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Thrombosis and hemorrhage experienced by hospitalized children with SARS-CoV-2 infection or MIS-C: Results of the PICNIC registry

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Abbreviations: BMI, body mass index; CHD, congenital heart disease; CVC, central venous catheters; ICU, intensive care unit; INR, international normalized ratio; ISTH, International Society of Thrombosis and Hemostasis; MIS-C, multisystem inflammatory syndrome in children; PTT, partial thromboplastin time; SIC, sepsis-induced coagulopathy; VTE, venous thromboembolism; WHO, World Health Organization.

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https://abstracts.isth.org/abstract/covid-19-related-abnormalities-in-the-hematologic-characteristics-among-inpatient-children-results-of-the-picnic-registry/

Abstract

Introduction: Coagulopathy and thrombosis associated with SARS-CoV-2 infection are well defined in hospitalized adults and leads to adverse outcomes. Pediatric studies are limited.

Methods: An international multicentered (n = 15) retrospective registry collected information on the clinical manifestations of SARS-CoV-2 and multisystem inflammatory syndrome (MIS-C) in hospitalized children from February 1, 2020 through May 31, 2021. This sub-study focused on coagulopathy. Study variables included patient demographics, comorbidities, clinical presentation, hospital course, laboratory parameters, management, and outcomes.

Results: Nine hundred eighty-five children were enrolled, of which 915 (93%) had clinical information available; 385 (42%) had symptomatic SARS-CoV-2 infection, 288 had MIS-C (31.4%), and 242 (26.4%) had SARS-CoV-2 identified incidentally. Ten children (1%) experienced thrombosis, 16 (1.7%) experienced hemorrhage, and two (0.2%) experienced both thrombosis and hemorrhage. Significantly prevalent prothrombotic comorbidities included congenital heart disease (p-value .007), respiratory support (p-value .006), central venous catheter (CVC) (p = .04) in children with primary SARS-CoV-2 and in those with MIS-C included respiratory support (p-value .03), obesity (p-value .002), and cytokine storm (p = .012). Comorbidities prevalent in children with hemorrhage included age >10 years (p = .04), CVC (p = .03) in children with primary SARS-CoV-2 infection and in those with MIS-C encompassed thrombocytopenia (p = .001) and cytokine storm (p = .02). Eleven patients died (1.2%), with no deaths attributed to thrombosis or hemorrhage.

Conclusion: Thrombosis and hemorrhage are uncommon events in children with SARS-CoV-2; largely experienced by those with pre-existing comorbidities. Understanding the complete spectrum of coagulopathy in children with SARS-CoV-2 infection requires ongoing research.

KEYWORDS
COVID-19, hemorrhage, MIS-C, pediatric, SARS-CoV-2, thrombosis, c

1 | INTRODUCTION

In hospitalized adults, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has been associated with coagulopathy, significantly elevated D-dimers, and venous thromboembolism (VTE). These complications lead to adverse outcomes in hospitalized adults, including increased mortality.[1–5] The etiology of the coagulopathy has been hypothesized to be related to a homeostatic imbalance associated with infections, similar to sepsis-induced coagulopathy (SIC). However, when compared to SIC, coagulopathy associated with SARS-CoV-2 is characterized by no or mild thrombocytopenia, higher rates of thrombosis, and a greater increase in D-dimer levels with infrequent hemorrhagic events.[6–8]

Children infected with SARS-CoV-2 are commonly asymptomatic or present with mild gastrointestinal (GI) or respiratory symptoms with a less than 1% mortality rate.[9–12] Children with underlying medical conditions such as chronic lung disease, congenital heart disease (CHD), obesity, and age <1 year are at an increased risk of severe illness

with multiorgan dysfunction.[13] Reports of hematologic complications of SARS-CoV-2 infection or multisystem inflammatory syndrome (MIS-C) in children are limited with recent observational studies reporting an increased risk of thrombosis in children over 12 years of age with MIS-C.[14,15] However, the current understanding of the clinical presentation of coagulopathy, optimal management, complications, and impact on disease prognosis is limited.

Given the impact of SARS-CoV-2 on hemostasis and its association with mortality in adults, understanding the spectrum of coagulopathy and its association with outcome in children is critical. The objectives of this study were to (a) determine the prevalence of hemorrhage and/or thrombosis; (b) describe the characteristics of hemorrhage and thrombosis with management; and (c) assess the relationship between thrombotic and bleeding complications and underlying comorbidities in hospitalized children with SARS-CoV-2 and MIS-C.

2 | METHODS

A multisite international registry was created by the PICNIC (Pediatric Investigators Collaborative Network on Infections in Canada) investigators, with the aim to collect data regarding clinical presentation, treatment, and outcome of hospitalized children up to 18 years of age with SARS-CoV-2 infection or MIS-C diagnosis. Fifteen hospitals participated in the study across three countries (Canada, Costa Rica, and Iran). Children who were hospitalized between February 1, 2020 and May 31, 2021, and diagnosed with SARS-CoV-2 or MIS-C were eligible for inclusion. This retrospective cohort sub-study presents data on coagulopathy, hemorrhage, and thrombosis among hospitalized children with SARS-CoV-2 or MIS-C.

