Observational Study

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The haemostatic profile in critically ill COVID-19 patients receiving therapeutic anticoagulant therapy

An observational study

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Abstract

Hypercoagulability and thrombosis remain a challenge in severe coronavirus disease 2019 (COVID-19) infections. Our aim is to investigate the hemostatic profile of critically ill COVID-19 patients on therapeutic anticoagulant treatment.

Forty one patients were enrolled into the study. We recruited 11 consecutive, COVID-19, patients who received therapeutic anticoagulant treatment on intensive care unit (ICU) admission. Disease severity indexes, biochemical, hematological and haemostatic parameters, endogenous thrombin potential (ETP), plasminogen activator inhibitor-1 (PAI-1) activity and extrinsically activated rotational thromboelastometry assay (EXTEM) were recorded on days 1, 3, 7. We also enrolled 9 ICU non-COVID-19, 21 non-ICU COVID-19 patients and 20 healthy blood donors as control populations.

Critically ill COVID-19 patients demonstrated a more hypercoagulable and hypofibrinolytic profile related to those with COVID-19 mild illness, based on EXTEM amplitude at 10 min (A10), maximum clot firmness (MCF) and lysis index at 60 min (LI60) variables ($p = 0.020$, 0.046 and 0.001, respectively). Similarly, a more hypercoagulable state was detected in COVID-19 ICU patients related to non-COVID-19 ICU patients based on A10 and MCF parameters ($p = 0.03$ and 0.04, respectively). On the contrary, ETP and EXTEM (clotting time) CT values were similar between patients with severe and mild form of the COVID-19 infection, probably due to anticoagulant treatment given.

Critically ill COVID-19 patients showed a hypercoagulable profile despite the therapeutic anticoagulant doses given. Due to the small sample size and the study design, the prognostic role of the hypercoagulability in this clinical setting remains unknown and further research is required in order to be assessed.

Abbreviations: A10 = clot strength at 10 minutes, A20 = clot strength at 20 minutes, A30 = clot strength at 30 minutes, ao = a angle, APACHE = Acute Physiology and Chronic Health Evaluation, ARDS = acute respiratory distress syndrome, AUC = curve included area under the curve, CFT = clot formation time, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, CT = clotting time, DIC = disseminated intravascular coagulopathy, ETP = endogenous thrombin potential, EXTEM = extrinsically activated rotational thromboelastometry assay, ICU = intensive care unit, LI60 = lysis index at 60 minutes, MCF = maximal clot firmness, ML = maximal lysis, PAI-1 = plasminogen activator inhibitor-1, ROTEM = rotational thromboelastometry, TEG = thromboelastography, TEM = thromboelastometry, TG = thrombin generation, VMs = viscoelastic methods.

Keywords: anticoagulant therapy, COVID-19 infection, hypercoagulability, hypofibrinolysis, rotational thromboelastometry

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1. Introduction

Recent observations suggest that respiratory failure in coronavirus disease 2019 (COVID-19) infections is not caused by the development of the acute respiratory distress syndrome (ARDS) alone,[1] but that microvascular thrombotic processes may contribute, also.[2] One of the most significant poor prognostic signs in those patients is the development of coagulopathy.[3,4] The level of D-dimer has been identified as a promising prognostic marker for survival of the disease and an early predictor of severe clinical presentations of COVID-19.[3,5,6] Based on the experience from published literature on septic coagulopathy, monitoring PT, D dimer, platelet count and fibrinogen has been suggested as helpful in determining prognosis in COVID-19 patients requiring hospital admission.[7–9]

In this context, the International Society of Thrombosis and Haemostasis (ISTH) recommends measuring D-dimers, prothrombin time and platelet count (decreasing order of importance) in all patients who present with COVID-19 infection,[10] in order to help in stratifying those who may need admission and close monitoring or not. Moreover the recommended management of COVID-19 coagulopathy is based on the only currently available evidence that markedly increased D-dimer is associated with high mortality in COVID-19 patients and that coagulopathy is associated with multi-organ failure in septic patients. In sepsis, the disturbance between components of the coagulation and fibrinolytic system, leads to a variable clinical picture, tilting from initial hypercoagulability towards a subsequent hypocoagulable disease state, depending on the phase of septic coagulopathy. Bleeding complications are rare in severe COVID-19 patients, suggesting that DIC is not a common complication of COVID-19, while pulmonary micro-thrombosis seems to be partially related with the pathophysiological mechanism of COVID-19 related ARDS.[2] Assessment of coagulation status in these patients is complex. The ability of conventional global coagulation tests to reflect in vivo hypo- or hypercoagulability accurately is questioned[11] as these assays reflect only a part of the coagulation system. Viscoelastic methods (VMs), like thromboelastography (TEG) and rotational thromboelastometry (ROTEM), are point-of-care tests, which evaluate whole-clot formation and dissolution.[12] A critical issue to be addressed is whether the use of viscoelastic tests performed on whole blood could contribute to both better explore hypercoagulability and predict thrombotic events in critically ill COVID-19 patients.[13–16]

