An Evaluation of Thrombotic Tendency by Whole-Body Enhanced CT Scan for Critical COVID-19 Pneumonia: A Case Series Study

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Case report

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Abstract

Background: Coronavirus disease (COVID-19) pneumonitis associated with severe respiratory failure has a high mortality rate. Based on recent reports, the most severely ill patients present with coagulopathy, and disseminated intravascular coagulation (DIC)-like massive intravascular clot formation is frequently observed. Coagulopathy has emerged as a significant contributor to thrombotic complications. Although recommendations have been made for anticoagulant use for COVID-19, no guidelines have been specified.

Case presentation: We describe four cases of critical COVID-19 with thrombosis detected by enhanced CT scan. The CT findings of all cases demonstrated typical findings of COVID-19 and pulmonary embolism or deep venous thrombus without critical exacerbation. Two patients died of respiratory failure due to COVID-19.

Discussion: Previous reports have suggested coagulopathy with thrombotic signs as the main pathological feature of COVID-19, but no previous reports have focused on coagulopathy evaluated by whole-body enhanced CT scan. Changes in hemostatic biomarkers, represented by an increase in D-dimer and fibrin/fibrinogen degradation products, indicated that the essence of coagulopathy was massive fibrin formation. Although there were no clinical symptoms related to their prognosis, critical COVID-19-induced systemic thrombus formation was observed.

Conclusions: Therapeutic dose anticoagulants should be considered for critical COVID-19 because of induced coagulopathy, and aggressive follow-up by whole body enhanced CT scan for systemic venous thromboembolism (VTE) is necessary.

Background

The coronavirus disease (COVID-19) pandemic, as declared by the World Health Organization, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (1, 2) Recent studies have reported a high prevalence of thrombotic events in COVID-19. (3, 4) In particular, venous thromboembolism (VTE) has emerged as an important consideration in the management of hospitalized COVID-19 patients. Early reports suggested a high incidence of VTE in hospitalized COVID-19 patients, particularly those with severe illness. This was similar to the high VTE rates observed in patients with other viral pneumonias, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS-CoV). (5–8) COVID-19 is associated with abnormalities in markers of hypercoagulability, including elevated levels of D-dimer, fibrinogen, and factor VIII, shortened activated partial thromboplastin time (APTT), and elevated sepsis-induced coagulopathy (SIC) score. (9) Hospitalized COVID-19 patients share similar strong clinical intrinsic and extrinsic risk factors for VTE, which include advanced age, obesity, immobility/stroke with paralysis, a history of cancer/active cancer, management in an intensive care unit setting, and prior history of VTE or known thrombophilia. (9, 10) However, risk stratification for VTE and

the optimal intensity and duration of anticoagulant thromboprophylaxis, including post-hospital discharge prophylaxis, remain uncertain in hospitalized COVID-19 patients.

In our institute, we have performed the severity classification and treatment strategies for patients with critical COVID-19, as shown in Table 1. Upon admission to our hospital, we assessed COVID-19 based on a positive reverse transcriptase–polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 in respiratory tract and laryngeal swab samples that were analyzed in a designated diagnostic laboratory.

Table 1
Severity Classification Criteria and Therapeutic Strategy for critical COVID-19

● **Criteria for severe COVID-19**		
1) SpO_2 < 92% at 10L/min. oxygen via a reservoir mask		
2) Shortness of breath with respiratory rate of > 30/min.		
3) Severe dyspnea due to COVID-19 pneumonia		
● Therapeutic strategy for critical COVID-19 (11)		
1)Mechanical ventilator	mode	pressure control
(primary setting)	PEEP	10–15 mmH_2O
	Driving Pressure	20–25 mmH_2O
	Respiratory Rate	12–16/min.
2) Antiviral therapy	Remdesivir (12)	10 days
3) Systemic steroid therapy	Dexamethasone (13)	10 days
4) Anticoagulant therapy	UFH with therapeutic dose according to APTT (1.5-2 times as normal)	
5) Protection for DVT	Intermittent air compression and elastic stocking	
6) Antibiotics	for CAP or secondary bacterial or fungus infection	
7) Rehabilitation	early intervention by NS, PT and OT	
8) Nutrition	early intervention via tube feeding or TPN	
9) Supportive therapy	sedation ,catecholamine support etc. via central venous catheter	
PEEP: positive end-expiratory pressure; PS: pressure support; UFH: unfractionated heparin; APTT: activated partial thromboplastin time; CAP: community associated pneumonia; NS: nurse; PT: physical therapist; OT: occupational therapist; TPN: total parenteral nutrition.		

Here, we describe four cases of critical COVID-19 patients with venous thrombosis admitted to intensive care.

Case Presentation

We treated 42 critical COVID-19 patients, who we got informed consent from all patients in document sheet before intubation, with intubation in our intensive care unit, from February 2020 onwards and performed enhanced CT scans for 15 critical COVID-19 patients after extubation or during mechanical ventilation to follow up their lung injury status. Of these, 11 patients did not have VTE and four patients had critical COVID-19 with VTE as demonstrated by via chest CT findings, as presented in Table 2. The characteristics showed no significant differences among all the subjects.

