—Original—

Coagulation Influencing Liberation from Respiratory Support in Patients with Coronavirus Disease 2019 : A Retrospective, Observational Study

Kota Shinada, Toru Miike, Ayaka Matsuoka, Mariko Miyazaki, Taku Goto, Akira Sasaki, Hirotaka Yamazaki, Kosuke Mori, Kento Nakayama, Ryota Sakurai, Miho Asahi, Kunimasa Yoshitake, Shogo Narumi, Mayuko Koba, Hiroyuki Koami and Yuichiro Sakamoto

Department of Emergency and Critical Care Medicine, Faculty of Medicine, Saga University, Saga, Japan

Background: Patients with coronavirus disease 2019 (COVID-19) occasionally develop respiratory failure and coagulopathy. We aimed to determine whether coagulation abnormalities at admission and during the course of hospitalization can predict the liberation from respiratory support in critically ill patients with COVID-19 by combining the results of rotational thromboelastometry (ROTEM) with standard laboratory tests.

Methods: This single-center, retrospective, observational study included 31 consecutive adult patients with COVID-19 who were admitted to the intensive care unit (ICU) and who required respiratory support between April 2021 and August 2021. We divided the patients into two groups according to the liberation from respiratory support and analyzed the differences between the groups.

Results: There were 20 patients in the liberation group and 11 in the non-liberation group. There were no significant differences in the overt disseminated intravascular coagulation scores or abnormal counts in the ROTEM parameters at admission between groups, although there was a significant difference in the highest score in the ICU. The Sequential Organ Failure Assessment and sepsis-induced coagulopathy scores were significantly different between both groups at admission and at the time when the highest values were reported during the ICU stay.

Conclusions: High sepsis-induced coagulopathy scores at admission to the ICU were found to be useful predictors of difficulties in the liberation from respiratory support in patients with severe COVID-19. However, increased overt disseminated intravascular coagulation scores and abnormal counts in the ROTEM parameters during the ICU stay were associated with difficulties in the liberation from respiratory support. (J Nippon Med Sch 2022; 89: 479–486)

Key words: COVID-19, intensive care units, respiratory insufficiency

Introduction

The coronavirus disease 2019 (COVID-19) has resulted in a pandemic on a global scale. Approximately 5%-10% of patients develop severe COVID-19 and require intensive care[1]. Many critically ill patients develop respiratory failure while some patients progress to multiple organ failure[2]. Patients with COVID-19 are more likely to experience coagulopathy and have an increased risk of thrombosis than healthy individuals[3,4]. Elevated D-dimer levels and prolonged prothrombin time (PT) have been reported in the mortality group[5]. Up to 55% of patients with COVID-19 have been shown to exhibit platelet reduction due to coagulopathy, which was also correlated with severity and mortality[6]. Therefore, the International Society of Thrombosis and Haemostasis (ISTH) recommends measuring the D-dimer level, PT, and platelet count of patients with COVID-19[2]. The sepsis-induced coagulopathy (SIC) and overt disseminated intravascular

Correspondence to Kota Shinada, MD, Department of Emergency and Critical Care Medicine, Faculty of Medicine, Saga University, 5–1–1 Nabeshima, Saga, Saga 849–8501, Japan
E-mail: st9137@cc.saga-u.ac.jp
https://doi.org/10.1272/jnms.JNMS.2022_89-506
Journal Website (https://www.nms.ac.jp/sh/jnms/)

coagulation (DIC) scores are clinical scores that comprise these values[7,8]. Increased SIC and overt DIC scores have been shown to be correlated with increased mortality in patients with COVID-19[9].

In addition to standard laboratory tests (SLTs), point-of-care testing (POCT), such as rotational thromboelastometry (ROTEM®; TEM International FZC, Munich, Germany), and thromboelastography (TEG; Haemonetics Corp., Braintree, MA, USA), involve tests for blood coagulation[10]. PT and activated partial thromboplastin time (APTT), which are part of SLTs, can be measured even when thrombin production is only 4% of the required limit[11]. Hence, these measures may not always reflect the coagulation ability of the body accurately because they do not reflect the effect of platelets by separating the plasma[12]. Therefore, POCT using whole blood may help detect coagulopathy that is not detected by SLT[13]. Some investigators have used POCT (e.g., ROTEM and TEG) for patients with COVID-19 and have reported that fibrinogen increases thrombus hardness[14]; however, no studies have performed frequent measurements on patients with severe COVID-19 whose conditions change rapidly every day.

