Clinical and Applied Thrombosis/Hemostasis
Volume 26: 1-7

DOI: 10.1177/1076029620912827
journals.sagepub.com/home/cat
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Supernormal Antithrombin Activity Is an Independent Predictor of In-Hospital Mortality in Patients With Sepsis: A Retrospective Observational Study

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Abstract

Supernormal antithrombin (AT) activity is rare in patients with sepsis. This study compared mortality rate of patients with sepsis and supernormal AT activity with that of other patients. This retrospective study included patients with sepsis from 42 intensive care units (ICUs) in Japan. Patients were included if their AT activity was measured on ICU admission, and if they did not receive AT concentrate. They were categorized into low, normal, and supernormal with respective AT activity of $\leq$70%, >70% to $\leq$100%, and >100%. The primary outcome was hospital in-patient mortality. Nonlinear regression analysis showed that mortality risk gradually increased with AT activity in the supernormal range, but without statistical significance. Survival rate was significantly lower in low (67%) and supernormal (57%) AT groups than in the normal AT group (79%; $P < .001$ and $P = .008$, respectively). After adjusting for disease severity and AT activity on day 2, supernormal AT activity was the only independent predictor of mortality. Sepsis with supernormal AT activity associated with high mortality, independent of disease severity, might be a predictor of in-hospital mortality.

Keywords

antithrombin, disseminated intravascular coagulation, mortality, prognosis, sepsis

Date received: 17 September 2019; revised: 11 February 2020; accepted: 18 February 2020.

Introduction

Antithrombin (AT) is a 58-kDa plasma glycoprotein synthesized in the liver and belongs to a family of serine protease inhibitors.[1,2] Antithrombin irreversibly inhibits activated factor X and thrombin in a 1-to-1 ratio, generating protease-AT complexes.[1,2] In addition to inhibiting activated factor X- and thrombin-induced inflammation, AT is involved in the inhibition of vascular endothelium inflammation.[1,2]

Sepsis and septic shock frequently induce blood coagulation activation and impair elements of the anticoagulation system, including AT.[3,4] Reduced AT activity is common in patients with sepsis[5,6] owing to excessive thrombin production, increased vascular permeability, impaired AT synthesis in the liver, and AT degradation by proteases.[7-10] Several studies have reported a relationship between reduced AT activity and poor outcomes.[6,11,12]

Patients with sepsis in the intensive care unit (ICU) rarely demonstrate supernormal AT[5]; therefore, the characteristics of these patients and their outcomes remain unclear. In the present study, we aimed to elucidate the characteristics of patients with

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both sepsis and supernormal AT activity and associated outcomes in a large cohort of patients.

Materials and Methods

This retrospective observational cohort study obtained data from the Japan Septic Disseminated Intravascular Coagulation (J-SEPTIC DIC) study, registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000012543) in 2013. The J-SEPTIC DIC study was conducted in 42 ICUs across 40 institutions in Japan[13,14] and was approved by the appropriate institutional review board of each hospital. The need for informed consent was waived due to the retrospective design of the current study.

Patient Selection and Data Collection

The J-SEPTIC DIC study included consecutive patients admitted to the ICU for treatment of severe sepsis/septic shock between January 2011 and December 2013. Severe sepsis and septic shock were defined based on recommendations from the International Sepsis Definitions Conference.[15] Sepsis was diagnosed based on judgments of individual attending physicians in respective clinical settings. Patients were excluded if they were younger than 16 years of age on admission or developed severe sepsis/septic shock after admission for the treatment of other severe diseases. Patients whose AT activity was measured on admission to the ICU and those who were not administered AT concentrate were included in this study. Patients were grouped according to their AT activity on admission: low AT (AT activity $\leq$70%), normal AT (70% < AT activity $\leq$100%), and supernormal AT (AT activity >100%). The lower limit of normal range AT activity is considered to be 70% and is the target of AT concentrate therapy for sepsis-induced DIC in Japan.[5,16]

