SCIEPublish

Article

Comparison of Blood Coagulation Function of Severe Patients Infected with SARS-CoV-2 Original Strain and Omicron Variant in China: A Single Center Retrospective Analysis

Yanhong Zhang [1,†], Li Li [1,†], Shangen Zheng [2], Yingkai Xu [2], Zihan Yuan [2], Chengyu Liu [1], Yu Zhang [1], Yao Zheng [1], Bicheng Hu [1], Wanbing Liu [2,*] and Lei Liu [2,*]

[1] Department of Transfusion, Wuhan First Hospital, Wuhan 430022, China; 1479522737@qq.com (Y.Z.); 992711239@qq.com (L.L.); liuchengyu0418@hotmail.com (C.L.); 25564106@qq.com (Y.Z.); 610206262@qq.com (Y.Z.); hubicheng211@sina.com (B.H.)

[2] Department of Transfusion Medicine, General Hospital of Central Theater Command of the PLA, Wuhan 430070, China; sxkzsg@sina.com (S.Z.); 18247918008@163.com (Y.X.); 15926674844@163.com (Z.Y.)

* Corresponding author. E-mail: wanbing1203x@163.com (W.L.); liulei890207@163.com (L.L.)

† These authors contributed equally to this work.

Received: 16 June 2024; Accepted: 14 November 2024; Available online: 30 December 2024

ABSTRACT: This study aims to analyze the characteristics of blood coagulation function in severe patients infected with Omicron variant in comparison to those infected with the original strain. Seventy-three severe patients infected with the Omicron variant and hospitalized at Wuhan First Hospital from 9 December 2022 to 9 January 2023, were included, as well as 71 severe patients infected with the original strain and hospitalized at the same institution from 12 February to 20 March 2020. Patients infected with Omicron demonstrated significant coagulation dysfunction, as evidenced by dramatically elevated levels of FIB, APTT, PT, INR, and D-D and decreased values of PLT compared to the healthy control group ($P < 0.01$). The patients infected with the Omicron variant exhibited more complex and worse coagulation disorders (dramatic elevation of FIB, APTT, PT, and D-D and decrease of PLT) than the patients infected with the original strain ($P < 0.05$). In addition, individuals infected with the Omicron variant experienced a decreased length of hospitalization but a higher mortality rate when compared to those infected with the original strain ($P < 0.01$). We found the FIB, D-D, LDH, and CRP values of non-survivors were much higher than those of survivors among patients infected with Omicron ($P < 0.05$). In general, patients with severe cases of Omicron infection consistently showed more pronounced coagulation dysfunction upon admission compared to those infected with the original strain, potentially due to their older age and higher prevalence of cardiovascular and cerebrovascular diseases. The study provides a realistic basis for clinical prevention and treatment of severe or critically ill cases of COVID-19 caused by the Omicron variant or new evolving variants in the future.

Keywords: Omicron variant; SARS-CoV-2 original strain; Blood coagulation; Clinical outcome

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in 700 million people experiencing the Coronavirus disease 2019 (COVID-19) globally [1]. SARS-CoV-2 is an RNA coronavirus (CoV) that contains four primary structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) and exhibits a mutation rate greater than that of DNA virus. The large genome (~30 kb) of SARS-CoV-2 and low-fidelity RNA-dependent RNA polymerase (RdRp) contribute to the elevated adaptive mutation rate observed during adaptation to new human hosts [2]. The infectivity, phenotypic characteristics, and immune evasion of SARS-CoV-2 will be changed upon the occurence of adaptive mutations, leading to the emergence of new variants such as Alpha, Beta, Gamma, Delta, and Omicron. Variant B.1.1.529 was initially detected on 11 November 2021 in Botswana and on 14 November 2021 in South Africa. The World Health Organization (WHO) defined it as the fifth variant of concern (VOC) and designated it Omicron on 26 November 2021. The Omicron variant was the most mutated strain among all of the SARS-CoV-2 variants during the COVID-19 pandemic [3]. The Omicron variant accumulates many mutations that are spread across

https://doi.org/10.70322/BG20240210006

the four main structural proteins, making it more transmissible and capable of producing immune escape [3]. According to the reported data, Omicron is believed to be over 10 times more infectious than the original SARS-CoV-2 strain and approximately twice as infectious as the Delta variant. The Omicron mutant continues to be the most common variant worldwide. Most people typically experience mild respiratory symptoms after the infection of Omicron. However, certain demographics, such as the elderly or individuals with important underlying diseases or immune deficiency, are more susceptible to severe or life-threatening cases.

The body's coagulation system can be activated by the infection of SARS-CoV-2 [4,5]. Coagulopathy was reported as a frequent complication in patients infected with SARS-CoV-2, with thrombotic complications observed in nearly 30% of severe COVID-19 cases [6–8]. Previous research has indicated that the extent of coagulation abnormalities was directly related to the severity of COVID-19 [9,10]. Our previous study also found that severe COVID-19 patients with pronounced coagulation dysfunction upon admission were more likely to experience deterioration in their health and mortality [5]. It is beneficial to understand disease progression and carry out precise treatment to clarify the characteristics and pathogenesis of coagulation disorder of COVID-19.

The Omicron variant was identified as exhibiting higher infectivity but lower pathogenicity, leading to milder clinical features compared to the original SARS-CoV-2 strain and other variants [11–13]. The strong infectivity of Omicron has resulted in a significant number of individuals contracting the virus globally, and the number of deaths and severe cases still cannot be underestimated. There were few reports on the coagulation function characteristics and their relationship with clinical outcomes of Omicron-infected patients. This study aims to elucidate the differences in coagulation function among patients infected with the Omicron variant and the original strain. Additionally, it seeks to analyze the variations in coagulation function among severe Omicron-infected patients with diverse clinical outcomes. These findings may help formulate appropriate therapeutic approaches for the Omicron variant or other evolving variants associated with coagulopathy in the future.