Table 2
Patients' Characteristics

	non-VTE (n = 11)	VTE (n = 4)	p value*
Age (year-old; median [IQR])	72 [68–78]	65 [63–69]	0.4255
Gender (Male: %)	91	75	0.4762
BMI (median [IQR])	23.7 [23–25]	23.5 [23–25]	0.8939
First Symptom (%)			
dyspnea	36	25	1.0000
fever	91	100	1.0000
cough	18	25	1.0000
Admission day after onset (day; median[IQR])	10 [8–11]	9 [8–11]	0.9272
Smoking History (%)	82	75	1.0000
Comorbidity (%)			
Diabetes	64	0	0.0769
Renal Dysfunction	36	50	1.0000
Hemodialysis	36	0	0.5165
Hypertension	82	50	0.5165
Hyperlipidemia	64	100	0.5165
Hyperuricemia	45	25	0.6044
Cardiovascular Disease	9	0	0.4762
Respiratory Disease	9	0	1.0000
Cancer	18	25	1.0000
Collagen Disease	0	25	0.2667
Thrombotic disease	36	0	0.5165
others	18	50	0.5165
*Mann-Whitney U test or Fisher's exact test; IQR; interquartile range, BMI; Body Mass Index.			

Patients with VTE cases (Table 3), were aged 59–79 years and had symptoms of only high fever and cough. Three of the patients were smokers. The patients had comorbidities which were as follows: none

of the patients had diabetes mellitus, 2 patients had renal dysfunction but without hemodialysis and hypertension, all patients had hyperlipidemia, and 1 patient was on oral systemic steroid therapy for systemic lupus erythematosus (SLE). The average number of days of illness before admission to our hospital and the start of our therapeutic strategy was 9.5 days (6–14 days) after onset. As a therapeutic strategy to prevent VTE, we maintained the APTT value in the range of 1.5-2 times the control value with continuous intravenous unfractionated heparin (UFH) under a therapeutic anticoagulant dose during intubation and UFH 5000 U twice a day by subcutaneous injection after extubation in all critical COVID-19 patients.

Table 3
Detailed characteristics of VTE patients

Patient	**1**	**2**	**3**	**4**
Age	66	59	79	64
Gender	Male	Male	Female	Male
BMI	28.0	22.6	22.4	24.4
First Symptom	fever	fever	cough	fever
Admission day after onset	8	14	10	6
Smoking History	+	+	-	+
Comorbidity				
Diabetes	-	-	-	-
Renal Dysfunction	+	+	-	-
Hemodialysis	-	-	-	-
Hypertension	+	+	-	-
Hyperlipidemia	+	+	+	+
Hyperuricemia	+	-	-	-
Cardiovascular Disease	-	-	-	-
Respiratory Disease	-	-	-	-
Cancer	-	-	+; Ov	-
Collagen Disease	-	+; SLE	-	-
others	-	+; HBV	-	+; HBV

BMI: Body Mass Index; Ov: Ovarian Cancer; SLE: Systemic Lupus Erythematosus; HBV: Hepatitis B virus.

Case 1

A 66-year-old male diagnosed with critical COVID-19 and fever was transferred to our hospital. He had renal dysfunction without hemodialysis, hypertension, hyperlipidemia, and hyperuricemia as comorbidities. After intubation, his condition gradually improved with our therapeutic strategy and he was extubated on the 8th day of admission. After he was moved to the general ward for rehabilitation, a sudden increase in D-dimer (20.47 μg/mL) was observed. We suspected VTE, which prompted enhanced CT screening. Internal jugular vein thrombosis (Fig. 1A) at the site of the central venous catheter, and pulmonary embolism (PE) (Fig. 1B, 1C) on the proximal side of the bilateral pulmonary artery were detected. As a result, we consulted a cardiologist and used direct oral anticoagulants (DOACs) as the standard treatment for PE. At this time, he had no symptoms such as dyspnea, desaturation, or chest pain. His rehabilitation was completed, and no conspicuous sequelae of COVID-19 were observed, and the patient was discharged from the hospital on the 35th day of admission. The patient' s clinical course is shown in Fig. 1D. One month later, we could not detect PE on follow-up enhanced chest CT.

Case 2

A 59-year-old male diagnosed with critical COVID-19 and fever was admitted to our hospital. He was on oral prednisolone for SLE and had other comorbidities such as hypertension, hyperlipidemia, and hepatitis B virus infection for which he was on oral entecavir hydrate. After intubation, his condition gradually improved with our therapeutic strategy. D-dimer (7.83 μg/mL) gradually elevated without any symptoms, which necessitated enhanced CT screening. As a result, internal jugular vein thrombosis (Fig. 2A) presented at the site of the central venous catheter, without other signs of VTE. The therapeutic dose of UFH was used as the standard treatment for internal jugular vein thrombosis. His condition improved, his requirement for ventilatory support decreased, and the inflammatory response also steadily reduced, so the patient was extubated on the 15th day of admission. His systemic condition was stable, and rehabilitation was completed, so he was followed up for SLE in the Department of Collagen Disease after admission. He was discharged from the hospital on the 26th day of admission. The patient' s clinical course is shown in Fig. 2B.

