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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 ($10^3/\mu L$) 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 Haemostasis (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[7] 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.[8] 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.[9] 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 with the Bonferroni correction 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 $74 \times 10^3/\mu L$ ($p = 0.007$) as well as the flat trend group (from 149 to $95 \times 10^3/\mu L$, $p = 0.028$) and the uptrend group (from 119 to $48 \times 10^3/\mu L$, $p = 0.006$). 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 $-108 \times 10^3/\mu L$ (IQR: −179 to −56), which was greater than the flat trend group ($-42 \times 10^3/\mu L$ [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)	Groups			p-Value
			Downtrend (n = 15)	Flat Trend (n = 30)	Uptrend (n = 15)	
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)	4 (4-5)	0.149
	Day 3	4 (3-4)	4 (3-5)	3 (3-4)	4 (4-4)	0.175
Overt DIC cases	Day 0	16	3	7	6	0.513
	Day 3	13	5	5	3	0.503
White blood cell ($x10^3/\mu L$)	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 ($x10^3/\mu L$)	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	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 (6.1-11.3)	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)	1.13 (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

[†] $p < 0.05$ versus the downtrend group.
[‡] $p < 0.05$ versus the flat trend group.
[§] $p < 0.05$ 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 downtrend 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.

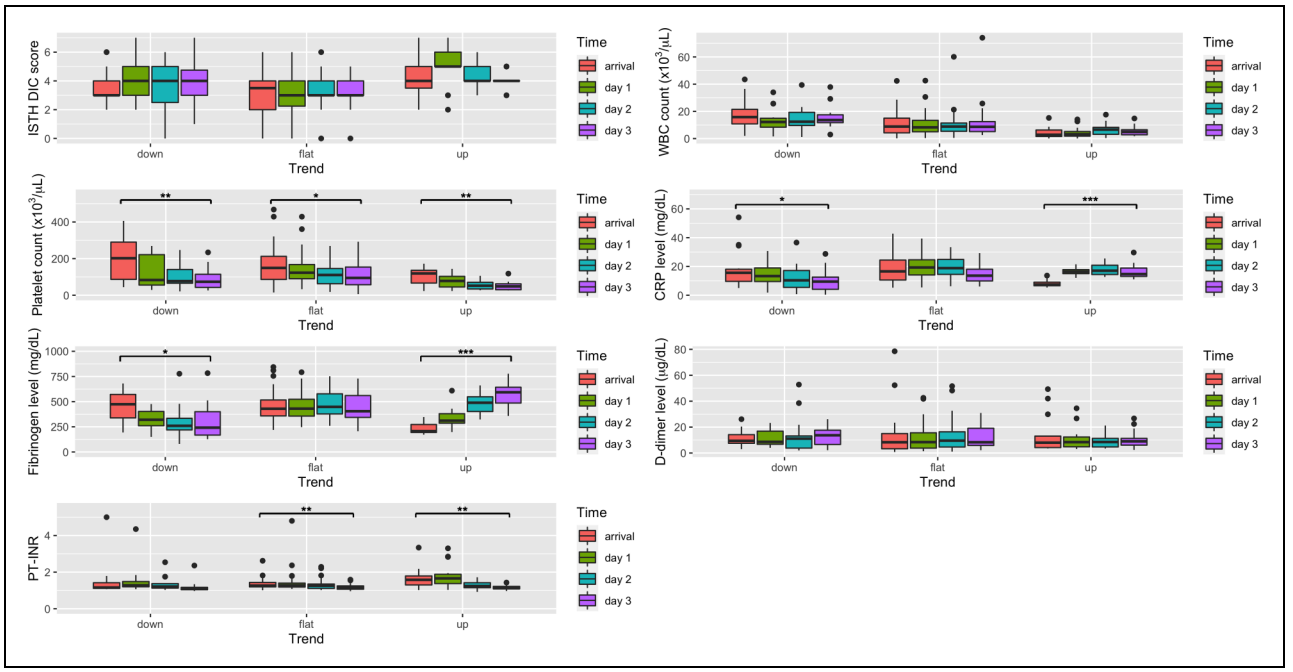

Figure 1. Time-course changes of ISTH DIC score, WBC count, platelet count, CRP level, fibrinogen level, D-dimer level, and PT-INR from the ICU arrival to day 3. Data were compared between the arrival and day 3, and presented as median and as first and third quantiles. *: $0.01 < P < 0.05$, **: $0.001 < P < 0.01$, and ***: $P < 0.001$.