Cases were identified by screening admission lists for children with positive testing for SARS-CoV-2 or MIS-C. Children were classified with primary SARS-CoV-2 if the infection led to hospital admission or prolonged the hospital stay for an existing admission. A child was classified with incidental SARS-CoV-2 infection if the infection caused mild or no symptoms, was not the reason for hospital admission, and did not extend the duration of the hospital stay. Children were classified with MIS-C based on the World Health Organization (WHO) criteria (Figure 1).[16]

Data collected included patient demographics, underlying risk factors for both pro-hemorrhagic and/or prothrombotic conditions, clinical presentation, including new hemorrhagic or thrombotic events during hospitalization, disease course, and severity as determined by admission to the intensive care unit (ICU), use of cardiorespiratory supports, treatments, and complications. Presence of hemorrhage was based on documentation from the clinical chart and classified according to the WHO-modified bleeding scale (Table S3).[17] Thrombotic events were identified based on any evidence of vessel occlusion on radiographic imaging with or without clinical features. Cytokine storm was defined based on the classification criteria from the Pediatric Rheumatologic Collaborative (Table S4).[18] Prothrombotic risk factors were defined based on the ISTH (International Society of Thrombosis and Hemostasis) criteria and included age >10 years, previous thrombosis, presence of a central venous catheter (CVC), active cancer, obesity, inherited thrombophilia, congenital/acquired heart disease, autoimmune disorders, hemoglobinopathy, systemic infection, use of respiratory support, or ICU admission.[19,20] Hemorrhagic risk factors were defined based on review of pediatric and adult literature and included age >10 years, male gender, CVC, thrombocytopenia, CHD, use of anticoagulation/antiplatelet therapy, congenital bleeding disorder, renal failure, systemic infection, and ICU admission.[21–23] Systemic infection was defined as laboratory detection of any virus, bacteria, or fungi concurrent with SARS-CoV-2 infection and treated with antimicrobials. Obesity was defined as documentation of obesity in the medical record and not based on the body mass index (BMI) criteria. Respiratory support was defined as the use of high-flow nasal cannula, noninvasive ventilation (BiPAP/CPAP), mechanical ventilation, or extracorporeal membrane support (ECMO) during hospital admission. Laboratory parameters included platelet count, international normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen, serum ferritin levels, C-reactive protein, erythrocyte sedimentation rate (ESR), D-dimer, triglycerides, liver function tests (AST, ALT, bilirubin), brain natriuretic peptide (BNP), troponin, urea, creatinine, and serum sodium. Data on clinical manifestations of bleeding and/or thrombosis, and management of these symptoms (including use of antithrombotic medications as prophylaxis and treatment) was recorded.

Ethics approval was obtained at all sites and the need for consent was waived. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were followed to ensure accurate and complete reporting of all observations for this retrospective cohort study.[24] The investigator of PICNIC registry (Joan Robinson) classified patients as MIS-C, primary infection, or incidental SARS-CoV-2, whereas the principal investigator (Sarah Tehseen) performed data review to ensure that all cases classified as having a hemorrhage, thrombosis, or cytokine storm met the study definitions.

Data were collected and managed using REDCap electronic data capture tools. From November 17, 2020 onwards, incidental SARS-CoV-2 cases had only demographic data collected. Therefore, these cases were not included in descriptive or comparative statistics (Figure 1). The "incidental SARS-CoV-2" cases entered before November 2020 had demographic and clinical data entered. Hence, they were included in descriptive statistics but not in the comparative analyses.

Comparative statistics were performed separately for patients with primary SARS-CoV-2 infection and MIS-C. Descriptive statistics were performed for continuous and categorical variables based on distribution of data. Comparisons of continuous variables between patients with hemorrhage and thrombosis and those without hemorrhage or thrombosis were conducted using parametric (independent sample *t*-tests) and nonparametric (Wilcoxon signed rank) tests depending on the distribution of data (normal distribution vs. non-normal distribution). Categorical variables were compared using chi-square or Fisher's exact test among patients with hemorrhage or thrombosis compared with those without hemorrhage or thrombosis. A *p*-value of .05 was considered statistically significant. All data were analyzed using SAS version 9.4.

