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Full Length Article

Significance of plasma fibrinogen level and antithrombin activity in sepsis: A multicenter cohort study using a cubic spline model

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ABSTRACT

Introduction: Sepsis leads to coagulopathy by the activation of inflammatory mediators and vascular endothelial cell injury. A number of biomarkers are used to evaluate coagulopathy on sepsis. Fibrinogen and antithrombin activity have been reported as biomarkers of coagulopathy; however, the utility of these two markers has not been well established. This study aimed to evaluate the detailed association between these two markers and clinical outcomes in sepsis patients.

Materials and methods: This was a post hoc analysis of a multicenter, prospective cohort study conducted in 59 intensive care units throughout Japan from January 2016 to March 2017. We included 1103 adult patients with severe sepsis based on the Sepsis-2 criteria. The associations between the coagulation markers and in-hospital mortality were examined using linear and non-linear logistic regression analyses. We also evaluated the associations between the coagulation markers and disseminated intravascular coagulation (DIC) scores. The International Society on Thrombosis and Haemostasis overt DIC score was calculated after subtracting the fibrinogen component.

Results: The decreased levels of the fibrinogen and antithrombin activity were significantly associated with an increase in mortality ($P = 0.011$ and 0.002, respectively). In addition, cubic spline regression demonstrated that mortality sharply increased at a fibrinogen level of approximately < 200 mg/dL and at an antithrombin activity of approximately < 50%. Similarly, the decreased levels of the two markers non-linearly correlated with the elevation of DIC score.

Conclusions: The fibrinogen level and antithrombin activity should be reconsidered as unique biomarkers for sepsis and sepsis-induced DIC.

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1. Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1] and causes coagulopathy by the activation of inflammatory mediators and vascular endothelial cell injury [2,3]. Sepsis-induced coagulopathy is considered to be caused by both systemic intravascular activation of coagulation and microvascular endothelial injury, which leads to widespread thrombosis in the microvasculature and organ failure [4]. A number of studies have reported that coagulopathy in sepsis is associated with organ failure and is a risk factor for mortality [5–8]. Thus, to accurately evaluate coagulopathy in sepsis, various coagulation hemostatic markers, such as fibrin/fibrinogen degradation products (FDP), prothrombin time (PT), platelet count, fibrinogen, and antithrombin activity are clinically measured in sepsis patients. In the complicated pathophysiology of sepsis and the accompanying coagulopathy, however, each marker alone cannot reflect the global picture of coagulation, and it is difficult to validate the usefulness of the markers. Thus, the clinical significance and validity of each hemostatic marker for sepsis management remain unknown [9].

Fibrinogen is reported to be highly specific but has low sensitivity in the diagnosis of coagulopathy based on sepsis [10,11]. Due to it being an acute-phase reactant, the marker remains at falsely normal or even higher levels until the late stage of disease progression [12,13]. Thus, whether fibrinogen accurately reflects the pathology of septic coagulopathy has been questioned [14]. Antithrombin activity consistently decreases in sepsis pathophysiology through several mechanisms, such as excessive thrombin generation, increased vascular leakage, impaired synthesis, and degradation by proteases [15,16]. Lower antithrombin activity was reportedly significantly associated with poor survival in coagulopathy induced by sepsis [17]. Hence, there are differences in the handling of fibrinogen and antithrombin activity between the disseminated intravascular coagulation (DIC) scoring systems. The Japanese Association for Acute Medicine (JAAM) DIC scoring system [10] removed the fibrinogen component, which is included in the Japanese Ministry of Health and Welfare (JMHW) [18] and the International Society on Thrombosis and Haemostasis (ISTH) overt DIC scoring systems [4]. However, a newly published DIC scoring system, the Japanese Society on Thrombosis and Haemostasis (JSTH) system, proposed including antithrombin activity as one of the components to diagnose DIC [18].

Here, we hypothesized that fibrinogen and antithrombin activity in sepsis-induced coagulopathy would affect mortality below certain numerical values rather than have a linear association with the prognosis. To date, most available evidence to satisfy this hypothesis has been constructed by linear association, and there is no consensus regarding the optimal activity levels of fibrinogen and antithrombin for increasing mortality; thus, the non-linear association between coagulation markers and clinical course in sepsis patients also needs to be elucidated. The present study aimed to evaluate the detailed association between these two markers and outcomes in sepsis using non-linear cubic spline models, a cutting-edge statistical method.

