

# Thromboelastometry Predicts Thromboembolic Events, Hospital Length of Stay, and Mortality in Patients with COVID-19 Infection and Mild Hypoxemia: A Prospective Observational Study

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**Background:** The aim of this study was to assess changes in hemostasis and associated outcome of hospitalized patients with COVID-19 infection and mild hypoxemia.

**Methods:** Adult patients with COVID-19 infection and hypoxemia admitted to ICU were included in this prospective observational study. The primary outcome was defined as an unfavorable course of the disease if a patient: (1) developed a thromboembolic event while receiving anticoagulation prophylaxis, (2) had prolonged ICU stay, or (3) died. Demographic data, laboratory parameters and thromboelastometry (ROTEM) test results were collected.

**Results:** Twenty-five patients were recruited into the study. There were 16 patients with an unfavorable course of the disease. Compared to the 9 patients in the favorable course group, patients with an unfavorable course had a lower platelet count, median difference of 154 (95% CI, 26 to 223  $\times 10^9/L$ ),  $P = 0.012$ , and lower clot firmness parameters in EXTEM assay: amplitude at 20 minutes (A20), median difference of 7 (95% CI, 2 to 11)  $P = 0.006$ , maximum clot firmness (MCF), median difference of 6 (95% CI, 3 to 10)  $P = 0.006$  and area under the curve (AUC) with a median difference of 671 (95% CI, 244 to 1029)  $P = 0.005$ . They also demonstrated suppression of fibrinolysis: higher lysis index 60, median difference of  $-3$  (95% CI,  $-6$  to 0),  $P = 0.023$ . Results of functional fibrinogen (FIBTEM) assay were similar between the groups.

**Conclusion:** The platelet count and the results of EXTEM assay, but not FIBTEM assay, were associated with the difference in clinical outcome among patients with COVID-19 infection and hypoxemia. The role of platelets in the outcome of COVID-19 infection calls for further investigation. Future studies on adjusting anticoagulant therapy based on the results of viscoelastic testing may be beneficial.

**Keywords:** intensive care unit, thromboelastometry, coronavirus disease 2019, hypoxemia, hemostasis, thrombosis, recovery, mortality

## Background

More than one million people have died in the US from the coronavirus infection (COVID-19) since the beginning of the pandemic.<sup>1</sup> In addition to severe pulmonary and renal injury, abnormality of hemostasis is recognized as a contributing factor to the severity of the disease.<sup>2</sup> Thromboembolic complications were diagnosed in 31% of patients with COVID-19 infection admitted to an intensive care unit, despite anticoagulation therapy.<sup>3</sup> Assessment of hemostasis with traditional plasma coagulation tests (eg, prothrombin time, activated thromboplastin time) is often not helpful because they evaluate only the initial phase of clot formation and frequently do not demonstrate significant abnormality.<sup>4</sup>

Viscoelastic tests (eg, thromboelastography (TEG), rotational thromboelastometry (ROTEM), or ClotPro) were developed to assess in real time all stages (dynamic) of clot formation and fibrinolysis using whole blood samples. In patients with bacterial sepsis abnormal coagulation detected by viscoelastic testing has shown to be of negative prognostic value.<sup>5</sup> Moreover, among critically ill patients with COVID-19 infection, viscoelastic tests have presented signs of hypercoagulation (elevated clot firmness parameters, ie, extrinsic rotational thromboelastometry (EXTEM) MCF > 70 mm) and suppression of fibrinolysis (high lysis indexes, ie, EXTEM LI60 >95%) and also associated with negative prognosis.<sup>6,7</sup> The association between the results of viscoelastic testing and the clinical outcomes may be different in critically ill patients compared to less critically ill hospitalized patients.<sup>8,9</sup> It is currently unknown if the results of viscoelastic testing in patients with COVID-19 infection and mild hypoxemia (patients who did not require mechanical ventilation or received treatment with vasopressors) are associated with severity of the infection and outcome of the disease.

