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

An observational study

Argiros E. Tsantes, MD, Frantzeska Frantzescaki, MD, Andreas G. Tsantes, MD, Evdoxia Rapti, PhD, Michalis Rizos, MD, Styliani I. Kokoris, MD, Elizabeth Paramythiotou, MD, Georgios Katsadiotis, MD, Vassiliki Karali, MD, Alkaterini Flevari, MD, Evangelia Chrysanthopoulou, MD, Eirini Maratou, PhD, Elias Kyriakou, MD, Argyri Gialeraki, PhD, Stefanos Bonovas, MD, George Dimopoulos, MD, Iraklis Tsangaris, MD, Apostolos Armaganidis, MD

Abstract

Hypercoagulability and thrombosis remain a challenge in severe coronavirus disease 2019 (COVID-19) infections. Our aim is to investigate the haemostatic 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, and 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 = 0.026, 0.046 and 0.001, respectively). Similarly, a more hypercoagulable state was detected in COVID-19 ICU patients related to non-COVID-19 ICU-based patients 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
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, but that microvascular thrombotic processes may contribute, also. One of the most significant poor prognostic signs in those patients is the development of coagulopathy. 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.

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.

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, 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 hypo-coagulable 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 associated with anticoagulant therapy and disease severity in critically ill COVID-19 patients.

The following parameters were recorded on days 1, 3, 7: PaO2/FiO2, PaCO2, HCO3, white blood cell count, platelets, total and direct bilirubin, 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. 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. 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); lyss 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. 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 ‘Artikon’ 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. 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.

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 ‘Artikon’ 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. 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: PaO2/FiO2, PaCO2, HCO3, white blood cell count, platelets, total and direct bilirubin, 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. 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. 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); lyss 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 obtained from 25 observations based on serial measurements, are COVID-19, ICU or non-ICU, patients. The correlations between Injury score (rho = 0.61 to 0.80 strong correlation, and 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.

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. 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.

In keeping with our findings, 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. Authors have reported the absence of abnormal conventional coagulation tests, which, in turn, supports the absence of consumption coagulopathy. 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.

In the current study, the prognostic value of high D-dimer levels was corroborated by their moderate correlation with SOFA and lung injury score. However, it should be noted that based on our

| 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 = 0.05 |
| Age (years)                                                                                 | 73.5 ± 12.9; 78.0 (67.0–71.0)                                                                 | 68.2 ± 20.4; 73.0 (50.0–88.0) | P < 0.001 |
| PTA-1 activity (s/ml)                                                                       | 2.7 ± 1.6; 2.1 (1.4–4.3)                                                                      | 1.4 ± 0.9; 1.5 (0.8–2.1) | P = 0.07 |
| Procalcitonin (ng/ml)                                                                       | 0.88 ± 1.02; 0.52 (0.23–1.25)                                                                | 0.20 ± 0.27; 0.1 (0.06–0.23) | P < 0.001 |
| INR                                                                                       | 1.19 ± 0.20; 1.10 (1.04–1.32)                                                                | 1.12 ± 0.16; 1.13 (1.03–1.18) | P = 0.45 |
| APTT (seconds)                                                                             | 36.1 ± 5.09; 36.0 (33.0–39.7)                                                                | 39.2 ± 6.7; 37.8 (34.3–41.9) | P = 0.38 |
| Fibrinogen (mg/dl)                                                                          | 486.1 ± 199.9; 439.5 (313.0–459.5)                                                           | 451.6 ± 131.2; 436.5 (399.0–503.0) | P = 0.98 |
| D-dimers (mg × 10^7/ml)                                                                     | 3.85 ± 3.47; 2.42 (1.47–7.32)                                                                | 1.32 ± 1.26; 0.86 (0.54–1.21) | P < 0.001 |
| WBC (count × 10^3/ml)                                                                        | 21.3 ± 30.6; 11.0 (7.1–20.0)                                                                  | 7.1 ± 4.4; 6.7 (4.5–8.2) | P < 0.003 |
| Neutrophils (%)                                                                             | 65.2 ± 26.8; 78.0 (61.0–82.0)                                                                | 60.1 ± 13.8; 60.5 (52.3–68.8) | P = 0.09 |
| Lymphocytes (%)                                                                            | 16.0 ± 21.1; 10.0 (4.0–15.0)                                                                  | 23.2 ± 15.1; 18.4 (14.6–28.8) | P < 0.033 |
| 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 = 0.59 |
| CRP (mg/L)                                                                                 | 78.6 ± 129.5; 48.0 (22.3–128.0)                                                               | 48.9 ± 60.9; 32.3 (9.2–55.0) | P = 0.17 |

