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Clinical Features and Risk Factors Associated With Multisystem Inflammatory Syndrome in Children With Cancer and COVID-19

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IMPORTANCE Little is known about the risk of post–COVID-19 multisystem inflammatory syndrome in children (MIS-C) in the setting of childhood cancer.

OBJECTIVE To evaluate factors associated with MIS-C and describe the clinical course of COVID-19 in the setting of MIS-C.

DESIGN, SETTING, AND PARTICIPANTS Multisite observational cohort study of a registry representing more than 100 US pediatric oncology sites. All included patients were registered between April 1, 2020, and May 18, 2022. Sites submitted deidentified data surrounding sociodemographics, cancer diagnosis and treatment, and COVID-19 course (symptoms, maximum support required, outcome). Patients with MIS-C (n = 24) were compared with matched controls (n = 96). Children (<21 years) with cancer who developed COVID-19 while receiving cancer treatment or within 1 year of completing treatment were characterized based on their development of MIS-C.

EXPOSURES (1) Clinical and sociodemographic characteristics of children with cancer and COVID-19; and (2) MIS-C.

MAIN OUTCOMES AND MEASURES (1) Development of MIS-C among children with cancer and COVID-19; and (2) symptoms and disease severity associated with MIS-C.

RESULTS Among 2035 children with cancer and COVID-19, 24 (1.2%) developed MIS-C. COVID-19 occurred at a median (IQR) age of 12.5 (5.5-17.1) years in those with MIS-C and 11 (6-16) years among matched controls (*P* = .86). The majority of children with MIS-C had a hematologic cancer (83.3% [n = 20]), were publicly insured (66.7% [n = 16]), and were Hispanic (54.2% [n = 13]). Half (n = 12) had 1 or more noncancer comorbidity. Those with comorbidities were more likely to develop MIS-C than those without (odds ratio [OR], 2.5 [95% CI, 1.1-5.7]). Among children with MIS-C, 100% (n = 24) were admitted to the hospital and 54.2% (n = 13) to the intensive care unit (ICU), while COVID-19 contributed to the death of 20.1% (n = 5); cancer therapy was changed in 62.5% (n = 15). Compared with matched controls, those with MIS-C had higher odds of symptoms classified as systemic (OR, 4.7 [95% CI, 1.4-15.8]) or gastrointestinal (OR, 5.0 [95% CI, 1.7-14.6]) along with higher odds of hospitalization (OR, 42.9 [95% CI, 7.1-258]), ICU admission (OR, 11.4 [95% CI, 3.6-36.4]), and changes to cancer therapy (OR, 24.9 [95% CI, 6.5-94.8]).

CONCLUSIONS AND RELEVANCE In this cohort study among children with cancer and COVID-19, those with MIS-C had a more severe clinical course than those without MIS-C. The risk of MIS-C and its severity are important to consider as clinicians monitor patients with COVID-19. These findings can inform their conversations with families regarding COVID-19 risks and the benefits of prevention strategies that are pharmacologic (vaccination) and nonpharmacologic (masking), as well as treatment (antivirals, monoclonal antibodies).

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Supplemental content

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Group Information: The members of the Pediatric Oncology COVID-19 Case Consortium appear in Supplement 2.

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Children with COVID-19 are uniquely susceptible to multisystem inflammatory syndrome in children (MIS-C). A constellation of clinical features represents this hyperinflammatory disease (fever, gastrointestinal symptoms, mucocutaneous changes, myocardial dysfunction, acute kidney injury), which progresses to shock and death in severe cases.[1] Although children with cancer are at risk of severe illness with COVID-19,[2-6] little is known about their risk for or clinical course with MIS-C.

In healthy children, MIS-C risk factors mirror those for COVID-19: being school-aged, male, Black, and Hispanic.[7,8] Underlying comorbidities (including cancer and/or immunosuppression) have been associated with severe COVID-19, although not with MIS-C[7-10]; to our knowledge, these have not been examined among children with cancer and COVID-19. We aimed to describe risk factors for and the clinical course of MIS-C among children with cancer and COVID-19.

