

Prevalence of thrombotic complications in children with SARS-CoV-2

David Aguilera-Alonso ^{1,2}, Sara Murias ³,
Amelia Martínez-de-Azagra Garde ⁴, Antoni Soriano-Arandes, ⁵, Marta Pareja,⁶
Enrique Otheo,⁷ Cinta Moraleda ^{8,9}, Alfredo Tagarro ^{9,10,11,12},
Cristina Calvo ¹³ on behalf of EPICO-AEP Working Group

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For numbered affiliations see end of article.

Correspondence to

Dr David Aguilera-Alonso, Department of Pediatrics, Hospital General Universitario Gregorio Marañón, Madrid 28009, Spain; david.aguilera@salud.madrid.org
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ABSTRACT

Knowledge of thrombosis in children with SARS-CoV-2 is scarce. In this multicentre national cohort of children with SARS-CoV-2 involving 49 hospitals, 4 patients out of 537 infected children developed a thrombotic complication (prevalence of 0.7% (95% CI: 0.2% to 1.9%) out of the global cohort and 1.1% (95% CI: 0.3% to 2.8%) out of the hospitalised patients). We describe their characteristics and review other published paediatric cases. Three out of the four patients were adolescent girls, and only two cases had significant thrombotic risk factors. In this paediatric cohort, D-dimer value was not specific enough to predict thrombotic complications. Adolescence and previous thrombotic risk factors may be considered when initiating anticoagulant prophylaxis on children with SARS-CoV-2 disease (COVID-19).

INTRODUCTION

The disease caused by SARS-CoV-2, named COVID-19, has spread rapidly. Among adult patients, a significant prevalence of thrombotic complications has been described. This risk has been linked to a hypercoagulability state, which has conditioned the publication of guidelines on anticoagulant management in patients with COVID-19.^{1,2}

However, due to the lower experience in COVID-19 disease in children, these guidelines have not included specific recommendations for paediatric patients. Based on adult recommendations, several authors have proposed some indications for anticoagulant prophylaxis that take into account individual risk factors.³ Nevertheless, to date, there is scarce information about thrombotic complications in children with COVID-19. We aimed to describe thrombotic complications among children infected with SARS-CoV-2.

METHODS

The Epidemiological Study of COVID-19 in children was launched and supported by the Spanish Society of Pediatrics (EPICO-AEP) as a multicentre prospective national cohort study aiming to describe paediatric COVID-19 in Spain. Children younger than 18 years of age infected by SARS-CoV-2 and attended at 49 hospitals are currently being enrolled in this registry. Inclusion criteria include positivity in real-time PCR (RT-PCR), IgM or IgG in lateral-flow rapid test, ELISA or

chemiluminescence serology, or disease suggestive of multi-inflammatory syndrome related to SARS-CoV-2 in children (MIS-C). From 1 March to 30 September 2020, children with thrombotic complications associated with SARS-CoV-2 enrolled in EPICO-AEP were included in this study.

Thrombotic complications associated with SARS-CoV-2 infection were defined as any radiologically confirmed thrombosis, arterial or venous, occurring close to the diagnosis of SARS-CoV-2 infection (up to 3 weeks). Microthrombi phenomena related or suspected to be related to SARS-CoV-2 (eg, acral chilblains) were not included. Two-sided 95% Clopper-Pearson exact CIs (95% CI) for binomial proportions were calculated for prevalence. Data were analysed using the Stata V.15 (College Station, Texas, USA).

RESULTS

By 30 September, 537 children were diagnosed with SARS-CoV-2 infection and included in the EPICO-AEP cohort. The median age was 61 months (IQR: 6–140 months), and 293 (54.6%) were boys. Of those, 368 (68.5%) were hospitalised, requiring paediatric intensive care unit admission (PICU), 58 (10.8%) cases. Forty-seven (8.8%) cases were diagnosed with MIS-C.

