Investigation of differences in coagulation characteristics between hospitalized patients with SARS-CoV-2 Alpha, Delta, and Omicron variant infection using rotational thromboelastometry (ROTEM): A single-center, retrospective, observational study

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Abstract
Background: The severe acute respiratory syndrome coronavirus 2 Omicron variant has a low rate of serious illness, is highly contagious, and has spread rapidly since January 2022. The number of severe cases and deaths remains problematic. Here, we aimed to elucidate the coagulation pathology of Omicron-infected patients using rotational thromboelastometry.

Methods: Patients with coronavirus disease 2019, hospitalized and treated from January 2021 to April 2022, were included. The Alpha–Delta and Omicron groups were defined during admission. Blood tests, clinical course, and rotational thromboelastometry measurements were compared using a propensity score-matched cohort.

Results: Both groups had 21 patients each. Lactate dehydrogenase (Alpha–Delta group [interquartile range] vs. Omicron group [interquartile range]; 449 [368–518] U/L vs. 241 [196–398] U/L, p = 0.01) and ferritin (1428 [1145–3061] ng/dl vs. 481 [188–881] ng/dl, p = 0.0002) levels were significantly lower in the Omicron group. In rotational thromboelastometry, the thrombus hardness indexes FIBTEM A5 (29 [23–34] mm vs. 23 [18–28] mm, p = 0.034) and maximum clot firmness (34 [27–40] mm vs. 26 [21–33] mm, p = 0.021) were significantly lower in the Omicron group, whereas the fibrinolysis index FIBTEM LI60 (98 [92–100] % vs. 100 [100–100] %, p = 0.0082) was higher.

Conclusion: Severe coagulation abnormalities may be less likely in Omicron-infected patients than in those infected with the previous Alpha and Delta variants.

KEYWORDS
coagulopathy, fibrinogen, point-of-care test
1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 rapidly spread worldwide after the outbreak in Wuhan, China, in December 2019, with an enormous impact on social activities and the economy.1

Infection with SARS-CoV-2 activates the coagulation system.2 COVID-19 coagulopathies differ from disseminated intravascular coagulation and sepsis-induced coagulopathy insofar as being extremely severe.3 Complications of coagulopathy have been reported frequently in patients with COVID-19.1,4,5 and thrombotic complications have been reported in 30% of patients with severe COVID-19.6 Conversely, hemorrhagic complications are less frequent, but may be a risk factor for death in patients with COVID-19.7 The degree of coagulation abnormalities reportedly reflects the severity of COVID-19,8,9 and the thrombotic tendency seen in patients with moderate or severe COVID-19 is not seen in those with mild disease.10 Thus, coagulation abnormalities in COVID-19 may affect prognosis and reflect disease status, emphasizing the need to elucidate the pathogenesis of coagulation disorders in COVID-19.

In addition to the standard laboratory tests (SLTs), point-of-care testing, such as rotational thromboelastometry (ROTEM®; TEM International FZC) and thromboelastography (TEG®; Haemonetics Co.), can be used clinically as tests for blood coagulation.11 SLTs, such as prothrombin time and activated partial thromboplastin time, reflect responses when thrombin production is only 4% of cases.12 They do not reflect the influence of platelets because they assess separate plasma components.12 Thus, they may not accurately appraise in vivo coagulability.13 Point-of-care testing using whole blood may detect coagulation disorders not seen through standard laboratory test (SLT).14 ROTEM has also been useful in elucidating coagulation abnormalities in COVID-19, and studies have demonstrated a hypercoagulable state in patients with COVID-19 using this technique.15–19

Omicron, a novel SARS-CoV-2 variant, is considered more infectious than other variants and is becoming more prevalent worldwide.20,21 The Omicron variant has relatively mild clinical features22 and is associated with lower hospitalization, intensive care unit admission, and mortality rates than the Alpha–Delta variants.21 However, owing to its strong infectivity, the absolute number of infected patients is high, and the number of deaths and severe cases remains a problem that should not be underestimated.23 Studies reporting coagulopathy in Omicron-infected patients have been scarce. Furthermore, there is little clinical information on coagulopathy in Omicron-infected patients with severe disease. In this study, we hypothesized that the pattern of coagulopathy in Omicron strains differs from that of previous variants. We aimed to clarify the coagulation characteristics of Omicron strains by using ROTEM.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This was a single-center, retrospective, observational study of COVID-19 patients in critical care beds at our institution. Patients with COVID-19 admitted to our hospital for multidisciplinary management from January 1, 2021, to March 31, 2022, were included. COVID-19 was diagnosed by RNA or antigen detection of SARS-CoV-2.