Key Points

Question Among children with cancer and COVID-19, what factors are associated with developing multisystem inflammatory syndrome in children (MIS-C), and what is its clinical course?

Findings Among 2035 children with cancer and COVID-19, those with MIS-C had higher odds of hospitalization (odds ratio [OR], 42.9) and intensive care unit admission (OR, 11.4). COVID-19 contributed to the death of children with MIS-C more often (20.1% vs 1.0%); children with MIS-C were also more likely to have their cancer therapy changed (OR, 24.9).

Meaning Among children with cancer and COVID-19, those with MIS-C faced a more severe clinical course than those without MIS-C; preventing COVID-19 in this vulnerable population will have the additional benefit of preventing MIS-C and its associated complications.

Methods

The Pediatric Oncology COVID-19 Case Report (POCC) captures deidentified sociodemographic (age, sex, race, ethnicity, insurance) and clinical (cancer diagnosis, blood/marrow transplantation [BMT] status, disease status, treatment, comorbidities) data for patients 39 years or younger who develop COVID-19 while receiving cancer-directed therapy or within 1 year of completing therapy. Clinical data regarding COVID-19 diagnoses include symptoms, vaccine status, level of medical support, changes in cancer therapy, and development of MIS-C; individuals completing POCC data forms reported MIS-C diagnosis based on clinical documentation. If vaccination status was missing, children were classified as unvaccinated if their form was submitted before vaccine availability for that age[11]; otherwise, they were classified as unknown. Cases of MIS-C were reviewed, and discrepancies discussed with treating institutions. Over 100 US institutions (>50% of US pediatric oncology sites) regularly submit data to POCC, including clinical information about the first 12 weeks following COVID-19 diagnoses; the methods have been described previously.[6] The University of Alabama at Birmingham institutional review board (IRB) approved the study; participating institutions adhered to local IRB policies. The need for consent was waived by the IRB because only deidentified data were used.

For this cohort study, we included children (<21 years at COVID-19 diagnosis) registered with POCC between April 1, 2020, and May 18, 2022. Propensity score matching matched each patient with MIS-C with 4 controls. A logistic regression model estimated the likelihood of developing MIS-C; this was used for matching. Covariate balance—age at COVID-19 diagnosis, race, cancer diagnosis, absolute lymphocyte count (ALC) at COVID-19 diagnosis, and presence of any comorbidity—was assessed between patients and controls using standardized difference scores before and after matching. Differences between patients with and without MIS-C were tested using appropriate descriptive statistics. After matching, logistic regression models assessed differences in odds of hospitalization, intensive care unit (ICU) admission, and changes in cancer-directed therapy between patients and controls. The whole cohort was used to examine factors associated with development of MIS-C. Statistical analyses used SAS, version 9.4 (SAS Institute).

Results

Study Population

Among the 2035 children with cancer and COVID-19, 24 (1.2%) (eTable 1 in Supplement 1) developed MIS-C at a median (IQR) age of 12.5 (5.5-17.1) years, having received chemotherapy a median (IQR) of 22.5 (10-39) days prior to COVID-19 diagnosis (**Table**; eTable 5 in Supplement 1). The majority of children with MIS-C had a hematologic cancer (83.3%; n = 20) and were male (75.0%; n = 18), publicly insured (66.7%; n = 16), and Hispanic (54.2%; n = 13). There were no statistically significant differences between children with MIS-C compared with matched controls in terms of age, sex, race, ethnicity, insurance, cancer diagnosis, BMT, disease status, ALC, or presence of 1 or more comorbidities (Table; eTable 4 in Supplement 1). In multivariable analyses, children with a comorbidity had higher odds of developing MIS-C (odds ratio [OR], 2.5 [95% CI, 1.1-5.7]) (eTable 2 in Supplement 1).