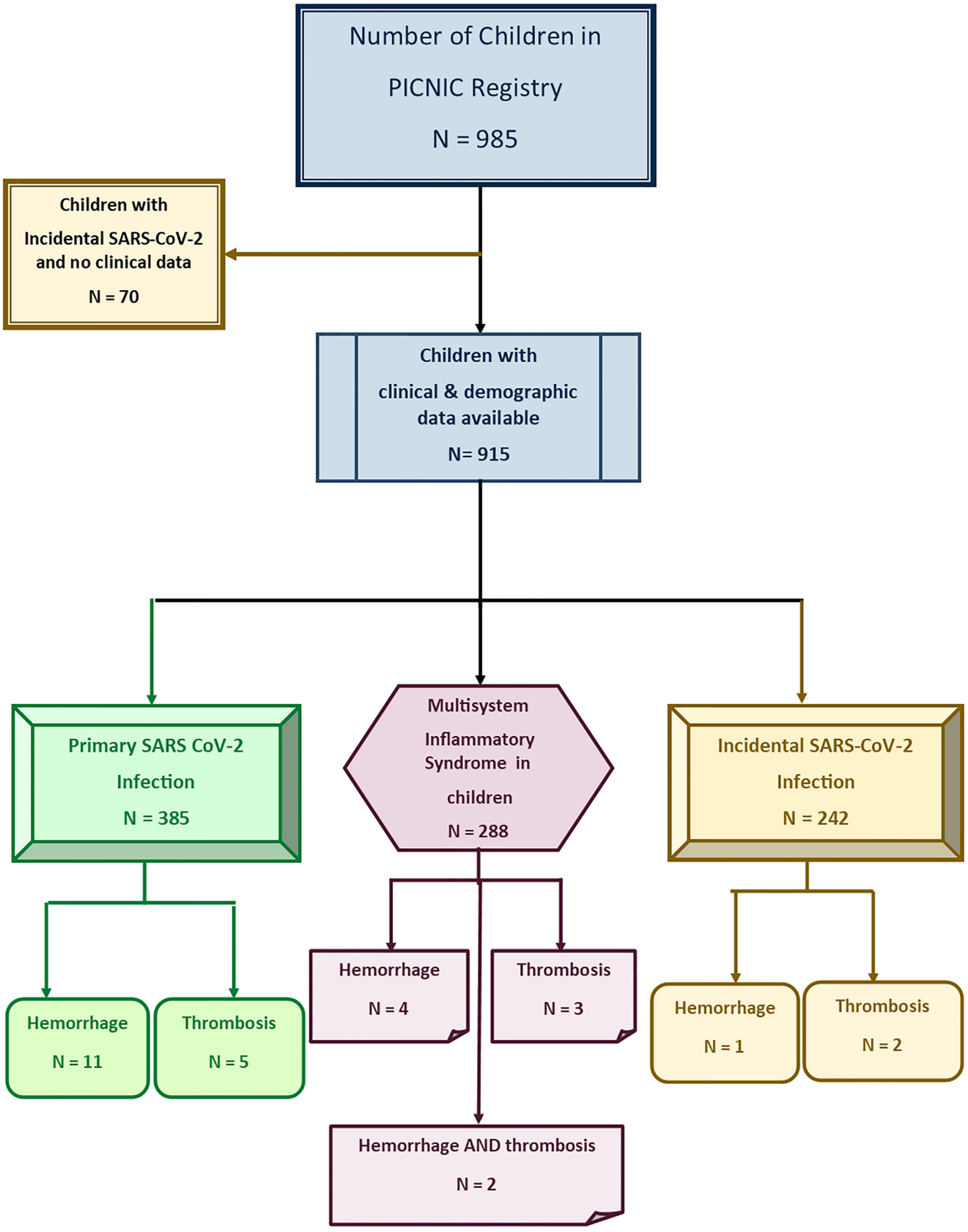

FIGURE 1 Classification of children enrolled in Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) registry with number of events of hemorrhage and thrombosis

TABLE 1 Demographic features of hospitalized children infected with SARS-CoV-2 or MIS-C (*N* = 915)

	All patients (*N* = 915)	Primary SARS-CoV-2 (*N* = 385)	MIS-C (*N* = 288)	Incidental SARS-CoV-2 (*N* = 242)
Age (years); median (IQR)	4.6 (1.1–11)	3 (0.8–11)	6.1 (3–10)*	4.3 (0.9–12)
Gender (male), *N* (%)	561 (74%)	282 (73%)	162 (57%)	43 (17%)
Total number of episodes of hemorrhage and thrombosis, *N* (%)				
Thrombosis	10 (1.0%)	5 (1.3%)	3 (1%)	2 (0.8)
Hemorrhage	16 (1.7%)	11 (2.8%)	4 (1.8%)	1 (0.4%)
Hemorrhage and thrombosis	2 (0.2%)	0	2 (0.7%)	0
Other clinical outcomes, *N* (%)				
ICU admission	256 (28%)	117 (30%)	116 (40%)	23 (9.5%)
Respiratory support	136 (15%)	111 (29%)	21 (8.6%)	4 (1.6%)
Death	11 (1.2%)	10 (2.5%)	0	1 (0.4%)
Anticoagulation therapy, *N* (%)				
Antiplatelet therapy	162 (18%)	18 (4.6%)	114 (39.5%)**	0
Anticoagulation	139 (15%)	58 (15%)	49 (17%)	1 (0.4%)
Anticoagulation and antiplatelet therapy	30	0	30 (10%)	0
Rationale for use of anticoagulation, *N* (% of total patients on anticoagulation, *N* = 139)				
Treatment of new thrombus	9 (6.5%)			
Thrombosis prophylaxis in MIS-C	79 (56%)			
Thrombosisprophylaxis for other indications[&]	51 (37%)			
Pharmacologic agents, *N* (% of total number on anticoagulation in each patient category)				
Unfractionated heparin (UFH)	*N* = 139	*N* = 58	*N* = 79	
	28 (20%)	20 (34%)	7 (9%)	1
Low molecular weight heparin (LMWH)	82 (59%)	34 (59%)	47 (59%)	1
Direct oral anticoagulants (DOAC)	29 (21%)	4 (7%)	25 (32%)	0

Note: None of the patients were receiving prophylactic or therapeutic anticoagulation prior to the current admission for SARS-CoV-2 infection/MIS-C. Age: age in years upon hospitalization.

