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Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C

Tracking no: BLD-2020-010218R1

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Abstract:
Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is associated with thrombotic complications in adults, but the incidence of COVID-19 related thrombosis in children and adolescents is unclear. Most children with acute COVID-19 have mild disease, but coagulopathy has been associated with multisystem inflammatory syndrome in children (MIS-C), a post-infectious complication. We conducted a multicenter retrospective cohort study to determine the incidence of thrombosis in children hospitalized with COVID-19 or MIS-C and to evaluate associated risk factors. We classified patients into one of three groups for analysis: COVID-19, MIS-C, or asymptomatic SARS-CoV-2. Among a total of 853 admissions (426 COVID-19, 138 MIS-C, and 289 asymptomatic SARS-CoV-2) in 814 patients, there were 20 patients with thrombotic events (TE) (including 1 stroke). Patients with MIS-C had the highest incidence (6.5%, 9/138) versus COVID-19 (2.1%, 9/426) or asymptomatic SARS-CoV-2 (0.7%, 2/289). In patients with COVID-19 or MIS-C, the majority of thrombotic events (89%) occurred in patients ≥12 years. Patients ≥ 12 years with MIS-C had the highest rate of thrombosis at 19% (9/48). Notably, 71% of TE that were not present on admission occurred despite thromboprophylaxis. Multivariable analysis identified the following as significantly associated with thrombosis: age ≥12 years, cancer, presence of a central venous catheter, and MIS-C. In patients with COVID-19 or MIS-C, hospital mortality was 2.3% (13/564), but was 28% (5/18) in patients with thrombotic events. Our findings may help inform pediatric thromboprophylaxis strategies.

Conflict of interest: COI declared - see note

COI notes: S.E.S serves on the advisory board for Alexion Pharmaceuticals, R.K. has attended advisory board meetings for Bayer, Genentech, and Kedrion. None of the other authors have competing financial interests.

Preprint server: No;

Author contributions and disclosures: H.W., S.E.S, R.K., K.A., L.B., M.B., C.T.C., R.D., C.D., N.A.G., J.J., A.G.R., S.R., A.S., L.S., A.Z., and L.R. contributed to study design. H.W., S.E.S, R.K., K.A., M.B., C.T.C., R.D., C.D., J.J., J.K., K.M., S.R., W.S.L., A.S., L.S., A.Z., and L.R. contributed to data collection. H.W., L.B., and L.R. analyzed data. H.W., S.E.S, R.K., K.A., L.B., M.B., C.T.C., R.D., C.D., N.A.G., J.J., A.G.R., S.R., A.S., L.S., A.Z., and L.R. wrote and edited the paper.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: The data is not currently publicly available. It exists as a deidentified dataset. Should another investigator be interested in the data, they can email the corresponding author and a data use agreement could be pursued.

Clinical trial registration information (if any):

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Title: Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C

Short title: Thrombosis in children with COVID-19 or MIS-C

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Text Word Count: 3705
Abstract Word Count: 237
Tables: 4
Figures: 1
References: 39

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Key Points

#1: Cancer, central venous catheter, older age, and MIS-C are risk factors for thrombosis in children and adolescents with COVID-19 or MIS-C.

#2: Mortality was high (28%) in the children and adolescents with MIS-C or COVID-19 who developed thrombosis.

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Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is associated with thrombotic complications in adults, but the incidence of COVID-19 related thrombosis in children and adolescents is unclear. Most children with acute COVID-19 have mild disease, but coagulopathy has been associated with multisystem inflammatory syndrome in children (MIS-C), a post-infectious complication. We conducted a multicenter retrospective cohort study to determine the incidence of thrombosis in children hospitalized with COVID-19 or MIS-C and to evaluate associated risk factors. We classified patients into one of three groups for analysis: COVID-19, MIS-C, or asymptomatic SARS-CoV-2. Among a total of 853 admissions (426 COVID-19, 138 MIS-C, and 289 asymptomatic SARS-CoV-2) in 814 patients, there were 20 patients with thrombotic events (TE) (including 1 stroke). Patients with MIS-C had the highest incidence (6.5%, 9/138) versus COVID-19 (2.1%, 9/426) or asymptomatic SARS-CoV-2 (0.7%, 2/289). In patients with COVID-19 or MIS-C, the majority of thrombotic events (89%) occurred in patients ≥12 years. Patients ≥ 12 years with MIS-C had the highest rate of thrombosis at 19% (9/48). Notably, 71% of TE that were not present on admission occurred despite thromboprophylaxis. Multivariable analysis identified the following as significantly associated with thrombosis: age ≥12 years, cancer, presence of a central venous catheter, and MIS-C. In patients with COVID-19 or MIS-C, hospital mortality was 2.3% (13/564), but was 28% (5/18) in patients with thrombotic events. Our findings may help inform pediatric thromboprophylaxis strategies.