Statistical Analysis

Data have been presented as numbers (%) or medians (interquartile ranges), as appropriate. We evaluated the association between in-hospital mortality and AT activity by logistic regression analysis defined by the odds ratio (OR) with 95% confidence interval (CI). The reference points were determined by 80% for AT activity as normal value. In addition, to evaluate the nonlinear associations, we fit restricted cubic spline models using a logistic regression model. 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.[17] Intergroup comparisons were made using the Mann-Whitney U or χ^2 tests. Kaplan-Meier analyses were performed to evaluate survival times, and the log-rank test was used to compare differences between groups. A Bonferroni correction was applied for repeated comparisons. Multiple logistic regression analysis was used to assess relationships between mortality and patients' characteristics. The Acute Physiology and Chronic Health Evaluation (APACHE) II score and AT activity on day 2 were used as covariates during multiple logistic regression analysis. Model 1 included data adjusted by APACHE II score, model 2 included data adjusted by AT activity on day 2, and model 3 included data adjusted by both, the APACHE II score and AT activity on day 2. The changes in AT activity from days 1 to 3 were evaluated using the Jonckheere-Terpstra test in each group. Cox regression model analysis was performed to evaluate the adjusted estimated survival curves in models 1, 2, and 3, as mentioned previously.

We performed multiple imputation for calculating the missing values for AT activity on days 2 and 3, as the probability of missing data for these markers was not considered 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 to each of the 10 imputed data sets. The results were combined based on the concepts developed by Rubin.[18] The SPSS 25 (IBM Japan, Tokyo, Japan) software package was used for all statistical analyses. A P value <.05 was considered significant.

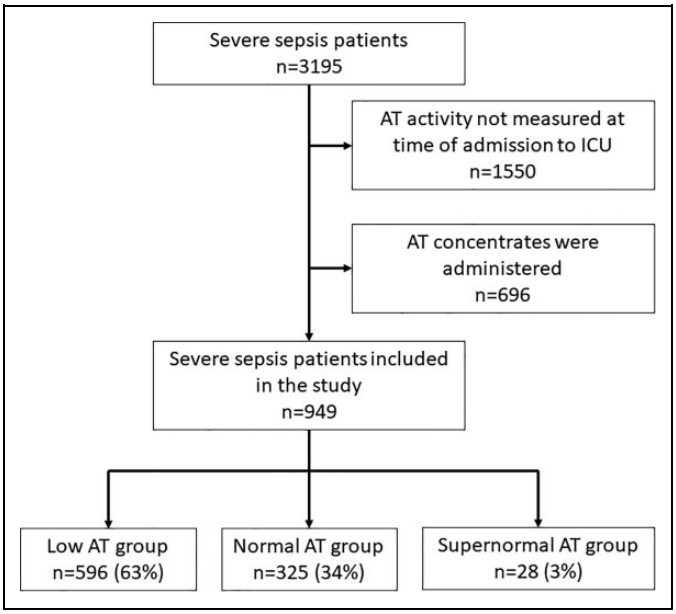

Figure 1. Flow chart of patient selection from the J-SEPTIC DIC study data set. AT indicates antithrombin; ICU, intensive care unit; J-SEPTIC DIC, Japan Septic Disseminated Intravascular Coagulation.

Results

A total of 949 patients with severe sepsis were included in this study (Figure 1). The histogram of AT activity on admission to the ICU is shown in Figure 2.