Abbreviations: ICU, intensive care unit; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome.

*Differences were significant at a *p*-value of <.001.

**p-Value of .02.

[&]Prothrombotic risk factors: low cardiac output, coronary aneurysms, and ≥2 prothrombotic factors (such as high D-dimer, CVC, systemic infection, etc.).

3 | RESULTS

Nine hundred eighty-five children were included in the registry; complete information available for 915 patients. Three hundred eighty-five (385/915; 42%) children were diagnosed with primary SARS-CoV-2 infection, 288 (288/915; 31%) with MIS-C, and 242 (242/915; 26.4%) with incidental SARS-CoV-2. Seventy patients with incidental SARS-CoV-2 had only demographic data entered (Table 1, Figure 1). The prevalence of thrombosis was 1.3% (5/385) in children with primary SARS-CoV-2 infection, 1.7% (5/288) in patients with MIS-C, and 0.8% (2/242) in children with incidental SARS-CoV-2 infection. The prevalence of hemorrhage was 2.8% (11/385) with primary SARS-CoV-2 infection, 2.1% (6/288) with MIS-C, and 0.4% (1/242) with incidental SARS-CoV-2. One hundred seventy-seven (19%) children were transferred to the ICU, and 11 (1.2%) died during the admission. None of the deaths were related to thrombotic or hemorrhagic events. Reasons for death included respiratory failure secondary to SARS-CoV-2 infection (n = 9/11; 80%), multiorgan failure in the setting of cytokine storm (n = 1/11; 10%), and deaths unrelated to SARS-CoV-2 (n = 1/11; 10%) (sudden infant death syndrome (SIDS). Ten children who died had underlying comorbidities, including chromosomal abnormalities, cancer, chronic kidney, and lung disease.

Twelve patients (12/915; 1.3%) developed new thromboses; five (5/385; 1.3%) with primary SARS-CoV-2 infection, five (5/288; 1.7%) with MIS-C, and two (2/242; 0.8%) with incidental SARS-CoV-2 infection (Table 2). None of the patients who developed thrombosis

TABLE 2 Clinical features of hospitalized children with SARS-CoV-2 infection or MIS-C and new thromboses ($N = 12$)

	Age (years)	Sex	Anatomic site	Case definition	Underlying comorbidities	ICU transfer	Thrombosis		SARS-CoV-2 or MIS-C treatment	Additional history
							Treatment	Prophylaxis		
1	0.2	M	Deep venous	Primary SARS-CoV-2 infection	Global developmental delay, congenital heart disease, seizures	Yes	LMWH	LMWH	None	
2	1	M	Deep venous -CVC related	Primary SARS-CoV-2 infection	Congenital heart disease,[a] systemic infection, seizures	Yes	LMWH	LMWH	None	
3	3	F	Deep venous-PICC line related	Primary SARS-CoV-2 infection	Systemic infection, seizure disorder	No	None	None	None	
4	1	F	Femoral artery	Primary SARS-CoV-2 Infection	Congenital heart disease[b] and trisomy 21	Yes	UFH	None	Tocilizumab	Cytokine storm, patient died
5	12	F	Large pulmonary embolism	Primary SARS-CoV-2 infection	Obesity	No	LMWH	None	None	
6	9	M	Cardiac	MIS-C	Obesity	Yes	LMWH	LMWH	IVIG, anakinra	Cytokine storm
7	5	M	Cardiac left ventricular	MIS-C	Obesity	Yes	LMWH	None	IVIG, anakinra aspirin	Cytokine storm
8	9	F	Internal jugular vein, right iliac vein, and segmental pulmonary artery with infarct	MIS-C	Antiphospholipid antibody syndrome$^{\Delta}$, asthma	No	LMWH	None	IVIG	30 days post-SARS-CoV-2 infection Patient was seropo sitive
9$^{\infty}$	10	M	Pulmonary micro-emboli	MIS-C	Obesitysystemic infection	No	LMWH	DOAC	IVIG, steroids	Also had GI hemorrhage
10$^{\infty}$	6	M	Renal artery infarcts	MIS-C	Factor V Leiden heterozygous	Yes	None	None	IVIG, aspirin	Also had hematuria
11	11	M	Internal jugular vein	Incidental SARS-CoV-2 infection	Mastoiditis, asthma	No	LMWH	None	None	Mastoiditis
12	3	M	Superficial venous upper extremity. Small CSVT	Incidental SARS-CoV-2 infection	Guillian–Barre syndrome$^{\Delta}$	No	None	None	IVIG	15 days post-SARS-CoV-2 seropositive

Note: Age: age in years upon hospital admission.