Case 3

A 79-year-old female diagnosed with critical COVID-19 and cough was admitted to our hospital. She had hyperlipidemia and cured ovarian cancer as a comorbidity. After intubation, her condition worsened under our therapeutic strategy, without any evidence of bacterial infection. During mechanical ventilation, the D-dimer level suddenly increased (8.58 μg/mL), which prompted enhanced CT screening. As a result, DVT presented in the right popliteal vein without other VTEs (Fig. 3A). We used therapeutic-dose UFH as the standard treatment for DVT. Her general condition and inflammatory response worsened, and oxygenation decreased, which subsequently led to death on the 21st day of admission. We thought that the cause of death in this case was not VTE; the deterioration of his condition was due to COVID-19 itself. The patient' s clinical course is shown in Fig. 3B.

Case 4

A 64-year-old male diagnosed with critical COVID-19 and fever was transferred to our hospital from another hospital. He had hyperlipidemia and hepatitis B virus infection with oral entecavir hydrate as comorbidities. After intubation, his condition gradually improved with our therapeutic strategy. However, under mechanical ventilation, the D-dimer level suddenly increased (54.53 μg/mL), and we suspected VTE, which prompted enhanced CT screening. As a result, a massive PE was detected on the distal side of the left pulmonary artery (Fig. 4A, 4B). We continued to use therapeutic-dose UFH as the standard treatment for PE. However, his condition suddenly worsened on the 12th day of admission, and he died on the 14th day of admission. We thought that his cause of death was massive PE or deterioration due to COVID-19 itself. The patient's clinical course is shown in Fig. 4C.

In all cases, the International Society on Thrombosis and Hemostasis (ISTH) score in the VTE group was less than 5 pts, the SIC score was less than 4 pts, and there was no evidence of DIC in their clinical course. After these results, we performed plain chest CT scan after extubation as a follow up of the lung condition in critical COVID-19 patients. However, we routinely took whole-body enhanced CT in all cases to follow up the condition of their lungs or systemic organs for the origin of infection, and search for whole body VTE because of the possibility of VTE due to a rapid increase in D-dimer or an originally high D-dimer in a critical COVID-19 patient.

Discussion

In our VTE cases, there were no dramatic differences in their clinical course compared with non-VTE patients, except for rapid elevation of D-dimer, for example, fundamental therapy for COVID-19, rehabilitation, nutrition, and supportive therapy. Patients 1 and 2 did not have massive VTE; in particular, patient 1 had a thrombus after extubation during rehabilitation in the intensive care unit, but his respiratory condition, blood pressure, and other vital signs were almost stable without any symptoms. In contrast, patients 3 and 4 had massive VTE, but we did not know the reason for their death. Patient 3 had just one side of the popliteal vein thrombus without lethal PE, so her reason for death was not VTE, but COVID-19 itself. He may have died from massive PE associated with COVID-19 because his clinical course was dramatic after elevated D-dimer and desaturation due to PE. Therefore, the exact timing of thrombosis in the course of the disease and optimal treatment for COVID-19 thrombosis remain unknown, but our experience suggests that comprehensive imaging should be considered soon after the presentation, as thrombosis may occur early and would warrant therapeutic-dose anticoagulant therapy. We inserted a central venous catheter for severe COVID-19 patients. Therefore, it tends to form a thrombus in the jugular vein or other insert place of the catheter, as in the two cases with jugular vein thrombus. Clearly, any benefit of thrombolysis should be balanced against the risk of bleeding, which was often considerable in ICU patients and can lead to intracranial hemorrhage. (14) Compared with white individuals, the incidence was higher in black people and lower in Asian people, (15) a disparity for which cause has not yet been elucidated but concerns regarding bleeding complications were accentuated in Asia, which led to the general reluctance for the use of pharmacological prophylaxis for VTE. However,

there was a paucity of studies investigating bleeding risk in Asian patients. (16) In fact, our two cases of hemorrhagic complications occurred in the non-VTE group, and complications of retroperitoneal hemorrhage and intra-abdominal hemorrhage were observed. Both patients had severe diabetes mellitus, chronic renal failure, and hemodialysis as comorbidities, and one case involved long-term steroid administration for lung lesions with thrombocythemia caused by COVID-19. Therefore, we must pay more attention to hemorrhagic complications in high-risk patients.

