Clin. Lab. 2022;68:XXX-XXX

ORIGINAL ARTICLE

Assessment of Coagulation Profiles by Rotational Thromboelastometry in COVID 19 Patients

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SUMMARY

Background: **According to recent studies, thrombotic complications frequently occur in Coronavirus Disease-19 (COVID-19) and are associated with increasing disease severity and poor prognosis. However, conventional coagulation assays are unable to identify these patients' hypercoagulable states, raising questions about the appropriate assessment tool. We aimed to evaluate coagulation abnormalities in patients with different severity of COVID-19 using viscoelastic tests.**

Methods: **This was a single center retrospective observational study in a group of 50 adult patients with SARS-COV-2 infection and different severity of pneumonia (20 moderate, 30 severe). Coagulation status was evaluated using rotational thromboelastometry (ROTEM®) in conjunction with conventional coagulation assays (platelet count, PT, aPTT, fibrinogen, and D-dimer levels).**

Results: **Shorter than normal EXTEM CFT, higher than normal A10 and MCF in INTEM, EXTEM, and FIBTEM and higher than normal α-angle were classified as markers of hypercoagulable state. Forty-four (88%) patients had at least two hypercoagulable ROTEM parameters. Seven patients developed thromboembolic complications. All were classified as having severe COVID-19 pneumonia. With increment increases in disease severity, we observed an increase in the number of patients with hypercoagulable parameters and higher INTEM, EXTEM, and FIBTEM MCF but without being statistically significant. On the other hand, we noted a significant decrement of PT ($p = 0.039$), higher fibrinogen ($p = 0.001$), higher D dimer ($p < 0.001$), and shorter CT EXTEM ($p < 0.001$).**

Conclusions: **Our findings support the presence of a hypercoagulable state in COVID-19 patients, especially in the severe forms. It also highlights the role of viscoelastic tests in assessing COVID-19 coagulopathy and, therefore, their potential use in thrombophrophylactic management.**

(Clin. Lab. 2022;68:xx-xx. DOI: 10.7754/Clin.Lab.2021.211026)

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Manuscript accepted November 26, 2021

KEY WORDS

rotational thromboelastometry, COVID-19, hypercoagulability, thrombosis

INTRODUCTION

Coagulation disorders were initially described in the first severe cases of SARS-CoV-2 infection during the Chinese epidemic; these data were confirmed later on by European teams. Coronavirus disease (COVID-19)

causes a state of hypercoagulability responsible for venous thromboembolism (VTE) [1-4]. This thrombotic tendency is also referred to as COVID-19 associated coagulopathy (CAC). CAC is likely different from sepsis induced disseminated intravascular coagulopathy (DIC). While DIC is characterized by a thrombogenic and bleeding phenotype, in CAC bleeding events are less frequent [4,5].

Conventional coagulation and fibrinolysis tests, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and D-dimers value are insufficient for hypercoagulation assessment. While fibrinogen and D-dimer levels are frequently elevated, neither parameter reliably identifies patients at an increased risk of thromboembolic complications [1,6]. In contrast, viscoelastic tests, such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM), are whole blood tests that have the advantage of providing information related to clot formation, clot firmness, and fibrinolysis process in real time [6-8].

Our aim was to describe the COVID-19 thromboelastometry profile using ROTEM Delta and compare it with standard laboratory findings. Moreover, the ROTEM parameters were analyzed according to the clinical spectrum of COVID-19 pneumonia, from moderate to severe, to determine the incidence of the hypercoagulable ROTEM profile and to assess its association with thromboembolic complications.

MATERIALS AND METHODS

Study design

This is a retrospective, observational study conducted at the University Hospital Sahloul Tunisia. Fifty adult patients with laboratory-confirmed SARS-CoV-2 infection and radiologically confirmed pneumonia were included in this study. Patients were recruited from January 2021 through March 2021.The Ethics Commission of university hospital approved the study.

Our exclusion criteria were the following: age < 18 years, pregnancy, active cancer and chemotherapy, liver and end-stage renal disease, and congenital bleeding. Laboratory confirmation of SARS-COV-2 infection was based on positive reverse transcriptase-polymerase chain-reaction (RT-PCR) assay based on the recommended World Health Organization standards [9]. Demographic and clinical data were retrieved from patients' medical records, including age, gender, preexisting illness (diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease), Sequential Organ Failure Assessment (SOFA) on ICU admission, need for non-invasive ventilation or mechanical ventilation, and ICU and hospital mortality. The disease severity was assessed according to national guidelines published by the ministry of public health:

- Moderate form of COVID-19 is defined by the presence of: dyspnea, respiratory rate > 30 breaths/min, oxygen saturation ≤ 92% on room air. Patients, in this case, are hospitalized in a medical service.
- Severe form of COVID-19 is defined by the presence of signs of vital distress, organ failure. Patients therefore are admitted to the ICU.