In-hospital survival rates for patients with severe sepsis are represented by AT activity in Figure 3A. Survival rates showed

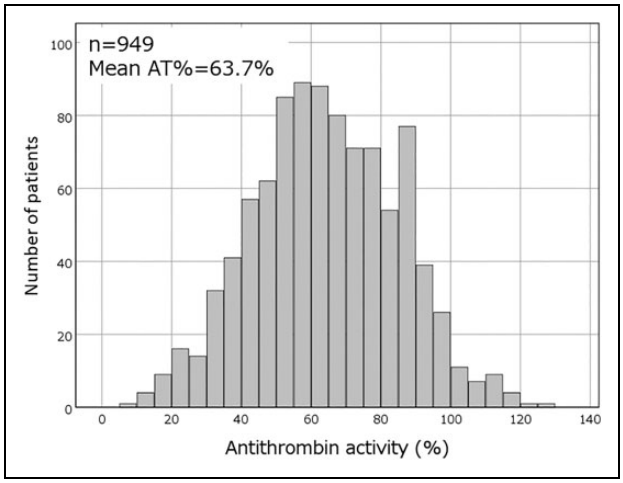

Figure 2. Antithrombin activity on admission to the intensive care unit.

a trend toward poorer survival as AT activity rose or fell from the normal range; the survival rate gradually declined with decreasing AT activity in the normal and low ranges, and also gradually declined with increasing AT activity in the supernormal range. Figure 3B shows nonlinear association between AT activity and OR for in-hospital mortality. The risks of mortality gradually increased with low levels of AT activity, while in supernormal range, the risks of mortality gradually increased with high levels of AT activity. However, statistical significance was not observed.

After categorizing patients into groups based on their AT activity at admission, the low, normal, and supernormal AT groups had 596, 325, and 28 patients, respectively. The supernormal AT group therefore comprised 3% of the total patients in this analysis (Figure 1). The patient characteristics for each group are presented in Table 1. The APACHE II score, DIC score, and frequency of DIC complications in the supernormal AT group were no higher than those of other groups. However, the sequential organ failure assessment (SOFA) scores on admission to the ICU were significantly higher in both, the low and supernormal AT groups compared to the normal AT group. Patients with supernormal AT activity were more likely to have an unknown primary infection site than those with either low or normal AT activity (14.3% vs 7.4% and 4.3%, respectively), and the sepsis-causing microorganisms were also more likely to be unknown (42.9% vs 19.1% and 23.1%, respectively); however, these differences did not attain statistical significance.

The Kaplan-Meier survival curves for the 3 groups have been presented in Figure 4. The survival rates in the low and supernormal AT groups were lower than that in the normal AT group ($P = .004$ and $P = .005$, respectively). However, there was no statistically significant difference in the survival rate between the low and supernormal AT groups. Data on the transfusion types and volumes and the incidence of bleeding complications during the 7 days following ICU admission are presented in Table 2. The transfused units for all types of transfusion were significantly higher in the low AT group than