Abbreviations: CSVT, cerebral venous sinus thrombosis; CVC, central venous catheter; DOAC, direct oral anticoagulants; GI, gastrointestinal; IVIG, intravenous immune globulin; LMWH, low molecular weight heparin; MIS-C, multisystem inflammatory syndrome in children; MOF, multiorgan failure; PICC, peripherally inserted central catheter; UFH, unfractionated heparin.

[a]Intraventricular communication, patent ductus arteriosus, congestive heart failure, and pulmonary hypertension.

[b]Pulmonary Hypertension, Patent ductus arteriosus.

$^{\Delta}$New autoimmune conditions that developed after SARS-CoV-2 infection. $^{\infty}$Patients 9 and 10 also had hemorrhage and hence mentioned in Table 4 as well.

TABLE 3 The prevalence of prothrombotic comorbidities in children hospitalized with SARS-CoV-2 infection or MIS-C

	Prothrombotic risk factors *N* (%)	No thrombosis (*N* = 380)	Thrombosis (*N* = 5)	*p*-Value
Children with Primary SARS-CoV-2 infection (*N* = 385)	Systemic infection	225 (59%)	2 (40%)	
	ICU admission	114 (30%)	3 (60%)	
	Age ≥10 years	92 (24%)	1 (28.6%)	
	Respiratory support	100 (26%)	5 (100%)	**<.00**
	Obesity	41 (11%)	1 (20%)	
	Cancer	35 (9%)	0	
	Presence of CVC	27 (7%)	2 (40%)	.04
	Cytokine storm	5 (1.3%)	1 (20%)	
	Congenital heart disease	9 (2.4%)	2 (40%)	.007
	Hemoglobinopathy	9 (2.4%)	0	
	Inherited thrombophilia	0	0	
	Previous history of thrombosis	4 (1%)	0	
		No thrombosis (*N* = 283)	**Thrombosis (*N* = 5)**	***p*-Value**
Children with MIS-C (*N* = 288)	ICU admission	114 (40%)	2 (40%)	
	Age ≥10 years	65 (23%)	1 (20%)	
	Respiratory support	19 (7%)	2 (40%)	.03
	Systemic infection	56 (20%)	1 (20%)	
	Presence of CVC	14 (5%)	1 (20%)	
	Obesity	6 (2%)	3 (60%)	.002
	Cancer	3 (1%)	0	
	Cytokine storm	9 (3%)	2 (40%)	.012
	Congenital heart disease	0	0	
	Inherited thrombophilia	0	1 (20%)	
	Previous history of thrombosis	1 (0.3%)	0	

Note: Respiratory support: use of high-flow nasal cannula, noninvasive ventilation (CPAP, BiPAP), mechanical ventilation, or ECMO.
Abbreviations: age, age ≥10 years upon admission to hospital; CVC, central venous catheter; ECMO, extracorporeal membrane support; ICU, intensive care unit; MIS-C, multisystem inflammatory syndrome in children.

during hospitalization had a previous history of thrombosis. Two of the 12 patients with thrombosis developed autoimmune conditions (Guillain–Barre and antiphospholipid antibody syndrome) following infection with SARS-CoV-2 and three of 12 developed cytokine storm. Two patients with MIS-C and thrombosis (2/5; 40%) had hemorrhage as well. Most patients with thrombosis (9/12; 75%) received standard pediatric anticoagulation management (low molecular weight or unfractionated heparin). Data on the dose, time, duration, and monitoring of anticoagulation were not available. The thrombotic events in those patients who did not receive anticoagulation included (a) a small CSVT (cerebral venous sinus thrombosis) and superficial upper extremity VTE; (b) peripherally inserted central catheter (PICC) line-related deep venous thrombosis (DVT) with spontaneous resolution; and (c) renal infarcts, postulated to be secondary to renal arterial thrombosis.

For children with primary SARS-CoV-2 infection and thrombosis (5/385; 1.3%), CHD (40% vs. 2.4%, *p*-value .007), use of respiratory support (100% vs. 0%, *p*-value <.001), and presence of CVC (40% vs. 7%, *p*-value .04) were more common compared to children without thrombosis (380/385). For children with MIS-C and thrombosis (5/288; 1.7%), obesity (60% vs. 2%, *p*-value .002), use of respiratory support (40% vs. 1%, *p*-value .03), and cytokine storm (40% vs. 3%, *p*-value .012) were more common than in children with MIS-C without thrombosis (283/288) (Table 3).

