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ORIGINAL ARTICLE

Thromboprophylaxis for children hospitalized with COVID-19 and MIS-C

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Abstract

Background: Limited data exist about effective regimens for pharmacological thromboprophylaxis in children with acute coronavirus disease 2019 (COVID-19) and multisystem inflammatory syndrome in children (MIS-C).

Objectives: Study the outcomes of institutional thromboprophylaxis protocol for primary venous thromboembolism (VTE) prevention in children hospitalized with acute COVID-19/MIS-C.

Methods: This single-center retrospective cohort study included consecutive children (aged less than 21 years) with COVID-19/MIS-C who received tailored intensity thromboprophylaxis, primarily with low-molecular-weight heparin, from April 2020 through October 2021. Thromboprophylaxis was given to those with moderate to severe disease based on the World Health Organization scale and exposure to two or more VTE risk factors. Therapeutic intensity was considered for severe illness. Clinical recovery along with D-dimer improvement determined thromboprophylaxis duration. Outcomes were incident VTEs, bleeding, and mortality.

Results: Among 211 hospitalizations, 45 (21.3%) received thromboprophylaxis (COVID-19, 16; MIS-C, 29). Median age was 14.8 years (interquartile range [IQR], 8.9–16.1). Among 35 (77.8%) with severe illness, 27 (60.0%) required respiratory support, and 19 (42.2%) required an intensive care unit stay. Median hospitalization was 6 days (IQR, 5.0–10.5). Median thromboprophylaxis duration was 19 days (IQR, 6.0–31.0) with therapeutic intensity in 24 (53.3%) and prophylactic in 21 (46.7%). Outcomes were as follows: VTE, 1 (2.2%); death, 1 (2.2%, unrelated to bleeding/thrombosis); major/clinically relevant nonmajor bleeding, 0; and minor bleeding, 7 (15.5%). D-dimer was elevated in a majority at diagnosis (median, 2.3; IQR, 1.2–3.3 mg/ml fibrinogen-equivalent units) and was noninformative in assessing disease severity. D-dimer normalized at thromboprophylaxis discontinuation.

Conclusions: Our experience of using clinically directed thromboprophylaxis with tailored intensity approach for children hospitalized with COVID-19 and MIS-C favors its

inclusion in current standard of care. The role of D-dimer in directing thromboprophylaxis management deserves further evaluation.

KEYWORDS
anticoagulants, child, COVID-19, heparin, low molecular weight, MIS-C, thrombosis, venous thromboembolism

Essentials

- Limited data exist about pharmacological thromboprophylaxis for children with acute coronavirus disease 2019/multisystem inflammatory syndrome in children.
- Thromboprophylaxis protocol was framed upon clinical parameters: illness severity and exposure to at least two VTE risk factors.
- Tailored-intensity thromboprophylaxis was administered without clinically significant bleeding or thrombotic events.
- D-dimer levels at diagnosis were not associated with disease severity but were useful in determining the duration of pharmacological thromboprophylaxis.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected more than 400 million people and caused more than 5 million deaths worldwide.[1,2] In children, the SARS-CoV-2 illness is generally mild and asymptomatic but approximately 2% require hospitalization with acute COVID-19 and SARS-CoV-2–related multisystem inflammatory syndrome in children (MIS-C).[3,4] These children generally present with acute respiratory distress syndrome (ARDS), hemodynamic instability, and multiple organ failure with an overall case fatality rate of 2%–5%.[1,2,5–12] Therefore, efforts are invested in evaluating interventions that will prevent fatal outcomes.

Hypercoagulable state, also known as COVID-19–associated coagulopathy (CAC), plays a pivotal role in the pathogenesis of SARS-CoV-2 infection and is associated with poor outcomes.[2,13] Early in the pandemic, almost a third of adult patients hospitalized with COVID-19 had a venous thromboembolic event such as deep vein thrombosis (DVT), pulmonary embolism (PE), or cerebral sinus venous thrombosis, and up to 70% of these adults had a fatal outcome.[14–17] Patients presenting with pneumonia or ARDS were particularly prone to de novo PE and at an eightfold increased risk of dying.[18] Elevated D-dimer level, a biomarker of thrombogenesis, has consistently emerged as an independent risk factor for poor outcomes, including death, in these patients.[19–21] Considering this association between hypercoagulability and adverse outcomes, pharmacological thromboprophylaxis, ranging from prophylaxis to therapeutic intensity, for primary venous thromboembolism (VTE) prevention remains the standard of care for adults hospitalized with COVID-19.[14,15,22–26]

Emerging data among hospitalized children with COVID-19 and MIS-C aligns with adult findings and confirms presence of prothrombotic *milieu*.[10,27–32] These patients have an increased rate of thrombosis and increased mortality, specifically among those with clinical thrombosis supporting a need for thromboprophylaxis.[10,33–36] Patients with MIS-C are at the highest risk of thrombosis (6.5%, 13 times higher than baseline) followed by COVID-19 (2.1%, 4 times higher than baseline).[35] Based on this premise, pediatric thrombosis experts from ISTH proposed a consensus recommendation that was extrapolated from adult experience. Experts recommended to have a low threshold (i.e., a single additional prothrombotic risk factor or markedly elevated plasma D-dimer levels 5 or more times the upper limit of normal [ULN]) for considering thromboprophylaxis with prophylaxis intensity in this population.[37] Some institutions developed thromboprophylaxis protocols of using prophylaxis intensity of anticoagulation based on local experience.[10,38] These protocols incorporated elevated D-dimer (5 or more times ULN) to direct the decision making despite limited data on utility of D-dimer in assessing severity of prothrombotic state in pediatric population. Moreover, concerns remain about efficacy of prophylaxis intensity of thromboprophylaxis for critically sick pediatric patients with COVID-19.[10]

Considering the potential clinical need of thromboprophylaxis in children hospitalized with acute COVID-19 and MIS-C, we implemented a pharmacological thromboprophylaxis protocol at our institute for primary VTE prevention. In this report, we aim to evaluate the outcomes of this prospectively implemented institutional thromboprophylaxis protocol. Additionally, we explored whether differences exist between the cohorts, COVID-19 versus MIS-C, with regards to clinical and laboratory features and whether there was association between disease severity and CAC markers.