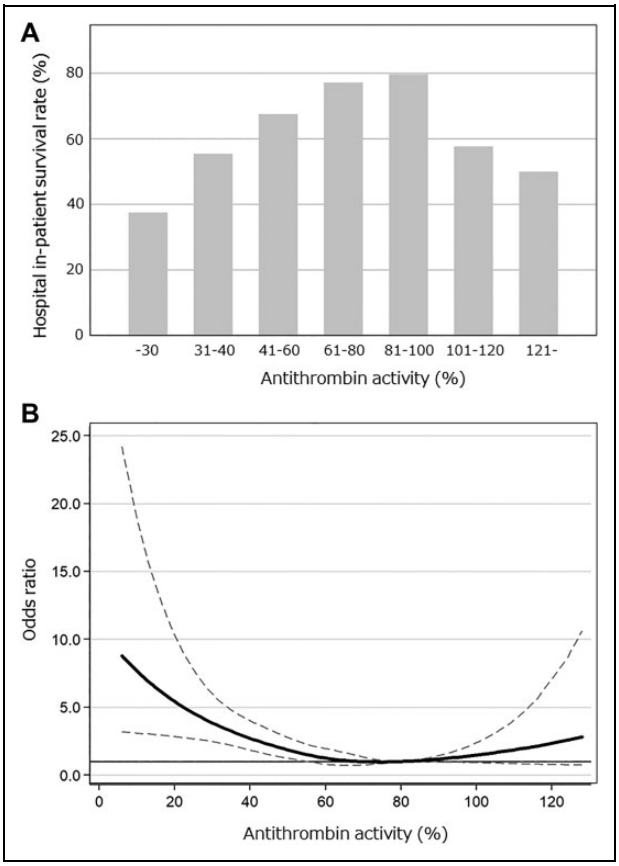

Figure 3. Relationship between AT activity and in-hospital survival rate. A, In-hospital survival rates of patients with severe sepsis, by AT activity. The in-hospital survival rate gradually declined with decreasing AT activity in the normal and low ranges. Furthermore, the survival rate also gradually declined with increasing AT activity in the supernormal range. B, Nonlinear cubic spline curve of AT activity against in-hospital mortality. The solid line represents the fitted line of the association between AT activity and estimated OR of in-hospital mortality risk. Dotted line represents the upper and lower 95% confidence intervals. The risks of mortality gradually increased with levels of AT activity in low range. In supernormal range, the risks of mortality gradually increased as well but without statistical significance. AT indicates antithrombin; OR, odds ratio.

in the normal AT group. The incidence of bleeding complications was similar between the groups.

Changes in AT activity following admission to the ICU according to the AT group are presented in Figure 5. The AT activity in the normal and supernormal AT groups gradually decreased from days 1 to 3, with statistical significance ($P < .001$ by the Jonckheere-Terpstra test, respectively), although marked changes in AT activity from days 1 to 3 were not observed in the low AT group ($P = .095$ by the Jonckheere-Terpstra test). However, the AT activity in the normal and supernormal AT groups on day 3 was higher than that in the low AT group ($P < .001$, respectively).

The adjusted ORs for in-hospital mortality are presented in Table 3. In model 1 (adjusted by APACHE II score), both low and supernormal AT activity were significantly associated with

Table 1. Clinical and Demographic Characteristics of Patients Treated for Sepsis[a]

	Low AT Group n = 596	Normal AT Group n = 325	Supernormal AT Group n = 28
Age, years	71 (61-80)	71 (57-80)	70 (58-75)
Male sex	358 (60.1)	184 (56.6)	14 (50)
Severity on admission to ICU			
APACHE II score	22 (17-29)[b]	21 (16-27)	22 (17-32)
SIRS score	3 (2-4)	3 (2-4)	3 (2-3)
Total SOFA score	9 (7-12)[b]	7.5 (5-10)	11 (6-12)[c]
DIC score	4 (3-6)[b]	3 (2-5)	3 (1-6)[d]
DIC	360 (60.4)[b]	145 (44.6)	13 (46.3)
Primary infection site[b,c]			
Lung	147 (24.7)	104 (32)	11 (39.3)
Urinary tract	84 (14.1)	72 (22.2)	4 (14.3)
Abdomen	188 (31.5)	53 (16.3)	8 (28.6)
Others	133 (22.3)	81 (25.0)	1 (3.6)
Unknown	44 (7.4)	14 (4.3)	4 (14.3)
Blood culture			
Positive	273 (45.8)	129 (39.7)	9 (32.1)
Negative	293 (49.2)	183 (56.3)	16 (57.1)
Not taken	30 (5)	13 (4)	3 (10.7)
Microorganisms causing sepsis[d]			
Gram-negative rod	211 (35.4)	114 (35.1)	10 (35.7)
Gram-positive coccus	161 (27)	75 (23.1)	1 (3.6)
Mixed infection	81 (13.6)	38 (11.7)	3 (10.7)
Other	29 (4.9)	23 (7.1)	2 (7.1)
Unknown	114 (19.1)	75 (23.1)	12 (42.9)
Anticoagulants in ICU			
Nafamostat mesilate	145 (24.3)	64 (19.7)	8 (28.6)
Heparin	66 (11.1)	33 (10.2)	4 (14.3)
Warfarin	8 (1.3)	4 (1.2)	0 (0.0)
Antiplatelet drugs	11 (1.8)	13 (4.0)	2 (7.1)
Others	3 (0.5)	4 (1.2)	0 (0.0)
Laboratory results on admission to ICU			
AT activity, %	53 (43-92)[b]	83 (76-88)	111 (105-114)[c,d]
White blood cell count, 10^9/L	12.3 (6-19.7)	11.6 (7-17.4)	11.8 (6.6-17.7)
Platelet count, 10^9/L	122 (64-188)[b]	168 (112-235)	153 (88-211)
Hemoglobin, mmol/L	10.5 (8.9-12.3)[b]	11.4 (9.8-12.9)	12.4 (10.2-14.7)[d]
PT-INR	1.36 (1.2-1.59)[b]	1.19 (1.08-1.33)	1.06 (0.98-1.24)[c,d]
Fibrinogen, g/L	396 (263-565)[b]	457 (346-622)	338 (271-567)[c]
FDP, mg/L	19.1 (10.7-37.6)	15.45 (8.65-33.2)	18.9 (8.3-30.5)
D-dimer, mg/L	8.7 (4-18.75)	6.6 (3.04-17.4)	8.21 (2.8-15.1)
Lactate, mmol/L	2.78 (1.67-5.66)[b]	2.32 (1.44-4.6)	2.42 (1.32-3.85)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; AT, antithrombin; DIC, disseminate intravascular coagulation; FDP, fibrin/fibrinogen degradation products; ICU, intensive care unit; PT-INR, prothrombin time–international normalized ratio; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