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. In addition, 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.

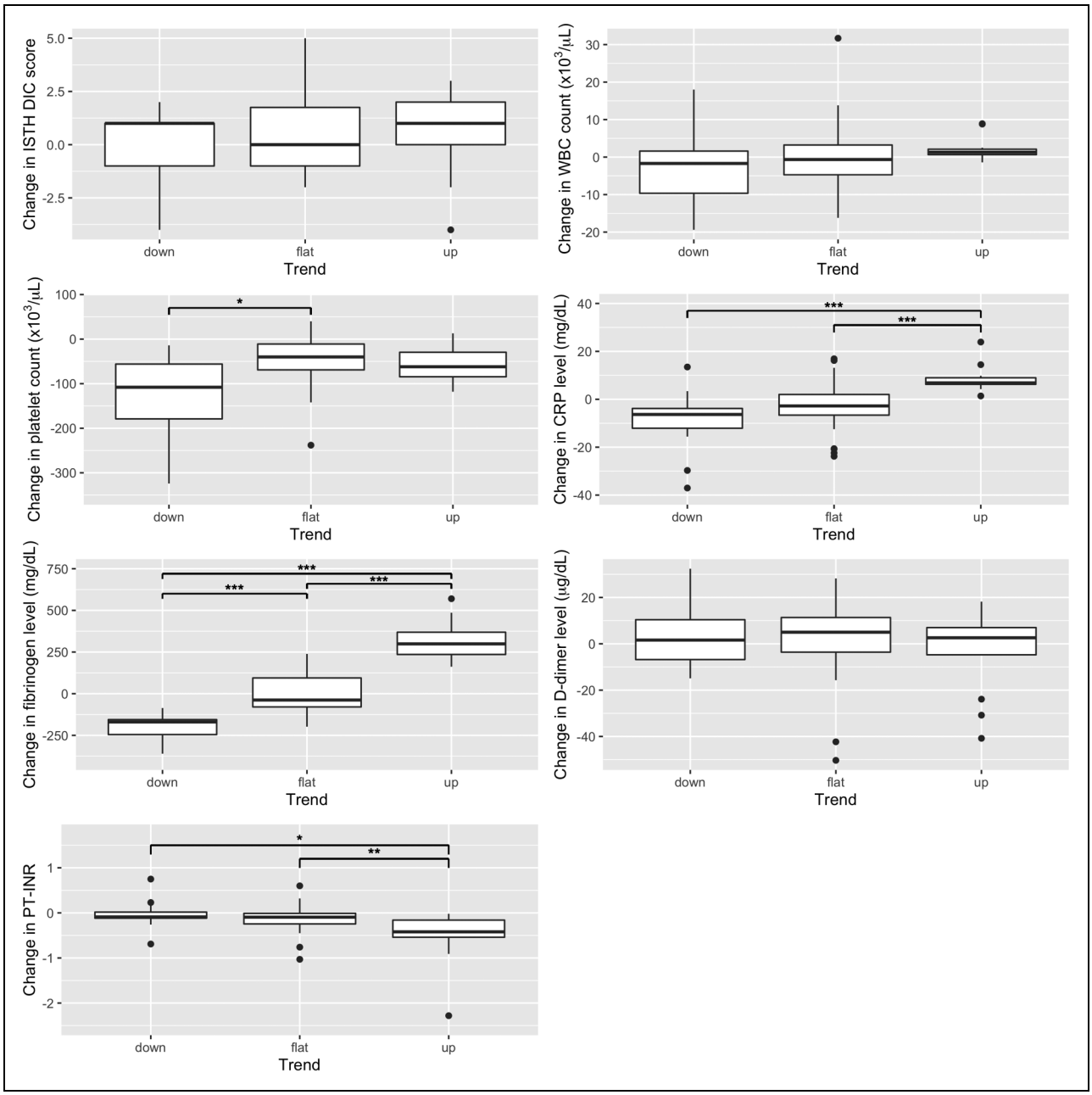

Figure 2. Degree of changes in ISTH DIC score, WBC count, platelet count, CRP level, fibrinogen level, D-dimer level, and PT-INR from ICU arrival to day 3. Data were compared between the three fibrinogen trend groups, and presented as median and as first and third quantiles. *: $0.01 < P < 0.05$, **: $0.001 < P < 0.01$, and ***: $P < 0.001$.

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.[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 fibrinogenolysis, as a course of immunohaemostasis.[12] Negatively charged

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.