2 | METHODS

2.1 | Cohort description

This retrospective cohort study included all consecutive patients, aged less than 21 years, admitted to our tertiary children's hospital with confirmed diagnosis of acute SARS-CoV-2 infection or MIS-C

between April 1, 2020, and October 31, 2021. Institutional review board approved the study. Consent was not required. Subjects were identified using International Classification of Diseases, Tenth Revision codes from the Centers for Disease Control and Prevention (CDC) guidance document (Appendix S1A).[39]

2.1.1 | Inclusion and exclusion criteria

Eligibility criteria required a laboratory-confirmed SARS-CoV-2 infection within 6 weeks of admission and hospitalized for at least 24 h. Exclusion criteria were (1) requirement of thromboprophylaxis for reasons unrelated to SARS-CoV-2 infection; and (2) hospitalization for VTE diagnosis requiring therapeutic anticoagulation for acute and subacute thrombosis, that is, secondary thromboprophylaxis. Follow-up information was collected for all eligible patients through November 30, 2021, at least 30 days after hospitalization. Hematology consultation was mandatory for thromboprophylaxis management.

2.1.2 | SARS-CoV-2 diagnosis

CDC recommendations were followed for diagnosis and surveillance of SARS-CoV-2 infection.[8] It required confirmation by reverse transcription polymerase chain reaction (PCR), antigen testing from respiratory swab, and/or serological evidence of SARS-CoV-2 antibody for MIS-C and clinical interpretation by epidemiology staff (Appendix S1B).[40]

2.1.3 | Data collection and variables

Data collection included demographic, disease, and treatment characteristics as well as status at last follow-up. The disease characteristics included clinical presentation, illness severity, and hospital course including intensive care unit (ICU) admission. Treatment characteristics included medications, type of respiratory support, and requirement of other interventions like extracorporeal membrane oxygenation or dialysis. Data on underlying comorbid conditions and known risk factors for VTE—obesity, presence of central venous line (CVL), invasive ventilation, severe dehydration, thrombophilia history (personal/family history of thrombophilia), immobilization (48 h or more), estrogen-containing hormonal therapy, pregnancy, cancer, asparaginase therapy, major trauma, and inflammatory conditions (MIS-C, nephrotic syndrome, Crohn disease, etc.)—were collected (Table 1).[37,41,42] Obesity was defined per the CDC as a body mass index of 95% or greater for those aged 2 years or above.[43] MIS-C was considered an inflammatory risk factor. Laboratory and imaging data at presentation and during hospitalization were collected.

2.2 | Definitions of cases and disease characterization

2.2.1 | Case classification

Cases were classified into three groups based on clinical presentation as "asymptomatic," "acute COVID-19," and "MIS-C." Those patients who were admitted for non–COVID-19 illness and were incidentally found to have a positive screen for SARS-CoV-2 in the absence of symptoms were classified as "asymptomatic." Those who were admitted for symptomatic SARS-CoV-2 infection (i.e., cough, shortness of breath, vomiting, headache, myalgias, symptoms of hemodynamic instability) were classified as "acute COVID-19." Patients with MIS-C met the CDC definition[44] and diagnosis was confirmed by local rheumatology experts.[34] If a patient presented with COVID-19 and overlapping MIS-C criteria, the patient was included under initial diagnosis at admission. Patients with multiple encounters were included separately for each qualifying encounter.

2.2.2 | Disease severity assessment

Coronavirus disease 2019 severity was classified according to the World Health Organization (WHO) progression scale as moderate (score 4 or 5) or severe (score 6, 7, 8, or 9) or dead (10) depending on oxygen requirement, ICU admission, and requirement of other interventions (Figure 1).[17] Oxygen requirement of less than 5 L/min by nasal canula was considered "low flow," while oxygen requirement of 5 L/min or greater, continuous positive airway pressure, bilevel positive airway pressure, and ventilator support were considered "high flow." For patients with MIS-C, the WHO progression scale was modified to assess severity as follows: those requiring therapy on an acute care floor were considered "moderate" and those requiring ICU admission for ventilator and/or vasopressor support were considered "severe" (Figure 1). Severity of cardiac involvement was determined by the cardiology team. Patients were managed according to national guidelines on COVID-19 and MIS-C treatment.[33,34]

2.3 | Pharmacological thromboprophylaxis protocol

Thromboprophylaxis, in consultation with hematology, was given to patients with moderate to severe disease and exposure to two or more risk factors for VTE without an overt risk of bleeding.[45] The intensity of anticoagulation, prophylaxis versus therapeutic, was determined on the basis of illness severity.[17] Figure 2 provides the basic framework of our thromboprophylaxis protocol. In general, children with moderate disease (WHO progression scale, 4 or 5) and admission on the regular floor generally received prophylaxis intensity of thromboprophylaxis, while children with

TABLE 1 Demographic characteristics, clinical presentation, and VTE risk factors of study cohort

Variables	COVID-19 with thromboprophylaxis (*n* = 16)	MIS-C with thromboprophylaxis (*n* = 29)	Thromboprophylaxis cohort (*N* = 45)
Age at hospitalization			
Median age, years (IQR)	15.4 (7.8–16.1)	14.6 (8.9–16.1)	14.8 (8.9–16.1)
Age category, years, *n* (%)			
0–1	2 (12.5)	1 (3.4)	3 (6.7)
2–12	4 (25.0)	12 (41.4)	16 (35.6)
13–21	10 (62.5)	16 (55.2)	26 (57.8)
Sex			
Female, *n* (%)	6 (37.5)	14 (48.3)	20 (44.4)
Race, *n* (%)			
African American/Black	3 (18.8)	4 (13.8)	7 (15.6)
Hispanic/Latino	3 (18.8)	7 (24.1)	10 (22.2)
White	7 (43.8)	16 (55.2)	23 (51.1)
Not Reported/Other[a]	3 (18.8)	2 (6.8)	5 (11.1)
Underlying medical condition, *n* (%)			
Malignancy	3 (18.8)	0 (0.0)	3 (6.7)
Type 1 diabetes	0 (0.0)	1 (3.4)	1 (2.2)
Autoimmune disease	0 (0.0)	1 (3.4)	1 (2.2)
Immunosuppressed,[c] *n* (%)	3 (18.8)	0 (0.0)	3 (6.7)
Pulmonary disease[d]	3 (18.8)	4 (13.8)	7 (15.6)
No medical illness[e]	5 (31.2)	15 (51.7)	20 (44.4)
Clinical presentation, *n* (%)			
Respiratory symptoms	16 (100.0)	14 (48.3)	30 (66.7)
GI symptoms	14 (87.5)	28 (96.6)	42 (93.3)
Cardiac symptoms	7 (43.8)	25 (86.2)	32 (71.1)
Neurological symptoms	5 (31.2)	9 (31.0)	14 (31.1)
Type of respiratory support, *n* (%)			
Any	15 (93.8)	12 (41.4)	27 (60.0)
Nasal cannula: Low flow	4 (26.7)	5 (41.7)	9 (33.3)
Nasal cannula: High flow	5 (33.3)	4 (33.3)	9 (33.3)
Noninvasive Ventilation, *n* (%)	1 (6.7)	1 (8.3)	2 (7.4)
Invasive ventilation	5 (33.3)	2 (16.7)	7 (25.9)
VTE risk factors			
Obesity[b]/patient numbers, (%)	7 (53.8)/(*N* = 13)	9 (34.6)/(*N* = 26)	16 (41.0)/(*N* = 39)
Central venous line (CVL), *n* (%)	8 (50.0)	5 (17.2)	13 (28.9)
Immobility	9 (56.2)	14 (48.3)	23 (51.1)
Cancer/Malignancy, *n* (%)	2 (12.5%)	0 (0%)	2 (4.4%)
Major trauma	0 (0)	0 (0)	0 (0.0)
Severe dehydration	3 (18.8)	11 (37.9)	14 (31.1)
Estrogen therapy	3 (18.8)	1 (3.4)	4 (8.9)
Inflammatory conditions[f]	7 (43.8)	29 (100.0)	36 (80.0)
Thrombophilia	0 (0)	3 (10.3)	3 (6.7)
Other	5 (31.2)	11 (37.9)	16 (35.6)