[a]Data are expressed as number (%) or median (interquartile range).

[b]$P < .017$ (after Bonferroni correction) between low and normal groups.

[c]$P < .017$ (after Bonferroni correction) between normal and high AT groups.[d] $P < .017$ (after Bonferroni correction) between low and high AT groups.

in-hospital mortality. However, in models 2 and 3 (adjusted by day 2 AT activity, and both, APACHE II score and day 2 AT activity, respectively) only supernormal AT activity was significantly associated with in-hospital mortality. In both models 2 and 3, some patients were excluded from analysis as the AT activity was not measured on day 2. The adjusted estimated survival curves in models 1, 2, and 3, same as those shown in Table 3, have been presented in Figure 6. The mortality rate in the supernormal AT group was high, with statistical significance in each model.

Certain sensitivity analyses were performed after multiple imputation. Supplemental Table 1 shows the adjusted ORs for in-hospital mortality after multiple imputation in the 3 models as shown in Table 3. The hazard ratios obtained from Cox regression analysis after multiple imputation are presented in Supplemental Table 2. These analyses indicated that as observed during complete case analyses, the supernormal AT activity after multiple imputation was significantly associated with in-hospital mortality.

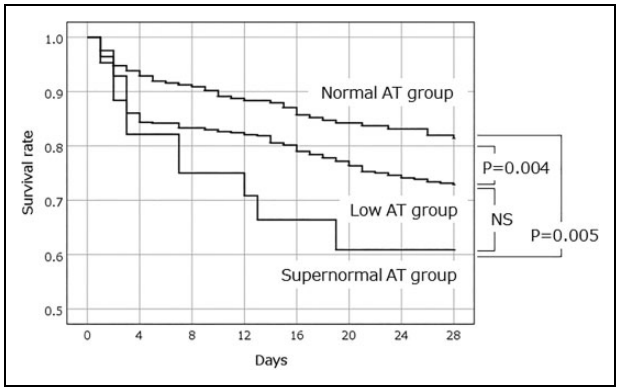

Figure 4. Kaplan-Meier survival curves during the 28 days in the hospital. The survival rates in the low and supernormal AT groups were lower than in the normal AT group. However, there was no statistically difference in survival rates between the low and supernormal AT groups. The statistical significance was $P < .017$ after Bonferroni correction. AT indicates antithrombin.