2. Materials and methods

2.1. Study setting and data source

The data source used in this study was a multicenter, prospective cohort of acutely ill patients with acute respiratory distress syndrome, sepsis, and trauma (JAAM FORECAST study). FORECAST used a sample of 59 ICUs in Japan and was conducted from January 2016 to March 2017. Patients included in the FORECAST sepsis cohort comprised adult patients (≥16 years old) with severe sepsis based on the Sepsis-2 criteria [19]. All patients were principally treated according to the strategy of the particular institution or at the discretion of the attending physician, and there was no predefined protocol for the use of anticoagulants.

2.2. Study population

This study included all adult patients with severe sepsis in the JAAM FORECAST Sepsis cohort. We excluded patients with the following pre-existing coagulation disorders that could potentially influence the markers of interest: serious liver disorder, history of hematologic malignancy (leukemia, lymphoma, and multiple myeloma), history of metastatic neoplasm, and others.

This study followed the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the ethics committee of all participating institutions in the JAAM study group in Japan. Specific approval for the present analysis was granted by Osaka General Medical Center (IRB No. 30-S11-004).

2.3. Data collection and definitions

The FORECAST database was compiled by the investigators in each institution. Collected patient data included age, sex, Charlson Comorbidity Index score, primary infection site, Systemic Inflammatory Response Syndrome (SIRS) score, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE) II score, the ISTH overt DIC score, the JAAM DIC score, and values of coagulation parameters such as platelet count, FDP, PT-INR (International Normalized Ratio), fibrinogen, and antithrombin activity at the time of ICU admission. We also obtained in-hospital mortality as a primary outcome.

DIC status was diagnosed using the ISTH overt DIC and JAAM DIC scoring systems as shown in Table 1, respectively [4,10,12]. For the ISTH overt DIC system, the FDP values were chosen as the fibrin-related marker instead of D-dimer values, and the cutoff levels and ranges were defined as follows: no increase, moderate increase, and strong increase were indicated by FDP values of < 10, 10–25, and > 25 mg/L, respectively [12]. PT-INR was chosen as the PT-related marker.

2.4. Statistical analysis

Descriptive statistics are summarized as group medians with the first and third quartiles for continuous variables and as frequencies with percentages for categorical variables. Baseline characteristics were compared between survivors and non-survivors by the Mann-Whitney *U*

Table 1
ISTH overt DIC and JAAM DIC scoring systems.

	Points	ISTH overt DIC	JAAM DIC
Platelet counts	3	–	$< 80 \times 10^9$/L or > 50% decrease/24 h
	2	$< 50 \times 10^9$/L	–
	1	≥50, $< 100 \times 10^9$/L	≥80, $< 120 \times 10^9$/L or 30–50% decrease/24 h
FDP	3	≥25 μg/mL	≥25 μg/mL
	2	≥10, < 25 μg/mL	–
	1	–	≥10, < 25 μg/mL
PT-INR	2	≥1.5	–
	1	≥1.25, < 1.5	≥1.2
Fibrinogen	1	< 100 mg/dL	–
SIRS score	1	–	≥3
Required points for criteria-positive		5 points	4 points

DIC indicates disseminated intravascular coagulation; FDP, fibrin/fibrinogen degradation product; ISTH, International Society on Thrombosis and Haemostasis; JAAM, Japanese Association for Acute Medicine; PT-INR, prothrombin time-international normalized ratio; and SIRS, systemic inflammatory response syndrome.

test or chi-square test.

We evaluated the association between in-hospital mortality and coagulation parameters by logistic regression analysis defined by the odds ratio (OR) with 95% confidence interval (CI). Besides, to evaluate nonlinear associations between mortality and coagulation parameters, we fit restricted cubic spline models also using a logistic regression model. The reference points were determined by the normal value of each parameter: 400 mg/dL for fibrinogen, 150×10^3/μL for platelet count, 1.0 for PT-INR, 2 points for SIRS score, 5 mg/dL for FDP, and 80% for antithrombin activity. The knot values were determined based on Harrell's recommended percentiles, with the knots placed at equally spaced percentiles of the original variable's marginal distribution [20]. The number of knots in each analysis was determined by the Wald test in such way that the explanatory variables at all the sections divided by the knots were significant [21]. Then, to evaluate the significance of the effect of fibrinogen and antithrombin activity on DIC status, we constructed scatter diagrams and fit curves between ISTH overt DIC and JAAM DIC scores and the two parameters. In this analysis, the ISTH overt DIC score was calculated subtracting the fibrinogen component.