2. Materials and Methods

2.1. Participants

This study included 73 severe patients infected with the Omicron variant who were hospitalized at Wuhan First Hospital from 9 December 2022 to 9 January 2023, as well as 71 severe patients infected with the original SARS-CoV-2 strain who were hospitalized at the same hospital from 12 February to 20 March 2020. All patients who were enrolled tested positive for nucleic acid, confirming a SARS-CoV-2 infection. They also underwent a coagulation function test within three days of admission. The data on coagulation function, liver function, and inflammatory factors from 61 healthy controls (elderly population with an average age of 69.8 ± 5.3 years) who conducted physical examinations at Wuhan First Hospital in February 2019 were used as control references. The patients infected with the Omicron variant were categorized into two groups based on their outcomes during hospitalization: non-survivor group (15 cases) and survivor group (58 cases). A patient was classified as a severe case if any of the following clinical scenes were present: (1) respiratory rate of 30 /min; (2) oxygen saturation ≤ 93%; and (3) arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤ 300 mmHg (1 mmHg = 0.133 kPa). The study was approved by the Ethics Committee of Wuhan First Hospital, and patient consent was waived given the retrospective nature of this study.

2.2. Data Collection

The general information (age, gender, initial symptoms, and coexisting disorders), clinical characteristics, and laboratory data of the patients included in the study were collected from electronic medical records at the time of admission. The initial results of the patients' coagulation data within three days of admission were presented and analyzed. The coagulation function was assessed through the following parameters: fibrinogen (FIB, normal range of 2–4 g/L), activated partial thromboplastin time (APTT, normal range of 20–40 s), prothrombin time (PT, normal range of 9–13 s), thrombin time (TT, normal range of 14–21 s), international normalized ratio (INR, normal range of 0.7–1.3), D-Dimers (D-D, normal range of 0–0.55 mg/L), and platelet count (PLT, normal range of 125–350 × 10^9 /L). For other laboratory data (alanine aminotransferase (ALT, normal range of 7–45 U/), aspartate aminotransferase (AST, normal range of 13–35 U/L), lactate dehydrogenase (LDH, normal range of 114–250 U/L), and C-reactive protein (CRP, normal range of 0–5 mg/L). The relevant results were recorded and analyzed based on the test time closest to the coagulation test.

2.3. Statistical Analysis

Continuous variables were characterized by their means and standard deviations or medians and interquartile ranges (IQR) values. Categorical variables were expressed in terms of counts and percentages. The independent group *t*-test was applied to continuous variables that were normally distributed; otherwise, the Mann-Whitney test was utilized. Categorical variables were compared using the chi-square test, while the Fisher exact test was used in situations where data were limited. Statistical analyses were performed using Graphpad Prism 9.0 software. A two-sided α of less than 0.05 was considered statistically significant.

3. Results

3.1. Demographics and Patient Characteristics

The demographics and clinical characteristics of the patients enrolled in this study are shown in Table 1. The median age of Omicron-infected patients was found to be higher compared to those infected with the original strain (74.0 years [IQR, 68.5–84.0] *vs.* 65.0 years [IQR, 56.5–71.5], $P < 0.001$). The proportion of male patients in the Omicron variant group was slightly higher than that in the original strain group, but there was no statistically significant difference (68.0% *vs*. 53.5%, $P = 0.065$). The median duration from the onset of illness to hospital admission for patients infected with the Omicron variant and the original strain infected patients was 8.0 days (IQR, 3.5–9.0) and 12.0 days (IQR, 7.0–21.0), respectively ($P < 0.001$). On admission, 91.7% of the Omicron-infected patients and 97.2% of those infected with the original strain exhibited a typical CT finding of ground-glass opacity and/or patchy shadowing. There was no difference in the initial symptom incidence between the two groups of patients except for shortness of breath. Fever, dry cough, chest tightness, and fatigue were the most common initial symptoms in both groups of patients. Hypertension, diabetes, cardiovascular, and cerebrovascular disease were the prevailing coexisting disorders. In addition, the proportions of Omicron-infected patients with hypertension (74.0% *vs*. 31.0%, $P < 0.001$) and cardiovascular/cerebrovascular disease (32.9% *vs*. 16.9%, $P < 0.001$) were significantly higher than those infected with the original strain.

Table 1. Comparison of demographic and baseline characteristics among patients infected with the original SARS-CoV-2 strain and the Omicron variant.

Characteristics	Original strain (*n* = 71)	Omicron variant (*n* = 73)	*P* value
Age, Median (IQR)—years	65.0 (56.5–71.5)	74.0 (68.5–84.0)	<0.001
Gender			
Male [*n* (%)]	38 (53.5)	50 (68.0)	0.065
Female [*n* (%)]	33 (46.5)	23 (32.0)	
Onset of symptom to hospital admission—days	12.0 (7.0–21.0)	8.00 (3.50–9.00)	<0.001
CT findings of ground-glass opacity and/or patchy shadowing [*n* (%)]	69 (97.2)	67 (91.7)	0.275
Initial symptoms [*n* (%)]			
Fever	48 (67.6)	53 (72.6)	0.512
Dry cough	33 (46.5)	39 (53.4)	0.405
Chest tightness	15 (21.1)	7 (9.6)	0.054
Fatigue	13 (18.3)	12 (16.4)	0.767
Chest pain	4 (5.6)	0 (0.0)	0.057
Shortness of breath	3 (4.2)	15 (20.5)	0.003
Dyspnea	2 (2.8)	4 (5.5)	0.681
Vomiting	2 (2.8)	2 (2.7)	>0.99
Chill	1 (1.4)	2 (2.7)	>0.99
Diarrhea	1 (1.4)	1 (1.4)	>0.99
Headache	1 (1.4)	2 (2.7)	>0.99
Nausea	1 (1.4)	0 (0.0)	0.493
Dizziness	1 (1.4)	7 (9.6)	0.063
Anorexia	1 (1.4)	2 (2.7)	>0.99
Coexisting disorders [*n* (%)]			
Hypertension	22 (31.0)	54 (74.0)	<0.001
Cardiovascular and/or cerebrovascular disease	12 (16.9)	35 (32.9)	<0.001

Diabetes	15 (21.1)	18 (24.7)	0.614
Chronic respiratory disease	4 (5.6)	9 (12.3)	0.161
Hepatopathy	4 (5.6)	3 (4.1)	0.717
Malignancy	1 (1.4)	2 (2.7)	>0.99

Data are median (IQR) or *n* (%). *P* values comparing patients in the original strain group and the Omicron variant group are from χ^2 test, Fisher's exact test, or Mann-Whitney U test. Original strain: the patients infected with the original SARS-CoV-2 strain. Omicron variant: the patients infected with the SARS-CoV-2 Omicron variant.

