

BRIEF REPORT

Multisystem inflammatory syndrome in children (MIS-C) and the prothrombotic state: Coagulation profiles and rotational thromboelastometry in a MIS-C cohort

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Abstract

Background: Adults infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have had high rates of thrombosis. A novel condition in children infected with SARS-CoV-2, multisystem inflammatory syndrome in children (MIS-C), has limited data on their prothrombotic state or need for thromboprophylaxis.

Objectives: We aimed to analyze the prothrombotic state using coagulation profiles, rotational thromboelastometry (ROTEM) parameters and clinical outcomes, to determine if this could aid in risk stratification for thromboprophylaxis.

Methods: This analysis included patients (<21 years of age) with a diagnosis of MIS-C ($n = 40$) and controls (presenting with suspicion of MIS-C but later ruled out; $n = 26$).

Results: MIS-C patients had higher levels of inflammatory markers including D-dimer ($p < .0001$), compared with controls, along with evidence of hypercoagulability on ROTEM with elevated evaluation of fibrinogen activity (FIBTEM) maximum clot firmness (MCF) ($p < .05$). For MIS-C patients with D-dimers >1000 ng/ml, there was a significant correlation of FIBTEM MCF ($p < .0001$) with a mean value of 37.4 (standard deviation 5.1). D-dimer >2144 ng/ml was predictive of intensive care unit admission (area under the curve [AUC] 0.80; 95% confidence interval, 0.60–0.99; $p < .01$; sensitivity: 82%, specificity: 75%), and elevated FIBTEM MCF (AUC 1 for >2500 ng/ml). MIS-C patients (50%) received enoxaparin thromboprophylaxis (in addition to aspirin) with significant improvement in their inflammatory and ROTEM parameters upon outpatient follow-up; none developed symptomatic thrombosis.

Conclusions: Despite an observed prothrombotic state, none of the MIS-C patients (on aspirin alone or in combination with enoxaparin) developed symptomatic thrombosis. ROTEM, in addition to coagulation profiles, may be helpful to tailor thromboprophylaxis in critically ill MIS-C patients.

KEYWORDS

COVID-19, MIS-C, pediatric, ROTEM, SARS-CoV-2, thrombosis

1 | INTRODUCTION

Adults infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have derangements of hemostasis characterized by a prothrombotic state marked by increased thrombin generation and decreased fibrinolysis.¹ This thrombotic propensity led to venous, arterial, and microvascular thromboembolic manifestations, reported in up to 69% of critically ill adults,² with anticoagulation decreasing mortality secondary to these events.³ However, the global pandemic caused by SARS-CoV-2 appears to have a relatively low incidence of acute infections in children, who present with mild symptoms and lower hospitalization rates.^{4,5}

A novel condition associated with SARS-CoV-2 in children (which emerges a few weeks after initial infection), primarily presented as a febrile inflammatory disorder with features of Kawasaki disease and toxic shock syndrome.⁶ This was termed multisystem inflammatory syndrome in children (MIS-C) and characterized by the Centers for Disease Control and Prevention as: an individual younger than age 21 years with fever, laboratory evidence of inflammation, clinical severity involving two or more organ systems requiring hospitalization, without another plausible diagnosis, and confirmed evidence of SARS-CoV-2.⁷ A multicenter study in severely ill MIS-C patients noted involvement of at least four organ systems including hematologic (76%) with a low (8%) prevalence of deep vein thrombosis or pulmonary embolism.⁸ Our institution previously identified 33 MIS-C patients, with elevated inflammatory markers (including fibrinogen and D-dimer levels) at presentation, without evidence of symptomatic thrombosis.⁹

