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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.

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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
PCT 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

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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...
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 \( \chi^2 \) 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 other cut-off value (7 days) and performed a sensitivity analysis of the primary and
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. Compared with the early-phase administration group, the late-phase administration group had significantly lower in-hospital mortality rate \( (4 \text{ (3.8\%)} \text{ vs. } 26 \text{ (27.7\%)} \text{ patients; } p < 0.001) \) and a lower rate of anticoagulation therapy-related adverse events \( (2 \text{ (1.9\%)} \text{ vs. } 12 \text{ (12.8\%)} \text{ patients; } p < 0.001) \).

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.

| Characteristic                          | All patients (n = 198) | Early-phase administration group (n = 104) | Late-phase administration group (n = 94) | p value |
|----------------------------------------|------------------------|-------------------------------------------|-----------------------------------------|---------|
| 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/m²), 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 (×10⁹/l), median [IQR] | 9200 [7400–10,800] | 10,500 [6100–11,800] | 7400 [6400–8600] | 0.133 |
| C-reactive protein (mg/dl), 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 (43.2)              | 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 meylate, 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.

| Outcome                          | 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.

| Outcome                          | 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.

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