Critical COVID-19 patients displayed coagulation abnormalities associated with respiratory deterioration and death. (17, 18) In addition, many critical COVID-19 patients developed venous thromboembolism, which appeared to be related to coagulopathy. (7, 19) In particular, VTE emerged as an important consideration in the management of hospitalized patients with COVID-19. However, these observations may have been limited by the low rates of cross-sectional imaging performed (10%) as reported in one study. (20) In recent years, common pathways for venous thrombosis have been described, with inflammation and hypercoagulation being key factors in the mechanism of venous thrombotic events. (21) These concerns should be balanced by emerging data that the incidence of VTE in hospitalized critical COVID-19 patients or in ICU settings was higher than that reported by historical data in similar patients, with an incidence of VTE of 27% in a previous study using standard thromboprophylaxis and an incidence of 25% in another study without prophylaxis.(5, 7) These findings were consistent with high rates of VTE in patients with other severe viral pneumonias, such as influenza H1N1, in whom there was an 18- to 23-fold higher risk for VTE compared with control patients. (8) Although the mechanisms underlying vascular thrombosis in COVID-19 have not yet been clearly defined, several have been postulated. The tropism of the virus for the angiotensin-converting enzyme-2 (ACE2) receptor of the endothelial cells resulted in endotheliopathy and endothelial cell apoptosis. (22) Activation of the complement system led to endothelial cell injury and death with subsequent vascular denudation and exposure of the thrombogenic basement membrane, which drives the activation of clotting cascades. These events resulted in inflammation, microvascular thrombosis, vessel edema, and hemorrhagic sequelae, all of which were prominent features of lung pathology in patients with COVID-19-associated pneumonia. (23) In an autopsy study of ten patients with COVID-19, small vessel thrombus formation in the lung periphery was associated with foci of alveolar hemorrhage. (24) In fact, two of our patients with VTE died after detecting VTE, but we do not know their final diagnosis for death. VTE may be a prognostic factor for critical COVID-19 patients.

The diagnostic assessment of suspected VTE in hospitalized COVID-19 patients is challenging, especially for critically ill patients in whom, typically, it is important to reliably confirm or exclude VTE. Imaging studies for DVT or PE may be avoided due to concerns about transmitting infection in non-COVID-19 hospital wards or to healthcare workers. The frequent finding of an elevated D-dimer level in severely hospitalized COVID-19 patients may prompt an aggressive diagnostic approach for VTE, despite the controversy that an elevated D-dimer level (> 4.0 mg/L) may not be a reliable predictor of VTE in this population, but rather a marker of poor overall outcome. (5, 25) A recent study found a 85.0% sensitivity and 88.5% specificity for diagnosing VTE in patients with D-dimer levels > 1.5 mg/L. (5)

In our critical COVID-19 patients, D-dimer values were almost over 4.0 mg/L, and except for six critical COVID-19 patients, we could not detect VTE by systemic enhanced CT scan. As one of the natural courses of coagulopathy, D-dimer levels on the day of admission were mostly elevated to levels higher than 4.0 mg/L, peaked a few days later, decreased during the recovery period of the disease, and normalized gradually. However, in these 4 cases, their coagulation data showed rapid elevation of D-dimer with the rapid elevation of fibrinogen degradation products (FDP) (data not shown), and decreased platelet count before VTE was detected by enhanced CT scan. Two of these patients died after the event. Therefore, the rapid change of elevated D-dimer and decreased platelet count may be an index to check VTE by enhanced CT scan during the clinical course of critical COVID-19.

The World Health Organization (WHO) recommended therapeutic anticoagulation rather than intermediate dosing, (26) but the optimal thromboprophylaxis strategy in the critically ill hospitalized COVID-19 patient population is uncertain (conditional recommendation, very low certainty). A previous report suggested that the use of either prophylactic or intermediate doses of low molecular weight heparin (LMWH) in critical COVID-19 was associated with improved outcomes and better prognosis. (27) A previous report that assessed a therapeutic-dose of UFH in patients with ARDS who were afflicted with influenza virus, found that patients with ARDS who received therapeutic-dose anticoagulation had 33-fold fewer VTE events than those treated with prophylactic UFH or LMWH. (8) In addition to intensive care management, thrombotic tendencies in COVID-19 promoted VTE formation, so therapeutic anticoagulant doses were more appropriate than intermediate-dose anticoagulants. Since LMWH had no control index, we preferred to use UFH, which can be monitored by the APTT value while paying attention to side effects such as bleeding. Nevertheless, during anticoagulant therapy with UFH we tried to maintain an APTT value at 1.5-2 times the control value, to prevent VTE. But some cases were uncontrollable even if the UFH was over than 20000 U/day continuous UFH. VTE, which was uncontrollable, occurred in four patients. Therefore, since coagulation ability varies personally, it was necessary to check other coagulation-related factors. The use of empiric therapeutic-dose anticoagulation has been advocated by some for critically-ill and hospitalized COVID-19 patients, especially in ICU settings; however, data on the efficacy and safety of this approach are limited; (7) We must prevent VTE by rigorous multimodal prophylaxis strategies (anticoagulant and mechanical) in the critically ill and completely immobile COVID-19 population. (9) We need further results of trials to assess the efficacy and safety of dose of anticoagulant in hospitalized COVID-19 patients.