Patients with COVID-19 sometimes develop respiratory failure and require respiratory support. Patients with severe COVID-19 cannot be liberated from respiratory support. Furthermore, respiratory support liberation may be associated with coagulopathy. This study combined the results of the ROTEM delta, a POCT method, using whole blood, with conventional SLTs and examined the indicators of coagulopathy at admission and during the treatment course in patients with severe COVID-19.

To the best of our knowledge, this study was the first to focus on coagulopathy and liberation from respiratory support in patients with severe COVID-19 and report on frequent ROTEM measurements.

Materials and Methods

Patients and Treatment

This single-center, retrospective, observational study was conducted at the Saga University Hospital (Saga City, Japan), designated by the Saga Prefecture to treat patients with COVID-19 who require respiratory support. This study was approved by the Ethics Committee of the Saga University Hospital (Approval no. 2021-04-R-08) and conforms to the provisions of the Declaration of Helsinki, as revised in Fortaleza, Brazil, October 2013. The need for informed consent was waived because of the retrospective nature of the study. We enrolled 31 consecutive adult patients with COVID-19 with severe respiratory failure who were admitted to the intensive care unit (ICU) and required respiratory support between April and August 2021, retrospectively. The severity and treatment were determined using the guidelines of the "Clinical Management of Patients with COVID-19 version 4.2," published by the Ministry of Health, Labour and Welfare[15]. Patients were administered anticoagulant therapy (unfractionated heparin) according to the anticoagulant therapy algorithm proposed by Sato et al.[16]

Data Collection and Definitions

Patient information, including age, sex, and medical history (e.g., hypertension, diabetes, cardiovascular disease, and respiratory disease), was extracted from the electronic medical records. The drugs used during the period from disease onset to ICU admission, were recorded as treatment information. The indicators of coagulation (i.e., platelet count, PT, APTT, fibrinogen, and D-dimer levels) and the indicators of inflammation (white blood cell count, lymphocytes, C-reactive protein, and ferritin) were extracted continuously from admission to discharge. The ROTEM® delta analyzed EXTEM, INTEM, and FIBTEM for all the patients on admission day, the day after admission, and every other day thereafter. The clotting time (CT), clot formation time (CFT), and maximum clot firmness (MCF) were extracted from each measurement. Overt DIC and SIC scores were calculated using the ISTH scoring system (Ding et al. and Taylor et al.)[7,8] and the Sequential Organ Failure Assessment (SOFA) scores were calculated every day from admission to discharge using the European Society of Intensive Care Medicine scoring system[17]. At admission, the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score was calculated according to the recommendations of Knaus et al.[18] Patients were divided into two groups: the liberation group (i.e., patients who could be liberated from respiratory support, including a high-flow nasal cannula (HFNC), at discharge) and the non-liberation group.

Statistical Analysis

All the statistical analyses were conducted using JMP Pro version 14 (SAS Inc., Cary, NC, USA). The categorical variables were compared using the Fisher's exact test. The mean and median differences in the continuous variables between both groups were evaluated using the independent Student's *t*-test and Wilcoxon rank sum test, respectively. The normality of the distribution of the continuous variables was assessed using the Shapiro-Wilk test. The normally distributed data were expressed as

Table 1 Characteristics of the patients in the liberation and non-liberation respiratory support groups

