatment timing, intensive care duration, or long-term outcomes. Several laboratory variables were available only as coded ranks, preventing definitive interpretation of direction. The 2020–2023 period also encompassed changes in definitions, circulating variants, population immunity, and clinical management.

Future prospective multicenter studies should analyze abdominal pain, vomiting, and diarrhea separately, distinguish common symptoms from severe gastrointestinal organ injury, collect standardized serial laboratory and cardiac data, and classify maximum disease severity longitudinally. Multivariable models should assess whether gastrointestinal phenotypes independently predict deterioration after adjustment for age, sex, illness duration, cardiovascular involvement, and inflammatory biomarkers.

Conclusions

Gastrointestinal manifestations were common among children with MIS-C but were more frequently documented in moderate than severe disease. They may represent an early or clinically prominent inflammatory phenotype rather than an isolated marker of advanced illness. Severe MIS-C was characterized more clearly by respiratory and neurocognitive involvement, shock, Kawasaki-like features, higher fever, and increased inflammatory activity. Clinical risk assessment should integrate gastrointestinal symptoms with hemodynamic, respiratory, neurologic, cardiac, and laboratory findings. Prospective multicenter studies with standardized gastrointestinal definitions and multivariable modeling are required to determine independent prognostic value.

Declarations

Author Contributions

Ana Maghradze: Conceptualization, methodology, investigation, data curation, formal analysis, writing—original draft, and writing—review and editing. Nani Kavlashvili: Methodology, clinical investigation, supervision, and critical revision. Ivane Chkhaidze: Supervision, validation, interpretation, and critical revision. All authors approved the final manuscript and agree to be accountable for the work.

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Conflicts of Interest

The authors declare no competing interests.

Data availability

De-identified data may be made available by the corresponding author upon reasonable request, subject to institutional ethics approval and applicable data-protection requirements.

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