Abbreviations: COVID-19, coronavirus 2019; CVL, central venous line; GI, gastrointestinal; MIS-C, multisystem inflammatory syndrome in children; SD, standard deviation; VTE, venous thromboembolism; WHO, World Health Organization.

[a]Other race combines categories of American Indian/Alaska Native, Asian, Multiracial/two or more races, and Native Hawaiian/Pacific Islander. Test for independence between race and group was conducted by Fisher's exact test of race categories as described, excluding subjects without a reported race.

[b]Obesity is defined as body mass index ≥95th percentile for patients <2 years old on the CDC growth chart.

[c]Immunosuppressed category includes primary immunodeficiency or acquired immunodeficiency due to immunosuppression.

[d]Pulmonary disease includes asthma and cystic fibrosis.

[e]No known prior medical illness.

[f]Includes chronic inflammatory conditions like nephrotic syndrome, Crohn disease, lupus, and MIS-C.

(A) WHO Progression Scale for COVID-19[17]

Patient State	Descriptor for COVID-19	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic : viral RNA detected	1
	Symptomatic : independent	2
	Symptomatic : assistance needed	3
Hospitalized : moderate disease	Hospitalized : no oxygen therapy	4
	Hospitalized : oxygen by mask or nasal prongs (< 5L/min)	5
Hospitalized : severe disease	Non-invasive ventilation or high flow	6
		7
	Invasive mechanical ventilation without other organ support	8
	Invasive Mechanical ventilation and vasopressor	9
	Invasive mechanical ventilation and vasopressor with other organ support (CRRT, ECLS)	
Dead	Dead	10

(B) Modified WHO Progression Scale for MIS-C for disease severity assessment

Patient State	Descriptor for COVID-19	Score
Hospitalized : moderate disease	Hospitalized on regular floor:	
	No hemodynamic instability or vasopressor support normal cardiac function, coronaries normal	4
	Oxygen by mask or nasal prongs (< 5L/min), normal cardiac function	4
	Hospitalized on regular floor and cardiac findings:	
	ECHO, cardiac function good or myocarditis+/- (>40% ejection fraction)	4
	ECHO, cardiac function good or myocarditis+/- (<40% ejection fraction), no vasopressor support;	5
	Presence of coronary dilatation+/- but no giant coronary aneurysm, no vasopressor support	4
	Presence of coronary dilatation: multiple and/or giant coronary aneurysm, no vasopressor support	5
	Any other finding on ECHO/EKG which is significant as per cardiology requiring duel therapy with antiplatelet and anticoagulation	5
Hospitalized : severe disease	Hospitalized on regular floor or ICU: Non-invasive ventilation or high flow	6
	Hospitalized on regular floor with multiple cardiac findings with high flow oxygen	7
	Hospitalized in ICU, Invasive mechanical ventilation without other organ support	8
	Hospitalized in ICU, requirement of vasopressor support	8
	History of cardiac arrest	9
	Invasive Mechanical ventilation and vasopressor with or without other organ support (CRRT, ECLS)	9
Dead	Dead	10

FIGURE 1 WHO Progression Scale for COVID-19 (A) and modified scale for MIS-C (B) for disease severity assessment. Abbreviations: COVID-19, coronavirus disease 2019; CRRT, continuous renal replacement therapy; ECLS, extracorporeal life support; MIS-C, multisystem inflammatory syndrome in children; WHO, World Health Organization

severe disease (WHO progression scale, 7–9) and admitted in ICU received therapeutic intensity. Whenever possible, coagulopathy testing including D-dimer was performed at the time of thromboprophylaxis initiation. Low-molecular-weight heparin (LMWH) was the preferred choice, but unfractionated heparin (UFH) was used when risk of bleeding was high and/or invasive interventions were anticipated. Anticoagulation dosing and monitoring was performed according to age- and weight-based dosing regimens.[46] In brief, LMWH was commenced at 0.5–1.7 mg/kg/dose (maximum, 80 mg/dose) twice daily and was titrated to maintain an anti-Xa level between 0.3–0.5 or 0.5–1.0 IU/ml depending on prophylaxis or therapeutic intensity, respectively. Children with acute kidney injury were started on 50% of the required dose to accommodate delayed excretion, and infants aged 2 months or younger received higher dosing. For UFH, established nomogram of partial thromboplastin time (PTT) monitoring was used.[46] The duration of anticoagulation was planned for 2 weeks and was extended or shortened based on clinical resolution and normalization of D-dimer. Cardiology contributed to extending the duration of thromboprophylaxis in addition to antiplatelet therapy based on improvement in cardiac status. Upon discharge, patients were followed primarily via telemedicine.

2.4 | Outcome assessment

Outcomes included duration of hospitalization, ICU admission rate and duration, incident VTEs, readmission due to SARS-CoV-2–related complications, bleeding diathesis, other thromboembolic events, and mortality (all-cause and VTE related). The thromboprophylaxis-specific outcomes—bleeding and incident VTE events—were classified according to ISTH recommendations.[47] Bleeding diathesis was evaluated as major, clinically relevant nonmajor bleeding (CRNMB) and minor bleeding. Major bleeding was defined as fatal bleeding, bleeding within vital organs, or requirement of blood transfusion for a drop in hemoglobin of more than 2 gm/dl and/or any bleeding requiring medical/surgical intervention, while CRNMB was defined as any bleeding requiring therapeutic intervention and discontinuation of anticoagulation. Any nonmajor bleeding such as easy bruising, injection site bleeding, and epistaxis that did not require therapeutic intervention and or discontinuation of anticoagulation was classified as minor. VTE events required objective confirmation by imaging.