	Liberation group (n = 20)	Non-liberation group (n = 11)	*p* value
Age (years)	50.5 [47.25–58.75]	71 [63–74]	$p < 0.0001$ *
Male	17 (85.0%)	6 (54.6%)	$p = 0.0947$ †
Onset to ICU admission (days)	9 [6.25–11.5]	8 [5–10]	$p = 0.3841$ *
Underlying conditions			
Hypertension	9 (45.0%)	3 (27.3%)	$p = 0.4516$ †
Diabetes	4 (20.0%)	3 (27.3%)	$p = 0.6757$ †
Respiratory disease	1 (5.0%)	2 (18.2%)	$p = 0.2814$ †
Heart disease	0 (0%)	1 (9.1%)	$p = 0.3548$ †
Intervention			
Methylprednisolone	20 (100%)	11 (100%)	
Tocilizumab	20 (100%)	8 (72.7%)	$p = 0.0367$ †
Remdesivir	20 (100%)	11 (100%)	
Mechanical ventilation	6 (30.0%)	11 (100%)	$p = 0.0002$ †
Anticoagulant drug	20 (100%)	11 (100%)	
Average dose of Unfractionated heparin (units/day)	12,000 [11,100–14,400]	9,600 [9,600–16,800]	$p = 0.5023$ *
Length of ICU stay (days)	8 [6–11.75]	18.5 [14.75–21.5]	$p = 0.0031$ *
Complication of pulmonary embolism			
Massive or Submassive	0 (0%)	0 (0%)	
Non-massive	2 (10.0%)	1 (9.1%)	$p = 1.0000$ †
At ICU admission			
White Blood Cell (/μL)	6,060 [4,375–7,775]	8,700 [4,600–10,200]	$p = 0.1664$ *
Lymphocyte (μL)	706 [478.25–1,006.25]	397 [222–1,367]	$p = 0.4089$ *
Platelet (10^3/μL)	219 [169.75–268.5]	145 [120–163]	$p = 0.0007$ *
PT. INR	1.09 [1.0125–1.155]	1.08 [1.05–1.47]	$p = 0.3524$ *
APTT (seconds)	34.1 [31.85–37.925]	37 [32.5–41.5]	$p = 0.3117$ *
Fibrinogen (mg/dL)	554.05 [454.625–726.75]	564.2 [370.7–625]	$p = 0.3020$ *
D-dimer (μg/mL)	1.15 [0.9775–1.555]	1.59 [1.15–2.4]	$p = 0.0692$ *
Ferritin (ng/dL)	1,346 [845.5–2,074]	1,963 [767.5–4,617.5]	$p = 0.5468$ *
CRP (mg/dL)	6.32 [2.5775–13.4675]	6.52 [2.31–10.17]	$p = 0.6497$ *
PaO_2/FiO_2 ratio	169.5 [141.25–199]	135.5 [62.25–215]	$p = 0.3219$ *
APACHE II score	9 [6.25–13.75]	24 [17–26]	$p = 0.0017$ *
GCS	15 [15–15]	3 [3–3]	$p = 0.0098$ *

ICU, intensive care unit; PT/INR, prothrombin time/international ratio; APTT, activated partial thromboplastin time; CRP, C-reactive protein; and APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II

* Based on Wilcoxon rank test results. † Based on Fisher's exact test results.

means (standard deviations), and the non-normally distributed data were expressed as medians. A *p*-value < 0.05 was considered to be statistically significant.

Results

All 31 patients who were admitted during the study period, were included in the analysis. There were 20 patients in the liberation group, and 11 in the non-liberation group. Patients in the non-liberation group were significantly older than those in the liberation group (50.5 [47.25-58.75] years vs. 71 [63-74] years; $p < 0.0001$), although the sex distribution and comorbidities were not significantly different between both groups. Regarding treatment, the non-liberation group were given a lower proportion of tocilizumab (100% vs. 72.7%; $p = 0.0367$), had a higher need of mechanical ventilation (30% vs. 100%; $p = 0.0002$), and had a longer median ICU stay (8 [6-11.75] days vs. 18.5 [14.75-21.5] days; $p = 0.0031$) than the liberation group. The average daily dose was not significantly different between both groups (12,000 [11,100-14,400 units/day] vs. 9,600 [9,600-16,800 units/day]; $p = 0.5023$). None of the patients had a complicated, massive, or submassive pulmonary embolism. Although some patients had a complicated, non-massive pulmonary embolism, there were no significant differences between both groups. Regarding SLT results and clinical scores, the non-liberation group had significantly lower median platelet counts (219 [169.75-268.5] vs. 145 [120-163]; $p = 0.0007$) and higher median APACHE II scores (9 [6.25-13.75] vs. 24 [17-26]; $p = 0.0017$) (**Table 1**) than the libera-