Patients with COVID-19 who were admitted to our hospital during the study period were eligible for inclusion. Patients with cardiac arrest on arrival, severe illness due to bacterial sepsis, pregnant women, and patients with insufficient data, were excluded from the analysis.

Since the start of the COVID-19 pandemic, the hospital has established dedicated beds for patients with severe COVID-19 and a special team of emergency physicians, intensive care physicians, anesthesiologists, infectious disease physicians, respiratory medicine physicians, cardiologists, and nurses to provide care for patients with COVID-19. In the prefecture, the hospital serves as a referral hospital for patients with COVID-19 who require respiratory support by tracheal intubation or high-flow nasal cannula. Anticoagulation was performed in accordance with the algorithm for anticoagulation with unfractionated heparin developed and proposed by Sato et al.24 for Japanese patients. The study was approved by the Ethics Committee of our institution. In addition, all participants were given the opportunity to opt out of the study if desired.

2.2 | Cohort definition

The first patient with COVID-19 was transported to our hospital on January 18, 2021. Patients with COVID-19 were admitted until September 23, 2021, after which there were none for approximately 3 months. Patients with COVID-19 were again admitted to our hospital between January 23, 2022, and April 16, 2022.

The Alpha strain was followed by the Delta strain worldwide until December 2021, and the Omicron strain rapidly expanded after January 2022.25 Therefore, all patients admitted to our hospital before December 2021 were defined as having Alpha or Delta variant infection; from December 2021 to January 23, 2022, no patients were admitted to our hospital with COVID-19; and patients admitted on or after January 23, 2022 were assumed to have Omicron variant infection. Previous reports have shown that patients infected with the Omicron variant have milder clinical disease and are less likely to have respiratory failure.20–22 Among patients admitted after January 23, 2022, the Omicron epidemic period, we suspected that those with extensive infiltrative shadows in the lungs on computed tomography and severe clinical disease such as acute respiratory distress syndrome could be infected with the Alpha or Delta variant.
Therefore, we performed polymerase chain reaction testing of patients admitted after January 23, 2022, who were suspected to be infected with the Alpha or Delta variant to confirm the variant type.

2.3 | Data collection and definition

Patient background information, past history, lifestyle, and blood test results were extracted from the medical records. Blood test data were extracted at the time of admission. Hemorrhagic complications were assessed according to the World Health Organization grading system and diagnosed if the bleeding was Grade 2 or higher. ROTEM® Delta analysis measured EXTEM, INTEM, FIBTEM, and APTEM on admission for all patients.

2.4 | Statistical analysis

All statistical analyses were performed using the JMP Pro Version 14 software package (SAS Institute Inc.). Continuous variables were presented as the median and quartiles. Patient background, history, the severity of illness, blood test results at presentation, and ROTEM parameters were compared using Fisher’s exact and Wilcoxon rank-sum tests. For all analyses, \( p < 0.05 \) was considered significantly different. Propensity score variables were defined using a logistic regression model with two variables, namely age and body mass index (BMI). The neighborhood matching method (1:1) was applied for propensity score matching, and the caliper width of the logit-transformed propensity score was set to 0.2. The same procedure was used to compare blood test results and ROTEM measurements between the Alpha–Delta and Omicron groups.

3 | RESULTS

3.1 | Participants

From January 2021 to April 2022, 97 patients with COVID-19 were admitted to our hospital. Patients with a cardiopulmonary arrest at presentation \( (N = 1) \), those with sepsis at presentation or sepsis considered the primary pathology \( (N = 4) \), pregnancy \( (N = 2) \), and those with missing ROTEM measurements or other data \( (N = 4) \) were excluded. The Alpha–Delta group consisted of 37 patients who were admitted between January 2021 and September 23, 2021, and the Omicron group consisted of 49 patients admitted between January 23, 2022, and April 16, 2022 (Figure 1).

