Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Therapeutic anticoagulation using heparin in early phase severe coronavirus disease 2019: A retrospective study

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ABSTRACT

Background: Although several reports recommend the use of systemic anticoagulation therapy in patients with severe coronavirus disease 2019 (COVID-19) pneumonia, appropriate target population and timing of administration are unknown. We assessed association between therapeutic anticoagulation administration with unfractionated heparin and outcomes in patients with severe COVID-19 pneumonia, assuming that anticoagulant administration effects are influenced by therapy timing.
Methods: This retrospective observational study included severe COVID-19 patients requiring mechanical ventilation in a tertiary emergency critical care hospital intensive care unit (ICU) in Japan from May 1, 2020 to September 30, 2021. All included patients were divided into early and late-phase administration groups based on therapeutic anticoagulant administration timing (≤5 and >5 days, respectively, after commencing oxygen therapy). Primary outcomes (in-hospital mortality and adverse events related to anticoagulation therapy) and secondary outcomes [veno-venous extracorporeal membrane oxygenation (ECMO), ventilator-free days (VFD), and ICU-free days] were compared between groups using univariate and multivariate models.
Results: Of 198 included patients 104 (52.5%) and 94 (47.5%) were in early-phase and late-phase administration groups, respectively. Although background characteristics were similar between the groups, the early-phase administration group had a significantly lower in-hospital mortality rate (3.8% vs. 27.7%; $p < 0.001$), lower adverse event rates (1.9% vs. 12.8%; $p < 0.001$), significantly longer VFD and ICU-free days, and lower ECMO rates, than the late-phase administration group, in the multivariate model.
Conclusions: Late administration of therapeutic-dose anticoagulation in patients with severe COVID-19 pneumonia was significantly associated with worse outcomes than early administration.

List of abbreviations

APACHE II	Acute Physiology and Chronic Health Evaluation
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
ECMO	extracorporeal membrane oxygenation
FDP	fibrin-fibrinogen degradation product
ICU	intensive care unit
PaO2/FiO2	arterial oxygen partial pressure to fractional inspired oxygen
RCT	randomized control trial
SARS-CoV-2	severe acute respiratory syndrome coronavirus disease 2
SOFA	Sequential Organ Failure Assessment
UFH	unfractionated heparin
VFD	ventilator-free days

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, an ongoing public health problem, has caused the death of more than 4.8 million people worldwide, as of the end of September 2021 [1]. COVID-19 induces a cytokine storm that activates a coagulation cascade, resulting in coagulopathy and thrombotic phenomena, which leads to multiple organ dysfunction and high mortality [2]. The inflammation and thrombosis associated with endothelial dysfunction and hypercoagulability lead to an increased risk of micro (or macro) vascular thrombosis [3,4]. Thus, guidelines from several medical organizations recommend the use of anticoagulation therapy in patients with COVID-19 [5].

A large cohort study [6,7] reported that the use of anticoagulation at therapeutic doses may be associated with a reduced risk of mortality among hospitalized patients with COVID-19. Although a recent randomized control trial (RCT) has reported that therapeutic-dose

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anticoagulation did not decrease the mortality rate and the number of organ support free days, the severity of included patients was relatively low, and the date of onset of symptoms was not considered [8]. Meanwhile, another recent RCT demonstrated a clear benefit of therapeutic dose anticoagulation for non-critically ill patients with COVID-19 [9]. Therefore, the appropriate target population and timing of the administration of therapeutic anticoagulants are still under debate.

Based on this background, in the present study, we assessed the association between the administration of therapeutic-dose anticoagulant therapy and the outcomes in patients with severe COVID-19 pneumonia, assuming that the effects of therapeutic anticoagulant administration are affected by the timing of the therapy.

2. Methods

2.1. Study design and setting

This was a single-center retrospective observational study conducted at the intensive care unit (ICU) of a tertiary emergency critical care hospital in Tokyo. The medical records of patients with COVID-19 with severe pneumonia who were admitted between May 1, 2020, and September 30, 2021, were reviewed. All patients with COVID-19 who underwent mechanical ventilation at our hospital received therapeutic doses of heparin during the study period. Clinical outcomes were compared between patients who received therapeutic doses of heparin in the early and late phases of COVID-19 treatment. The study was approved by the institutional review board of our hospital (approval number: M2020–130). The board waived the need for written informed consent given the retrospective nature of the study.