D-dimer was available from 169 patients, with a median of 1071 µg/L (IQR: 291–2858 µg/L). Anticoagulant drugs (heparin in all cases) were administered to 29 (5.4%) patients: as prophylaxis in 24 (82.8%) cases, and as treatment in 5 (17.2%) cases. Most of the patients on thromboprophylaxis had severe COVID-19 (79.2% admitted to PICU and 56.5% received inotropic support). Four cases, which correspond to 0.7% (95% CI: 0.2% to 1.9%) out of the global cohort and 1.1% (95% CI: 0.3% to 2.8%) out of the hospitalised patients, developed some thrombotic complication. A fifth case receiving anticoagulant treatment was a patient who had a history of venous thrombosis not related to SARS-CoV-2 infection and was not included in this report.

Three out of these four patients were adolescent girls (table 1, cases 1–4). None of the cases was diagnosed with MIS-C. Two patients (patients 1 and 2) had several significant thrombotic risk factors. Patients 3 and 4 did not have any previous personal or family risk factors for thrombosis. However, in patient 3, after thrombosis diagnosis,



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Table 1 Characteristics of children with SARS-CoV-2 infection and thrombosis from EPICO-AEP cohort (cases 1–4) and from literature review (cases 5–13)

N	Age	Sex	Medical background/ risk factors	Other thrombotic risk factors	Family thrombotic history	Thrombotic complication	Other signs/symptoms	SARS-CoV-2 RT-PCR	SARS-CoV-2 Abs	D-dimer (µg/L)	Thrombo- prophylaxis*	Anticoagulation treatment	Thrombophilia work-up	Outcome†
1	4 years	Female	Systemic juvenile idiopathic arthritis on treatment with steroids and canakinumab	Central venous catheter	No	Right iliac vein thrombosis	Fever, cough and rhinorrhoea	Positive	Negative	5953‡	No	LWH	NA	Discharged without sequelae
2	12 years	Female	B cell acute lymphoblastic leukaemia on induction chemotherapy and obesity	Central venous catheter and asparaginase treatment	No	Thrombosis of the right upper limb	Dyspnoea and thoracic pain (pulmonary embolism was ruled out)	Positive	IgG positive	232‡	LWH	LWH	Decreased protein C activity (58%)	Discharged without sequelae
3	13 years	Female	No	No	No	Left common and superficial femoral vein thrombosis	Fever, hyporexia, headache, asthena, rash, abdominal pain and vomiting	Positive	NA	1194‡	No	LWH and cava filter	Lupus anticoagulant positive (remained positive 5 months later)	Discharged without sequelae
4	13 years	Female	No	No	No	Thrombosis of the transverse sinuses and of the jugular vein, pulmonary embolism and femoral thrombosis	Fever and odynophagia	Positive	NA	35 420‡	No	Continuous unfractionated heparin followed by LWH	Normal	Discharged without sequelae
5	16 years	Female	Homozygous sickle cell disease	No	ND	Bilateral pulmonary embolism	Fever, cough, anosmia, acute chest syndrome	Positive	ND	23 611	No	Yes (not fully described)	ND	Discharged
6	5 years	Male	No	ECMO	ND	Right middle cerebral artery infarction, cerebral oedema and diffuse contralateral subarachnoid haemorrhages	Fever, cough, and abdominal pain; cardiogenic shock with cardiopulmonary failure	ND	Positive	15 000	Yes	ND	ND	Brain dead
7	2 months	Male	Tracheomalacia requiring tracheostomy	ECMO	ND	Bilateral middle cerebral artery and posterior cerebral artery territory infarction with haemorrhagic transformations	Respiratory failure, pneumomediastinum, and bilateral pneumothoraces	ND	Negative	ND	ND	ND	ND	Admitted
8	12 years	Female	No	No	No	Popliteal-to-common iliac vein thrombosis and massive pulmonary embolism	No	Negative	IgM positive	1953	No	Percutaneous mechanical venous thrombectomy, thrombolysis and infrahepatic venous filter	Antiphospholipid antibodies	Discharged without neurological deficits
9	16 years	Male	ND	Sphenoid sinusitis	ND	Cavernous sinus thrombosis and left middle cerebral artery stroke	Aseptic meningitis associated with stupor	Positive	ND	ND	No	Yes (not fully described)	ND	Died
10	16 years	Male	ND	ND	ND	Deep venous thrombosis of the lower limbs with pulmonary emboli	ND	Positive	ND	ND	ND	ND	ND	ND
11	6 years	Male	ND	ND	ND	Small segmental pulmonary emboli	MIS-C (fever, hypoxic respiratory failure, abdominal pain)	Positive	ND	ND	ND	ND	ND	ND
12	5 years	Male	No	ECMO	ND	Right anterior and middle cerebral artery ischaemic infarction§	MIS-C (fever, vomiting, cough, abdominal pain)	Negative	Positive	18 300	Heparin	ND	ND	Brain dead
13	2 years	Female	No	Miliary tuberculosis	ND	Thrombosis of the superior sagittal sinus and the transverse sinuses and cerebral infarction involving the anterior limb of the right internal capsule, lentiform nucleus and thalamus	Weakness, lethargy and cervical lymphadenopathy	Positive	ND	14 800	No	Aspirin	ND	Discharged with residual left haemiparesis

