

Coagulation Abnormalities and Management in Hospitalized Pediatric Patients With COVID-19

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Background: The incidence and severity of coagulation abnormalities have not been extensively studied in pediatric populations with coronavirus disease 2019 (COVID-19). Moreover, their association with an increased risk for thromboembolic events remains unclear, and there is a lack of evidence for optimal prophylactic antithrombotic management. The aim of our study was to present our experience in evaluation, management, and long-term outcomes of coagulation abnormalities in pediatric hospitalized patients with COVID-19.

Methods: A prospective study was performed in all children hospitalized for COVID-19 during a 6-month period focusing on patients' coagulation abnormalities, the normalization of the coagulation profile with or without anticoagulation prophylaxis and the clinical outcome of the disease.

Results: Two hundred twenty-three patients (median age: 11.4 months) were enrolled in the study. Coagulation abnormalities were detected in 92.4% of patients with increased D-dimer levels to be the most common abnormality detected in 84.3% of patients. Prophylactic anticoagulation was initiated only in 7 (3.1%) selected patients with severe COVID-19 and at least 2 risk factors for venous thromboembolism (VTE) and in all patients with previous history of VTE. Follow-up coagulation profile in 85 patients showed that changes over time had a tendency towards normalization irrespective of the initiation of anticoagulant thromboprophylaxis. No thrombotic complications were observed 3 months upon discharge.

Conclusions: Although abnormal findings in coagulation profile were very common, they were not associated with risk for VTE even in severe cases. A trend of normalization early in the course of the disease was observed regardless of the use of anticoagulant thromboprophylaxis.

Keywords: COVID-19, children, D-dimer levels, thrombotic risk, prophylactic anticoagulation

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Coronavirus disease 2019 (COVID-19) in adult populations has been associated with significant coagulation dysfunction resulting in venous thromboembolism (VTE).¹ Extended coagulation abnormalities such as elevated D-dimer and fibrin degradation product levels, prolongation of the prothrombin time (PT) and activated partial thromboplastin time (aPTT), thrombocytopenia, decreased antithrombin, and increased activity of von Willebrand factor and factor VIII have been detected and associated with poor

prognosis.^{2,3} In this context, international guidelines have been published for the risk stratification at admission for an adult COVID-19 patient and management of COVID-19 coagulopathy.^{4,5}

In pediatric populations with COVID-19, coagulation abnormalities have also been reported and according to recent consensus-based clinical recommendations, pediatric risk assessment, and consideration of prophylactic anticoagulation should be performed routinely for all hospitalized children.^{6,7}

Recently, the International Society on Thrombosis and Haemostasis (ISTH) published recommendations for anticoagulant thromboprophylaxis in children hospitalized for COVID-19 relying mainly on D-dimer levels and, second, on prothrombotic risk factors despite the fact that it has not been clarified yet whether SARS-CoV-2 confers, like in adults, a unique risk for thrombosis. According to ISTH recommendations, anticoagulant thromboprophylaxis should be administered in symptomatic hospitalized children for COVID-19 who have either markedly elevated plasma D-dimer levels (e.g., 5-times more than normal values) or one or more clinical risk factors for hospital-associated VTE and in asymptomatic hospitalized children with more than 3 risk factors for hospital-associated VTE. Continued anticoagulant thromboprophylaxis upon discharge was considered in patients who have markedly elevated plasma D-dimer levels at hospital discharge and clinical risk factors for VTE until resolution of clinical risk factors or 30 days postdischarge.⁷

The aim of the study was to share our experience in evaluating and managing coagulopathy in pediatric hospitalized patients with COVID-19.