This study had some limitations. First, this study was performed in a single hospital with a small study population, since there are currently few confirmed and recovered cases of COVID-19 in Japan. Second, no therapeutic treatment for VTE in patients with severe COVID-19 was available for use in a parallel control group. However, we believe that the credibility of the therapeutic effect is high, as our study provides a comprehensive examination, including clinical features, laboratory findings, and physical findings, at a single institution. Third, we did not check for antithrombin III (ATIII), factor Xa, protein S, and protein C, because previous reports suggested that the effects and complications of heparin had some individual differences between metabolism and some enzymes. (16, 28) Therefore, these factors must be checked for COVID-19 patients during intensive care. In the future, we hope to collaborate with other

medical institutes in our area to design a control group that will allow us to improve the reliability of our study.

Conclusion

We suggest that it is very important for critical COVID-19 patients' therapeutic-dose anticoagulants to be strictly monitored by APTT tests, and early whole-body enhanced CT scans are done for the detection of VTE and the follow-up of these patients. Further studies on detailed and early laboratory, clinical, and imaging characterization are needed to better understand the pathophysiology of the thrombotic nature of COVID-19.

Abbreviations

COVID-19, Coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MERS-CoV, Middle East respiratory syndrome; DIC, disseminated intravascular coagulation; VTE, venous thromboembolism; PE, pulmonary embolism; UFH, unfractionated heparin; LMWH, low molecular weight heparin; DOACs, direct oral anticoagulants; APTT, activated partial thromboplastin time; SIC, sepsis-induced coagulopathy; ISTH, International Society on Thrombosis and Hemostasis; RT-PCR, reverse transcriptase–polymerase chain reaction; SLE, systemic lupus erythematosus; WHO, World Health Organization

Declarations

Ethics approval and consent to participate

Ethical approval to report this case was obtained from Yokohama City University Hospital (No.B200200048). Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Consent for publication

Written consent was obtained from patients for the publication of this case report and the relevant images. A copy of the written consent is available for review by the Editor-in-Chief of Thrombosis Journal

Availability of data and materials

Data requests should be made to the corresponding authors.

Competing interests

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Authors' contributions

FO prepared the manuscript and collected the references. IT coordinated the authors. FO, KN, RM, TN, TM and YO provided clinical support.

YO and TA helped to draft the manuscript. All authors have read and approved the final manuscript.