DIC was defined using the International Society on Thrombosis and Hemostasis (ISTH) scoring system. All patients were on thromboprophylaxis anticoagulation with Enoxaparin, a Low Molecular Weight Heparin (LMWH), at a dose of 60 × 2 mg/day.

Conventional coagulation tests

The following coagulation tests were assessed from citrated plasma: PT, aPTT, fibrinogen, and D-dimer levels. All tests were performed using the ACL TOP 750® coagulometer. The platelet count was assessed from an EDTA tube with a Sysmex XN- 1000® cell counter.

ROTEM tests

ROTEM tests (ROTEM® Delta, TEM Innovations, Munich, Germany) were performed in citrated whole blood according to the manufacturer's instructions. Extrinsic and intrinsic coagulation were evaluated by using the EXTEM and INTEM tests, respectively. The influence of fibrinogen on clot firmness was estimated by using the platelet inactivating with cytochalasin D (FIBTEM test). The heparin effect was determined by comparing the clotting time of the INTEM with the clotting time of the HEPTEM, in which heparinase is added.

The following parameters were recorded: 1) Clotting time (CT, s), time from the beginning of the coagulation analysis until an increase in the amplitude of thromboelastogram of 2 mm; 2) Clot formation time (CFT, s), time between an increase in the amplitude of thromboelastogram from 2 to 20 mm; 3) Maximum clot firmness (MCF, mm) or maximum amplitude reached in the thromboelastogram; 4) A10: amplitude reached in the thromboelastogram at 10 minutes; 5) α-angle, the slope of the tangent at 2 mm amplitude; 6) LI30 and 60: lysis indexes at 30 (LI30), and 60 (LI60) minutes defined as the residual clot firmness in percentage of MCF at 30 or 60 minutes after CT, respectively; 7) Maximum lysis (ML, %) defined as the decrease in clot firmness, expressed in percentage of MCF during run time (10).

Statistics

Data are reported as mean with standard deviation (SD), median with interquartile range (IQR), or number with percentage. The Mann-Whitney test was used to compare differences between patient groups in continuous variables while the chi-squared test was used for categorical data. Correlations were assessed with Pearson's correlation coefficients. P-values below 0.05 were considered statistically significant. Statistical analyses were performed using SPSS® version 23.

RESULTS

Patient characteristics

Fifty patients were enrolled into the study. The median age was 63 years (20 - 87). The sex ratio was 2.8. Thirty patients (60%) had underlying chronic diseases. All patients required mechanical ventilation. In order to assess the degree of organ dysfunction, SOFA Score was calculated for 29 ICU patients. They all had a SOFA score ≥ 2. During hospitalization, seven patients (14%) developed thromboembolic complications, comprising deep vein thrombosis (n = 2), pulmonary embolism (n = 2), and ischemic stroke (n = 3). All these patients were classified as having severe COVID-19 pneumonia and among them only two had a history of thrombosis.

Platelet count < 150 10^9/L was noticed in six (12%) patients, prolonged PT and aPTT in 18 (36%) and 10 (20%) patients, respectively. Higher than normal fibrinogen level (> 4 g/L) were noted in 24 (48%) cases whereas 46 (92%) had a high D-dimer value (> 0.5 µg/mL). The mean length of stay of these patients was six (1 - 31) days with a mortality of 54%. The demographic and clinical characteristics of studied patients are shown in Table 1.

ROTEM parameters

Median values for all INTEM, EXTEM, and FIBTEM parameters are presented in Table 1. Hypercoagulable state was seen in 44 (88%) patients. ROTEM® showed decreased clot formation in 6 cases (12%) (i.e CT and CFT are shortened in INTEM and EXTEM). The EXTEM angle was increased in 8 cases (16%). A substantially higher clot firmness above standard values via high A10 and MCF in INTEM, EXTEM, and FIBTEM was observed in 22 (44%), 28 (56%), and 43 (86%) patients, respectively. Among patients with thrombosis, 6/7 (71.4%) had more than two (≥ 2) hypercoagulable ROTEM parameters (Figure 1), and 1/7 (14.3%) had a normal coagulation profile.