We performed multiple imputation technique to calculate missing values for fibrinogen, platelet count, PT-INR, SIRS score, and antithrombin activity as the probability of missing data for these markers could be assumed not to depend on the unobserved data themselves (missing at random). We created 10 imputations for each missing value using the other available variables and then fit the desired models separately on each of the 10 imputed datasets and combined the results based on the concepts developed by Rubin [22].

All hypotheses were two-sided, and a P value of < 0.05 indicated statistical significance. All statistical analyses were conducted using STATA Data Analysis and Statistical Software version 14.0 (StataCorp, College Station, TX).

3. Results

3.1. Study population and baseline characteristics

The patient flow diagram is shown in Fig. 1. During the study period, 1184 patients fulfilling the inclusion criteria were registered in the FORECAST study database. After excluding 81 patients who met at least one exclusion criterion, we analyzed 1103 patients as the final study cohort in this study.

The baseline characteristics and severity of illness in the 862 survivors and 241 non-survivors are shown in Table 2. The non-survivors had significantly higher age and Charlson Comorbidity Index score. Also, illness severity, as indicated by the SIRS, SOFA, APACHE II, and DIC scores was significantly higher in the non-survivors. Regarding the coagulation profile, non-survivors had significantly lower levels of the fibrinogen and antithrombin activity and higher levels of PT-INR. The levels of FDP and platelet counts were similar between the survivors and non-survivors.

3.2. Effect of coagulation parameters on mortality

Table 3 shows the results of multivariate logistic regression analysis for in-hospital mortality including coagulopathy-related parameters. The decrease of antithrombin activity and fibrinogen and the increase of PT-INR were independently associated with the increased risk of in-hospital mortality.

3.3. Non-linear association between coagulation parameters and outcomes

To deeply assess a nonlinear association between the abnormality of coagulation parameters and mortality, restricted cubic splines were performed in the multivariate logistic models. As shown in Fig. 2A, although no remarkable increase in mortality was observed according to the increase of fibrinogen, there was a significant J-shaped increase in mortality as the levels of fibrinogen decreased. The risks of mortality sharply rose as the levels of fibrinogen decreased below the level of approximately 200 mg/dL. Similarly, a significant J-shaped association between the decreased levels of antithrombin activity and in-hospital mortality are shown in Fig. 2B. The risks of mortality rose sharply as levels of antithrombin activity decreased below approximately 50%. For the changes in PT-INR, an increase in the marker was associated with increased mortality although the association appeared to be linear. None of the changes in SIRS score, FDP, and platelet count showed remarkable associations with mortality even in the non-linear analysis.

We classified the study patients into the anticoagulants group and non-anticoagulants group and separately evaluated the associations between the coagulation markers and mortality. Consequently, the shapes of the non-linear cubic spline curves between two groups were similar both for fibrinogen and antithrombin activity (Fig. S1).

3.4. Effect of fibrinogen and antithrombin activity on DIC status

We then assessed the significance of fibrinogen and antithrombin activity on the progression of DIC status (Fig. 3). Both the decrease of fibrinogen and antithrombin activity nonlinearly correlated with the elevation of the JAAM DIC score. There was a sharp increase in the JAAM DIC score when the fibrinogen level was lower than 200 mg/dL. For antithrombin activity, there was a gradual increase in the JAAM

