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ORIGINAL RESEARCH

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Investigation of predictors of bleeding complications in COVID-19 using rotational thromboelastometry (ROTEM®): A retrospective study

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Abstract

Background: Hemorrhagic complications in patients with coronavirus 19 disease (COVID-19) are infrequent but associated with a prognosis. This study aimed to elucidate the risk factors for bleeding complications in patients with COVID-19 using rotational thromboelastometry (ROTEM) parameters and blood tests performed at admission.

Methods: In total, 31 patients with severe COVID-19 treated intensively at Saga University Hospital were included in this study. Patients were divided into two groups according to the presence or absence of hemorrhagic complications. Results from the blood tests performed at admission and during hospitalization, and ROTEM values acquired upon admission, were compared between the two groups.

Results: There were significant differences in ROTEM values upon admission between the bleeding and non-bleeding groups. Receiver operating curve analysis showed that the area under the curve for prothrombin time international normalized ratio (PT-INR) and extrinsically-activated test with tissue factor (EXTEM) amplitude at 10 min (A10) were 0.82 (0.52–0.92) and 0.81 (0.58–0.93), respectively. Logistic regression analysis with PT-INR and EXTEM A10 as factors calculated an odds ratio of 1.94 (1.04–3.62) and EXTEM A10 0.86 (0.71–1.05) for bleeding complications occurrence.

Conclusion: ROTEM may be a sensitive predictor for bleeding complications in patients with COVID-19.

KEYWORDS

anticoagulation, coagulopathy, point of care testing, prothrombin time

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has rapidly spread worldwide after the outbreak in Wuhan, China, in December 2019. The COVID-19 pandemic has had a global, social, and economic impact.[1]

COVID-19 causes acute respiratory distress syndrome by inducing a cytokine storm, which can lead to rapid respiratory deterioration and ultimately, death.[2] In addition, COVID-19 is known to induce coagulopathy by a mechanism different from sepsis-induced coagulopathy or disseminated intravascular coagulopathy.[3,4] Infection with SARS-CoV-2 causes a marked elevation in fibrinogen, D-dimer, and fibrin/fibrinogen degradation products (FDP), leading to hypercoagulability throughout the body and a high incidence of thromboembolism.[5] Therefore, anticoagulants are often used in combination with other drugs to treat COVID-19, even though an increased risk of bleeding complications has been reported.[6]

Although the frequency of bleeding complications in COVID-19 is not as high as that of thromboembolism, it can be a serious complication.[5] A retrospective study by Atschl et al.[7] found that bleeding events were more likely to occur in the COVID-19 death group than in the survival group and that bleeding events are a risk factor for death. Codagnone et al.[8] reported seven cases of hemorrhagic complications in patients with severe COVID-19, resulting in death. It is important to identify patients with COVID-19 at risk for hemorrhagic complications, which are linked to poor outcomes and premature death. In addition to the standard laboratory test (SLT), point-of-care testing (POCT), such as rotational thromboelastometry (ROTEM®; TEM International FZC) and thromboelastography (TEG®; Haemonetics Co.) are known for their ability to predict blood coagulability.[9] The SLTs prothrombin time (PT) and activated partial thromboplastin time (APTT) reflect the response at a time when thrombin production is only 4% of the total amount.[10] PT and APTT may not accurately reflect coagulability in vivo because the plasma component is separated and does not reflect the activity of platelets.[11] POCT using whole blood has the potential to detect coagulopathies that are not detected using SLT coagulation tests.[12]

Since 2013, ROTEM® has been used at our hospital to diagnose patients in intensive care and monitor coagulopathies during hospitalization. This study examined the risk factors for bleeding complications in COVID-19 using the SLTs and ROTEM® parameters.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This was a single-center, retrospective, observational study conducted at the intensive care unit (ICU) of the Saga University Hospital. This hospital is a facility that treats critically ill patients with COVID-19 from the Saga Prefecture who require respiratory support by tracheal intubation or high-flow nasal cannula (HFNC). Thirty-one patients with severe COVID-19 who were admitted to the hospital between April 1, 2021, and August 31, 2021, were included in the study. COVID-19 was diagnosed using SARS-CoV-2 RNA detection or antigen detection. Anticoagulation was performed according to the anticoagulation algorithm with unfractionated heparin developed and proposed by Sato et al.[13] for Japanese patients. This study was approved by the Ethics Committee of Saga University (2021-04-R-08). All participants were given an opportunity to opt-out.

