SHOCK, Vol. 46, No. 6, pp. 623–631, 2016

OPEN

ANTITHROMBIN SUPPLEMENTATION AND MORTALITY IN SEPSIS-INDUCED DISSEMINATED INTRAVASCULAR COAGULATION: A MULTICENTER RETROSPECTIVE OBSERVATIONAL STUDY

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Contributions of authors and collaborators: MH, DK, SS, SU, KY, YI, MS, KT, and TM designed the study and reviewed the data set. MH interpreted the data and drafted the manuscript. KO performed the statistical analysis. MH, DK, SS, YI, KT, TA, FI, SY, KH, TN, TO, EN, YN, RS, YY, MS, KU, YO, MW, AT, NS, YK, HT, IK, YK, WM, SN, TM, HT, ST, KU, TT, HK, KA, TK, YI, HA, MM, MY, KS, and NH collected and assessed the data at each institution.

All authors also read and approved the final manuscript.

MH received a grant for basic research and a lecturer's fee from Asahi Kasei Pharma Co.

The other authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.shockjournal.com).

DOI: 10.1097/SHK.0000000000000727

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Received 4 May 2016; first review completed 16 May 2016; accepted in final form 29 Jun 2016

ABSTRACT—Supplemental doses of antithrombin (AT) are widely used to treat sepsis-induced disseminated intravascular coagulation (DIC) in Japan. However, evidence on the benefits of AT supplementation for DIC is insufficient. This multicenter retrospective observational study aimed to clarify the effect of AT supplementation on sepsis-induced DIC using propensity score analyses. Data from 3,195 consecutive adult patients admitted to 42 intensive care units for severe sepsis treatment were retrospectively analyzed; 1,784 patients were diagnosed with DIC (n = 715, AT group; n = 1,069, control group). Inverse probability of treatment-weighted propensity score analysis indicated a statistically significant association between AT supplementation and lower in-hospital all-cause mortality (n = 1,784, odds ratio [95% confidence intervals]: 0.748 [0.572–0.978], $P = 0.034$). However, quintile-stratified propensity score analysis (n = 1,784, odds ratio: 0.823 [0.646–1.050], $P = 0.117$) and propensity score matching analysis (461 matching pairs, odds ratio: 0.855 [0.649–1.125], $P = 0.263$) did not show this association. In the early days after intensive care unit admission, the survival rate was statistically higher in the propensity score-matched AT group than in the propensity score-matched control group ($P = 0.007$). In DIC patients without concomitant heparin administration, similar results were observed. In conclusion, AT supplementation may be associated with reduced in-hospital all-cause mortality in patients with sepsis-induced DIC. However, the statistical robustness of this connection was not strong. In addition, although the number of transfusions needed in patients with AT supplementation increased, severe bleeding complications did not.

KEYWORDS—Antithrombin, coagulation abnormality, disseminated intravascular coagulation, mortality, sepsis

INTRODUCTION

Disseminated intravascular coagulation (DIC) is a serious and frequent complication in patients with severe sepsis and septic shock (1–3). The pathogenesis of sepsis-induced DIC is characterized by systemic generation of thrombin, reduction of coagulation inhibitors, and impairments to fibrinolytic components (2). Antithrombin (AT), formerly known as antithrombin III, is an important physiologic coagulation inhibitor, similar to protein C and tissue factor pathway inhibitor (4). In sepsis-induced DIC, a decrease in AT activity is frequently observed, and baseline AT activity is an independent predictor of prognosis in patients with sepsis-induced DIC (5–7).

The KyberSept trial, which was a large-scale randomized controlled trial, did not find any benefits to high-dose AT administration (total 30,000 IU over 4 days) in patients with severe sepsis (8). Furthermore, a meta-analysis of 20 randomized trials concluded that AT treatments should not be recommended for critically ill patients; notably, the patients in this analysis were not limited to those with sepsis (9). These reports also indicated that AT treatment, particularly with heparin, increased bleeding complications (8, 9). Therefore, AT treatment is not recommended as an adjunct therapy for sepsis according to international sepsis guidelines (10). However, in *post hoc* analyses of the KyberSept trial, high-dose AT administration without concomitant heparin increased survival time in patients with severe sepsis (11, 12). In a systematic review of AT treatment in patients with sepsis-induced DIC, AT treatment increased overall survival in comparison to a control group (13). Thus, AT treatment should perhaps target not patients with sepsis, but those with sepsis-induced DIC. Moreover, it may be important that AT is administered without heparin to prevent bleeding complications.