2.5 | Statistical analysis

Summary statistics and descriptive analyses were performed according to total number of eligible encounters. Categorical measures were assessed using counts and percentages. Continuous measures were assessed using medians and interquartile ranges (IQRs) due to the skewed nature of the data. Comparisons between groups (COVID-19 and MIS-C) were performed using Fisher's exact tests for categorical measures and Wilcoxon rank-sum tests for continuous measures. Additional analyses were performed for COVID-19 patients according to WHO classification,[17] in which Wilcoxon rank-sum tests were used to evaluate whether individuals with moderate versus severe

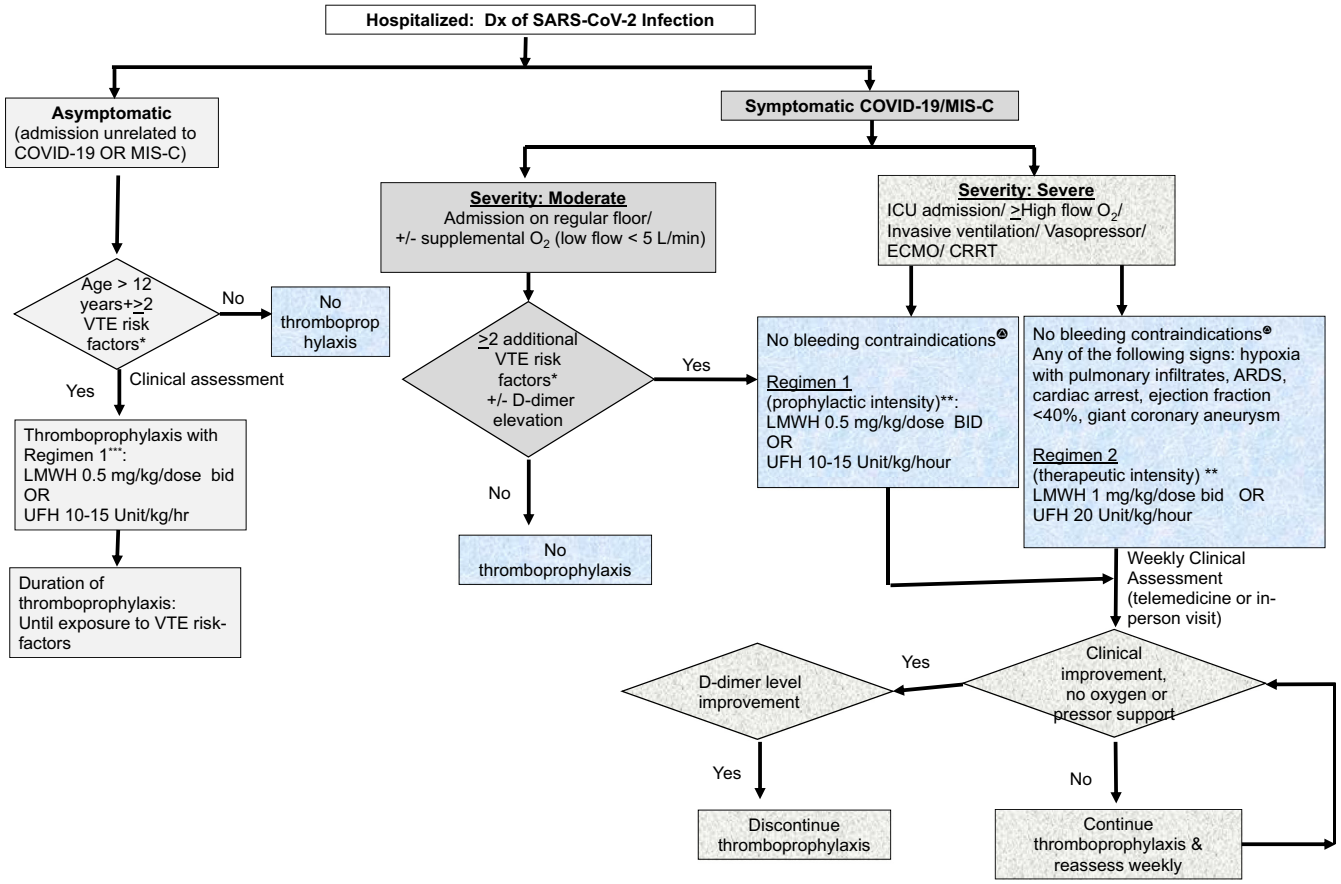

FIGURE 2 Clinical framework for pharmacological thromboprophylaxis for primary venous thromboembolism prevention. Abbreviations: COVID-19, Coronavirus disease 19; MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

COVID-19 and MIS-C had different D-dimer levels at presentation. Post hoc *p* values were employed to quantify the likelihood of observing discrepancies between different groups according to chance alone. Two-sided *p* values of less than 0.05 were considered to indicate statistical significance. Due to the exploratory nature of this analysis, *p* values were not adjusted for multiple comparisons. Analyses were performed using R software version 4.1.1 (R Foundation for Statistical Computing).

3 | RESULTS

A total of 296 hospitalizations in 268 patients with a positive SARS-CoV-2 PCR test or diagnosis of MIS-C were identified. Eighty-five encounters were excluded as they did not fulfill study inclusion criteria (Figure 3). The remaining 211 hospitalizations were as follows: asymptomatic, 104 (49.2%); symptomatic COVID-19, 71 (33.6%), and MIS-C, 36 (17.1%). The median age was 10 years with more males than females (54% vs. 46%) and predominantly White (63.5%), followed by African American (12.3%) and Hispanic/Latino (10.9%). The demographics and patient characteristics of the entire cohort is illustrated in Appendix S1C. Among these 211 encounters, 53 received thromboprophylaxis (asymptomatic, 6 [11.3%]; COVID-19, 18 [34.0%]; MIS-C, 29 [54.7%]). Upon further review, 8 of these 53 (6 asymptomatic, 2 COVID-19) were excluded from analyses, as they did not qualify for thromboprophylaxis. Thus, the final thromboprophylaxis cohort consisted of 45 (21.3%) patients with 45 encounters.

3.1 | Thromboprophylaxis cohort (*n* = 45)

Thromboprophylaxis cohort demography is illustrated in Table 1. The median age was 14.8 years (IQR, 8.9–16.1) and a majority (57.8%; *n* = 26) were older than 12 years. More than half (55.6%; *n* = 25), had one or more preexisting comorbid medical conditions. Among 39 patients older than 2 years, 16 (41.0%) were obese. A majority of the COVID-19 cohort (77.8%; *n* = 35) had severe disease and required respiratory support, while the majority of the MIS-C cohort (86.2%; *n* = 25) presented with cardiac complications.