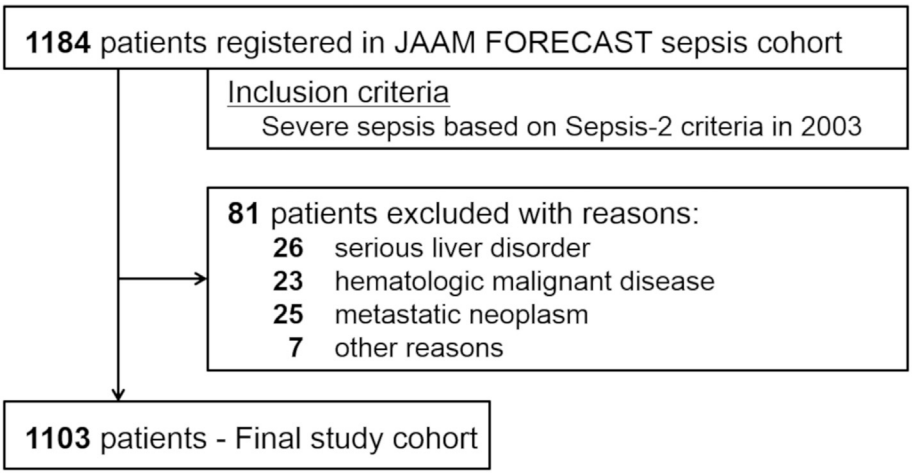

Fig. 1. Patient flow diagram. JAAM FORECAST indicates Japanese Association for Acute Medicine Focused Outcome Research on Emergency Care for ARDS, Sepsis and Trauma.

Table 2
Baseline characteristics in included populations.

Patient characteristics	Overall (n = 1103)	Survivors (n = 862)	Non-survivors (n = 241)	P*	Missing data
Age in years	73 (64–82)	71 (61–79)	75 (67–84)	< 0.001	0
Sex (male), n (%)	647 (60.2%)	500 (59.9%)	147 (60.1%)	0.77	0
Illness severity					
SIRS score	3 (2–4)	3 (2–4)	3 (3–4)	0.044	65 (5.9%)
SOFA score	9 (6–11)	8 (5–11)	11 (8–13)	< 0.001	200 (18.1%)
APACHE II score	22 (17–29)	21 (16–27)	29 (23–35)	< 0.001	146 (13.2%)
ISTH overt DIC score	3 (2–4)	3 (2–4)	3 (2–5)	< 0.001	251 (22.8%)
JAAM DIC score	4 (2–5)	3 (2–5)	4 (3–6)	< 0.001	185 (16.8%)
Charlson Comorbidity Index score	1(1–2)	1(1–2)	1(1–3)	< 0.001	28 (2.5%)
Primary site of infection				< 0.001	79 (7.2%)
Lung	304 (28%)	217 (20%)	87 (8%)	–	–
Abdomen	248 (23%)	198 (18%)	50 (5%)	–	–
Urinary tract	206 (19%)	182 (17%)	24 (2%)	–	–
Central nervous system	32 (3%)	22 (2%)	10 (1%)	–	–
Blood	16 (1.5%)	13 (1.2%)	3 (0.3%)	–	–
Other/unknown	192 (17%)	142 (13%)	50 (4%)	–	–
Coagulation parameters					
Platelet count, ($\times 10^9$/L)	17.7 ± 0.5	17.7 ± 0.5	17.4 ± 0.9	0.59	30 (2.7%)
FDP, (μg/mL)	42.5 ± 3.1	39.9 ± 3.8	51.8 ± 7.2	0.07	360 (32.6%)
PT-INR	1.41 ± 0.02	1.32 ± 0.03	1.65 ± 0.05	< 0.001	60 (2.7%)
Fibrinogen (mg/dL)	472.0 ± 7.4	491.9 ± 8.4	417.9 ± 16.3	< 0.001	236 (21.4%)
AT activity (%)	63.8 ± 0.9	66.3 ± 1.0	57.5 ± 1.9	< 0.001	535 (48.5%)

APACHE indicates Acute Physiology and Chronic Health Evaluation; AT, antithrombin activity; DIC, disseminated intravascular coagulation. FDP, fibrin/fibrinogen degradation products; ISTH, International Society on Thrombosis and Haemostasis; JAAM, Japanese Association for Acute Medicine; PT-INR, prothrombin time-international normalized ratio; SIRS, systemic inflammatory response syndrome; and SOFA, Sequential Organ Failure Assessment.

* *P* value from Mann-Whitney U test for continuous variables and from χ^2 test for categorical variables. Data are expressed as group medians (interquartile range), number (percentage) or mean (SE).

Table 3
Multiple logistic regression analysis for in-hospital mortality.

Coagulation parameter	OR	95% CI	*P*
Fibrinogen	0.89	0.82–0.98	0.01
PT-INR	1.55	1.21–1.96	0.02
AT	0.85	0.77–0.94	< 0.01
FDP	1.000	0.98–1.01	0.96
Platelet count	1.01	0.98–1.20	0.21
SIRS	1.20	0.99–1.45	0.06

Data are expressed as the OR of various factors to the outcome calculated using multiple logistic regression analysis for in-hospital mortality with multiple imputation. AT indicates antithrombin activity; CI, confidence interval; FDP, fibrin/fibrinogen degradation products; OR; odds ratio; PT-INR, prothrombin time-international normalized ratio; and SIRS, systemic inflammatory response syndrome.