Table 2 Results of rotational thromboelastometry performed at admission

	Liberation group (n = 20)	Non-liberation group (n = 11)	*p* value
EXTEM			
CT	77.5 (67.75–91.25)	91 (67–94)	$p = 0.4204$ *
CFT	67.5 (59–80.75)	84 (71–124)	$p = 0.0334$ *
MCF	67.5 (65–69.75)	65 (60–68)	$p = 0.1203$ *
INTEM			
CT	233 (205–263.5)	240 (204–283)	$p = 0.8526$ *
CFT	67 (58.75–82.75)	84 (73–106)	$p = 0.1600$ *
MCF	65 (61.5–66.75)	60 (55–67)	$p = 0.1852$ *
FIBTEM			
CT	73.5 (65.25–75.75)	76 (55–85)	$p = 0.5615$ *
CFT	81.5 (68.25–136.5)	127 (84–218.5)	$p = 0.2024$ *
MCF	32 (27.25–38.75)	28 (24–39)	$p = 0.2381$ *

CT, clotting time; CFT, clot formation time; and MCF, maximum clot firmness

* Based on the Wilcoxon rank test results.

Table 3 Number of patients with abnormal values for each measurement parameter during the intensive care unit stay

	Lower/Upper limits	Liberation group (n = 20)	Non-liberation group (n = 11)	*p* value
EXTEM				
CT	<38	1 (5%)	0 (0%)	$p = 1.0000$ *
	>79	14 (70.0%)	10 (90.9%)	$p = 0.3717$ *
CFT	<34	0 (0%)	0 (0%)	
	>159	1 (5.0%)	6 (54.6%)	$p = 0.0036$ *
MCF	<50	0 (0%)	5 (45.5%)	$p = 0.0027$ *
	>72	4 (20.0%)	1 (9.1%)	$p = 0.6310$ *
INTEM				
CT	<100	1 (5.0%)	0 (0%)	$p = 1.0000$ *
	>240	17 (85.0%)	11 (100%)	$p = 0.5350$ *
CFT	<30	0 (0%)	0 (0%)	
	>110	8 (40.0%)	9 (81.8%)	$p = 0.0570$ *
MCF	<50	4 (20.0%)	5 (45.5%)	$p = 0.2175$ *
	>72	0 (0%)	1 (9.1%)	$p = 0.3548$ *
FIBTEM				
MCF	<9	0 (0%)	2 (18.2%)	$p = 0.1183$ *
	>25	18 (90.0%)	7 (63.6%)	$p = 0.1510$ *

CT, clotting time; CFT, clot formation time; and MCF, maximum clot firmness

* Based on Fisher's exact test result

tion group. As a component of the APACHE II score, the median Glasgow Coma Scale (GCS) scores were significantly lower in the non-liberation group (15 [15-15] in the liberation group vs. 3 [3-3] in the non-liberation group; $p = 0.0098$) (**Table 1**). The mortality of patients requiring mechanical ventilation was 47.1%. Fourteen patients were able to avoid mechanical ventilation; however, required HFNC. They also had a low PaO_2/FiO_2 ratio and showed no significant differences compared with the intubated patients (180 [142.75-202] in the HFNC patients vs. 140 [70.25-200] in the intubated patients; $p = 0.2120$).