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Introduction

The emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in late 2019 led to a global pandemic of a highly transmissible and severe disease called coronavirus disease 2019 (COVID-19).[1] While severe pneumonia is the cardinal presentation of COVID-19 in adults, a proclivity to cause thrombotic coagulopathy became apparent early in the pandemic.[1–10] Many patients had elevated levels of D-dimer and fibrinogen with mild thrombocytopenia and mild prolongation of the prothrombin time (PT).[1–3] Studies in adults reported a high venous thromboembolism (VTE) rate, often occurring despite prophylactic anticoagulation.[4–9] A recent meta-analysis estimated an overall VTE incidence of 21% in adults hospitalized for COVID-19, rising to 31% in those admitted to the intensive care unit (ICU).[10] The pooled odds of mortality were 74% higher among adult patients with thrombotic events (TE), compared to those without TE (23% vs 13%, respectively).[10]

Compared to adults, most children and adolescents with COVID-19 have minimal disease and many infected with SARS-CoV-2 are asymptomatic.[11] Persons <21 years of age accounted for only 8% of reported cases and 0.08% of deaths in the U.S.[12] Starting in April 2020, reports emerged of previously healthy children presenting with fever, cardiovascular shock and/or Kawasaki disease features, hyperinflammation, and multisystem involvement with a temporal association to SARS-CoV-2 exposure.[13,14] Many patients were SARS-CoV-2 negative on respiratory testing but had positive antibody titers. Public health alerts from the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) published criteria for this new disease called multisystem inflammatory syndrome in children (MIS-C).[15–17] Coagulopathy was listed as a potential presenting feature of MIS-C.

As hospitalizations for COVID-19 increased, pediatric hematologists developed guidelines for thromboprophylaxis.[18] The Pediatric/Neonatal Scientific and Standardization Subcommittee of the International Society of Thrombosis and Haemostasis (ISTH) published consensus guidelines recommending pharmacological prophylaxis in children with additional risk factors for VTE or those with an elevated D-dimer.[19] These guidelines were based on extrapolation of adult data and expert opinion, and not supported by data on the incidence and risk factors for thrombosis in children and adolescents with COVID-19 or MIS-C. Therefore, the primary objective of this study was to determine the incidence of thrombotic complications in hospitalized

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children and adolescents with COVID-19 or MIS-C. We additionally sought to evaluate risk factors associated with TE and describe the current practices for thromboprophylaxis in this cohort.

Methods

Study Cohort

We conducted a retrospective cohort study of consecutive children ages 0 to <21 years admitted from March 1, 2020 through August 15, 2020 with a positive SARS-CoV-2 polymerase chain reaction (PCR) or a diagnosis of MIS-C across 7 pediatric hospitals in 6 U.S. states: Boston Children's Hospital (MA), Children's Hospital of Los Angeles (CA), Children's Hospital of Philadelphia (PA), Children's Medical Center of Dallas (TX), Johns Hopkins All Children's Hospital (FL), Joseph M. Sanzari Children's Hospital at Hackensack University Medical Center (NJ), and Texas Children's Hospital (TX). This study was approved for a waiver of informed consent by each center's Institutional Review Board.

Eligible patients were identified by one or more means: 1) from COVID-19 or MIS-C patient databases maintained at participating institutions; 2) from electronic medical record queries for patients with both an ICD10 COVID-19 diagnosis code and an inpatient admission code; 3) from electronic medical record queries for patients with a positive SARS-CoV-2 test and coded for inpatient admission. Additionally, MIS-C patients were identified from electronic medical record queries of inpatients who had a consult order with the consult reason "MIS-C"; and/or from electronic medical record queries for patients who had a COVID-19 related lab test and at least one of the following tests sent: ferritin, IL-2, or IL-6.

The following data were collected and entered into Research Electronic Data Capture software (REDCap):[20,21] demographics, comorbidities, COVID-19 exposure history and presenting symptoms, hospital course (intensive care unit (ICU) admission, need for ventilator, vasopressors, or ECMO, presence of bacterial co-infection, presence of a central venous catheter (CVC), length of stay, death), use of prophylactic anticoagulation (drug, dose, duration), use of COVID-19 or MIS-C-directed therapies, hematologic and inflammatory laboratory parameters, presence of "COVID toes,"[22] presence of thrombosis up to 30 days post-discharge, and presence of bleeding during hospitalization.

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Study Definitions

Admissions were categorized into one of four subgroups at the discretion of the investigator: 1) COVID-19: a positive PCR and COVID-19 symptoms (fever, cough, diarrhea, loss of smell, headache, sore throat, or congestion); 2) MIS-C: requiring all 5 CDC criteria of fever, evidence of inflammation on laboratory testing, ≥2 organ systems involved, no other plausible diagnosis, and a positive SARS-CoV-2 PCR or antibody test or known exposure[23]; 3) "MIS-C like": patients with symptoms and laboratory findings highly suggestive of MIS-C who were assessed and treated for MIS-C but did not fully meet the CDC criteria and 4) Asymptomatic SARS-CoV-2: a positive SARS-CoV-2 PCR test without symptoms of COVID-19 (listed above) and admitted with alternative diagnoses. Patients with asymptomatic SARS-CoV-2 were included primarily as a comparison group.

Clinically apparent thrombosis was defined as a radiologically confirmed arterial or venous thrombus. Superficial vein thrombosis was not included. In patients with thrombosis, data on clot location, symptoms, and anticoagulation treatment were collected. Bleeding was categorized as "major" or "clinically relevant non-major" based on the ISTH consensus definition.[24] COVID-19 directed therapies included systemic steroids, convalescent plasma, remdesivir, tocilizumab, hydroxycholoroquine, and anakinra. MIS-C directed therapies included systemic steroids, IVIG, anakinra, tocilizumab, and aspirin. Type, duration, and dosing of post-discharge thromboprophylaxis were collected. Laboratory parameters were collected as maximum and/or minimum values during hospitalization and included platelet count, hemoglobin, PT, lupus anticoagulant, D-dimer, and fibrinogen.

Obesity was defined using the CDC definition for BMI greater than or equal to the 95th percentile for age for children greater than 24 months.[25] If height and weight were not available, the patient was classified as obese if documented as such in the patient's medical record.