	Day 0				Day 3			
	Overt DIC		Non-Overt DIC		Overt DIC		Non-Overt DIC	
	Total/Death	Proportion	Total/death	Proportion	Total/Death	proportion	Total/death	Proportion
Total	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.

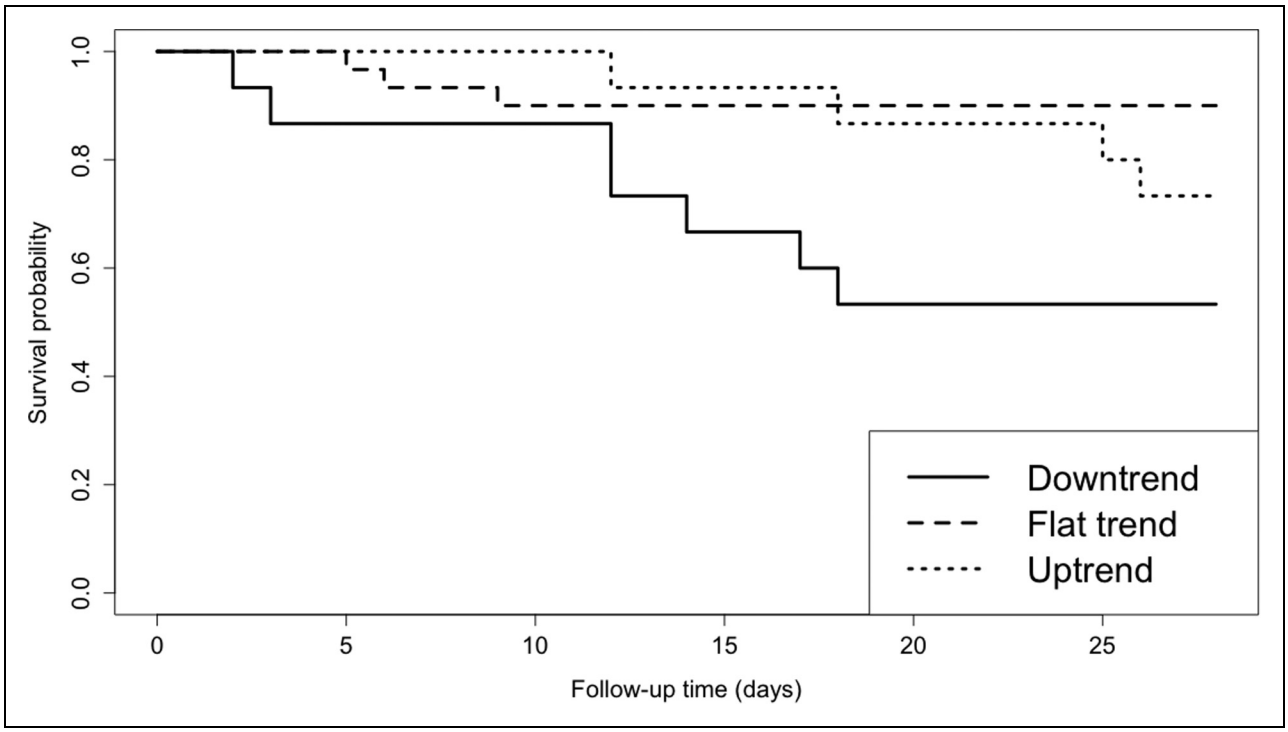

Figure 3. Kaplan-Meier 28-day survival curves for the three trend groups. The global *p*-value for the three group comparison is 0.020; the *p*-value of each pair-wise comparison shows significant differences between the down- and flat trend groups.

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

	Univariate Analysis			Multivariate Analysis		
	OR (95% CI)	*P* (Wald's test)	*P* (LR test)	Adj. OR (95% CI)	*P* (Wald's test)	*P* (LR test)
Downward fibrinogen trend	4.75 (1.30-17.35)	0.018	0.018	4.60 (1.13-18.67)	0.033	0.031
SOFA score	1.29 (1.06-1.56)	0.011	0.005	1.29 (1.05-1.59)	0.016	0.008

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

would sensitively reflect hypercoagulation on day 0 and hyperfibrinogenolysis 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 hypofibrinogenemia in patients with septic DIC is associated with high mortality rate and platelet loss.[10] 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 pathophysiological 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 mortality. The ISTH DIC scores on admission predicted the mortality 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 performed statistical analyses. K. Mori drafted the manuscript. Y. Eguchi designed and guided the study.

Declaration of Conflicting Interests

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