FDP Fluctuation in Severe COVID-19 is Associated With the Development of Thrombotic or Bleeding Complications and Systemic Coagulopathy

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Abstract

Purpose COVID-19 is sometimes associated with coagulation disorders. In such cases, patients developed elevated D-dimer and fibrin degradation products (FDP) levels, both of which are associated with high risks of thromboembolic complications and poor prognosis. To date, time course changes of FDP values in COVID-19 patients has not been well evaluated. The aim of this study is to evaluate whether FDP fluctuation in COVID-19 patients are associated with systemic coagulopathy.

Methods We retrospectively analyzed the changes in coagulofibrinolytic markers including FDP in 42 COVID-19-ARDS patients. FDP elevation as the fluctuation was defined as follows: 1) FDP>10μg/mL for the first time after admission and 2) 10μg/mL or more elevation after the improvement of the first or subsequent FDP elevations.

Results FDP elevation was observed a total of 30 times in 21 patients (50%). Marked intravascular coagulofibrinolytic activation occurred at the same time as the FDP elevation (soluble fibrin: SF, 27.0 [14.9–80.0] μg/mL; thrombin-antithrombin complex: TAT, 7.5 [2.9–17.8] μg/L; plasmin-α_2-plasmin inhibitor complex: PIC, 2.4 [1.4–4.2] μg/mL). FDP was elevated in all patients who met sepsis-induced coagulopathy (SIC) or disseminated intravascular coagulation (DIC) diagnosis criteria. Thrombotic or bleeding complications developed in 12 patients (28.6%) and were significantly correlated with FDP elevation (*OR* [odds ratio] 4.50, 95% CI [confidence interval] 1.01–20.11, $p = 0.049$). However, there were no significant differences in coagulofibrinolytic activities between the patients with and without SIC or DIC.

Conclusions Coagulation activation which can lead to the development of systemic coagulopathy such as DIC occurred with FDP fluctuation in severe COVID-19 patients. However, there is a limit of the application of existing DIC and SIC diagnosis criteria to COVID-19.

Introduction

Coronavirus Disease-2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) infection, has rapidly become a global pandemic since it was first reported in Wuhan, China in December 2019 [1]. The lung is the primary target organ of SARS-CoV-2, which sometimes leads to the development of acute respiratory distress syndrome (ARDS) [2]. COVID-19 has also been associated with coagulation disorders; such cases are characterized by elevated D-dimer and fibrin degradation products (FDP) levels, which are associated with high risk of thromboembolic complications and poor prognosis [3–7]. In this context, several guidelines recommend routine anticoagulant agents in the treatment of COVID-19 [8, 9].

In its early phase, SARS-CoV-2 is thought to cause a localized coagulation disorder in the lung, which differs from systemic coagulopathies such as sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC) in some key ways [10, 11]. The main features of SIC and DIC, decreased platelet count and prolonged prothrombin time, are uncommon in COVID-19-associated coagulopathy [12,

13]. In spite of these differences, COVID-19 associated coagulopathy can progress to DIC as the underlying disease progresses or due to secondary bacterial infections, resulting in poor prognosis [14].

DIC is characterized by intravascular activation of coagulation with loss of localization [15]. One of its hallmarks is coagulofibrinolytic activity including thrombin generation. In DIC arising out of COVID-19 associated coagulopathy, however, this activity has not been adequately evaluated [16]. We hypothesize that dynamic coagulofibrinolytic responses with the capacity to progress from local to systemic coagulopathy might develop at the times of FDP elevation. The aim of our study is to evaluate time course changes of FDP values in COVID-19 patients and to determine their association with the development of systemic coagulopathy such as DIC and thrombotic or bleeding complications.

Methods

Study design

This was a single-center, retrospective, observational study of COVID-19-ARDS patients at a tertiary care university hospital in Japan. Our university hospital is a local designated center for patients with COVID-19-ARDS in Ehime, Japan. This study complied with the Declaration of Helsinki and was approved by the Institutional Local Ethics Committee for Clinical Studies. The written informed consent requirement was waived because of the retrospective design.