New hemorrhagic events were reported in 18 children (18/915; 2%); 11 with primary SARS-CoV-2 infection (11/385; 2.8%), six with MIS-C (6/288; 2%), and one with incidental SARS-CoV-2 infection (1/242; 0.4%) (Table 4). All hemorrhagic episodes occurred during the course of hospitalization, with none observed at the time of presentation. Information about previous episodes of hemorrhage was not

TABLE 4 Clinical features of hospitalized children with SARS-CoV-2 infection or MIS-C and new episodes of hemorrhage ($N = 18$)

	Age (years)	Sex	Lowest platelet count ($\times 10^9$/L)	Anatomic site	Severity	Case definition	Underlying comorbidity	Anticoagulation	Management		Additional history
									Hemorrhage	SARS CoV-2 or MIS-C	
1	13	M	18	Nose	4	Primary SARS-CoV-2 infection	Relapsed ALL thrombocytopenia fungal infection	Yes (LMWH)	Tranexamic acid, transfusion-packed RBCs, plasma platelets cryoprecipitate	Famipinavir	Patient died
2	2.5	F	15	Nose, abdominal intratumor	3	Primary SARS-CoV-2 infection	Neuroblastoma thrombocytopenia CMV infection	No	Surgical intervention, transfusion: packed RBCs, plasma platelets	IVIG, remdesivir	
3	0.5	M	17	Lower GI	3	Primary SARS-CoV-2 infection	Bernard Soulier syndrome	No	Transfusion: packed RBCs, platelets		
4	17	F	202	Postpartum vaginal	3	Primary SARS-CoV-2	Gestational HTN, asthma	Yes (LMWH)	Transfusion: packed RBCs		
5	0.5	M	172	Lung	3	Primary SARS-CoV-2 infection	Congenital heart disease	No	Transfusion: plasma	IVIG, tocilizumab interferon	Cytokine storm
6	1	M	236	Lower GI	2	Primary SARS-CoV-2 infection	None	Yes (LMWH)	None		
7	17	M	169	Nose, lung	2	Primary SARS-CoV-2 infection	Kidney injury, hepatitis, asthma	Yes (DOAC)	None	Steroids	
8	17	F	142	Lung	2	Primary SARS-CoV-2 infection	None	No	None		
9	5	F	210	Upper GI	2	Primary SARS-CoV-2 infection	Global developmental delay, Mallory Weiss tear	No	None		
10	9	F	318	Upper GI	2	Primary SARS-CoV-2 infection	Global developmental delay, seizures	No	None		
11	3.5	M	219	Upper GI	2	Primary SARS-CoV-2 infection	Obesity	No	Pantoprazole		
12	16	M	<5	CNS	4	MIS-C	ALL, thrombocytopenia systemic infection	No	Transfusion: platelets, packed RBCs	IVIG, prednisone	Past history of DVT
13	8	F	236	Upper GI	3	MIS-C	Systemic infection, cerebral palsy	Yes (aspirin)	Transfusion: frozen plasma	IVIG, anakinra, aspirin	Cytokine storm

(Continues)

TABLE 4 (Continued)

	Age (years)	Sex	Lowest platelet count ($\times 10^9$/L)	Anatomic site	Severity	Case definition	Underlying comorbidity	Anticoagulation	Management		Additional history
									Hemorrhage	SARS CoV-2 or MIS-C	
14	13	M	202	Lower GI	2	MIS-C	None	No	None	IVIG, steroids interferon	
15	13	F	56	Nose	1	MIS-C	Castleman's disease thrombocytopenia	Yes (aspirin)	None	IVIG, anakinra aspirin	Cytokine storm
16	10	M	73	Upper GI	3	MIS-C	Obesity systemic infection	Yes (DOAC)	Transfusion: packed RBCs	IVIG, steroids	Also had pulmonary micro-emboli[a]
17	86	M	189	Urinary tract	1	MIS-C	Factor V Leiden heterozygous	No	None	IVIG, aspirin	Also had hematuria[a]
18	6	M	35	Upper GI	3	Incidental SARS-CoV-2	ALL thrombocytopenia	No	Transfusion: platelets, packed RBCs		Febrile neutropenia

Note: Lowest platelet count recorded during hospital admission; not correlated with timing of hemorrhage. Age: age in years upon hospital admission; severity: determined based on World Health Organization-modified bleeding scale.

Abbreviations: ALL, acute lymphoblastic leukemia; DVT, deep vein thrombosis; GI, gastrointestinal tract; IVIG, intravenous immune globulin; MIS-C, multisystem inflammatory syndrome in children; PRBCs, packed red blood cells; TXA, tranexamic acid.

[a] Patients 16 and 17, also mentioned in Table 2, had thrombosis.

TABLE 5 The prevalence of pro-hemorrhagic comorbidities in children hospitalized with SARS-CoV-2 infection or MIS-C