Patients with COVID-19 admitted between January 23, 2022, and April 16, 2022, with possible Alpha or Delta strain infections based on clinical symptoms and computed tomography lung imaging, underwent polymerase chain reaction testing for strain identification. However, no patients were included in the Alpha or Delta strain group during this period.

3.2 | Comparison of SLT and ROTEM parameters between the Alpha–Delta and Omicron groups

Standard laboratory test and ROTEM measurements of the target population are shown in Table 2.

Lactate dehydrogenase (LDH; Alpha–Delta vs. Omicron; 436 [342–518] U/L vs. 282 [220–377] U/L, \( p < 0.0001 \)) and ferritin (1339 [750–1871] ng/dl vs. 525 [217–876] ng/dl, \( p < 0.0001 \)) levels were significantly lower in the Omicron group than in the Alpha–Delta group. The background factors, severity, and outcome of each of the included groups are shown in Table 1.

Age was significantly higher (Alpha–Delta vs. Omicron; 58 [48–70] years vs. 76 [68–84] years, \( p < 0.0001 \)), and BMI was lower (25.3 [22.3–28.3] kg/m\(^2\) vs. 21.3 [17.5–24.5] kg/m\(^2\), \( p = 0.0004 \)) in the Omicron group than that for the Alpha–Delta group. History of heart failure and dementia were also significantly more prevalent. Significantly more patients in the Alpha–Delta group were on regular anticoagulants. Although there was no significant difference in the respiratory rate at presentation, the partial pressure of oxygen/fraction of inspired oxygen ratio (P/F) was significantly higher in the Omicron group (180 [139–200] vs. 300 [145–450], \( p < 0.0001 \)). However, the rate of high-flow nasal cannula use during hospitalization (25 [67.6%] vs. 12 [24.5%], \( p < 0.0001 \)) and tracheal intubation (17 [46%] vs. 2 [4.1%], \( p < 0.0001 \)) during hospitalization was significantly lower.
### Table 1: Characteristics comparison between the Alpha–Delta and Omicron groups

