Decreasing Plasma Fibrinogen Levels in the Intensive Care Unit Are Associated with High Mortality Rates in Patients With Sepsis-Induced Coagulopathy

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Abstract
Plasma fibrinogen levels increase in response to infection, but they could also decrease due to degradation as in severe coagulopathy. We evaluated 60 septic patients with their CRP levels over 5.00 mg/dL. The patients were classified into three groups based on the ratio of the maximum or minimum fibrinogen concentration within day 3 to the initial concentration on day 0: down-, flat, and uptrend groups (n = 15, 30, and 15, respectively). Both down- and flat trend groups showed reduced inflammatory markers on day 3, and the degree of platelet loss (10³/µL) and the mortality rate (%) were more remarkable in the down-trend group (−108 vs −42 [p = 0.026] and 46.7 vs 10.0 [p = 0.027]). On day 0, in total 12 and 9 patients were diagnosed with non-overt DIC in the down- and uptrend groups, of which 5 (41.7%) and 1 (11.1%) died within 28 days after admission. In conclusion, decreasing fibrinogen levels in the ICU are associated with high mortality in patients with sepsis followed by decreasing platelet counts, even when they are diagnosed with non-overt DIC.

Keywords
sepsis-induced coagulopathy, SOFA score, fibrinogen, mortality, sepsis

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Introduction
Fibrinogen, a well-known coagulation factor, is also known to be an acute-phase protein that is rapidly produced following the onset of infection and inflammation. It serves as a protective barrier by acting as bacteria-entrapping fibrin matrices, which activate the host immune system either directly or indirectly.1 Due to its role in coagulation, fibrinogen was previously considered a diagnostic criterion for sepsis-induced disseminated intravascular coagulation (DIC). In the DIC diagnostic criteria released by the Japanese Ministry of Health and Welfare (JMHW) in 1983, fibrinogen < 150 mg/dL was considered as a potential risk factor.2 The International Society on Thrombosis and Hemostasis (ISTH) diagnostic criteria released in 2001 also included fibrinogen < 100 mg/dL.3 However, plasma fibrinogen was found to have no effect on the 28-day mortality, and thus was omitted from the new diagnostic criteria proposed by the Japanese Association for Acute Medicine in 2006 and the Japanese Society on Thrombosis and Hemostasis in 2016.4,5 This concept was continued later in the sepsis-induced coagulopathy diagnostic criteria in 2017, which consisted of prothrombin time-international normalized ratio (PT-INR), platelet count, and Sequential Organ Failure Assessment (SOFA) score.6

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This study aimed to investigate the prognostic significance of plasma fibrinogen levels in patients with sepsis-induced coagulopathy. Even though plasma fibrinogen was not currently considered as a risk factor, we hypothesized that changes, and not absolute values, in plasma fibrinogen levels were useful for predicting the prognosis of sepsis patients.

Materials and Methods

Study Design and Participants

This was a single-center, retrospective cohort study of intensive care unit (ICU) patients who were diagnosed with sepsis based on the Sepsis-3 criteria between April 2017 and March 2019.

Measurements

The following data were collected: age, sex, SOFA score, 28-day mortality, white blood cell (WBC) count, platelet count, C-reactive protein (CRP) level, fibrinogen level, D-dimer level, PT-INR, activated partial thromboplastin time (APTT), sites of infection, and treatments provided. The date when CRP concentration reached ≥ 5.00 mg/dL was set as day 0, and data were collected until day 4. DIC scores were calculated based on the ISTH diagnostic criteria with updated cut-off values for D-dimer in 2018. For the scoring for PT-INR, values of < 1.3, 1.3–1.7, and 1.7 < were considered as 0, 1, and 2 points, respectively. A score of ≥ 5 was defined as overt DIC.

Grouping

Patients were classified into three groups based on the pattern of fibrinogen concentration changes. The patterns were determined based on the ratio of the maximum or minimum concentration within day 3 to the initial fibrinogen concentration on day 0. In patients with increasing fibrinogen, the ratio of the maximum to the initial value was calculated. In patients with decreasing fibrinogen, the ratio of the minimum to the initial value was calculated. In patients with a relatively stable fibrinogen trend, the maximum or minimum value was selected as the numerator such that the difference from the initial value became larger. Next, the first and third quantiles of the calculated sets of ratios were obtained, and patients with a fibrinogen level less than the first quantile, patients with the level lying between the first and third quantiles, and patients with a level greater than the third quantile were categorized to the downtrend (n = 15), flat trend (n = 30), and uptrend (n = 15) groups, respectively.