Statistical Analysis

Standard statistical methods were used to summarize the data: frequency and percent for categorical variables and median and interquartile range (IQR) for continuous scaled variables. The incidence of

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thrombotic events was calculated, along with the 95% confidence interval (CI) for each subgroup (COVID-19, MIS-C/MIS-C like, and asymptomatic SARS-CoV-2). Comparisons of demographic and clinical characteristics among patients with and without thrombosis was performed using non-parametric statistical tests. For the univariable analyses, categorical variables were analyzed using count and percentages with the Fisher's exact test and continuous variables using median, inter-quartile range (IQR), and Kruskal-Wallis rank test. Missing values were excluded from the analyses.

Multivariable analysis was performed using a Binomial Logit model with Wald test statistics. Given the low event rate (thrombotic events), we only carried through a subset of the variables from the univariable analysis based on those that we believed to be independently associated. The primary analysis employed patients with COVID-19 or MIS-C/MIS-C like. Due to the low number of TE, these groups were combined and asymptomatic SARS-CoV-2 cases were excluded. A sensitivity analysis was performed excluding MIS-C like patients.

All calculated p-values were 2-sided and an alpha level of 0.05 was used for assessing significance; all analyses were conducted using SAS 9.4.

Data Sharing Statement

For original data, please contact raffini@email.chop.edu.

Results

Between March 1 to August 15, 2020, we identified 853 hospital admissions in 814 patients meeting eligibility criteria. Of these, 426 admissions (50%) were for COVID-19, 138 (16%) for MIS-C (n=130) or MIS-C like illness (n=8), and 289 (34%) admissions for asymptomatic SARS-CoV-2 infection. Of the 8 patients who did not meet full MIS-C criteria, 1 did not have documented fever, 5 did not have a positive SARS-CoV-2 test or known exposure, and 2 had an alternative diagnosis. All had other features highly suggestive of MIS-C and were treated for MIS-C with steroids, IVIG, aspirin, anakinra, and/or infliximab. Demographic and clinical characteristics of the cohort including therapies received are provided in Table 1 by clinical subgroup. For all

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subsequent analyses, MIS-C like patients were combined with MIS-C patients. The MIS-C cohort had the highest proportion of patients without underlying co-morbidities, more evidence of coagulopathy (elevated D-dimer, fibrinogen, and PT, and lower platelet count), and had the highest proportion of patients who required critical care (Table 1).

Thrombotic events

There were 20 patients with 1 or more TE; 9 patients admitted with COVID-19, 9 patients with MIS-C and 2 patients with asymptomatic SARS-CoV-2. One patient admitted with COVID-19 developed a second TE during the admission (total 21 TE). Patients with MIS-C had the highest incidence, 6.5% (95% CI 3-12%), followed by those with COVID-19 at 2.1% (95% CI 1-4%), and those with asymptomatic SARS-CoV-2 at 0.7% (95% CI 0.1-2.4%). The majority of TE (89%) in COVID-19 or MIS-C patients occurred in those ≥12 years. The incidence of TE in patients with COVID-19 or MIS-C ≥ 12 years was 6.8% (16/237), compared to 0.6 % (2/327) in those <12 years. In the subgroup of patients with MIS-C who were ≥12 years old, the incidence was 19% (9/48). Clinical details regarding patients with thrombosis are provided in Table 2. Of the 19 TE in patients with COVID-19 or MIS-C, there were 11 deep vein thrombosis (DVT), 3 pulmonary embolism (PE), 3 intracardiac thrombosis, 1 acute ischemic stroke, and 1 cerebral sinovenous thrombosis. Four TE were clinically apparent on admission to the hospital (Table 2). Thirteen (68%) were symptomatic, while the rest were asymptomatic, detected on imaging performed for another indication. Nine (47%) were catheter-related. Death from all causes occurred in 5 (28%) of the 18 patients with COVID-19 or MISC and thrombosis. The vast majority of COVID-19 and MIS-C patients with thrombosis (17/18) identified as either Hispanic ethnicity or African American race. One COVID-19 patient was diagnosed with "COVID" toes, but this was not included in the overall TE.

We evaluated several clinical, demographic, and laboratory risk factors for thrombosis in the combined cohort of COVID-19 and MIS-C, listed in Table 3. Older age, African American race and/or Hispanic ethnicity, MIS-C, admission to the ICU, need for a ventilator, length of stay, presence of a CVC, cancer, D-dimer > 5 times the upper limit of normal (x ULN), PT > 1.5 x ULN, elevated fibrinogen, reduced platelet count, and death during admission were all statistically significant variables on univariable analysis. In a univariable analysis

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specifically comparing the rate of thrombosis in COVID-19 patients versus asymptomatic SARS-CoV-2 patients, COVID-19 was not significantly associated with TE (p=0.2).

D-dimer > 5 x ULN was significantly associated with TE in the univariable analysis. However, there was a high proportion (36%) of missing D-dimer values, which was a problem for all the laboratory variables. Rather than imputing values, we ran the multivariable modeling in two ways: without laboratory values and including only admissions that had a D-dimer performed. In the model without laboratory values, the following variables were significantly associated with thrombosis: age ≥12 years, cancer, CVC, and MIS-C (Table 4). When D-dimer was included in the model, it was significant, but MIS-C was no longer statistically significant (Table 4).

In a sensitivity analysis that excluded the 8 MIS-C like patients, the results of the multivariable analyses were similar to the primary analysis (data not shown).