Our aim is to evaluate the potential role of ROTEM and other specific assays in the assessment of haemostatic profile and their association with anticoagulant therapy and disease severity in critically ill COVID-19 patients.

2. Methods

The study population consisted of 11 consecutive patients tested positive for COVID-19 with real-time reverse-transcriptase-polymerase chain reaction (rRT-PCR) assay (VIASURE Sars-CoV-2, CERTEST Biotec SL, Zaragoza, Spain) and treated in the Intensive Care Unit (ICU) of the 'Attikon' University Hospital of Athens due to acute respiratory distress syndrome (ARDS) development. Nine non-COVID-19 ICU patients and 21 COVID-19 patients presented with a mild form of the disease were used as control populations. Twenty healthy blood donors were also used as controls to establish normal values for standard extrinsically activated ROTEM assay (EXTEM) and Endogenous Thrombin Potential (ETP) assay. ICU COVID-19 patients were on therapeutic anticoagulant doses with low molecular weight heparin (LMWH), as per our ICU specific protocol (enoxaparin 1 mg/kg every 12 hours), while non-ICU COVID-19 and ICU non-COVID-19 patients were on thromboprophylaxis with LMWH (enoxaparin 1 mg/kg every 24 hours). All patients were enrolled within 24 h after ICU admission. The study was performed in accordance with the Declaration of Helsinki and was approved by the hospital's institutional review board (180;14/04/2020). Informed consent was obtained from all participants or relatives.

Diagnosis of ARDS was made according to Berlin Definition.[17] Demographic were recorded on study enrolment. Clinical data and samples for laboratory testing were collected from ICU COVID-19 patients on days 1, 3, 7. Disease severity indexes, including Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA), lung compliance, lung injury score, sepsis induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC) scores, were also calculated.

Biochemical, hematological and haemostatic parameters.

The following parameters were recorded on days 1, 3, 7: PaO_2/FiO_2, $PaCO_2$, HCO_3, white blood cell count, platelets, total and direct billirubin, creatinine, blood urea nitrogen, aminotransferases, C-reactive protein (CRP), procalcitonin, activated partial thromboplastin time and prothrombin time, fibrinogen, ROTEM analysis, Plasminogen activator inhibitor-1 (PAI-1) activity, Endogenous Thrombin Potential (ETP) and D-dimer levels in plasma.

PAI-1 activity was determined on an automated coagulation analyzer (Behring Coagulation System, Marburg, Germany) with reagents (Berichrom PAI; Dade Behring, Milton Keynes, UK) and protocols from the manufacturer.

INNOVANCE ETP (Siemens Healthcare Diagnostics) is a global hemostasis function test to assess the ETP of plasma samples and was performed on the BCS XP system hemostasis analyzer as previously described.[18] The estimated parameters of the thrombin generation (TG) curve included area under the curve (AUC), also referred to as ETP and maximum TG depicted by peak height (Cmax).

For ROTEM analysis, the EXTEM test was performed on the ROTEM analyzer (Tem Innovations GmbH, Munich, Germany) as formerly described.[19] The following ex-TEM variables were measured: clotting time (CT, seconds), the time from the beginning of measurement until the formation of a clot 2 mm in amplitude; clot formation time (CFT, seconds), the time from CT (amplitude of 2 mm) until a clot firmness of 20 mm was achieved; amplitude was recorded at 10 min (A10, mm); a angle (a°), the angle between the central line (x-axis) and the tangent of the TEM tracing at the amplitude point of 2 mm, describing the kinetics of clot formation; maximum clot firmness (MCF, mm), the final strength of the clot; Maximum clot elasticity (MCE) is calculated using the following formula: MCE = (MCF*100)/(100-MCF); lysis index at 60 min (LI60, %), the percentage of remaining clot stability in relation to the MCF following the 60-min observation period after CT which indicates the speed of fibrinolysis and maximum lysis (ML) index which reflects the percent decrease of maximal amplitude over time.