3.2 | Thromboprophylaxis characteristics

Among the 45 children, 53.3% (*n* = 24) received therapeutic intensity, while 46.7% (*n* = 21) received prophylactic intensity (Table 2). Twenty-three patients were on concurrent aspirin therapy at 3–5 mg/kg/day (COVID-19, 1; MIS-C, 22). For thromboprophylaxis, 3 received initial treatment with UFH (COVID-19, 2; and MIS-C, 1)

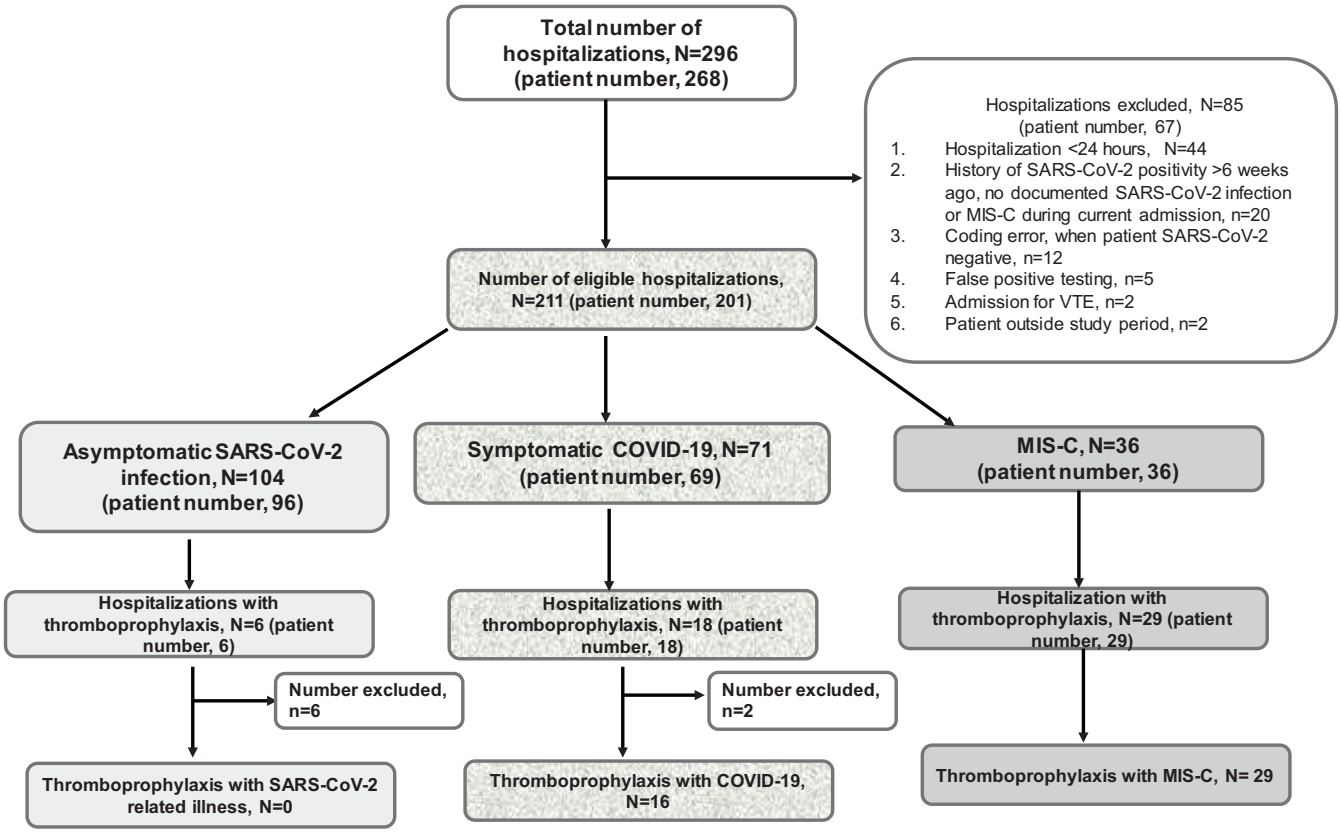

FIGURE 3 Flow diagram showing eligible cohort who received pharmacological thromboprophylaxis for prevention of VTE due to SARS-CoV-2 infection, COVID-19, and/or MIS-C. Flow diagram showing cohort selection. Abbreviations: COVID-19, coronavirus disease 2019; MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

and one patient with MIS-C received fondaparinux due to concern for heparin-induced thrombocytopenia (HIT). LMWH was resumed upon negative HIT assay. Anti-Xa monitoring was performed in 43 (95.6%) patients; 25 (58%) achieved the goal within 48 hours, while the remaining 18 (42%) required at least one dose titration to achieve required goal of thromboprophylaxis. The median dose of LMWH for prophylaxis and therapeutic intensity was 0.5 mg/kg/dose (IQR, 0.5–1.0) and 1.0 mg/kg/dose (IQR, 1–1) twice daily, respectively. The median duration of anticoagulation was 19 days (IQR, 6–31); 30 (66.6%) continued anticoagulation after discharge, for a median of 16 days (IQR, 9–24). MIS-C patients received anticoagulation for longer duration 22 days (IQR, 12–39) versus 12 days (IQR, 6–21.5) for COVID-19.

3.3 | Cohort outcomes

Cohort outcomes are given in Table 3. The median duration of hospitalization was 6 days (IQR, 5.0–10.5), while the median follow-up was 296 days. The ICU admission rate was higher for the MIS-C cohort, 44.8% (n = 13), compared to 37.5% (n = 6) for the COVID-19 cohort (p = 0.634). The median duration of ICU stay was longer for the COVID-19 cohort compared to MIS-C, 19.0 versus 3.0 days respectively (p = 0.014). One patient with MIS-C was readmitted due to ongoing cardiac problems. No event of major bleeding or CRNMB was reported. Seven (15.5%) experienced minor bleeding (severe, 4; moderate, 3): epistaxis, 3; injection site hematoma and bruising, 4. Five of these seven were on concurrent aspirin therapy. One patient developed CVL-related VTE, 2.2% (95% CI, 0.06–11.8%). This patient with severe COVID-19 required invasive ventilation and needed therapeutic intensity of thromboprophylaxis. However, he received prophylaxis intensity of thromboprophylaxis with UFH due to recent intracranial hemorrhage (ICH). One patient with severe MIS-C developed superficial thrombophlebitis while on therapeutic UFH. He was suspected to have HIT. No event of arterial thrombosis or PE was documented. All-cause mortality was 2.2% (95% CI, 0.06%–11.8%), with one death reported in a medically complex patient with MIS-C and supraventricular tachycardia. The patient died 3 months after discharge.