Significant positive correlations were seen between A10 INTEM and platelets (p < 0.001), fibrinogen (p = 0.011); MCF INTEM and platelets (p < 0.001), fibrinogen (p = 0.002); ML INTEM and fibrinogen (p = 0.009). A10 EXTEM and platelets (p <0.001), fibrinogen (p = 0.003); MCF EXTEM and platelets (p < 0.001), fibrinogen (p < 0.001); ML EXTEM and platelets (p = 0.011), fibrinogen (p = 0.028); A10 FIBTEM and fibrinogen (p < 0.001); MCF FIBTEM and fibrinogen (p = 0.009), D-dimer (p = 0.002). A negative correlation was seen between CT EXTEM and PT (p = 0.008) (Table 2).

Impaired fibrinolysis was observed in COVID-19 patients. Hypofibrinolysis was noted in 14 (28%) patients with an ML ≤ 2 in INTEM and EXTEM, whereas, hyperfibrinolysis was seen in 3 patients with an ML > 15 in INTEM and EXTEM. Among patients with reduced fibrinolysis, 4/14 (28.57%) had thrombosis. Among patients with hyperfibrinolysis, 2/3 patients (66.6%) had septic shock.

Comparison of clinical and laboratory data according to different disease severity groups:

Severe form of COVID 19 was observed in 30 (60%) while moderate in 20 (40%) patients. Comparisons of clinical and laboratory data are shown in Table 3. Significant differences between groups were confirmed in terms of lung damage (p = 0.002), PT (p = 0.039), fibrinogen (p = 0.001), D-dimer (p < 0.001) levels and CT EXTEM (p < 0.001). No significant relationship was noted between the number of patients with hypercoagulable ROTEM patterns and disease severity (moderate 80%, severe 93.3%, p = 0.748). We observed a significant relationship between the number of patients with thrombosis and disease severity (moderate 0%, severe 23.3%, p = 0.020).

DISCUSSION

Hypercoagulability is a frequent phenomenon among COVID-19 patients. Recent studies reported the occurrence of venous thromboembolism and stroke in approximately 20% and 3% of patients, respectively. A higher frequency seems to be present in severely ill patients, in particular those admitted to intensive care units [11,12].

Our study supports the presence of a hypercoagulable state in COVID-19 patients. More than 80% of patients had at least two hypercoagulable ROTEM® parameters. This hypercoagulability is characterized by the acceleration of the clot formation as shown by a decreased EXTEM CFT and/or an increased EXTEM α angle and very high clot strength by an increased INTEM, EXTEM A10 and MCF. The increased CT in EXTEM corresponds with prolonged PT in the conventional coagulation test. Standard coagulation variables showed higher fibrinogen and D-dimer levels in COVID-19 patients compared to normal, consistent with findings in other studies [2,8]. The influence of fibrinogen on clot firmness was confirmed by the high A10 and MCF in FIBTEM. As depicted in Table 2, EXTEM MCF, FIBTEM-MCF, and fibrinogen; FIBTEM MCF and D-dimer values were highly correlated in COVID-19 patients.

Currently, coagulation viscoelastic tests are increasingly used to characterize the coagulation profile of these patients. All of them have reported a procoagulant profile on ICU admission in COVID-19 patients with acute respiratory distress syndrome, as indicated by the detection of an increased clot firmness strength [7,10-18]. Boss K et al. [11] analyzed ROTEM measurements in 20 COVID-19 patients with a severe disease course and in patients with severe sepsis in an ICU. They found that MCF was significantly higher among COVID-19 patients than among non-COVID-19 (FIBTEM: 38.4 ± 10.1 mm vs. 29.6 ± 10.8 mm; p = 0.012; EXTEM: 70.4 ± 10.4 mm vs. 60.6 ± 14.8 mm; p = 0.022).

Laboratory findings showed a robust increase in D-dimer and fibrinogen levels pointing towards the presence

Table 1. Clinical characteristics and laboratory data.