MATERIALS AND METHODS

A single-center cohort study was performed from November 2020 to April 2021 at the COVID-19 unit of the First Department of Pediatrics of the Medical School of the National and Kapodistrian University of Athens at the "Aghia Sophia" Children's Hospital in Athens, which is the largest tertiary children's Hospital in Greece. All pediatric patients with COVID-19 who were hospitalized in the COVID-19 unit during this period were included in the study. SARS-CoV-2 infection was confirmed by real time RT-PCR performed on nasal or pharyngeal swabs. Cases of multisystem inflammatory syndrome in children (MIS-C) were defined according to WHO criteria.⁸ Hospitalization was considered necessary for every child who had a history of underlying chronic disease, abnormal chest radiograph imaging results, worsening symptoms, or age less than 3 months. Based on National Institutes of Health (NIH) COVID-19 Treatment Guidelines, patients were grouped in those who had "mild/moderate" illness and those who had "severe/critical" illness. Patients with mild illness had any of the various signs and symptoms of COVID-19 (eg, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste, and smell) but who did not have shortness of breath, dyspnea, or abnormal chest imaging, while patients with moderate illness showed evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO₂) ≥94% on room air at sea level. Severe illness referred to patients who had SpO₂ <94% on room air at sea level, a ratio of arterial

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partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%, while critical illness to patients who had respiratory failure, septic shock, or multiple organ dysfunction.⁹

Data regarding demographic characteristics, clinical status, laboratory tests, and radiological findings were collected for all patients. Coagulation profile test was performed in all patients upon admission and included D-dimers, PT, aPTT, antithrombin III (ATIII), fibrinogen, and factor VIII (FVIII). Abnormal findings were defined as D-dimer levels over 0.5 µg/mL, PT values over 14 seconds, aPTT values over 39 seconds, ATIII levels less than 80%, fibrinogen levels over 400 mg%, and FVIII levels over 150%.

Repeated coagulation profile was performed during hospitalization depending on the severity of the abnormalities and the general condition of the patient and in the follow-up visit within 14 days after discharge, when possible.

In our study population, anticoagulation management was based on both, our previous experience from the first 9 months of the pandemic, where rapid normalization of coagulation abnormalities had been observed without any treatment, and the very low incidence of VTE in pediatric COVID-19 reported in the literature. Prophylactic treatment was initiated in: (i) patients admitted to the intensive care unit (ICU) caused by critical illness; (ii) patients with severe COVID-19 and ≥2 risk factors for hospital-associated VTE; (iii) patients with “mild/moderate” illness and a previous history of VTE. According to ITSH, risk factors for hospital-associated VTE included central venous catheter, mechanical ventilation, complete immobility, obesity, active malignancy, nephrotic syndrome, cystic fibrosis exacerbation, sickle cell disease vaso-occlusive crisis, flare of underlying inflammatory disease, congenital or acquired cardiac disease with venous stasis or impaired venous return, previous history of VTE, first degree family history of VTE before age of 40 years, known thrombophilia, pubertal or age >12 years, receiving estrogen-containing oral contraceptive pill and status-post splenectomy for

underlying hemoglobinopathy.^{7,10} Thromboprophylaxis was discontinued after normalization of patient’s coagulation profile or 14 days after discharge depending on the severity of COVID-19 disease.

Descriptive analysis was performed for all variables. Categorical data were expressed as absolute number and proportions (%). Continuous variables were reported as mean ± SD in the case of normal distribution or the median and interquartile range (IQR) in the case of nonnormal (Gaussian) distribution. Continuous data were tested for normality using statistical tests (Kolmogorov-Smirnoff test) and graphical methods (histogram, Q–Q plot). For normally distributed variables, Student’s *t* test was used to assess differences between 2 groups, whereas for skewed variables, the Mann-Whitney *U* test was performed. For categorical data, we performed χ^2 tests for comparisons or Fisher’s exact tests if data were not suitable for χ^2 testing. The nonparametric Wilcoxon test was used to determine if there are differences between 2 related groups on the same continuous, dependent variable. Logistic regression analysis was performed, when necessary, to identify independent associations. All statistical analyses were performed with the statistical package PSAW Statistics v23 (SPSS, Inc., Chicago, IL, USA). Statistical significance was set at *P* < 0.05.