Symptoms

Children with MIS-C were more often symptomatic (100% [n = 24] vs 67.7% [n = 65]; $P < .001$) and had higher rates of systemic (79.2% [n = 19] vs 53.1% [n = 51]; $P = .02$) and gastrointestinal (41.7% [n = 10] vs 15.6% [n = 15]; $P < .001$) symptoms than matched controls (**Figure 1**A). These differences persisted in multivariable analyses (systemic: OR, 4.7 [95% CI, 1.4-15.8]; gastrointestinal: OR, 5.0 [95% CI, 1.7-14.6]) (**Figure 2**A; eTable 3 in Supplement 1). Children with MIS-C more often died with COVID-19 as a contributing cause (20.1% [n = 5] vs 1.0% [n = 1]; $P = .002$) (Figure 1C).

Support for COVID-19

Children with MIS-C were admitted more often to the hospital (100% [n = 24] vs 34.4% [n = 33]; $P < .001$) or the ICU (54.2%

Table. Characteristics of the Study Population: Patients With MIS-C and Matched Controls

Characteristic	No. (%)			P value
	All study patients (n = 120)	Patients with MIS-C (n = 24)	Non-MIS-C matched controls (n = 96)	
Age, median (IQR), y	12 (6-16)	12.5 (5.5-17.1)	11 (6-16)	.86
Time from chemotherapy, median (IQR), d	22 (9-42)	22.5 (10-39)	16 (4-52)	.67
Age group, y				
<5	27 (22.5)	6 (25.0)	21 (21.9)	.74
≥5	93 (77.5)	18 (75.0)	75 (78.1)	
Sex				
Female	43 (35.8)	6 (25.0)	37 (38.5)	.21
Male	77 (64.2)	18 (75.0)	59 (61.5)	
Race and ethnicity				
Black	9 (7.5)	2 (8.3)	8 (8.3)	.30
Hispanic/Latino	68 (56.7)	13 (54.2)	55 (57.3)	
Non-Hispanic White	41 (34.2)	8 (33.3)	33 (34.4)	
Unknown	1 (0.8)	1 (4.2)	0	
Insurance				
Public	84 (70.0)	16 (66.7)	68 (70.8)	.69
Private	36 (30.0)	8 (33.3)	28 (29.2)	
Diagnosis				
Hematologic cancer	100 (83.3)	20 (83.3)	80 (83.3)	>.99
Solid tumor	20 (16.7)	4 (16.7)	16 (16.7)	
Relapse/refractory	25 (20.8)	7 (29.2)	18 (18.8)	.60
BMT				
No	109 (90.8)	20 (83.3)	89 (92.7)	.40
Yes	11 (9.3)	4 (16.7)	7 (7.3)	
ALC at time of COVID-19				
0-999 cells/μL	85 (70.8)	17 (70.8)	68 (70.8)	>.99
≥1000 cells/μL	15 (12.5)	3 (12.5)	12 (12.5)	
Unknown	20 (16.7)	4 (16.7)	16 (16.7)	
≥1 Comorbidity	60 (50)	12 (50)	48 (50)	>.99
COVID-19 vaccination status				
No	111 (92.5)	22 (91.7)	89 (92.7)	.82
Yes	3 (2.5)	1 (4.2)	2 (2.1)	
Unknown	6 (5.0)	1 (4.2)	5 (5.2)	
12-wk Follow-up complete	116 (96.7)	23 (95.8)	93 (96.9)	.79

Abbreviations: ALC, absolute lymphocyte count; BMT, blood/marrow transplantation; MIS-C, multisystem inflammatory syndrome in children.