In Japan, a supplemental dose of AT (total 4,500 IU over 3 days) is commonly administered to patients with sepsis-induced DIC and low AT levels. Two studies by Tagami et al. (14, 15) analyzed the effects of AT supplementation using a nationwide administrative database and reported that AT treatment was beneficial in treating sepsis-induced DIC patients. A major limitation of these studies was that the database did not contain laboratory data or information regarding the clinical severity of the patients' conditions (14, 15). Furthermore, the etiologies of sepsis were solely restricted to pneumonia (14) and perforation of the lower intestinal tract (15). Gando et al. (16) performed a randomized trial of AT supplementation in sepsis-induced DIC patients with low risk of death. Although the study did not have enough power to prove with statistical significance that AT supplementation was associated with a reduction in 28-day mortality, the results did suggest that AT supplementation improved outcomes in DIC patients (28-day mortality: 13% vs. 10%, n = 60, $P = 1.0$) (16). Furthermore, several studies have indicated that AT supplementation does not increase bleeding complications in patients with sepsis-induced DIC (16–18).

Although supplemental doses of AT are often administered to patients with sepsis-induced DIC in Japan, the evidence for this practice is insufficient. Therefore, we conducted a multicenter retrospective observational study and analyzed the effect of AT supplementation in patients with sepsis-induced DIC using propensity score analyses.

PATIENTS AND METHODS

This retrospective observational study (referred to as the Japan Septic Disseminated Intravascular Coagulation [J-SEPTIC DIC] study) (UMIN000012543 [University hospital Medical Information Network Clinical Trials Registry]) was conducted in 42 intensive care units (ICUs) across 40 institutions throughout Japan (Supplemental Tables 1 and 2, http://links.lww.com/SHK/A458) and was approved by the Institutional Review Board at each hospital. The boards waived the need for informed consent, as this was a retrospective study. We performed the present analyses of AT using the same methods used for previous analyses of recombinant human thrombomodulin (19).

Patient selection and data collection

The J-SEPTIC DIC study retrospectively included patients admitted consecutively to the ICU for treatment of severe sepsis/septic shock from January 2011 to December 2013. The definitions from the international sepsis definitions conference were used to classify cases of severe sepsis/septic shock (20). Patients were excluded if they were younger than 16 years of age or developed severe sepsis/septic shock after admission to the ICU. Patients who died on the day of ICU admission were not excluded.

This study collected data on the following variables: ICU characteristics; ICU admission route; patient age, sex, and body weight; pre-existing organ dysfunction; pre-existing hemostatic disorders; Acute Physiology and Chronic Health Evaluation (APACHE) II score; Sequential Organ Failure Assessment (SOFA) score on Days 1, 3, and 7; systemic inflammatory response syndrome (SIRS) score on Days 1, 3, and 7; primary infection site; blood culture results; microorganisms causing sepsis; daily results of laboratory tests during the first week after ICU admission; lactate levels on Days 1, 3, and 7; treatments administered; number of transfusions needed during the first week after ICU admission; bleeding complications during the first week after ICU admission; and hospital outcomes.

The DIC score was calculated using a scoring algorithm from the Japanese Association for Acute Medicine DIC criteria (21). Missing values were scored as zeroes. DIC patients were considered to be those without a pre-existing hemostatic disorder and with a single-day DIC score $\geq$4 during the first week after ICU admission (on Days 1, 3, or 7). The number of event-free days (events were defined as ICU admission, renal replacement therapy, mechanical ventilator use, and vasopressor administration) within a 28-day period was calculated by subtracting the duration from 28 days (or survival days after ICU admission). If a patient was discharged before 28 days after ICU admission, the number of event-free days was calculated by subtracting each duration from 28 days.

Patients were divided into the following two groups: the AT group (i.e., patients who received AT treatment) and the control group (i.e., patients who did not receive AT treatment). For DIC patients who experienced a decline in AT levels, AT therapy was used at the discretion of the attending physician. There was no predefined protocol regarding AT treatment. Typically, 1500 IU of AT per day were intravenously administered to DIC patients with AT levels $\leq$70%. The AT treatment was continued for 3 days or until there was improvement to the patient's DIC.