Table 2. Transfusions and Bleeding Complications.[a]

	Low AT Group n = 596	Normal AT Group n = 325	Supernormal AT Group n = 28
Transfusion during 7 days after ICU admission			
Red blood cell concentration, units	0 (0-4)[b]	0 (0-2)	0 (0-4)
Fresh frozen plasma, units	0 (0-0)[b]	0 (0-0)	0 (0-0)
Platelet concentration, units	0 (0-0)[b]	0 (0-0)	0 (0-0)
Bleeding complications during the 7 days following ICU admission			
Bleeding requiring transfusion	56 (9.4)	28 (8.6)	1 (3.6)
Bleeding requiring a therapeutic intervention	4 (0.7)	1 (0.3)	0 (0.0)
Intracranial hemorrhage	1 (0.2)	2 (0.6)	0 (0.0)
Bleeding-related death	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AT, antithrombin; ICU, intensive care unit.
[a]Data are expressed as number (%) or median (interquartile range).
[b]$P < .017$ (after Bonferroni correction) between low and normal group.

Discussion

There was small proportion (3%) of patients with supernormal AT activity among patients with sepsis admitted into ICU. In the nonlinear regression analysis, although we observed the trend that the risk of in-hospital mortality gradually increased with levels of AT activity in the supernormal range, but this was not statistically significant. Moreover, after categorizing patients into groups based on their AT activity, the mortality rate of patients with supernormal AT activity was higher than that of those with normal AT activity levels. Furthermore, supernormal AT activity on day 1 of ICU admission was a predictor of in-hospital mortality, independent of disease severity (APACHE II score) and AT activity on day 2.

To our knowledge, no previous studies have investigated supernormal AT activity in sepsis. Since this study indicated

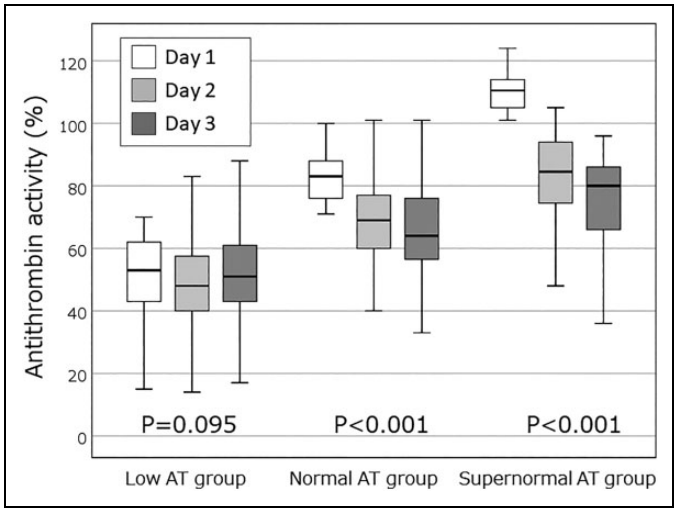

Figure 5. Changes in antithrombin (AT) activity following admission to the intensive care unit, by initial antithrombin activity. The AT activity in normal and supernormal AT groups gradually decreased from days 1 to 3 with statistical significances ($P < .001$ by the Jonckheere-Terpstra test, respectively), although marked changes in AT activity from days 1 to 3 were not observed in the low AT group ($P = .095$ by the Jonckheere-Terpstra test). However, the AT activity in the normal and supernormal AT groups on day 3 was higher than in the low AT group ($P < .001$, respectively). Day 1 indicates day of admission to intensive care unit; ICU, intensive care unit.

Table 3. Adjusted Odds Ratios for In-Hospital Mortality.