3.4 | D-Dimer and other coagulopathy testing

Table 2 shows the laboratory testing for the thromboprophylaxis patients. D-dimer was available for 44 (97.8%) patients at diagnosis and in 38 (84.4%) at the end of treatment. The D-dimer levels were elevated at least 2 times the ULN at diagnosis and improved in all with most normalized (78.9%; n = 38) at therapy discontinuation. Median D-dimer levels were significantly higher in the MIS-C cohort compared to the COVID-19 cohort (p = 0.001; Figure 4). No association was noted

TABLE 2 Characteristics of disease severity, VTE risk factors, primary thromboprophylaxis therapy, and laboratory testing

Variables	COVID-19 with thromboprophylaxis (*n* = 16)	MIS-C with thromboprophylaxis (*n* = 29)	Thromboprophylaxis cohort (*N* = 45)
Disease severity (WHO progression scale),[a] *n* (%)			
Moderate (4–5)	4 (25.0)	6 (20.7)	10 (22.2)
Severe (6–9)	12 (75.0)	23 (79.3)	35 (77.8)
Median number of VTE risk factors (IQR)	3.00 (2.75–3.00)	3.00 (2.00–3.00)	3.00 (2.00–3.00)
Antiplatelet therapy, *n* (%)			
Aspirin	1 (6.2)	22 (75.9)	23 (51.1)
Anticoagulation therapy			
Therapeutic intensity, *n* (%)	8 (50.0)	16 (55.2)	24 (53.3)
Prophylactic intensity, *n* (%)	8 (50.0)	13 (44.8)	21 (46.7)
Duration (days), median (IQR)	12.0 (6.0–21.5)	22.0 (12.0–39.0)	19.0 (6.0–31.0)
Coagulation testing, median (IQR)			
D-Dimer at Presentation (ULN, 0.5 mg/L FEU)	1.2 (0.9–1.6) (*N* = 16)	2.9 (21.9–3.8) (*N* = 28)	2.3 (1.2–3.3) (*N* = 44)
D-Dimer at discontinuation (ULN, 0.5 mg/L FEU)	0.43 (0.32–0.56) (*N* = 15)	0.28 (0.23–0.39) (*N* = 23)	0.32 (0.25–0.46) (*N* = 38)
Prothrombin Time(s)/IQR (Range: 9–12 s)	11.0 (11.0–11.0) (*N* = 15)	12.5 (12.0–13.0) (*N* = 26)	12.0 (11.0–13.0) (*N* = 41)
Partial thromboplastin time (s)/ IQR (range: 22–31 s)	29.0 (27.0–32.5) (*N* = 15)	29.5 (27.0–31.0) (*N* = 26)	29.0 (27.0–31.0) (*N* = 41)
von Willebrand Factor antigen, VWF:Ag (%) (range, 50%–160%)	244 (240–247) (*N* = 2)	313 (272–363) (*N* = 14)	286 (261–355) (*N* = 16)
Factor VIII (range, 48–150)	255 (199–283) (*N* = 3)	319 (251–394) (*N* = 13)	283 (241–379) (*N* = 16)
Fibrinogen (mg/dl) (range: 198–448 mg/dl)	405 (257–511) (*N* = 14)	540 (501–677) (*N* = 27)	518 (371–554) (*N* = 41)
Lupus anticoagulant (positive) (Normal: negative), *n* (%)	0 (0.0) (*N* = 4)	2 (15.4) (*N* = 13)	2 (11.8) (*N* = 17)
Inflammatory markers			
Ferritin (ng/ml) (range,13–150 ng/ml)	742 (204–1870) (*N* = 14)	425 (272–657) (*N* = 25)	445 (267–890) (*N* = 39)
NT-proBNP (pg/ml) (range, 10–242 pg/ml)	100 (13–1637) (*N* = 13)	2930 (822–6088) (*N* = 26)	1628 (210–4450) (*N* = 39)
CRP (mg/dl) (range, <0.5 mg/dl)	4.1 (1.0–8.1) (*N* = 14)	14.6 (10.8–20.6)	11.8 (4.7–18.1) (*N* = 41)
Blood counts			
WBC (k/mm^3)/IQR (range, 4.5–13 k/mm^3)	5.0 (3.2–7.9) (*N* = 16)	9.1 (6.6–12.8) (*N* = 28)	8.3 (4.4–12.4) (*N* = 44)
ANC (k/mm^3)/IQR (range, 1700–7500)	3.5 (2.1–5.9) (*N* = 16)	7.0 (5.2–9.3) (*N* = 28)	5.8 (3.3–8.9) (*N* = 44)
ALC (k/mm^3)/IQR (range, 1200–7500)	0.7 (0.5–1.5) (*N* = 15)	0.9 (0.7–1.2) (*N* = 29)	0.9 (0.6–1.3) (*N* = 44)
Platelets (k/mm^3)/IQR (range, 150–400 k/mm^3)	206 (150–221) (*N* = 16)	198 (129–273) (*N* = 28)	203 (145–267) (*N* = 44)

Abbreviations: +ve, positive; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; FEU, fibrinogen-equivalent units; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ULN, upper limit of normal; WBC, white blood cell count.

[a]Reference [17].

between the WHO disease severity score and D-dimer values at presentation (Figure 4). No difference was noted between the moderate and severe category within COVID-19 (1.79 vs. 1.11 mg/ml fibrinogen-equivalent units [FEU]) and MIS-C cohort (3.75 vs. 2.69 mg/ml FEU).

Median blood counts and screening coagulation testing was done in a majority of patients and was within normal range. Other coagulation tests like fibrinogen, von Willebrand factor (VWF) antigen and factor VIII activity levels were available for limited number of patients, and all were elevated twice the ULN. Inflammatory markers, C-reactive protein (CRP) and ferritin were significantly higher for MIS-C cohort compared to COVID-19. Lupus anticoagulants were available in 17 (37.8%) and 2 (11.8%) were positive, both with MIS-C diagnosis.

4 | DISCUSSION

This report summarizes the outcomes of a prospectively implemented pharmacological thromboprophylaxis in pediatric patients with acute COVID-19 and MIS-C. To our knowledge, this is the second pediatric report of using thromboprophylaxis for this population[48] and the first one to have a provision to tailor the intensity of anticoagulation. Before the COVID-19 pandemic, our practice of using thromboprophylaxis for adolescents and young adults was limited to select patients, as the baseline risk of VTE in hospitalized children is extremely low, at 0·01–0·05 per 1000 children per year,[49,50] which is 20–100 times lower than in adults.[51,52] During this pandemic, we

TABLE 3 Hospitalization and outcomes of the pharmacological thromboprophylaxis population (analyses based on hospital encounters)