Table 2 shows the measurement results obtained from the ROTEM at admission. There were no differences between both groups in most of the measurement parameters, and only the median EXTEM CFT in the non-liberation group was extended compared to that in the liberation group (67.5 [59-80.75] vs. 84 [71-124]; $p = 0.0334$). **Table 3** shows the number of patients with ab-

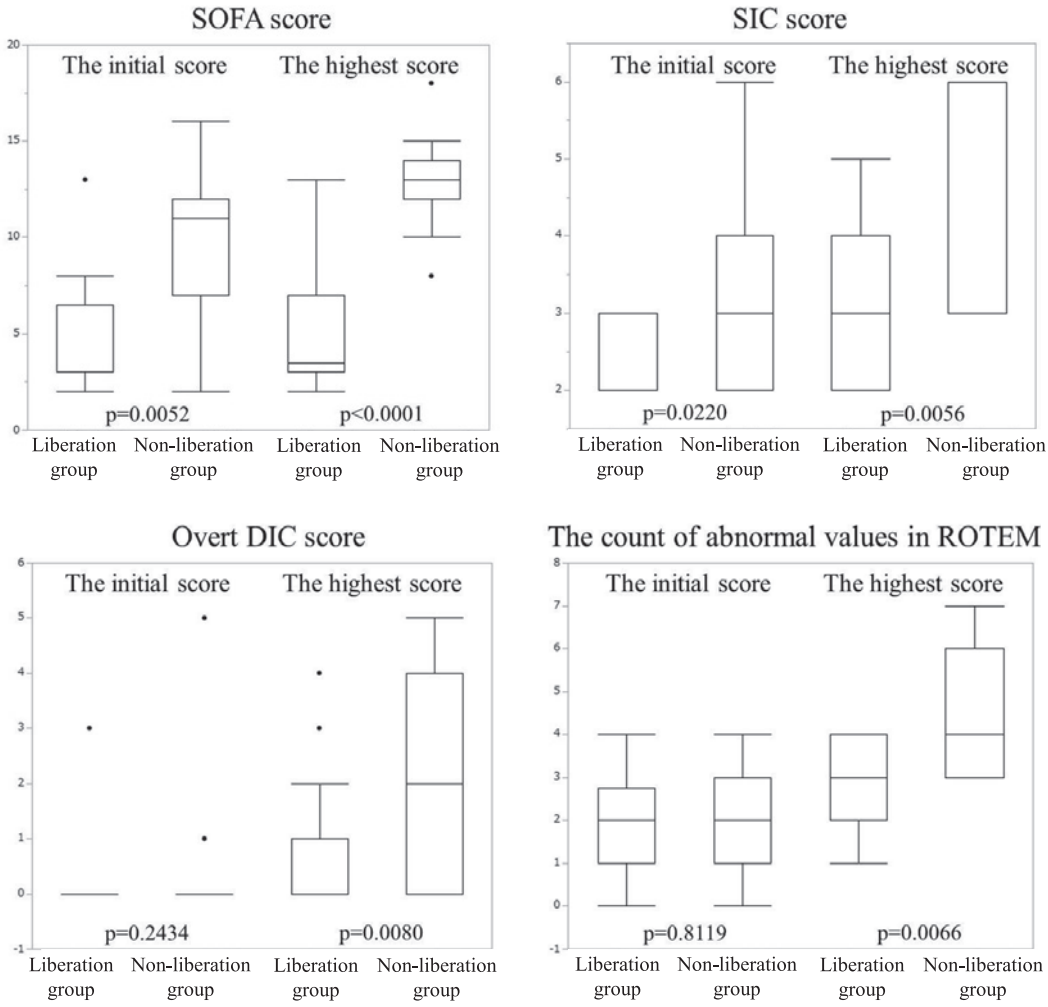

Fig. 1 Changes in the initial and highest SOFA, SIC and overt DIC scores, and the counts of the ROTEM abnormal values.
SOFA, Sequential Organ Failure Assessment; SIC, sepsis-induced coagulopathy; DIC, disseminated intravascular coagulation; and ROTEM, rotational thromboelastometry

normal values (i.e., lower or higher than the normal value limits) for each measurement item during the ICU stay. The proportion of patients with a prolonged EXTEM CFT (5.0% vs. 54.6%; p = 0.0036) and decreased EXTEM MCF (0% vs. 45.5%; p = 0.0027) was significantly higher in the non-liberation group than in the liberation group.