Patients

We included all adult patients who were admitted or transferred to the ICU for COVID-19-induced ARDS from April 2020 to June 2021. As a control group, we also included 10 healthy participants.

During the study period, the patients received various treatments according to changing international recommendations. We considered all patients receiving anticoagulants for thrombosis prophylaxis or treatment at any time during in-hospital stay; the anticoagulant regimen considered of either 1) prophylactic dose: unfractionated heparin (UFH) 10000-15000U/day, adjusted depending on patient status, or 2) therapeutic dose: UFH in the quantity necessary to bring the patient's activated partial thromboplastin time (APTT) to within 1.5 to 2.5 times the control value or direct oral anticoagulants (DOACs). The choice of dosage and the initiation or discontinuation of anticoagulants was left to each physician's discretion depending on the patient's status.

Data collection and definition

COVID-19 was confirmed by reverse-transcription polymerase chain reaction. ARDS was diagnosed according to the Berlin definition [17].

The patients' demographic characteristics, comorbidities, examinations, therapeutic interventions, severity scores and mortality were recorded from the day of admission to our hospital until death, hospital discharge, or transfer to another hospital.

Laboratory tests including coagulofibrinolytic biomarkers such as platelet count (PLT), fibrinogen (Fbg), prothrombin time (PT), fibrin/fibrinogen degradation product (FDP), plasmin-α_2-plasmin inhibitor complex (PIC), thrombin-antithrombin complex (TAT), soluble fibrin (SF) and antithrombin (AT) activity were evaluated during the treatment period at the discretion of the physicians depending on the status of each patient. For the purpose of evaluating FDP fluctuation in the present study, we defined FDP elevation as follows: 1) FDP > 10μg/mL for the first time after admission and 2) 10μg/mL or more elevation after the improvement of the first or subsequent FDP elevations.

We evaluated COVID-19-associated coagulopathy according to the sepsis-induced coagulopathy (SIC) criteria [18], the Japanese Association for Acute Medicine (JAAM)-DIC criteria [19] and the International Society on Thrombosis and Hemostasis (ISTH) overt-DIC criteria [15]. The outcome of COVID-19-associated coagulopathy was assessed in terms of composite of thrombotic and bleeding events. Thrombotic events were defined by composite venous and arterial thrombosis confirmed with imaging. Although screening was not standardized, each patient was actively examined for deep vein thrombosis (DVT) using doppler ultrasound of the limbs, and CT was requested if indicated based on clinical status including the suspicion of thrombosis. Bleeding events were defined according to the ISTH as overt bleeding of any of the following kinds: fatal bleeding, symptomatic bleeding in a critical area or organ (i.e., intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, intramuscular with compartment syndrome), bleeding causing a fall in hemoglobin level of 2g/dL or more or leading to transfusion of two or more units of whole blood or red cells [20].

Statistical analysis

Statistical analysis was performed using the IBM SPSS statistics 22 software package (IBM, Tokyo, Japan). All data are expressed as medians (interquartile range: IQR). Two-group comparisons were performed using the Mann-Whitney U test, while three-group comparisons were performed using the Kruskal-Wallis test. A stratified logistic regression analysis was used to generate odds ratios (ORs) and confidence intervals (CIs) for categorical valuables. A *p* value less than 0.05 was considered as significant.

Results

Patient characteristics

A total of 42 patients (32 males, 10 females) with a median age of 61.5 (IQR: 52.8–69.0) years and a median body mass index (BMI) of 26.7 (23.8–28.3) kg/m^2 were admitted to the ICU with the diagnosis of ARDS induced by COVID-19. By the end of the data collection period, five (11.9%) patients had died, 34 (81.0%) had been discharged alive and three were still hospitalized. Patient characteristics are shown in Table 1.

