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Review Article

Thrombotic risk in children with COVID-19 infection: A systematic review of the literature

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ARTICLE INFO

Keywords:
 COVID-19
 SARS-CoV-2
 Children
 Childhood
 Thrombosis
 Thrombophilia

ABSTRACT

Objective: Coagulation and inflammatory parameters are mildly altered in children with SARS-CoV-2 (COVID-19) infection, and laboratory evidence of a proinflammatory and procoagulant state has been noted in multisystem inflammatory syndrome in children (MIS-C). It is not clear whether this pediatric condition is related to thrombotic events. With this study we reviewed the literature for thrombotic complications in children with COVID-19 infection and MIS-C.

Data sources: We searched the Medline PubMed Advanced Search Builder, Scopus, Web Of Science, and Google Scholar electronic databases (until 1 January 2021) using the medical subject headings (MeSH) terms and text words (their combinations and truncated synonyms): (THROMBOSIS OR THROMBOPHILIA) AND (CHILD OR CHILDREN OR INFANT) AND (COVID-19 OR SARS-CoV-2).

Study eligibility criteria: Inclusion criteria were children with COVID-19 or SARS-COV-2 infection. The search was limited to articles published in English. Exclusion criteria were: reviews of published studies, studies published only as abstracts, letters or conference proceedings, discussion papers, animal studies, or editorials.

Results: After screening for duplicates, the initial search yielded 86 records: 12 were case reports involving 19 children; comorbidities were absent or mild in 73.7%. The most common site of thrombosis the lung (21%); the most often used drug was heparin (42%). Two studies were an international survey ($n = 337$ patients) and a large multicenter study ($n = 186$ patients with MIS-C). The risk of ischemic stroke in SARS-CoV-2 infection (0.82%) and deep venous thrombosis in MIS-C (4.3%) was lower in children than in adults.

Conclusions: Thrombotic or thromboembolic events are rare in pediatric patients with COVID-19 infection and MIS-C. Nonetheless, as in adults, a high index of suspicion should be maintained in children with COVID-19 infection or MIS-C, particularly in those with comorbidities predisposing to thrombotic events.

1. Introduction

Between 2020 and early 2021, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) rapidly spread in a worldwide pandemic. At the time of writing, more than 2.4 million people have died from coronavirus disease 2019 (COVID-19) and nearly 109 million are currently infected [1]. About 1.6% of children with a known diagnosis of COVID-19 have been hospitalized and 0.01% have died in the United

States alone [2].

COVID-19 patients present with coagulation disorders and marked predisposition to thrombosis. The cytokine storm described in COVID-19 patients is a major pathophysiological bridge between inflammation and thrombosis [3]. In adults, complications related to coagulation abnormalities include pulmonary and renal microangiopathy, arterial and venous thromboembolism presenting as acute ischemic stroke, deep venous thrombosis (DVT), pulmonary embolism, and arterial and

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<https://doi.org/10.1016/j.thromres.2021.07.011>

Received 17 March 2021; Received in revised form 9 July 2021; Accepted 13 July 2021

Available online 16 July 2021

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venous catheter thrombosis [4,5] [6]. A recent meta-analysis showed that patients with COVID-19 who develop DVT are more likely to be older [7].

Although SARS-CoV-2 infection in children is generally mild and non-fatal, there is increasing recognition of a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, also known as MIS-C associated with COVID-19, which can lead to serious illness and long-term side-effects [8] [9]. MIS-C usually arises weeks after an infection. The clinical spectrum in children ranges from persistent fever and inflammation to characteristic features of Kawasaki-like disease, and shock, multiple organ failure, and death in the severely ill [8,10].

Coagulation and inflammatory parameters are mildly altered in COVID-19 infection, whereas MIS-C is characterized by laboratory evidence of a proinflammatory and procoagulant state [11]. It is not clear, however, whether this pediatric condition is related to thrombotic events. To fill this gap, we reviewed the literature on thrombotic complications in children with COVID-19 infection or MIS-C.