Supplementary Material 1 (https://doi.org/10.1272/jnms.JNMS.2022_89-506) shows the trend of the scores of the SOFA, overt DIC, and SIC scores, and the median abnormal counts on ROTEM parameters for each of both groups, during the ICU stay. **Figure 1** shows the relationship between the median SOFA, overt DIC, and SIC scores; the median abnormal counts on ROTEM parameters; liberation from respiratory support at admission; and the median time of the highest score, during ICU stay. The median overt DIC scores and abnormal counts of the ROTEM parameters at admission were not significantly different (overt DIC score: 0 [0-0] vs. 0 [0-0], p = 0.2434; abnormal counts in ROTEM parameters: 2 [1-2.75] vs. 2 [1-3], p = 0.8119), although significant differences existed between both groups when the highest values were reported in the ICU (median overt DIC score: 0 [0-1] vs. 2 [0-4], p = 0.0080; abnormal counts in the ROTEM parameters: 3 [2-4] vs. 4 [3-6], p =0.0066). Although all the highest scores were reflected, the death date was not. The SOFA and SIC scores were significantly different between both groups at admission and when the highest values were reported during the ICU stay. **Supplementary Material 2** (https://doi.org/10.1272/jnms.JNMS.2022_89-506) shows the Receiver Operating Characteristic curves for the prediction of liberation from respiratory support in the highest scores of SIC, DIC, and the counts of the abnormal values in the ROTEM. The areas under the curve were 0.7955 for the SIC score, 0.7705 for the

overt DIC score, and 0.7909 for the counts of the abnormal values in the ROTEM. Compared with the counts of the abnormal values in the ROTEM, there were no significant differences in both the SIC and overt DIC scores (p = 0.9578 for the SIC score and p = 0.8019 for the overt DIC score).

Discussion

In this study, we investigated whether coagulation abnormalities at admission and during hospitalization can predict the liberation from respiratory support in critically ill patients with COVID-19. When combining the ROTEM and SLT results, we found that a high SIC score at ICU admission, an increased overt DIC score, and the counts of the abnormal values in the ROTEM parameters during the ICU stay were useful in this regard. The mortality rate of patients requiring mechanical ventilation was 47.1%, which was nearly the same as the mortality rate (44.3%) of ICU patients in a previous study by Grasselli et al.[19] Furthermore, no significant bias was observed. The non-liberation group was significantly older, which was similar to the findings of a study that investigated extubation failure in patients with COVID-19[20]. The significant difference in the administration of tocilizumab may be attributed to the inclusion of patients with severe COVID-19 symptoms who may have had occasional infections in the non-liberation group. Fourteen (70%) patients in the liberation group were able to avoid mechanical ventilation. They also had a low PaO_2/FiO_2 ratio of 180 (142.75-202) at ICU admission and required HFNC as respiratory support, which was liberated at discharge.

Previous studies have reported that thrombocytopenia is correlated with severity and mortality[6]. Therefore, the significant difference in the platelet count may have been due to the inclusion of patients with severe COVID-19 symptoms in the non-liberation group. The APACHE II scores have been correlated with the subsequent risk of death in ICU patients[18] and patients with high scores tended to require a tracheostomy[21]. In this study, the median APACHE II score was significantly higher in the non-liberation group. However, the proportion of patients with mechanical ventilation differed between both groups, resulting in extreme differences in the median Glasgow Coma Scale (GCS) scores, which were affected by sedation. The limitations of GCS for critically ill patients with tracheal intubation and sedation have been described in a previous report[22]. The effectiveness of the APACHE II score may be limited in the prediction of liberation from respiratory support, including a HFNC.

In the ROTEM results at admission, the EXTEM CFT alone showed a significant prolongation in the non-liberation group. Since the EXTEM reflects the activation of coagulation in the extrinsic pathway, and the CFT represents the speed of fibrin formation, which is influenced by platelets. It was possible that the EXTEM CFT may have been especially affected. In the non-liberation group, the CT and CFT were prolonged, and the MCF decreased, in all the measurement parameters, although the differences between the groups were not significant. The abnormal values for the prolonged EXTEM CFT and decreased EXTEM MCF during the ICU stay were significantly different between both groups. The findings of the prolonged CFT and decreased MCF in the ROTEM were similar to those reported in previous studies on coagulopathy in patients with fatal COVID-19 symptoms and may be useful parameters for estimating prognosis[23,24].