*Thromboprophylaxis before thrombosis diagnosis.

†Outcome when this article or the reviewed articles were published.

‡Highest value during the episode.

§These cases were supposed to be hypercoagulable manifestations of COVID-19/MIS-C.

¶Abs, antibodies; ECMO, extracorporeal membrane oxygenation; LWH, low-weight heparin; MIS-C, multi-inflammatory syndrome related to SARS-CoV-2 in children; NA, not available; ND, not described; RT-PCR, real-time PCR.

a thrombophilia work-up was performed, which revealed a positive lupus anticoagulant, remaining positive 5 months later.

The only patient receiving thromboprophylaxis (low-weight heparin) before thrombosis was patient 2. D-dimer levels were severely increased in patients 1 (5953 µg/L) and 4 (35 420 µg/L) but were only slightly increased in the other cases (1194 and 232 µg/L, respectively). All cases except patient 3 had SARS-CoV-2 RT-PCR confirmation coinciding with thrombosis diagnosis. In patient 3, COVID-19 was initially suspected but not microbiologically confirmed until 3 weeks after thrombosis. All cases had thrombosis affecting the limbs, with cerebral venous sinus thrombosis and pulmonary embolism in one of them. All patients were treated with heparin and discharged without sequelae.

DISCUSSION

To the best of our knowledge, this is the first study that describes thrombotic complications in children with SARS-CoV-2 infection in a large cohort. Only four patients developed a thrombotic complication (1.2% of hospitalised children with non-MIS-C SARS-CoV-2 infection). Although this prevalence is not as high as in hospitalised adults with COVID-19,¹ it is slightly higher than that previously described in hospitalised children without COVID-19 (0.13%–0.55%). Among the factors associated with a lower incidence of thromboembolic complications in children with COVID-19, a different balance in coagulation homeostasis, with a higher concentration of antithrombotic serum factors (eg, alpha-2-macroglobulin) in children compared with adults, a protective ‘healthy’ endothelium or fewer comorbidities have been proposed.

Only two of our four cases had significant thrombotic risk factors (central venous catheter, obesity, malignancy or asparaginase treatment), highlighting the difficulty of predicting thrombotic complications in children with COVID-19 to initiate anticoagulant prophylaxis. Thrombosis is very uncommon in patients under 18 years old, and systemic anticoagulant prophylaxis may have adverse events that outweigh its benefit. Of note, one patient was diagnosed with antiphospholipid syndrome, showing lupus anticoagulant persistently elevated. Transient lupus anticoagulant has been described in patients with COVID-19, but its significance is unclear.