2. Methods

2.1. Search strategy

We searched the electronic databases Medline PubMed Advanced Search Builder, Scopus, Web of Science and Google Scholar (until January 1, 2021) using medical subject headings (MeSH) terms and text words (their combinations and truncated synonyms): (THROMBOSIS OR THROMBOPHILIA) AND (CHILD OR CHILDREN OR INFANT) AND (COVID-19 OR SARS-CoV-2). The abstracts were screened after removal of duplicate records. The full text was analyzed and the references were screened for further articles missed in the primary search. This review is not limited to geographical area, race or gender. Inclusion criteria were children with COVID-19 (or SARS-CoV-2) infection. The search was limited to articles published in English. Exclusion criteria were: reviews of published studies, studies published only as abstracts, letters or conference proceedings, discussion papers, animal studies, or editorials.

Potentially relevant studies were identified by screening of titles, screening of abstracts and then full-text review. All titles and abstracts were independently evaluated by two reviewers (MZ, MF), not blinded to authors, journals, results for consistency of inclusion/exclusion. Disagreement was solved by consensus; if no agreement could be reached, a third review author (GPG) was consulted to solve disagreement. No ethical approval was required for this study.

2.2. Study review and data extraction

Two independent reviewers (MZ, MF) evaluated the articles potentially meeting the inclusion criteria and retrieved the full text. Studies that did not fulfil the inclusion criteria were excluded; the reasons for exclusion are reported. When the data from the same cohort were presented in more than one article, only the reports that most directly evaluated COVID-19 (or SARS-CoV-2) in pediatrics (age, years) were included in the study. Full texts were screened, and bibliographic details, as well as data on study design, participants, disease severity, intervention, and outcomes were recorded on predefined forms. All data, numerical calculations, and graphic extrapolations were independently confirmed. Full articles, assessed for eligibility, but excluded from the review because not pertinent to the present study were summarized. We did not deal with missing data. Due to the lack of study homogeneity, a narrative synthesis of the results was conducted.

3. Results

After screening for duplication, the initial search yielded 86 records, as detailed in the PRISMA flow diagram (PRISMA, Fig. 1). The records included one article not published in English [12]. Screening of abstracts

excluded 67 records because: full articles were unrelated to the subject ($n = 23$), full related articles involved adults ($n = 12$), reviews of studies involving adults ($n = 16$), and a review related article on children ($n = 14$). In all, 21 articles were assessed for eligibility. After reading the full texts, 7 were excluded (summarized in the Supplementary Table [13–16,11,17,18]). Twelve articles were case reports (Table 1) [19–30]. In addition, an international survey [31] and a prospective multicenter study were included [32] (Table 2).

Table 1 presents the 12 case reports (involving 19 children). The age range was 9 mos [20] to 17 yrs. [30]. In total, 3 studies were conducted in the United States [24,25,27], 4 in Europe [23,26,29,30], 3 in Asia [19,20,22], 1 in South America [28], and 1 in South Africa [21]. Nine studies were published in 2020 [19,21–25,28–30]. The total number of patients was 10 females [19,21,23,25–27,29,30] and 9 males [20,22,24,26,28,30]. Eight case reports included patients without comorbidity ($n = 14$ children) [19,20,22,23,25,26,28,30]; comorbidities ($n = 5$) included: tuberculous meningitis ($n = 1$) [21], sickle cell disease ($n = 1$) [29], asthma ($n = 1$) [24], and obesity ($n = 2$) [26,27].

Diagnosis of COVID-19 infection was based on RT-PCR assay results of nasopharyngeal swab in 10 studies [19–26,29,30], SAR-CoV-2-IgM antibody in 1 study [27] and post mortem histopathological examination of the heart showing spherical viral particles consistent with the Coronaviridae family in 1 study [28].