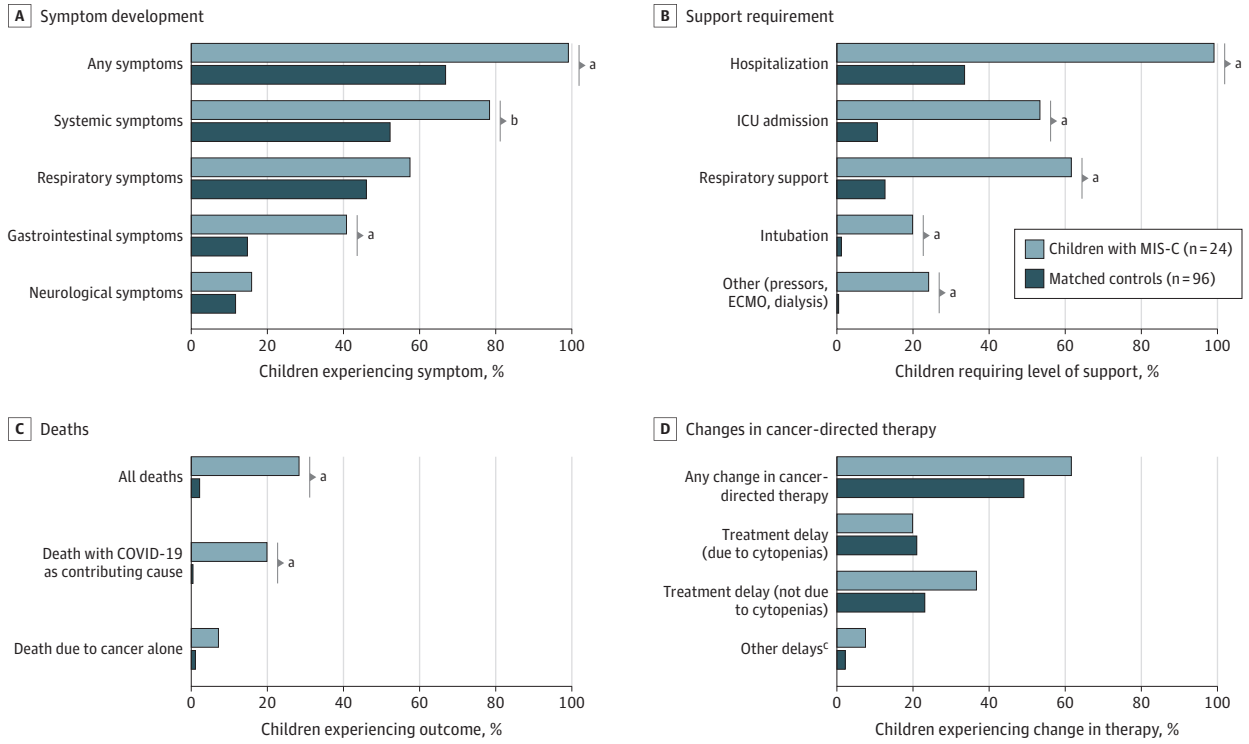
[n = 13] vs 11.5% [n = 11]; $P < .001$); they required respiratory support (62.5% [n = 15] vs 13.5% [n = 13]; $P < .001$) including intubation (20.8% [n = 5] vs 2.1% [n = 2]) more often than matched controls (Figure 1B). They also more often had their cancer therapy changed (62.5% [n = 15] vs 50.0% [n = 48]; $P = .27$) (Figure 1D). These differences persisted in multivariable analyses (hospitalization: OR, 42.9 [95% CI, 7.1-258]; ICU: OR, 11.4 [95% CI, 3.6-36.4]; respiratory support: OR, 27.0 [95% CI, 5.9-123]; changes in therapy: OR, 24.9 [95% CI, 6.5-94.8]) (Figure 2B).

Discussion

In this cohort study, we report that children with cancer are potentially facing MIS-C at higher rates (1.2% of infected patients) than the general pediatric population (0.6%).[7] The presence of a comorbidity was the only factor significantly associated with developing MIS-C. While children with cancer already experience a more severe clinical course than healthy children,[6,12] we report that those with cancer and COVID-19 who developed MIS-C had an even more severe clinical course as evidenced by higher rates of hospitalization, ICU admission, respiratory support, and death than in those without MIS-C.[6] Furthermore, the majority of children with MIS-C experienced changes in cancer treatment. Treatment intensity is critical for long-term survival in pediatric oncology, and these delays have unknown implications on the long-term cancer outcomes.[13]

Reported outcomes in previously healthy children with MIS-C similarly include high rates of ICU admission (63%-80% vs 79% in the present study), respiratory support (33%-56% vs 63% in the present study) including intubation (10%-18% vs 21% in the present study), and death (0.8%-3% vs 21% in the present study).[7-9] Among healthy children, the inci-

Figure 1. Rates of Symptom Development, Support Requirement, Deaths, and Changes in Cancer-Directed Therapy in Patients With MIS-C vs Matched Controls



ECMO indicates extracorporeal membrane oxygenation; ICU, intensive care unit; MIS-C, multisystem inflammatory syndrome in children.