Ethical Approval

Data were collected with complete anonymity and study protocol was approved by the Research Ethics Board of “Aghia Sophia” Children’s Hospital.

RESULTS

Characteristics of the Study Population

Two hundred twenty-three patients (130; 58.3% males) were included in the study. Patients’ characteristics are presented in Table 1. The median age was 11.4 months (IQR: 3.2 months–6.5 years). Thirty-five (15.7%) patients had at least 1 comorbidity

TABLE 1. Patients’ characteristics

	Total (n = 223)	Mild/moderate illness (n = 209)	Severe/critical illness (n = 14)	<i>P</i>
Male	130 (58.3%)	118 (56.5%)	12 (85.7%)	0.03
Age (mo)	11.4 (3.2–77.9)	9.8 (3.2–71.6)	112.3 (8.5–170.4)	0.05
Roma, immigrants	54 (24.2%)	48 (23.0%)	6 (42.9%)	0.09
Comorbidities	35 (15.2%)	26 (12.4%)	9 (64.3%)	<0.001
Symptoms				0.32
Only fever	47 (22.3%)	46 (23.4%)	1 (7.1%)	
Respiratory symptoms	62 (29.4%)	56 (28.4%)	6 (42.9%)	
Gastrointestinal symptoms	27 (12.8%)	23 (11.7%)	4 (28.6%)	
Other symptoms*	75 (35.5%)	72 (36.5%)	3 (21.4%)	
Hospitalization (d)	3 (2–5)	2 (1.5–4)	9.5 (6.8–19.3)	<0.001
Coagulation profile				
Ferritin (µg/L, normal range 10–150)	117.5 (59.8–296.2)	107.0 (58.5–282.5)	314 (187.0–453.0)	0.008
PT (s)	13.5 (12.3–14.6)	13.4 (12.3–14.5)	14.7 (13.1–16.6)	0.01
PT over 14 s	81 (36.3%)	73 (34.9%)	8 (57.1%)	0.09
aPTT (s)	32.1 (29.2–35.6)	32.0 (29.2–35.4)	35.1 (29.1–39.1)	0.26
aPTT over 39 s	28 (12.6%)	25 (12.0%)	3 (21.4%)	0.25
Fibrinogen (mg%)	249.0 (196.8–305.0)	249.0 (195.0–300.8)	397.0 (263.0–489.3)	<0.001
Fibrinogen over 400 mg%	19 (8.5%)	12 (5.7%)	7 (50.0%)	<0.001
d-dimers (µg/mL)	1.1 (0.7–2.2)	1.1 (0.7–2.0)	1.7 (0.8–4.0)	0.13
d-dimers over 0.5	188 (84.3%)	175 (83.7%)	13 (92.9%)	0.37
d-dimers over 2.5	43 (19.3%)	37 (17.7%)	6 (42.9%)	0.04
Factor VIII (%)	116 (90.0–152.5)	115.5 (90.0–149.5)	152.5 (111.5–197.0)	0.03
FVIII >150%	46 (20.6%)	40 (19.1%)	7 (50.0%)	0.06
ATIII (%)	99.6 (±23.5)	99.3 (±22.3)	103.7 (±35.3)	0.68
ATIII <80%	27 (12.1%)	25 (12.0%)	2 (14.3%)	0.67

Categorical data are presented as number (%). Not normally distributed data are presented as median (interquartile range, IQR) except ATIII, which had normal distribution and presented as mean (±SD).

aPTT indicates activated partial thromboplastin time; ATIII, antithrombin III; PT, prothrombin time; VTE, venous thromboembolism.

P values in bold are considered statistically significant.

*Other symptoms: headache, feeding difficulties, drowsiness, seizures.

including inflammatory bowel disease, congenital heart disease, prematurity, obesity, and so on. There were, also, 12 asymptomatic patients who have other health problems and have an incidental finding of a positive SARS-CoV-2 test.