The main objective of the current investigation was to evaluate if assessments of hemostasis by traditional and research thromboelastometry tests among patients with COVID-19 infection and mild hypoxemia performed at the time of admission to the intensive care unit were associated with higher risk of thromboembolic events, prolonged hospitalization or death. We hypothesized that patients with an unfavorable course of COVID-19 disease would demonstrate higher clot firmness parameters using ROTEM analysis compared to the patients with a favorable course of the disease.

## Methods

This single center prospective cohort study complied with the Declaration of Helsinki and was approved by the Lifespan Institutional Review Board (IRB# 1591584, October 27, 2020). Written informed consent was obtained from all participants and the study period extended from January 27, 2021 to April 2, 2021. The study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies.<sup>10</sup>

## Inclusion and Exclusion Criteria

All consecutive patients 18 years or older who were admitted to the step-down unit or intensive care unit of our hospital due to respiratory insufficiency were considered for inclusion on the first morning following admission. Inclusion criteria were a positive PCR COVID-19 test result and respiratory insufficiency requiring supplemental oxygen. Exclusion criteria included patient's refusal to participate or the inability of the patient to consent due to their physical condition. All patients received medications and respiratory treatment (supplemental oxygen and respiratory support) for COVID-19 related hypoxemic respiratory failure and pre-existing medical conditions according to standards of care. No patients received mechanical ventilation prior to enrollment. All patients received prophylactic anticoagulation therapy (heparin or low-molecular-weight heparin).

## Data Collection

Data collection was performed by using a pre-designed collection form and included the following variables: (1) patient demographics (eg, age, gender, body mass index), (2) clinical characteristics (eg, comorbidities and vaccination status), (3) laboratory results (eg, white blood cell count, hematocrit, platelet count, potassium, albumin, glucose, D-dimer, C-reactive protein), and (4) treatment information (eg, antiviral medication, glucocorticoid treatment, antibiotics and anticoagulants). The blood sampling for the routine laboratory panels was performed by the patient's clinical providers. All patients were followed until discharge from the hospital or death.

## Study Grouping

The primary study endpoint was an unfavorable course of the disease defined by the presence of one or more of the following outcomes: (1) development of a thromboembolic event (deep venous thrombosis or pulmonary embolism) while receiving prophylactic anticoagulation (2) prolonged (greater than 30 days) intensive care unit (ICU) stay, and (3) death. It is well documented that patients with respiratory insufficiency due to COVID-19 are at higher risk for

thromboembolic events, mortality, and prolonged ICU stays.<sup>11–13</sup> Patients who did not develop these conditions were assigned to the favorable course of the disease group.

## Thromboelastometry Procedure

Rotational thromboelastometry was performed by trained personnel (DS) using a ROTEM delta device (TEM Innovations GmbH, Munich, Germany). Quality control tests were performed in accordance with manufacturer's recommendations. After obtaining consent, the blood samples for the ROTEM analysis were collected within two to three hours after the administration of the next scheduled dose of the prescribed anticoagulant medication. Venous blood samples (3.6 mL) were collected in blue top tubes containing sodium citrate anticoagulant. The blood specimens were processed at 37°C within 30 minutes of collection.

The following ROTEM tests were performed: (1) EXTEM assay consisting of recombinant tissue factor and Polybrene (heparin inhibitor) added to re-calcified whole blood to activate the extrinsic pathway and initiate coagulation, (2) In the FIBTEM assay, the contribution of platelets to clot formation is eliminated allowing to assess fibrinogen contribution (functional fibrinogen) to hemostasis. It is performed by an addition of recombinant tissue factor, polybrene and platelet inhibitor cytochalasin D added to the whole blood sample to activate the extrinsic pathway while suppressing platelets.