2.2. Patient population

Consecutive patients with severe COVID-19 requiring mechanical ventilation who were admitted to ICU of Tokyo Medical and Dental University Hospital in Japan were included. A diagnosis of COVID-19 diagnosis was made based on the findings of a nasopharyngeal swab test for severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2) using real-time reverse transcriptase-polymerase chain reaction in all patients. We excluded patients with 'do not attempt resuscitation' orders [including veno-venous extracorporeal membrane oxygenation (ECMO) and renal replacement therapy (RRT)], those who had received systemic anticoagulant therapy at intubation time, and patients with missing or insufficient data regarding the study variables.

2.3. Patient management

Patients with COVID-19 were transferred to the ICU and underwent mechanical ventilation if they could not maintain an arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) ratio of less than 200 after oxygen therapy in our hospital. All included patients received unfractionated heparin (UFH) within the first 6 h after ICU admission, and their activated partial thromboplastin time was monitored and maintained at 1.5 to 2.5 times that of the control. During the study period, when anticoagulation therapy-related adverse events occurred, or the patients were discharged from the ICU, these therapies were discontinued immediately.

2.4. Data collection

Data were collected by trained medical doctors, and a standard abstraction form was used to ensure uniform data handling. Collected data were monitored, and suspected outliers were confirmed or corrected by other chart abstractors. The following information was retrospectively collected from the patients' medical records: age, sex, body mass index, date of disease onset, date of oxygen therapy, history of anticoagulant and/or antiplatelet therapy, smoking history, Charlson Comorbidity Index score [10], administration of ECMO, drug treatment for COVID-19, and status on hospital discharge (i.e., dead or alive). The clinical course, length of ventilation, and ICU stay for each patient were also recorded. Furthermore, we collected laboratory results such as D-dimer, fibrin-fibrinogen degradation products (FDP), white blood cell count, and C-reactive protein (CRP) levels. All blood samples evaluated in this study were obtained after the institution of mechanical ventilation and before administering anticoagulation therapy. For all included patients, the worst Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores within the first 24 h of mechanical ventilation were assessed.

2.5. Definitions and outcome measures

In this study, severe COVID-19 pneumonia was defined as an acute need for invasive mechanical ventilation. The "early-phase administration group" was defined as patients who received therapeutic anticoagulation within 5 days after the commencement of oxygen therapy, while the "late-phase administration group" was defined as those who received it 6 days or after, based on the fact that almost all patients who need oxygen therapy require hospitalization. A cut-off value of "5 days" was determined as the median number of days from oxygen therapy administration to therapeutic anticoagulation administration. The date of disease onset was defined as the day that the symptoms were observed. COVID-19-related sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, according to the 2016 Third International Consensus Definition [11]. Secondary infection was diagnosed when patients showed clinical symptoms or signs of pneumonia, urinary tract infection, or central line-associated bloodstream infection; or when patients had a positive culture of a new pathogen from blood, lower respiratory tract (qualified sputum or endotracheal aspirate), or urine specimens after ICU admission [12].

We defined the primary efficacy outcome as in-hospital mortality. The primary safety outcomes included anticoagulation therapy-related adverse events, defined as any of the following events: (1) hemoglobin level < 7 g/dL and any red blood cell transfusion, (2) at least two units of red blood cell transfusion within 48 h, or (3) clinical diagnosis of major bleeding (defined as symptomatic intracranial hemorrhage or hemorrhage requiring surgical or radiological intervention). Secondary outcomes were defined as the administration of ECMO, ventilator-free days (VFD) 28 days after admission, and ICU-free days within the first 28 days after admission.

2.6. Statistical analysis

In the univariate analysis, continuous variables were compared using Student's *t*-test or the Mann–Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. First, using a multivariable logistic regression model, we evaluated the interaction between therapeutic-dose anticoagulant therapy and the days from commencement of oxygen therapy to the anticoagulant therapy for the primary outcome, to determine whether the timing of therapeutic anticoagulation influenced the outcomes. We incorporated age and SOFA score, which are known a priori to be associated with outcomes in patients with severe COVID-19 pneumonia [13-15], and selected variables based on clinical plausibility and the number of outcomes (10 events per variable rule) as covariates in the multivariate model. Second, we divided the enrolled patients into two groups: the early-phase administration group (≤5 days after the commencement of oxygen therapy) and the late-phase administration group (>5 days after the commencement of oxygen therapy) based on the median number of days from oxygen therapy administration to therapeutic anticoagulation administration. We then compared the characteristics, severity, and outcomes of both groups. Furthermore, we divided the enrolled patients into two groups based on the another cut-off value (7 days) and performed a sensitivity analysis of the primary and