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Figures

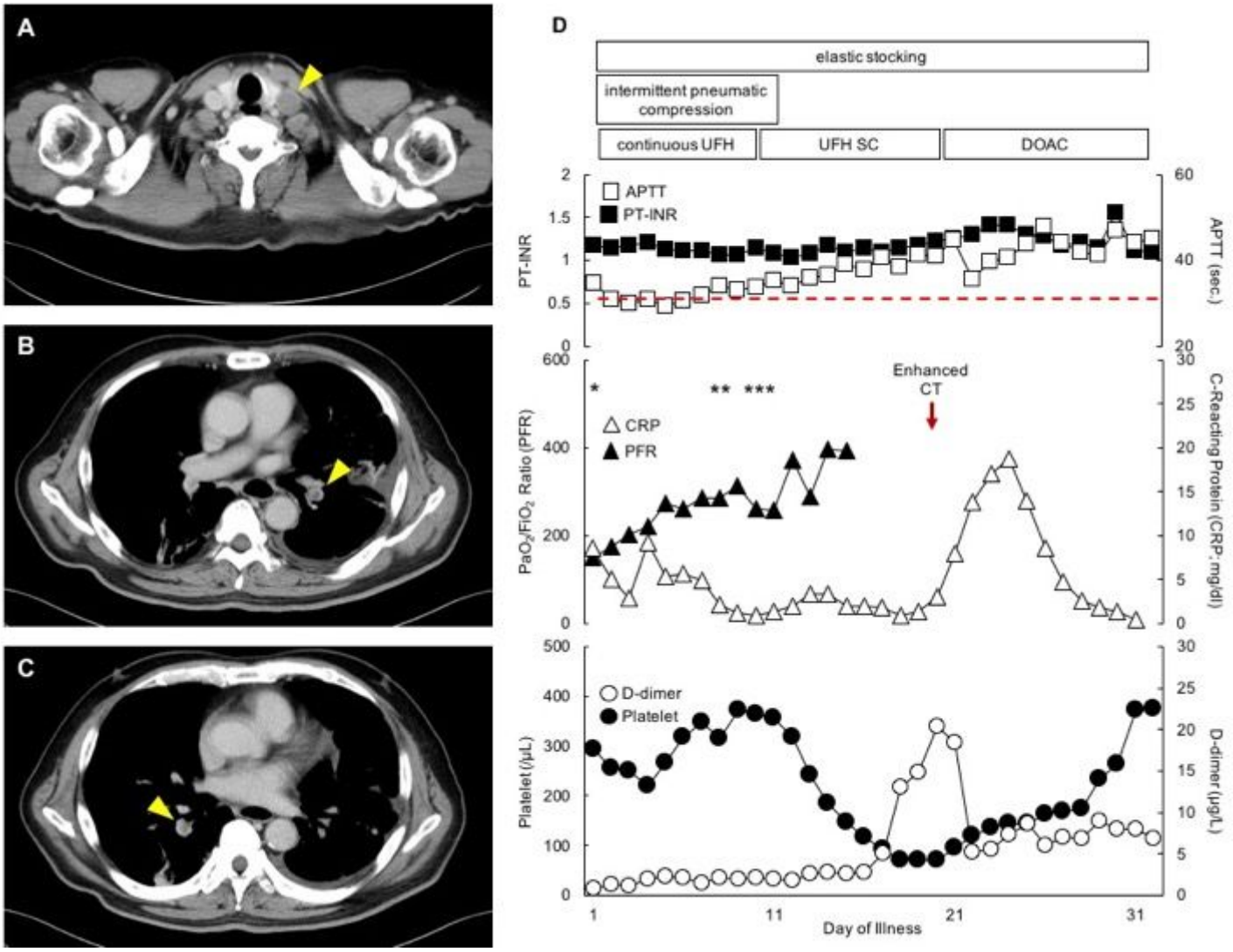

Figure 1

Computed tomography (CT) scan images and time course of PFR, CRP, D-dimer and platelet in case 1: (A) , (B) , (C) enhanced CT images (arrow head indicated thrombus); (D) clinical course X-axis: day of illness

(day). Y-axis: each parameter. Abbreviations: PT-INR: prothrombin time-international normalized ratio; APTT: activated partial thromboplastin time; PFR: PaO2/FiO2 ratio; CRP: C-reacting protein; UFH: unfractionated heparin; SC: subcutaneous injection; DOAC: direct oral anticoagulant Red border line; standard value of APTT *, intubation, **, extubation, ***, discharge from intensive care unit