## Thromboelastometry Parameters

The following ROTEM parameters were recorded for all of the assays: (1) Clotting time (CT) in seconds from the beginning of the measurement until the beginning of clotting illustrated by a clot firmness amplitude of 2 mm; (2) Clot formation time (CFT) measured in seconds is the time needed for the clot firmness amplitude to increase from 2 to 20 mm; (3) Alpha angle (ALP) which is tangent to the clotting curve at the 2 mm clot firmness amplitude point; (4) A10 and A20 represent clot amplitude in millimeters reached at 10 and 20 minutes after CT, respectively; (5) Maximum clot firmness (MCF) measured in millimeters is the maximum amplitude of clot firmness reached during testing run time; (6) Lysis index LI30 and LI60 indicates the percentage of the remaining clot firmness in percentage of MCF at 30 and 60 minutes after CT. (7) Maximum lysis (ML) clot firmness reduction in percentage of MCF during the run time of 90 minutes.

ROTEM parameters reflecting the velocity of clot formation are recognized in the European Union; however, they are still considered research parameters in the United States. The research parameters we analyzed included: (1) Maximum clot velocity (maxV) measured in mm/second; (2) time to maximum velocity (maxV-t) is measured in seconds, (3) Area under the velocity curve (AUC) is defined as the area under the first derivative curve from start of the derivative curve until MCF is reached. It correlates to endogenous thrombin potential.<sup>14,15</sup> The velocity parameters MaxV, maxV-t and AUC are the first derivative of the ROTEM curve.

## Statistical Analysis

No statistical power calculation was performed due to the investigative nature of the study. Data were tested for normality using Kolmogorov–Smirnov test. Categorical variables were evaluated by using a Chi-square test of independence or Fisher exact test were appropriate. Non-normally distributed interval and ordinal data are reported as median (interquartile range) and compared among groups by using Mann–Whitney *U*-test. The estimate median difference was calculated using the Hodges-Lehmann method. All statistical tests were two-tailed and a *p* value <0.05 was considered statistically significant. The analyses were performed using Stata 11.1 (Stata Corporation, College Station, TX) and SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina).

## Results

Thirty-one patients were approached and 25 patients agreed to participate in the study. Four patients refused to participate, one patient was unable to consent and one patient was missed by the recruitment team. Sixteen patients were assigned to the unfavorable course group as they developed deep venous thrombosis (*n* = 5), pulmonary embolism (*n* = 3), prolonged hospitalization (*n* = 5) or died during their hospitalization (*n* = 8). Nine patients were assigned to the

favorable course group as they recovered from respiratory failure within three weeks of admission and did not develop any thromboembolic events. One patient quickly recovered from COVID-19 related respiratory failure but died following re-admission due to a perforated bowel in the setting of newly discovered obstructive colon cancer. The patient refused surgery and died 3 days after their initial discharge from the hospital.

Patients' demographics and hospital stay are presented in Table 1. There were no differences between the two study groups in patients' age, body mass index, or gender distribution. There was no difference in the time period from admission to ROTEM sampling between groups with a median time of 3 days (range 1–15). Pre-existing medical conditions were also similar in both groups, with hypertension, cardiovascular disease, and diabetes as the most frequent co-morbidities. Patients in the favorable course group experienced a shorter hospital stay than those patients in the unfavorable course group, median difference of -10 (95% CI, -22 to -1),  $P = 0.014$ .

Patients received antiviral, antibiotics, glucocorticoids, and prophylactic anticoagulation therapy treatment as directed (Table 2). At the time of our study, other treatment modalities such as anti-interleukin-6 receptor monoclonal antibody, tocilizumab was not routinely used for patient care.

The laboratory parameters are presented in Table 3. There was no difference between the groups regarding white blood cell count, hematocrit, potassium, albumin, glomerular filtration rate, blood glucose, D-dimer and C-reactive protein. The