Elevated fibrinogen and D-dimer levels are observed in children with infections and autoimmune diseases, including SARS-CoV-2 and MIS-C, but D-dimers may lack specificity for deep vein thrombosis prediction. Furthermore, the prevalence of thromboembolic complications in children with MIS-C has not been fully determined and there are no pediatric evidence-based thromboprophylaxis guidelines. Most institutions have adapted guidelines from Kawasaki disease, an inflammatory vasculitis described in children, with clinical manifestations similar to MIS-C. A survey by the International Kawasaki Registry¹⁰ on the management of patients with MIS-C revealed that anticoagulation practices were variable and based on risk assessment (decreased mobility, coronary artery aneurysms, and increased D-dimer levels). Goldenberg et al¹¹ have published a consensus of expert opinions recommending prophylactic anticoagulation in patients with MIS-C with elevated D-dimer levels and superimposed clinical risk factors, whereas others have recommended against universal anticoagulant prophylaxis, but using concurrent risk factors not taking into account D-dimer values.¹² Therefore, there remains a need in the MIS-C population for additional risk assessment tools to guide clinical decision making for thromboprophylaxis.

Essentials

- Multisystem inflammatory syndrome in children (MIS-C) is a novel condition related to SARS-CoV-2.
- Adults with SARS-CoV-2 have elevated inflammatory markers and hypercoagulability with thrombosis.
- Multisystem inflammatory syndrome in children patients demonstrate similar inflammation as in adults (also noted on thromboelastometry).
- Multisystem inflammatory syndrome in children patients did not develop thrombosis and anticoagulant prophylaxis should be tailored.

We have reported feasibility of using rotational thromboelastometry (ROTEM), a viscoelastic point of care device that evaluates whole blood coagulation parameters¹³ in a small case series of children infected with SARS-CoV-2.¹⁴ Multiple studies in adults with SARS-CoV-2 revealed a prothrombotic state characterized by an acceleration of propagation of blood clot formation and higher clot strength, using viscoelastic testing.^{15,16} Given the stark differences between children and adults infected with SARS-CoV-2, this study aimed to determine whether pediatric patients with MIS-C demonstrated prothrombotic parameters using coagulation profiles and ROTEM. A secondary aim was to determine if the use of prophylactic anticoagulation or aspirin could be tailored based on these data.

2 | METHODS

This retrospective analysis included patients younger than 21 years of age presenting to Cohen Children's Medical Center between April 17 and July 9, 2020, with suspicion of MIS-C. The study was approved by the Northwell Health Institutional Review Board as minimal-risk research and waived the requirement for informed consent. MIS-C patients met Centers for Disease Control and Prevention criteria and controls were those who presented with concerns for MIS-C but did not formally meet criteria. Aspirin was instituted by the infectious disease and cardiology teams based on clinical presentation and echocardiogram findings. The decision to initiate thromboprophylaxis was made by the treating team extrapolated from adult institutional guidelines: severity of illness, end organ damage, obesity, oxygen requirement >3L/min, and D-dimer >6 times upper limit of normal.¹⁷ Prophylactic enoxaparin (0.5 mg/kg/dose twice a day subcutaneously) was used without monitoring anti-Xa levels. Enoxaparin was continued after discharge (weight <50 kg)

or transitioned to apixaban 2.5 mg twice a day (weight ≥ 50 kg), with outpatient follow-up within 2 weeks of discharge. Exclusion criteria: age >21 years, underlying coagulopathy, or anticoagulant use upon presentation.

Clinical demographics, laboratory data including baseline coagulation and inflammatory markers and ROTEM parameters (ROTEM delta, Instrumentation Laboratory, Werfen, Barcelona, Spain) were recorded. ROTEM analyses was completed within 1 to 4 days of admission by obtaining native whole blood (2.7 ml in a vacutainer with 3.2% concentration of sodium citrate using a 22 G needle) from a peripheral draw, hand delivered to the laboratory and tested within 2 hours. Specifically, the following ROTEM parameters were analyzed: (a) clotting time (CT), corresponding to clot initiation; (b) clot

formation time (CFT), corresponding to clot propagation; (3) maximum clot firmness (MCF), for clot strength. Hypercoagulability was defined by a shortened CT or CFT, or an increased MCF based on pediatric reference ranges.¹⁸ We previously determined intra- and inter-assay precision (four individual samples for each in eight measurements for ages 4-12 months, 2-5 years, 6-10 years, 11-16 years) by calculating coefficient of variation for parameters EXTEM, INTEM, FIBTEM. The intra-assay variability was $<5\%$ for all three parameters and the inter-assay coefficient of variation is available in Table S1. Therefore, these low variabilities suggested a good reproducibility of the method.