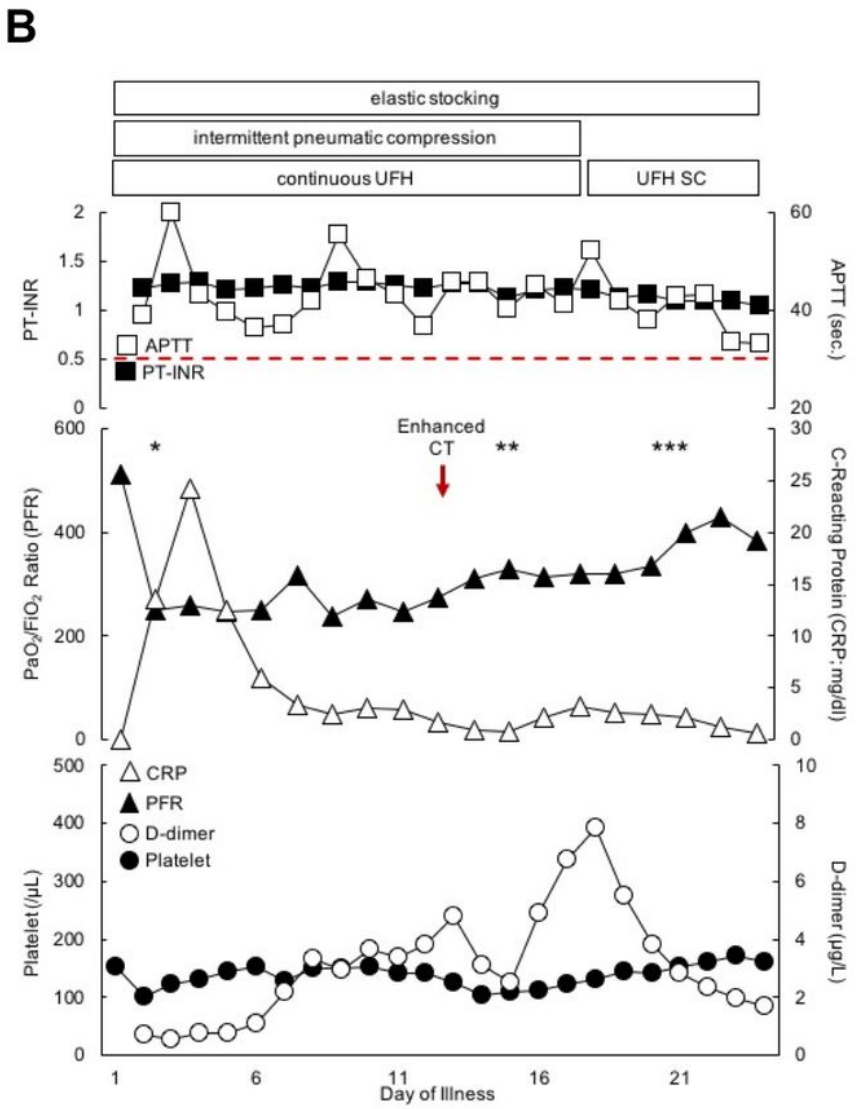

Figure 2

CT scan images and time course of PFR, CRP, D-dimer and platelet in case 2: (A) enhanced CT image (arrow head indicated thrombus); (B) clinical course X-axis: day of illness (day). Y-axis: each parameter. Abbreviations: PT-INR: prothrombin time-international normalized ratio; APTT: activated partial thromboplastin time; PFR: PaO2/FiO2 ratio; CRP: C-reacting protein; UFH: unfractionated heparin; SC: subcutaneous injection; Red border line; standard value of APTT *, intubation, **, extubation, ***, discharge from intensive care unit

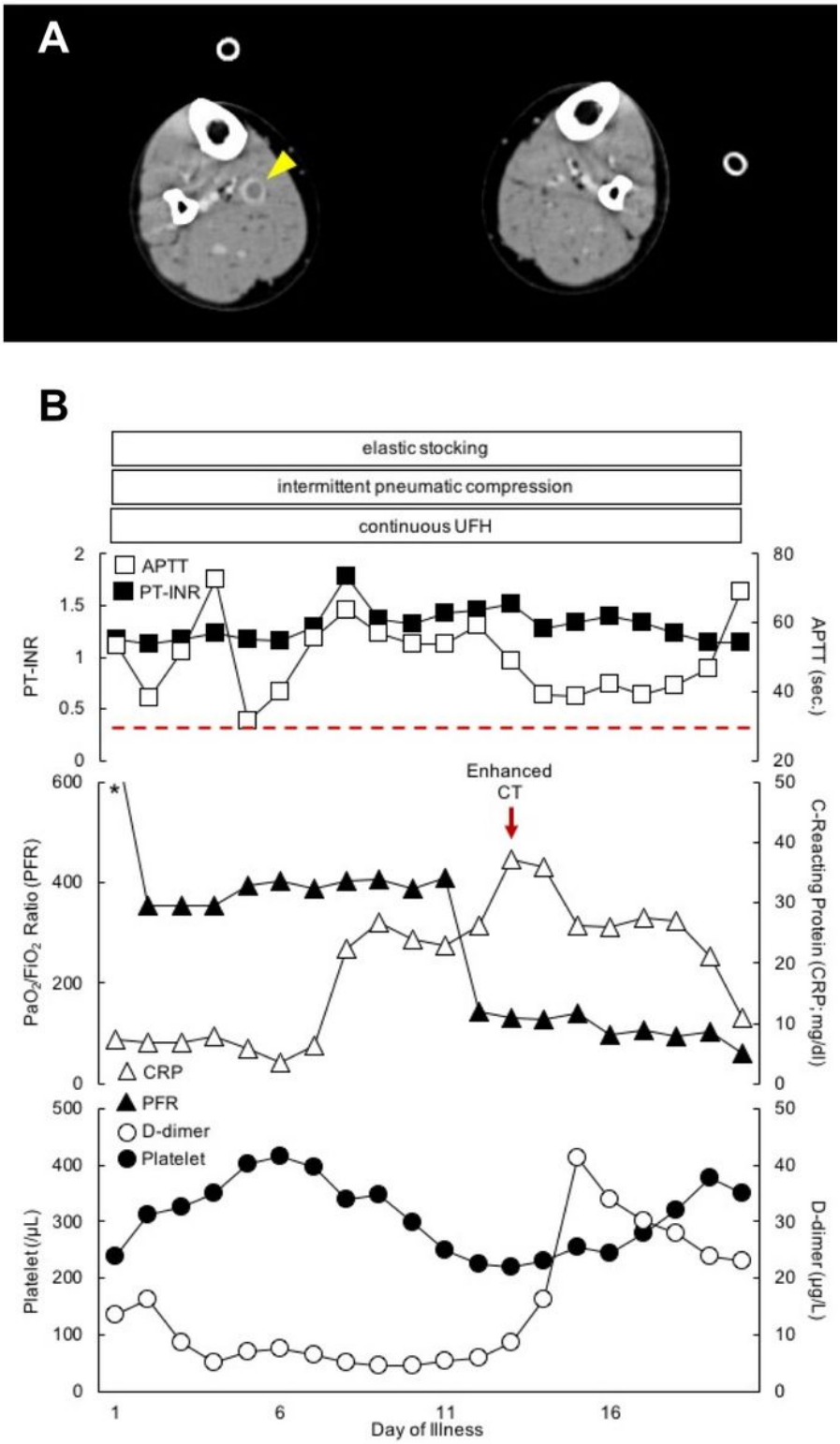

Figure 3

CT scan images and time course of PFR, CRP, D-dimer and platelet in case 3: (A) enhanced CT image (arrow head indicated thrombus); (B) clinical course X-axis: day of illness (day). Y-axis: each parameter. Abbreviations: PT-INR: prothrombin time-international normalized ratio; APTT: activated partial thromboplastin time; PFR: PaO2/FiO2 ratio; CRP: C-reacting protein; UFH: unfractionated heparin; Red border line; standard value of APTT; *, intubation