**Table 1** Patient Characteristics and Hospital Stay

	Total COVID Patients (n=25)	Unfavorable Course (n=16)	Favorable Course (n=9)	P value
Age, (years)	66 (62 to 74)	70 (63 to 78)	64 (53 to 71)	0.164
Sex, n (%)				
Male	14 (56)	9 (56)	5 (56)	1
Female	11 (44)	7 (44)	4 (44)	
Body mass index, (kg/m <sup>2</sup> )	30 (25 to 39)	31 (25 to 36)	29 (24 to 40)	0.840
Body mass index > 40, (kg/m <sup>2</sup> )	4 (17)	2 (12)	2 (22)	0.602
Comorbidities, n (%)				
Cardiovascular disease	14 (56)	9 (56)	5 (56)	0.973
Chronic kidney disease	5 (20)	4 (25)	1 (11)	0.621
Diabetes	15 (60)	8 (50)	7 (78)	0.229
Hypertension	20 (80)	12 (75)	8 (89)	0.621
Malignancy	9 (36)	7 (44)	2 (22)	0.401
Smoker*	8 (32)	7 (44)	1 (11)	0.182
COPD/Asthma	10 (28)	6 (25)	4 (33)	0.673
Oxygen-dependent	3 (12)	1 (6)	2 (22)	0.238
OSA	6 (24)	4 (25)	2 (22)	1
COVID vaccine, n (%)				
1 dose	2 (8)	1 (6)	1 (11)	1
2 dose	2 (8)	2 (12)	0	0.520
Length of hospitalization (days)	14 (8 to 26)	20 (11 to 31)	10 (4 to 12)	0.013

**Notes:** Data is presented as median (interquartile range) or n %. \*Previous or current smoker.

**Abbreviations:** BMI, body mass index; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.

**Table 2** Patient Treatment and Prophylactic Anticoagulation Therapy During Hospital Course

	Total COVID Patients (n=25)	Unfavorable Course (n=16)	Favorable Course (n=9)	P value
Medication/Treatment				
Antiviral medication				
Remdesivir	21 (84)	14 (88)	7 (78)	0.524
Glucocorticoid				
Dexamethasone	23 (92)	16 (100)	7 (78)	0.120
Antibiotics	20 (80)	13 (81)	7 (78)	0.835
Anticoagulants				
Lovenox	14 (56)	8 (50)	6 (67)	0.420
Heparin				
SQ	8 (32)	4 (25)	4 (44)	0.317
IV	2 (8)	1 (6)	1 (11)	0.667
Quality of Insurance				
Commercial Payer	17 (68)	10 (63)	7 (78)	0.432
Government Payer	8 (32)	6 (37)	2 (22)	0.432

**Note:** Data is presented as n, %.

**Abbreviations:** SQ, subcutaneous; IV, intravenous.

**Table 3** Laboratory Parameters

	Reference Range	Total COVID Patients (n= 25)	Unfavorable Course (n=16)	Favorable Course (n=9)	P value
White Blood Cell Count, ( $\times 10^9/L$ )	3.5–11.0	8.6 (7.5 to 12.6)	8.9 (7.7 to 12.3)	8.5 (6.8 to 13)	0.651
Hematocrit, (%)	32–45	36 (28 to 40)	36 (31 to 40)	33 (27 to 40)	0.734
Platelet counts, ( $\times 10^9/L$ )	150–400	231 (161 to 348)	191 (132 to 248)	348 (273 to 364)	0.011
Potassium, (mEq/L)	3.6–5.1	3.9 (3.7 to 4.2)	4 (3.5 to 4.3)	3.8 (3.7 to 4.1)	0.777
Albumin, (g/dL)	3.5–5.0	3.2 (2.9 to 3.6)	3.2 (2.7 to 3.5)	3.1 (2.9 to 3.6)	0.929
Glucose, (mg/dL)	67–99	153 (120 to 210)	156 (111 to 208)	153 (139 to 210)	0.865
D-dimer, (ng/mL)	0–300	442 (338 to 1253)	462 (300 to 1046)	356 (338 to 1301)	0.910
C-reactive protein, (mg/L)	0–10	79 (38 to 138)	107 (49 to 144)	54 (35 to 100)	0.246

**Note:** Data is presented as median (interquartile range) or n, %.

median platelet count was within normal range in both groups; however, patients in the favorable course had higher platelet counts compared to patients in the unfavorable course, median difference of 154 (95% CI, 26 to 223  $\times 10^9/L$ ,  $P = 0.012$ ).