Thrombosis involved the lung [25,27–29], the digestive tract [19,23], the heart [20,26], the brain [21], the legs [22], the eyes [24], the kidney [26] or the skin [30]. Four patients were diagnosed with MIS-C [23,26,28].

Increased serum D-dimer level was reported by in 7 studies [19,21,23,25,27–29]. In addition, one study reported increased D-dimer but assessed it in 1/7 patients [30]. Fibrinogen level was reported in 3 studies [19,21,28], in 2 of which it was significantly increased [21,28]; platelet levels were reported in 5 studies [20–22,25,28], in 3 of which they were elevated [20–22], in 1 study the levels were decreased [25] and in 1 study they were normal [28]. NT-pro-BNP levels were reported in 1 study in which they were increased [20]. Ferritin level was reported in 5 studies [19,21,24,27,28], in 3 of which it was increased [21,27,28] and near normal in 2 [19,24].

The most frequently administered additional drug treatment was anticoagulation with low-molecular-weight (LMW) heparin or heparin in 8 studies [19,20,22–27]; 1 study did not state the anticoagulant name [29], acetylsalicylic acid was administered in 3 studies [20–22], hydroxychloroquine in 2 [22,24], IVIg in 1 study [20] and tocilizumab (8 mg/kg) in a patient with sickle cell disease [29].

Patient outcomes were reported as full recovery and/or discharge from hospital ($n = 6$ patients) [19,22,23,25,26,30], improvement but requiring medical assistance/rehabilitation ($n = 6$ patients) [20,21,24,26,27,29], and one patient with MIS-C died suddenly after hospital admission [28].

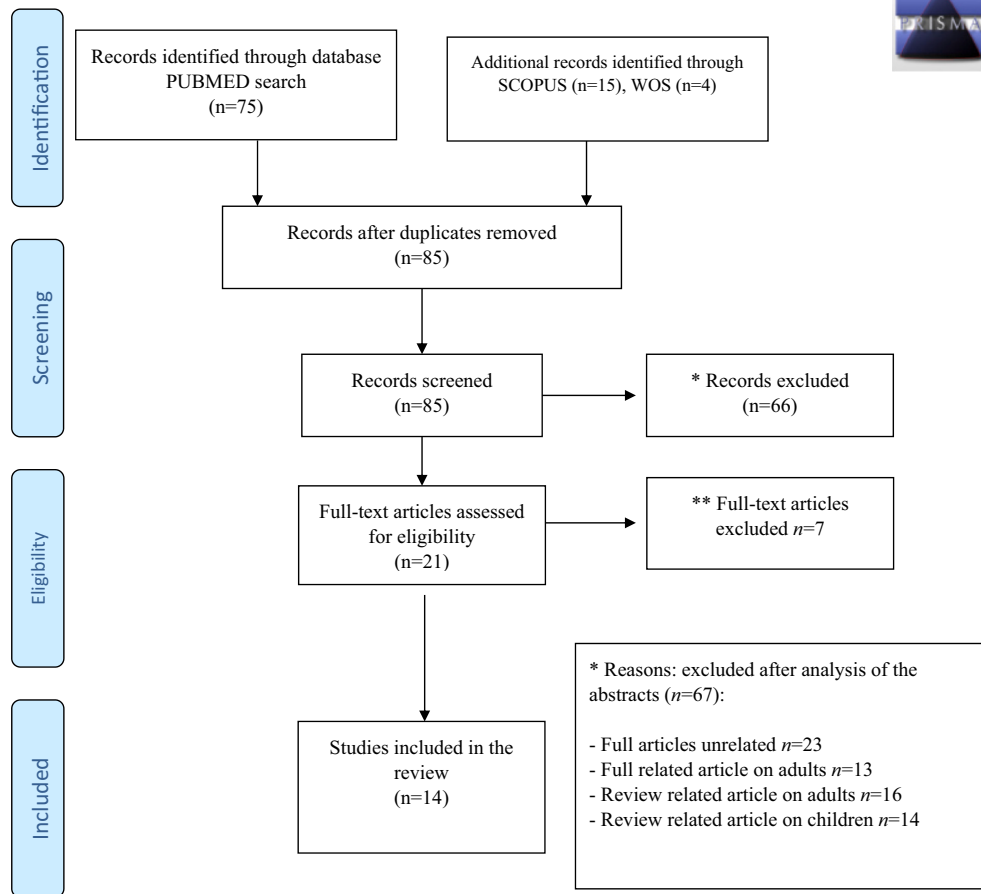
Table 2 presents two studies on the topic [31,32]. An international survey [31] involved 26 countries and several pediatric specialists. A total of 337 patients (<21 years of age), positive for SARS-CoV-2 infection, were enrolled. Eight children had ischemic stroke, including 1/108 newborns with cerebral synovial thrombosis (CSVT; 0.9%), 6/166 children with arterial ischemic stroke (AIS; 0.82%), and 1/54 children with CSVT (1.9%) [31]. In a large multicenter study [32] ($n = 186$ MIS-C), 8 children developed deep vein thrombosis (DVT). The authors concluded that DVT was a rare complication in children positive for SARS-CoV-2 infection [32].