Fourteen (6.3%) patients were defined as experiencing “severe/critical” illness. One patient presented with thrombosis and 13 patients experienced severe respiratory disease. Among them, there was 1 neonate who died 23 days after symptoms onset caused by severe respiratory distress and sepsis. The neonate was diagnosed with COVID-19 at 15 days of life. It was a full-term infant with no congenital abnormalities of other health problems. Patients with “severe/critical” illness were older (median 9.3 years versus 9.8 months, $P = 0.05$), showed a higher rate of comorbidities (64.3% versus 12.4%, $P < 0.001$), were predominantly males (85.7% versus 56.5%, $P = 0.03$), and had increased levels of ferritin as inflammation marker (median 314 $\mu\text{g/L}$ versus 107 $\mu\text{g/L}$, $P = 0.008$). Older age ($P = 0.03$) and the presence of comorbidities ($P < 0.001$) were independently associated with the severity of the disease.

No thrombotic events have been observed during our study period during hospitalization and 3 months upon discharge. However, during the whole period of the pandemic, we had only 1 patient with many underlying prothrombotic risk factors who developed deep vein thrombosis (DVT) and pulmonary embolism (PE) before admission, received anticoagulant treatment and fully recovered after 3 months (case report submitted for publication).

Coagulation Profile of Study Population

In our study population, 203 (92.4%) patients had at least one abnormal parameter and 46 (20.6%) patients had at least 3 abnormal findings. One hundred eighty-eight (84.3%) patients had abnormal D-dimer levels, 81 (36.3%) abnormal PT values, 46 (20.6%) abnormal FVIII levels, 28 (12.6%) abnormal aPTT values, 27 (12.1%) decreased ATIII levels, and 19 (8.5%) patients had increased fibrinogen levels. Moreover, 43 (19.3%) patients were detected having increased D-dimer levels over 2.5 $\mu\text{g/mL}$ (Table 1).

Patients with “severe/critical” illness tended to have higher PT and FVIII values (median 14.7 seconds versus 13.4 seconds, $P = 0.01$; median 152.5% versus 115.5%, $P = 0.03$, respectively) than those with “mild/moderate” illness. Moreover, abnormal fibrinogen levels (50% versus 5.7%, $P < 0.001$) and D-dimer levels over 2.5 $\mu\text{g/mL}$ were more often observed in “severe/critical” than in “mild/moderate” illness (42.9% versus 18%, $P = 0.04$) (Table 1).

Prophylactic Anticoagulation

Based on ISTH recommendations, all patients were evaluated for the presence of risk factors for hospital-associated VTE. Forty-three (19.3%) patients had at least 1 risk factor for hospital-associated VTE. Interestingly, risk factors were more often detected in “severe/critical” than “mild/moderate” illness (42.9% versus 17.7%, $P = 0.021$).

After our anticoagulation management protocol, prophylactic anticoagulation was initiated only in 7 (3.1%) patients who

fulfilled our criteria (Table 2). In details, there were 2 patients, one with severe and one with critical illness admitted to the ICU and 3 patients with severe illness and ≥ 2 risk factors for hospital-associated VTE. Two patients with “mild/moderate” illness and a previous history of VTE also received prophylactic anticoagulation. The first patient was a female 2-year-old toddler with moderate illness and a history of short bowel disease and prolonged hospitalization and the second was a female 15-year-old adolescent with mild illness and a history of cerebral tumor and diabetes insipidus.

Follow-up Coagulation Profile

Follow-up coagulation profile was performed in 85 patients with abnormal findings.

Eighty-one (95.3%) of them did not receive prophylactic anticoagulation. Changes of coagulation parameters over time showed a tendency to normalization in most of the parameters. In details, significantly lower values were detected regarding PT, aPTT, and D-dimer levels ($P < 0.001$) before discharge or at a follow-up visit within 14 days after discharge (Figure 1).