Hemostatic parameters

Fbg values were significantly higher in COVID-19 patients on admission than in healthy volunteers, though there were no differences between these groups in PLT, PT-INR or AT activity (Fbg, 268 [243–361] vs 521 [464–589] mg/dL, $p < 0.001$; PLT, 18.5 [14.6–35.1] vs 21.6 [14.7–25.0] $\times 10^4/\mu L$, $p = 0.889$; PT-INR, 0.98 [0.91–1.05] vs 0.96 [0.93–1.06], $p = 0.981$; AT activity, 94.7 [82.4–100.8] vs 89.2 [82.6–103.3] %, $p = 0.693$) (Fig. 1). On admission, COVID-19 patients showed slightly higher TAT, SF and PIC values than healthy volunteers, as well as significantly higher FDP values (TAT, 0.9 [0.6–1.1] vs 2.9 [2.2–6.1] μg/L, $p < 0.001$; SF, 3 [3–3] vs 6.8 [3.2–19.8] μg/mL, $p < 0.001$; PIC, 0.9 [0.6–1.0] vs 1.8 [1.1–2.4] μg/mL, $p < 0.001$; FDP, 2.5 [2.0–3.1] vs 5.5 [3.9–8.5] μg/mL, $p < 0.001$) (Fig. 1).

Many patients with severe COVID-19 patients showed rapid and abrupt FDP fluctuations. FDP elevation as defined above was observed a total of 30 times in 21 patients (50%) (Fig. 2). Patient characteristics and laboratory values on admission were similar between COVID-19 patients with and without the FDP elevation, however, all patients who received ECMO and RRT were included in the group with FDP elevation (Table 1). Median levels of coagulofibrinolytic markers such as TAT, SF and PIC were markedly higher at the time of the FDP elevation than they were on admission (TAT, 7.5 [2.9–17.8] μg/L, p = 0.006; SF, 27.0 [14.9–80.0] μg/mL, $p < 0.001$; PIC, 2.4 [1.4–4.2] μg/mL, $p = 0.034$) (Fig. 2).

The association of the FDP elevation with the development of SIC, DIC and thrombotic or bleeding complications

Of all COVID-19 patients, seven patients met the SIC criteria, 11 met the JAAM-DIC criteria and three met the ISTH-overt DIC criteria. All patients who developed SIC or DIC exhibited FDP elevation during the study period (Table 1). However, there were no significant differences in coagulofibrinolytic activities between the patients with and without SIC or DIC (Table 2). Thrombotic or bleeding complications occurred in 12 patients (28.6%); seven patients developed DVT, four developed muscular hemorrhage, three developed gastrointestinal hemorrhage, one developed cerebral hemorrhage, one developed cerebral infarction and one developed splenic infarction (Table 1). A simple logistic regression analysis revealed that the development of thrombotic or bleeding complications was significantly correlated with FDP elevation during the study period (OR [odds ratio] 4.50, 95% CI [confidence interval] 1.01–20.11, $p = 0.049$).

Discussion

In the present study, many cases of severe COVID-19 were complicated with FDP fluctuations during the treatment period. Our results revealed that episodes of marked intravascular coagulofibrinolytic activation coincided in time with episodes of FDP elevation. Furthermore, these FDP elevations were associated with the development of thrombotic or bleeding complications, occasionally leading to meet SIC or DIC diagnostic criteria. This suggests that increasing FDP values may serve as a sign of the systemic progression of coagulofibrinolytic disorders with loss of localization in severe COVID-19. However, there were some differences in coagulofibrinolytic responses between CAC and SIC or DIC. Our results demonstrated that coagulation activation which can cause the development of systemic

coagulopathy such as DIC, and suggested the limitation of the application of existing DIC and SIC diagnosis criteria to COVID-19.

In this study we evaluated coagulofibrinolytic responses by assessing changes in plasma biomarkers in ARDS-COVID-19 patients. We measured TAT and SF values as markers for coagulation activation and PIC levels as a marker for fibrinolytic activation. Because TAT is a covalent stable stoichiometric 1:1 complex of thrombin and antithrombin, TAT values reflect intravascular thrombin formation. SF, a marker of hypercoagulation, is generated during thrombin-fibrinogen reactions. PIC is a product of the inactivation of activated plasmin by α_2 plasmin inhibitor, which represents fibrinolytic activity. The half-lives of TAT, SF and PIC are short, so these markers represent real time profiles of coagulofibrinolytic activity. Measuring these markers is essential for accurately evaluating systemic intravascular coagulofibrinolytic pathophysiology in COVID-19 patients [21]. Activated plasmin lyses fibrinogen and fibrin to make FDP, which reflects primary and secondary fibrinolysis. This means that, especially in enhanced fibrinolytic conditions, FDP is a more sensitive indication of fibrinolysis than D-dimer, which reflects secondary fibrinolysis [4, 6, 21]. FDP values increase when coagulofibrinolytic activation occurs, we measured marker levels during episodes of FDP elevation and compared them to the levels observed on admission, i.e., not during FDP elevation.