4. Discussion

COVID-19 has been recently recognized as a systemic disorder that induces a prothrombotic state via hyper-activation of the inflammatory and hemostatic pathways [33]. While thrombotic complications in adults with COVID-19 have been widely recognized (overall venous thromboembolism rate 21%, 95% confidence interval [CI] 17–26) and



Fig. 1. PRISMA 2009 flow diagram.
 Legend: * Review fully unrelated to the subject: review that mentions neither pregnancy nor convalescent plasma (CP); review partially related to the subject: review that mentions either only pregnancy or only convalescent plasma; review related article: mentions both pregnancy and CP. **test excluded after analysis of the full text.



extensively studied [34] together with their associated therapeutic implications, little is known about the burden of COVID-19-associated hypercoagulable state in children.

This is the first review of the literature to investigate the relationship between thrombosis and COVID-19 infection in children. Most of the studies are case reports ($n = 19$ children), 73.7% had no or mild comorbidity. The hematological biochemical profile was often incomplete: the most frequently assessed was serum D-dimer levels. None received convalescent plasma therapy [35]. The most common site of thrombosis was the lung (21%) and the most frequently used drug was heparin (42%). Two large multicenter studies reported that the risk of ischemic stroke in SARS-CoV-2 infection (0.82%) and DVT in MIS-C (4.3%) was lower than in adults (1.2% and 21%, respectively). Current data suggest that thrombotic or thromboembolic events are rare in children with COVID-19 infection or MIS-C.

The prevalence of COVID-19 in children and adolescents is relatively low, accounting for about 2.4% of all reported cases [36]. The mortality rate is negligible in this age group [37]. Although most children rarely progress to severe disease, there is concern about an inflammatory cascade [38]. SARS-CoV-2 rarely progresses to MIS-C, while MIS-C leads to serious, life-threatening illness in previously healthy children and adolescents [32]. Children with COVID-19 present with upper respiratory symptoms; symptoms of MIS-C include fever (100%), vomiting (68.2%), and abdominal pain/diarrhea [39]. Similar to Kawasaki-like disease, MIS-C is associated with inflammation, dermatologic, mucocutaneous, gastrointestinal manifestations [40], and cardiac dysfunction [18]. Severity of MIS-C can be life-threatening. The mortality rate is less than 0.1% of reported cases in children [39].

Coagulation and inflammatory parameters are mildly altered in COVID-19; laboratory signs of a proinflammatory and procoagulant

state have been reported in MIS-C cases [11] [26]. In a recent review, Mitchell underlined the need for studies on coagulopathy of COVID-19 in children [41].