We conducted a systematic search in order to review reported paediatric patients diagnosed with SARS-CoV-2 infections with any thrombotic complication (search strategy in online supplemental material). Ten cases were found (full references in online supplemental material); one of them included in our series (case 4). **Table 1** (cases 5–13) shows the main characteristics of the reported cases. Additionally, three (3.8%) and four (2.2%) cases diagnosed with MIS-C from two other national cohorts developed a venous thrombosis, but their full clinical information was not available.⁴

The central nervous system was the most commonly affected site (six cases), followed by the lung (five cases) and lower limbs (three cases). Similar to our data, most of the patients were adolescents. This age distribution is also seen in patients with MIS-C, in which the prevalence of thrombosis increases with the age of the patients: 0 of 66 (0%), 1 of 75 (1.3%) and 3 of 45 (6.7%) in patients aged <5 years, 5–12 years and 13–20 years, respectively.⁴ This peak of cases with thrombosis affecting adolescents is similar to what is seen in hospitalised children without COVID-19.

Markedly elevated plasma D-dimer levels (eg, ≥ 5 times the upper limit of normal values) has been proposed as an indication

for anticoagulant prophylaxis in children hospitalised with SARS-CoV-2-related illness.³ In our cohort, 68 of 169 (40.2%) had a value >1500 µg/L. However, only 2 of 68 (2.9%) cases developed a thrombotic complication. Therefore, the use of the D-dimer value is not specific enough to make decisions regarding anticoagulant prophylaxis in children. In our opinion, other factors, such as the age (considering adolescents especially vulnerable), coexistence of risk factors (eg, malignancy, indwelling central venous catheter, obesity, immobility, etc),⁵ or MIS-C diagnosis, should be considered when initiating anticoagulant prophylaxis in children with COVID-19. Of note, a clinical trial is currently evaluating the safety and efficacy of thromboprophylaxis in children hospitalised with signs and/or symptoms of SARS-CoV-2 infection (ClinicalTrials.gov NCT04354155).

Our study has some limitations, such as the variability of tests that were used to diagnose infection, not only the gold standard PCR, which could make false results. Additionally, since ultrasound was not routinely performed in all patients, subclinical thrombosis may not have been diagnosed.

In conclusion, except in the MIS-C, unlike adults, thrombotic complications seem very uncommon in children with SARS-CoV-2. Adolescence and previous thrombotic risk factors may be considered when initiating thromboprophylaxis in children with COVID-19. Further studies are needed to clarify risk factors among children with COVID-19 in order to develop specific recommendations.

Author affiliations

¹Pediatric Infectious Diseases Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain

²Instituto de Investigación Sanitaria Gregorio Marañón (IISGM), Hospital General Universitario Gregorio Marañón, Madrid, Spain

³Pediatric Rheumatology Department, Hospital La Paz, Madrid, Spain

⁴Pediatric Intensive Care Unit, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

⁵Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Vall d'Hebron, Barcelona, Spain

⁶Department of Pediatrics, Hospital General de Albacete, Albacete, Spain

⁷Department of Pediatrics, Hospital Ramón y Cajal, Madrid, Spain

⁸Pediatric Infectious Diseases Unit, Hospital Universitario 12 de Octubre, Madrid, Spain

⁹Fundación de Investigación Biomédica Hospital 12 de Octubre. Instituto de Investigación 12 de Octubre (imas12), Hospital 12 de Octubre, Madrid, Spain

¹⁰Pediatrics Department, Hospital Universitario Infanta Sofía, Madrid, Spain

¹¹Fundación para la Investigación, Hospital Universitario Infanta Sofía y del Henares, Madrid, Spain

¹²Universidad Europea, Madrid, Spain

¹³Department of Pediatrics, Infectious and Tropical Diseases, Hospital Universitario La Paz, Madrid, Spain

Correction notice This paper has been updated since it was published online. There has been a change to an author's first name in the EPICO-AEP Working Group.