3.2. Comparison of Blood Coagulation between Patients Infected with the Omicron Variant and the Original Strain

Compared with the healthy controls, patients with Omicron infection had significant performances with coagulation dysfunction, abnormal liver function, and inflammatory manifestations characterized by substantial elevations in values of FIB, APTT, PT, INR, D-D, ALT, AST, LDH, CRP, and a decrease in PLT count ($P < 0.05$) (Figure 1 & Table 2). Furthermore, the FIB, APTT, PT, and D-D values of patients with Omicron infection were even markedly higher than those of patients with the original strain infection ($P < 0.05$), while the PLT count of patients with Omicron infection was dramatically lower than that of patients with original strain infection ($P < 0.001$) (Figure 1 & Table 2). The proportions of Omicron-infected patients with FIB, APTT, PT, and D-D above normal reference values, as well as PLT levels below normal reference values, were significantly elevated ($P < 0.01$) (Table 2). The FIB value of patients with Omicron infection was much higher than that of patients with the original strain infection (5.07 g/L [IQR, 4.28–6.25] *vs*. 3.96 g/L [IQR, 3.42–4.17]; $P < 0.001$). However, the values of APTT (36.30 s [IQR, 32.50–42.20] *vs*. 26.30 s [IQR, 24.10–28.90]; $P < 0.001$) and PT (12.8 s [IQR, 11.45–13.80] *vs*. 11.60 s [IQR, 11.00–12.10]; $P < 0.001$) were significantly elevated in patients with Omicron infection than those infected with the original strain (Table 2). Furthermore, the PLT value of patients with Omicron infection was much lower than that of patients with the original strain infection (168.00×10^9 /L [IQR, 129.00–211.00] *vs*. 240.00×10^9 /L [IQR, 194.00–333.00]; $P < 0.001$). Simultaneously, D-D was significantly higher in the Omicron-infected patients compared to those infected with the original strain (0.83 mg/L [IQR, 0.52–1.63] *vs*. 0.55 mg/L [IQR, 11.00–12.10], $P < 0.05$). Nevertheless, no difference could be observed in the TT and INR values between the two groups of patients ($P > 0.05$).

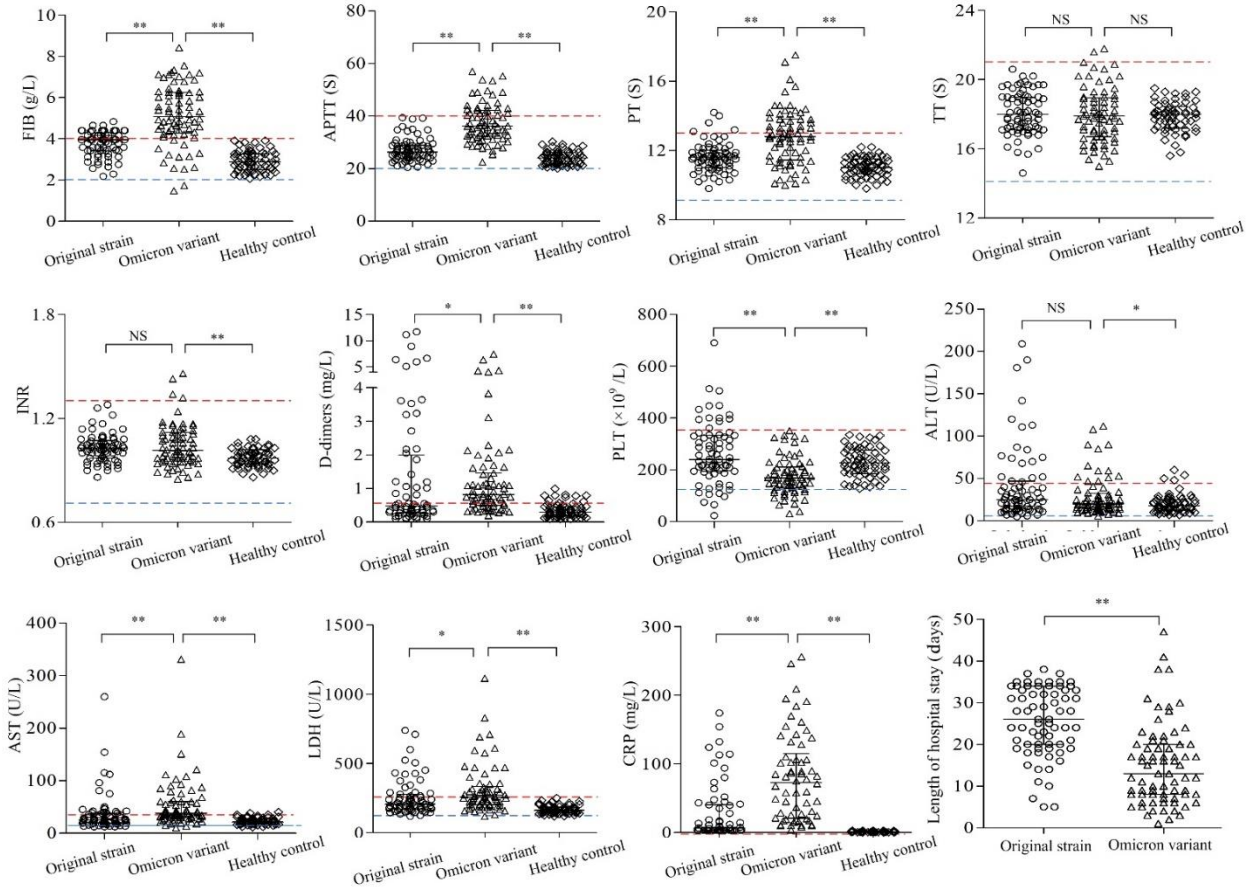

Figure 1. Comparison of blood coagulation, liver function indicators, and inflammatory factors between patients with Omicron infection and original strain infection. The values of blood coagulation parameters (FIB, PT, APTT, TT, INR, D-D, and PLT), liver

function indicators (ALT and AST), and inflammatory factors (LDH and CRP) of the original strain-infected patients (circle), Omicron-infected patients (triangle), and healthy controls (diamond) on admission are shown and compared. FIB: fibrinogen; APTT: activated partial thromboplastin time; PT: prothrombin time; TT: thrombin time; INR: international normalized ratio; D-D: D-Dimers; PLT: platelet count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive protein; NS: no significance. * $P < 0.05$. ** $P < 0.01$.