	Adjusted Odds Ratio	95% CI	*P* Value
Model 1, n = 949			
APACHE II score	1.098	1.078-1.119	<.001
AT activity on day 1			
Normal AT activity	Reference		
Low AT activity (≤70%)	1.663	1.188-2.331	.003
Supernormal AT activity (>100%)	2.483	1.053-5.848	.038
Model 2, n = 593			
AT activity on day 2	0.974	0.960-0.988	<.001
AT activity on day 1			
Normal AT activity	Reference		
Low AT activity (≤70%)	0.867	0.513-1.466	.594
Supernormal AT activity (>100%)	3.676	1.312-10.309	.013
Model 3, n = 593			
APACHE II score	1.074	1.047-1.101	<.001
AT activity on day 2	0.981	0.967-0.996	.014
AT activity on day 1			
Normal AT activity	Reference		
Low AT activity (≤70%)	1.007	0.584-1.736	.979
Supernormal AT activity (>100%)	3.378	1.160-9.901	.026

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; AT, antithrombin; CI, confidence interval.

that supernormal AT activity is only present in a small proportion (3%) of patients with sepsis, it is likely that this condition may only be studied in a large cohort, such as the

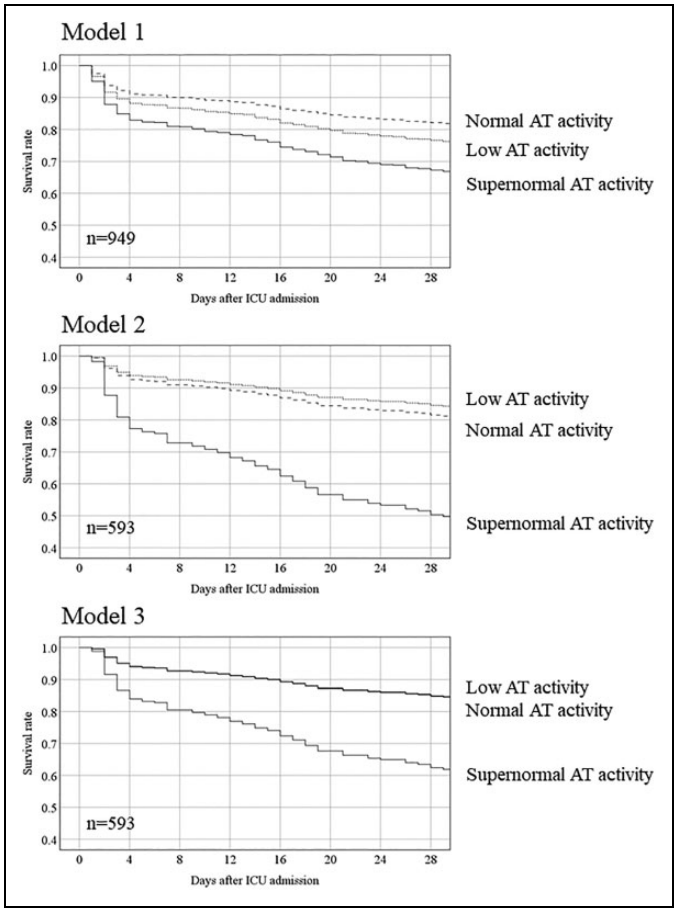

Figure 6. Adjusted estimated survival curves in Cox regression models. Model 1: the estimated survival curves adjusted by APACHE II score. Compared with the normal AT group, the low and supernormal AT groups had higher mortality rates (adjusted hazard ratio [HR] 95% CI, *P* value: 1.35 (1.03-1.78), $P = .032$ and 2.01 (1.09-3.73), $P = .26$, respectively). Model 2: the estimated survival curves adjusted by AT activity on day 2. Compared with the normal AT group, the supernormal AT group had higher mortality rates (adjusted HR [95% CI], *P* value: 3.36 [1.45-7.80], $P = .005$). The difference between the low and normal AT activity groups was not statistically significant (adjusted HR [95% CI], *P* value: 0.82 [0.51-1.31], $P = .403$). Model 3: the estimated survival curves adjusted by the APACHE II score and AT activity on day 2. Compared with the normal AT group, the supernormal AT group had higher mortality rates (adjusted HR [95% CI], *P* value: 2.85 [1.23-6.59], $P = .015$). The difference between the low and normal AT activity groups was not statistically significant (adjusted HR [95% CI], *P* value: 0.99 [0.62-1.58], $P = .952$). APACHE indicates Acute Physiology and Chronic Health Evaluation; AT, antithrombin; CI, confidence interval.