Parameters		Reference values	Values
Age (years, median (IQR))			63 (20 - 87)
Genre (male, number (%))			37 (74%)
Comorbidities (yes, number (%))			30 (60%)
DIC Score		< 5	2 (0 - 4)
History of thrombosis (number (%))			5 (10%)
Lung damage (number (%))	No or minimal damage	< 10%	3 (6%)
	Moderate damage	10 - 25%	8 (16%)
	Extensive damage	25 - 50%	12 (24%)
	Severe damage	50 - 75%	20 (40%)
	Critical damage	> 75%	7 (14%)
Mechanically ventilated (number, (%))			50 (100%)
Platelet count ($\times 10^9$/L)		150 - 450	268.8 ± 126.6
PT (%)		70 - 100	71.9 ± 14.4
aPTT (s)		24 - 36	33.8 ± 14.1
Fibrinogen (g/L)		2 - 4	4.23 ± 1.24
D-dimer (µg/L)		< 0.5	5.5 ± 11.3
INTEM	CT (s)	100 - 240	217.5 ± 97.5
	CFT (s)	30 - 110	74.2 ± 40.8
	α (°)	70 - 83	75.5 ± 6.5
	A10 (mm)	44 - 66	63.6 ± 9.8
	MCF (mm)	50 - 72	70.3 ± 7.7
	LI30 (%)	94 - 100	99.7 ± 1.5
	ML (%)	≤ 15	3.2 ± 3.5
EXTEM	CT (s)	38 - 79	83.5 ± 41.1
	CFT (s)	34 - 159	63.0 ± 33.1
	α (°)	63 - 83	77.9 ± 5.8
	A10 (mm)	43 - 65	65.6 ± 8.7
	MCF (mm)	50 - 72	72.0 ± 6.3
	LI30 (%)	94 - 100	99.8 ± .6
	ML (%)	≤ 15	4.5 ± 4.5
FIBTEM	A10 (mm)	7 - 23	37.9 ± 13.9
	MCF (mm)	9 - 25	43.1 ± 17.0
Hypercoagulable ROTEM (number (%))			44 (88%)
Thrombosis (number (%))			7 (17%)
Length of stay in hospital (days, median (IQR))			6 (1 - 31)
Outcome, death (number (%))			27 (54%)

Comorbidities: hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, chronic obstructive pulmonary disease. Disseminated Intravascular Coagulation (DIC) scores are calculated from platelet count, prothrombin time, fibrinogen, and D-dimer according to guidelines of the International Society on Thrombosis and Hemostasis (ISTH), aPTT - activated Partial Thromboplastin Time, PT - Prothrombin Time, CT - clotting time, CFT - clot formation time, LI - lysis index, ML - maximum lysis, MCF - maximum clot firmness.

Table 2. Correlation between ROTEM parameters and platelets, fibrinogen, and D-dimer.

			Platelets	Fibrinogen	D-dimer
INTEM	CT	r	-0.199	0.088	-0.045
		p	0.166	0.542	0.756
	CFT	r	-0.219	-0.056	0.027
		p	0.127	0.702	0.852
	α	r	0.249	0.70	-0.39
		p	0.081	0.627	0.786
	A10	r	0.524	0.356	-0.114
		p	<0.001	0.011	0.429
	MCF	r	0.540	0.419	-0.106
		p	< 0.001	0.002	0.462
	ML	r	0.170	0.364	-0.100
		p	0.237	0.009	0.489
EXTEM	CT	r	-0.128	0.231	0.050
		p	0.376	0.106	0.732
	CFT	r	-0.204	-0.043	0.148
		p	0.154	0.766	0.304
	α	r	0.170	0.14	-0.119
		p	0.239	0.925	0.412
	A10	r	0.514	0.413	-0.104
		p	< 0.001	0.003	0.472
	MCF	r	0.490	0.556	-0.142
		p	< 0.001	<0.001	0.326
	ML	r	0.358	0.311	-0.023
		p	0.011	0.028	0.873
FIBTEM	A10	r	0.335	0.504	-0.111
		p	0.017	< 0.001	0.442
	MCF	r	0.280	0.368	0.435
		p	0.049	0.009	0.002

CT - Clotting Time, CFT - Clot Formation Time, A10 - Amplitude 10, ML - maximum lysis, MCF - Maximum Clot Firmness.

of CAC [4]. Platelet counts were almost within their normal range. Similar correlations were found in our study suggesting that high clot firmness is caused by a high fibrinogen level and platelet count in COVID-19 patients.

The physiopathology of hypercoagulability state observed in COVID-19 patients is a multifactorial process involving endothelial dysfunction; systemic inflammation, characterized by Toll-like receptor activation and a procoagulatory state, characterized by the activation of the tissue factor pathway [17,19-21]. Published data suggest that both hypercoagulability and a significant increase in proinflammatory cytokines (cytokine storm) are the leading causes of multiple organ failure in critically ill COVID-19 patients [10].