Thromboprophylaxis

Anticoagulant thromboprophylaxis was used during 30% (128/426) of COVID-19 and 58% (80/138) of MIS-C admissions, as well as 61% of ICU admissions in those patients (Figure 1A). Nonetheless, 10 of the 14 (71%) TE that were not identified on admission occurred in patients receiving thromboprophylaxis (regimens listed in Table 2). There were 220 regimens used in the 208 COVID-19 or MIS-C admissions that received prophylactic anticoagulation. The most common anticoagulant was enoxaparin (89%), followed by unfractionated heparin (UFH) in 6.8%, and other anticoagulants (4.5%). The variation with respect to drug and intensity is shown in Figure 1B. Once-daily enoxaparin accounted for 20%, while the majority (62%) received twice daily prophylactic enoxaparin (~0.5 mg/kg every 12 hours). Full therapeutic intensity prophylaxis with enoxaparin (~1 mg/kg every 12 hours) or UFH was used in 9.1%.

Notably, 45/417 (11%) patients with COVID-19 and 32/129 (25%) MIS-C who did not develop thrombosis were discharged on prophylactic anticoagulation. The majority were discharged on enoxaparin (56), followed by DOACs (16), aspirin (4), and warfarin (1). The only patient known to develop thrombosis after discharge was a patient with cancer, found to have a catheter associated intracardiac thrombosis within 30

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days after an admission with asymptomatic SARS-CoV-2 when he was re-admitted for COVID-19; this patient had not been discharged on anticoagulation.

Bleeding

There were 9 admissions with major bleeding and 8 with clinically relevant non-major bleeding among the COVID-19 and MIS-C subgroups (Table 1). The COVID-19 cohort had 7 (1.6%) admissions with major bleeding events, 2 of which occurred while on anticoagulation, and there were 2 (1.4%) in the MIS-C cohort with major bleeding and both events occurred on anticoagulation. Of the 4 COVID-19 or MIS-C patients with major bleeding on anticoagulation, 1 was receiving prophylactic daily enoxaparin, 1 was receiving therapeutic dose unfractionated heparin for ECMO and treatment of TE, and 2 were receiving therapeutic dose enoxaparin for treatment of TE.

Mortality

The all-cause mortality rate in our cohort of COVID-19 and MIS-C patients was 2.3% (13/564). The majority of deaths (11) occurred in patients hospitalized with COVID-19. All patients who died had an underlying comorbidity; the most common was cancer (7 patients). Respiratory failure was the most common reason for death (7). The cause of death was attributed, at least in part, to malignancy in 3 patients. One patient had a hemothorax while on therapeutic anticoagulation that was thought to contribute to death. Other reported contributors to death included renal failure (1), thrombotic microangiopathy (1), complex congenital heart disease (1), bowel obstruction with abdominal compartment syndrome (1), and septic shock (1). Five of the 18 patients (28%) with COVID-19 or MIS-C and TE died.

Discussion

This is the first study to evaluate the incidence of thrombosis in a large, multicenter cohort of children hospitalized with COVID-19-related complications.[16,26–28] The incidence of TE in hospitalized children with COVID-19 was 2.1% and 6.5% in those with MIS-C, compared to 0.7% in those with asymptomatic SARS-CoV-2 infection. We identified several important laboratory (elevated D-dimer) and clinical variables (age ≥12

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years, cancer, MIS-C, CVC) that were associated with a much higher risk of TE. Importantly, over two-thirds of TE that occurred in hospitalized children with COVID-19 or MIS-C occurred in patients receiving thromboprophylaxis. These findings have important implications for clinicians and provide new evidence regarding the risk of TE in children hospitalized with COVID-19 or MIS-C. Mortality was 28% in pediatric patients with TE and COVID-19 or MIS-C, although most patients who died had comorbid conditions that were risk factors for TE and contributed to mortality.[10]

To put our findings into perspective, the rate of VTE in children admitted to U.S. tertiary care hospitals in 2007 was estimated at 58 per 10,000 admissions (0.58%) using the Pediatric Health Information System (PHIS) database, with those ages 12-18 years having the highest rate (94 per 10,000; 0.94%).[29] The rate observed in our study is much higher, particularly in patients ≥12 years (6.8%) with COVID-19 or MIS-C. However, this comparison is limited for several reasons. Patients hospitalized with COVID-19 are known to have a high prevalence of underlying medical conditions, e.g., cancer, diabetes, obesity, which may have increased the rate. In addition, the age distribution of patients in this study is skewed toward older patients compared to the PHIS study, which would also result in a higher rate. Nonetheless, the rates of TE that we observed, particularly in the MIS-C population and those ≥12 years of age, suggest that COVID-19 and MIS-C are unique risk factors for thrombosis in hospitalized children.

Consistent with this conclusion is the finding that a D-dimer > 5 x ULN was significantly associated with TE in our study. This is the first pediatric COVID-19 study to demonstrate the association between elevated D-dimer and TE, and is consistent with multiple studies of adults with COVID-19.[8,30,31] In addition, elevated fibrinogen, prolonged PT, and reduced platelet count were also associated with TE in our study on univariable analysis, similar to reports of adults with COVID-19.[1–3] A limitation of our analysis is that there was a high proportion of missing laboratory values and that we limited the collection of laboratory parameters to the maximum or minimum values during the hospitalization, regardless of timing (i.e. early in hospitalization and/or prior to TE). Therefore, it is possible that elevations in D-dimer levels may have occurred after a TE in some of the patients, reducing this variable's predictive value. Future studies will be necessary to better evaluate the predictive value of an elevated D-dimer in this setting.