DIC score in accordance with the decrease in antithrombin activity below 80%. Similar associations of fibrinogen and antithrombin activity were also seen for the ISTH overt DIC score (Fig. 4).

4. Discussion

This study investigated the association between coagulopathy and outcomes in a large cohort study of patients with sepsis in Japan. The results revealed that decreases in both fibrinogen and antithrombin activity showed “J-shaped” associations with the increase in mortality in the cubic spline analysis. The risks of mortality rose sharply as levels of fibrinogen and antithrombin activity decreased below approximately 200 mg/dL and 50%, respectively. Moreover, we found similar non-linear associations between fibrinogen/antithrombin activity and DIC status. This study was conducted to revalidate the clinical significance of fibrinogen and antithrombin activity, not to compare these markers with each other or to determine cutoff values. Our findings can enhance the clinical value of these markers and can help in decision making by using the values of fibrinogen and antithrombin activity in the clinical setting. The overall findings in this study may suggest that the established scoring system for DIC could be revised according to the changing patterns and characteristics of each hemostatic marker.

Several studies have previously reported that plasma levels of fibrinogen and antithrombin activity are significantly lower in patients with a poor prognosis [5–8]. Our findings in this analysis confirm those of these previous reports, whereas we added new knowledge about the non-linear association between the markers and mortality and the optimal cut-off points of the markers. Inflammation and coagulation constitute two host defense systems with complementary roles against infection, which means that a crushing systemic inflammatory reaction in sepsis is accompanied by severe coagulopathy, and both contribute to tissue damage in the early phase of sepsis [23]. Fibrinogen and antithrombin activity play an important role in this cascade. Generally, fibrinogen is the marker indicating consumption of hemostatic factors and reflecting the excessive hyper-coagulation and hyper-fibrinolysis state in sepsis-induced coagulopathy [9]. However, the marker is considered to be an acute-phase reactant, and thus it typically increases in patients with infection and/or inflammation [24]. These controversial pathophysiologic features of fibrinogen in sepsis partly make this hemostatic marker too complicated to use in clinical situations. Actually, it has been reported that most DIC patients do not show a decreased level of fibrinogen at the time of intensive care admission [25]. In our study, the risks of mortality exponentially rose as plasma fibrinogen decreased below approximately 200 mg/dL. This finding might suggest that the consumption of fibrinogen by coagulopathy, rather than the production of fibrinogen, is predominantly increased in extremely severe patients at high risk of death.

Antithrombin activity, an important physiologic anticoagulant, inhibits an estimated 80% of the coagulation activities of thrombin and coagulation factors VII, IX, X, XI, and XII [26]. Antithrombin activity is frequently decreased in sepsis-induced coagulopathy [16,27] and is associated with high disease severity and mortality [28,29]. The decrease of antithrombin activity in sepsis-induced coagulopathy is reportedly due to consumption, extravasation, and degradation by several proteolytic enzymes [28]. The reduced antithrombin activity level results in a decreased ability to undertake thrombin inactivation, leading to further acceleration of the coagulopathy, and even subsequent multiple organ dysfunction. Iba et al. [30] reported that the