COVID-19-associated coagulopathy, CAC has been associated with coagulation disorders; such cases are characterized by elevated D-dimer and fibrin degradation products (FDP) levels [3–7]. In the early stages of COVID-19, CAC is thought to occur and be localized overwhelmingly in the lungs [10, 11, 21–23]. On the other hand, CAC is associated with the development of systemic thromboembolic complications, suggesting a risk of progression from local to systemic coagulopathy [3–7, 14]. It is known that sepsis following an acute infection can be complicated by systemic coagulopathy, DIC [15]. CAC overlaps with this sepsis-associated coagulopathy, although there are some differences between these two pathophysiologies [14, 16, 22].

One of the manifestations of DIC is dysregulated intravascular coagulation [15], excessive thrombin generation has not been definitively established in COVID-19 patients [16]. High fibrinogen levels and thromboelastographic findings have revealed that hypercoagulation sometimes occurs in connection with COVID-19 [24, 25]. While some studies have reported mild intravascular coagulation activation on admission [23, 26, 27], it remains unclear whether this mild response causes the development of DIC. As in previous reports, no crucial coagulofibrinolytic activation was observed on admission in this study. However, our results revealed that many patients with severe COVID-19 exhibited FDP fluctuations during the treatment period. Furthermore, our results clearly demonstrated that significant intravascular coagulofibrinolytic activations, as evidenced by TAT, SF and PIC levels, coincide with episodes of FDP elevation, a finding that supports similarity between the pathogenesis of COVID-19-associated coagulopathy and that of DIC. Many studies have assessed coagulofibrinolytic status in COVID-19 patients on admission, but FDP elevations occur not only at the time of admission, but also in the middle of treatment. Furthermore, many of the FDP elevations observed in this study were fast and transient

responses. Thus, there is a possibility that we may miss or underestimate these rapid responses if the markers are not measured regularly.

Our results demonstrated that severe COVID-19 patients could suffer coagulofibrinolytic activation with FDP elevation and also the thrombotic or bleeding complications, which is consistent with the definition of DIC. On the other hand, regarding consumption coagulopathy, it is known that decreased platelet count and a prolonged prothrombin time are uncommon or mild in COVID-19, in contrast to both SIC and DIC [12, 13]. In fact, we found that patients with severe COVID-19 have preserved PLT and PT-INR values. Moreover, in this study, the application of existing diagnosis criteria for DIC and SIC to CAC did not show certain tendency for coagulofibrinolytic responses; further these responses did not match a suppressed-fibrinolytic phenotype of DIC often seen in sepsis. Systemic coagulofibrinolytic activation due to disease exacerbation or secondary bacterial infection thought to cause a progression from local coagulopathy to DIC in COVID-19 [14]. However, the existing diagnosis criteria for DIC and SIC could not evaluate the state of CAC adequately. The rate of COVID-19 complicated by DIC remains rare, but its mortality rate is very high [4, 12]. Furthermore, COVID-19 patients show a markedly high incidence of thrombotic and bleeding complications in connection with minimal coagulofibrinolytic abnormalities. We need to develop a specific diagnostic method for COVID-19-associated coagulopathy. Even though thrombus formation or bleeding can directly cause coagulofibrinolytic activation and FDP elevation, we cannot assume that local thrombosis events such as DVT lead to the development of DIC. It is likely that marked FDP elevation might be a sign reflecting the progression from local coagulopathy to DIC. We should assess the usefulness of FDP fluctuations as signs for early detection of the development of DIC and thrombotic or bleeding complications during the treatment period.