Twitter David Aguilera-Alonso @DavidAguileraAl, Antoni Soriano-Arandes, @tonisorianoo66 and Cristina Calvo @CclavoreyRITIP

Collaborators EPICO-AEP Working Group: Mar Santos, Marisa Navarro, Jesús Saavedra, Elena Rincón, Begoña Santiago (Hospital Universitario Gregorio Marañón); Pablo Rojo, Daniel Blázquez, Luis Prieto, Elisa Fernández-Cooke, Cristina Epalza, Sara Domínguez-Rodríguez, Serena Villaverde (Hospital 12 de Octubre); María José Mellado, Teresa del Rosal, Carlos Grasa, Paula Rodríguez Molino (Hospital La Paz); Francisco José Sanz-Santaufemia, José Antonio Alonso Cadenas, Gero Calleja, María Isabel Iglesias Bouzas, Blanca Herrero (Hospital Universitario Niño Jesús); Victoria Fumadó, Miguel Lanasa; Silvia Simó (Hospital Sant Joan de Déu); Susana Melendo, Pere Soler-Palacin (Hospital Vall d'Hebron); María Urretavizcaya, Mercedes Herranz (Complejo Hospitalario de Navarra); Fátima Ara, Fernando Cabañas (Hospital Universitario Quirónsalud Madrid); Rut del Valle, María Fernández, Teresa Raga, María de la Serna, Ane Plazaola (Hospital Infanta Sofía); María Dolores Martín (BR Salud); Enrique Otheo, José Luis Vázquez (Hospital Ramón y Cajal); Lola Falcón, Olaf Neth, Peter Olbrich, Walter Goicoechea (Hospital Universitario Virgen del Rocío); Laura Martín (Hospital Universitario Regional de Málaga); Lucía Figueroa (Hospital de Villalba); María Lorente (Hospital Universitario del Sureste); María Penn,

Claudia García, María García, Teresa Alvaredo (Hospital Príncipe de Asturias); Ma Inmaculada Olmedo, Agustín López (Hospital Puerta de Hierro); Elvira Cobo (Hospital Fundación Alcorcón); Mariam Tovizi (Hospital del Tajo); Pilar Galán (Hospital Fundación Fuenlabrada); Beatriz Soto, Sara Guillén (Hospital de Getafe); Adriana Navas (Hospital Infanta Leonor); M Luz García (Hospital de Leganés); Sara Pérez (Hospital de Torrejón); Amanda Bermejo, Pablo Mendoza (Hospital de Móstoles); Gema Sabrido (Hospital Rey Juan Carlos); María José Hernández (Hospital Central de la Defensa); Ana Belén Jiménez (Fundación Jiménez Díaz); Arantxa Berzosa, Marta Illán (Hospital Clínico San Carlos); Nerea Gallego, Ana López (Hospital Universitario Son Espases); Beatriz Ruiz (Hospital Universitario Reina Sofía); Santiago Alfayate, Ana Menasalvas, Eloísa Cervantes (Hospital Clínico Universitario Virgen de la Arrixaca); María Méndez (Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol); Ángela Hurtado (Instituto Hispalense de Pediatría); Cristina García, Inés Amich, Yolanda Ruiz (Hospital San Pedro); Manuel Oltra, Álvaro Villaroya (Hospital Universitario i Politècnic La Fe); Angustias Ocaña (Hospital La Moraleja); Isabel Romero, María Fernanda Guzmán (Hospitales Madrid); MJ Pascual (Hospital Nisa); María Sánchez-Códez (Hospital Universitario Puerta del Mar); Elena Montesinos (Consorci Hospital General Universitari de València); Julia Jensen, María Rodríguez (Hospital Infanta Cristina); Gloria Caro (Hospital Infanta Elena); Neus Rius, Alba Gómez (Hospital Universitari Sant Joan de Reus); Rafael Bretón (Hospital Clínico Universitario de Valencia); Margarita Rodríguez, Julio Romero (Hospital Universitario Virgen de las Nieves); Ana Campos (Hospital Universitario Sanitas La Zarzuela); Mercedes García (Hospital de Mérida); Rosa María Velasco (Complejo Hospitalario de Toledo); Zulema Lobato (Althia, Xarxa Assistencial Universitària de Manresa); Fernando Centeno, Elena Pérez (Hospital Universitario Río Hortega); Paula Vidal (Hospital Clínico Universitario Lozano Blesa); Corsino Rey, Ana Vivanco, Maruchi Alonso (Hospital Universitario Central de Asturias); Pedro Alcalá, Javier González de Dios (Hospital General Universitario de Alicante); Eduard Solé, Laura Minguell (Hospital Universitari Arnau de Vilanova); Itziar Astigarraga (Hospital Universitario de Cruces); Ma Ángeles Vázquez, Miguel Sánchez (Hospital Universitario Torrecárdenas); Elena Díaz (Hospital Virgen de la Luz); Eduardo Consuegra (Hospital Universitario de Salamanca); María Cabanillas (Complejo Asistencial Universitario de Palencia); Luis Peña (Hospital Universitario Materno Infantil de las Palmas); Elisa Garrote, Maitte Goicoechea (Hospital Universitario de Basurto); Irene Centelles (Hospital General Universitari de Castelló); Santiago Lapeña, Sara Gutiérrez, Soraya Gutiérrez (Complejo Asistencial Universitario de León); Amparo Cavalle (PIUS Hospital de Valls); José María Olmos (Hospital Mare de Déu dels Liris); Alejandro Cobo, Sara Díaz (Hospital Universitario de Canarias); Beatriz Jiménez (Hospital Universitario Marqués de Valdecilla); Raúl González (Hospital Sant Joan d'Alacant); Miguel Lafuente, Matilde Bustillo (Hospital Infantil de Zaragoza); Natividad Pons, Julia Morata (Hospital Lluís Alcanyis); Elsa Segura (Hospital Universitario Son Llatzer de Palma de Mallorca); and María Bernardino (Universidad Europea de Madrid).

