rpth
research & practice
in thrombosis & haemostasis

Rotational thromboelastometry in critically ill COVID-19 patients does not predict thrombosis

Romein W. G. Dujardin MD[1,2] | Gabriel Garcia Rosenbaum MD[3] | Timo C. J. Klercq BSc[1] | Jecko Thachil MD[4] | Nathan D. Nielsen MD[5,6] | Nicole P. Juffermans MD, PhD[1,2]

[1]Department of Intensive Care, OLVG Hospital, Amsterdam, The Netherlands

[2]Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam UMC, Amsterdam, The Netherlands

[3]Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, New Mexico, USA

[4]Department of Haematology, Manchester Royal Infirmary, Manchester, UK

[5]Division of Pulmonary, Critical Care and Sleep Medicine, University of New Mexico School of Medicine, Albuquerque, New Mexico, USA

[6]Department of Pathology, University of New Mexico School of Medicine, Albuquerque, New Mexico, USA

Correspondence
Romein W. G. Dujardin, Department of Intensive Care Medicine OLVG Hospital, Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam UMC, Location AMC, Meibergdreef 9, room G3 – 227, 1105 AZ, Amsterdam, The Netherlands.
Email: r.w.dujardin@amsterdamumc.nl

Handling Editor: Dr Henri Spronk

Abstract

Background: Critically ill COVID-19 patients are in a hypercoagulable state with increased risk of thrombotic complications. Rotational thromboelastometry (ROTEM) is a viscoelastic test with the potential to reflect COVID-19-associated hypercoagulability and may therefore be useful to predict thrombotic complications.

Objective: To investigate the potential of ROTEM profiles to predict thrombotic complications in critically ill COVID-19 patients.

Patients/Methods: Retrospective multicenter cohort study in 113 adult patients with confirmed COVID-19 infection admitted to the intensive care unit (ICU) of two large teaching hospitals in the United States and in the Netherlands. ROTEM profiles of the EXTEM, INTEM, and FIBTEM tracings were measured within 72 h of ICU admission. Thrombotic complications encompass both arterial and venous thromboembolic complications, diagnosed with electrocardiogram, ultrasound, or computed tomography. ROTEM profiles were compared between patients with and without thrombosis. Univariable logistic regression followed by receiver operating characteristic (ROC) curves analysis was performed to identify ROTEM parameters associated with thrombosis.

Results and Conclusions: Of 113 patients, 27 (23.9%) developed a thrombotic event. In the univariable analysis, EXTEM clot amplitude at 10 min (CA10) and EXTEM maximum clot formation (MCF) were associated with thrombosis with a $p < 0.2$ ($p = 0.07$ and $p = 0.05$, respectively). In ROC curve analysis, EXTEM CA10 had an area under the curve (AUC) of 0.58 (95% CI 0.47–0.70) and EXTEM MCF had an AUC of 0.60 (95% CI 0.49–0.71). Thereby, ROTEM profiles at ICU admission did not have the potential to differentiate between patients with a high and low risk for thrombotic complications.

KEYWORDS
COVID-19, critical care, hypercoagulability, thromboelastometry, thrombosis

Essentials

- Severe COVID-19 is associated with hypercoagulability and thrombosis.
- This study assessed the potential of rotational thromboelastometry to predict thrombosis.
- Rotational thromboelastometry reflects hypercoagulability and diminished clot breakdown.
- Rotational thromboelastometry in critically ill COVID-19 patients does not predict thrombosis.

1 | INTRODUCTION

Critically ill patients with coronavirus disease 2019 (COVID-19) are in a hypercoagulable state that is accompanied by a high risk of thrombotic complications, despite intensified thromboprophylaxis or even preemptive therapeutic anticoagulation.[1–4] Thrombotic complications most frequently consist of various forms of venous thromboembolic events but can also present as stroke or myocardial infarction.[2,5–7] Consequently, a tool with the potential to differentiate between patients with a high or low risk of thrombosis will likely improve both the diagnostic efficiency of imaging studies as well as the early initiation of therapeutic anticoagulant therapy.

A low D-dimer has a strong potential to rule out thrombosis, but D-dimer levels can rise due to several pathologies that are common in critically ill patients and as such, D-dimer levels have low specificity in the intensive care unit (ICU).[8,9] In COVID-19 patients, a sudden D-dimer elevation can be useful to predict thrombosis, especially when combined with a concomitant increase in C-reactive protein (CRP).[10,11] However, steroids and immunomodulating therapies such as tocilizumab can suppress CRP rise. Also, many critically ill patients with COVID-19 already have markedly increased D-dimer levels, even in the absence of thrombi. As such, a robust marker for thrombotic events in COVID-19 remains elusive, though potentially highly beneficial.