Descriptive statistics were generated to assess data distributions. Statistical comparisons were conducted for continuous measures

TABLE 1 Characteristics and laboratory values of MIS-C patients and controls

			MIS-C (n=40)		Controls (n=26)	p-value	
CHARACTERISTICS	Mean Age (SD)		9 (4.1)		8.8 (5.7)	0.87	
	Gender, females		54.5%		50.0%	0.45	
	BMI in kg/m²		21.4 (6.5)		20.7 (8.3)	0.76	
	PICU Admission		70%		3.9%	<0.001	
	Oxygen Use		47.5%		3.9%	<0.001	
	Mean LOS in days		6.4 (3.7)		4.6 (3.7)	0.06	
	Thrombosis		0%		0%	1	
			Initial	Follow up	P-value	Initial	P-value (initial)
INITIAL LABS	WBC (K/μl)		12.23 (9.0)	8.89 (4.1)	<0.05	8.3 (3.5)	<0.05
	Hb (g/dl)		9.91 (1.41)	11.57 (1.1)	<0.0001	11.3 (1.1)	<0.001
	Plt (K/μl)		230 (121)	339 (111)	<0.001	281 (132)	0.2
	PT (s)		15.6 (2.2)	11.6 (1.1)	<0.0001	14.6 (2.8)	0.29
	PTT (s)		31.5 (4.7)	28.6 (5.3)	0.51	32.5 (7.6)	0.67
	Fibrinogen (mg/dl)		667 (187)	376 (74)	<0.0001	577 (272)	0.25
	D-dimer (ng/mL)		2384 (1080)	179 (56)	<0.0001	413 (242)	<0.001
	Ferritin (ng/mL)		975 (1184)	270 (564)	<0.001	384 (690)	<0.05
	Creatinine (mg/dl)		0.52 (0.23)	0.46 (0.12)	<0.05	0.49 (0.30)	0.74
	Albumin (g/dl)		2.7 (0.5)	4.3 (0.3)	<0.0001	3.7 (0.7)	<0.001
	CRP (mg/L)		166 (87.6)	2.8 (4.8)	<0.0001	56.2 (55.2)	<0.001
	Procal (ng/mL)		11.75 (19.12)	0.63 (0.025)	<0.05	-	-
ROTEM	EXTEM	CFT (s)	68.4 (22.7)	75.8 (18)	0.14	74.1 (23.0)	0.394
		A10 (mm)	60.8 (8.3)	60.4 (19.8)	0.93	58.6 (9.4)	0.424
		MCF (mm)	67.1 (6.5)	64.4 (5)	0.08	65.2 (7.5)	0.393
	INTEM	CFT (s)	58.6 (16.5)	65.1 (17.6)	0.09	69.6 (37.5)	0.272
		A10 (mm)	60.4 (7.8)	54.1 (103)	<0.01	56.9 (13.3)	0.334
		MCF (mm)	66.2 (7.2)	59.9 (11.07)	<0.01	61.9 (13.1)	0.226
	FIBTEM	CFT (s)	79.05 (43.94)	30.7 (28.8)	0.24	141.4 (170.3)	0.280
		A10 (mm)	33.4 (6.2)	17.6 (3.5)	<0.0001	25.6 (11.1)	<0.05
		MCF (mm)	35.6 (6.5)	18.2 (3.3)	<0.0001	27.1 (11.3)	<0.05

Note: Red = significant *p* value. Values presented as means (with standard deviation in parentheses), unless otherwise stated.