Several limitations of the present study should be addressed. First, the sample size of this observational study was small, so even though we obtained the present results using appropriate statistical methods, larger-scale studies are still needed to clarify our hypotheses. Second, imaging for the detection of thrombotic events was at the discretion of the treating clinician, which may have introduced additional bias and skewed the reporting of thrombotic events. Lastly, possible causes of FDP elevation other than SARS-CoV-2 infection, such as bacterial infection and anticoagulant prophylaxis, were not assessed in this study. Accordingly, a future study considering other factors affecting COVID-19-associated coagulopathy is needed.

Conclusion

Coagulation activation which can lead to the development of systemic coagulopathy such as DIC occurred with FDP fluctuation in severe COVID-19 patients. However, there is a limit of the application of existing DIC and SIC diagnosis criteria to COVID-19.

Abbreviations

APTT: activated partial thromboplastin time; ARDS: acute respiratory distress syndrome; AT: antithrombin; COVID-19: Coronavirus Disease-2019; DIC: disseminated intravascular coagulation; DVT: deep vein thrombosis; Fbg: fibrinogen; FDP: fibrin/fibrinogen degradation product; PIC: plasmin-α_2-plasmin inhibitor complex; PT: prothrombin time; SF: soluble fibrin; SIC: sepsis-induced coagulopathy; TAT: thrombin-antithrombin complex

Declarations

Ethics approval and consent to participate

This study was approved by the Local Institutional Ethics Committee for Clinical Studies at Ehime University Graduate School of Medicine. The written informed consent requirement was waived because of the retrospective design.

Consent for publication

Not applicable.

Availability of data and materials

The datasets for the current study are available from the corresponding author upon reasonable request.

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Authors' contributions

HM, SM and NS conceived and designed the study. HM, MO, YH, SA, NM, YN, SK, SO and MO prepared the data for analysis. HM and SM conducted the data analysis. SK, JT and NS assisted with the interpretation of the results and supervised the study. HM and JT drafted the article. All authors read and approved the manuscript. HM and JT take responsibility for the paper as a whole.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Patient characteristics and outcomes

	All patients N=42	FDP elevation(+) N=21	FDP elevation(-) N=21	p value
Characteristics				
Age, years	61.5 (52.8-69.0)	63.0 (54.0-70.0)	57.0 (50.5-66.5)	0.279
Sex (Male/Female), n (%)	32 (76.2) / 10 (23.8)	18 (85.7) / 3(14.3)	14 (66.7) / 7 (33.3)	0.147
BMI, kg/m^2	26.7 (23.8-28.3)	26.6 (23.6-28.1)	26.7 (24.2-28.9)	0.538
Comorbidities, n (%)				
Heart diseases	3 (7.1)	2 (9.5)	1 (4.8)	0.549
Hypertension	17 (40.5)	10 (47.6)	7 (33.3)	0.346
Diabetes	15 (35.7)	8 (38.1)	7 (33.3)	0.747
Hyperlipidemia	11 (26.2)	5 (23.8)	6 (28.6)	0.726
Chronic renal failure	1 (2.4)	1 (4.8)	0 (0.0)	0.311
Respiratory diseases	2 (4.8)	1 (4.8)	1 (4.8)	1.000
Liver cirrhosis	0 (0.0)	0 (0.0)	0 (0.0)	NA
Neurological disorders	1 (2.4)	0 (0.0)	1 (4.8)	0.311
Time from illness onset to admission, days	8 (6-11)	8 (6-12)	8 (7-11)	0.640
PaO_2:FiO_2 ratio	81.6 (59.4-162.2)	76.4 (58.1-157.7)	109.1 (60.0-169.8)	0.414
Respiratory support, n (%)				
Invasive positive pressure ventilation	39 (92.9)	20 (95.2)	19 (90.5)	0.549
ECMO	5 (11.9)	5 (23.8)	0 (0.0)	0.017
Renal replacement therapy, n (%)	4 (9.5)	4 (19.0)	0 (0.0)	0.035
Medication, n (%)				
Favipiravir	12 (28.6)	7 (33.3)	5 (23.8)	0.495
Remdesivir	32 (76.2)	14 (66.7)	18 (85.7)	0.147
Hydroxychloroquine	2 (4.8)	2 (9.5)	0 (0.0)	0.147
Tocilizumab	2 (4.8)	0 (0.0)	2 (9.5)	0.147