Expert opinions suggested the administration of LMWH subcutaneously as anticoagulant thromboprophylaxis in children hospitalized for COVID-19-related illness (including MIS-C) who have markedly elevated D-dimer levels or clinical risk factors for hospital-associated venous thromboembolism [42]. Furthermore, antithrombotic therapy was also recommended in children with markedly elevated plasma D-dimer levels (e.g., ≥ 5 times) at hospital discharge [37,42,43].

Two prospective studies on children hospitalized for COVID-19 ($n = 44$) and MIS-C ($n = 12$) did not report complications of thrombosis/embolism [11,13]. A descriptive analysis of clinical presentation, complications, and outcomes ($n = 99$ MIS-C patients) reported no thrombosis/embolism complications [18]. A retrospective study ($n = 33$ children with MIS-C) investigating the incidence of abnormal cardiac testing on admission and at hospital discharge reported no thrombosis/embolism complications [14]. Debate continues to surround anticoagulation therapy in this population, with little clinical evidence to guide treatment decisions in patients with increased risk for thrombosis [44].

The main limitation of the present study is the reporting of isolated cases with thrombotic complications, which itself precludes representativeness of the entire pediatric population. This limitation notwithstanding, two large multicenter studies showed that ischemic stroke and DVT are rare events in children [31] [32]. Severe illness and complications in children with COVID-19 infection is much less frequent and fatal than in adults [10,45] and thrombosis or thromboembolism in children with COVID-19 infection and MIS-C is uncommon.

Table 1
Characteristics of case reports of children affected by Covid-19 infection and thrombosis events.