Viscoelastic tests such as rotational thromboelastometry (ROTEM) have been suggested to have the potential to detect COVID-19-associated hypercoagulability.[12,13] ROTEM parameters may also be useful to distinguish between critically ill COVID-19 patients with a high or a low risk of thrombosis. The aim of this study was to develop a prediction model for thrombotic complications in critically ill COVID-19 patients based on ROTEM profiles at ICU admission.

2 | METHODS

2.1 | Study design and participants

This retrospective multicenter cohort study included all adult patients (≥18 years of age) with a polymerase chain reaction positive for COVID-19 admitted to the ICU of the New Mexico University School of Medicine in Albuquerque or the OLVG Hospital in Amsterdam between May 2020 and January 2021. Patients were excluded for analysis if they received therapeutic anticoagulation, were already diagnosed with a thrombotic event at the time of ROTEM measurement, or if the thrombotic event occurred more than 21 days after ROTEM was performed.

Thrombosis prophylaxis at Amsterdam was nadroparin dosed at 5700 IU once daily for patients with a body weight <100 kg and 7600 IU once daily for patients >100 kg. In Albuquerque, enoxaparin 40 mg/kg was given to patients with a body mass index <35 kg/m^2 or 80 mg/kg in case of a body mass index ≥35 kg/m^2.

Collected laboratory data at ICU admission were white blood cells, hemoglobin, platelet count, CRP, prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer, factor XIII, plasminogen activator inhibitor-1, plasminogen, and antithrombin, processed by the clinical laboratory.

Formal approval was waived by the Medical Ethics Review Committee as the Medical Research Involving Human Subjects Act does not apply to this retrospective study in which measurements were done as part of standard care.

2.2 | Thrombotic events

A thrombotic event was defined as an arterial thrombosis, deep venous thrombosis, pulmonary embolism, catheter-related thrombosis, cardiac cavity thrombus, and organ support membrane filter clotting. Diagnosis of a thromboembolic event was based on ultrasound, performed weekly as standard care to screen for thrombosis in patients, or computed tomography imaging performed on clinical suspicion by the treating physician, or visual inspection of the filter.

2.3 | ROTEM analysis

Early during the pandemic, ROTEM measurements were implemented as part of standard care to better assess the coagulation abnormalities that were apparent in COVID-19 patients. ROTEM analysis was performed within 72 h of ICU admission on a ROTEM Delta (TEM international GmbH) at both sites. Three ROTEM tracings were analyzed in this study: first, the EXTEM tracing which assesses the tissue factor-dependent coagulation pathway. Second, the INTEM tracing that assesses the contact pathway of coagulation and, finally, the FIBTEM tracing that assesses the contribution of fibrinogen to clot strength by inhibiting platelet function in the blood sample. Collected ROTEM parameters included: clotting time, clot amplitude at 10 min (CA10), maximal clot firmness (MCF), the lysis index at 30 min, which represents the remaining percentage of the MCF at 30 min, and maximum lysis. ROTEM results between centers were compared to ensure there were no major differences between sites.

2.4 | Statistical analysis

After assessing for normality using histograms, numerical variables are presented as median with interquartile range; categorical variables are presented as percentage (%). Differences between the group with and without thrombosis were computed using a Mann–Whitney U test for numerical variables and with a χ^2 test for categorical variables. A two-tailed p value <0.05 was considered statistically significant.

Univariable logistic regression was performed to identify ROTEM parameters that were predictive of a thrombotic event. Of all ROTEM variables with a significance of $p<0.2$ in univariable analysis, receiver operating characteristics (ROC) curves were constructed with subsequent calculation of the corresponding area under the curve (AUC).

Statistical analysis was performed with SPSS, version 26.0 (IBM). Figures were made using Prism GraphPad version 9.1.0.