Abbreviations: A10, amplitude at 10 minutes; BMI, body mass index; CFT, clot formation time; CRP, C-reactive protein; Hb, hemoglobin; LOS, length of stay; MCF, maximal clot firmness; MIS-C, multisystem inflammatory syndrome in children; mm, millimeters; PICU, pediatric intensive care unit; Plt, platelet count; Procal, procalcitonin; PT, prothrombin time; PTT, partial thromboplastin time; ROTEM, rotational thromboelastometry machine; s, seconds; WBC, white blood cells.

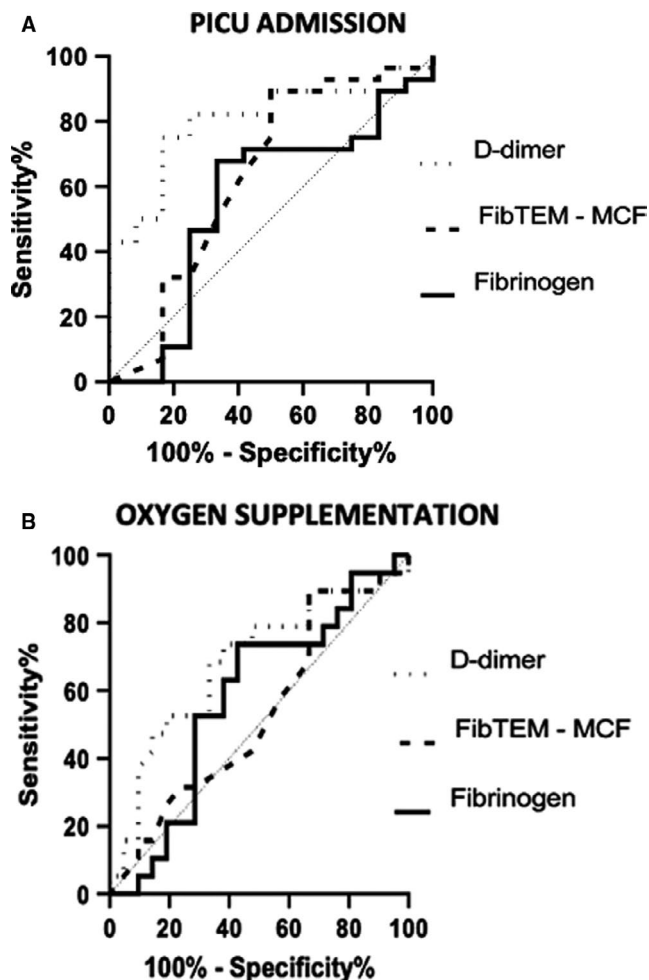


FIGURE 1 (A) ROC curves for PICU admissions of MIS-C patients: D-dimer AUC 0.80 (95% CI, 0.66–0.94, $p < .01$), FIBTEM-MCF AUC 0.64 (95% CI, 0.43–0.85, $p > .1$), fibrinogen AUC 0.56 (95% CI, 0.35–0.77, $p > .5$). (B) ROC curves for oxygen use of MIS-C patients: D-dimer AUC 0.68 (95% CI, 0.51–0.85, $p < .05$), FIBTEM-MCF AUC 0.53 (95% CI, 0.35–0.72, $p > .5$), fibrinogen AUC 0.58 (95% CI, 0.40–0.77, $p > .1$). AUC, area under the curve; CI, confidence interval; MIS-C, multisystem inflammatory syndrome in children; PICU, pediatric intensive care unit; ROC, receiver operating characteristic

with *t*-tests or Wilcoxon rank-sum tests for skewed data, chi-square tests for categorical data with Fisher's exact tests used in cross-tabulations for small patient numbers. For testing between two time points, the paired *t*-test (continuous measures) and McNemar's test (categorical measures) were implemented. The area under the curve (AUC) and the 95% confidence interval (CI) of the receiver operator characteristic (ROC) curve and logistic regression were computed using the predicted probability of the D-dimer, fibrinogen and FIBTEM MCF for pediatric intensive care unit (PICU) admission and oxygen requirement. Pearson correlation coefficients were generated to assess the relationship between hospital length of stay and lab values. Statistical analysis was performed with R Statistical Software (v. 4.0.2; Windows) and GraphPad Prism (v. 8.4.3, Windows).