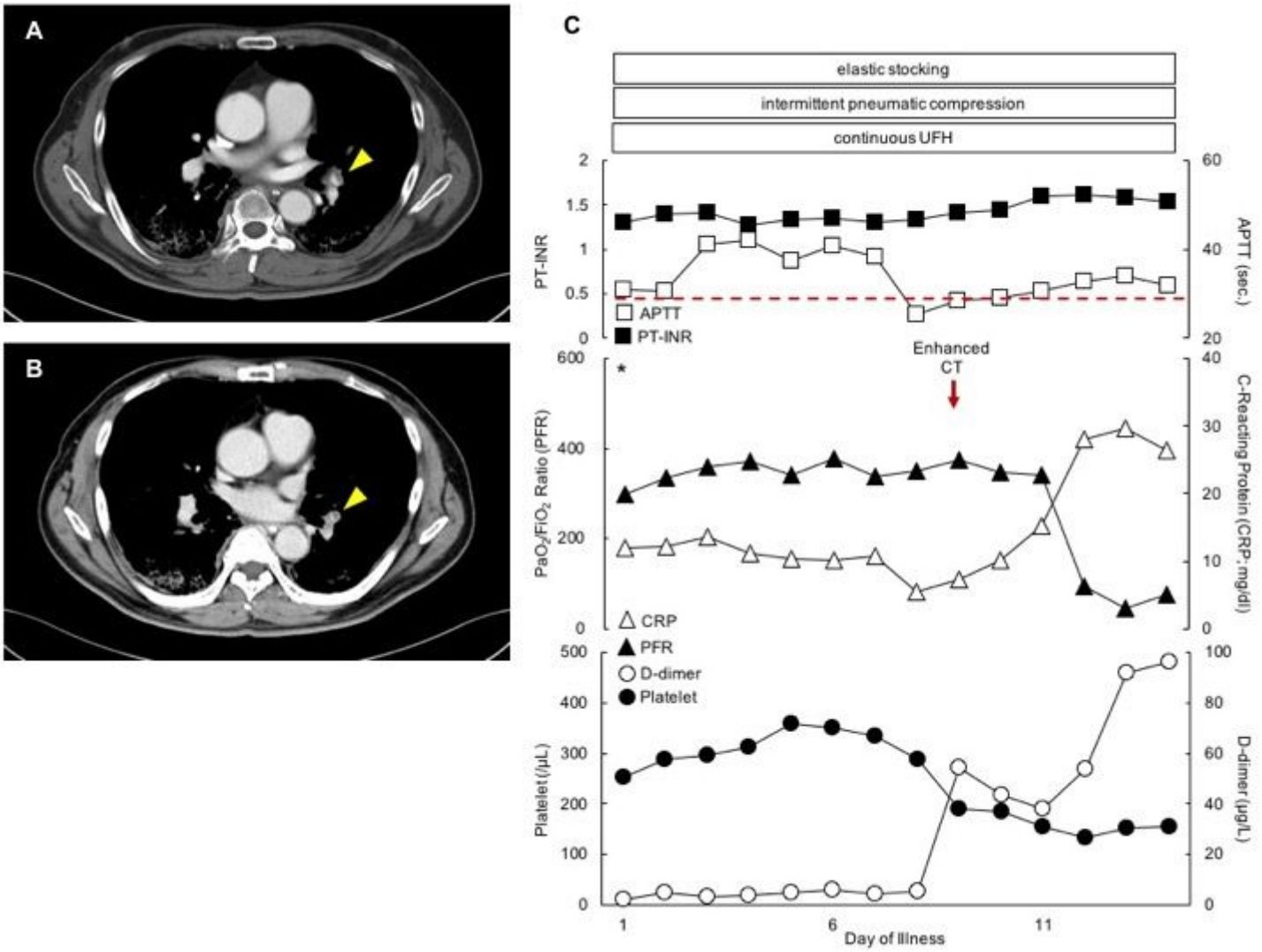

Figure 4

CT scan images and time course of PFR, CRP, D-dimer and platelet in case 4: (A), (B) enhanced CT images (arrow head indicated thrombus); (C) clinical course X-axis: day of illness (day). Y-axis: each parameter. Abbreviations: PT-INR: prothrombin time-international normalized ratio; APTT: activated partial thromboplastin time; PFR: PaO2/FiO2 ratio; CRP: C-reacting protein; UFH: unfractionated heparin; Red border line; standard value of APTT *, intubation,