Author (year)	Country	Age	Sex	Comorbidity	Presentation	Diagnosis	Severity of disease	Site of thrombosis	D – dimer	Fibrinogen	Platelet	NT – pro – BNP	Ferritin	Procedures	Medications	Outcome
Kenchappa, 2020 [19]	India	10 y	F	None	Nausea, acute abdominal pain	Nasopharyngeal swab RT-PCR	Extensive gangrenous small bowel	Venules partially obliterated by platelets and fibrin thrombi	1496 ng/ m ↑	480 mg/ dL ≈	NA	NA	186 ng/ mL ≈	Surgical excision	LMWH	Recovered
Ghatasheh, 2021 [20]	Arab region	9 m	M	None	2-wk history fever, erythematous rash, watery diarrhea, conjunctival injection	Nasopharyngeal swab RT-PCR	Aneurysm of right coronary artery and left circumflex coronary artery	Aneurysms with multiple filling defects indicated contrast dilution or partial thrombus	NA	NA	653 × 10 ⁹ /L↑	1393 ng/ L↑	NA	–	IVIg (2 g/kg), acetylsalicylic acid (100 mg/kg/d), triple antithrombotic therapy, LMWH	Giant coronary aneurysms, stable general condition
Essajee, 2020 [21]	South Africa	2 y, 7 m	F	Tuberculous meningitis	Left-sided weakness, lethargy, coma	Nasopharyngeal swab RT-PCR	Pan-hydrocephalus, infarction internal capsule, lentiform nucleus and thalamus	Cerebral sinus venous thrombosis	14.8 mg/ L↑	5.2 g/ L↑	253 × 10 ⁹ /L↑	NA	711 μg/ L↑	–	Soniazid 20 mg/kg, rifampicin 20 mg/kg, pyrazinamide 40 mg/kg, ethionamide 20 mg/kg, prednisone (2 mg/kg), acetylsalicylic acid 3 mg/kg/d	Discharged, physiotherapy
Hussain, 2020 [22]	India	14 y	M	None	Frivial blunt trauma, chest pain, cough, fever	Nasopharyngeal swab RT-PCR	Acute osteomyelitis	Femoral vein thrombus	NA	NA	398 × 10 ⁹ /L↑	NA	NA	–	Antibiotics, idexamethasone, hydroxychloroquine, acetylsalicylic acid, injection LMWH 40 mg (followed by warfarin)	Discharged after 40 d hospitalization
Lang, 2020 [23]	Germany	10 y	F	None	Fever (>40 °C), diffuse abdominal pain	Nasopharyngeal swab RT-PCR	Ileitis, aschitis, pleural and pericardial effusions, MIS-C	Clot firmness (3 mm)	4.7 mg/ L↑	NA	NA	NA	NA	–	Defibrotide (start 25 mg/kg/d), low-dose heparin	Discharged 17d after admission
Turbin, 2020 [24]	USA	15 y	M	Mild asthma	Painful unilateral orbital swelling, rhinorrhea, migraine	Nasopharyngeal swab for SARS-CoV-2	Sinusitis, orbital cellulitis, bilateral lung opacities	Thrombophlebitis of right superior ophthalmic vein	NA	NA	NA	NA	1382 ng/mL ≈	Endoscopic frontal sinusotomy, total ethmoidectomy and maxillary antrostomy	Antimicrobial, enoxaparin 2 mg/kg, hydroxychloroquine (start 400 mg bid)	Near resolution of orbital findings and stability of small epidural fluid collection
Visveswaran, 2020 [25]	USA	12 y	F	None	Painful erythema of the left thigh, ecchymotic left foot	Nasopharyngeal swab for SARS-CoV-2 (hospitalization d 16/d 20)	Cellulitis	Iliac vein thrombosis, massive pulmonary embolism	1953 ng/ mL↑	NA	126,000/ μL↓	NA	NA	ClotTriever mechanical thrombectomy, ECMO, Plasmapheresis	Solumedrol, prednisone, enoxaparin	Discharged home on 20 d
Minen, 2021 [26]	UK	14 y 12 y	1) M 2) F	1) Obesity 2) None	1) Complicated Kawasaki disease 2) Vasoplegic shock, bradycardia, Shortness of breath, syncope	Nasopharyngeal swab for SARS-CoV-2	1) [Renal replacement therapy], MIS-C 2) Coronary artery dilatation, MIS-C	1) Renal two filters clotted after 9 and 48 h of hemofiltration 2) Right atrial thrombus	NA	NA	NA	NA	NA	1) ECMO 2) ECMO	1) Antifactor Xa, heparin (35 IU/kg/h), 2) Antifactor Xa, High-dose acetylsalicylic acid, methylprednisolone, infliximab tPA at 0.5 mg/h, heparin,	1) Acute right anterior and middle cerebral artery infarction 2) Resolution
Kotula, 2021 [27]	USA	15 y	F	Obesity	Shortness of breath, syncope	SAR-CoV-2-IgM antibody	Cardiorespiratory failure	Bilateral pulmonary emboli, superior vena cava thrombus	>20 mg/ L↑	NA	NA	NA	4670 ng/ mL ↑	Intubated, hemodialysis	Intubated, heparin,	Inpatient neurological rehabilitation

(continued on next page)

Table 1 (continued)

Author(year)	Country	Age	Sex	Comorbidity	Presentation	Diagnosis	Severity of disease	Site of thrombosis	D – dimer	Fibrinogen	Platelet	NT – pro – BNP	Ferritin	Procedures	Medications	Outcome
Dolhnikoff, 2020 [28]	Brazil	11 y	M	None	Odynophagia, myalgia, abdominal pain, persistent fever	Histopathological examination heart (Coronaviridae family)	Cardiac failure, MIS-C	Microthrombi in pulmonary arterioles, and renal glomerular capillaries	54,153↑ ng/mL	513 mg/dL↑	191 × 10 ³ /μL=	NA	1501 ng/mL↑	Mechanical ventilation	Antimicrobials, epinephrine, furosemide	Ventricular fibrillation, died 1 d after admission
Odievre, 2020 [29]	France	16 yr	F	Sickle cell disease, bilateral ischemic retinopathy	Fever, cough, anosmia, acute chest syndrome, respiratory distress	Nasopharyngeal swab for SARS-CoV-2	Respiratory distress syndrome	Bilateral pulmonary embolisms	23,611 ng/mL	–	–	–	–	ICU, non invasive ventilation; transfusion	Acetaminophen, anti-coagulation, tocilizumab (8 mg/kg)	Discharge 11 d after admission; anticoagulation for 6 w
Colmenero, 2020 [30]	Spain (April to May 2020)	11–17 y (case series, n = 7)	N	None	Pernioteic acral ischemic lesions present for 4–30 d (n = 7; feet) Respiratory and GI (n = 1); respiratory (n = 4); none (n = 2) Before biopsy lesions (chilblains)	Nasopharyngeal swab for SARS-CoV-2 (negative in all)	–	Skin biopsy showed fibrinoid necrosis of vessels (n = 2); microthrombosis (n = 4); fibrinoid necrosis or thrombosis (n = 1)	900↑ ng/mL (n.1, ↑)	–	–	–	–	–	Methylphenidate hydrochloride (n = 2)	Gradual spontaneous resolution (8 w)