Baricitinib	4 (9.5)	1 (4.8)	3 (14.3)	0.293
Steroid	41 (97.6)	20 (95.2)	21 (100.0)	0.331
Unfractionated heparin	41 (97.6)	20 (95.2)	21 (100.0)	0.331
Laboratory values on admission				
White blood cell, /μL	8450 (5300-12625)	9000 (5350-12800)	7200 (5050-11400)	0.601
Hemoglobin, g/dL	15.0 (13.2-15.6)	15.0 (13.9-16.1)	14.3 (13.0-15.4)	0.314
Platelet, $\times 10^4$/μL	21.6 (14.7-25.0)	20.4 (12.6-24.4)	22.3 (17.5-25.9)	0.247
Fibrinogen, mg/dL	521 (464-589)	530 (463-624)	497 (468-557)	0.660
PT activity, %	89.4 (72.7-97.2)	91.3 (77.8-99.5)	89.2 (63.9-96.1)	0.308
PT-INR	0.96 (0.93-1.06)	0.96 (0.93-1.02)	0.98 (0.94-1.14)	0.371
FDP, μg/dL	5.5 (3.9-8.5)	7.3 (4.5-11.3)	4.5 (3.8-5.6)	0.008
AT activity, %	89.2 (82.6-103.3)	89.1 (82.6-98.2)	95.0 (81.8-107.1)	0.372
CRP, mg/dL	6.8 (3.1-11.3)	9.7 (3.7-15.1)	4.8 (2.3-8.2)	0.061
LDH, mg/dL	458 (357-580)	422 (348-655)	500 (376-576)	0.910
APACHE score	17.0 (14.0-22.8)	19.0 (16.5-29.5)	15.0 (13.5-17.5)	0.012
SOFA score	4 (3-7)	5 (3-7)	4 (3-6)	0.203
Outcome				
Bleeding or thrombotic complications, n(%)				
DVT, n(%)	6 (14.3)	4 (19.0)	2 (9.5)	0.378
Muscular hemorrhage, n(%)	4 (9.5)	3 (14.3)	1 (4.8)	0.293
Gastrointestinal hemorrhage, n(%)	3 (7.1)	3 (14.3)	0 (0.0)	0.072
Cerebral hemorrhage, n(%)	1 (2.4)	1 (4.8)	0 (0.0)	0.311
Cerebral infarction, n(%)	1 (2.4)	1 (4.8)	0 (0.0)	0.311
Splenic infarction, n(%)	1 (2.4)	1 (4.8)	0 (0.0)	0.311
Diagnosis of coagulopathy				

SIC	7 (16.7)	7 (33.3)	0 (0.0)	0.008
JAAM-DIC	11 (26.2)	10 (52.4)	0 (0.0)	<0.001
ISTH-overt DIC	3 (7.1)	3 (14.3)	0 (0.0)	0.072
ICU mortality, n(%)	5 (11.9)	4 (19.0)	1 (4.8)	0.153

Values are presented as medians (interquartile range: IQR) or numbers (%) if appropriate.

BMI, body mass index; ECMO, extracorporeal membrane oxygenation; PT, prothrombin time; FDP, fibrin/fibrinogen degradation product; AT, antithrombin; DVT, deep venous thrombosis; SIC, sepsis-induced coagulopathy; DIC, disseminated intravascular coagulation; JAAM, Japanese Association for Acute Medicine; ISTH, the International Society on Thrombosis and Hemostasis.

Table 2.