2.2 | Data collection and definition

Basic patient information, medical history, life history, and blood test results were extracted from electronic medical records. The diagnosis of bleeding complications was based on the World Health Organization (WHO) grading system.[14] All patients were divided into two groups: a bleeding group and a group without bleeding complications (no bleeding group). Patients with grade 2 bleeding scores or higher were defined as those with bleeding complications (bleeding group). First, blood test data were collected at admission. For the bleeding group, the highest or lowest value of each laboratory test up to the day of the bleeding event was extracted. For the nonbleeding group, the highest or lowest value of each laboratory test for the entire hospital stay was extracted. For analysis by ROTEM® delta, extrinsically-activated test with tissue factor (EXTEM), internally-activated test with tissue factor (INTEM), and fibrin-based EXTEM and the platelet inhibitor cytochalasin D (FIBTEM)[15] were measured in all patients. The timing of analysis was at ICU admission, the day after admission, and every other day thereafter. The acute physiology and chronic health evaluation II (APACHE II) score was calculated on the day of admission based on the acute physiologic assessment and chronic health evaluation second edition proposed by Kanus et al.[16]

2.3 | Statistical analysis

All statistical analyses were performed using the JMP Pro version 14 software package (SAS Inc.). Continuous variables were described as the median and quartiles. Comparisons of each parameter were performed using Fisher's exact test and Wilcoxon rank-sum test. Statistical significance was set at $p < 0.05$. The distribution of values for factors with a $p < 0.01$ was shown in box plots. Receiver operating characteristic (ROC) curve analysis was performed for the risk factors that showed statistically significant differences between the bleeding and nonbleeding groups at the univariate level.

Youden's index was used to determine the cutoff value, sensitivity, and specificity of each risk factor. Logistic regression analysis was performed using the factors identified as having a high area under the curves (AUCs) in this univariate analysis to search for independent risk factors for bleeding complications occurrence. Bleeding prediction by these combined factors was also performed to obtain AUC, sensitivity, and specificity.

TABLE 1 Baseline characteristics of participants.

Background	
Male, *N* (%)	23 (74.1)
Age, median (IQR), years	59 (50–71)
Height, median (IQR), m	167 (160–175)
Weight, median (IQR), kg	73.5 (59–79.5)
BMI, median (IQR), kg/m^2	25.3 (22.7–28.6)
Occasional drinker, *N* (%)	11 (36.7)
Smoker (%)	8 (25.1)
Charlson index, median (IQR)	1 (0–1)
Severity	
PaO_2/FiO_2 on admission, median (IQR)	180 (130–200)
APACHE II score, median (IQR)	7 (3–16)
SOFA score on admission, median (IQR)	4 (3–7)
Clinical course	
HFNC, *N* (%)	14 (45.1)
Intubation, *N* (%)	17 (54.8)
CRRT, *N* (%)	2 (6.5)
ECMO, *N* (%)	3 (9.7)
Outcome	
Bleeding, *N* (%)	9 (29.0)
Airway hemorrhage, *N* (%)	3 (33.3)
Gastrointestinal bleeding, *N* (%)	3 (33.3)
Urinary system bleeding, *N* (%)	2 (22.2)
Bleeding from the catheter and drain insertion sites, *N* (%)	1 (11.1)
Death in ICU, *N* (%)	8 (25.8)
Length of ICU stay, median (IQR)	10 (7–29)

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; BMI, body mass index; CRRT; continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HFNC, high flow nasal cannula; ICU, intensive care unit; IQR, interquartile range; SOFA sequential organ failure assessment.

3 | RESULTS

The baseline characteristics of the 31 patients included in this study are shown in Table 1. All patients admitted to our hospital required respiratory support with HFNC or oral tracheal intubation. The overall mortality rate was 25.8%, and the median length of hospital stay was 10 (7–29) days. A WHO grade 2 or higher bleeding occurred in 9/31 (29.0%) patients. Bleeding complications occurred in all patients who required oral tracheal intubation. The ROTEM values on the date of admission and hemorrhagic complications onset for the 9 patients with hemorrhagic complications are listed in Supporting Information 1.