Unfractionated heparin is an agent that can affect coagulation and fibrinolysis. The dose that was administered was lower in the non-liberation group, although the average daily dose was not significantly different between both groups. Both groups were significantly different with respect to the EXTEM, which was less susceptible to heparin than the other parameters. Coagulopathy due to COVID-19 was more prominent in the non-liberation group than in the liberation group. Therefore, this finding implied that coagulopathy is a factor that makes the liberation from respiratory support difficult. In fact, respiratory support during ICU stay could not be liberated for patients with four or more abnormalities in the ROTEM parameters.

The SOFA score, an indicator of organ damage, is a predictor of successful extubation[25]. In this study, the SOFA score was also significantly different between the two groups at admission, although as with APACHE II, which includes the GCS, the score may have been limited in the prediction of the liberation from respiratory support, including a HFNC. The overt DIC score was not significantly different at admission. However, the highest value during the ICU stay was significantly higher in the non-liberation group, suggesting that coagulopathy was associated with the liberation from respiratory support.

The SIC score is a new scoring system that was devised in 2016 for septic coagulopathy, following the Sepsis-3 Guidelines[26]. The SIC score is more sensitive to coagulopathy than the overt DIC score of patients with sepsis, and it is useful as an early detection tool for DIC with high mortality[27]. The SIC score comprises the platelet count, the PT/international normalized ratio, and a

part of the SOFA score (other than GCS and platelet count). It is unaffected by a sedation-induced decline in consciousness. In this study, the SIC score and highest value during ICU stay were significantly different between both groups. Confirming the SIC score was useful for the early detection of coagulopathy and as a predictor of the liberation from respiratory support.

This study has a few limitations. First, it was difficult to completely distinguish between COVID-19-induced coagulopathy and coagulopathy associated with complications that occurred during the course of hospitalization, such as bacterial infection and bleeding. Such complications are important factors that make the liberation from respiratory support difficult. Hence, it is essential to identify coagulopathy in patients with severe COVID-19. Second, this was a single-center, retrospective, observational study. Therefore, bias may have been present with respect to the selection of patients and the treatment protocols. Moreover, the number of patients was small, and it is possible that there may not have been sufficient detection power. Furthermore, all the patients were Japanese; hence, our results cannot be generalized to patients of other ethnicities. It is recommended that in the future, studies with diverse study samples and treatment protocols, involving multiple facilities, be conducted.

Despite these limitations, to the best of our knowledge, this study was the first to focus on coagulopathy and liberation from respiratory support in patients with severe COVID-19 and report frequent ROTEM measurements.

In conclusion, regarding the coagulation scores of patients with severe COVID-19, a high SIC score at admission to the ICU was found to be a useful predictor of the non-liberation of respiratory support. Moreover, an increase in the overt DIC scores and abnormal values in the ROTEM parameters during the ICU stay were associated with the non-liberation of respiratory support.

Acknowledgements: The authors would like to thank all staff of the Saga University Hospital (Saga City, Japan) for their involvement in the treatment of COVID-19 patients.

Funding: This study did not receive any funding from the private or non-profit sector.

Conflict of Interest: The authors have no potential conflicts of interest to disclose.