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In a multivariable regression model that excluded laboratory values, MIS-C, age ≥12 years, presence of a CVC, and cancer were significantly associated with TE. With the exception of MIS-C, these mirror previously established risk factors for TE in hospitalized children.[32,33] When D-dimer was included in the multivariable model, it was significant, however MIS-C was no longer significant. We hypothesize that this is due to the collinearity of these variables, as well as the proportion of missing laboratory values. Interestingly, cancer was identified as an independent risk factor for TE in multivariable models with and without D-dimer. Although COVID-19 was not found to be a risk factor for TE, 30% of patients with COVID-19 received thromboprophylaxis which may have reduced the rate of thrombosis in this group. In addition, our ability to evaluate COVID-19 as a risk factor may have been limited by the small sample size. Due to the small sample size, missing laboratory values, and lack of a validation cohort, we did not develop a clinical prediction model. Future studies, focused on TE risk prediction in children with SARS-CoV-2 should address these points, and also include other potentially important variables such as blood type and pubertal status (rather than age).

We decided to include asymptomatic patients with SARS-CoV-2 for several reasons. First, we wanted to evaluate the risk of thrombosis in these children because hematologists are frequently consulted to address the role of thromboprophylaxis in this setting. Second, if patients were truly asymptomatic and had no effects from viremia, this group could potentially serve as a control group. The overall incidence of TE in the asymptomatic SARS-CoV-2 group was low (0.7%), and the 2 patients with TE in this subgroup had several pro-thrombotic risk factors (Table 2). Therefore, we believe that asymptomatic SARS-CoV-2 infection may not significantly increase the risk of thrombosis.

In our study, all 9 of the TE in the MIS-C cohort occurred in patients ≥ 12 years, for a rate of 19% (9/48) in this subgroup. This is higher than an earlier report from a multicenter registry of 186 MIS-C patients, where 3/45 (6.7%) patients > 12 years had TE.[16] This difference may be due to variation in thromboprophylaxis, the severity of the disease, inclusion of different centers, or because our study was designed to focus on TE. We did not identify any TE in the 90 MIS-C admissions that occurred in children < 12 years of age, confirming the low incidence of TE in younger children with MIS-C observed in the prior study.

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Similar to other studies, we observed a high prevalence of Hispanic (51%) and African American (23%) children hospitalized with COVID-19 or MIS-C.[34] Of the 18 patients with TE and COVID-19 or MIS-C, 17 identified as either Hispanic ethnicity or African American race. These racial disparities associated with worse outcomes in both children and adults are likely linked to similar socioeconomic disadvantages that have been suggested by others.[12,34,35]

The majority of TE in our study developed while patients were receiving thromboprophylaxis, which is similar to adult reports.[7,8] This has raised questions regarding the optimal intensity of prophylactic anticoagulation for patients with SARS-CoV-2. We are unable to answer this question since thromboprophylaxis practices varied across institutions and changed during the study period. However, it is notable that 4/9 of the major bleeding events in COVID-19 and MIS-C patients occurred on anticoagulation. This is limited by the fact that we could not assess all clinical risk factors for bleeding in these patients, however anticoagulation likely contributed to these bleeding events. Optimal thromboprophylaxis dose intensity may be more carefully addressed by an ongoing clinical trial to evaluate the safety of enoxaparin in children with SARS-CoV-2 associated illness, administered twice daily to achieve a 4-hour post-dose anti-factor Xa level of 0.20-0.49 anti-Xa U/ml.[36]

There are several limitations to this retrospective study. First, our findings must be contextualized recognizing that a significant proportion of patients received inpatient and post-discharge thromboprophylaxis. Given the lack of a comparator group, it is plausible that the rate of thrombosis in this cohort would have been higher in the absence of thromboprophylaxis. Second, participating hospitals were large pediatric referral centers, and patients may have been more medically complex or transferred from outside hospitals for a higher level of care. Thus, the risk of thrombosis may actually be an overestimate, and results from our study may not be generalizable to smaller pediatric centers or community hospitals. In contrast, some patients may have died due to unrecognized TE or PE; this number is likely low, but would have resulted in an underestimate of the risk. Third, there was some variation over time regarding the practice of testing all admitted patients for SARS-CoV-2 (particularly earlier on in the pandemic), so patients with mild disease may have been missed. Last, is important to note that a proportion of patients in this study (estimated at <10%) have been reported in prior

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publications or included in other registries.[16,37–39] To the best of our knowledge, none of the TE have been previously reported.

For the first time, we provide data regarding the rate of thrombotic complications in patients < 21 years hospitalized with SARS-CoV-2 associated illness. Our findings, including the low rate of TE in children < 12 years with COVID-19 or MIS-C, and the low rate of post-discharge TE, along with factors associated with an increased risk (age ≥ 12 years, MIS-C, CVC, and cancer) may help inform thromboprophylaxis strategies at pediatric centers. Future studies focused on the intensity of anticoagulation as well as at novel targets, are well underway in adults with COVID-19, and will likely be relevant to high-risk adolescent patients with COVID-19 and MIS-C, in whom the rate of thrombosis and mortality rate were highest.

Acknowledgements

H.W. was supported by the National Institutes of Health T32 HL007971. C.D. was supported by a scholarship from the Institute for Translational Medicine and Therapeutics at the University of Pennsylvania.