TABLE 2 Comparison of patient characteristics between bleeding and nonbleeding groups.[a]

	Bleeding (*N* = 9)	No bleeding (*N* = 22)	*p*
Physical background			
Male, *N* (%)	6 (26.1)	17 (54.8)	0.543
Age, median (IQR), y	63 (51–71)	58 (48–66)	0.2579
Height, median (IQR), m	166 (156–169)	172 (161–175)	0.2395
Weight, median (IQR), kg	74.5 (57.5–79.1)	73 (59–81)	0.7772
BMI, median (IQR), kg/m^2	25.8 (23.7–29.3)	24.9 (21.6–28.9)	0.9106
Occasional drinker, *N* (%)	4 (36.3)	7 (63.6)	0.5628
Smoker, *N* (%)	2 (25)	6 (19.4)	0.7705
Past history			
Charlson index, median (IQR)	1 (0.5–4)	1 (0–1)	0.3367
Myocardial infarction, *N* (%)	1 (11.1)	0	0.112
Congestive heart failure, *N* (%)	1 (11.1)	0	0.112
Peripheral vascular disease, *N* (%)	0	0	
Cerebrovascular disease, *N* (%)	0	0	
Dementia, *N* (%)	0	1 (4.6)	0.5156
COPD, *N* (%)	2 (22.2)	0	0.0223
Connective tissue disease, *N* (%)	1 (11.1)	0	0.112
Peptic ulcer disease, *N* (%)	1 (11.1)	1 (4.55)	0.4994
Mild liver disease, *N* (%)	2 (22.2)	3 (13.6)	0.5552
Diabetes mellitus, *N* (%)	4 (44.4)	5 (22.7)	0.2266
Severe diabetes mellitus, *N* (%)	0	0	
Hemiplegia, *N* (%)	0	0	
Chronic kidney disease, *N* (%)	1 (11.1)	2 (9.1)	0.8629
Solid tumor, *N* (%)	2 (22.2)	1 (4.6)	0.1308
Leukemia, *N* (%)	0	0	
Lymphoma, *N* (%)	0	0	
Severe liver disease, *N* (%)	0	0	
Metastasis, *N* (%)	0	1 (4.6)	0.5156
AIDS, *N* (%)	0	0	
Hypertension (%)	3 (33.3)	11 (50)	0.3973
Medication			
Aspirin (%)	0	0	–
Warfarin (%)	0	0	–

(Continues)

TABLE 2 (Continued)

	Bleeding (*N* = 9)	No bleeding (*N* = 22)	*p*
Anticoagulants (%)	5 (55.5)	10 (45.5)	0.7043
Steroid (%)	9 (100)	13 (59.1)	0.0315
Antiviral (%)	7 (77.8)	13 (59.1)	0.429
IL-6 receptor inhibitor (%)	1 (11.1)	2 (9.1)	1
Severity			
P/F on admission, median (IQR)	180 (111–230)	163 (120–197)	0.6913
APACHE II score, median (IQR)	17 (7.5–23)	6 (3–11.2)	0.0183
JAAM DIC score, median (IQR)	1 (0–3)	0 (0–1)	0.0808
SOFA score on admission, median (IQR)	7 (4–9)	3 (3–5)	0.0806
Clinical course			
Intubation, *N* (%)	9 (100)	8 (36.4)	0.0013
CRRT, *N* (%)	1 (11.1)	1 (4.6)	0.5032
ECMO, *N* (%)	2 (22.2)	1 (4.6)	0.1949
Outcome			
Death in ICU, *N* (%)	4 (50)	5 (21.7)	0.1293
Length of ICU stay, median (IQR)	16 (8–22.5)	10 (5.8–18.5)	0.1272

Abbreviations: AIDS, acquired immunodeficiency syndrome; APACHE II, acute physiology and chronic health evaluation II; BMI, body mass index; COPD, chronic obstructive pulmonary disease; Cre, Creatinine; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IL-6, interleukin 6; IQR, interquartile range; JAAM DIC, Japanese Association for Acute Medicine disseminated intravascular coagulation; P/F, PaO2/FoI2 ratio; SOFA sequential organ failure assessment.