Statistical analysis

Data are expressed as a number (%), mean $\pm$ standard deviation, or median (interquartile range), as appropriate. To estimate the propensity scores, we fit a logistic regression model for AT treatment as a function of variables related to patient characteristics, therapeutic interventions, and ICU characteristics. This resulted in models based on age; sex; body weight; admission route to the ICU; pre-existing organ dysfunction; pre-existing hemostatic disorder; APACHE II score; SOFA score for each organ (except coagulation) on Day 1; SIRS score on Day 1; DIC score on Day 1; primary infection site; blood culture results; microorganisms responsible for sepsis; laboratory tests (including white blood cell count, platelet count, hemoglobin level, and prothrombin time-international normalized ratio) on Day 1; use of anti-DIC drugs; use of other anticoagulants; immunoglobulin use; low-dose steroid use; surgical interventions at the infection site; renal replacement therapy; renal replacement therapy for non-renal indications; polymyxin B direct hemoperfusion; extracorporeal membrane oxygenation; intra-aortic balloon pumping; ICU characteristics; ICU policy; and number of beds in the ICU. Some laboratory tests (fibrinogen, fibrin/fibrinogen degradation products, D-dimer, antithrombin, and lactate) were not used to estimate the propensity score because the proportion of missing data was >10%. In the present analysis, we used various therapeutic interventions to estimate the propensity score, because they were usually performed simultaneously with AT treatment.

To evaluate statistical robustness, we performed a propensity score matching analysis, inverse probability of treatment-weighted (IPTW) analysis, and quintile-stratified propensity score analysis. For the propensity score matching analysis, we performed one-to-one nearest-neighbor matching without replacement between the AT and control groups based on estimated propensity scores for each patient. A caliper width of 0.15 of the standard deviation of the logit of the propensity score was used. The standardized difference was used to evaluate covariate balance. An absolute standardized difference >10% was determined to represent meaningful imbalance (22). We performed logistic regression analysis fitted with generalized estimating equations to examine the association between AT treatment and in-hospital all-cause mortality, accounting for the matched nature of matched pairs (23). AT supplementation alone was used as the independent variable for the logistic regression analysis fitted with generalized estimating equations, IPTW analysis, and the Cox regression analysis. For the quintile-stratified propensity score analysis, we used AT supplementation and propensity score strata as independent variables. The generalized Wilcoxon test was used to assess differences in in-hospital survival rates in the propensity score-matched groups. Intergroup comparisons were assessed using the Wilcoxon signed-rank test or McNemar test in the propensity score-matched groups. For the subgroup that included DIC patients without concomitant heparin administration, we performed the same analyses as mentioned above.

R version 3.1.3 with the "MATCHIT" package was used for propensity score estimation and matching (24, 25), and SAS version 9.4 (SAS Institute Inc, Cary, NC) was used for other analyses.

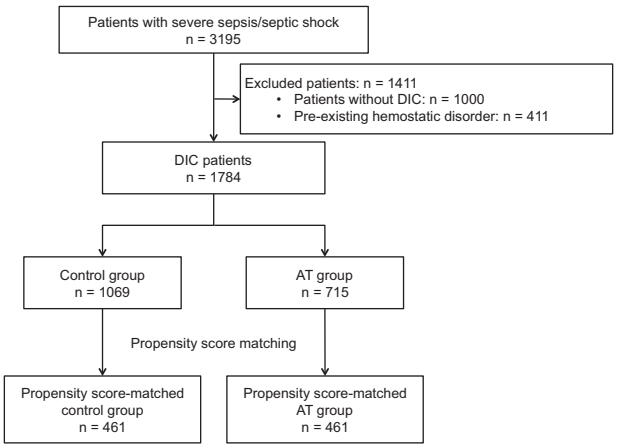

FIG. 1. **Study flow design for selection of patients who received antithrombin supplementation.** AT indicates antithrombin; DIC, disseminated intravascular coagulation.

RESULTS

A total of 3,195 consecutive patients with severe sepsis/septic shock were enrolled in this study. Among patients with severe sepsis/septic shock, 1,784 patients were diagnosed with DIC; of these, 715 patients received AT therapy, and 1,069 patients did not (Fig. 1).

Propensity score matching created 461 matched pairs (Fig. 1). The ICU characteristics, according to the unmatched and propensity score-matched groups, are presented in Table 1, while the characteristics of the patients in the unmatched and propensity score-matched groups are shown in Table 2. Although some data regarding laboratory test results upon ICU admission were missing for some patients, all data for other variables were collected. Clinical severity and intensity of therapeutic interventions were imbalanced between the two groups. After propensity score matching, all of the standardized differences in the matched patients were <10%, except for fibrinogen and AT levels, and the characteristics of the two groups were appropriately balanced. For DIC patients who did not receive concomitant heparin, the characteristics of the propensity score-matched groups were appropriately balanced (Supplemental Table 3, http://links.lww.com/SHK/A458).