3195-patient cohort of the J-SEPTIC DIC study.[13,14] A recent multicenter cohort study using a cubic spline model demonstrated a relationship between AT activity and mortality in patients with sepsis.[19] In the study, the mortality rate of patients with supernormal AT activity was higher than that of those with normal AT activity.[19] However, the study focused on the high mortality rate of patients with low AT activity, and the characteristics of patients with supernormal AT activity were not discussed.[19]

Supernormal AT activity on day 1 was found to be a predictor of in-hospital mortality independent from day 2 AT activity in this study. Based on these findings, a reduction or increase in AT activity following ICU admission may therefore have little or no impact on the effect of supernormal AT levels on mortality. Although both supernormal and low AT activity on day 1 were associated with an increased mortality rate, it is likely that the causative pathophysiology differs between these groups of patients. In severe sepsis, decreases in the AT activity are usually induced by an increase in vascular permeability, which results from inflammation.[9,10] Therefore, patients with sepsis with low AT activity are likely to have severe vascular permeability[9,10] and related organ dysfunction, including acute respiratory distress syndrome.[10,20] Consequently, the outcome of patients with low AT activity may be poor. Conversely, patients with supernormal AT activity do not demonstrate vascular permeability. In our study, patients with supernormal AT activity had complicated organ dysfunction and were admitted to the ICU. Organ dysfunction without vascular permeability, which requires admission to the ICU, may affect the outcome in patients with supernormal AT activity.

The SOFA scores on admission to the ICU were higher in patients with supernormal AT activity than those with normal AT activity; however, the APACHE II scores were similar between the groups. This apparent contradiction may be attributed to differences in the degree of organ dysfunction between patients with different levels of AT activity; therefore, the degree of organ dysfunction on admission may affect the in-hospital mortality of patients with sepsis. Furthermore, the tendency of patients with supernormal AT activity to have unknown primary infection sites and unknown sepsis-causing microorganisms may indicate that a pathophysiology other than sepsis may be responsible for multiple organ dysfunction and high mortality rates in these individuals.

The methods used to measure AT activity in the J-SEPTIC DIC study were not recorded; however, the factor Xa-inhibition method was commonly used in Japan during the study period. It is therefore possible that other molecules with anti-Xa activity may have affected the AT activity values. Oral direct factor Xa inhibitors, such as rivaroxaban, may induce pseudo-high AT activity owing to its anti-Xa effect[21]; however, patients in the supernormal AT group of this study had not received oral direct anticoagulants during their stay in the ICU (Table 1).

The present study has several limitations. First, the AT antigen levels in plasma were not considered, as they are not routinely measured in clinical settings. Second, in the nonlinear regression analysis, the relationship between the risk of in-hospital mortality and AT activity in the supernormal range was not statistically significant. This result was affected by large 95% CI resulting from small number of patients with supernormal AT activity. We speculated that the relationships between the mortality risk and AT activity in the supernormal range might become significant when a larger cohort is used. Third, the pathophysiology associated with the higher mortality rate in the supernormal AT group was not identified from this analysis. Fourth, owing to the retrospective nature of the study,

several patients had to be excluded from multiple regression analyses owing to missing data regarding AT activity on day 2.

Conclusions

This study identified a subgroup of patients with sepsis with supernormal AT activity from a large cohort of patients with sepsis. This subgroup of patients represented 3% of patients with sepsis treated in the ICU. The in-hospital mortality of patients with low or supernormal AT activity was similar. However, the pathophysiology causing mortality in patients with supernormal AT activity may differ from that causing mortality in patients with low AT activity. Further studies are needed to elucidate the pathophysiology associated with higher mortality in patients with supernormal AT activity.

Authors' Note

The data sets used in this study are available from Hayakawa et al.[13]

Acknowledgments

The authors would like to thank Editage (https://online.editage.jp/) for English language editing.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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