3 | RESULTS AND DISCUSSION

Of 138 patients assessed for eligibility, 25 were excluded based on the exclusion criteria, leaving 113 patients for the analysis. Included patients showed elevated levels of fibrinogen and D-dimer with a concomitant decrease in plasminogen levels compared with reference values (Table 1). Other coagulation markers remained within reference range. Twenty-seven (23.9%) patients developed a thrombotic event, with a median time from ICU admission to thrombosis of 10 days. Venous thromboembolic complications were the most frequently observed thrombotic complication, occurring in 22 patients (81.5%). These presented in 12 patients as a pulmonary embolism, in five patients as deep venous thrombosis, in four patients as filter clotting, and in one patient as central venous catheter-related thrombosis. Three patients (11.1%) had an arterial thrombotic complication, consisting of limb ischemia, an ST-elevation myocardial

TABLE 1 Baseline characteristics of the whole cohort and subgroups of patients with and without a thrombotic event

Variable	All patients N = 113	Thrombotic event[a] N = 27	No thrombotic event[b] N = 86	p value
Age (y)	62 (52–69)	60 (47–69)	64 (53–70)	0.17
Male (%)	75 (66.4%)	17 (63.0%)	58 (67.4%)	0.67
BMI (kg/m^2)	30.6 (26.5–33.7)	31.6 (28.1–38.2)	30.2 (26.4–33.1)	0.23
SOFA score (points)	6 (4–9)	6 (4–9)	6 (4–9)	0.73
Hb [12–18] (g/dl)	13.4 (11.4–14.8)	14.0 (10.8–15.3)	13.1 (11.4–14.5)	0.17
WBC [4.5–11.0] (×10^9/L)	9.0 (6.3–13.6)	9.7 (7.2–13.7)	8.5 (6.2–13.5)	0.67
Platelets [150–450] (×10^9/L)	253 (196–356)	267 (199–368)	250 (195–350)	0.60
PT [11.0–12.5] (s)	13.4 (12.0–15.7)	13.3 (12.6–15.8)	13.4 (11.9–15.6)	0.65
APTT [22–29] (s)	29.0 (26.2–34.5)	27.0 (25.0–32.0)	29.2 (26.8–35.1)	0.085
CRP [<10] (mg/L)	21.7 (11.4–46.0)	20.7 (11.6–33.5)	21.7 (11.4–69.5)	0.69
Fibrinogen [200–400] (mg/dl)	707 (488–760)	750 (643–842)	645 (360–727)	0.003
D-dimer [0.00–0.50] (mcg/ml)	1.44 (0.80–3.65)	1.99 (1.02–5.83)	1.35 (0.70–2.83)	0.51
Factor XIII [70–140] (%)	97 (81–116)	103 (88–117)	95 (80–116)	0.39
PAI-1 [2–46] (ng/ml)	15 (5–31)	18 (8–39)	10 (4–32)	0.42
Plasminogen [150–250] (ng/L)	111 (85–129)	122 (89–134)	105 (84–129)	0.085
Antithrombin [80–140] (%)	116 (97–125)	100 (100–117)	115 (94–125)	0.64
Outcome				
ICU duration (days)	11 (5–23)	18 (7–37)	10 (4–20)	0.01
Mechanical ventilation, n (%)	98 (86.7%)	26 (96.3%)	72 (83.7%)	0.093
Discharged from ICU, n (%)	59 (52.2%)	10 (37%)	49 (57%)	0.07
Died in ICU, n (%)	41 (36.3%)	13 (48.1%)	28 (32.6%)	0.14
Transfer to other ICU, n (%)	13 (11.5%)	4 (14.8%)	9 (10.5%)	0.53

Note: Data presented as median (first–third quartile). Reference ranges for laboratory values provided between square brackets.

Abbreviations: APTT, activated partial thromboplastin time; BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin; ICU, intensive care unit; PAI-1, plasminogen activator inhibitor-1; PT, prothrombin time; SOFA, sequential organ failure assessment; WBC, white blood cell.

[a]Missing values: missing for PT: 1, missing for APTT: 6, missing for CRP: 6, missing for fibrinogen: 13, Missing for D-dimer: 5, missing for factor XIII: 7, missing for PAI-1: 7, missing for plasminogen: 7, missing for antithrombin: 24.

[b]Missing values: missing for PT: 4, missing for APTT: 14, missing for CRP: 21, missing for fibrinogen: 60, missing for D-dimer: 15, missing for factor XIII: 37, missing for PAI-1: 38, missing for antithrombin: 77.

infarction, and an ischemic stroke, respectively. Two patients (7.4%) had both arterial thrombosis as well as venous thromboembolic events. With the exception of a more marked elevation of fibrinogen in the group that developed thrombosis compared with the group without thrombosis, admission coagulation parameters were similar between both groups.