2.1. Statistical analysis

Statistical analysis of the population data included descriptive statistics, presented as means ± SD, medians and interquartile

ranges (IQR), or as frequencies (percentages) when appropriate. The demographic characteristics, the clinical parameters, the conventional laboratory values and the ROTEM parameters between the study groups (COVID-19 ICU patients, non COVID-19 ICU patients, COVID-19 non-ICU patients and healthy subjects) were compared using the Chi-square test for categorical variables, and the two-sample Wilcoxon rank-sum (Mann-Whitney) test or the Kruskal-Wallis test for continuous variables. The assessment of correlation between laboratory values and certain clinical parameters was performed using the Spearman rank correlation coefficient test. Spearman's rho of < 0.20 indicates very weak correlation, 0.21 to 0.40 weak correlation, 0.41 to 0.60 moderate correlation, 0.61 to 0.80 strong correlation, and > 0.81 very strong correlation. For statistical analysis, we used the R software (version 3.6). For all tests, a p-value < 0.05 indicates statistical significance.

3. Results

The demographics, clinical and conventional laboratory parameters of COVID-19 ICU patients, and COVID-19 non-ICU patients are presented in Table 1. The results of ETP measurements and the EXTEM parameters among the 3 study groups (COVID-19 ICU patients, non-COVID-19 ICU patients, COVID-19 non-ICU patients) and healthy controls are summarized in Table 2. COVID-19 ICU patients had significantly higher A10 and MCF than non-COVID-19 ICU patients ($p = 0.030$ and 0.049, respectively). Moreover, COVID-19 ICU patients had significantly higher A10 ($p = 0.020$), MCF ($p = 0.046$), LI60 ($p = 0.001$), alpha angle ($p = 0.008$) and significantly lower CFT ($p = 0.042$) and ML ($p = 0.001$) compared to non-ICU COVID-19 patients. Furthermore, as shown in Table 2, most EXTEM parameters were significantly different ($p < 0.05$) between healthy subjects and COVID-19, ICU or non-ICU, patients. The correlations between laboratory and clinical parameters in ICU COVID-19 patients, obtained from 25 observations based on serial measurements, are summarized in Table 3. LI60 was found to be moderately positively correlated with procalcitonin levels (rho = +0.49, $p = 0.045$), while a moderate positive correlation was shown between D-dimers and SOFA score (rho = +0.51, $p < 0.001$) and, D-dimers and Lung Injury score (rho = +0.50, $p = 0.013$).

4. Discussion

Based on ROTEM measurements, critically ill COVID-19 patients demonstrated a more hypercoagulable and hypofibrinolytic profile related to those with COVID-19 mild illness, while hypercoagulability and hypofibrinolysis were evident in both patient groups as compared to healthy controls. This indicates that hypercoagulability in COVID-19 infection might be associated with disease severity.

The exactly same pattern of shorter EXTEM-CFT and increased EXTEM-MCF in hospitalized COVID-19 positive patients compared with healthy controls, which became more pronounced in patients with more severe disease, has recently been reported.[20,21] It is noteworthy that in our hands, a more hypercoagulable state was also detected in COVID-19 ICU patients compared with non-COVID-19 ICU patients with similar critical illness severity.

On the other hand, prolonged PT/APTT, reduced platelet counts and abnormal fibrinogen levels, which are pathognomonic signs of DIC were absent in ICU COVID-19 patients. The association between severe COVID-19 infection and hypercoagulability has recently been demonstrated by whole blood thromboelastography and thromboelastometry.[13,14,16] Authors have reported the absence of abnormal conventional coagulation tests, which, in turn, supports the absence of consumption coagulopathy.[13] Similarly, in the current study, based on SIC or DIC score, coagulopathy was detected in only two critically ill patients. Thus, it is confirmed that coagulopathy in most ICU COVID-19 patients does not conform to classic DIC.[2]