Author contributions

H.W., S.E.S, R.K., K.A., L.B., M.B., C.T.C., R.D., C.D., N.A.G., J.J., A.G.R., S.R., A.S., L.S., A.Z., and L.R. contributed to study design. H.W., S.E.S, R.K., K.A., M.B., C.T.C., R.D., C.D., J.J., J.K., K.M., S.R., W.S.L., A.S., L.S., A.Z., and L.R. contributed to data collection. H.W., L.B., and L.R. analyzed data. H.W., S.E.S, R.K., K.A., L.B., M.B., C.T.C., R.D., C.D., N.A.G., J.J., A.G.R., S.R., A.S., L.S., A.Z., and L.R. wrote and edited the paper.

Conflict of interest disclosures

S.E.S serves on the advisory board for Alexion Pharmaceuticals, R.K. has attended advisory board meetings for Bayer, Genentech, and Kedrion. None of the other authors have competing financial interests.

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Table 1. Clinical characteristics of all three COVID-19 cohorts (asymptomatic SARS-CoV-2, COVID-19, MIS-C/MIS-C-like)

	Asymptomatic SARS-CoV-2 n=289	**COVID-19 n=426**	**MIS-C* n=138**
Age, yrs median (IQR)	10 (3-15)	10 (1-16)	10 (6-14)
Sex, male N (%)	144 (50)	226 (53)	75 (54)
Ethnicity N (%)			
Hispanic	125 (43)	228 (54)	57 (41)
Non-Hispanic	139 (48)	167 (39)	69 (50)
Unknown/Other	25 (9)	31 (7)	12 (9)
Race N (%)			
White	151 (52)	234 (55)	77 (56)
African American	74 (26)	89 (21)	39 (28)
Asian	2 (1)	6 (1)	4 (3)
Other/Unknown	62 (21)	97 (23)	18 (13)
African American race and/or Hispanic ethnicity	198 (69)	315 (74)	96 (70)
Length of stay d median (IQR)	3 (1-7)	3 (2-7)	6 (4-10)
Comorbidities N (%)			
Respiratory	22 (8)	90 (21)	16 (12)
Cardiac	13 (5)	38 (9)	5 (4)
Cancer	25 (9)	39 (9)	5 (4)
Obesity	61 (21)	114 (27)	45 (33)
Diabetes	17 (6)	15 (4)	0
Immunodeficiency	10 (3)	18 (4)	1 (1)
Sickle cell disease	8 (3)	26 (6)	1 (1)
Neurologic	38 (13)	49 (12)	4 (3)
Gastrointestinal	36 (12)	38 (9)	1 (1)
None	77 (27)	114 (27)	70 (51)
ICU admission N (%)	46 (16)	136 (32)	86 (62)
Ventilator	11 (4)	46 (11)	22 (16)
ECMO	1 (0.4)	4 (1)	3 (2)
Central venous catheter N (%)	47 (16)	74 (17)	53 (38)
COVID-19 directed treatment N (%)	0	105 (25)	39 (28)
MIS-C directed treatment N (%)	1 (0.3)	6 (1)	130 (94)
Maximum D-dimer			
Not done	214 (74)	197 (46)	5 (4)
Normal range	14 (5)	36 (8)	1 (1)
1-5 x ULN	34 (12)	131 (31)	32 (23)
>5 x ULN	27 (9)	62 (15)	100 (72)
Minimum platelet count K/uL median (IQR)	259 (199-320)	208 (140-273)	148 (103-204)
Maximum fibrinogen mg/dl median (IQR)	421 (282-583)	463 (325-583)	551 (462-657)
Maximum Prothrombin time			
Not done	183 (63)	204 (48)	7 (5)
Normal range	55 (19)	121 (28)	38 (27)
1-1.5 x ULN	48 (17)	90 (21)	86 (62)
>1.5 x ULN	3 (1)	11 (3)	7 (5)
Thromboprophylaxis N (%)	31 (11)	128 (30)	80 (58)
Admissions with thrombotic events N (%)	2 (0.7)	9 (2)	9 (7)
Deep vein thrombosis	2	4	7
Pulmonary embolism	0	3	0
Stroke	0	0	1
Intracardiac	0	2	1
Cerebral sinovenous thrombosis	0	1	0
Major bleeding N (%)	4 (1)	7 (2)	2 (1)
Death during hospitalization (or < 30 days) N (%)	2 (0.7)	11 (2.6)	2 (1.4)

*Includes MIS-C like patients

yrs:years; IQR:interquartile range; d:days; ICU:intensive care unit; ULN:upper limit of normal range

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Table 2. Clinical characteristics of patients who developed thrombosis