Table 2. Comparison of laboratory findings on admission and clinical outcomes between patients infected with the original SARS-CoV-2 strain and Omicron variant.

Parameters	Original strain (*n* = 71)	Omicron variant (*n* = 73)	Healthy control (*n* = 61)	*P* value	
				P1	*P2*
Coagulation function					
FIB (g/L; normal range 2.00–4.00)	3.96 (3.42–4.17)	5.07 (4.28–6.25)	2.89 (2.50–3.26)	0.000	0.000
Increased cases [*n* (%)]	27 (38.0)	60 (82.2)	0 (0.0)	0.000	0.000
APTT (s; normal range 20.00–40.00)	26.30 (24.10–28.90)	36.30 (32.5–42.2)	24.10 (21.75–26.15)	0.000	0.000
Increased cases [*n* (%)]	0 (0.0)	26 (35.6)	0 (0.0)	0.000	0.000
PT (s; normal range 9.00–13.00)	11.60 (11.00–12.10)	12.80 (11.45–13.80)	11.00 (10.65–11.50)	0.000	0.000
Increased cases [*n* (%)]	6 (8.5)	32 (43.8)	0 (0.0)	0.000	0.000
TT (s; normal range 14.00–21.00)	18.00 (17.10–19.00)	17.90 (16.70–18.95)	18.00 (17.20–18.45)	0.499	0.996
Increased cases [*n* (%)]	0 (0.0)	2 (2.7)	0 (0.0)	0.497	0.500
INR (normal range 0.70–1.30)	1.03 (0.97–1.08)	1.02 (0.96–1.12)	0.97 (0.94–1.02)	>0.99	0.001
Increased cases [*n* (%)]	1 (1.4)	5 (6.8)	0 (0.0)	0.209	0.063
D-D (mg/L; normal range 0.00–0.55)	0.55 (0.30–3.24)	0.83 (0.52–1.63)	0.29 (0.18–0.46)	0.029	0.000
Increased cases [*n* (%)]	33 (46.5)	52 (71.2)	8 (13.1)	0.003	0.000
PLT (10^9/L; normal range 125–350)	240.00 (194.00–333.00)	168.00 (129.00–211.00)	226.00 (185.50–276.00)	0.000	0.000
Decreased cases [*n* (%)]	8 (11.3)	16 (21.9)	0 (0.0)	0.086	0.019
Liver function					
ALT (U/L; normal range 7–45)	25.00 (14.00–47.00)	20.00 (14.00–33.50)	18.00 (12.50–25.50)	0.357	0.049
Increased cases [*n* (%)]	19 (26.8)	14 (19.1)	4 (6.6)	0.966	0.033
AST (U/L; normal range 13–35)	25.00 (19.00–38.00)	38.00 (29.00–60.00)	21.00 (17.00–27.50)	0.000	0.000
Increased cases [*n* (%)]	21 (29.6)	39 (53.4)	2 (3.3)	0.004	0.000
Inflammatory indicators					
LDH (U/L; normal range 114–250)	207.00 (171.00–278.00)	250.00 (185.00–317.00)	162.00 (143.50–184.00)	0.034	0.000
Increased cases [*n* (%)]	20 (28.2)	35 (47.9)	0 (0.0)	0.015	0.000
CRP (mg/L; normal range 0.00–5.00)	6.27 (3.11–41.30)	49.20 (10.80–104.05)	1.20 (0.65–2.20)	0.000	0.000
Increased cases [*n* (%)]	35 (49.3)	60 (82.2)	0 (0.0)	0.000	0.000
Clinical outcomes					
Length of hospital stay—d	26.00 (20.00–34.00)	20.00 (13.00–29.00)	/	0.000	/
Death cases [*n* (%)]	4 (5.6)	15 (20.5)	/	0.008	/

Data are median (IQR) or *n* (%). *P1* values comparing patients in the original strain group and in the Omicron variant group, and *P2* values comparing patients in the Omicron variant group and the healthy controls were from χ^2 test, Fisher's exact test, or Mann-Whitney U test. Original strain: patients infected with the original SARS-CoV-2 strain. Omicron variant: patients infected with the SARS-CoV-2 Omicron variant. FIB: fibrinogen; APTT: activated partial thromboplastin time; PT: prothrombin time; TT: thrombin time; INR: international normalized ratio; D-D: D-Dimers; PLT: platelet count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive protein.

Moreover, it was observed that the Omicron-infected patients displayed elevated levels of AST (38.00 U/L [IQR, 29.00–60.00] *vs*. 25.00 U/L [IQR, 19.00–38.00], $P < 0.001$), LDH (250.00 U/L [IQR, 185.00–317.00] *vs*. 207.00 U/L [IQR, 171.00–278.00], $P < 0.05$), and CRP (49.20 mg/L [IQR, 10.80–104.05] *vs*. 6.27 mg/L [IQR, 3.11–41.30], $P < 0.001$) compared to those of the original strain-infected patients (Figure 1 & Table 2). The Omicron-infected patients possessed a reduced duration of hospitalization (20 days [IQR, 13–29] *vs*. 26 days [IQR, 20–34, $P < 0.001$] but a higher rate of mortality (20.5% *vs*. 5.6%, $P < 0.01$) compared to patients infected with the original strain (Table 2). Above all, individuals with Omicron infection exhibited more severe coagulation disorders, worse liver function, and stronger inflammatory responses than those infected with the original strain.