[a]Comparisons were performed using Fisher's exact test and Wilcoxon rank-sum test.

There was no significant difference in patient physical background between the bleeding and nonbleeding groups. With regard to comorbidities, patients in the bleeding group had significantly higher chronic obstructive pulmonary disease and APACHE II scores compared to patients in the nonbleeding group (Table 2).

There were no significant differences in mortality or hospital stay between the bleeding and nonbleeding groups. There was a significant difference in the PT test international normalized ratio (PT-INR) at admission between the two groups. There were also significant differences in EXTEM, coagulation time (CT), EXTEM clot formation time (CFT), EXTEM maximum clot firmness (MCF), EXTEM amplitude at 10 min (A10), INTEM CFT, INTEM MCF, INTEM A10, and FIBTEM A10 between the two groups (Table 3).

PT-INR and EXTEM A10 values differed significantly between the bleeding and nonbleeding groups ($p < 0.01$), as shown in Figure 1. ROC curve analysis showed that the AUC of PT-INR and EXTEM A10 was 0.82 (0.6–0.93) and 0.81 (0.58–0.92), while the cutoff values were 1.14 and 59 mm, respectively (Table 4). Logistic regression analysis with PT-INR and EXTEM A10 as factors calculated an odds ratio of 1.94 (1.04–3.62) and EXTEM A10 0.86 (0.71–1.05) for bleeding complications occurrence. The model for hemorrhagic complications occurrence composed of these combined factors was calculated to have 0.90 AUC (0.71–0.97), 0.89 sensitivity, and 0.82 specificity (Table 4; b)

4 | DISCUSSION

This study found that the frequency of hemorrhagic complications was higher in patients with COVID-19 under endotracheal intubation management. PT-INR and several ROTEM parameters were independent predictors of hemorrhagic complications.

The incidence of thrombosis in COVID-19 is high.[17–21] Bleeding complications are less frequent than thrombosis but are more likely to occur in severe cases of COVID-19.[7] An increased incidence of bleeding events and a significantly higher mortality rate have also been reported in patients receiving therapeutic anticoagulation.[22] Al-Samkari et al.[1] reported that the incidence of bleeding complications in 400 patients with COVID-19 receiving standard-dose prophylactic anticoagulation (144 of whom were critically ill) was 4.8%, and the incidence of major bleeding was 2.3%. In the present study, the incidence of bleeding complications of grade 2 or higher in patients with COVID-19 was as high as 29%, all of which occurred in patients undergoing tracheal intubation. The increased severity of COVID-19 resulted in more severe coagulation abnormalities,[23–25] requiring therapeutic anticoagulation, which may have increased the frequency of hemorrhagic complications. In this study, no significant association was found between anticoagulants initiated at the time of admission and the development of bleeding complications during hospitalization in the bleeding and nonbleeding groups. However, INTEM CT, which is supposed to reflect coagulation abnormalities caused by anticoagulants such as unfractionated heparin, was already abnormal at admission in the bleeding group. This result suggests that the coagulopathy caused by anticoagulants started before admission may have contributed to hemorrhagic complications that occur after admission. In severe cases of COVID-19, both disease-related coagulation abnormalities and anticoagulants used for therapeutic purposes are thought to increase the possibility of bleeding complications, and vigilance is necessary. David et al.[7] reported that a high PT-INR is a risk factor for bleeding complications in COVID-19, which is consistent with the present study results.

ROTEM uses whole blood and has the potential to detect coagulation abnormalities that cannot be detected by conventional SLT.[12] In EXTEM, which mainly reflects extrinsic coagulability, univariate analysis in the bleeding and non-bleeding groups showed significant differences in CT, CFT, MCF, and A10. There were no significant differences in platelets, APTT, fibrinogen, D-dimer, FDP, and other coagulation factors other than PT-INR between the two groups, despite significant differences in multiple ROTEM items. Coagulation abnormalities in COVID-19 can be assessed in more detail using ROTEM.[21,25]

TABLE 3 Comparison of SLTs and ROTEM in bleeding and nonbleeding groups.[a]