Statistical Analysis

Categorical variables are presented as numbers and percentages and compared using the Fisher’s exact test. Meanwhile, continuous variables were presented as medians and interquartile ranges (IQRs) and compared using the Kruskal-Wallis test and the Mann-Whitney U-test. P-values were adjusted using the Bonferroni method, and values of < 0.05 were considered statistically significant. Survival was estimated using the Kaplan-Meier method, and between-group differences in survival were evaluated using the log-rank test. Univariate and multivariate analyses were performed using logistic regression. All statistical tests were performed using the R version 4.0.3.

Results

Among the 66 patients initially evaluated, 6 patients were excluded due to death within day 4 or low CRP levels < 5.00 mg/dL. Finally, 60 patients were included in the analysis. Plasma fibrinogen concentration reached its maximum or minimum within day 3: median: 57 (IQR: 32–74) hours after the initial measurement. The first quantile, median, and third quantile of the ratio of the maximum or minimum concentration to the initial fibrinogen within days 0 to 3 were 0.744, 0.908, and 1.625, respectively. The ratios were < 0.744, 0.744–1.625, and > 1.625 in the down-, flat, and uptrend groups, respectively.

The patient characteristics were presented in Table 1. Age, sex, SOFA score, the ISTH DIC score, site of infection, and treatment provided were not significantly different among the groups. The medians of WBC counts, platelet counts, CRP levels, and fibrinogen levels at the initial measurement were significantly different, whereas those of coagulation factors, except PT-INR, were not. The uptrend group had significantly lower WBC, CRP, and fibrinogen than the downtrend group (p = 0.002, p = 0.005, and p < 0.001, respectively) and the flat trend group (p = 0.012, p < 0.001, and p < 0.001, respectively). The Kruskal-Wallis test of platelet counts and PT-INR showed significant difference upon arrival (p = 0.041 and p = 0.032, respectively); however, the Mann-Whitney U-tests did not reveal which comparison was significant.

As time progressed from day 0 to 3, platelet counts decreased in all the three groups. The downtrend group showed a decrease from 202 to 74 × 10³/µL (p = 0.007) as well as the flat trend group (from 149 to 95 × 10³/µL, p = 0.028) and the uptrend group (from 119 to 48 × 10³/µL, p = 0.006). The CRP and fibrinogen levels decreased in the downtrend group (p = 0.036 and p = 0.021, respectively), while they increased in the uptrend group (p < 0.001 and p < 0.001, respectively). PT-INR exhibited a statistically significant decrease in the flat and uptrend groups (p = 0.006 and p = 0.001, respectively), but did not in the downtrend group (p = 0.121). Time-course changes in the ISTH DIC score, WBC count, and D-dimer level were not statistically significant among the groups (Figure 1).

The degree of platelet loss in the downtrend group was − 108 × 10³/µL (IQR: − 179 to − 56), which was greater than the flat trend group (− 42 × 10³/µL [IQR: − 76 to − 12], p = 0.026). The CRP level decreased by − 6.34 mg/dL (IQR: − 12.09 to − 3.83) and − 2.78 mg/dL (IQR: − 6.62 to 2.01) in the down- and flat trend groups, but increased by 6.84 mg/dL (IQR: 6.25–8.97) in the uptrend group (down vs flat: p = 0.165; down vs up: p < 0.001; flat vs up: p < 0.001). Comparison of changes in PT-INR revealed that a decrease in the uptrend group (− 0.42 [IQR: − 0.54 to − 0.16]) was greater than the downtrend (− 0.09 [IQR: − 0.19 to − 0.01], p = 0.017) and the
Table 1. Clinicodemographic Patient Characteristics.