In the EXTEM assay, there were signs of elevated coagulation activity in both groups (EXTEM AUC >7000), though patients in the favorable course had significantly higher clot firmness parameters compared to patients in the unfavorable course group: A10 median difference of 8 (95% CI, 2 to 13),  $P = 0.012$ , A20 median difference of 7 (95% CI, 2 to 11),  $P = 0.006$  and MCF median difference of 6 (95% CI, 3 to 10),  $P = 0.006$  (Table 4). They also had higher fibrinolytic activity, which was demonstrated by a lower LI60, median difference of  $-3$  (95% CI,  $-6$  to 0),  $P = 0.023$  and higher ML, median difference of 4 (95% CI, 1 to 7),  $P = 0.018$ . Values of CT, CFT and alfa angle were approaching, but did not

**Table 4** Results of the Thromboelastometry Extrinsic Activation (EXTEM) Assay

Characteristics	Unfavorable Course (n=16)	Favorable Course (n=9)	Hodges Lehmann Estimator of Shift (95% CI)	P value
CT, (sec)	75 (72 to 87)	68 (64 to 73)	-9 (-22 to 0)	0.057
CFT, (sec)	59 (53 to 78)	53 (47 to 56)	-9 (-27 to 0)	0.051
MCF, (mm)	66 (63 to 69)	73 (71 to 74)	6 (3 to 10)	0.006
Alpha angle	78 (76 to 79)	79 (79 to 80)	1 (0 to 5)	0.057
A10	61 (56 to 66)	68 (67 to 69)	8 (2 to 13)	0.012
A20	66 (62 to 69)	73 (70 to 74)	7 (2 to 11)	0.006
LI30	100 (99 to 100)	99 (99 to 100)	0 (-1 to 0)	0.100
LI60	95 (92 to 97)	90 (90 to 94)	-3 (-6 to 0)	0.023
ML	10 (7 to 12)	15 (11 to 16)	4 (1 to 7)	0.018
Max V	22 (18 to 25)	23 (22 to 27)	2 (-1 to 8)	0.221
MaxV-t	100 (91 to 132)	112 (98 to 115)	2 (-27 to 21)	0.799
AUC	6590 (6312 to 6847)	7282 (7032 to 7384)	671 (244 to 1029)	0.005

**Notes:** Data presented as medians (IQR). Comparison between groups was performed Mann-Whitney U-Test and Hodges-Lehmann Estimator.

**Abbreviations:** CT, clotting time; CFT, clotting formation time; MCF, maximum clotting firmness; A10, amplitude 10 minutes after clotting time; A20, amplitude 20 minutes after clotting time; LI30, lysis index 30 minutes after clotting time; LI60, lysis index 60 minutes after clotting time; ML, maximum lysis; Max V, maximum clot velocity; MaxV-t, time to maximum velocity; AUC, area under the curve reflecting the overall platelet aggregation.

reach, significant difference ( $P = 0.057$ ,  $0.051$  and  $0.057$ , respectively). Among the research parameters, clot velocity maxV and maxV-t was not different, but AUC demonstrated a significant increase in the favorable course group, with a median difference of 671 (95% CI, 244 to 1029),  $P = 0.005$ .

In the FIBTEM assay, the parameters A10, A20, and MCF were above the normal limits in both groups but did not demonstrate significant difference between patients who had favorable compared to unfavorable outcomes. Similarly, there was no significant difference in fibrinolytic parameters and AUC in FIBTEM between the groups (Table 5).

**Table 5** Results of the Thromboelastometry Extrinsic Activation (FIBTEM) Assay

Characteristics	Unfavorable Course (n=16)	Favorable Course (n=9)	Hodges Lehmann Estimator of Shift (95% CI)	P value
A10	33 (29 to 37)	35 (28 to 45)	2 (-6 to 12)	0.630
A20	35 (30 to 39)	38 (30 to 49)	2 (-6 to 13)	0.650
MCF, (mm)	36 (32 to 40)	38 (31 to 49)	2 (-6 to 13)	0.630
LI30	100 (100 to 100)	100 (100 to 100)	0 (0 to 0)	0.211
LI60	99 (98 to 100)	96 (95 to 100)	-2 (-5 to 0)	0.057
ML	2 (1 to 3)	7 (0 to 10)	4 (-1 to 8)	0.196
AUC	3611 (3163 to 4057)	3817 (3031 to 4883)	216 (-626 to 1240)	0.671

**Notes:** Data presented as medians (IQR). Comparison between groups was performed Mann-Whitney U-Test and Hodges-Lehmann Estimator.