A second key finding of this study is the occurrence of significant fibrinolysis shutdown among COVID-19 patients, represented by ML EXTEM reduction in 14/50 patients, but with paradoxical increased D-dimer levels, typically seen in hyperfibrinolysis. This decreased fibrinolytic function has been described in severe sepsis and is correlated with increased morbidity and mortality [11, 16,17,22-24].

To explain high D-dimer levels in COVID-19 patients with the global viscoelastic test showing a hypofibrinolytic pattern, Ibanez et al. [25] suggested that the lungs could potentially be the main source of D-dimers, which is due to the fibrinolysis acting on intra-alveolar fibrin membranes or local microthrombi. In fact, he postulated that damaged epithelial alveolar cells release the urokinase, a fibrinolysis activator, in the lungs of patients with severe COVID19, and therefore the coexistence of a local imbalance between increased fibrin formation and insufficiently increased fibrinolytic activity in rela-

Table 3. Comparison of clinical and laboratory data by the severity group.

Parameters		Disease severity		p
		Moderate (n = 20)	Severe (n = 30)	
Age (years, median (range))		62 (30 - 87)	63.5 (20 - 82)	0.271
Genre (male, number (%))		20 (40%)	30 (60%)	0.148
Comorbidities (number (%))		15 (75%)	15 (50%)	0.185
Lung damage (number (%))	Minimal damage	3 (15%)	0 (0%)	0.002
	Moderate damage	3 (15%)	5 (16.7%)	
	Extensive damage	9 (45%)	3 (10%)	
	Severe damage	5 (25%)	15 (50%)	
	Critical damage	0 (0%)	7 (23.3%)	
History of thrombosis (number (%))		1 (5%)	4 (13.3%)	0.235
Platelet count (× 10^9/L)		251.8 ± 93.5	280.1 ± 144.9	0.552
PT (%)		77.0 ±12.2	68.5 ± 14.9	0.039
aPTT (s)		30.7 ± 6.5	35.9 ± 17.2	0.120
Fibrinogen (g/L)		3.4 ± 0.6	4.7 ± 1.2	0.001
D-dimer (µg/L)		1.4 ± 1.2	8.2 ± 14	< 0.001
INTEM	CT (s)	193.4 ± 34.9	233.6 ± 120.8	0.073
	CFT (s)	67.7 ± 24.4	78.5 ± 48.8	0.494
	α (°)	76.4 ± 4.7	74.9 ± 7.5	0.662
	A10 (mm)	62.9 ± 9.6	64.0 ± 10.0	0.613
	MCF (mm)	68.8 ± 7.9	71.37 ± 7.6	0.246
	LI30 (%)	99.4 ± 2.4	99.93 ± 0.3	0.336
	ML (%)	2.5 ± 2.8	3.6 ± 3.8	0.355
EXTEM	CT (s)	62.2 ± 9.6	97.8 ± 47.6	< 0.001
	CFT (s)	52.9 ± 21.6	69.7 ± 37.8	0.087
	α (°)	79.8 ± 4.1	76.7 ± 6.5	0.073
	A10 (mm)	65.0 ± 8.0	65.9 ± 9.3	0.585
	MCF (mm)	70.8 ± 6.0	72.8 ± 6.5	0.156
	LI30 (%)	99.9 ± 0.3	99.8 ± 0.7	0.705
	ML (%)	3.0 ± 2.8	5.6 ± 5.2	0.088
FIBTEM	A10 (mm)	37.9 ± 18.2	37.9 ± 17.2	0.532
	MCF (mm)	39.0 ± 12.1	45.9 ± 19.3	0.223
Hypercoagulable ROTEM (number, (%))		16 (80%)	28 (93.3%)	0.748
Thrombosis (number, (%))		0 (0%)	7 (23.3%)	0.020
Length of stay in hospital (days, median (IQR))		3.5 (1 - 17)	7 (1 - 31)	0.075
Outcome, death (number, (%))		2 (10%)	25 (83.3%)	0.008

Comorbidities: hypertension, Diabetes mellitus, dyslipidemia, cardiovascular disease, chronic obstructive pulmonary disease. Disseminated Intravascular Coagulation (DIC) scores are calculated from platelet count, prothrombin time, fibrinogen, and D-dimer according to guidelines of the International Society on Thrombosis and Haemostasis (ISTH), aPTT - activated Partial Thromboplastin Time, PT - Prothrombin Time, CT - clotting time, CFT - clot formation time, LI - lysis index, ML - maximum lysis, MCF - maximum clot firmness.

tion to the high burden of fibrin, leads to high D-dimer levels in COVID19 patients with systemic hypofibrinolysis.