Contributors DA-A, CC, CM and AT designed the study. SM, AM-d-A, AS-A, MP and EO did the follow-up of patients with COVID-19 and thrombosis. DA-A and CC drafted the initial manuscript. CM, AT, SM, AM-d-A, AS-A, MP and EO reviewed and edited the manuscript. All authors approved the final version of the manuscript.

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ORCID iDs

David Aguilera-Alonso <http://orcid.org/0000-0003-1017-2386>

Sara Murias <http://orcid.org/0000-0002-3309-0722>

Amelia Martínez-de-Azagra Garde <http://orcid.org/0000-0002-7997-0821>

Antoni Soriano-Arandes, <http://orcid.org/0000-0001-9613-7228>

Cinta Moraleda <http://orcid.org/0000-0002-8335-903X>

Alfredo Tagarro <http://orcid.org/0000-0003-2860-3455>

Cristina Calvo <http://orcid.org/0000-0002-6503-3423>

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Prevalence of thrombotic complications in children with SARS-CoV-2

- Supplementary material -

Search strategy

We searched 2 electronic databases, PubMed and the medical preprint server medRxiv, on November 21st, 2020. We used the following search terms in PubMed: ((stroke) OR (coagulopathy) OR (coagulation) OR (thrombosis) OR (thromboembolism) OR (thromboembolic) OR (embolism)) AND ((children[Title]) OR (child[Title]) OR (childhood[Title]) OR (paediatric[Title]) OR (pediatric[Title]) OR (paediatrics[Title]) OR (pediatrics[Title]) OR (infant[Title]) OR (infants[Title]) OR (youth[Title]) OR (youths[Title]) OR (adolescent[Title]) OR (adolescents[Title]) OR (neonate[Title]) OR (neonates[Title]) OR (newborn[Title]) OR (newborns[Title])) AND ((covid[Title]) OR (coronavirus[Title]) OR (sars[Title])). In medRxiv, we undertook separate searches for “child and covid-19” and “covid-19 and thrombosis”, as more complex Boolean searches are not available.