| Characteristic                  | Total (n = 60) | Down trend (n = 15) | Flat Trend (n = 30) | Uptrend (n = 15) | p-Value |
|--------------------------------|---------------|---------------------|---------------------|-----------------|---------|
| Age (years)                    | 74 (68-78)    | 72 (68-76)          | 75 (68-78)          | 75 (69-80)      | 0.456   |
| Sex (% female, F/M)            | 36.7, 22/38   | 40.0, 6/9           | 36.7, 11/19         | 33.3, 5/10      | 1       |
| SOFA score                     | 11 (8-13)     | 12 (9-14)           | 10 (7-13)           | 11 (8-14)       | 0.546   |
| 28-day mortality (%), deaths/survivals | 23.3, 14/46     | 46.7, 7/8           | 10.0, 3/27          | 26.7, 4/11      | 0.023   |
| ISTH DIC score                 | Day 0         | 4 (3-5)             | 3 (3-4)             | 4 (2-4)         | 0.149   |
|                                | Day 3         | 4 (3-4)             | 4 (3-5)             | 3 (3-4)         | 0.175   |
| Overt DIC cases                | Day 0         | 16                  | 3                   | 7               | 0.513   |
|                                | Day 3         | 13                  | 5                   | 5               | 0.503   |
| White blood cell (x10^3/μL)    | Day 0         | 8.1 (2.8-15.6)      | 15.8 (10.8-21.5)§   | 8.9 (4.2-15.0)§ | 2.8 (1.6-6.3)‡‡ | < 0.001 |
|                                | Day 3         | 8.9 (4.7-13.7)      | 13.7 (11.8-17.5)‡   | 8.7 (5.2-12.5)‡ | 4.9 (2.8-6.5)‡  | < 0.001 |
| Platelet (x10^3/μL)            | Day 0         | 145 (81-209)        | 202 (87-290)        | 149 (86-212)    | 119 (67-136) | 0.041   |
|                                | Day 3         | 66 (41-122)         | 74 (43-114)         | 95 (57-154)     | 48 (30-62)‡  | 0.021   |
| CRP (mg/dL)                    | Day 0         | 13.0 (8.1-18.6)     | 15.6 (9.6-18.1)§    | 16.6 (10.6-24.4)§ | 7.4 (6.6-9.0)‡ | < 0.001 |
|                                | Day 3         | 13.0 (9.9-17.6)     | 9.5 (4.1-12.6)‡     | 13.6 (9.9-18.1)‡ | 14.7 (13.1-18.9)‡ | 0.019   |
| Fibrinogen (mg/dL)             | Day 0         | 372 (263-489)       | 474 (339-572)§      | 430 (358-517)§  | 207 (194-273)‡ | < 0.001 |
|                                | Day 3         | 421 (326-570)       | 242 (168-400)       | 405 (344-560)§  | 593 (486-643)‡ | < 0.001 |
| Hypofibrinogenemia <150 mg/dL  | Day 0         | 0                   | 0                   | 0               | -       |
|                                | Day 3         | 4                   | 4                   | 0               | 0       |
| D-dimer (μg/dL)                | Day 0         | 8.8 (4.1-14.8)      | 9.4 (7.5-14.15)§    | 8.3 (3.3-15.0)  | 8.0 (4.2-13.1) | 0.515   |
|                                | Day 3         | 9.4 (5.7-18.2)      | 13.7 (6.6-17.6)§    | 8.3 (5.9-19.1)  | 9.0 (6.1-13.3) | 0.703   |
| PT-INR                         | Day 0         | 1.30 (1.15-1.54)    | 1.16 (1.12-1.42)    | 1.27 (1.20-1.44) | 1.58 (1.30-1.79) | 0.032   |
|                                | Day 3         | 1.14 (1.07-1.24)    | 1.16 (1.04-1.17)    | 1.16 (1.07-1.25) | 1.12 (1.09-1.22) | 0.711   |
| APTT (sec)                     | Day 0         | 42.1 (34.3-58.9)    | 37.2 (29.0-56.8)    | 41.2 (35.3-54.6) | 49.4 (38.8-80.0) | 0.141   |
|                                | Day 3         | 51.5 (41.6-65.6)    | 52.9 (39.5-59.1)    | 49.8 (40.5-66.5) | 46.5 (42.7-64.8) | 0.848   |
| Site of infection              | Lung          | 13                  | 2                   | 10              | 1       | 0.108   |
|                                | Abdomen       | 24                  | 7                   | 9               | 8       | 0.276   |
|                                | Urinary Tract | 4                   | 0                   | 3               | 1       | 0.799   |
|                                | Others        | 8                   | 3                   | 4               | 1       | 0.555   |
|                                | Unknown       | 11                  | 3                   | 4               | 4       | 0.564   |
| Treatment                     | Plasmapheresis | 18                  | 6                   | 5               | 7       | 0.079   |
|                                | Antithrombin III | 32                   | 10                  | 11              | 11      | 0.169   |