Table 1. **Characteristics of ICUs that admitted DIC patients in the unmatched and propensity score-matched groups**

	Unmatched group		Unmatched	Matched group		Matched
	Control n = 1,069	AT n = 715	Standardized Difference (%)	Control n = 461	AT n = 461	Standardized Difference (%)
ICU characteristics						
General ICU	526 (49.2%)	358 (50.1%)	−1.73	226 (49.0%)	228 (49.5%)	−0.87
Emergency ICU	543 (50.8%)	357 (49.9%)		235 (51.0%)	233 (50.5%)	
ICU policy						
Closed policy	584 (54.6%)	342 (47.8%)	−13.63	224 (48.6%)	231 (50.1%)	3.04
Open policy	365 (34.1%)	231 (32.3%)	−3.90	151 (32.8%)	143 (31.0%)	−3.72
Other	120 (11.2%)	142 (19.9%)	24.00	86 (18.7%)	87 (18.9%)	0.56
Bed number	12 (8–19)	10 (7–15)	−33.11	10 (8–18)	11 (8–16)	−1.59

AT indicates antithrombin; DIC, disseminated intravascular coagulation; ICU, intensive care unit. Data are presented as the median (interquartile range) or number (%).

Table 2. **Characteristics of the DIC patients in the unmatched and propensity score-matched groups**

	Unmatched group		Unmatched	Matched group		Matched
	Control n = 1069	AT n = 715	Standardized difference (%)	Control n = 461	AT n = 461	Standardized difference (%)
Age, year	70 ± 14	70 ± 14	−5.01	69 ± 15	70 ± 14	4.26
Male	610 (57.1%)	403 (56.4%)	1.41	265 (57.5%)	268 (58.1%)	1.32
Body weight, kg	55.5 ± 14.1	56.2 ± 13.5	4.94	56.5 ± 14.0	56.2 ± 14.1	−1.88
Admission route to ICU						
Emergency department	494 (46.2%)	316 (44.2%)	−4.05	196 (42.5%)	201 (43.6%)	2.19
Other hospital	314 (29.4%)	202 (28.3%)	−2.48	147 (31.9%)	146 (31.7%)	−0.47
Hospital ward	261 (24.4%)	197 (27.6%)	7.16	118 (25.6%)	114 (24.7%)	−2.00
Pre-existing organ dysfunction						
Liver insufficiency	10 (0.9%)	7 (1.0%)	0.45	4 (0.9%)	4 (0.9%)	0.00
Chronic respiratory disorder	44 (4.1%)	20 (2.8%)	−7.22	15 (3.3%)	17 (3.7%)	2.37
Chronic heart failure	57 (5.3%)	32 (4.5%)	−3.97	26 (5.6%)	26 (5.6%)	0.00
Chronic hemodialysis	109 (10.2%)	47 (6.6%)	−13.10	34 (7.4%)	32 (6.9%)	−1.68
Immunocompromised	115 (10.8%)	75 (10.5%)	−0.87	54 (11.7%)	50 (10.8%)	−2.74
Severity						
APACHE II score	23 (17–29)	24 (18–29)	2.99	23 (17–29)	24 (18–29)	−0.76
SOFA score, total	10 (7–12)	11 (8–13)	26.54	10 (8–13)	11 (8–13)	−0.18
Respiratory	2 (1–3)	2 (1–3)	5.86	2 (1–3)	2 (1–3)	1.28
Renal	2 (0–3)	2 (1–3)	18.15	2 (0–3)	2 (1–3)	2.90
Liver	0 (0–1)	0 (0–1)	12.71	0 (0–1)	0 (0–1)	−0.69
Cardiovascular	3 (1–4)	3 (2–4)	27.24	3 (1–4)	3 (2–4)	6.08
Coagulation	1 (0–2)	2 (0–2)	15.72	2 (1–2)	1 (0–2)	−9.11
Central nervous	1 (0–3)	1 (0–3)	−3.79	1 (0–3)	1 (1–3)	−2.78
SIRS score	3 (3–4)	3 (2–4)	−4.69	3 (3–4)	3 (2–4)	1.01
DIC score	5 (4–6)	5 (4–7)	24.90	5 (4–7)	5 (4–7)	−2.20
Primary infection site						
Abdomen	370 (34.6%)	283 (39.6%)	10.30	176 (38.2%)	181 (39.3%)	2.23
Lung/thoracic	247 (23.1%)	128 (17.9%)	−12.92	90 (19.5%)	85 (18.4%)	−2.77
Urinary tract	196 (18.3%)	129 (18.0%)	−0.76	74 (16.1%)	83 (18.0%)	5.20
Bone/soft tissue	103 (9.6%)	91 (12.7%)	9.82	58 (12.6%)	55 (11.9%)	−1.98
Cardiovascular	30 (2.8%)	14 (2.0%)	−5.57	13 (2.8%)	12 (2.6%)	−1.34
Central nervous system	29 (2.7%)	15 (2.1%)	−4.01	16 (3.5%)	12 (2.6%)	−5.06
Catheter-related	13 (1.2%)	8 (1.1%)	−0.90	7 (1.5%)	7 (1.5%)	0.00
Others	15 (1.4%)	17 (2.4%)	7.16	7 (1.5%)	8 (1.7%)	1.71
Unknown	66 (6.2%)	30 (4.2%)	−8.93	20 (4.3%)	18 (3.9%)	−2.18
Blood culture						
Positive	502 (47.0%)	385 (53.8%)	13.81	246 (53.4%)	248 (53.8%)	0.87
Negative	500 (46.8%)	308 (43.1%)	−7.44	194 (42.1%)	196 (42.5%)	0.88
Not taken	67 (6.3%)	22 (3.1%)	−15.16	21 (4.6%)	17 (3.7%)	−4.37
Microorganisms caused sepsis						
Gram-negative rod	406 (38.0%)	320 (44.8%)	13.79	188 (40.8%)	200 (43.4%)	5.27
Gram-positive-coccus	243 (22.7%)	178 (24.9%)	5.08	124 (26.9%)	118 (25.6%)	−2.96
Fungus	20 (1.9%)	4 (0.6%)	−11.99	5 (1.1%)	4 (0.9%)	−2.21
Virus	9 (0.8%)	4 (0.6%)	−3.39	4 (0.9%)	3 (0.7%)	−2.50
Mixed infection	141 (13.2%)	86 (12.0%)	−3.50	60 (13.0%)	64 (13.9%)	2.54