3.3. Comparison of Blood Coagulation between Survivors and Non-Survivors with Omicron Infection

To elucidate the relationship between blood coagulation and clinical outcomes in the Omicron-infected patients, several hematological findings in the laboratory are presented and compared between survivors and non-survivors (Figure 2 & Table 3). The values of FIB (6.11 g/L [IQR, 4.87–6.34] *vs*. 4.88 g/L [IQR, 4.17–5.89], $P < 0.05$) and D-D

(1.12 mg/L [IQR, 1.07–2.13] *vs*.0.74 mg/L [IQR, 0.64–1.33], $P < 0.05$) were found to be higher in individuals who did not survive as compared to those who survived. Nevertheless, no statistical differences could be found in the values of APTT, PT, TT, INR, and PLT. The values of LDH (358.00 U/L [IQR, 248.00–575.00] *vs*. 238.50 U/L [IQR, 172.50–297.25], $P < 0.01$) and CRP (85.50 mg/L [IQR, 57.80–149.00] *vs*. 33.85 mg/L [IQR, 9.91–101.25], $P < 0.05$) were significantly higher in non-survivors compared to survivors. However, no differences were observed in the values of ALT and AST.

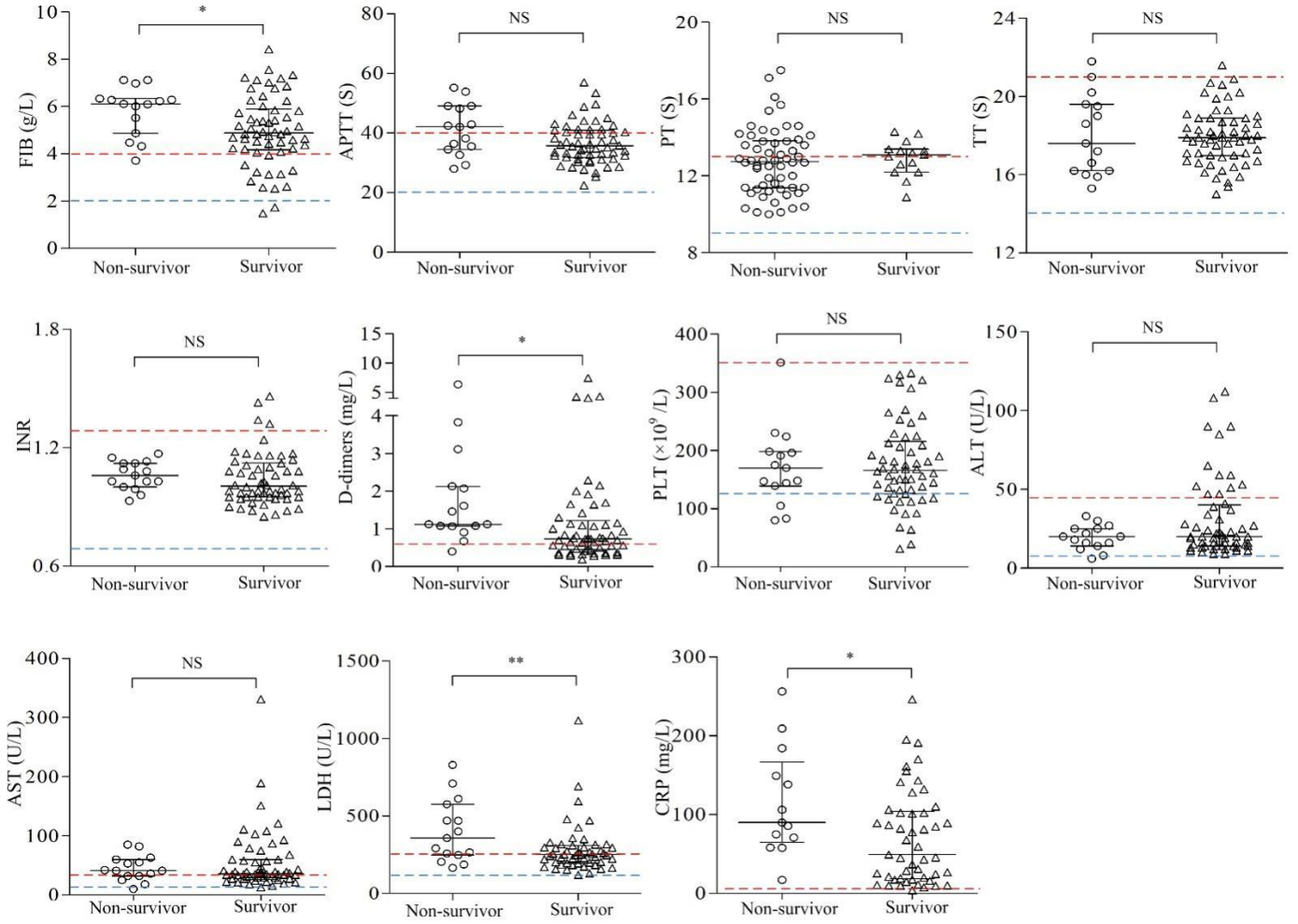

Figure 2. Comparison of blood coagulation, liver function indicators, and inflammatory factors between survivors and non-survivors with Omicron infection. The values of blood coagulation parameters (FIB, PT, APTT, TT, INR, D-D, and PLT), liver function indicators (ALT and AST), and inflammatory factors (LDH and CRP) of the survivors (triangle) and non-survivors (circle) on admission are shown and compared. FIB: fibrinogen; APTT: activated partial thromboplastin time; PT: prothrombin time; TT: thrombin time; INR: international normalized ratio; D-D: D-Dimers; PLT: platelet count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive protein; NS: no significance. * $P < 0.05$. ** $P < 0.01$.