Similarly, in 4 patients who received prophylactic anticoagulation, changes over time towards normalization were also detected especially for PT and D-dimer levels.

DISCUSSION

To our knowledge, this is the largest single-center study, which focuses on the coagulation profile of hospitalized children with “mild/moderate” or “severe/critical” COVID-19. Our findings indicate that abnormalities in coagulation profile are very common in pediatric COVID-19 but normalization even in “severe/critical” illness, occurs early and irrespectively of the initiation of prophylactic anticoagulation. Moreover, in contrast to what has been reported in adults, the absence of VTE events among our patients, indicates that in the majority of pediatric patients with COVID-19, coagulation abnormalities should not be considered as a risk factor for VTE.

The majority of our patients experienced “mild/moderate” illness, whereas 14 patients experienced “severe/critical” illness. Similarly, to previous reports, we found that “severe/critical” illness was more frequent in older children with increased rates of comorbidities.^{11–13} Abnormal findings in our patients’ coagulation profile were quite common including increased D-dimer levels, decreased ATIII levels, increased FVIII, and fibrinogen levels and were more often detected among patients with “severe/critical” illness. Similar coagulation abnormalities were reported in a multicenter retrospective cohort study.¹⁴ During our study period, despite the high incidence of coagulation abnormalities among our patients, no thrombotic events have been observed except of the single case of the teenager who presented VTE.

Interestingly, according to ISTH recommendations, which have been developed based mainly on adult data, we should have offered prophylactic anticoagulation to 73 (32.8%) patients; 41

TABLE 2. Patients’ characteristics who received prophylactic anticoagulation

Patient	Sex	Age	Clinical characteristics	ICU	Risk factors for hospital-associated VTE	D-dimers ($\mu\text{g/mL}$; normal range <0.5)
1	Male	2 mo	Severe respiratory disease	Yes		3.2
2	Female	10 mo	Severe respiratory disease		Obesity, pulmonary artery stenosis	35
3	Male	15 d	Severe respiratory distress, death	Yes		1.8
4	Male	13 y	Severe respiratory disease		Age > 12 y, obesity	1.5
5	Female	20 y	Severe respiratory disease		Immobility, age > 12 y	3.9
6	Female	2 y	Moderate illness		Previous history of VTE	0.9
7	Female	15 y	Mild illness		Previous history of VTE	2.5

ICU indicates intensive care unit; MIS-C, multisystem inflammatory syndrome in children; VTE, venous thromboembolism.