		No hemorrhage ($N = 374$)	Hemorrhage ($N = 11$)	p-Value
Children with primary SARS-CoV-2 infection ($N = 385$)	Gender	274 (73%)	8 (73%)	
	Systemic infection	226 (60%)	3 (27%)	
	Anticoagulation therapy and/or antiplatelet therapy	157 (42%)	8 (73%)	
	ICU admission	113 (30%)	4 (36%)	
	Age ≥10 years	86 (23%)	5 (45%)	.04
	Thrombocytopenia	33 (8%)	2 (18%)	
	Presence of CVC	26 (7%)	3 (27%)	.03
	Congenital heart disease	13 (3.4%)	1 (9%)	
	Cytokine storm	5 (1.3%)	1 (9%)	
	Kidney disease (acute or chronic)	4 (1%)	1 (9%)	
		No hemorrhage (N = 282)	**Hemorrhage (N = 6)**	p-Value
Children with MIS-C ($N = 288$)	Anticoagulation therapy and/or antiplatelet therapy	219 (78%)	3 (50%)	
	Gender	155 (55%)	4 (57%)	
	ICU admission	114 (41%)	2 (33%)	
	Age ≥10 years	64 (23%)	3 (50%)	
	Systemic infection	53 (20%)	3 (50%)	
	Presence of CVC	15 (5.3%)	2 (33%)	
	Cytokine storm	9 (3.2%)	2 (33%)	.001
	Thrombocytopenia	1 (0.3%)	2 (33%)	.02
	Congenital heart disease	0	0	
	Kidney disease (acute or chronic)	0	0	

Note: Age ≥10 years: age at the time of admission to hospital.
Abbreviations: CVC, central venous catheter; MIS-C, multisystem inflammatory syndrome in children.

recorded. Two (2/6; 34%) patients with hemorrhage and MIS-C developed cytokine storm and two (2/6; 34%) experienced both hemorrhage and thrombosis.

Six patients (6/18; 33%) who experienced hemorrhage had thrombocytopenia, five were receiving anticoagulation or antiplatelet therapy (5/18; 28%), and one (1/15; 5%) was thrombocytopenic and receiving anticoagulation prophylaxis as well.

Fifty percent of the patients ($N = 9/18$) had severe hemorrhage (WHO grade 3 or higher) and required transfusion of blood products and/or surgical intervention to control the bleeding. Children with severe hemorrhage (WHO grades 3–4) were more likely to have thrombocytopenia (5/6; 83%; p-value .04) versus those with minor hemorrhage (grades 1–2). The proportion of children with severe hemorrhage was similar with (4/7) and without the use of anticoagulation or antiplatelet therapy (4/10). However, as the temporal relationship between use of anticoagulation and hemorrhage occurrence during hospital admission was not available, comparative statistics could not be performed. Seven patients (7/18; 39%) required ICU admission. One patient died due to sepsis and relapse of leukemia.

Comorbid medical conditions that predispose to hemorrhage were compared between children who developed hemorrhage during hospitalization and those without (Table 5). In children with primary SARS-CoV-2 infection and hemorrhage (11/385), a significantly higher proportion had age >10 years at the time of hospitalization (5/11, 50% vs. 86/374, 23%; p-value .04) and a CVC present (26/374, 30% vs. 3/11, 7%; p-value .03). Thrombocytopenia (2/6, 28.5% vs. 1/282, 0.3%; p-value .001) and cytokine storm (2/6, 28.5% vs. 9/282, 3%; p-value .02) were significantly common in children with MIS-C and hemorrhage (6/288) versus MIS-C patients without hemorrhage.

Overall, patients with MIS-C did not have a higher prevalence of hemorrhage (2.1% vs. 2.6%; p-value .8) or thrombosis (1.7% vs. 1.3%; p-value .2) compared to patients with primary SARS-CoV-2 infection. All children with thrombosis had at least one prothrombotic factor in addition to SARS-CoV-2 and hospitalization with seven having

two or more additional factors. Majority of children with hemorrhage (16/18; 89%) also had additional comorbid conditions predisposing to hemorrhage.

The hematologic laboratory parameters (white blood cell count [WBC], hemoglobin, platelet count, INR, PTT, D-dimer, and fibrinogen) were collected but could not be linked by time with thrombosis or hemorrhage (Tables 1 and 2). Median D-dimer levels were noted to be significantly higher in patients with thrombosis; both among the ones with MIS-C and SARS-CoV-2 infection (12.6 vs. 3.1 mg/dl, *p*-value .01; 11 vs. 1.5 mg/dl, *p*-value .02).

4 | DISCUSSION

This study describes the clinical spectrum of new bleeding and thrombotic events in a large cohort of hospitalized children with SARS-CoV-2 infection or MIS-C. When compared to hospitalized adults, the rates of thrombosis and hemorrhage in children were markedly lower and were not associated with mortality.[8] The majority of children with new bleeding or thrombotic events had predisposing comorbid conditions. In children with primary SARS-CoV-2 infection, thrombosis was more common for children on respiratory support, who had a CVC or a diagnosis of CHD. In children with MIS-C, thrombosis was more likely for obese patients, those receiving respiratory support, or diagnosed with cytokine storm. Children with primary SARS-CoV-2 infection were more likely to experience bleeding if older than 10 years upon admission or if they had a CVC. For children with MIS-C, hemorrhage was more likely in those with thrombocytopenia or those diagnosed with cytokine storm.