3 | RESULTS AND DISCUSSION

Study cohort included 66 patients (MIS-C: 40; controls: 26), Table 1. All MIS-C patients had a positive coronavirus disease 2019 (COVID-19) nasopharyngeal polymerase chain reaction test or COVID-19 antibodies. The groups were comparable in age, sex, body mass index, and race. MIS-C patients had significantly higher white blood cell count, D-dimer levels, ferritin, and C-reactive protein (CRP), with significantly lower hemoglobin and albumin compared with controls upon presentation. MIS-C patients also had higher rates of admission to the PICU (70% vs. 3.9%; $p < .001$) and a higher percentage required supplemental oxygen (47.5% vs. 3.9%; $p < .001$). All MIS-C patients received treatment including intravenous immunoglobulin, along with aspirin (95%) and steroids (82.5%).

Upon admission, ROTEM parameters of MIS-C patients showed evidence of a hypercoagulable state with elevated FIBTEM MCF ($p < .05$) with resolution of this hypercoagulable state at outpatient follow-up ($p < .0001$). For MIS-C patients, there was a significant correlation of FIBTEM MCF with a mean value of 37.4 (standard deviation 5.1) with D-dimers >1000 ng/ml compared with those with ≤ 1000 ng/ml ($p < .0001$). All controls had D-dimers below 1000 ng/ml, with 85% of MIS-C patients ($n = 34$) having D-dimers >1000 ng/ml.

The AUC using D-dimer to predict PICU admission and supplemental oxygen requirement for MIS-C patients was 0.80 (95% CI, 0.66–0.99; $p < .01$) and 0.68 (95% CI: 0.51–0.85 $p < .05$), respectively (Figure 1). A D-dimer value greater than 2144 ng/ml was sensitive (82%) and specific (75%) for predicting PICU admission. Receiver operating characteristic curves also showed an improved prediction of FIBTEM MCF values with D-dimer levels: AUC 0.875 for D-dimers <1000 and AUC of 0.998 and 1 for levels between 1001–2500 and >2500 , respectively.

The 50% of MIS-C patients ($n = 20$) who received enoxaparin thromboprophylaxis (in addition to aspirin initiated by the primary team) were observed to have higher prothrombin time ($p < .01$), fibrinogen ($p < .05$), D-dimer levels ($p < .05$), CRP ($p < .01$), and EXTEM MCF ($p < .05$) compared with MIS-C patients who received aspirin alone (Table 2), with near normalization at outpatient follow-up 2 weeks later. Initial and follow-up ROTEM parameters of a patient with MIS-C who received enoxaparin thromboprophylaxis is shown in Figure 2. Note the significant decrease (improvement in hypercoagulable state) in MCF in EXTEM, INTEM, and FIBTEM upon follow-up compared with initial presentation. There were no symptomatic thrombotic events, bleeding side effects, or deaths in MIS-C or control patients.

Despite the well-described prothrombotic state and thrombotic events in adults with SARS-CoV-2, children (and those with MIS-C) have not demonstrated similar thromboembolic complications.⁸ Although the exact etiology for MIS-C is unknown, experts have suggested a dysfunctional immune response leading to cytokine release and organ damage.¹⁹ In that sense, MIS-C has been compared with cytokine release syndrome, Kawasaki disease, and other autoimmune disorders, conditions that are associated with a prothrombotic state.^{20,21} In addition, it has recently been shown that antibody

TABLE 2 Multisystem inflammatory syndrome in children patients who received thromboprophylaxis