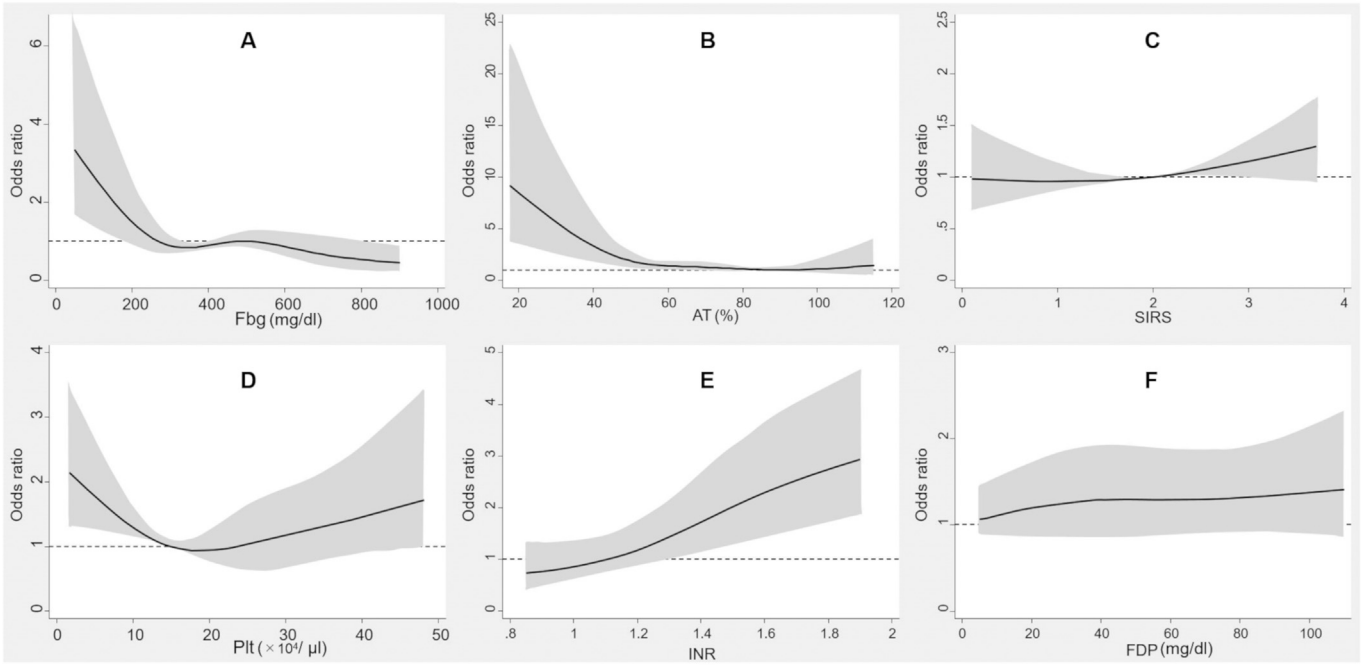

Fig. 2. Non-linear cubic spline curve of coagulation parameters against mortality in sepsis. (A) Fibrinogen, (B) Antithrombin activity, (C) SIRS score, (D) Platelet count, (E) PT-INR, and (F) FDP. The black line represents the fitted line of the association between coagulation parameters and the estimated odds ratio (OR) of mortality risk, and the shaded region represents the 95% confidence interval. Fbg indicates fibrinogen; AT, antithrombin activity; FDP, fibrin/fibrinogen degradation products; INR, international normalized ratio; Plt, platelets; and SIRS, systemic inflammatory response syndrome score.

antithrombin activity level decreases to approximately 80% of normal in infectious patients without organ dysfunction, whereas it decreases to approximately 60% in sepsis patients with organ dysfunction and to 40% in sepsis patients complicated with DIC [30]. Similarly, in the present study, antithrombin activity decreased to approximately 64% in sepsis and was nonlinearly associated with mortality at an antithrombin activity level of approximately 50% or less. These findings suggested that antithrombin activity decreased in accordance with the progression of organ dysfunction and coagulopathy in sepsis and correlated very strongly with mortality when it decreased below a specific threshold.

Several potential limitations should be acknowledged. First, there were missing values of plasma fibrinogen levels and antithrombin activity in our study. Therefore, in this study we performed a multiple imputation technique to calculate missing values for hemostatic markers and DIC score; however, this may have influenced the results due to the large amount of missing data for some variables. Second, the methods used for the measurement of the hemostatic markers such as fibrinogen, antithrombin, FDP, and D-dimer were not uniform between the participating hospitals in the present study. In Japan, fibrinogen and AT assays are mainly performed by automated Clauss assays and anti-Xa-based AT assays, respectively. The variation between the assays may have slightly influenced the levels of these markers and the main findings in this analysis.

In conclusion, we showed the non-linear association between both plasma fibrinogen level and antithrombin activity and mortality in patients with sepsis, using a multicenter cohort study database in Japan. These findings suggested that plasma fibrinogen levels and antithrombin activity have unique clinical features and may be potentially useful in sepsis management to identify the patients at high risk for death or DIC status.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.07.002.