In comparing ROTEM parameters according to COVID-19 severity, EXTEM CT was shown to be increased with the severity of the disease, alongside with a prolonged PT in the conventional coagulation test, which suggested that patients with advanced disease have a delay in activation of hemostasis; however, once initiated, clot formation is exaggerated with reduced fi-

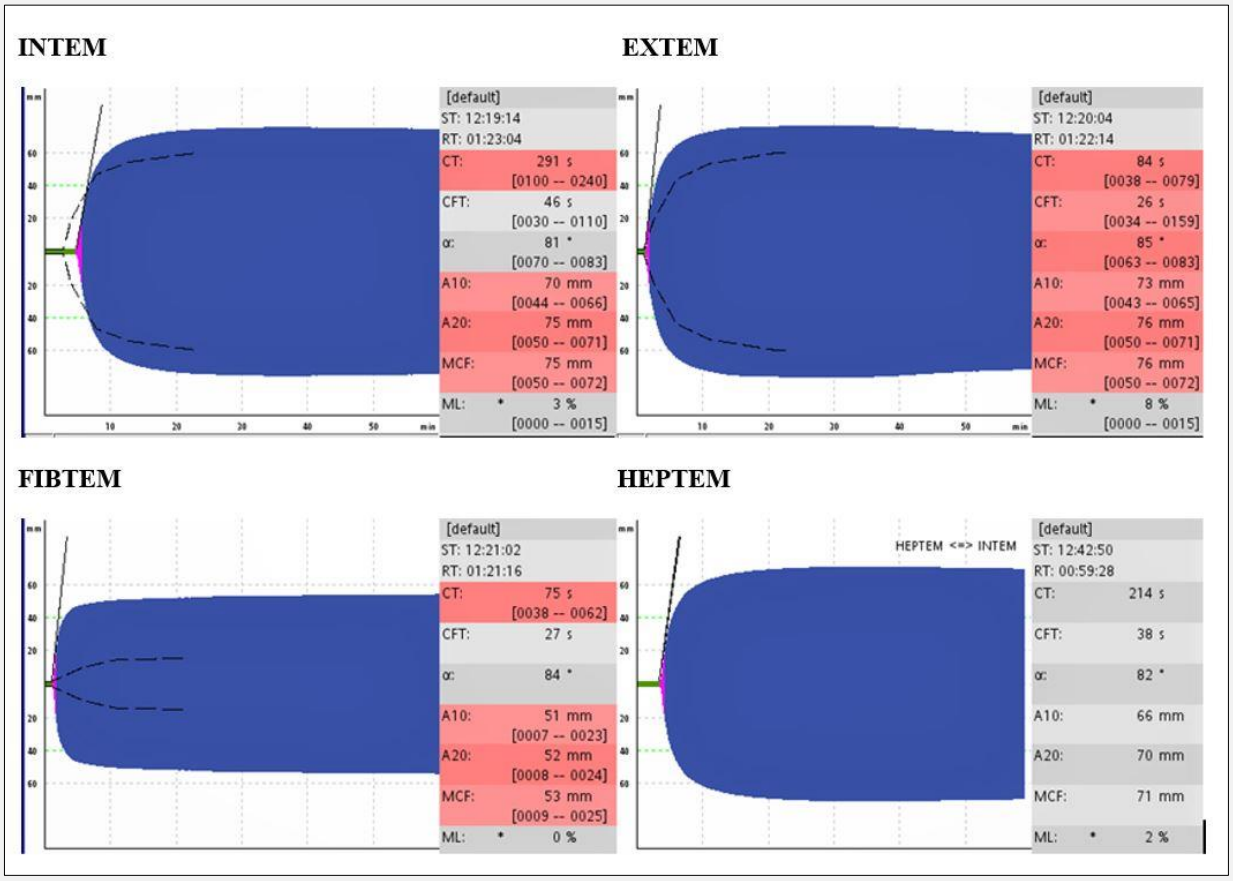

Figure 1. Hypercoagulability profile of a COVID 19 patient.

brinolysis [14,22]. Conversely, a correlation between ROTEM parameters and severity illness scores has not been reported in other studies [25].