Outcome variable	COVID-19 with thromboprophylaxis (*N* = 16)	MIS-C with thromboprophylaxis (*N* = 29)	Thrombo-prophylaxis cohort (*N* = 45)	Posthoc *p* value[c]
ICU admission, *n* (%)	6 (37.5)	13 (44.8)	19 (42.2)	0.634
Days in ICU				
Median (IQR)	19.0 (13.8–28.0)	3.0 (2.0–4.0)	3.0 (3.0–18.5)	0.014
Range	3–38	1–25	1–38	
Days in hospital				
Median (IQR)	11.0 (5.0–21.5)	6.0 (4.0–7.0)	6.0 (5.0–10.5)	0.036
Range	1–55	2–30	1–55	
ARDS, *n* (%)	4 (28.6)	4 (14.8)	8 (19.5)	0.411
Pneumonia, *n* (%)	12 (87.5)	3 (11.1)	15 (36.6)	<0.001
Hypotension, *n* (%)	6 (40.0)	12 (42.9)	18 (41.9)	>0.999
Cardiac complications, *n* (%)	1 (6.2)	9 (31.0)	10 (22.2)	0.071
Readmission,[b] *n* (%)	0 (0.0)	1 (3.4)	1 (2.2)	>0.999
VTE,[a] *n* (%)	0 (0.0)	1 (3.4)	1 (2.2)	>0.999
Major bleeding/CSNMB, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Mortality/Death, *n* (%)	0 (0.0)	1 (3.4)	1 (2.2)	>0.999
Follow-up duration, days, median (IQR)	86 (74–392)	312 (232–349)	296 (89–355)	0.115

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CSNMB, clinically significant non-major bleeding; ICU, intensive care unit; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; NA, not applicable; SD, standard deviation; VTE, venous thromboembolic events; WHO, World Health Organization.

[a]Thrombotic event occurred before commencement of anticoagulation.

[b]Readmission was counted only if the patient continued to meet study inclusion criteria.

[c]*p* values are between symptomatic COVID-19 and MIS-C cohort.

broadened the scope of thromboprophylaxis to children with all ages presenting with SARS-CoV-2–related illness. The development and successful implementation of our thromboprophylaxis protocol required a multidisciplinary consensus, as there was a paucity of high-quality evidence to support this practice. The unique features of our thromboprophylaxis approach and key observations are discussed as follows: (1) reasoning for using the clinical framework alone for directing the decision of thromboprophylaxis intervention; (2) utility of D-dimer for thromboprophylaxis management; (3) insight about coagulopathy; (4) consideration of a tailored-intensity approach for thromboprophylaxis; (5) bleeding and thrombosis outcomes of thromboprophylaxis; and (6) study limitations.

4.1 | Clinical framework for thromboprophylaxis intervention

The reasons for choosing the clinical framework for directing thromboprophylaxis were multifold. First, we were unsure about the feasibility of timely blood draws due to strict isolation precautions and requirement of minimizing patient contact with this population. Second, there is limited experience of using thromboprophylaxis in this population. Third, the diagnostic and prognostic utility of D-dimer in pediatrics (with and without acute COVID-19/MIS-C) for incident VTE events is unclear[10,37,38,53–56] and hence to inform thromboprophylaxis decision in this population. Therefore, the choice of clinically driven decision making (over biomarker-driven decision making) was felt to be appropriate for patient care.[57,58] The incorporation of the WHO scale to have a uniform approach for assessing COVID-19/MIS-C severity and careful assessment by hematology to weight the risk of bleeding versus risk of VTE predisposition helped identify high-risk patients and ensured patient safety.

4.2 | Utility of D-dimer for thromboprophylaxis management

Considering the significance of D-dimer in CAC, we attempted to clarify if D-dimer could be used to direct the decision of thromboprophylaxis. Our data suggested that D-dimer levels were elevated (2 times ULN or greater) in a majority of patients with COVID-19/MIS-C; patients with MIS-C had significantly higher values (greater than 5 times ULN) than COVID-19 (greater than 2 times ULN), but no association was observed between the WHO severity score and D-dimer values. Since the VTE event rate was low in our study (occurred in one patient with suboptimal thromboprophylaxis), our data

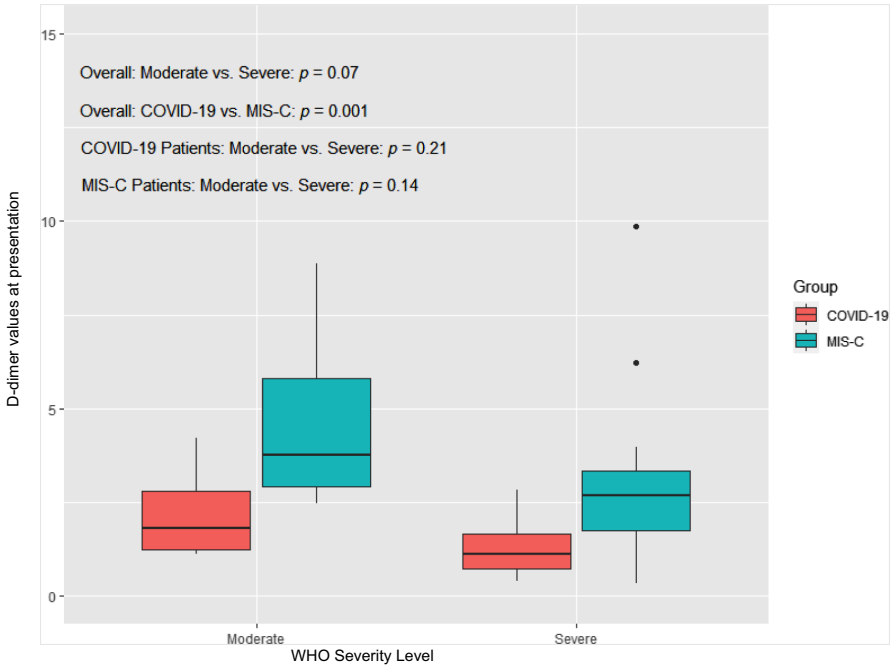

FIGURE 4 D-Dimer values at presentation and COVID-19 and MIS-C severity levels for pharmacological thromboprophylaxis cohort. Abbreviations: COVID-19, coronavirus disease 2019; MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

are insufficient to recommend a specific cutoff value for D-dimer to direct the thromboprophylaxis decision. On the same note, current literature clarifying the utility of D-dimer as a predictor of VTE in this population is inconsistent. For example, two recent reports, though underpowered, did not find an association between D-dimer values and disease severity and the prothrombotic state in this population.[31,59] The largest multicenter cohort study to date found that D-dimer levels greater than 5 times ULN was significantly associated with thromboembolic events in a cohort of 814 patients with SARS-CoV-2 infection.[35] Besides being a retrospective study, the high proportion of patients in this cohort had missing laboratory values, making it challenging to apply these results in clinical decision making. Similarly, Mitchell et al.[10] identified a trend of D-dimer levels greater than 5 μg/ml among patients with acute COVID-19 and VTE, and acknowledges that D-dimer levels were not a statistically significant risk factor for VTE potentially due to small sample size of the cohort (odds ratios of D-dimer as a risk factor was fairly high but failed to reach significance due to the small sample size and approximately 25% of patients with missing values). Thus, it is possible that D-dimer levels above a certain threshold (i.e., greater than 5 times ULN) may indeed have predictive value on the development of VTE in this population, particularly among children diagnosed with MIS-C.