| Characteristic                                      | Alpha–Delta group (N = 37) | Omicron group (N = 49) | p-Value |
|-----------------------------------------------------|---------------------------|------------------------|---------|
| **Background**                                      |                           |                        |         |
| Age, median (IQR), years                           | 58 (48–70)                | 76 (68–84)             | <0.0001 |
| Sex, male (%)                                      | 25 (67.6)                 | 32 (65.3)              | 1       |
| BMI, median (IQR), kg/m²                            | 25.3 (22.3–28.3)          | 21.3 (17.5–24.5)       | 0.0004  |
| Occasional drinker (%)                             | 12 (32.4)                 | 13 (27)                | 0.6366  |
| Smoker (%)                                          | 8 (21.6)                  | 10 (20.8)              | 1       |
| **Past history**                                    |                           |                        |         |
| Hypertension (%)                                    | 15 (40.5)                 | 18 (36.7)              | 0.8236  |
| Myocardial infarction (%)                           | 1 (2.7)                   | 4 (8.2)                | 0.3853  |
| Congestive heart failure (%)                        | 1 (2.7)                   | 9 (18.4)               | 0.0384  |
| Peripheral vascular disease (%)                    | 0 (0)                     | 1 (2.0)                | 1       |
| Cerebrovascular disease or TIA (%)                  | 1 (2.7)                   | 6 (12.2)               | 0.2308  |
| Dementia (%)                                        | 1 (2.7)                   | 13 (26.5)              | 0.0028  |
| COPD (%)                                            | 2 (5.4)                   | 6 (12.2)               | 0.457   |
| Connective tissue disease (%)                       | 2 (5.4)                   | 7 (14.3)               | 0.289   |
| Peptic ulcer disease (%)                            | 3 (8.1)                   | 1 (2.0)                | 0.3102  |
| Mild liver disease (%)                              | 5 (13.4)                  | 1 (2.0)                | 0.0801  |
| Diabetes mellitus (%)                               | 10 (27.0)                 | 11 (22.5)              | 0.8004  |
| Hemiplegia (%)                                      | 0 (0)                     | 0 (0)                  | —       |
| Chronic kidney disease (%)                          | 2 (5.4)                   | 4 (8.2)                | 0.6955  |
| Solid tumor (%)                                     | 3 (8.1)                   | 6 (12.2)               | 0.7261  |
| Leukemia (%)                                        | 0 (0)                     | 0 (0)                  | —       |
| Lymphoma (%)                                        | 0 (0)                     | 2 (4.1)                | 0.504   |
| Severe liver disease (%)                            | 0 (0)                     | 0 (0)                  | —       |
| Metastasis (%)                                      | 1 (2.7)                   | 0 (0)                  | 0.4302  |
| AIDS (%)                                            | 0 (0)                     | 0 (0)                  | —       |
| Charlson comorbidity index, median (IQR)            | 1 (0–1)                   | 1 (0–3)                | 0.0613  |
| **Medication**                                      |                           |                        |         |
| Aspirin (%)                                         | 0 (0)                     | 4 (8.2)                | 0.1309  |
| Warfarin (%)                                        | 0 (0)                     | 2 (4.1)                | 0.504   |
| Unfractionated heparin (%)                          | 15 (40.5)                 | 8 (16.3)               | 0.015   |
| **Severity**                                        |                           |                        |         |
| P/F, median (IQR)                                   | 180 (139–200)             | 300 (145–450)          | <0.0001 |
| Respiratory rate, median (IQR)                      | 25 (20–30)                | 21 (20–27)             | 0.2027  |
| JAAM DIC score, median (IQR)                        | 0 (0–1)                   | 1 (0–2)                | 0.078   |
| SOFA score on admission, median (IQR)               | 4 (3–5.5)                 | 3 (1.5–5)              | 0.081   |
| APACHE II score, median (IQR)                       | 9 (6–17)                  | 11 (8–17)              | 0.1989  |
| **Clinical course**                                 |                           |                        |         |
| High-flow nasal canula (%)                          | 25 (67.6)                 | 12 (24.5)              | <0.0001 |
| Intubation (%)                                      | 17 (46)                   | 2 (4.1)                | <0.0001 |
| ECMO (%)                                            | 3 (8.1)                   | 0 (0)                  | 0.076   |
| CRRT (%)                                            | 1 (2.7)                   | 1 (2.0)                | 1       |
| **Complications on admission**                      |                           |                        |         |
| Bacterial pneumonia (%)                             | 9 (24.3)                  | 14 (28.6)              | 0.8065  |
| Thrombotic complications (%)                        | 1 (2.7)                   | 1 (2.0)                | 1       |
TABLE 1 (Continued)

|                      | Alpha–Delta group (N = 37) | Omicron group (N = 49) | p-Value |
|----------------------|----------------------------|------------------------|---------|
| Bleeding complications (%) | 9 (24.3)                  | 5 (10.2)               | 0.1382  |
| Outcome              |                            |                        |         |
| Death in ICU(%)      | 8 (21.6)                   | 3 (6.1)                | 0.0494  |

Abbreviations: AIDS, acquired immune deficiency syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; JAAM DIC, Japanese Association for Acute Medicine Disseminated Intravascular Coagulation; P/F, partial pressure of oxygen/fraction of inspired oxygen ratio; SOFA, Sequential Organ Failure Assessment; TIA, transient ischemic attack.

TABLE 2 Comparison between SLT and ROTEM data between the Alpha–Delta and Omicron groups