3.1 | Analysis of ROTEM profiles

Compared with reference values, ROTEM profiles showed an increased CA10 and MCF in the EXTEM, INTEM, and most markedly in the FIBTEM trace, with a concomitant hypofibrinolytic profile (Table 2).

In the univariable logistic regression analysis, EXTEM CA10 and EXTEM MCF were identified as possible predictors for a thrombotic event with a $p < 0.2$ ($p = 0.07$ and $p = 0.05$, respectively). However, in a subsequent ROC curve analysis, EXTEM CA10 had an AUC of 0.58 (95% CI 0.47–0.70) and EXTEM MCF had an AUC of 0.60 (95% CI 0.49–0.71; Figure 1), indicating poor diagnostic performance.

Collectively, our results indicate that in critically ill patients with COVID-19, ROTEM profiles indeed reflect increased clot strength with concomitant hypofibrinolysis as noted elsewhere.[14] Interestingly, parameters of clot strength such as CA10 and MCF

were elevated in all ROTEM traces, with the most marked elevation in the FIBTEM assay, whereas parameters of clot initiation remained within the reference range. Increases in CA10 and MCF parameters tended to be more pronounced in the group of patients that developed thrombosis compared with patients without thrombosis, but not to a statistically significant level. We found similar elevations in D-dimer levels between patients with and without thrombosis, which can be explained by the fact that D-dimer elevation is not necessarily specific to thrombus formation but can also be the result of inflammation.[15,16] Overall, however, ROTEM profiles did not differentiate between patients with high and low risk of thrombosis. In fact, AUCs revealed a diagnostic potential comparable to flipping a coin. Therefore, we think it unlikely that early ROTEM testing is a useful thrombosis diagnostic tool in COVID-19, even if larger patient populations were to be investigated. Our findings are in contrast with the results of a previous study that found an association between ROTEM-detected hypofibrinolysis and the occurrence of thrombosis.[17] Possible explanations for this difference are that in that study, ROTEM sigma was used whereas ROTEM parameters in our cohort were determined with ROTEM delta, possibly leading to different results. Alternatively, the case mix differed between studies, with 25% of the included population in the previous study receiving extracorporeal membrane oxygenation, which could have contributed to thrombotic complications.

TABLE 2 Baseline ROTEM parameters of the whole cohort and subgroups of patients with and without a thrombotic event

Variable	All patients $N = 113$	Thrombotic event $N = 27$	No thrombotic event $N = 86$	p value
EXTEM				
CT [38–79] (s)	73 (61–83)	78 (66–82)	71 (61–84)	0.27
CFT [34–159] (s)	58 (46–75)	56 (46–70)	58 (45–78)	0.55
CA10 [43–63] (mm)	68 (61–73)	69 (64–73)	66 (60–73)	0.20
MCF [50–72] (mm)	73 (69–77)	74 (71–77)	72 (67–76)	0.12
Li30 [100–94] (%)	100 (100–100)	100 (100–100)	100 (100–100)	0.86
ML [<15] (%)	4 (1–6)	4(2–6)	4 (0–6)	0.49
INTEM				
CT [100–240] (s)	186 (161–220)	184 (155–199)	187 (163–222)	0.45
CFT [30–110] (s)	57 (49–73)	52 (46–62)	60 (51–78)	0.061
CA10 [43–63] (mm)	67 (51–74)	59 (49–67)	68 (56–74)	0.29
MCF [50–72] (mm)	71 (66–75)	73 (68–78)	70 (65–74)	0.17
Li30 [100–94] (%)	100 (100–100)	100 (100–100)	100 (100–100)	0.53
ML [<15%] (%)	3 (0–6)	3 (1–5)	3 (0–6)	0.78
FIBTEM				
CT (s)	69 (60–80)	72 (64–83)	69 (60–79)	0.24
CA10 (mm)	36 (27–41)	36 (30–44)	34 (25–41)	0.27
MCF [9–25] (mm)	39 (31–45)	40 (32–47)	36 (29–45)	0.26
Li30 (%)	100 (100–100)	100 (100–100)	100 (100–100)	0.52
ML [<15%] (%)	0 (0–3)	1 (0–4)	0 (0–3)	0.16

Note: Data presented as median (first–third quartile). Reference range as provided per manufacturer between square brackets.