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

*APTT = activated partial thromboplastin time, CRP = C-reactive protein, INR = international normalization rate, PAI-1 = plasminogen activator inhibitor, PLTs = platelets, WBCs = white blood cells.
|                         | 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 (sec)**           | 74.1 ± 30.3    | 79.1 ± 21.6   | 80.3 ± 30.5    | 95.3 ± 13.4    | .16       | P=.84 | P=.31 | P=.04 | P=.52 | P=.22 | P=.30 |
| **TG Omax (mm)**        | 98.4 ± 27.5    | 116.5 ± 33.5  | 101.3 ± 27.5   | 114.5 ± 28.2   | .42       | P=.64 | P=.86 | P=.10 | P=.68 | P=.18 | P=.47 |
| **CT (sec)**            | 73.5 ± 15.5    | 70.5 ± 8.5    | 73.5 ± 12.0    | 68 ± 10.6      | .20       | P=.68 | P=.49 | P=.71 | P=.18 | P=.048|
| **CFT (sec)**           | 40.7 ± 13.0    | 63.7 ± 34.7   | 59.5 ± 24.9    | 89.2 ± 24.7    | <.001     | P=.10  | P=.042| P=.001| P=.85 | P=.013| P=.001|
| **A10 (mm)**            | 70.2 ± 8.1     | 60.7 ± 11.0   | 65.0 ± 5.4     | 59.9 ± 3.1     | <.001     | P=.03  | P=.020| P=.031| P=.34 | P=.013| P=.004|
| **MCF (mm)**            | 75.3 ± 5.0     | 69.4 ± 8.5    | 72.4 ± 4.0     | 72.0 ± 7.0     | .42       | P=.04  | P=.046| P=.032| P=.13 | P=.001| P=.001|
| **Alpha angle (°)**     | 82.3 ± 2.1     | 79.7 ± 3.4    | 78.1 ± 4.7     | 72.9 ± 4.1     | <.001     | P=.07  | P=.008| P=.73  | P=.011| P=.001| P=.001|
| **MCE (min)**           | 396.6 ± 98.1   | 258.9 ± 78.9  | 269.1 ± 51.6   | 171.5 ± 35.1   | <.001     | P=.08  | P=.054| P=.002| P=.06 | P=.001| P=.001|

**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).

ETP=endogenous thrombin potential, TG=thrombin generation, CT=clotting time, CFT=clot formation time, A10=cot amplitude at 10 min, MCF=maximum clot firmness, LI60=lysis index at 60 min, MLE=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.

**Note:** The absence of correlation between thrombin generation and disease severity might reflect the presence of a high prothrombotic ischemia-reperfusion injury and the corresponding difficulties in the assessment of thrombin generation with the current methodology.
inappropriate to assess each hemostatic component individually and independently. 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.

**Author contributions**

**Conceptualization:** Argirios Tsantes, Andreas G Tsantes, Michalis Rizos, Stefanos Bonovas, Apostolos Armaganidis.

**Data curation:** Andreas G Tsantes, Evdoxia Rapti, Michalis Rizos, Styliani I Kokoris, Elizabeth Paramythiotou, Georgios Katsiadiotis, Vassiliki Karali, Evangelia Chrysanthopoulou, Eirini Maratou, Argyri Gialeraki, Irakis Tsangaris.

**Formal analysis:** Andreas G Tsantes, Michalis Rizos, Elizabeth Paramythiotou.

**Investigation:** Argirios Tsantes, Frantzeska Frantzeskaki, Evdoxia Rapti, Georgios Katsiadiotis, Vassiliki Karali, Aikaterini Flevari, Elias Kyriakou, Argyri Gialeraki, Stefanos Bonovas, Irakis Tsangaris.

**Methodology:** Andreas G Tsantes, Evdoxia Rapti, Styliani I Kokoris, Elizabeth Paramythiotou, Argyri Gialeraki, Stefanos Bonovas, George Dimopoulos, Irakis Tsangaris.

**Supervision:** Argirios Tsantes, Apostolos Armaganidis.

**Validation:** Styliani I Kokoris, Georgios Katsiadiotis, Aikaterini Flevari, Eirini Maratou.

**Writing – original draft:** Argirios Tsantes, Frantzeska Frantzeskaki, Stefanos Bonovas.

**Writing – review & editing:** Argirios Tsantes, Frantzeska Frantzeskaki, Andreas G Tsantes, Evdoxia Rapti, Michalis Rizos, Styliani I Kokoris, Elizabeth Paramythiotou, Georgios Katsiadiotis, Vassiliki Karali, Aikaterini Flevari, Evangelia Chrysanthopoulou, Eirini Maratou, Elias Kyriakou, Argyri Gialeraki, Stefanos Bonovas, George Dimopoulos, Irakis Tsangaris, Apostolos Armaganidis.