|                      | Alpha–Delta group (N = 37) | Omicron group (N = 49) | p-Value |
|----------------------|----------------------------|------------------------|---------|
| SLT                  |                            |                        |         |
| White blood cell, median (IQR), ×10³ | 6.4 (4.6–7.9) | 7.2 (4.1–9.3) | 0.4458  |
| Hemoglobin level, median (IQR), g/dl | 13.9 (12.9–14.5) | 12.7 (11.3–13.9) | 0.0085  |
| Platelets, median (IQR), 10⁴/μl | 20.7 (16–26.3) | 17.5 (14.6–21.9) | 0.0956  |
| PT-INR, median (IQR) | 1.07 (1.03–1.15) | 1.14 (1.04–1.3) | 0.1339  |
| APTT, median (IQR), seconds | 35.6 (32.1–41) | 35.4 (32.8–43.5) | 0.7262  |
| Fibrinogen, median (IQR), mg/dl | 564 (405–683) | 489 (399–638) | 0.1941  |
| FDP, median (IQR), μg/ml | 5 (3.6–8.8) | 5.2 (4.1–11.2) | 0.4261  |
| D-dimer, median (IQR), μg/ml | 1.27 (1.08–2.68) | 1.65 (1.09–4.26) | 0.4301  |
| Creatine, median (IQR), mg/dl | 0.73 (0.58–0.91) | 0.86 (0.61–1.19) | 0.2437  |
| LDH, median (IQR), U/L | 436 (342–518) | 282 (220–377) | <0.0001 |
| Lactate level, median (IQR), mmol/L | 1.7 (1.3–2.1) | 1.7 (1.3–2.4) | 0.6411  |
| CRP, median (IQR), mg/dl | 6.6 (2.4–11.2) | 7.2 (2.1–15.9) | 0.3948  |
| Ferritin, median (IQR), ng/dl | 1339 (750–1871) | 525 (217–876) | <0.0001 |

ROTEM*

|                      | Alpha–Delta group (N = 37) | Omicron group (N = 49) | p-Value |
|----------------------|----------------------------|------------------------|---------|
| EXTEM CT (N: 38–79), median (IQR), seconds | 79 (69–94) | 65 (61–76) | 0.0009  |
| EXTEM A5 (N: –), median (IQR), mm | 52 (46–55) | 49 (46–53) | 0.2728  |
| EXTEM CFT (N: 34–159), median (IQR), seconds | 71 (59–83) | 71 (63–81) | 0.6721  |
| EXTEM MCF (N: 50–72), median (IQR), mm | 68 (64–70) | 65 (62–69) | 0.1327  |
| EXTEM LI60, median (IQR), % | 91 (88–94) | 92 (89–94) | 0.6966  |
| INTEM CT (N: 100–240), median (IQR), seconds | 226 (203–262) | 240 (205–310) | 0.5102  |
| INTEM A5 (N: –), median (IQR), mm | 49 (44–55) | 49 (43–53) | 0.3637  |
| INTEM CFT (N: 30–110), median (IQR), seconds | 67 (56–83) | 68 (59–90) | 0.5017  |
| INTEM MCF (N: 50–71), median (IQR), mm | 65 (61–68) | 64 (59–66) | 0.2688  |
| INTEM LI60, median (IQR), % | 90 (87–94) | 90 (88–93) | 0.9093  |
| FIBTEM CT (N: –), median (IQR), seconds | 75 (61–83) | 61 (55–71) | 0.0057  |
| FIBTEM A5 (N: –), median (IQR), mm | 29 (23–34) | 23 (17–28) | 0.0003  |
| FIBTEM CFT, median (IQR), seconds | 89 (70–138) | 112 (79–269) | 0.0841  |
| FIBTEM MCF (N: 9–25), median (IQR), mm | 33 (28–39) | 27 (21–32) | 0.0003  |
| FIBTEM LI60, median (IQR), % | 96 (92–100) | 100 (100–100) | <0.0001 |

Abbreviations: APTT, activated partial thromboplastin clotting time; CRP, C-reactive protein; EXTEM, CT, CFT, MCF, INTEM, FIBTEM; FDP, fibrin/fibrinogen degradation products; IQR, interquartile range; LDH, lactate dehydrogenase; PT-INR, prothrombin time-international normalized ratio; ROTEM, rotational thromboelastometry; SLT, standard laboratory test.