Furthermore, several authors have demonstrated that COVID-19 infection is associated with a high rate of venous and arterial thrombotic manifestations [12]. In our study, we detected severe ischemic events in 7 of 50 (14%) COVID-19 patients despite anticoagulation with heparin. All patients with thrombosis were classified as having severe form of COVID-19 and were hospitalized in ICU. More than 85% had at least two hypercoagulable ROTEM parameters, whereas one patient had a normal coagulation profile but had a history with thrombosis. Four out of seven (57.14%) patients with venous thrombosis met the diagnostic criteria for fibrinolysis shutdown. The failure of LMWH to reduce the incidence of thrombosis was reported by Creel-Bulos et al. [26] and was attributed to the presence of fibrinolysis shutdown.

The number of thromboembolic events among COVID-19 patients as reported in published studies is variable [21,24,27-29]. The pooled incidence of VTE was 17.0% (95% CI, 13.4 and 20.9), 12.1% (95% CI, 8.4 and 16.4) for deep vein thrombosis, and 7.1% (95% CI, 5.3 and 9.1) for pulmonary embolism [24]. Mitrovic et al. [7] showed a significant relationship between the number of patients with ≥ 2 hypercoagulable factors and disease severity (moderate 23.5%, severe 60.0%, critical 74.3%, $p < 0.001$). Boscolo et al. [30] showed that COVID-19 patients with mild respiratory failure had less severe hypercoagulability and lower incidence of symptomatic VTE as compared with more critically ill patients. Therefore, in order to assess a predictive value of ROTEM measurements for the occurrence of thromboembolic events, sequential ROTEM measurements and corresponding CT-scans should be performed in a prospective study design [11].

Inflammation-induced coagulopathy is a very dynamic process, ranging from the initial hypercoagulability towards a subsequent hypocoagulable profile, depending on the critical illness evolvement. Interestingly, the degree of hypocoagulation has been found to be associated

with DIC which is associated with a high mortality rate [4,5,17]. Tang et al. [2] noted 11.5% mortality in patients with COVID-19 pneumonia and reported that 71.4% of deceased patients had abnormal coagulation profile consistent with DIC. Nevertheless, we did not observe consumption coagulopathy (score DIC < 5). Our results are in agreement with other studies that did not show DIC in patients with severe COVID-19 [12, 31].

Study limitations

First, it is a single-center study with a relatively small sample size that could not be representative of all hospitalized COVID-19 patients. Second, inclusion of a healthy control group was not possible due to the lock down conditions. Finally, the use of thromboelastometry to assess CAC could be questioned because of the lack of standardization limiting comparison of results between centers. Our findings highlight the role of ROTEM when monitoring the coagulation system in COVID-19 patients. Future studies should investigate the potential use of ROTEM in optimizing thromboprophylaxis strategies in these patients.

CONCLUSION

In our study, we confirmed the presence of a hypercoagulable state in COVID-19 patients, characterized by acceleration of blood clot formation, high clot strength, and reduced fibrinolysis. This state was more frequent in severely ill patients, in whom thrombotic complications mainly occurred.

Ethics Commission:

The study was approved by the local Ethics Commission of the hospital.

Declaration of Interest:

The authors have no conflict of interest to declare.

References:

1. WuZ, McGooganJM.Characteristics of and important lessons from the coronavirus disease 2019 (covid-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA 2020;323(13):1239-42. (PMID: 32091533)

2. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18(4):844-7. (PMID: 32073213)

3. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med 2020;58(7):1116-20. (PMID: 32172226)

4. Herrmann J, Notz Q, Schlesinger T, et al. Point of care diagnostic of hypercoagulability and platelet function in COVID-19 induced acute respiratory distress syndrome: a retrospective observational study. Thromb J 2021;19(1):39. (PMID: 34078393)

5. Tsantes AE, Tsantes AG, Kokoris SI, et al. COVID-19 Infection-Related Coagulopathy and Viscoelastic Methods: A Paradigm for Their Clinical Utility in Critical Illness. Diagnostics (Basel) 2020; 10(10):817. (PMID: 33066390)

6. Tynngård N, Lindahl TL, Ramström S. Assays of different aspects of haemostasis - what do they measure? Thromb J 2015; 13:8. (PMID: 25688179)

7. Mitrovic M, Sabljic N, Cvetkovic Z, et al. Rotational Thromboelastometry (ROTEM) Profiling of COVID-19 Patients. Platelets 2021;4;32(5):690-6. (PMID: 33561381)