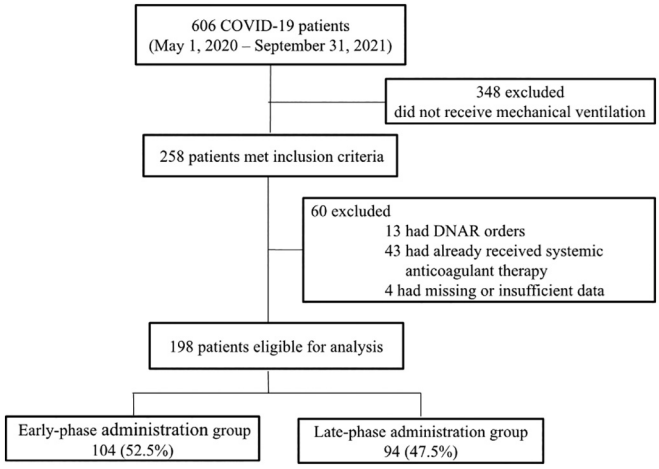

Fig. 1. Patient flow diagram.
COVID-19, coronavirus disease 2019; ICU, intensive care unit; DNR, do not attempt resuscitation.

secondary outcomes. All statistical analyses were conducted using R software (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

3. Results

The patient selection process is shown in Fig. 1. Among 606 potentially eligible patients with COVID-19, 198 (32.7%) patients with severe pneumonia underwent mechanical ventilation during the study period. Of these, 104 (52.5%) patients were treated with therapeutic anticoagulation in the early phase. Table 1 shows the main clinical characteristics, laboratory data at the initiation of mechanical ventilation, the worst clinical scores during the first 24 h after intubation, and the administered drugs during the ICU stay. The patients' laboratory data and severity scores were similar between the two groups. However, D-dimer and CRP levels, FDP, and severity scores tended to be higher in the late-phase administration group. Although the patients in both groups received similar treatments, the frequency of clinical complications was significantly higher in the late-phase administration group than in the early phase administration group. Table 2 provides the univariate analysis results for the outcomes between the early- and late-phase administration groups. Compared with the late-phase administration group, the early phase administration group had a significantly lower in-hospital mortality rate [4 (3.8%) vs. 26 (27.7%) patients; $p < 0.001$] and a lower rate of anticoagulation therapy-related adverse events [2 (1.9%) vs. 12 (12.8%) patients; $p < 0.001$]. Furthermore, compared to the late-phase administration group, the early phase administration group had significantly longer VFD and ICU-free days and lower rates of ECMO therapy.

The *p*-value for the interaction between therapeutic-dose anticoagulant therapy and the days from the commencement of oxygen therapy to the anticoagulant therapy for in-hospital mortality was 0.004, indicating that the effect of therapeutic-dose anticoagulation was significantly affected by the duration from oxygen therapy to the commencement of therapeutic-dose anticoagulation therapy. Table 3 presents the multivariate logistic regression analysis results adjusted for age and SOFA score. The late-phase administration of therapeutic-dose anticoagulants, compared to early phase administration, was significantly associated with higher in-hospital mortality, rates of adverse events, rates of ECMO administration, and shorter VFD and ICU-free days. Supplementary Tables 1, 2 and 3 show the result of the sensitivity analysis wherein the patients were grouped according to different criteria. The results were similar to the main findings.

4. Discussion

In this retrospective observational study, we found that the timing of therapeutic anticoagulation therapy significantly influenced the outcomes in 198 patients with COVID-19 pneumonia requiring mechanical ventilation. Furthermore, our findings indicated that late administration compared to early administration of therapeutic-dose anticoagulation was significantly associated with higher in-hospital mortality, adverse events, and ECMO administration, as well as shorter VFD and ICU-free days. To the best of our knowledge, this is the first study to report the association between the timing of therapeutic dose anticoagulation and outcomes in patients with severe COVID-19 pneumonia.