	JAAM-DIC			SIC			ISTH-overt DIC		
	(+), n=17	(-), n=13	p value	(+), n=11	(-), n=19	p value	(+), n=3	(-), n=27	p value
FDP, μg/mL	41.7 (23.4–77.1)	16.7 (11.4–23.3)	0.001	26.5 (14.2–43.1)	23.3 (12.0–62.4)	0.785	36.6 (14.2–43.1)	23.3 (14.1–62.4)	0.762
PLT, $\times 10^4$/μL	10.6 (5.8–26.0)	22.6 (14.3–26.8)	0.068	7.9 (5.7–10.6)	25.8 (17.4–27.9)	<0.001	5.8 (5.1–10.6)	19.4 (8.6–26.7)	0.056
PT-INR	1.05 (1.00–1.16)	1.01 (0.94–1.11)	0.099	1.15 (0.98–1.35)	1.02 (0.95–1.08)	0.081	1.36 (0.98–1.64)	1.04 (0.97–1.13)	0.149
Fbg, mg/dL	431 (305–547)	530 (370–559)	0.595	496 (232–552)	461 (361–542)	0.967	520 (232–588)	461 (361–542)	0.920
AT activity, %	78.8 (68.9–89.5)	94.0 (77.2–100.1)	0.072	74.8 (44.7–89.8)	90.6 (77.5–100.7)	0.018	65.4 (35.6–89.8)	87.8 (75.0–98.0)	0.135
PIC, μg/mL	3.2 (1.6–7.4)	2.2 (1.3–2.7)	0.055	2.3 (1.3–3.8)	2.6 (1.7–5.2)	0.553	1.3 (0.5–2.3)	2.7 (1.7–4.6)	0.079
TAT, μg/L	9.1 (2.3–22.0)	7.2 (3.9–11.5)	0.698	6.8 (2.6–15.0)	7.6 (3.3–18.3)	0.693	9.1 (0.6–25.9)	7.2 (3.0–17.6)	0.944
SF, μg/mL	52.1 (15.7–80.0)	24.7 (10.4–63.1)	0.080	22.2 (15.5–80.0)	42.7 (12.2–80.0)	0.845	18.7 (15.0–80.0)	29.9 (14.6–80.0)	0.971

Figures

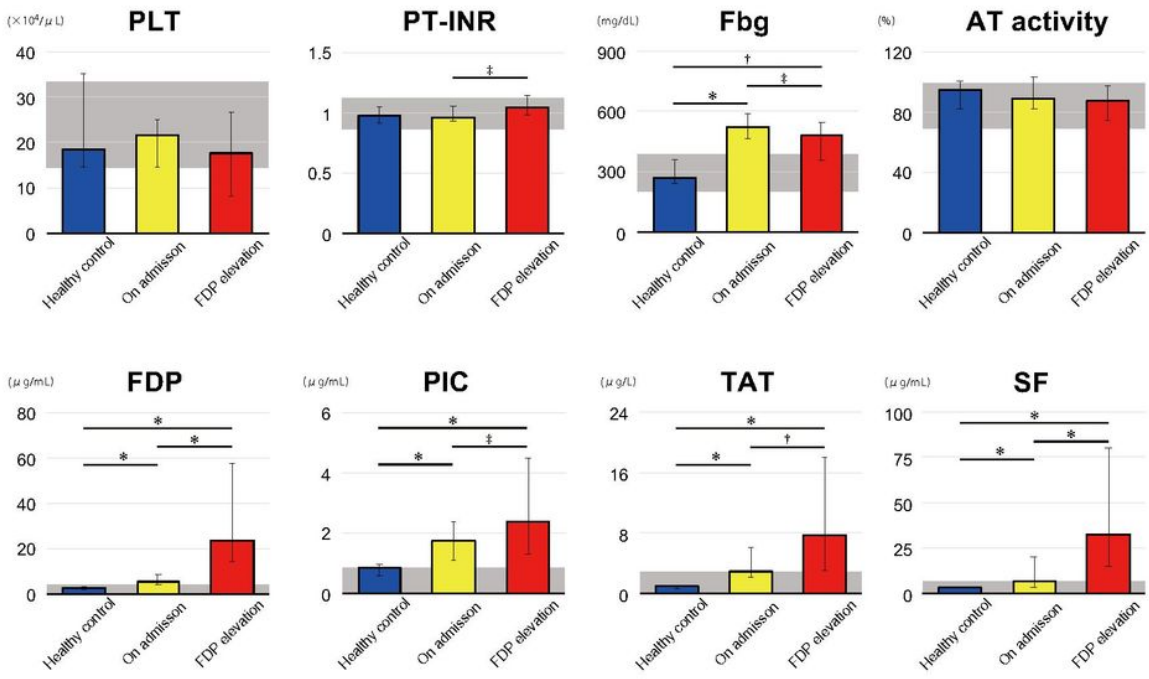

Figure 1

Comparison of coagulofibrinolytic marker levels: healthy volunteers vs COVID-19 patients on admission vs COVID-19 patients at the time of FDP elevation

The central boxes and peripheral horizontal bars indicate the median values and 25th to 75th percentiles, respectively. The gray area represents the normal range of each marker.