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Case 4 (included in our case series): Alberto García-Salido, Inés Leoz-Gordillo, Amelia Martínez de Azagra-Garde, Montserrat Nieto-Moro, María Isabel Iglesias-Bouzas, María Ángeles García-Teresa, et al. Children in Critical Care Due to Severe Acute Respiratory Syndrome Coronavirus 2 Infection: Experience in a Spanish Hospital. *Pediatr Crit Care Med* 2020;21.

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National cohorts describing MIS-C:

USA: thrombosis in 4 (2.2%) cases.

Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med* 2020;383:334–46.

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EPICO-AEP WORKING GROUP:

Mar Santos, Marisa Navarro, Jesús Saavedra, Elena Rincón, Begoña Santiago, (Hospital Universitario Gregorio Marañón), Pablo Rojo, Daniel Blázquez, Luis Prieto, Elisa Fernández-Cooke, Cristina Epalza, Sara Domínguez-Rodríguez, Serena Villaverde (Hospital 12 de Octubre), María José Mellado, Teresa del Rosal, Carlos Grasa, Paula Rodríguez Molino (Hospital La Paz), Francisco José Sanz-Santaefemia, José Antonio Alonso Cadenas, Gero Calleja, María Isabel Iglesias Bouzas, Blanca Herrero (Hospital Universitario Niño Jesús), Victoria Fumadó, Miguel Lanaspá (Hospital Sant Joan de Déu), Susana Melendo, Pere Soler-Palacin, Silvia Simó (Hospital Vall d'Hebron), María Urretavizcaya, Mercedes Herranz (Complejo Hospitalario de Navarra), Fátima Ara, Santiago Cabañas (Hospital Universitario Quirónsalud Madrid), Rut del Valle, María Fernández, Teresa Raga, María de la Serna, Ane Plazaola (Hospital Infanta Sofía), María Dolores Martín (BR Salud), Enrique Otheo, José Luis Vázquez (Hospital Ramón y Cajal), Lola Falcón, Olaf Neth, Peter Olbrich, Walter Goicoechea (Hospital Universitario Virgen

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(Complejo Hospitalario de Toledo), Zulema Lobato (Althaia, Xarxa Assistencial Universitària de Manresa), Fernando Centeno, Elena Pérez (Hospital Universitario Río Hortega), Paula Vidal (Hospital Clínico Universitario Lozano Blesa), Corsino Rey, Ana Vivanco, Maruchi Alonso (Hospital Universitario Central de Asturias), Pedro Alcalá, Javier González de Dios (Hospital General Universitario de Alicante), Eduard Solé, Laura Minguell (Hospital Universitari Arnau de Vilanova), Itziar Astigarraga (Hospital Universitario de Cruces), M^a Ángeles Vázquez, Miguel Sánchez (Hospital Universitario Torrecárdenas), Elena Díaz (Hospital Virgen de la Luz), Eduardo Consuegra (Hospital Universitario de Salamanca), María Cabanillas (Complejo Asistencial Universitario de Palencia), Luis Peña (Hospital Universitario Materno Infantil de las Palmas), Elisa Garrote, Maite Goicoechea (Hospital Universitario de Basurto), Irene Centelles (Hospital General Universitari de Castelló), Santiago Lapeña, Sara Gutiérrez, Soraya Gutiérrez (Complejo Asistencial Universitario de León), Amparo Cavalle (PIUS Hospital de Valls), José María Olmos (Hospital Mare de Déu dels Liris), Alejandro Cobo, Sara Díaz (Hospital Universitario de Canarias), Beatriz Jiménez (Hospital Universitario Marqués de Valdecilla), Raúl González (Hospital Sant Joan d'Alacant), Miguel Lafuente, Matilde Bustillo (Hospital Infantil de Zaragoza), Natividad Pons, Julia Morata (Hospital Lluís Alcanyis) and Elsa Segura (Hospital Universitario Son Llatzer de Palma de Mallorca), María Bernardino (Universidad Europea de Madrid).