*Normal ranges (N:) are shown for each ROTEM parameter.

the two groups, with FIBTEM A5 [29 [23–34] mm vs. 23 [17–28] mm, p = 0.0003] and FIBTEM maximum clot firmness (MCF) [33 [28–39] mm vs. 27 [21–32] mm, p = 0.0003] being significantly lower in the Omicron group. However, FIBTEM LI60 was significantly higher in the Omicron group [96 [92–100] % vs. 100 [100–100] %, p < 0.0001].
3.3 | Comparison between SLT and ROTEM parameters in the matched cohort

After propensity score matching for age and BMI, univariate analysis showed no significant differences in the prevalence of heart failure or dementia between the Alpha–Delta and Omicron groups. The number of patients taking anticoagulants was also comparable between the two groups. However, P/F was significantly higher in the Omicron group in the matched cohort (180 [87–223] vs. 245 [135–450], \( p = 0.0011 \)), while tracheal intubation rates were significantly lower in the Omicron group (12 [57.1%] vs. 1 [4.8%], \( p = 0.0005 \)). Hemorrhagic complications occurred only in the Delta group, at a rate of 23.8% (Table 3).

Lactate dehydrogenase (Alpha–Delta group vs. Omicron group; 449 [368–518] U/L vs. 241 [196–398] U/L, \( p = 0.001 \)) and ferritin levels (1428 [1145–3061] ng/dl vs. 481 [188–881] ng/dl, \( p = 0.0002 \)) were significantly lower in the Omicron group than in the Alpha–Delta group. In ROTEM, FIBTEM A5 (29 [23–34] mm vs. 23 [18–28] mm, \( p = 0.034 \)) and FIBTEM MCF (34 [27–40] mm vs. 26 [21–33] mm, \( p = 0.0211 \)) were lower in the Omicron group. However, FIBTEM LI60 was significantly higher (98 [92–100] % vs. 100 [100–100] %, \( p = 0.0082 \)) (Table 4).

4 | DISCUSSION

With regard to the target population of this study, there was a significant difference in age between the two groups. Because of the strong infectivity of Omicron, it may be more prevalent among younger patients than the Alpha or Delta variants; however, cases are relatively milder as one of the factors contributing to the severity of COVID-19 include older age. Nonetheless, during the Alpha–Delta infection period, many young patients in our institution also had severe cases, which may have contributed to the low average age of the Alpha–Delta group in our study.

When compared to the groups before propensity score matching, BMI was significantly higher in the Alpha–Delta group; Campello et al. reported an association between a high BMI and hypercoagulability in a study using ROTEM. The difference in the ROTEM profile between the Alpha–Delta and Omicron groups, in the pre-matching cohort, may have been partially related to differences in BMI between patients in the two groups.

Prior to propensity score matching, the percentage of patients administered unfractionated heparin prior to transport to our hospital was significantly higher in the Alpha–Delta group. This suggests that more patients in the Alpha–Delta group had hypercoagulability on blood tests.

The P/F on admission was significantly lower in the Alpha–Delta group, even after propensity score matching, and the proportion requiring oxygen via a high-flow nasal canula was also lower in the Alpha–Delta group. Patients infected with the Omicron variant have been reported to develop milder disease than those infected with the Alpha and Delta variants, and our results are consistent with these reports. Despite respiratory failure being significantly milder in the Omicron group, the SOFA and APACHE II scores tended to be lower in the Omicron group after propensity score matching, although the difference was not statistically significant. This suggests that in patients with severe Omicron variant infection, the disease may be more severe in conditions other than respiratory failure.

Furthermore, bleeding complications were significantly more common in the Alpha–Delta group compared with the propensity score-matched group. Hemorrhagic complications are known to be associated with COVID-19 severity and death. In this study, the incidence of hemorrhagic complications was lower in the Omicron group, which may also indicate differences in coagulation characteristics between the Alpha–Delta and Omicron groups.

Our hospital aggregates severely ill patients from all over the Prefecture, and there was no difference in the Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores, which assess the severity of illness and organ function of the Alpha–Delta and Omicron groups. However, the Omicron group had a significantly higher P/F and was considered to have a milder degree of hypoxemia. The proportion of patients requiring ventilators was also significantly lower, and the mortality rate was also lower, consistent with the reported epidemiology of Omicron-infected patients.