1p < 0.05 versus the down trend group.
2p < 0.05 versus the flat trend group.
3p < 0.05 versus the uptrend group.

SOFa, Sequential Organ Failure Assessment; DIC, disseminated intravascular coagulation; CRP, C-reactive protein; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time.

flat trend (−0.10 [IQR: −0.25 to −0.01], p = 0.004) groups. While changes in fibrinogen level were all statistically significant (p < 0.001 in all comparisons), those in the ISTH DIC score, WBC count, and D-dimer level were not (Figure 2).

Table 2 shows the number of deaths in patients with overt DIC diagnosed by the ISTH criteria. On day 3, 13 patients were diagnosed with overt DIC. Of these, 7 patients died within 28 days (mortality: 53.8%). This was statistically significant compared with non-overt DIC patients (mortality: 14.9%, 7/47 patients, p = 0.007). On day 0, the mortality rate of patients with overt DIC (37.5%, 6/16 patients) was not significantly higher than that of patients with non-overt DIC (mortality: 18.2%, 8/44 patients, p = 0.168). The ISTH DIC scoring system on day 0 successfully detected critically ill patients, who died within 28 days, in the uptrend group. The mortality rate of patients with overt DIC in the uptrend group was 50.0% (3/6 patients), while that of patients with non-overt DIC was 11.1% (1/9 patients). In the downtrend group, 66.7% (2/3 patients) of overt DIC patients died, but 41.7% (5/12 patients) also died within 28 days. In contrast, DIC scores on day 3 highlighted critical cases in the downtrend group. In total, 4 out of 5 overt DIC patients died in the down-trend group (80.0%), but the mortality of non-overt DIC patients remained at 30.0% (3/10 patients).

In total, 23.3% (14/60 patients) of the patients died within 28 days of ICU admission. The 28-day mortality in the downtrend group was 46.7% (7/15 patients) and was significantly higher than that in the flat trend group (10.0%, 3/30 patients, p = 0.027). The Kaplan-Meier curve of 28-day mortality is shown in Figure 3. The global p-value for the three-group comparison was 0.020. Pairwise log-rank tests with the Bonferroni correction showed a significant difference between the down- and flat trend groups (p = 0.020), but not in other group comparisons.
Considering the significantly higher 28-day mortality of the downtrend group, the flat and uptrend groups were combined into one group, and univariate and multivariate analyses were performed to evaluate the association of the 28-day mortality with the fibrinogen trends and SOFA scores (Table 3). In both analyses, fibrinogen trends and SOFA scores were associated with the 28-day mortality (OR [95% CI]: 4.60 [1.13-18.67], p = 0.031 and 1.29 [1.05-1.59], p = 0.008, respectively).

**Discussion**

Fibrinogen is an acute phase protein whose concentration increases during infection. However, a quarter of patients in this study showed a decreasing trend of fibrinogen concentration as time progressed due to severe coagulopathy. In these patients, the 28-day mortality rate was higher than that in patients with non-decreasing fibrinogen trends.

The JMHW and the ISTH diagnostic criteria for DIC include fibrinogen cut-off values of 150 and 100 mg/dL, respectively.2,3 In our data, only one patient showed a fibrinogen level < 100 mg/dL, three patients had 100–150 mg/dL, and majority (n = 56) had a level > 150 mg/dL. Recent study also showed that hypofibrinogenemia (fibrinogen levels < 150 mg/dL) was observed in 10.3% of patients with infectious diseases.10 These findings suggest that the previously used cut-off value would be applicable to only a small number of sepsis patients. In contrast, the trend classification in our study covered all patients with sepsis regardless of fibrinogen levels. As such, our criterion could be more useful for detecting life-threatening complications in patients with sepsis followed by decreasing platelet counts, namely sepsis-induced coagulopathy.