3.4. Correlation Analysis of Blood Coagulation with Liver Function and Inflammatory Factors in Omicron-Infected Patients

The correlation analysis results of coagulation function parameters with the indexes of liver function and inflammatory factors in the Omicron-infected patients are displayed in Figure 3. FIB was positively correlated with LDH ($r = 0.446$, $P < 0.001$) and CRP ($r = 0.557$, $P < 0.001$). PT exhibited a positive correlation with CRP levels ($r = 0.254$, $P < 0.05$). APTT was positively correlated with AST ($r = 0.330$, $P < 0.01$) and CRP ($r = 0.310$, $P < 0.05$). No relevance was found between D-D levels with liver function parameters and inflammatory indexes. Overall, the coagulation parameters have a close connection to the indexes of liver function and inflammatory factors, suggesting that the blood coagulation of Omicron-infected patients may be extensively influenced by liver function and inflammation.

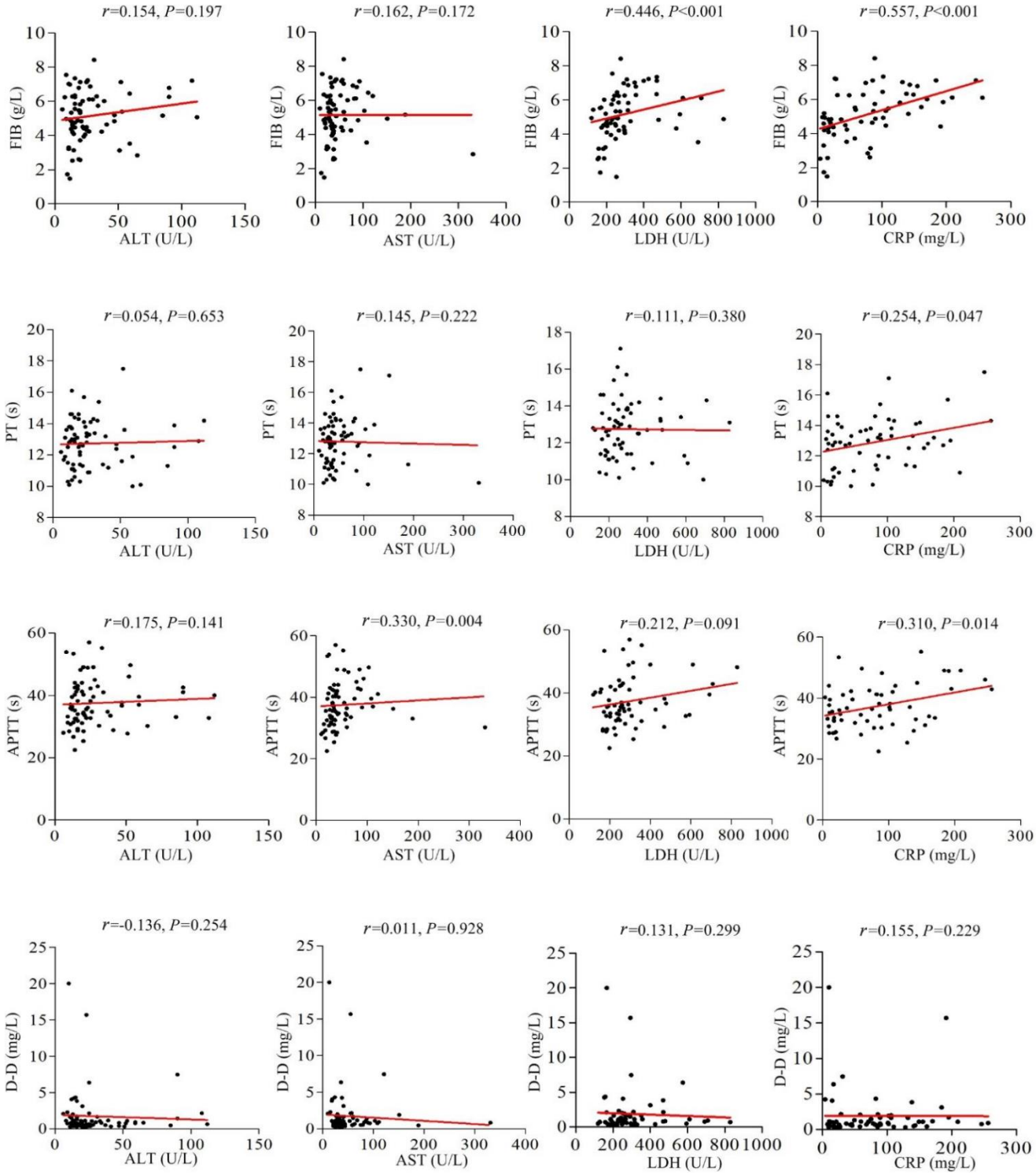

Figure 3. Correlation analysis of blood coagulation with liver function indicators and inflammatory factors in patients infected with the Omicron variant. The correlation of blood coagulation parameters (FIB, PT, APTT, and D-D) with liver function indicators (ALT and AST) and inflammatory factors (LDH and CRP) were analyzed by nonparametric Spearman correlation test. Spearman correlation coefficients (*r*) and *P* value are depicted in plots. FIB: fibrinogen; APTT: activated partial thromboplastin time; PT: prothrombin time; D-D: D-Dimers; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive protein.

Table 3. Comparison of laboratory findings on admission and clinical outcomes between survivors and non-survivors infected with the SARS-CoV-2 Omicron variant.