In COVID-19 pneumonia, despite anticoagulant prophylaxis or therapy, several studies have reported life-threatening arterial or venous thrombosis, including frequent severe pulmonary embolisms [16,17]. Such disease characteristics have led to the empirical treatment of patients with severe COVID-19 with heparin at therapeutic doses than at the usual thromboprophylaxis doses [18]. In addition to its known anticoagulant properties, heparin has been reported to have potential therapeutic effects in severe lung inflammation, impaired pulmonary gas exchange, and high viral load [19-21]. Because SARS-CoV-2 infection causes an excessive inflammatory response that may lead to coagulation hyperactivity, anticoagulation therapy using heparin is expected to have positive effects on the outcomes based on potential antiviral mechanisms [21] in addition to anticoagulative effects. However, the optimal anticoagulant regimen remains unknown. A recent RCT did not support the hypothesis that routine therapeutic dose anticoagulation benefits patients with severe COVID-19 pneumonia [8], possibly because the net effect of anticoagulation on clinical outcomes may depend on the timing of initiation in relation to disease course or severity. Further RCTs considering the timing of commencement are warranted to assess the effects of therapeutic anticoagulation.

In severe COVID-19 pneumonia cases, dramatic changes in the coagulation/fibrinolytic status on illness days 7–10 have been reported, where the status is changed from a hypofibrinolytic state to a hyperfibrinolytic state [22,23]. In this respect, late administration of therapeutic-dose anticoagulation in patients with severe COVID-19 could influence the fibrinolytic state, increasing bleeding risk. However, since the underlying mechanisms of the late-phase administration of therapeutic anticoagulation could not be elucidated by our clinical data, further research is warranted to reveal the differences in the effect between the early and late phases in patients with severe COVID-19.

Lymphopenia has been reported in most patients with severe COVID-19 pneumonia [24], and immunosuppression is more obvious in severe cases than in mild cases [25]. In severe cases, immunosuppression has been reported to develop after more than 7 days of illness onset [26]. In this study, we found that the prevalence of secondary infection in the late-phase administration group was higher than that in the early-phase administration group (22.3% vs. 3.8%). Previous studies reported high mortality in patients with COVID-19 with secondary infections [27,28], and the higher incidence of secondary infection observed in the late-phase administration group might have affected the outcomes in this study. Although details regarding the immune effect of heparin and the immune status of the patients could not be assessed in the present study, the immune effect, in addition to the anticoagulative effect, might have influenced the worse outcomes in the late-phase administration group.

The present study had several limitations. First, this was a retrospective observational study conducted at a single hospital with a limited sample size. Accordingly, the number of variables used in the multivariate analysis had to be limited, and there is a risk of residual confounding and type II error. Additional research is necessary to provide more definitive data, including large-scale studies adjusted for covariates. Second, we did not consider the coronavirus variant type or the days from disease onset to therapeutic anticoagulation administration, which could influence the outcomes and coagulation state. Third, patients who had

Table 1
Comparison of characteristics and laboratory data at ICU admission between the early-phase and the late-phase administration groups.

	All patients ($n = 198$)	Early-phase administration group ($n = 104$)	Late-phase administration group ($n = 94$)	p value
Characteristic				
Age (y), median [IQR]	62 [52–75]	59 [50–73]	66 [55–77]	0.180
Male, n (%)	167 (84.3)	87 (83.7)	80 (85.1)	0.503
Body mass index (kg/m^2), median [IQR]	26.3 [24.2–27.9]	26.8 [24.9–28.4]	25.5 [23.9–28.1]	0.302
History of smoking, n (%)	93 (47.0)	50 (48.7)	44 (46.8)	0.252
History of anticoagulant and/or antiplatelet therapy, n (%)	35 (17.7)	19 (18.3)	16 (17.0)	0.595
Days from the oxygen therapy to the administration of mechanical ventilation, median [IQR]	5 [4–6]	5 [3–5]	7 [5–11]	<0.001
Days from illness onset to the administration of mechanical ventilation, median [IQR]	8 [7–10]	6 [5–7]	10 [8–13]	<0.001
Laboratory data				
D-dimer level, median [IQR]	3.5 [2.2–6.1]	2.4 [1.5–5.8]	4.3 [2.4–6.8]	0.104
Fibrin-fibrinogen degradation products, median [IQR]	7.1 [5.8–9.6]	5.8 [4.3–7.3]	8.2 [6.6–10.8]	0.161
White blood cell count (/μl), median [IQR]	9200 [7400–10,800]	10,500 [8100–11,800]	7400 [6400–8600]	0.133
C-reactive protein (mg/dl) level, median [IQR]	5.6 [3.4–7.8]	4.0 [3.1–7.2]	7.4 [3.9–9.8]	0.085
Clinical scores				
SOFA score, median [IQR]	4 [3–5]	4 [3–5]	5 [3–5]	0.208
APACHE II score, median [IQR]	15 [11–16]	12 [11–15]	16 [11–17]	0.178
Treatment drugs				
Favipiravir, n (%)	82 (41.4)	42 (40.4)	40 (42.6)	0.712
Tocilizumab, n (%)	85 (42.3)	48 (46.2)	37 (39.4)	0.328
Remdesivir, n (%)	75 (37.9)	38 (36.5)	37 (39.4)	0.389
Baricitinib, n (%)	41 (20.7)	23 (22.1)	18 (19.1)	0.412
Nafamostat mesylate, n (%)	24 (12.1)	13 (12.5)	11 (11.7)	0.314
Corticosteroid, n (%)	196 (99.0)	103 (99.0)	93 (98.9)	0.913
Clinical complications				
Severe sepsis, n (%)	96 (48.5)	31 (29.8)	65 (69.1)	<0.001
Secondary infection, n (%)	25 (12.6)	4 (3.8)	21 (22.3)	<0.001