The initial WBC count, CRP level, and fibrinogen level were significantly different in the uptrend group. This could be attributed to the fact that grouping was performed based on the fibrinogen ratio, and the denominator of this ratio was fixed at the initial fibrinogen level. The uptrend group involved patients with milder inflammation on ICU admission whose CRP and fibrinogen levels were initially lower but then increased. Meanwhile, the CRP levels of the down- and flat trend groups were higher on ICU admission then decreased. Additionally, the 28-day mortality was the highest in the downward trend group, whereas it was the lowest in the flat trend group. These findings indicate that the impact of inflammation upon arrival and consequent admission is not associated with prognosis, and sequential changes in fibrinogen concentrations could predict the prognosis of patients with sepsis.

Logistic regression analyses revealed that fibrinogen trends and SOFA scores were associated with 28-day mortality. There was no significant difference in the median SOFA scores among the three groups, indicating that there was a uniform probability of multiple organ failure regardless of time-course fibrinogen changes. This is reasonable because the coagulation component of SOFA scores is solely explained by platelet counts and is independent of fibrinogen concentration. The 28-day mortality is well-explained from the point of SOFA scores in recent diagnostic criteria but not from the perspective of fibrinogen.6 Our result also supports the importance of measuring fibrinogen levels in sepsis patients with serum levels of CRP > 5.00 mg/dL.

![Figure 1. Time-course changes of ISTH DIC score, WBC count, platelet count, CRP level, fibrinogen level, D-dimer level, and PT-INR from the ICU arrival to day 3. Data were compared between the arrival and day 3, and presented as median and as first and third quantiles. #: 0.01 < P < 0.05, **: 0.001 < P < 0.01, and ###: P < 0.001.](image-url)
The pathophysiological mechanisms of changes in fibrinogen concentration during infection are unclear. We hypothesize that these changes are attributed to differences in the main players in infection, inflammation, and coagulation. Tissue factor (TF) is expressed on the surface of activated endothelial cells and monocytes in response to pathogen-associated molecular patterns and damage-associated molecular patterns. Neutrophil extracellular traps (NETs) are another source of TF that activate the extrinsic pathway of coagulation, form microvascular thrombi, and localize invaded pathogens. This concept is known as immunothrombosis and plays a pivotal role in infection control in microvessels.\textsuperscript{11} Given that fibrinogen is an acute-phase protein, its increase following the onset of infection, which was observed in the uptrend group, is a natural physiological response. In this study, the uptrend group showed high PT-INR and low inflammatory markers on ICU admission. This indicated that as infection was established, inflammatory markers gradually increased over a few days. In contrast, TF promptly activated the extrinsic pathway of coagulation in the course of immunothrombosis, and prolonged PT-INR was observed from day 0.

The contact pathway of coagulation can trigger fibrinolysis, as a course of immunohaemostasis.\textsuperscript{12} Negatively charged

\begin{figure}
\includegraphics[width=\textwidth]{figure2.png}
\caption{Degree of changes in ISTH DIC score, WBC count, platelet count, CRP level, fibrinogen level, D-dimer level, and PT-INR from ICU arrival to day 3. Data were compared between the three fibrinogen trend groups, and presented as median and as first and third quantiles. *: 0.01 < \(P\) < 0.05, **: 0.001 < \(P\) < 0.01, and ***: \(P\) < 0.001.}
\end{figure}
molecules derived from neutrophils (eg, NETs) and activated platelets or pathogens (eg, polyphosphates) induce factor XII (FXII) activation, which in turn lead to the activation of the contact pathway of coagulation, high-molecular-weight kininogen (HK), and the complement system. HK can activate urokinase, which has a catalytic activity towards fibrinogen.\(^{13}\) The differences in the down- and flat trend groups may be attributed to the degree of immunohaemostatic activity. Severer fibrinogen and platelet losses were observed in the downtrend than the flat trend group. In the downtrend group, activation of FXII might be more prominent, urokinase further degraded fibrinogen, and excessive complement activation resulted in thrombocytopenia.