Pt	Age ^ (yrs)	Sex	Race/ Ethnicity	Thrombosis location	Catheter related	Underlying medical conditions	Thromboprophylaxis	ICU	Other
Patients with COVID-19									
1	16-18	F	White/ Hispanic	Pulmonary embolism	No	Cancer (relapsed sarcoma), CVC, obesity	Enoxaparin 30 mg q12	Yes	Critically ill; died due to cardiac arrest, COVID pneumonia, hemothorax
2	16-18	M	African-American	DVT of upper extremity	Yes	Congenital heart disease, cerebral palsy, CVC, bacterial tracheitis	Enoxaparin q12, goal anti-Xa 0.2-0.5 IU/ml	Yes	Critically ill; died due to cardiac arrest
3	18-21	M	White/ Hispanic	Pulmonary embolism	No	Cancer (AML), CVC	No- thrombosis present on admission	Yes	Critically ill; died due to intracranial hemorrhage, COVID, multisystem organ failure
4	16-18	M	White/ Hispanic	Lower extremity DVT	No	Obesity	No	Yes	
5	< 1	F	White/ Hispanic	Intracardiac thrombosis	Yes	Cancer (AML), CVC	No	Yes	Died due to AML
6	10-12	F	African-American	Pulmonary embolism	No	Obesity	Enoxaparin 0.5 mg/kg q12	Yes	Critically ill
7	12-14	M	White/ Hispanic	Cerebral sinovenous thrombosis	No	Cancer	No	No	Major bleeding event on anticoagulation
8	14-16	F	African-American	DVT of upper extremity x 2	Yes	Cancer, obesity, CVC	No – thrombosis present on admission, second thrombosis occurred while on enoxaparin 1 mg/kg q12	No	
9	14-16	M	Other/ Hispanic	Intracardiac thrombosis	Yes	Cancer, CVC	No – thrombosis present on admission	No	Readmitted after asymptomatic SARS-CoV2 admission with symptomatic COVID-19, thrombosis on chest CT
Patients with MIS-C									
10	16-18	M	African-American	Acute ischemic stroke	No	Neurologic disorder, CVC	No – stroke on admission	Yes	Critically ill; admitted with acute MCA stroke and MIS-C 1 month after acute COVID-19 admission
11	12-14	F	African-American	Asymptomatic extremity DVT	No	Respiratory, CVC	No	Yes	Critically ill; admitted in shock and with decreased cardiac function
12 *	14-16	F	Unknown/ Non-Hispanic	Lower extremity DVT	No	None, CVC	Enoxaparin q12, goal anti-Xa 0.3-0.5 IU/ml	Yes	Critically ill, on ECMO
13	16-18	M	African-American	Lower extremity DVT	No	None, CVC	Unfractionated heparin, goal anti-Xa 0.1-0.3 IU/ml	Yes	Critically ill
14	16-18	M	Unknown/ Hispanic	Intracardiac thrombosis	Yes	Obesity, CVC	Unfractionated heparin, goal anti-Xa 0.3-0.7 IU/ml	Yes	Critically ill; thrombosis found post-ECMO

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15	16-18	F	African-American	UE DVT	Yes	Obesity, CVC	Heparin 5000u q12 then enoxaparin, goal anti-Xa 0.5-1.0 IU/ml	Yes	Critically ill
16 *	14-16	F	White/ Hispanic	Asymptomatic upper extremity DVT	Yes	Cancer, obesity, respiratory, CVC	Enoxaparin daily	No	Died due to multi-organ failure
17 *	18-21	M	African-American	Upper extremity DVT	No	Cancer, obesity, CVC	Enoxaparin, goal anti-Xa 0.3-0.5 IU/ml	No	Symptomatic COVID then readmitted with MIS-C, relapsed ALL, bacteremia
18	16-18	F	African-American	Upper extremity DVT	Yes	Obesity, CVC	Enoxaparin, goal anti-Xa 0.2-0.5 IU/ml	No	Urinary tract infection
Patients with asymptomatic Sars-CoV2									
19	16-18	F	White/ Hispanic	Asymptomatic lower extremity DVT	No	Cancer (ALL in induction)	Enoxaparin 40 mg daily	Yes	Died due to complications of ALL; bacteremia
20	< 1	F	African-American	lower extremity DVT	Yes	Acute liver failure, CVC	No	Yes	

*MIS-C like; ^ Age range to be less identifying; Critically ill: required mechanical ventilation, vasopressors, and/or ECMO; CVC: central venous catheter; DVT: deep vein thrombosis; q12: every 12 hours; ALL: acute lymphoblastic leukemia; AML: acute myelogenous leukemia

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Table 3. Comparison of patients with thrombosis to those without in patients with COVID-19 or MIS-C/MIS-C like

	Thrombosis N=18	**No Thrombosis** N=546	**P Value**
Age, yrs (median, IQR)	16 (14-17)	10 (2-15)	.0001
Age group N (%)			.0002
0-6 yrs	1 (6)	209 (38)	
6-12 yrs	1 (6)	116 (21)	
≥12 yrs	16 (89)	221 (40)	
Sex, male N	9 (50)	292 (53)	.81
Ethnicity N (%)			
Hispanic	8 (44)	277 (51)	.64
Race N (%)			
White	6 (33)	305 (56)	.09
African American	9 (50)	119 (22)	.009
Asian	0	10 (2)	1
Other/Unknown	3 (17)	112 (21)	1
African American race and/or Hispanic ethnicity	17 (94)	394 (72)	.03
SARS-CoV-2 Disease category N (%)			
COVID-19	9 (50)	417 (76)	.02
MIS-C	9 (50)	129 (24)	
Length of stay d median (IQR)	18 (10-41)	4 (2-8)	<.0001
Comorbidities N (%)			
Respiratory	3 (17)	103 (19)	1
Cardiac	1 (6)	42 (8)	1
Cancer	8 (44)	36 (7)	<.0001
Obesity	9 (50)	150 (27)	.06
Neurologic	2 (11)	51 (9)	.68
Sickle Cell Disease	0	27	1
None	2 (11)	182 (33)	.07
ICU admission N (%)	13 (72)	209 (38)	.006
Ventilator	9 (50)	59 (11)	.004
ECMO	2 (11)	5 (1)	.06
Central Venous Catheter N (%)	15 (83)	112 (21)	<.0001
Maximum D-dimer			.002
Not done	2 (11)	200 (37)	
Normal range	0	37 (7)	
1-5 x ULN	2 (11)	161 (29)	
>5 x ULN	14 (78)	148 (27)	
Maximum fibrinogen mg/dl median (IQR)	632 (449-788)	499 (386-602)	.034
Minimum platelet count K/uL median (IQR)	71 (54-152)	189 (131-266)	.0001
Prothrombin time			0.03
Not done	1 (6)	210 (38)	
Normal range	3 (17)	156 (29)	
1-1.5 x ULN	12 (67)	164 (30)	
>1.5 x ULN	2 (11)	16 (3)	
Thromboprophylaxis N (%)	10 (56)	198 (36)	.134
Bacterial Co-infection N (%)	5 (28)	67 (12)	.07
Death during hospitalization (or < 30 days) N (%)	5 (28)	8 (1)	<.0001

yrs:years; d:days; ICU:intensive care unit; ULN:upper limit of normal range

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Table 4. Multivariable model for factors associated with thrombosis in COVID-19 and MIS-C/MIS-C like patients