ICU, intensive care unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation.

Table 2
Treatment outcomes of both groups.

	All patients (n = 198)	Early-phase administration group (n = 104)	Late-phase administration group (n = 94)	p value
Primary outcomes				
In-hospital mortality, n (%)	30 (15.2)	4 (3.8)	26 (27.7)	<0.001
Anticoagulation therapy-related adverse events, n (%)	14 (7.1)	2 (1.9)	12 (12.8)	<0.001
Secondary outcomes				
ECMO, n (%)	20 (10.1)	3 (2.9)	17 (18.9)	<0.001
VFD, median days [IQR]	15 [8–19]	17 [12−21]	11 [6–18]	<0.001
ICU-free days, median days [IQR]	13 [3–17]	15 [10–18]	8 [4–15]	<0.001

ECMO, extracorporeal membrane oxygenation; VFD, ventilator-free days; ICU, intensive care unit; IQR, interquartile range;

Table 3
Multivariate analysis of the impact of the late-phase therapeutic anticoagulation.

	Adjusted odds ratio [95% CI]	Adjusted difference [95% CI]	p value
Primary outcome			
In-hospital mortality	8.86 [5.45–11.3]	–	<0.001
Anticoagulation therapy-related adverse events	6.34 [3.35–8.13]	–	<0.001
Secondary outcomes			
ECMO	7.82 [4.15–9.92]	–	<0.001
VFD		−4.7 [−6.9–1.6]	<0.001
ICU-free days	–	−4.1 [−7.0–2.1]	<0.001

CI, confidence interval; ECMO, extracorporeal membrane oxygenation; VFD, ventilator-free days; ICU, intensive care unit.

already received anticoagulants and/or antiplatelet agents were excluded from this study. The proportions were similar between the two groups in our study (early-phase administration group, 18.3% vs. late-phase administration group, 17.0%), although these agents could influence the coagulable state and anticoagulation sensitivity.

Despite these limitations, we showed a novel and significant association between the timing of therapeutic anticoagulation therapy and the outcomes in patients with severe COVID-19 pneumonia. Further large-scale research is necessary to confirm the results of the present study.

5. Conclusion

The results of this study suggest that late administration of therapeutic-dose anticoagulation in patients with COVID-19 pneumonia

requiring mechanical ventilation was significantly associated with worse outcomes compared to early administration. Further studies are necessary to validate our results.

Ethics approval and consent to participate

The study was approved by the institutional review board of our hospital (approval number: M2020–130). The board waived the need for written informed consent because the study was retrospective.

Consent for publication

This study was approved by the institutional review board, and written informed consent was waived because of the retrospective design.

Availability of data and materials

The datasets analyzed in this study are not publicly available due to privacy issues, but are available from the corresponding author upon reasonable request.

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Authors' contributions

WT, AE, and YO participated in the study conception and design, data collection, and drafting of the manuscript. All authors read and approved the final manuscript.

Credit authorship contribution statement

Wataru Takayama: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Akira Endo:** Data curation, Investigation, Validation, Writing – review & editing. **Yasuhiro Otomo:** Writing – review & editing, Validation, Supervision.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2022.05.031.

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