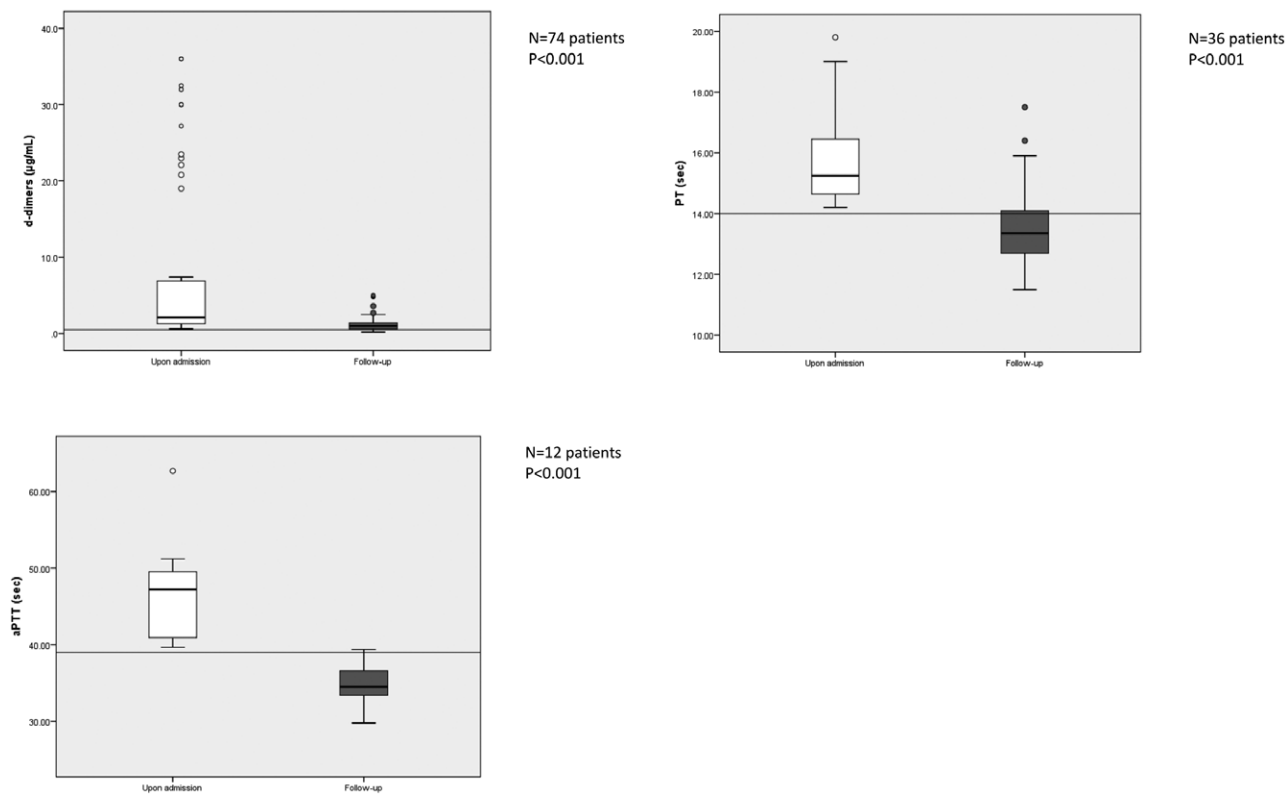


FIGURE 1. Changes over time in coagulation profile in patients not receiving prophylactic anticoagulation. Changes over time in d-dimers, PT, and aPTT levels showed a tendency to normalization before discharge or at a follow-up visit within 14 days after discharge. Abnormal findings were defined as D-dimer levels over 0.5 µg/mL, PT values over 14 seconds, and aPTT values over 39 seconds. aPTT indicates activated partial thromboplastin time; PT, prothrombin time. [full color online](#)

symptomatic patients with D-dimer levels 5-times more than normal values and 32 symptomatic patients with at least 1 risk factor for hospital-associated VTE. Instead, based on our assessment, prophylactic anticoagulation was initiated only in 7 patients.

We decided not to initiate prophylaxis when D-dimer levels were more than 5-times, the upper normal level for the after reasons; in pediatric population, it is well-known that D-dimer assays are prone to several confounders, which may limit their reliability such as the quality of blood specimen and, most importantly patient's age. According to several studies, there is an age dependency of coagulation parameters, such as D-dimer levels, during infancy and childhood highlighting the need for age-specific reference ranges to correctly assess and manage thrombotic events in pediatric populations.¹⁵ More importantly, despite the fact that they are widely recognized as a biochemical marker in the diagnostic approach of VTE, they lack specificity as they tend to increase in all inflammatory conditions.¹⁶ In COVID-19, inflammation-induced endothelial cell injury could result in massive release of plasminogen activators, which could explain the high concentrations of D-dimer and fibrin degradation products in patients with severe disease.¹⁷ Our findings that none of our patients with increased D-dimer levels developed VTE, provide further evidence that D-dimer levels lack specificity as a risk factor for VTE in pediatric populations.