Lactate dehydrogenase and ferritin levels, previously reported as factors of COVID-19 severity, were significantly lower in the Omicron group in the propensity score-matched cohort as well. It is difficult to determine whether this is because hypoxemia was less severe in the Omicron group, or due to differences in the strains themselves. Furthermore, LDH and ferritin levels may not be applicable in predicting the severity of illness in Omicron-infected patients, and there may be other markers of severity for Omicron strains.

The coagulopathy that occurs in COVID-19 differs from that of disseminated intravascular coagulation, which can be caused by other severe diseases in terms of both its clinical and biochemical features. Several studies on coagulation disorders characteristic of COVID-19 that assessed patients using ROTEM parameters have also reported signs of hypercoagulability. The coagulation disorders of COVID-19 are characterized by high fibrinogen levels, and elevated fibrinogen levels are an indicator of severe disease. Although there were no significant differences in fibrinogen values between the Alpha–Delta and Omicron groups, significant differences in A5 and MCF, indicators of thrombus hardness, were noted in the FIBTEM parameters of ROTEM. These parameters were increased beyond the normal range in the Alpha–Delta group, indicating higher thrombus hardness and a hypercoagulable state.

Boscolo et al. reported that COVID-19 patients requiring ICU care show more severe hypercoagulability than patients with mild disease. In the present study, both the Alpha–Delta and Omicron groups required ICU management due to respiratory failure or other severe medical conditions. The Alpha–Delta group showed EXTEM...
### TABLE 3  Comparison of characteristics in the matched cohort of the Alpha–Delta and Omicron groups

|                          | Alpha–Delta group (N = 21) | Omicron group (N = 21) | p-Value |
|--------------------------|-----------------------------|------------------------|---------|
| **Background**           |                             |                        |         |
| Age, median (IQR), years | 64 (56–72)                  | 70 (62–75)             | 0.3449  |
| Sex, male (%)            | 6 (28.6)                    | 4 (19.1)               | 0.7186  |
| BMI, median (IQR), kg/m² | 22.9 (21.1–26.1)            | 24.2 (19.3–28.8)       | 0.9499  |
| Occasional drinker (%)   | 8 (38.1)                    | 10 (47.6)              | 0.7557  |
| Smoker (%)               | 5 (23.8)                    | 8 (38.1)               | 0.5055  |
| **Past history**         |                             |                        |         |
| Hypertension (%)         | 10 (47.6)                   | 8 (38.1)               | 0.7557  |
| Myocardial infarction (%)| 1 (4.8)                     | 1 (4.8)                | 1       |
| Congestive heart failure (%)| 1 (4.8)                   | 4 (19.1)               | 0.3433  |
| Peripheral vascular disease (%)| 0 (0)                   | 1 (4.8)                | 1       |
| Cerebrovascular disease or TIA (%)| 0 (0)                   | 2 (9.5)                | 0.4878  |
| Dementia (%)             | 1 (4.8)                     | 1 (4.8)                | 1       |
| COPD (%)                 | 2 (9.5)                     | 3 (14.3)               | 1       |
| Connective tissue disease (%)| 0 (0)                     | 2 (9.5)                | 0.4878  |
| Peptic ulcer disease (%) | 2 (9.52)                    | 0 (0)                  | 0.4878  |
| Mild liver disease (%)   | 3 (14.3)                    | 0 (0)                  | 0.2317  |
| Diabetes mellitus (%)    | 6 (28.6)                    | 5 (23.8)               | 1       |
| Hemiplegia (%)           | 0 (0)                       | 0 (0)                  | —       |
| Chronic kidney disease (%)| 2 (9.5)                    | 2 (9.5)                | 1       |
| Solid tumor (%)          | 2 (9.5)                     | 1 (4.8)                | 1       |
| Leukemia (%)             | 0 (0)                       | 0 (0)                  | —       |
| Lymphoma (%)             | 0 (0)                       | 2 (9.5)                | 0.4878  |
| Severe liver disease (%) | 0 (0)                       | 0 (0)                  | —       |
| Metastasis (%)           | 1 (4.8)                     | 0 (0)                  | 1       |
| AIDS (%)                 | 0 (0)                       | 0 (0)                  | —       |
| Charlson comorbidity index, median (IQR) | 1 (0–1) | 1 (0–2.5) | 0.599 |
| **Medication**           |                             |                        |         |
| Aspirin (%)              | 0 (0)                       | 2 (9.5)                | 0.4878  |
| Warfarin (%)             | 0 (0)                       | 2 (9.5)                | 0.4878  |
| Unfractionated heparin (%)| 7 (33.3)                   | 4 (19.1)               | 0.4841  |
| **Severity**             |                             |                        |         |
| P/F, median (IQR)        | 180 (87–223)                | 245 (135–450)          | 0.0011  |
| Respiratory rate, median (IQR) | 27 (18–35)                | 20 (20–25)             | 0.3486  |
| JAAM DIC score, median (IQR) | 1 (0–1.5)                  | 1 (0–2)                | 0.7013  |
| SOFA score on admission, median (IQR) | 4 (3–6.5)                 | 3 (1–4.5)              | 0.058   |
| APACHE II score, median (IQR) | 10 (7.5–17)                | 9 (6–12)               | 0.0981  |
| **Clinical course**      |                             |                        |         |
| High-flow nasal canula (%)| 11 (52.4)                   | 8 (38.1)               | 0.5359  |
| Intubation (%)           | 12 (57.1)                   | 1 (4.8)                | 0.0005  |
| ECMO (%)                 | 2 (9.5)                     | 0 (0)                  | 0.4878  |
| CRRT (%)                 | 1 (4.8)                     | 0 (0)                  | 1       |
| **Complications at the time of admission** | | | |
| Bacterial pneumonia (%)  | 7 (33.3)                    | 5 (23.8)               | 0.7337  |
| Thrombotic complications (%) | 1 (4.8)                  | 1 (4.8)                | 1       |
CT prolongation and FIBTEM MCF elevation, consistent with the findings of Boscolo et al. However, in the cohort of patients infected with the Omicron variant, abnormal ROTEM values were rare, even in patients with severe disease. This may be due to differences in the severity of respiratory...
failure between the Alpha–Delta and Omicron groups. However, it may also be because coagulation abnormalities are less likely to occur in patients infected with the Omicron variant.