	Bleeding (*N* = 9)	No bleeding (*N* = 22)	*p*
SLTs			
Hemoglobin level, median (IQR) g/dl	13.6 (12.6–14.4)	14.1 (12.8–14.6)	0.4992
Min hemoglobin level, median (IQR) g/dl	12.1 (9.3–12.9)	12.3 (11.5–13.8)	0.5709
Platelets, median (IQR) 10^4/μl	16.4 (10.7–22.6)	19.9 (14.9–28.2)	0.1171
Min platelets, median (IQR) 10^4/μl	13.5 (6.9–17.5)	18.5 (12.7–24.1)	0.0502
PT-INR, median (IQR)	1.21 (1.08–1.48)	1.06 (1.0–1.11)	0.0053
Max PT-INR, median (IQR)	1.47 (1.13–1.58)	1.22 (1.18–1.31)	0.184
APTT, median (IQR) s	34.3 (30.7–43.1)	36.3 (32.2–46.1)	0.8961
Max APTT, median (IQR) s	47.8 (36.3–123.9)	54.7 (36.1–82.1)	0.9653
Fibrinogen, median (IQR) mg/dl	392 (358–683)	565 (457–649)	0.1843
Max fibrinogen, median (IQR) mg/dl	381 (363–647)	554 (457–688)	0.1026
Antithrombin III, median (IQR) %	112 (84–124)	96 (88–114)	0.3493
Min Antithrombin III, median (IQR) %	102 (66–124)	86 (79–102)	0.3606
FDP, median (IQR) μg/ml	3.9 (3.3–28.7)	5.1 (3.8–6.9)	0.6166
Max FDP, median (IQR) μg/ml	7.2 (3.4–43.4)	6.7 (3.8–22.2)	0.4594
D-dimer, median (IQR) μg/ml	1.27 (1.13–12.3)	1.19 (1.05–2.3)	0.5138
Max D-dimer, median (IQR) μg/ml	3.9 (1.5–17.6)	2.42 (1.16–8.74)	0.3196
BUN, median (IQR) mg/dl	23.3 (15.7–38.1)	16.8 (15.9–16.8)	0.1637
Max BUN, median (IQR) mg/dl	42.3 (23.8–55.7)	29.6 (22.6–45.6)	0.3607
Cre, median (IQR) mg/dl	0.88 (0.56–1.08)	0.75 (0.58–1.13)	0.7175
Max Cre, median (IQR) mg/dl	0.89 (0.68–1.5)	0.8 (0.7–1.6)	0.6476
Bilirubin, median (IQR) mg/dl	0.6 (0.5–1)	0.6 (0.4–0.6)	0.1448
Max bilirubin, median (IQR) mg/dl	0.7 (0.6–1)	0.7 (0.6–1)	0.9473
AST, median (IQR) U/L	55 (36–79)	55 (34–83)	0.9574
Max AST, median (IQR) U/L	55 (36–64)	70 (46–97)	0.1916
LDH, median (IQR) U/L	458 (331–606)	436 (335–524)	0.7432
Max LDH, median (IQR) U/L	565 (403–917)	497 (402–832)	0.6321
Lactate, median (IQR) mmol/L	1.9 (1.3–2.2)	1.7 (1.2–2.0)	0.6553
Max lactate, median (IQR) mmol/L	2.6 (1.9–2.9)	3 (2.3–3.4)	0.1272
CRP, median (IQR) mg/dl	3.2 (1.1–12.0)	6.6 (3.3–10.6)	0.5175
Max CRP, median (IQR) mg/dl	3.2 (1.1–13.8)	7.0 (3.3–12.6)	0.4094
Ferritin, median (IQR) ng/dl	1301 (944–3077)	1411 (908–1788)	0.8521
Max ferritin, median (IQR) ng/dl	2138 (1351–3336)	1855 (1382–3309)	0.8961
ROTEM[b]			
EXTEM CT (*N*:38–79), median (IQR) s	93 (77–103)	75 (63–85)	0.0235
EXTEM CFT (*N*: 34–159), median (IQR) s	84 (74–115)	68 (65–70)	0.0347
EXTEM MCF (*N*: 50–72), median(IQR) mm	62 (60–66)	68 (65–70)	0.0145
EXTEM A10(*N*: 43–65), median (IQR) mm	53 (50–59)	62 (58–64)	0.0072
EXTEM ML (*N*: –), median (IQR)	21 (12–29)	23 (17–28)	0.4852