8. Collett LW, Gluck S, Strickland RM, Reddi BJ. Evaluation of coagulation status using viscoelastic testing in intensive care patients with coronavirus disease 2019 (COVID-19): An observational point prevalence cohort study. Aust Crit Care 2021 Mar; 34(2):155-9. (PMID: 32773357)

9. World Health Organization. 2020. Clinical management of severe acute respiratory infection when novel coronavirus infection is suspected: interim guidance 2020. https://apps.who.int/iris/handle/10665/330893

10. Görlinger K, Pérez-Ferrer A, Dirkmann D, et al. The role of evidence-based algorithms for rotational thromboelastometry-guided bleeding management. Korean J Anesthesiol 2019;72(4):297-322. (PMID: 31096732)

11. Boss K, Kribben A, Tyczynski B. Pathological findings in rotation thromboelastometry associated with thromboembolic events in COVID-19 patients. Thromb J 2021;19:10. (PMID: 33573670)

12. Corrêa TD, Cordioli RL, Campos Guerra JC, et al. Coagulation profile of COVID-19 patients admitted to the ICU: An exploratory study. PLoS One 2020;15(12):e0243604. (PMID: 33320874)

13. van de Berg TW, Hulshof AM, Nagy M, et al. Suggestions for global coagulation assays for the assessment of COVID-19 associated hypercoagulability. Thromb Res 2021;201:84-9. (PMID: 33662799)

14. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. J. Thromb. Haemost 2020;18:1738-42. (PMID: 32302438)

15. Spiezia L, Boscolo A, Poletto F, et al. COVID-19 Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. Thromb. Haemost 2020;120: 998-1000. (PMID: 32316063)

16. Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis Shutdown Correlation with Thromboembolic Events in Severe COVID-19 Infection. J Am Coll Surg 2020;231:193-203.e1. (PMID: 32422349)

17. Pavoni V, Gianesello L, Pazzi M, Stera C, Meconi T, Frigieri FC. Evaluation of coagulation functions by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. J Thromb Thrombolysis 2020;20:281-6. (PMID: 32394236)

18. Mortus JR, Manek SE, Brubaker LS, et al. Thromboelastographic Results and Hypercoagulability Syndrome in Patients With Coronavirus Disease 2019 Who Are Critically Ill. JAMA Netw Open 2020;3(6):e2011192. (PMID: 32501489)

19. Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of Coronavirus Disease 2019. Crit Care Med 2020;48(9):1358-64. (PMID: 32467443)

20. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020;18(8):1995-2002. (PMID: 32369666)

21. Aggarwal M, Dass J, Mahapatra M. Hemostatic Abnormalities in COVID-19: An Update. Indian J Hematol Blood Transfus 2020; 36(4):616-26. (PMID: 32837053)

22. Kruse JM, Magomedov A, Kurreck A, et al. Thromboembolic complications in critically ill COVID-19 patients are associated with impaired fibrinolysis. Crit Care 2020;24 (1):676. (PMID: 33287877)

23. Bachler M, Bösch J, Stürzel DP, et al. Impaired fibrinolysis in critically ill COVID-19 patients. Br J Anaesth 2021;126(3):590-8. (PMID: 33422287)

24. Görlinger K, Almutawah H, Almutawaa F, et al. The role of rotational thromboelastometry during the COVID-19 pandemic: a narrative review. Korean J Anesthesiol 2021;74(2):91-102. (PMID: 33440114)

25. Ibañez C, Perdomo J, Calvo A, et al. High D dimers and low global fibrinolysis coexist in COVID19 patients: what is going on in there? J Thromb Thrombolysis 2020;51(2):308-12. (PMID: 32671609)

26. Creel-Bulos C, Auld SC, Caridi-Scheible M, et al. Fibrinolysis Shutdown and Thrombosis in a COVID-19 ICU. Shock 2021; 55(3):316-20. (PMID: 32769822)

27. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-7. (PMID: 32291094)

28. Helms J, Tacquard C, Severac F,et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;46(6):1089-98. (PMID: 32367170)

29. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 2020;136(4):489-500. (PMID: 32492712)

30. Boscolo A, Spiezia L, Correale C, et al. Different Hypercoagulable Profiles in Patients with COVID-19 Admitted to the Internal Medicine Ward and the Intensive Care Unit. Thromb Haemost 2020;120(10):1474-7. (PMID: 32702757)

31. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9-14. (PMID: 32353746)