References

1. Joly BS, Siguret V, Veyradier A. Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19. Intensive Care Med. 2020;46(8):1603–6.
2. 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(5):102–6.
3. Lippi G, Sanchis-Gomar F, Favaloro EJ, Lavie CJ, Henry BM. Coronavirus disease 2019-associated coagulopathy. Mayo Clin Proc. 2021;96(1):203–17.
4. Thachil J, Srivastava A. SARS-2 coronavirus-associated hemostatic lung abnormality in COVID-19: is it pulmonary thrombosis or pulmonary embolism? Semin Thromb Hemost. 2020;46(7):777–80.
5. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844–7.
6. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta. 2020;506:145–8.
7. Ding R, Wang Z, Lin Y, Liu B, Zhang Z, Ma X. Comparison of a new criteria for sepsis-induced coagulopathy and International Society on Thrombosis and Haemostasis disseminated intravascular coagulation score in critically ill patients with sepsis 3.0: a retrospective study. Blood Coagul Fibrinolysis. 2018;29(6):551–8.
8. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M. Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost. 2001;86(5):1327–30.
9. Long X, Zhang Z, Zou W, et al. Coagulopathy of patients with COVID-19 is associated with infectious and inflammatory markers. Risk Manag Healthc Policy. 2020;13:1965–75.
10. Whiting D, DiNardo JA. TEG and ROTEM: technology and clinical applications. Am J Hematol. 2014;89(2):228–32.
11. Mann KG, Butenas S, Brummel K. The dynamics of thrombin formation. Arterioscler Thromb Vasc Biol. 2003;23(1):17–25.
12. Kashuk JL, Moore EE, Sabel A, et al. Rapid thrombelastography (r-TEG) identifies hypercoagulability and predicts thromboembolic events in surgical patients. Surgery. 2009;146(4):764–72;discussion 772–4.
13. Müller MC, Meijers JC, Vroom MB, Juffermans NP. Utility of thromboelastography and/or thromboelastometry in adults with sepsis: a systematic review. Crit Care. 2014;18(1):R30.
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. Ministry of Health, Labour and Welfare. Clinical Management of Patients with COVID-19 version 4.2 [Internet]. 2021 Feb 19 [cited 2022 Feb 1]. Available from: https://www.mhlw.go.jp/content/000742297.pdf
16. Sato R, Ishikane M, Kinoshita N, et al. A new challenge of unfractionated heparin anticoagulation treatment for moderate to severe COVID-19 in Japan. Glob Health Med. 2020;2(3):190–2.
17. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on

Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–10.
18. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818–29.
19. Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med. 2020;180(10):1345–55.
20. Ionescu F, Zimmer MS, Petrescu I, et al. Extubation failure in critically ill COVID-19 patients: risk factors and impact on in-hospital mortality. J Intensive Care Med. 2021;36(9):1018–24.
21. Matic I, Titlic M, Dikanovic M, Jurjevic M, Jukic I, Tonkic A. Effects of APACHE II score on mechanical ventilation; prediction and outcome. Acta Anaesthesiol Belg. 2007;58 (3):177–83.
22. Teasdale G, Maas A, Lecky F, Manley G, Stocchetti N, Murray G. The Glasgow Coma Scale at 40 years: standing the test of time. Lancet Neurol. 2014;13(8):844–54.
23. Kong R, Hutchinson N, Görlinger K. Hyper- and hypocoagulability in COVID-19 as assessed by thromboelastometry -two case reports. Korean J Anesthesiol. 2021;74(4): 350–4.
24. Mitrovic M, Sabljic N, Cvetkovic Z, et al. Rotational thromboelastometry (ROTEM) profiling of COVID-19 patients. Platelets. 2021;32(5):690–6.
25. Gnanapandithan K, Agarwal R, Aggarwal AN, Gupta D. Weaning by gradual pressure support (PS) reduction without an initial spontaneous breathing trial (SBT) versus PS-supported SBT: a pilot study. Rev Port Pneumol. 2011;17(6):244–52.
26. Iba T, Nisio MD, Levy JH, Kitamura N, Thachil J. New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. BMJ Open. 2017;7(9):e017046.
27. Iba T, Arakawa M, Di Nisio M, et al. Newly proposed sepsis-induced coagulopathy precedes International Society on Thrombosis and Haemostasis overt-disseminated intravascular coagulation and predicts high mortality. J Intensive Care Med. 2020;35(7):643–9.

(Received, December 27, 2021)
(Accepted, March 23, 2022)
(J-STAGE Advance Publication, May 30, 2022)