Parameters	**Survivors (*n* = 58)**	**Non-survivors (*n* = 15)**	***P* value**
Coagulation function			
FIB (g/L; normal range 2.00–4.00)	4.88（4.17–5.89）	6.11(4.87–6.34)	0.032

Increased cases [*n* (%)]	46 (79.3)	14 (93.3)	0.375
APTT (s; normal range 20.00–40.00)	35.75 (31.78–41.03)	42.10 (34.50–49.10)	0.060
Increased cases [*n* (%)]	18 (31.0)	8 (53.3)	0.108
PT (s; normal range 9.00–13.00)	12.75 (11.38–13.83)	13.10 (12.20–13.40)	0.512
Increased cases [*n* (%)]	23 (39.7)	8 (53.3)	0.339
TT (s; normal range 14.00–21.00)	17.90 (16.98–18.90)	17.60 (16.20–19.60)	0.946
Increased cases [*n* (%)]	1 (1.7)	1 (6.7)	0.371
INR (normal range 0.70–1.30)	1.01 (0.95–1.12)	1.06 (1.00–1.12)	0.221
Increased cases [*n* (%)]	5 (8.6)	0 (0.0)	0.576
D-D (mg/L; normal range 0.00–0.55)	0.74 (0.64–1.33)	1.12 (1.07–2.13)	0.012
Increased cases [*n* (%)]	38 (65.5)	14 (93.3)	0.072
PLT (10^9/L; normal range 125–350)	166.00 (125.75–215.50)	170.00 (139.00–198.00)	0.978
Decreased cases [*n* (%)]	13 (22.4)	3 (20.0)	>0.99
Liver function			
ALT (U/L; normal range 7–45)	20.00 (14.00–42.50)	20.00 (14.00–25.00)	0.302
Increased cases [*n* (%)]	14 (24.1)	0 (0.0)	0.080
AST (U/L; normal range 13–35)	36.00 (29.00–60.00)	41.00 (32.00–60.00)	0.800
Increased cases [*n* (%)]	29 (50.0)	10 (66.7)	0.249
Inflammatory indicators			
LDH (U/L; normal range 114–250)	238.50 (172.50–297.25)	358.00 (248.00–575.00)	0.006
Increased cases [*n* (%)]	24 (41.4)	11 (84.6)	0.027
CRP (mg/L; normal range 0.00–5.00)	33.85 (9.91–101.25)	85.50 (57.80–149.00)	0.031
Increased cases [*n* (%)]	47 (81.0)	13 (86.7)	0.897

Data are median (IQR) or n (%). *P* values comparing patients in the survivor group and in the non-survivor group are from χ^2 test, Fisher's exact test, or Mann-Whitney U test. Survivors: patients in the surviving group. Non-survivors: patients in the dead group. FIB: fibrinogen; APTT: activated partial thromboplastin time; PT: prothrombin time; TT: thrombin time; INR: international normalized ratio; D-D: D-Dimers; PLT: platelet count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive protein.

4. Discussion

The overall pathogenicity of the Omicron variant is prominently reduced, with a notably high transmission speed [14]. Although the proportion of patients experiencing severe disease is relatively low, the absolute number of severe cases remains significant due to a large population base, especially the enormous elderly population in China. Numerous reports were carried out on coagulation dysfunction following infection with the original SARS-CoV-2 strain, yet the characteristics of coagulation function of patients with Omicron infection remain to be elucidated. In this study, we observed the coagulation function characteristics of the patients infected with the Omicron variant in comparison to those infected with the original strain and healthy elderly individuals. The median age of the Omicron-infected patients was greater than that of the original strain-infected patients. This indicates that older individuals are at a higher risk of experiencing severe COVID-19 symptoms and necessitate hospitalization treatment during the COVID-19 Omicron wave, which is consistent with findings from previous studies [15,16]. Additionally, we found that patients infected with the Omicron variant required a shorter duration from onset to hospitalization compared to those infected with the original strain. We analyze the reasons from two perspectives: firstly, the enhanced guarantee and treatment capabilities of medical resources have led to an improvement in providing timely medical care to patients during the rapid transmission period of the Omicron variant; secondly, the period from onset to severe illness requiring medical treatment is shorter, indicating a rapid progression of the disease after the elderly population being infected with the Omicron variant. The proportions of concomitant hypertension and cardiovascular and cerebrovascular diseases in the Omicron-infected patients significantly increased when compared to those infected with the original strain. The mechanism by which the merging of these underlying diseases is more likely to progress to severe illness remains unclear. We believe that these comorbidities can affect vascular function and may subsequently impact the characteristics of coagulation disorders.

The coagulation function parameters FIB, APTT, PT, and D-Dimers were significantly elevated in patients infected with the Omicron variant than those infected with the original strain and the healthy controls. These findings suggest that patients with Omicron infection may exhibit significant coagulation dysfunction, potentially influenced by multiple factors such as advanced age, concomitant cardiovascular and cerebrovascular diseases, medication selection for underlying diseases, and infection with Omicron. An increase in FIB typically signifies a clinical manifestation of blood hypercoagulability, while elevation of APTT, PT, and INR generally means a clinical presentation of low coagulation. These results prompt that most of severe cases with Omicron infection may be associated with disseminated

intravascular coagulation (DIC) [17–19], as evidenced by elevated levels of D-D and decreased value of PLT. The liver is responsible for the synthesis and transportation of numerous coagulation factors and anticoagulants [20,21], and inflammation also plays a significant role in coagulation regulation cascade network [22,23]. ALT and AST can reflect the liver injury. Besides, AST also reflects myocardial damage. LDH widely exists in human organs and tissues and reflects the inflammation and injury present in the liver. CRP is one kind of acute proteins that significantly increases in the plasma when the body is infected or injured, and it is a non-specific and momentous marker of inflammation. The values of AST, LDH, and CRP were significantly higher in patients infected with the Omicron variant compared to those infected with the original strain. The Omicron variant infection seemed to cause more severe organ damage (especially liver and heart) and inflammatory storm in severely ill patients, which may be attributed to the fact that these patients with Omicron variant infection have older age and more underlying diseases combined and the possibility that SARS-CoV-2 infection of different strains may only serve as a triggering factor.

In patients infected the original strain, coagulation abnormalities were considered to be indicators of severe disease and adverse clinical outcomes [10,24,25]. In this study, the enrolled Omicron-infected patients were divided into the survivor group and the non-survivor group. The values of FIB, D-D, LDH, and CRP were significantly higher in the non-survivor group than those in the survivor group. These results align with the conclusions drawn from our previous research on patients with the original strain of infection [5]. Therefore, FIB, D-D, LDH, and CRP can serve as effective biomarkers for predicting disease prognosis and clinical outcomes both in patients with original strain infection and Omicron variant infection. Furthermore, early monitoring of coagulation function, liver function, and inflammatory may be essential for establishing an accurate therapeutic strategy, particularly in preventing disease progression.