In our study, D-dimer levels did reflect disease course with elevation at presentation due to SARS-CoV-2–induced inflammation and normalization or reduction as inflammation improved by 2–3 weeks. This timeline aligns with the median duration of anticoagulation, 2 weeks for COVID-19 and slightly over 3 weeks for MIS-C. Therefore, it is reasonable to interpret that follow-up D-dimer levels at 2- to 3-week time points may be helpful to guide discontinuation of anticoagulation in patients with COVID-19 and MIS-C, respectively.

4.3 | COVID-19– and MIS-C–associated coagulopathy

Since coagulopathy workup was not done consistently in our cohort, we cannot comment about the utility of these biomarkers in this population. Unlike the adult experience, the majority had normal platelet count, and normal prothrombin time/PTT, limiting their usefulness for informing anticoagulation intervention. Elevated fibrinogen, VWF, and factor VIII levels supported existing data that underlying vasculopathy and endothelial activation contributes to coagulopathy.[60,61] As expected, the MIS-C cohort had significantly higher levels of inflammatory markers including CRP, fibrinogen, and D-dimer compared to COVID-19 due to the ongoing cytokine storm driving mutually amplifying loops of coagulation, inflammation and hyperfibrinolysis.[32,62–64] Based on this a priori knowledge, our decision to consider MIS-C as one of the inflammatory risk factors for VTE is justified.

4.4 | Tailored approach for thromboprophylaxis intensity

We tailored the thromboprophylaxis intensity depending on disease severity due to increased risk of de novo thrombosis despite prophylaxis intensity of anticoagulation.[18] We used therapeutic intensity of anticoagulation for patients with severe disease typically with respiratory failure and hemodynamic instability.[17] Our approach is supported by Mitchell et al.[10] These investigators shared concerns that "prophylaxis intensity" of anticoagulation with LMWH offered suboptimal protection in their study cohort (n = 27), specifically for those with respiratory failure. Among these 27 children, 40% developed VTE, and

those who died had VTE. Therefore, Mitchell et al.[10] recommended therapeutic intensity of anticoagulation for children presenting with hypoxia and requiring high levels of respiratory support. One of their patients developed a VTE 2 weeks after discharge, suggesting a need for anticoagulation after discharge, perhaps until resolution of inflammation. A recent Phase II study by Sochet et al.[48] showed that prophylaxis intensity of LMWH was safe in this population (n = 38) and more than 90% of the cohort achieved target anti-Xa levels during hospitalization with 0.5 mg/kg/dose every 12 h dosing. Although this study did not discuss illness severity, it calls into question our approach of using therapeutic intensity of LMWH in select patients and raises concerns as to why approximately 40% of our cohort did not achieve the target anti-Xa. Clearly, the need for therapeutic intensity of thromboprophylaxis for a subset of population needs further evaluation.

4.5 | VTE outcomes

We did not use thromboprophylaxis for asymptomatic patients. Since no VTE event was reported in this population, it is reasonable to assume that children hospitalized with asymptomatic SARS-CoV-2 may not need thromboprophylaxis for CAC. Whitworth et al.[35] have also reported that asymptomatic SARS-CoV-2 infection does not increase a patient's VTE risk. We observed two thrombotic events after initiation of thromboprophylaxis in patients with moderate to severe COVID-19/MIS-C. Both were related with vascular access trauma.[65] One of our patients received prophylaxis intensity thromboprophylaxis despite severe illness due to risk of ICH. The other developed a superficial thrombosis and died after discharge. Sochet et al.[48] have also reported two CVL-related VTE events (5.2%; 90% CI, 1.0–15.7%) in their Phase II thromboprophylaxis trial. Occurrence of CVL-related thrombosis despite thromboprophylaxis is not unexpected, as the meta-analysis by Vidal et al. has previously shown that LMWH does not prevent CVL-related VTE (relative risk, 1.13; 95% CI, 0.51–2.50).[65] We did not experience PE or fatal VTE. Therefore, it is reasonable to conclude that our thromboprophylaxis approach was overall effective in our cohort.

4.6 | Bleeding outcomes

We did not observe any major or CRNM bleeding diathesis supporting that tailored-intensity thromboprophylaxis was safe in this population. The minor bleeding events were noted in 15.5% of patients, and the majority were also receiving concurrent antiplatelet therapy. While the rate of minor bleeding seems high, it is comparable with previous reports of minor bleeding events ranging from 15 to 20%.[66,67] Regardless, this bleeding risk is acceptable as the VTE risk without anticoagulation is 10–20 times higher in the context of COVID-19/MIS-C.[35]

4.7 | Study limitations

The limitations of the study deserve discussion. First, the results of our study should be interpreted with caution due to its small sample size. Second, the single institutional experience limits the generalizability of the results. Nevertheless, clinical presentation of our patients was comparable to national reports of COVID-19/MIS-C, implying that our intervention could benefit this population beyond our institute.[36,68] Third, the retrospective study design may have contributed to selection bias. We emphasize that the thromboprophylaxis protocol was implemented prospectively, and investigators used the uniform approach for managing these children to reduce this weakness. Fourth, the clinical approach for directing initiation of thromboprophylaxis and using D-dimer for determining the therapy duration was not derived from high-quality data and may reflect investigator bias. Our data did provide an insight about D-dimer trend and clinical improvement that could be used to determine duration of thromboprophylaxis for future studies. Fifth, the clinical framework allows for subjective variability in provider judgment. We suggest involvement of local thrombosis experts to identify the population with VTE predisposition to reduce this variability. Finally, we may have underestimated incident VTEs as we did not routinely screen patients for VTE with imaging studies. On the same note, we may have underreported minor bleeding events, as these data were not collected systematically. Therefore, we may have overestimated the efficacy and safety of our regimen.

In conclusion, our study is timely and favors inclusion of clinically directed tailored-intensity thromboprophylaxis approach into the current standard of care for children hospitalized with moderate to severe COVID-19 and MIS-C as the pandemic transitions towards an endemic state. Ongoing efforts related to developing an effective thromboprophylaxis regimen for this population should focus on evaluating the optimal intensity of thromboprophylaxis and utility of D-dimer for informing thromboprophylaxis management.

AUTHOR CONTRIBUTIONS

Conceptualization and study design: ASK; methodology: AS, KW, EB, and ASK; data analysis: EB and LW; data interpretation and writing: AS, ASK, EB, LW, BK, and AB. All authors have read and approved the final manuscript and agree to the published version of the article.

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RELATIONSHIP DISCLOSURE

The authors have no conflict of interest to declare in relation to this study.

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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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