Variable	Multivariable model without D-dimer		Multivariable model including D-dimer (missing values excluded)	
	OR (95% CI)	P value	OR (95% CI)	P value
Cancer	6.34 (1.56-25.73)	0.01	13.74 (2.36-79.95)	0.004
Obesity	0.89 (0.24- 3.25)	0.856	1.16 (0.21-6.35)	0.863
No comorbidity	0.31 (0.04-2.17)	0.236	0.43 (0.05-3.79)	0.447
Bacterial co-infection	1.63 (0.41-6.48)	0.484	1.31 (0.27-6.43)	0.741
Central venous catheter	7.22 (1.71-30.45)	0.007	25.71 (2.65-249.01)	0.005
ICU admission	2.17 (0.56-8.40)	0.263	0.35 (0.04-3.04)	0.339
MIS-C	6.44 (1.65-25.24)	0.008	3.18 (0.57-17.55)	0.185
COVID-19	Reference		Reference	
Age <6 yrs	1.30 (0.06-27.71)	0.871	1.19 (0.05-30.28)	0.916
Age 6-12 yrs	Reference		Reference	
Age ≥12 yrs	16.84 (1.93-147.1)	0.011	20.05 (2.18-184.29)	0.008
African American race and/or Hispanic ethnicity	7.14 (0.83-61.36)	0.073	9.74 (0.91-104.45)	0.06
D-dimer >5x ULN	Not included		21.16 (2-223.94)	0.011

OR: Odds ratio; yrs:years; d:days; ICU:intensive care unit; ULN:upper limit of normal range

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Figure

Figure 1. Prophylactic anticoagulation regimens in COVID-19 and MIS-C patients. (A) proportion of admissions receiving prophylactic anticoagulation in clinical subgroups by dose intensity (n=208 admissions). When >1 regimen was used per admission, the regimen with either the longest duration or highest dose intensity was included. For patients with TE, only those without TE on admission were included (n=14). (B) Prophylactic anticoagulation regimens in patients with COVID-19 or MIS-C (n=220 regimens) (other: rivaroxaban, apixaban, bivalirudin, warfarin, aspirin; UFH: unfractionated heparin, TE: thrombotic event)

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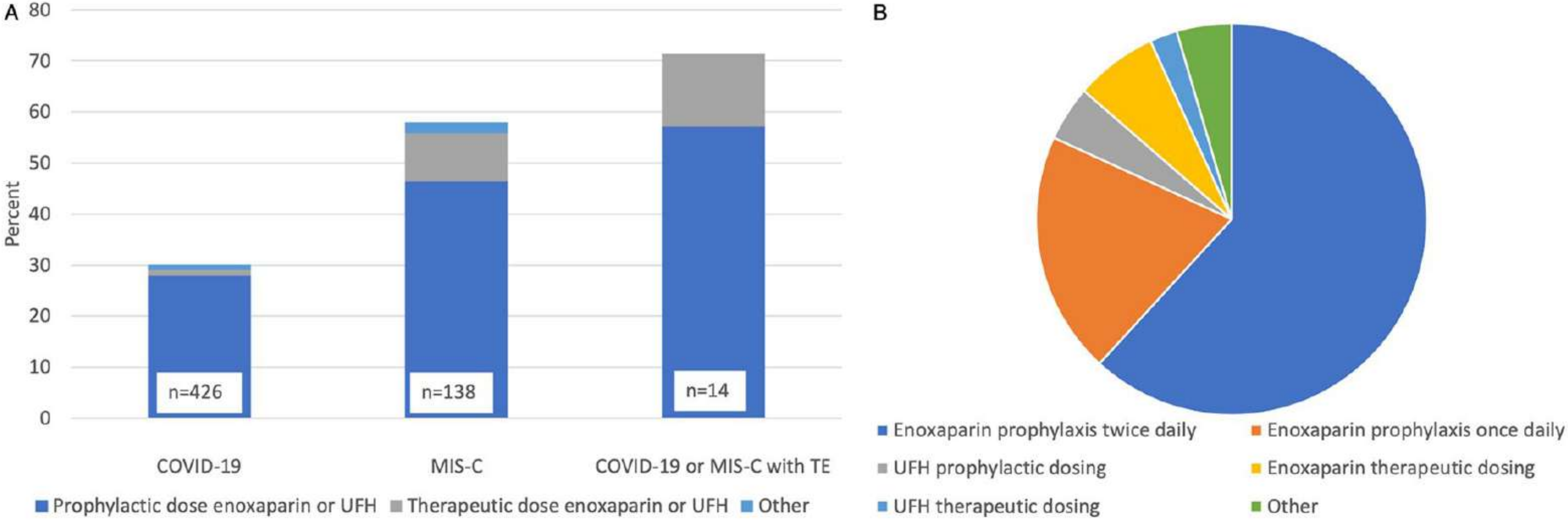

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