(Continues)

TABLE 3 (Continued)

	Bleeding (*N* = 9)	No bleeding (*N* = 22)	*p*
INTEM CT (100–240), median (IQR) s	253 (221–355)	228 (201–255)	0.1509
INTEM CFT (30–110), median (IQR) s	84 (70–156)	67 (57–83)	0.0263
INTEM MCF (50–71), median (IQR) mm	60 (53–65)	65 (62–67)	0.0495
INTEM A10 (44–66), median (IQR) mm	54 (43–58)	60 (55–63)	0.0107
INTEM ML (*N*: –), median (IQR)	19 (11–20)	23.5 (16–25.3)	0.0737
FIBTEM CT (*N*: –), median (IQR) s	75 (69–92)	73 (59–76)	0.1316
FIBTEM MCF (9–25), median (IQR) mm	25 (23–34)	32 (28–38)	0.0606
FIBTEM A10 (7–23), median (IQR) mm	22 (30)	31 (26–36)	0.0275

Abbreviations: A10, amplitude at 10 min; APTT, activated partial thromboplastin time, AST, aspartate aminotransferase; BUN, blood urea nitrogen; CFT, clot formation time; Cre, Creatinine; CRP, C–reactive protein; CT, clotting time; EXTEM, extrinsically-activated test with tissue factor; FDP, fibrin/fibrinogen degradation products; FIBTEM, fibrin-based extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin D; INTEM, intrinsically-activated test using ellagic acid; IQR, interquartile range; LDH, lactate dehydrogenase; MCF, maximum clot firmness; ML, maximum lysis; P/F, PaO2/FiO2 ratio; PT-INR, prothrombin time test international normalized ratio; ROTEM, rotational thromboelastometry; SLT, standard laboratory test.

[a]Comparisons of each parameter were performed using Fisher's exact test and Wilcoxon rank-sum test

[b]Normal ranges (N:) are shown for each item in ROTEM parameters.

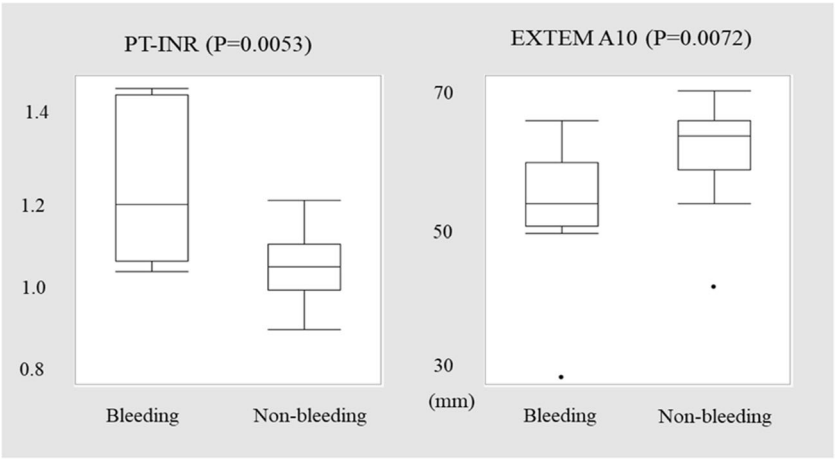

FIGURE 1 Box-and-whisker diagram of PT-INR and EXTEM A10 in bleeding and nonbleeding groups. EXTEM, extrinsically-activated test with tissue factor; PT-INR, prothrombin time test international normalized ratio.

Therefore, ROTEM may be useful in assessing the risk of bleeding complications associated with COVID-19.

In the ROC analysis of factors that showed significant differences at the univariate level, higher AUCs were found for PT-INR and EXTEM A10. EXTEM A10 is a parameter that reflects the influence of platelets and fibrinogen in addition to exogenous coagulation factors. Although platelets and fibrinogen alone were not significantly different between the bleeding and nonbleeding groups in univariate analysis, EXTEM A10, which considers these effects, was different, maybe because it more realistically reflects the coagulation abnormalities in the bleeding group, which may be an advantage to using ROTEM. In addition, referring to the sensitivity and specificity calculated using Youden's index, PT-INR had the disadvantage of high specificity, although it had low sensitivity. In contrast, extrinsic coagulation indices such as EXTEM CT, CFT, MCF, and A10 had lower specificity but tended to be more sensitive than PT-INR. A test method with higher sensitivity may be more useful in predicting hemorrhagic complications because of the possibility of severe outcomes in patients with COVID-19.