This study had several limitations. First, the study was conducted at a single institution, and the number of cases was small. In addition, the data did not entirely show the characteristics of the Omicron strains, since data were aggregated from patients that were determined to be severely ill. Second, we did not distinguish between vaccinated and unvaccinated patients. It is likely that vaccinated coverage was higher in patients in the Omicron group than in the Alpha–Delta group, because vaccination coverage improved with time. Although thrombosis has been reported to be associated with COVID-19 vaccination, another study found no increased risk for hypercoagulability associated with COVID-19 vaccination. In this study, we were unable to assess whether there is an association between vaccination and coagulopathy. Third, in this study, there was a significant difference in P/F between the Alpha–Delta and Omicron groups. It is unclear whether the results of this study also apply to the patients with Omicron infection who have poor respiratory status. In other words, the results may differ from the results of this study in patients with Omicron infection who have respiratory failure comparable with that of the Alpha–Delta group. Further data are necessary to resolve this question.

However, this is the first ROTEM study to evaluate coagulability in severely Omicron-infected patients. Further studies may lead to better elucidation of the coagulation characteristics of Omicron-infected patients and the optimization of anticoagulation therapy.

5 | CONCLUSIONS

Patients infected with the Omicron variant have lower values of lactate dehydrogenase and ferritin than those infected with Alpha or Delta variants. FIBTEM A5 and MCF were significantly higher, and FIBTEM Li60 was lower, in patients infected with the Omicron variant than in those infected with the Alpha or Delta variants. These results suggest that patients have different blood test and coagulation characteristics according to the infecting variant type and that coagulation abnormalities are less severe in patients infected with the Omicron variant, than in those infected with the Alpha or Delta variants.

AUTHOR CONTRIBUTIONS

AM, HK, and YS conceptualized and designed the study and drafted the article. AM, KS, and acquired the data. AM and HK analyzed the data. AM and YS interpreted the data. HK and YS supervised the study. All authors approved the final version of the article.

ACKNOWLEDGMENTS

We would like to thank Editage (www.editage.com) for English language editing. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PATIENT CONSENT

All participants were provided the opportunity to opt out of the study, if desired.

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