In keeping with our findings, PT and APTT levels did not significantly differ between mild and severe COVID-19 cases,[6,22] although this has not been a constant finding.[3,23] The fact that inflammation-induced coagulopathy is a very dynamic process, ranging from initial hypercoagulability towards a subsequent hypocoagulable profile, depending on the critical illness evolvement,[24] might account for this inconsistency. Unlike other conventional coagulation tests, increased D dimer levels were identified as a predictor for the development of severe disease and were significantly associated with the need for ICU admission, in accordance with previous studies.[3,6,10,25,26] In the current study, the prognostic value of high D dimers levels was corroborated by their moderate correlation with SOFA and lung injury score. However, it should be noted that based on our

Table 1

Clinical characteristics and conventional laboratory values of COVID-19 ICU patients and COVID-19 non-ICU patients.

	COVID-19 ICU patients (n = 11)	COVID-19 non-ICU patients (n = 21)	*P* value
Gender (males, %)	10 (90.9)	11 (52.3)	$P = .050$
Age (years)	73.5 ± 12.9; 78.0 (67.0–71.0)	68.2 ± 20.4; 73.0 (50.0–88.0)	$P < .001$
PAI-1 activity (U/ml)	2.7 ± 1.6; 2.1 (1.4–4.3)	1.4 ± 0.9; 1.5 (0.8–2.1)	$P = .07$
Procalcitonin (ng/Ml)	0.88 ± 1.02; 0.52 (0.23–1.25)	0.20 ± 0.27; 0.1 (0.06–0.23)	$P < .001$
INR	1.19 ± 0.20; 1.10 (1.04–1.32)	1.12 ± 0.16; 1.13 (1.03–1.18)	$P = .45$
APTT (seconds)	36.1 ± 5.09; 36.0 (33.0–39.7)	39.2 ± 6.7; 37.8 (34.3–41.9)	$P = .38$
Fibrinogen (mg/dl)	486.1 ± 199.9; 439.5 (313.0–439.5)	451.6 ± 131.2; 436.5 (399.0–503.0.)	$P = .98$
D-dimers (ng × 10^3/ml)	3.85 ± 3.47; 2.42 (1.47–7.32)	1.32 ± 1.28; 0.86 (0.54–1.21)	$P = .001$
WBC (count × 10^3/ml)	21.3 ± 30.6; 11.8 (7.1–20.0)	7.1 ± 4.4; 6.7 (4.5–8.2)	$P = .003$
Neutrophils (%)	65.2 ± 26.8; 78.0 (61.0–82.0)	60.1 ± 13.8; 60.5 (52.3–68.8)	$P = .09$
Lymphocytes (%)	16.0 ± 21.1; 10.0 (4.0–15.0)	23.2 ± 15.1; 18.4 (14.6.3–28.8)	$P = .033$
PLTs (count × 10^3/ml)	248.0 ± 130.2; 262.0 (120.0–350.0)	285.6 ± 120.2; 253.0 (207.0–396.0)	$P = .59$
CRP (mg/L)	78.6 ± 62.8; 48.0 (22.8–128.0)	48.9 ± 60.9; 32.3 (9.2–55.0)	$P = .17$

Data are presented as means ± SD, medians and interquartile ranges (IQR), or as absolute values (percentages) when appropriate.

aPTT = ctivated partial thromboplastin time, CRP = C-reactive protein, INR = international normalization rate, PAI-1 = plasminogen activator inhibitor, PLTs = platelets, WBCs = white blood cells.

Table 2

Comparison of thrombin generation indices and ROTEM parameters among Covid-19 patients in ICU (group A), non-Covid-19 patients in ICU (group B), Covid-19 patients hospitalized not in ICU (group C), and healthy controls (group D).