Legend: d, day/s; m, month/s; w, week/s; y, year/s; ECMO, extracorporeal membrane oxygenation; F, female; GI, gastrointestinal; ICU, intensive care unit; IVIg, intravenous immunoglobulin; LMWH, low-molecular-weight heparin; M, male; MIS-C, Multisystem Inflammatory Syndrome in Children; NA, not available; RT-PCR, reverse transcriptase-polymerase chain reaction; tPA, tissue polypeptide antigen.

Table 2
Characteristics of studies of children with Covid-19 infection and thrombosis events.

Author year	Type of design	Country	Population	Age (mean)	Case selection	Cases with SARS-CoV-2	Diagnosis	Comment
Beslow, 2020 [31]	International survey, 61 centers, 26 countries	USA (March - May 2020)	971 SARS-CoV-2 patients	0–18 y	Stroke hospitalized patients with SARS-CoV-2 infection: AIS; CSVT	8/337 children positive for SARS-CoV-2 had ischemic stroke (2.4%). Neonates: 1/108 positive for SARS-CoV-2 had AIS (0.9%), 0/9 positive for SARS-CoV-2 no CSVT 6/166 with SARS-CoV-2 had AIS (3.6%), 1/54 with CSVT (1.9%). 8 DVT cases of 186 (1/8 < 5 y, 7/8 13-20 y)	SARS-CoV-2 polymerase chain reaction OR antigen tests	Ischemic strokes rare (< 1% of patients with SARS-CoV-2).
Feldstein, 2020 [32]	Prospective and retrospective surveillance, multicenter	USA, 26 states (16 March – 20 May)	186 MIS-C patients (M, 65%)	Median 8.3 y (IQR 3.3–12.5); (M, 62%)	–		RT-PCR, antibody testing or exposure to persons with COVID-19	DVT rare

Legend: AIS, arterial ischemic stroke; CSVT, cerebral sinovenous thrombosis; DVT, deep vein thrombosis; IQR, interquartile range; y, year/s; M, male/s; MIS-C, Multisystem Inflammatory Syndrome in Children; RT-PCR, reverse transcriptase-polymerase chain reaction.

5. Conclusion

Thrombotic or thromboembolic events are rare in children with COVID-19 infection or MIS-C. As in adults, however, a high index of suspicion should be maintained in children with COVID-19 infection, especially in those with comorbidities predisposing to a thrombotic event. These preliminary observations require larger and more in-depth studies on thrombosis/embolism risk in children with COVID-19 infection to guide both prevention and treatment decisions.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.thromres.2021.07.011>.

CRedit authorship contribution statement

Marco Zaffanello; Conceptualization, Data curation, Roles/Writing - original draft; **Giorgio Piacentini**; Supervision, Validation, Writing - review & editing; **Luana Nosetti** and **Stefania Ganzarolli**; Data curation, Validation; **Massimo Franchini**; Roles/Writing - original draft, Methodology, Writing - review & editing.

Funding source

This study received no grants from funding agencies in the public, commercial or not-for-profit sector.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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