			Thromboprophylaxis, Initial		Thromboprophylaxis, Follow-up	Initial vs. Follow-up
	Received Thromboprophylaxis		Yes (n = 20, 50.0%)	No (n = 20, 50.0%)	p Value	Yes (n = 20, 50.0%)
Laboratory values	WBC (K/ul)		14.8 (11.4)	9.7 (4.8)	.08	10.2 (4.0)
	Hb (g/dl)		10.2 (1.6)	9.7 (1.2)	.3	11.4 (1.1)
	Plt (K/ul)		218 (71)	241 (155)	.55	314 (108)
	PT (s)		16.5 (2.3)	14.6 (1.7)	<.01	11.4 (1.3)
	PTT (s)		31.9 (5.4)	31.1 (4.0)	.61	27.1 (5.5)
	Fibrinogen (mg/dl)		740 (153)	594 (194)	<.05	391 (82)
	D-dimer (ng/ml)		2779 (1071)	1999 (967)	<.05	175 (38)
	LDH (U/L)		275 (106)	292 (125)	.68	342 (159)
	Ferritin (ng/ml)		984 (1249)	967 (1147)	.96	383 (749)
	Albumin (g/dl)		2.68 (0.64)	2.75 (0.42)	.69	4.3 (0.3)
	CRP (mg/L)		204 (82)	128 (77)	<.01	3.6 (6.5)
ROTEM	EXTEM	CFT (s)	65.1 (21.6)	71.45 (24.0)	.23	80.4 (22.9)
		A10 (mm)	62.3 (6.7)	59.25 (9.5)	.12	55.8 (6.3)
		MCF (mm)	68.7 (5.29)	65.45 (7.22)	<.05	63.1 (5.2)
	INTEM	CFT (s)	56.5 (15.3)	60.7 (17.8)	.26	69.8 (22.3)
		A10 (mm)	60.9 (7.1)	59.9 (8.6)	.34	51.6 (8.6)
		MCF (mm)	67 (7.3)	65.5 (7.2)	.15	57.8 (9.3)
	FIBTEM	A10 (mm)	34.7 (5.2)	32.1 (7)	<.001	17.9 (3.9)
		MCF (mm)	37.5 (5.6)	33.8 (7))	<.0001	18.4 (3.5)

Note: Red = significant *p* value. Values presented as means (with standard deviation in parentheses), unless otherwise stated.

Abbreviations: A10, amplitude at 10 min; CFT, clot formation time; CRP, C-reactive protein; Hb, hemoglobin; MCF, maximal clot firmness; MIS-C, multisystem inflammatory syndrome in children; Plt, platelet count; Procal, procalcitonin; PT, prothrombin time; PTT, partial thromboplastin time; ROTEM, rotational thromboelastometry machine; WBC, white blood cells.

responses in adults with SARS-CoV-2 and MIS-C patients are different²³, positing that MIS-C maybe a distinct disease entity.

Our results demonstrate a hyperinflammatory state in patients with MIS-C with elevations in white blood cells, D-dimer, ferritin, and CRP, along with ROTEM parameters suggestive of increased clot strength, which are associated with a hypercoagulable state.¹⁴ Interestingly, although patients with MIS-C demonstrated a prothrombotic state on ROTEM at presentation, these parameters improved after discharge, similar to an adult study using Quantra, another viscoelastic tool.²²

A ROTEM study completed in adult patients with SARS-CoV-2 by Spiezia et al¹⁶ revealed hypercoagulability on EXTEM CFT (*p* = .01) and EXTEM MCF (*p* < .001) compared to healthy controls, along with elevated FIBTEM MCF (*p* = .001), which was the major ROTEM parameter of hypercoagulability noted in our MIS-C patients. With these similar findings, incidence of thrombosis in our cohort was 0% vs. 23% for hospitalized patients in the Spiezia study.

It is plausible that children with MIS-C, unlike adults infected with SARS-CoV-2, do not have vasculopathy from smoking, atherosclerosis, diabetes, or hypertension and therefore do not develop significant thrombosis despite laboratory evidence of a hyperinflammatory and prothrombotic state. Whether impaired fibrinolysis observed in adults with SARS-CoV-2 plays a role in determining

propensity to develop clinical thrombosis, in addition to hypercoagulability, is unclear.