Similarly, other coagulation abnormalities observed were not associated with poor outcome, increased mortality and early-onset VTE as has been reported in adult populations.¹⁸⁻²¹ Similarly, to our retrospective observations and after repeating the coagulation profile in 85 patients, we observed that normalization of abnormalities occurs very early upon admission and prophylactic anticoagulation

did not seem to make a difference in that. Comparable results about the kinetics of coagulation abnormalities were reported from Del Borello et al according to which abnormalities detected in 35 patients returned to normal upon disease resolution.²²

Our assessment took into consideration the clinical severity of COVID-19, the presence of known risk factors for hospital-associated VTE and preexisting severe comorbidities regardless any abnormalities detected in patients' coagulation profile. Prophylactic anticoagulation was initiated in all patients with "severe/critical" illness transferred to the ICU or those who had ≥2 risk factors for hospital-associated VTE. For selected cases with "mild/moderate" illness, prophylactic coagulation was initiated only in patients with a previous history of VTE.

Such approach is further supported by recent findings, where several clinical variables such as age ≥12 years, cancer, MIS-C, and presence of central venous catheter have been associated with an increased risk of VTE in pediatric populations.^{14,23,24} Regarding MIS-C cases, rates of VTE varies from 3 to 6.5% and it is believed that this risk might be driven by a procoagulant highly inflammatory milieu and increased venous stasis secondary to decreased myocardial function.^{14,23,24} In our study, we did not include MIS-C cases because we focused on the importance of anticoagulant thromboprophylaxis upon admission in the vast majority of pediatric patients with "mild/moderate" or "severe/critical" COVID-19.

Our management can be considered successful since none of our patients developed VTE during hospitalization or during the 3 months' follow-up. During the whole period of the pandemic, we had only 1 patient who developed VTE. This low rate of VTE is in line with the one of a multicenter Italian study, where the rate of

VTE was 0.6% as only 1 patient experienced peripheral vasculitis during hospitalization among 168 hospitalized children.²⁵ In a multicenter study from United States, the rate of VTE was 2.3% and 20 cases of VTE were reported among 853 admissions.¹⁴ This low incidence of VTE in pediatric populations is strikingly different from what has been repeatedly reported in adult populations where VTE incidence is estimated approximately 21% in hospitalized patients, rising to 31% in those admitted to the ICU and in whom it has been associated with increased mortality.²⁶ Such striking differences in the incidence and outcome of VTE between adult and pediatric populations could be attributed to the healthier vascular system of children as well as to the developmental differences in their hemostatic system, which probably confers a protective mechanism contributing to a decreased risk of VTE.²⁷

Taking into consideration the low incidence of VTE, the extended use of prophylactic anticoagulation is further questioned by the lack of data regarding its efficacy and safety in hospitalized children with COVID-19. A significant number of VTEs as well as bleeding events were reported recently among patients receiving prophylactic anticoagulation, and it is believed that variation of thromboprophylactic practices across hospitals might have contributed to these events.¹⁴ An ongoing clinical trial evaluating the safety of enoxaparin in children with COVID-19 is expected to shed light in this field soon.²⁸

The relatively small number of patients with “severe/critical” COVID-19, which are considered at higher risk of developing thrombotic events, is main limitations of the study. However, given the fact that “severe/critical” illness is not quite common in pediatric population cumulative experience from different pediatric centers is necessary for future revision of existing guidelines. Interestingly, our observations, are in line with those of Del Borrello et al²² according to whom prophylactic anticoagulation should be restricted only in specific patients with multiple prothrombotic risk factors without taking into consideration solely the abnormal D-dimer levels.

In conclusion, according to our experience, the increased incidence of coagulation abnormalities does not seem to be connected with a high rate of VTE and children hospitalized for COVID-19 should receive a more personalized anticoagulant management that should take into consideration mainly the presence of multiple prothrombotic risk factors that could justify the use of anticoagulant thromboprophylaxis in “severe/critical” COVID-19. Future multicenter, prospective placebo-controlled studies are necessary for the identification of the selected pediatric patients who may benefit from optimal anticoagulant prophylaxis.

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