	Group A (n = 11)	Group B (n = 9)	Group C (n = 21)	Group D (n = 21)	Overall *P*	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
ETP	74.1 ± 30.3; 78.0 (46.0–102.0)	79.1 ± 21.6; 87.0 (65.0–98.0)	89.3 ± 30.5; 92.0 (62.0–99.0)	95.3 ± 13.4; 95.5 (90.0–103.0)	.16	*P* = .64	*P* = .31	*P* = .040	*P* = .52	*P* = .22	*P* = .30
TG Cmax	98.4 ± 27.5; 96.0 (80.0–121.0)	116.5 ± 33.5; 108.5 (100.0–114.0)	101.3 ± 27.5; 107.0 (79.0–117.0)	114.5 ± 28.2; 107.0 (102.0–115.0)	.42	*P* = .64	*P* = .86	*P* = .10	*P* = .68	*P* = .18	*P* = .47
CT (sec)	73.5 ± 15.5; 67.5 (65.0–72.0)	70.5 ± 8.5; 69.0 (67.0–79.0)	73.5 ± 12.0; 71.0 (66.0–81.0)	68 ± 10.6; 65.0 (60.0–73.0)	.20	*P* = .68	*P* = .49	*P* = .27	*P* = .71	*P* = .18	*P* = .048
CFT (sec)	40.7 ± 13.0; 39.5 (30.0–51.0)	63.7 ± 34.7; 59.0 (41.0–77.0)	59.5 ± 24.9; 48.0 (45.0–61.0)	89.2 ± 24.7; 79.0 (72.0–96.0)	<.001	*P* = .10	*P* = .042	*P* < .001	*P* = .85	*P* = .013	*P* < .001
A10 (mm)	70.2 ± 6.1; 70.5 (69.0–76.0)	60.7 ± 11.0; 63.0 (56.0–66.0)	65.0 ± 5.4; 66.0 (63.0–69.0)	54.0 ± 5.6; 56.0 (49.0–58.0)	<.001	*P* = .03	*P* = .020	*P* < .001	*P* = .31	*P* = .024	*P* < .001
MCF (mm)	75.7 ± 5.0; 77.0 (75.0–78.0)	69.4 ± 8.5; 72.0 (67.0–73.0)	72.4 ± 4.0; 72.0 (70.0–74.0)	59.9 ± 13.1; 63.5 (60.0–66.0)	<.001	*P* = .04	*P* = .046	*P* < .001	*P* = .32	*P* = .013	*P* < .001
Alpha angle	82.3 ± 2.1; 82.0 (81.0–84.0)	79.7 ± 3.4; 80.0 (78.0–83.0)	78.1 ± 4.7; 80.0 (78.0–81.0.)	72.0 ± 4.1; 74.0 (71.0–75.0)	<.001	*P* = .07	*P* = .008	*P* < .001	*P* = .73	*P* < .001	*P* < .001
LI60 (%)	99.5 ± 1.0; 100.0 (100.0–100.0)	98.4 ± 2.1; 99.0 (98.0–100.0)	96.3 ± 2.9; 97.0 (94.0–99.0)	93.1 ± 4.2; 94.0 (91.0–96.0)	<.001	*P* = .14	*P* = .001	*P* < .001	*P* = .046	*P* < .001	*P* = .008
ML (%)	1.8 ± 2.3; 1.0 (0.0–2.0)	3.2 ± 3.7; 1.0 (0.0–5.0)	6.2 ± 3.5; 6.0 (4.0–8.0)	8.4 ± 4.6; 8.0 (5.0–11.0)	<.001	*P* = .55	; *P* = .001	*P* < .001	*P* = .058	*P* = .006	*P* = .22
MCE	336.6 ± 89.1; 351.0 (297.0–415.0)	259.8 ± 78.9; 259.5 (206.0–304.5)	269.1 ± 51.6; 262.0 (235.0–289.0)	171.5 ± 35.1; 176.0 (152.0–190.0)	<.001	*P* = .08	*P* = .054	*P* < .001	*P* = .66	*P* = .002	*P* < .001

ETP = endogenous thrombin potential, TG = thrombin generation, CT = clotting time, CFT = clot formation time, A10 = clot amplitude at 10 min, MCF = maximum clot firmness, LI60 = lysis index at 60 min, ML = maximal lysis, MCE = maximum clot elasticity.
Data are presented as mean ± SD; median and interquartile range. The Kruskal–Wallis test was used for the overall comparison, while the Mann–Whitney test was used for the pairwise comparisons.

data there was no difference between COVD ICU and non-COVID ICU patients. Thus, it is not clear whether D dimmers increase is a specific marker of COVID infection or may be just a marker of being critically ill.