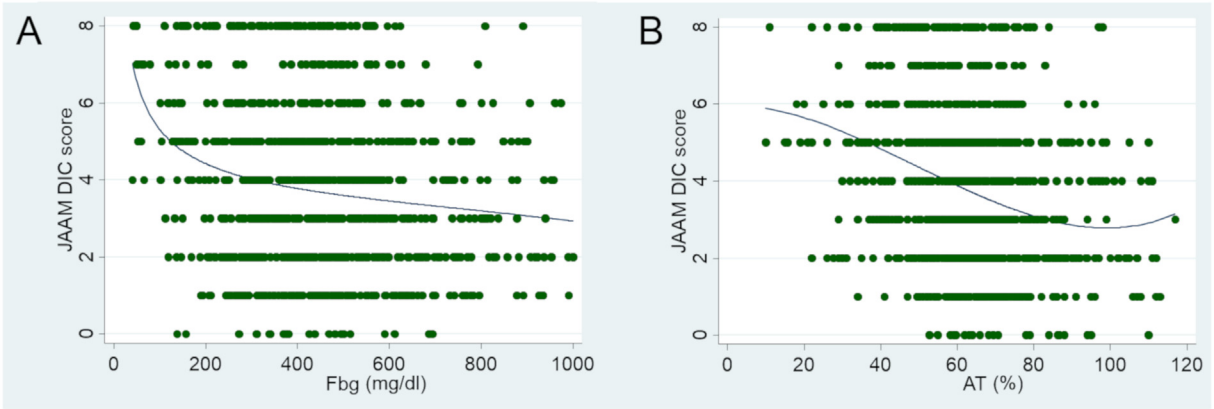

Fig. 3. Scatter diagram and fit curve of fibrinogen and antithrombin against JAAM DIC score. (A) Fibrinogen and (B) antithrombin activity. The blue line represents the fitted line of the scatter diagram. JAAM indicates Japanese Association for Acute Medicine; and DIC, disseminated intravascular coagulation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

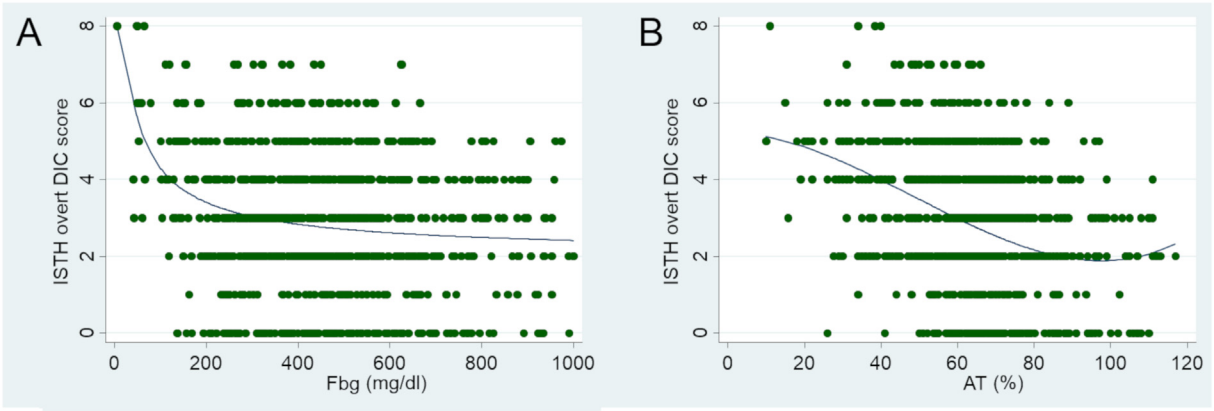

Fig. 4. Scatter diagram and fit curve of fibrinogen and antithrombin against ISTH overt DIC score. (A) Fibrinogen and (B) antithrombin. The blue line represents the fitted line of the scatter diagram. ISTH indicates International Society on Thrombosis and Haemostasis; and DIC, disseminated intravascular coagulation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Contribution: T. Matsubara, K. Yamakawa, and Y. Umemura analyzed the data, interpreted the results, drafted the figures and tables, and wrote the manuscript. S. Gando, H. Ogura, Y. Otomo, T. Tarui and S. Fujimi gave advice on the analytical methods, interpreted the results, and critically inspected the manuscript. A. Shiraishi and A. Hagiwara advised on the statistics and reviewed the manuscript. S. Gando, A. Shiraishi, H. Ogura, S. Kushimoto, and T. Abe designed the study and organized the data collection and critically reviewed the manuscript. All authors approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare no competing financial interests.

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