**Abbreviations:** A10, amplitude 10 minutes after clotting time; A20, amplitude 20 minutes after clotting time; MCF, maximum clotting firmness; LI30, lysis index 30 minutes after clotting time; LI60, lysis index 60 minutes after clotting time; ML, maximum lysis; AUC, area under the curve reflecting the overall platelet aggregation.



## Discussion

This prospective cohort study identified early changes in hemostasis among patients with COVID-19 infection and mild hypoxemia, which were associated with clinical outcomes. The changes in hemostasis were demonstrated among patients who, at the time of ROTEM testing, did not have signs of thrombosis, require mechanical ventilation for respiratory failure, exhibit signs of hemodynamic instability or were treated with vasopressors. Contrary to our expectations, higher pro-coagulation activity detected by thromboelastometry at the time of admission to the ICU was associated with shorter hospitalization, lower incidence of thromboembolic event or death among patients with COVID-19 related hypoxemia. A higher platelet count, higher EXTEM clot firmness parameters (A10, A20 and MCF), a higher EXTEM AUC together with fibrinolytic activity indexes (lower LI60 and higher ML at 90 minutes, but not LI30) were associated with a favorable course of the disease.

Our findings demonstrated that fibrinolytic shutdown is associated with negative prognosis not only in critically ill COVID-19 patients, as reported previously,<sup>6,7,16</sup> but in less severely ill patients with mild hypoxemia, who did not require treatment with vasopressors and/or mechanical ventilation. The association between lower clot firmness parameters, lower (but still within normal limits) platelet count and worse clinical outcome in COVID-19 patients is presented for the first time.

Alterations observed in the hemostasis of patients with COVID-19 infections is not well understood; however, it is likely related to the hyperinflammatory response due to the COVID-19-infection with significant and prolonged increase in the production of cytokines such as IL-6, TNF- $\alpha$ .<sup>17</sup> This hyperinflammatory response is different from the cytokine storm observed in patients with bacterial sepsis or other types of severe respiratory infection and is correlated with the disease severity and patient prognosis.<sup>17</sup> The hyper-production of proinflammatory cytokines is associated with elevated levels of fibrinolysis inhibitors such as plasmin activator inhibitor 1 (PAI-1) and thrombin activated fibrinolysis inhibitor.<sup>18,19</sup> This creates an imbalance between fibrinolysis activators and inhibitors which results in fibrinolytic shutdown. Other potential factors that may contribute to the development of fibrinolysis suppression such as consumption of the pro-enzyme plasminogen or a lack of fibrinolysis activators (tissue plasminogen activator, tPA) have not been demonstrated in patients with COVID-19.<sup>6,7</sup> Furthermore, elevated factor XIII activity is unlikely the cause of fibrinolysis suppression in patients with COVID-19, since COVID-19 infection is associated with acquired factor XIII deficiency.<sup>20</sup>

The hypercoagulable status observed in patients with COVID-19 disease is different from patients with other severe respiratory infections.<sup>21,22</sup> In addition to elevated levels of D-Dimer, elevated clot firmness parameters such as maximum clot firmness (MCF), clot amplitude at 20 minutes (A20) and area under the curve (AUC) were previously reported.<sup>21,22</sup> The increase in proinflammatory cytokines, an elevated release of neutrophil extracellular traps and the expression of tissue factor by monocytes may contribute to the increase in clot firmness parameters.<sup>23</sup> The changes in the dynamics of clot development demonstrated by viscoelastic testing, such as an increase in clot firmness parameters and suppression of fibrinolysis, reflect the prothrombotic profile of hemostasis in patients with COVID-19 infection. It is interesting to note that contrary to our expectations, those changes in the results of viscoelastic testing had an opposite prognostic value among our COVID-19 patients. While fibrinolytic shutdown was associated with an unfavorable outcome, more significantly elevated clot firmness parameters were associated with a favorable outcome.