Abbreviations: CA10, clotting amplitude at 10 min; CFT, clot formation time; CT, clotting time; Li30, lysis index at 30 min; MCF, maximum clot formation; ML, maximum lysis.
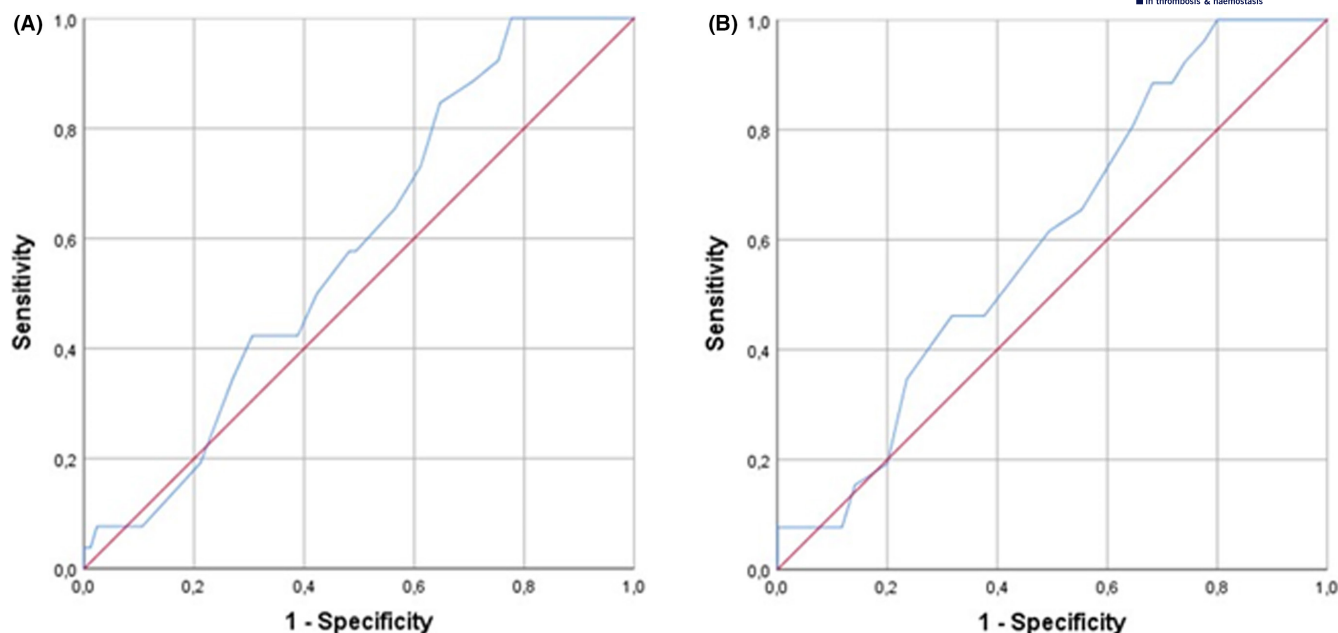
FIGURE 1 Receiver operating characteristics curves with thrombosis as outcome for (A) EXTEM CA10, AUC 0.58 (95% CI 0.47–0.70) and (B) EXTEM MCF, AUC 0.60 (95% CI 0.49–0.71)

The major limitation of this study is the timing of sampling. Because we used ROTEM profiles obtained in the first 3 days of ICU admission, it remains to be determined whether diagnostic performance would be improved if ROTEM was performed on the day of clinical suspicion or event. However, previous research has already demonstrated that ROTEM parameters in critically ill patients measured at consecutive time points do not reveal major changes and it could therefore be argued that repeated testing will not influence diagnostic performance.[18] Also, because of the retrospective design of the study, underreporting of thromboembolic events in patient records and other factors could have led to bias of uncertain nature. Last, racial differences in intrinsic thrombogenicity have been described in the literature but data on sociocultural background were not collected in this study.[19] However, we do not think this affected results of this study because ROTEM parameters reflect individual coagulation profiles and thereby also intrinsic thrombogenicity. Also, this is one of the biggest cohort studies on coagulation and fibrinolysis parameters reported and we therefore feel that our results are generalizable to critically ill patients with COVID-19.