Thrombosis is reported in 20% of hospitalized adults with SARS-CoV-2 infection and is associated with increased morbidity and mortality.[25] The reasons for lower rate of thrombosis in children with SARS-CoV-2 infection are multifactorial and possibly related to differences in the immunologic response to SARS-CoV-2 infection and age-related variation in thrombosis risk factors (e.g., age, cardiovascular disease, smoking, etc.) between children and adults.[26,27] In this study, thrombosis prevalence in hospitalized children with SARS-CoV-2 or MIS-C was higher when compared to published rates in hospitalized children without SARS-CoV-2 infection (1.7% vs. 0.5%), highlighting the pro-inflammatory and prothrombotic aspects of this disease.[28,29]

The majority of children who developed thrombosis in the study had well-identified, and sometimes, multiple prothrombotic risk factors. The significantly prevalent prothrombotic conditions identified in this study (CHD, obesity, cytokine storm, and presence of CVC) have previously been associated with the development of thrombosis in children or are surrogate markers of disease severity and inflammation (utilization of respiratory support).[30–33] Information on their additive impact on thrombosis in SARS-CoV-2 infection or MIS-C is limited. Cytokine storm usually presents with prothrombotic coagulopathy,[34,35] but children with cytokine storm in this study had a high rate of both hemorrhage and thrombosis (2/5 and 2/6), likely due to presence of additional pro-hemorrhagic factors such as thrombocytopenia, sepsis, and CHD. Therefore, thromboprophylaxis decisions in children with SARS-CoV-2 infection or MIS-C should account for their individual pro-thrombotic and pro-hemorrhagic factors as well as presence of severe inflammation (as evidenced by D-dimer greater than five times the upper limit of normal, diagnosis of MIS-C, or cytokine storm).

Published pediatric literature on thrombosis in SARS-CoV-2 infection provides variable rates of thrombosis. From March 2020 to December 2020, the reported prevalence of thrombotic events in children with primary SARS-CoV-2 infection was 0.8% (N = 8/971), 1.2% (5/398), and 26% (7/27).[36–39] Between January 2021 to November 2021, the prevalence was 0.7% (4/537) to 2.1% (9/426).[14,40] In children with MIS-C, the reported rate of thrombosis ranged from 4.3% (8/186) to 6.5% (9/138) in larger studies,[14,41] with two small studies reporting no thrombotic events in MIS-C patients (N = 6 and N = 30).[15,42] The prevalence of thrombosis in children with primary SARS-CoV-2 infection in the current study is in alignment with previous reports. However, the thrombosis rates are markedly lower in MIS-C patients of this cohort compared with previous studies. The specificity of diagnostic criteria used for MIS-C in this study, younger age of admission to hospital (median age 6 vs. 10 years in previous large cohort[14]), and male predominance are some of the potential reasons for a lower thrombosis prevalence in MIS-C patients.

Hemorrhage occurred in 2% of children, and was graded as severe in half of the cases. The rate of hemorrhage and its severity is in alignment with previously reported adult and pediatric literature on SARS-CoV-2 infection and MIS-C.[14] Hemorrhage was most frequently observed in children with underlying pro-hemorrhagic conditions (thrombocytopenia, cytokine storm, and CHD)[43] or with severe disease (older age and CVC presence likely the surrogate markers of disease severity).[21,22,44] As expected, children with thrombocytopenia had a higher risk of severe hemorrhage; however, hemorrhage prevalence or severity was not altered by administration of anticoagulation or antiplatelet agents. Adult COVID-19 inpatients are reported to have a similar rate of hemorrhagic episodes (2.8%), linked with increased mortality at 28 days.[45] Previous data on hemorrhage in pediatric SARS-CoV-2 patients have indicated no correlation of hemorrhage with mortality, and the current study affirms this observation.[14]

The relationship between SARS-CoV-2 infection and hemorrhage severity in pediatric inpatients is currently unclear. In those with pre-existing hemorrhagic conditions, SARS-CoV-2 or MIS-C may alter the overall bleeding risk and severity, but additional research is needed to ascertain that effect.

This study is unique as it describes hematologic complications of a large, diverse cohort of pediatric inpatients with SARS-CoV-2 infection. The main limitations include its retrospective design and missing patient data. It was not possible to link the time of the laboratory results with clinical events (hemorrhage/thrombosis). Information on the time of initiation of anticoagulation in relation to the timing of hemorrhage or thrombosis during hospitalization, its dose, and duration were not recorded consistently. Hence, the correlation of hemorrhage with the use of anticoagulation agents could not be analyzed conclusively. Small or subsegmental pulmonary embolic events may have not been diagnosed, as CT angiogram of chest was used in a very small

number of children (63/915; 7%) and hence underreported. Rate of obesity in this cohort may also be underreported, as it was not defined based on BMI. The event rate for hemorrhage and thrombosis was low, which led to inability in performing regression analyses and provided uncertainty in the results of comparative statistics.

In conclusion, the dysregulation of hemostasis in hospitalized children with SARS-CoV-2 and MIS-C is more likely to occur among those with underlying comorbid conditions. The rates of thromboses in children are markedly lower than adults, with no observed correlation to prognosis. Ongoing research is critical to determine appropriate management of coagulopathy and thromboprophylaxis in pediatric patients, especially with the advent of variant strains of SARS-CoV-2 virus.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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