Since the difference in clot firmness parameters was observed in the EXTEM assay and not in the FIBTEM assay (where contribution of platelets to clot formation is eliminated), we postulate that the difference in hemostasis and clinical outcomes observed between the study groups may be associated with the difference in platelet contribution to clot formation. Moreover, even though the patients in both study groups had normal platelet counts, the patients in the favorable course group had significantly higher platelet count. In two previous reports that investigated platelet function between healthy controls and COVID-19+ patients reported no significant differences between groups.<sup>24,25</sup> At the same time, it has been shown that in patients with COVID-19 infection, an increase in platelet function as assessed by ROTEM platelet ARATEM (stimulation with arachidonic acid) and ADPTM (stimulation with adenosine diphosphate) during a 14-day study period was associated with a favorable outcome.<sup>26</sup> The hyperproduction of proinflammatory mediators seen in patients with COVID-19 infection, such as increased von Willebrand Factor, may affect platelet activity and

contribute to the observed difference in platelet count, ROTEM results and clinical outcomes observed in our study.<sup>27</sup> The role of platelets in the pathogenesis of COVID-19 disease and alteration of platelet function as a possible therapeutic goal will need further investigation.

Here, it is important to consider that COVID-19-associated coagulopathy is a very dynamic process and can change significantly during the course of the disease,<sup>28–30</sup> which may require adjustment of anticoagulation therapy. Indeed, a recent randomized controlled trial did not demonstrate a benefit of therapeutic anticoagulation over prophylactic anticoagulation among critically ill COVID-19 patients.<sup>31</sup> The implementation of a personalized anticoagulation regimen adapted to the individual coagulation status might be advantageous.<sup>32</sup> Thromboelastometry testing may be a viable strategy to optimize coagulation status and the subsequent prognosis for patients with COVID-19 related hypoxemia.

## Limitations

Our study does have several limitations. Due to the small sample size, our statistically significant results should be confirmed with future randomized clinical trials with sample size calculation and power analysis. Second, the absence of dynamic observation of changes in hemostasis. Serial measurements of the hemostasis components would provide a more accurate description of the dynamic changes occurring in hemostasis in this population. However, a larger study population employing continuous or repeated measures over time is needed to assess whether the prognostic value of platelet count and EXTEM clot firmness are modified by bacterial superinfection and organ failure. Last, the COVID-19 infection has affected racial minorities in the United States more severely than any other racial group. The majority of patients in our study were Caucasian and thus our findings cannot be generalized to other racial groups.<sup>33–35</sup>

## Conclusions

Suppression of fibrinolysis, lower (though still within normal limits) platelet count and lower clot firmness parameters (in EXTEM, but not FIBTEM assay) were associated with unfavorable course of the disease in patients with COVID-19 infection and mild hypoxemia. The role in the outcome of COVID-19 infection calls for further investigation. An investigation into adjusting anticoagulant therapy based on the results of viscoelastic testing may be beneficial.

## Abbreviations

ALP, alpha angle; A10, amplitude 10 minutes after clotting time; CCT, conventional coagulation tests; CFT, clot formation time; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CT, clotting time; DVT, deep vein thrombosis; ICU, intensive care unit; INR, international normalized ratio; LI60, lysis index 60 minutes after clotting time; Max V, maximum velocity; MaxV-t, time to maximum velocity; MCF, maximum clot firmness; ML, maximum lysis; ROTEM, rotational thromboelastometry; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TEG, thromboelastogram.

## Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

## Ethics Approval

This study was approved by the Lifespan Institutional Review Board (IRB# 1591584, October 27, 2020). Our study conforms to provisions of the Declaration of Helsinki. Written consent was obtained from all participants.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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## Disclosure

Dr. Klaus Görlinger has been the Medical Director of TEM Innovations GmbH, Munich, Germany since 2012 and reports no other potential conflicts of interest in relation to this work. All other authors (DS, MCK, AL, RS, DP, and GDO) report no conflicts of interest in relation to this work.

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