Acknowledgments

We extend our gratitude to all healthcare workers and patients who were involved in this study.

Author Contributions

Y.Z. (Yanhong Zhang) and L.L. (Li Li) contributed equally to this study. Conceptualization, methods, and investigation, Y.Z. (Yanhong Zhang) and L.L. (Li Li); formal analysis, S.Z., Y.X., Z.Y., C.L., and Y.Z. (Yu Zhang); writing—original draft preparation: W.L.; writing—review and editing: L.L. (Lei Liu); visualization and data curation, Y.Z. (Yao Zheng) and B.H.; supervision, W.L. and L.L. (Lei Liu). All authors have read and agreed to the published version of the manuscript.

Ethics Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Wuhan First Hospital ([2023]004-01 on 1 March 2023).

Informed Consent Statement

Patient consent was waived due to the retrospective nature of this study.

Funding

This work was supported by the Medical Youth Top Talents of Hubei Province (Eweitong [2023] 65th) and the Open Foundation of Hubei Province Key Laboratory (ZZYKF202201).

Declaration of Competing Interest

The authors declared no conflict of interests.

References

1. WHO coronavirus (COVID-19) dashboard. Available online: https://covid19.who.int (accessed on 22 August 2023).
2. Pachetti M, Marini B, Benedetti F, Giudici F, Mauro E, Storici P, et al. Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase variant. *J. Transl. Med.* **2020**, *18*, 179.
3. Tian D, Sun Y, Xu H, Ye Q. The emergence and epidemic characteristics of the highly mutated SARS-CoV-2 Omicron variant. *J. Med. Virol.* **2022**, *94*, 2376–2383.
4. Long X, Zhang Z, Zou W, Ling J, Li D, Jing L, et al. Coagulopathy of patients with COVID-19 is associated with infectious and inflammatory markers. *Risk. Manag. Healthc. Policy* **2020**, *13*, 1965–1975.

5. Zhang Y, He L, Chen H, Lu S, Xiong Y, Liu J, et al. Manifestations of blood coagulation and its relation to clinical outcomes in severe COVID-19 patients: retrospective analysis. *Int. J. Lab. Hematol.* **2020**, *42*, 766–772.
6. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood* **2020**, *136*, 489–500.
7. Kruse JM, Magomedov A, Kurreck A, Münch FH, Koerner R, Kamhieh-Milz J, et al. Thromboembolic complications in critically ill COVID-19 patients are associated with impaired fibrinolysis. *Crit. Care* **2020**, *24*, 676.
8. Wool GD, Miller JL. The impact of COVID-19 disease on platelets and coagulation. *Pathobiology* **2021**, *88*, 15–27.
9. Arachchillage DRJ, Laffan M. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J. Thromb. Haemost.* **2020**, *18*, 1233–1234.
10. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin. Chim. Acta.* **2020**, *506*, 145–148.
11. Shuai H, Chan JF, Hu B, Chai Y, Yuen TT, Yin F, et al. Attenuated replication and pathogenicity of SARS-CoV-2 B.1.1.529 Omicron. *Nature* **2022**, *603*, 693–699.
12. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, et al. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. *Lancet* **2022**, *399*, 437–446.
13. Meo SA, Meo AS, Al-Jassir FF, Klonoff DC. Omicron SARS-CoV-2 new variant: global prevalence and biological and clinical characteristics. *Eur. Rev. Med. Pharmacol. Sci.* **2021**, *25*, 8012–8018.
14. Kandeel A, Moatasim Y, Fahim M, Bahaaeldin H, El-Shesheny R, Roshdy WH, et al. Comparison of SARS-Cov-2 omicron variant with the previously identified SARS-Cov-2 variants in Egypt, 2020–2022: insight into SARS-Cov-2 genome evolution and its impact on epidemiology, clinical picture, disease severity, and mortality. *BMC Infect. Dis.* **2023**, *23*, 542.
15. Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and outcomes of hospitalized patients in South Africa during the COVID-19 omicron wave compared with previous waves. *JAMA* **2022**, *327*, 583–584.
16. Wei YY, Wang RR, Zhang DW, Chen SH, Tan YY, Zhang WT, et al. Differential characteristics of patients for hospitalized severe COVID-19 infected by the omicron variants and wild type of SARS-CoV-2 in China. *J. Inflamm. Res.* **2023**, *16*, 3063–3078.
17. Kawano N, Wada H, Uchiyama T, Kawasugi K, Madoiwa S, Takezako N, et al. Analysis of the association between resolution of disseminated intravascular coagulation (DIC) and treatment outcomes in post-marketing surveillance of thrombomodulin alpha for DIC with infectious disease and with hematological malignancy by organ failure. *Thromb. J.* **2020**, *18*, 2.
18. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.* **2020**, *382*, 1708–1720.
19. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J. Thromb. Haemost.* **2020**, *18*, 844–847.
20. Hoffman M. Coagulation in liver disease. *Semin. Thromb. Hemost.* **2015**, *41*, 447–454.
21. He Y, Yao H, Ageno W, Méndez-Sánchez N, Guo X, Qi X. Review article: thromboelastography in liver diseases. *Aliment. Pharmacol. Ther.* **2022**, *56*, 580–591.
22. Witkowski M, Landmesser U, Rauch U. Tissue factor as a link between inflammation and coagulation. *Trends. Cardiovasc. Med.* **2016**, *26*, 297–303.
23. Loof TG, Mörgelin M, Johansson L, Oehmcke S, Olin AI, Dickneite G, et al. Coagulation, an ancestral serine protease cascade, exerts a novel function in early immune defense. *Blood* **2011**, *118*, 2589–2598.
24. Bi X, Su Z, Yan H, Du J, Wang J, Chen L, et al. Prediction of severe illness due to COVID-19 based on an analysis of initial fibrinogen to albumin ratio and platelet count. *Platelets* **2020**, *31*, 674–679.
25. van de Berg TW, Hulshof AM, Nagy M, van Oerle R, Sels JW, van Bussel B, et al. Suggestions for global coagulation assays for the assessment of COVID-19 associated hypercoagulability. *Thromb. Res.* **2021**, *201*, 84–89.