In this study, the ISTH DIC score on day 3 predicted the mortality rate of patients with sepsis, but that on day 0, when CRP concentration reached \(\geq 5.00\) mg/dL, did not. Previous studies revealed that DIC scoring was capable of predicting mortality of septic patients.\(^{3,8}\) Hence, we speculate that this discrepancy on day 0 could be due to small sample size of our dataset. Even though the ISTH DIC score is useful to identify critical cases in patients with sepsis, it does not reflect underlying pathophysiological mechanisms of DIC, and thus may ignore some of life-threatening cases. When we divided patients with overt DIC into three fibrinogen trend groups, our result showed that day 0 DIC scores more sensitively detected deaths in the uptrend than downtrend group. In contrast, DIC scores on day 3 enabled to catch critical cases in the downtrend, but not in the uptrend group. Therefore, this finding implies that both day 0 and 3 DIC scores indicate the severity of sepsis, but

### Table 2. The Number of Total and Dead Patients Who Were Diagnosed With Overt DIC and Non-Overt DIC Based on the ISTH DIC Diagnostic Criteria on Day 0 and Day 3.

|                | Overt DIC | Non-Overt DIC | Overt DIC | Non-Overt DIC |
|----------------|-----------|---------------|-----------|---------------|
|                | Total/Death | Proportion | Total/Death | Proportion | Total/Death | Proportion | Total/Death | Proportion |
| Day 0          | 16/6       | 37.5%        | 44/8       | 18.2%        | 13/7        | 53.8%      | 47/7        | 14.9%      |
| Downtrend      | 3/2        | 66.7%        | 12/5       | 41.7%        | 5/4         | 80.0%      | 10/3        | 30.0%      |
| Flat trend     | 7/1        | 14.3%        | 23/2       | 8.7%         | 5/2         | 40.0%      | 25/1        | 4.0%       |
| Uptrend        | 6/3        | 50.0%        | 9/1        | 11.1%        | 3/1         | 33.3%      | 12/3        | 25.0%      |

DIC, Disseminated Intravascular Coagulation; ISTH, International Society of Thrombosis and Haemostasis.

![Figure 3. Kaplan-Meier 28-day survival curves for the three trend groups. The global \(p\)-value for the three group comparison is 0.020; the \(p\)-value of each pair-wise comparison shows significant differences between the down- and flat trend groups.](image)

6. Clinical and Applied Thrombosis/Hemostasis
would sensitively reflect hypercoagulation on day 0 and hyper-
brinogenolysis on day 3.

The limitation of this study was the relatively small sample
size due to the single-center design. In addition, most critically
ill patients who died within a few days after ICU admission
were not accessed due to lack of time-course data. For severe
cases, study in 2021 has already reported that hypofibrinogenema-
inia in patients with septic DIC is associated with high mortality
rate and platelet loss.14 Our data, together with the previous
study, suggest that a decrease in plasma fibrinogen levels in
patients with sepsis followed by decreasing platelet counts is
associated with a higher mortality rate and greater platelet loss.
The downtrend group exhibited higher CRP and fibrinogen
levels on day 0, and these promptly decreased by day 3. This
could be interpreted as a consequence of deteriorative pathophys-
iological activities, even though infection was ameliorated.
Decreasing fibrinogen levels in non-survivors were also observed
in cases of novel coronavirus pneumonia.14 Hence, we propose
that fibrinogen trends should be monitored in sepsis patients to
identify high-risk patients and provide timely treatments.

Conclusion
Changes in fibrinogen levels in the ICU are associated with the
prognosis of sepsis patients. Both down- and flat-fibrinogen
groups had high WBC counts, CRP levels, and fibrinogen
levels upon arrival. In both groups, infection was under
control on day 3, but coagulopathy was more prompt in the
down-fibrinogen group, resulting in higher rates of 28-day mor-
tality. The ISTH DIC scores on admission predicted the mortal-
ity of patients with increasing fibrinogen, but may not be
sufficient to identify critical cases with decreasing fibrinogen.
Thus, consecutive measurement of fibrinogen could predict
and help improve the prognosis of patients with sepsis.