Expanding on these results, predictions using a combination of factors were considered. In this study, the bleeding group was small ($n = 9$), so the analysis was limited; however, for reference, we devised a Logistic regression analysis that suggested that PT-INR may be an independent predictor for bleeding complications. Validation of models using these factors also confirmed high AUC, sensitivity, and specificity. It is difficult to conclude that the results are statistically meaningful due to the small number of data in this study. However, the combination of multiple factors may be able to predict hemorrhagic complications with higher accuracy. Further analysis with more data is desirable with the accumulation of more cases in the future.

This study had several limitations. First, it was a single-center, retrospective study with a small sample size. Second, the results of this study may be limited because coagulation capacity is known to vary by race.[26] Third, not all patients underwent regular imaging tests such as computed tomography. We cannot deny the possibility that central hemorrhage was overlooked in patients under sedation and whose level of consciousness could not be confirmed. Fourth,

TABLE 4 ROC analysis of factors that showed statistically significant differences in univariate analysis.

	AUC (95% CI)	Cut off	Sensitivity	Specificity
(a) Univariate analysis[a]				
APACHE II score	0.77 (0.52–0.92)	16	66.7	90.9
PT-INR	0.82 (0.6–0.93)	1.14	66.7	81.8
EXTEM CT	0.76 (0.55–0.9)	74	100	50
EXTEM CFT	0.74 (0.53–0.88)	72	88.9	59.1
EXTEM MCF	0.78 (0.53–0.92)	66	88.9	68.2
EXTEM A10	0.81 (0.58–0.93)	59	88.9	68.1
INTEM CFT	0.76 (0.54–0.89)	65	100	40.9
INTEM MCF	0.73 (0.49–0.88)	60	55.6	81.8
INTEM A10	0.8 (0.58–0.92)	60	100	45.5
FIBTEM A10	0.76 (0.51–0.9)	25	77.8	77.3
(b) Logistic regression analysis[b]				
Model	0.90 (0.71-0.97)		88.9	81.8

Abbreviations: 95% CI, 95% confidence interval; A10, amplitude at 10 min; APACHE II, acute physiology and chronic health evaluation II; AUC, area under the curve; CFT, clot formation time; CT, clotting time; EXTEM, extrinsically-activated test with tissue factor; INTEM, intrinsically-activated test using ellagic acid; MCF, maximum clot firmness; PT-INR, prothrombin time test international normalized ratio; ROC, receiver operating characteristic.

[a]Univariate analysis of risk factors for bleeding complications.

[b]Model; logistic regression analysis using PT-INR and EXTEM A10 as factors.

medication and treatment before the patient was transferred to the hospital were not considered. However, this is the first study to suggest the importance of focusing on ROTEM parameters in predicting bleeding complications in patients with COVID-19.

5 | CONCLUSION

The characteristics of SLT and ROTEM measurements in patients with hemorrhagic complications of COVID-19 were clarified. Our findings suggest that ROTEM use may be more sensitive in predicting the hemorrhagic complications of COVID-19 compared to traditional tests.

AUTHOR CONTRIBUTIONS

Ayaka Matsuoka: Conceptualization; data curation; formal analysis; investigation; methodology; writing–original draft; and writing–review and editing. **Hiroyuki Koami**: Conceptualization and methodology. **Kota Shinada**: Formal analysis and methodology. **Akira Sasaki**: Data curation. **Hirotaka Yamazaki**: Data curation. **Kosuke Mori**: Data curation. **Kento Nakayama**: Data curation and investigation. **Miho Asahi**: Data curation and investigation. **Kunimasa Yoshitake**: Data curation and investigation. **Shogo Narumi**: Data curation and investigation. **Mayuko Koba**: Methodology and supervision. **Atsushi Kawaguchi**: Formal analysis and methodology.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

TRANSPARENCY STATEMENT

We ensured that the manuscript was an honest, accurate, and transparent account of the reported study, that no important aspects of the study were omitted, and that there were no discrepancies with the planned study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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