[a] $P < .001$.

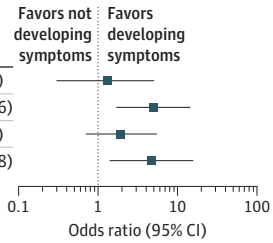
[b] $P = .02$.

[c] Other delays include delays in radiation therapy, transplant, and surgery.

Figure 2. Odds Ratios and 95% Confidence Intervals of Developing Symptoms and Requiring Support in Children With Cancer and COVID-19: Patients With MIS-C vs Matched Controls

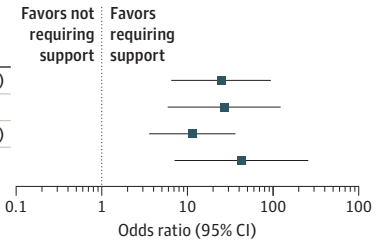
A Developing symptoms

Symptom	Odds ratio (95% CI)
Neurologic	1.3 (0.3-5.1)
Gastrointestinal	5.0 (1.7-14.6)
Respiratory	1.9 (0.7-5.5)
Systemic	4.7 (1.4-15.8)



B Requiring support in children with cancer and COVID-19

Outcome	Odds ratio (95% CI)
Changes in cancer therapy	24.9 (6.5-94.8)
Respiratory support	27.0 (5.9-123)
ICU admission	11.4 (3.6-36.4)
Hospitalization	42.9 (7.1-258)



Adjusted for age, race and ethnicity, diagnosis, absolute neutrophil count, comorbidities, and blood/marrow transplantation status. Full models in eTables 2 and 3 in Supplement 1. ICU indicates intensive care unit; MIS-C, multisystem inflammatory syndrome in children.

dence of MIS-C is apparently increasing while the severity is apparently decreasing; this may reflect differences in viral variants and/or vaccine uptake.[14]

The only significant difference between those with and without MIS-C with respect to baseline clinical or sociodemographic factors was the presence of a comorbidity. While identifying clinical and sociodemographic risk factors for developing MIS-C among children with cancer and COVID-19 would be ideal to guide clinical management, our study is not sufficiently powered to fully answer this question due to the limited number of children with MIS-C (n = 24). Nevertheless, the risk factors for developing COVID-19 in children with cancer (hematologic cancers, Hispanic ethnicity, public insurance) inherently are associated with a greater risk of MIS-C.[6] As the pandemic persists, it will be critical to continue to examine risk factors for MIS-C among children with cancer as more cases develop.

Limitations

This study needs to be placed in the context of its limitations. The small number of patients with MIS-C (n = 24) was under-

powered to detect risks for developing this rare syndrome in children with cancer. While POCC expedited regulatory approvals by excluding protected health information (PHI), the lack of PHI also prevents understanding the time course and some granular detail surrounding MIS-C and symptom evolution. Additionally, the data set includes only children with cancer and COVID-19, not allowing for comparisons between children with and without cancer. Also, we did not collect data regarding viral variants for each infection; thus, we cannot compare different variants' propensity to cause MIS-C. Limitations notwithstanding, these findings can assist clinicians in understanding the clinical course and risk of MIS-C in the setting of childhood cancer.

Conclusions

In this cohort study among children with cancer and COVID-19, those with MIS-C had a more severe clinical course than those without MIS-C. Given the severity of disease with MIS-C and associated changes in cancer treatment required, MIS-C is a serious outcome for children with cancer and COVID-19. Preventing COVID-19, and therefore MIS-C, in this population is critical. The severity of MIS-C among children with cancer is yet another reason to encourage vaccines and other risk mitigation behaviors in this population.[15]

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Group Information: This work builds on the contributions of all members of the Pediatric Oncology COVID-19 Case Consortium. The full list of consortium members is in eTable 6 in Supplement 1 and in Supplement 2.

Data Sharing Statement: See Supplement 3.

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