**References**

[1] Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res 2020;220:1–3.

[2] Joly BS, Siguret V, Veyradie A. Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19. Intensive Care Med 2020;46:1603–6.

[3] Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844–7.

[4] Guan WJ, Ni ZY, Hu Y, et al. China medical treatment expert group for COVID-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.

[5] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus – infected pneumonia in Wuhan, China. JAMA 2020;323:1061–9.

[6] Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. Prelease from Journal of Medical Virology 2020;92:791–6.

[7] Taylor FB, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001;86:1327–30.

[8] Levi M, Toh CH, Thachil J, et al. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol 2009;145:24–33.

[9] di Nisco M, Baudo F, Cosmi B, et al. on behalf of the Italian Society for Thrombosis and Haemostasis. Diagnosis and treatment of disseminated intravascular coagulation: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET). Thromb Res 2012;129:e177–84.

[10] Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020;18:1023–6.

[11] Levi M, Meijers JC. DIC: which laboratory tests are most useful. Blood Rev 2011;25:33–7.

[12] Mallett SV, Cox DJ. Thrombelastography. Br J Anaesth 1992;69:307–13.

[13] 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.

[14] Spurza L, Boscolo A, Polletto 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.

[15] Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis shutdown correlates to thromboembolic events in severe COVID-19 infection. J Am Coll Surg 2020;231:193–203.

[16] Mortus JR, Manek SE, Brubaker LS, et al. Thromboelastographic results and hypercoagulability syndrome in patients with coronavirus disease 2019 who are critically ill. JAMA Newl Open 2020;3:e2001192.

[17] Ranieri VM, Rubenfeld GD. The ARDS Definition Task Force.Acute respiratory distress syndrome: The Berlin definition. JAMA 2012; 307:2526–33.

[18] Katsiadiotis, Vassiliki Karali, Aikaterini Flevari, Evangelia Chrysanthopoulou, Eirini Maratou, Elias Kyriakou, Argyri Gialeraki, Stefanos Bonovas, George Dimopoulos, Irakis Tsangaris, Apostolos Armaganidis.

**Table 3**

| Variables | Procalcitonin | SOFA score | Lung Injury score |
|-----------|---------------|------------|-------------------|
|           | 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     |
| CTf       | 0.08           | .75       | −0.15           | 0.54    | 0.21            | .54     |
| LDI60     | 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           | .51       | 0.011           | 0.50    | .013            |         |

CT = clotting time, CTf = clot formation time, ML = maximal lysis, LDI60 = lysis index at 60 min.
Han H, Yang L, Liu F, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med 2020;58:1116–20.

Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934–43.

Brenner T, Schmidt K, Delang M, et al. Viscoelastic and aggregometric point-of-care testing in patients with septic shock: cross-links between inflammation and haemostasis. Acta Anaesthesiol Scand 2012;56:1277–90.

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

Tu W-J, Cao J, Yu L, et al. Clinicolaboratory study of 25 fatal cases of COVID-19 in Wuhan. Intensive Care Med 2020;46:1117–20.

Nougier C, Benoit R, Simon M, et al. Hypofibrinolytic state and high thrombin generation may play a major role in sars-cov2 associated thrombosis. J Thromb Haemost 2020. doi: 10.1111/jth.13016.

Maatman TK, Jalali F, Feizpour C, et al. Routine Venous Thromboembolism Prophylaxis May Be Inadequate in the Hypercoagulable State of Severe Coronavirus Disease 2019. Crit Care Med 2020.

Wu YP, Wei R, Liu ZH, et al. Analysis of thrombotic factors in severe acute respiratory syndrome (SARS) patients. Thromb Haemost 2006;96:100–1.

Ciceri F, Beretta L, Scandroglio AM, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (Micro-CLOTS): an atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc 2020;22:95–7.

Gertler R, Wiesner G, Tassani-Prell P, et al. Are the point-of-care diagnostics MULTIPLATE and ROTEM valid in the setting of high concentrations of heparin and its reversal with protamine? J Cardiothorac Vasc Anesth 2011;25:981–626.

Lampridou M, Sokou R, Tsantes AG, et al. ROTEM diagnostic capacity for measuring fibrinolysis in neonatal sepsis. Thromb Res 2020;192:105–8.