Probably, due to treatment with therapeutic and prophylactic anticoagulant doses in patients with severe and mild form of the COVID-19 infection, respectively, ETP and EXTEM CT values were similar between them. The use of therapeutic anticoagulant doses in our ICU COVID-19 patients has resulted in significantly greater suppression on thrombin generation compared to healthy controls. It is noteworthy, that anti-Xa activity was within therapeutic ranges in almost all ICU COVID-19 patients. Besides CT, all other EXTEM variables showed significant hypercoagulability in ICU COVID-19 patients compared to non-ICU COVID-19, but also to ICU non-COVID-19 patients, indirectly supporting the use of anticoagulants in this clinical setting. The anticoagulant treatment given has probably prevented excessive generation of thrombin which, in turn, could have possibly led to a more intense hypercoagulable state than the currently observed. In a recent study, all ICU COVID-19 patients on prophylactic anticoagulation had ETP within the normal range suggesting a major hypercoagulability that could not be controlled with prophylactic heparin therapy.[27] Recent data showed that routine chemical venous thromboembolism prophylaxis may be inadequate in preventing venous thromboembolism in severe COVID-19.[28] However, no correlation of these EXTEM parameters with disease severity scores was found. Small sample size might partially account for this.

Regarding fibrinolysis, severe COVID-19 infection was associated with a trend to increased PAI-1 activity levels which might result in a decreased fibrinolytic activity compared to mild COVID-19 cases, as detected by both EXTEM LI60 and ML variables. It is of note the moderate association between LI60 and procalcitonin levels, supporting the well established, close interrelation among fibrinolysis shutdown and inflammation severity. Fibrinolysis shutdown, as demonstrated by complete lack of clot lysis on TEG, and its correlation with thromboembolic events in severe COVID-19 infection has also been previously noted,[15] while Nougier et al showed that hypofibrinolysis is mainly associated with increased PAI-1 levels in ICU COVID-19 patients, while they reported significantly higher plasma levels of PAI-1 in ICU patients, as compared to non-ICU COVID-19 patients.[27] Moreover, increased PAI-1 levels were measured in the blood of SARS-CoV-infected patients during the 2002–2003 epidemic.[29] However, taking into account that in the current study, PAI1 activity did not significantly differ between ICU COVID and ICU non-COVID patients, it is hard to say, if fibrinolysis shutdown is driven by COVID or just by severity of patient's condition. In any case, COVID-19-related proinflammatory cytokines induce an endothelial injury resulting in primary hemostasis activation and the overexpression of tissue factor.[2] A reduced capacity to cleave and remove fibrin deposits in association with the enhanced procoagulant activity probably contributes to fibrin deposition forming localized/disseminated microthrombi and worse clinical outcome.[24,30]

EXTEM assay was selected to monitor the coagulation system in this clinical setting because EXTEM measurements are valid in the presence of very high heparin concentrations.[31] The fact that VMs assess the kinetics of clot formation and clot lysis simultaneously, providing overall information on coagulation and fibrinolysis equilibrium, renders them more suitable to evaluate the current hemostatic state as compared to conventional coagulation assays. However, they are considered

Table 3

Correlation of laboratory and clinical parameters in COVID positive ICU patients.

	Procalcitonin		SOFA score		Lung Injury score	
Variables	**Spearman's rho**	***P* value**	**Spearman's rho**	***P* value**	**Spearman's rho**	***P* value**
CT	−0.46	.057	−0.13	0.56	−0.31	.16
CFT	0.08	.75	−0.13	0.54	−0.21	.34
LI60	0.49	**.045**	0.20	0.36	0.02	.90
ML	0.40	.10	−0.27	0.22	−0.06	.77
D-dimers	0.38	.10	0.51	**0.011**	0.50	**.013**

CT = clotting time, CFT = clot formation time, ML = maximal lysis, LI60 = lysis index at 60 min.

inappropriate to assess each hemostatic component individually and independently.[32] Based on our results, critically ill COVID-19 patients showed hypercoagulability and fibrinolysis shutdown despite the administration of therapeutic anticoagulant treatment. The clinical significance of this finding remains unknown, since the small sample size and the study design did not allow to estimate its clinical impact. However, this is the first study investigating the haemostatic state of ICU COVID-19 patients on therapeutic anticoagulant treatment. Studies with larger sample sizes and use of specific assays evaluating certain hemostatic components in association with clinical outcome are required to delineate the prognostic role of the intense hypercoagulable profile in severe COVID-19 infection and determine the appropriate anticoagulant treatment strategy.

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