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Author Contributions
K. Mori, Y. Tsujita, and T. Yamane collected the clinical data and per-
fomed statistical analyses. K. Mori drafted the manuscript. Y. Eguchi
designed and guided the study.

Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to
the research, authorship, and/or publication of this article.

Table 3. Univariate and Multivariate Logistic Regression Analyses for 28-Day Mortality

|                      | Univariate Analysis | Multivariate Analysis |
|----------------------|---------------------|-----------------------|
|                      | OR (95% CI)         | P (Wald’s test)       | OR (95% CI)         | P (Wald’s test) |
| Downward fibrinogen  | 4.75 (1.30-17.35)   | 0.018                 | 1.29 (1.06-1.56)    | 0.011          |
| trend                |                     |                       |                      |                |
| SOFA score           | 6.12 (1.06-35.39)   | 0.021                 | 6.12 (1.06-35.39)   | 0.021          |
|                      | 0.018               | 0.033                 | 0.018               | 0.033          |

OR, Odds Ratio; CI, Confidence Interval; P, P-value; LR Test, Likelihood Ratio Test; Adj. OR, Adjusted Odds Ratio; SOFA, Sequential Organ Failure Assessment.

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References
1. Ko YP, Flick MJ. Fibrinogen is at the interface of host defense and
pathogen virulence in Staphylococcus aureus infection. Semin
Thromb Hemost. 2016;42(4):408-421.
2. Kobayashi N, Maekawa T, Takada M, et al. Criteria for diagnosis
dIC of DIC based on the analysis of clinical and laboratory findings in
345 DIC patients collected by the Research Committee on DIC in
Japan. Bibl Haematol. 1983;(49):265-267.
3. Taylor FB, Toh CH, Hoots WK, et al. Towards definition, clinical
and laboratory criteria, and a scoring system for disseminated
intraocular coagulation. Thromb Haemost. 2001;86(5):1327-
1330.
4. Gando S, Iba T, Eguchi Y, et al. A multicenter, prospective vali-
dation of disseminated intravascular coagulation diagnostic crite-
ria for critically ill patients: comparing current criteria. Crit Care
Med. 2006;34(3):625-631.
5. Asakura H, Takahashi H, Uchiyama T, et al. Proposal for new
diagnostic criteria for DIC from the Japanese Society on
Thrombosis and Hemostasis. Thromb J. 2016;14:42.
6. Iba T, Nisio MD, Levy JH, et al. New criteria for sepsis-induced
coagulopathy (SIC) following the revised sepsis definition: a re-
trospective analysis of a nationwide survey. BMJ Open. 2017;7(9):e017046.
7. Singer M, Deutschman CS, Seymour CW, et al. The third interna-
tional consensus definitions for sepsis and septic shock (sepsis-3).
JAMA. 2016;315(8):801-810.
8. Suzuki K, Wada H, Imai H, et al. A re-evaluation of the D-dimer
cut-off value for making a diagnosis according to the ISTH
overt-DIC diagnostic criteria: communication from the SSC of
the ISTH. J Thromb Haemost. 2018;16(7):1442-1444.
9. Statz S, Sabal G, Walborn A, et al. Angiopoietin 2 levels in the
risk stratification and mortality outcome prediction of sepsis-associated
coagulopathy. Clin Appl Thromb Hemost. 2018;24(8):1223-1233.
10. Kawasugi K, Wada H, Honda G, et al. Hypofibrinogenemia is
associated with a high degree of risk in infectious diseases: a post-hoc analysis of post-marketing surveillance of patients with
disseminated intravascular coagulation treated with thrombomo-
dulin alfa. Thromb J. 2021;19(1):12.
11. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. *Nat Rev Immunol*. 2013;13(1):34-45.

12. Delabranche X, Helms J, Meziani F. Immunohaemostasis: a new view on haemostasis during sepsis. *Ann Intensive Care*. 2017;7(1):117.

13. Weitz JI, Leslie B. Urokinase has direct catalytic activity against fibrinogen and renders it less clottable by thrombin. *J Clin Invest*. 1990;86(1):203-212.

14. 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(4):844-847.