Prevalence of thrombotic complications in children with SARS-CoV-2

- Supplementary material -

Search strategy

We searched 2 electronic databases, PubMed and the medical preprint server medRxiv, on November 21st, 2020. We used the following search terms in PubMed: ((stroke) OR (coagulopathy) OR (coagulation) OR (thrombosis) OR (thromboembolism) OR (thromboembolic) OR (embolism)) AND ((children[Title]) OR (child[Title]) OR (childhood[Title]) OR (paediatric[Title]) OR (pediatric[Title]) OR (paediatrics[Title]) OR (pediatrics[Title]) OR (infant[Title]) OR (infants[Title]) OR (youth[Title]) OR (youths[Title]) OR (adolescent[Title]) OR (adolescents[Title]) OR (neonate[Title]) OR (neonates[Title]) OR (newborn[Title]) OR (newborns[Title])) AND ((covid[Title]) OR (coronavirus[Title]) OR (sars[Title])). In medRxiv, we undertook separate searches for “child and covid-19” and “covid-19 and thrombosis”, as more complex Boolean searches are not available.

References of cases included from literature review:

Case 4 (included in our case series): Alberto García-Salido, Inés Leoz-Gordillo, Amelia Martínez de Azagra-Garde, Montserrat Nieto-Moro, María Isabel Iglesias-Bouzas, María Ángeles García-Teresa, et al. Children in Critical Care Due to Severe Acute Respiratory Syndrome Coronavirus 2 Infection: Experience in a Spanish Hospital. *Pediatr Crit Care Med* 2020;21.

Case 5: Odièvre M, Marcellus C, Ducou Le Pointe H, Allali S, Romain A, Youn J, et al. Dramatic improvement after tocilizumab of severe COVID-19 in a child with sickle cell disease and acute chest syndrome. *Am J Hematol* 2020;95:E192–4.

Cases 6 and 7: Schupper AJ, Yaeger KA, Morgenstern PF. Neurological manifestations of pediatric multi-system inflammatory syndrome potentially associated with COVID-19. *Child's Nerv Syst* 2020;36:1579–80.

Case 8: Visveswaran G, Morparia K, Narang S, Sturt C, Divita M, Voigt B, et al. SARS-CoV-2 Infection and Thrombosis: Phlegmasia Cerulea Dolens Presenting with Venous Gangrene in a Child. *J Pediatr* 2020. <https://doi.org/10.1016/j.jpeds.2020.07.032>.

Case 9: Oualha M, Bendavid M, Berteloot L, Corsia A, Lesage F, Vedrenne M, et al. Severe and fatal forms of COVID-19 in children. *Arch Pediatr* 2020;27:235.

Case 10: Caro-Dominguez P, Shelmerdine SC, Toso S, Secinaro A, Toma P, Damasio MB, et al. Thoracic imaging of coronavirus disease 2019 (COVID-19) in children: a series of 91 cases. *Pediatr Radiol* 2020:1–15.

Case 11: Winant AJ, Blumfield E, Liszewski MC, Kurian J, Foust A, Lee EY. Thoracic Imaging Findings of Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19: What Radiologists Need to Know Now. *Radiol Cardiothorac Imaging* 2020;2:e200346.

Case 12: Kaushik S, Ahluwalia N, Gangadharan S, Esperenza M, Murthy R, Ofori-Amanfo G, Aydin SI. ECMO support in SARS-CoV2 multisystem inflammatory syndrome in children in a child. *Perfusion*. 2020 Sep 9:267659120954386.

Case 13: Essajee F, Solomons R, Goussard P, Van Toorn R. Child with tuberculous meningitis and COVID-19 coinfection complicated by extensive cerebral sinus venous thrombosis. *BMJ Case Rep*. 2020 Sep 14;13(9):e238597.

National cohorts describing MIS-C:

USA: thrombosis in 4 (2.2%) cases.

Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med* 2020;383:334–46.

UK: thrombosis in 3 (3.8%) cases.

Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. *Lancet Child Adolesc Heal* 2020;4:669–77.

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