Currently, there are no published studies demonstrating laboratory evidence of a prothrombotic state in MIS-C. Moreover, guidelines recommending primary thromboprophylaxis are based on expert consensus and we await results of a multicenter phase 2 clinical trial in children with SARS-CoV-2, including MIS-C.¹¹ Although patients who received enoxaparin thromboprophylaxis demonstrated significantly higher inflammatory markers (D-dimer and CRP) and prothrombotic markers (EXTEM and FIBTEM MCF) compared with those who received aspirin alone, there were no symptomatic thromboses. Furthermore, a D-dimer cut-off level >2144 ng/ml correlated with MIS-C severity based on higher rates of PICU admission and need for supplemental oxygen. In addition, elevated FIBTEM MCF parameters significantly correlated with the higher D-dimer levels, suggesting a need for thromboprophylaxis in this subset of MIS-C patients.

Our study limitations include its retrospective design, and most notably, the confounding of MIS-C therapies given concurrently. Also, some of our ROTEM studies were completed after starting aspirin/anticoagulation (due to timing of patient admissions and varying availability of experienced technologists to process the ROTEM samples at the beginning of the pandemic);

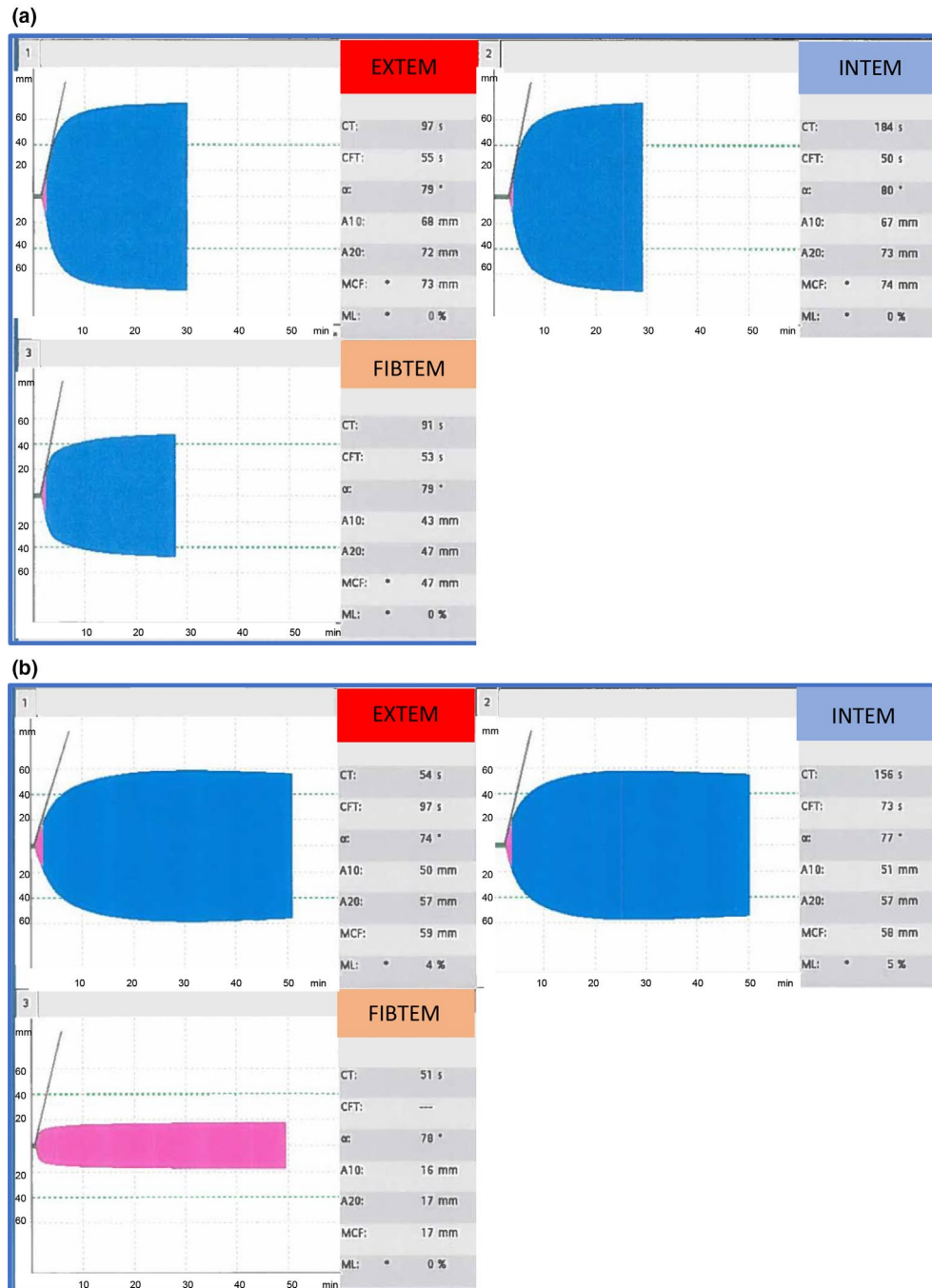


FIGURE 2 Temograms of a MIS-C patient upon (A) initial presentation and subsequent (B) outpatient follow up with time in minutes (x-axis) and clot thickness in mm (y-axis). A10: amplitude at 10 min (clot thickness at 10 min, in mm); CFT, clot formation time (time from initiation of clot to a thickness of 20 mm, in seconds); CT, clotting time (time to start of clot formation, in seconds); EXTEM, evaluation of the extrinsic pathway; FIBTEM, evaluation of fibrinogen activity; INTEM, evaluation of the intrinsic pathway; MCF, maximum clot firmness (the highest clot thickness, in mm); ML, maximal lysis (percentage of clot lysis)

therefore, the absolute disease-related prothrombotic state is difficult to discern. We also did not perform platelet mapping, had incomplete data on antithrombin III levels ($n = 8$, all of which were normal between 86–140%), and also had incomplete data on fibrinolysis parameters ($n = 10$, no hyperfibrinolysis demonstrated at 30 min).