* $p < 0.001$; † $p < 0.01$; ‡ $p < 0.05$.

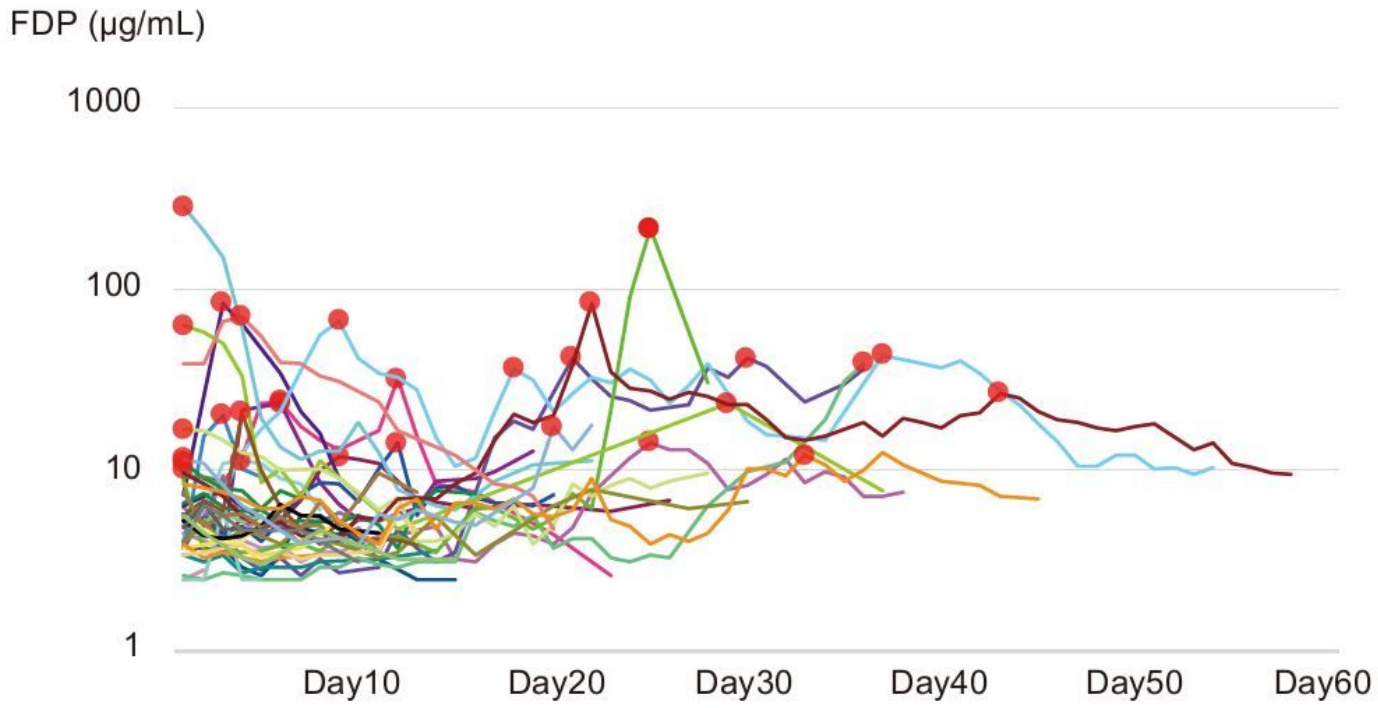

Figure 2

Fluctuations of FDP values in COVID-19-ARDS patients

Lines represent FDP values in each patient. Red closed circles indicate the episodes of FDP elevation as defined in the present study.