Our results have relevance, implicating that viscoelastic testing using ROTEM early after ICU admission does not have the potential to identify patients at a high risk of thrombosis. Whether a follow-up ROTEM in a later course of the disease has a higher diagnostic performance remains to be elucidated. Of note, study results have been obtained in the first wave. It could be argued that relevance of our results may be diminished due to altered virus strains, vaccination, and evolved treatment of COVID-19. We argue that this is unlikely because acute respiratory distress syndrome due to COVID-19 requiring ICU admission is still the same syndrome, despite altered treatment. Although the number of ICU admissions are decreasing,

it is generally thought that COVID-19 will not disappear entirely, including a protracted course.

In conclusion, this study found no evidence to suggest a predictive capability of ROTEM profiles obtained early in the ICU course to differentiate between patients at high and low risk for thrombotic complications.

AUTHOR CONTRIBUTIONS

R.W.G. Dujardin: data analysis and writing of the manuscript; G. Garcia Rosenbaum: data collection; T.C.J. Klercq: data collection and data analysis; J. Thachil: study design; N. D. Nielsen: study design and data collection; and N.P. Juffermans: study design and writing of the manuscript. All authors provided feedback on the writing of the manuscript.

RELATIONSHIP DISCLOSURE

The authors declare no competing interests.

ORCID

Romein W. G. Dujardin https://orcid.org/0000-0003-1095-3502
Jecko Thachil https://orcid.org/0000-0001-7218-0993

REFERENCES

1. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: incidence, pathophysiology, and management. *Thromb Res*. 2020;194:101-115.
2. Kaptein FHJ, Stals MAM, Grootenboers M, et al. Incidence of thrombotic complications and overall survival in hospitalized patients with COVID-19 in the second and first wave. *Thromb Res*. 2021;199:143-148.

3. Sadeghipour P, Talasaz AH, Rashidi F, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. *JAMA*. 2021;325(16):1620-1630.

4. REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators, et al. Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. *N Engl J Med*. 2021;385(9):777-789.

5. Jenner WJ, Kanji R, Mirsadraee S, et al. Thrombotic complications in 2928 patients with COVID-19 treated in intensive care: a systematic review. *J Thromb Thrombolysis*. 2021;51(3):595-607.

6. Smit JM, Lopez Matta JE, Vink R, et al. Coronavirus disease 2019 is associated with catheter-related thrombosis in critically ill patients: a multicenter case-control study. *Thromb Res*. 2021;200:87-90.

7. Endres P, Rosovsky R, Zhao S, et al. Filter clotting with continuous renal replacement therapy in COVID-19. *J Thromb Thrombolysis*. 2021;51(4):966-970.

8. Minet C, Potton L, Bonadona A, et al. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. *Crit Care*. 2015;19(1):287.

9. Sathe PM, Patwa UD. D dimer in acute care. *Int J Crit Illn Inj Sci*. 2014;4(3):229-232.

10. Rauch A, Labreuche J, Lassalle F, et al. Coagulation biomarkers are independent predictors of increased oxygen requirements in COVID-19. *J Thromb Haemost*. 2020;18(11):2942-2953.

11. Dujardin RWG, Hilderink BN, Haksteen WE, et al. Biomarkers for the prediction of venous thromboembolism in critically ill COVID-19 patients. *Thromb Res*. 2020;196:308-312.

12. Slomka A, Kowalewski M, Zekanowska E. Haemostasis in coronavirus disease 2019 - lesson from viscoelastic methods: a systematic review. *Thromb Haemost*. 2021;121:1181-1192.

13. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost*. 2020;18(7):1747-1751.

14. Bareille M, Hardy M, Douxfils J, et al. Viscoelastometric testing to assess hemostasis of COVID-19: a systematic review. *J Clin Med*. 2021;10(8):1740.

15. Crawford F, Andras A, Welch K, Sheares K, Keeling D, Chappell FM. D-dimer test for excluding the diagnosis of pulmonary embolism. *Cochrane Database Syst Rev*. 2016;2016(8):CD010864.

16. Lippi G, Bonfanti L, Saccenti C, Cervellin G. Causes of elevated D-dimer in patients admitted to a large urban emergency department. *Eur J Intern Med*. 2014;25(1):45-48.

17. 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.

18. Hulshof AM, Brüggemann RAG, Mulder MMG, et al. Serial EXTEM, FIBTEM, and tPA rotational Thromboelastometry observations in the Maastricht intensive care COVID cohort-persistence of hypercoagulability and Hypofibrinolysis despite anticoagulation. *Front Cardiovasc Med*. 2021;8:654174.

19. White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. *Thromb Res*. 2009;123(suppl 4):S11-S17.