The use of ROTEM in a number of settings demonstrating a prothrombotic state has been helpful to guide anticoagulation strategies

in adults.²⁴ Our data indicate that children with MIS-C are prothrombotic, D-dimer is predictive of disease severity and increased clot strength on ROTEM, but inconclusive as to whether aspirin alone and/or concomitant anticoagulation may be most effective for thromboprophylaxis. Future multi-institutional studies using D-dimer and ROTEM parameters, along with superimposed clinical risk factors, may aid in risk stratification to guide thromboprophylaxis in MIS-C disease.

ACKNOWLEDGMENTS

The authors acknowledge Vijay Nandi (MPH) for statistical analysis; Pooja Desai (MD) and Sibgha Zaheer (MD, MPH) for coordinating studies; Cohen Children's Medical Center fellows, residents, and nursing staff caring for children infected with SARS-CoV-2; the Northwell Covid-19 Research Consortium; and the Robert Chasanoff family for funding the ROTEM tool.

CONFLICT OF INTEREST

This manuscript was read and approved by all authors and there are no conflicts of interest to declare. All authors have agreed to this change in authorship.

AUTHOR CONTRIBUTIONS

Maha Al-Ghafry, Anshul Vagreacha, and Mariam Malik performed research, analyzed data, and wrote the paper; Banu Aygun, Abena Appiah-Kubi, Adrianna Vlachos, Lawrence C. Wolfe, and Jeffrey M. Lipton interpreted data and revised the paper; Linda Shore-Lessersson provided expertise on ROTEM interpretation and revised the paper; Chana Levine and Eliza Uster helped with data entry and patient care; Sujatha Rajan, Christine A. Capone, Nilanjana Misra, Elizabeth C. Mitchell, and Nancy Palumbo took care of patients through a multidisciplinary approach and made decisions about aspirin therapy; and Suchitra S. Acharya designed research, interpreted data and wrote the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Al-Ghafry M, Vagreacha A, Malik M, et al. Multisystem inflammatory syndrome in children (MIS-C) and the prothrombotic state: Coagulation profiles and rotational thromboelastometry in a MIS-C cohort. *J Thromb Haemost.* 2021;19:1764-1770. <https://doi.org/10.1111/jth.15340>