Table 2. (*continued*)

	Unmatched group		Unmatched	Matched group		Matched
	Control n = 1069	AT n = 715	Standardized difference (%)	Control n = 461	AT n = 461	Standardized difference (%)
Others	23 (2.2%)	4 (0.6%)	−13.80	3 (0.7%)	3 (0.7%)	0.00
Unknown	227 (21.2%)	119 (16.6%)	−11.74	77 (16.7%)	69 (15.0%)	−4.75
Laboratory test on admission to ICU						
White blood cell counts, 10^9/L	11.2 (5.2–18.3)	11.2 (3.7–18.0)	−1.72	11.2 (4.6–18.5)	11.2 (3.6–18.1)	−2.07
Missing data, n (%)	0 (0.0%)	1 (0.1%)		0 (0.0%)	0 (0.0%)	
Platelet counts, 10^9/L	106 (60–68)	88 (51–149)	−15.76	97 (54–149)	95 (57–160)	3.71
Missing data, n (%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Hemoglobin, mmol/L	6.7 (5.6–7.8)	6.5 (5.6–7.7)	−8.51	6.7 (5.6–7.8)	6.5 (5.6–7.8)	−2.10
Missing data, n (%)	0 (0.0%)	1 (0.1%)		0 (0.0%)	0 (0.0%)	
PT-INR	1.31 (1.17–1.56)	1.41 (1.25–1.68)	10.94	1.36 (1.19–1.60)	1.41 (1.24–1.64)	0.97
Missing data, n (%)	32 (3.%)	19 (2.7%)		0 (0.0%)	0 (0.0%)	
Fibrinogen, g/L	4.00 (2.72–5.59)	3.54 (2.26–5.13)	−19.68	3.99 (2.63–5.51)	3.60 (2.80–5.05)	−16.54
Missing data, n (%)	228 (21.3%)	94 (13.1%)		59 (12.8%)	58 (12.6%)	
FDP, mg/L	25.6 (13.5–55.0)	25.5 (13.6–29.5)	7.64	27.0 (14.5–62.4)	23.8 (13.0–51.5)	2.14
Missing data, n (%)	334 (31.2%)	154 (21.5%)		112 (24.3%)	102 (22.1%)	
D-dimer, mg/L	12.8 (5.7–27.3)	12.4 (5.8–27.1)	8.69	13.1 (6.1–29.8)	11.0 (5.7–24.7)	7.76
Missing data, n (%)	220 (20.6%)	156 (21.8%)		91 (19.7%)	102 (22.1%)	
Antithrombin, %	60 (48–75)	51 (40–61)	−53.82	60 (47–74)	51 (41–62)	−43.73
Missing data, n (%)	540 (50.8%)	206 (28.8%)		200 (43.4%)	139 (30.2%)	
Lactate, mmol/L	3.0 (1.7–6.0)	3.9 (2.2–6.8)	12.30	3.2 (2.0–6.0)	3.9 (2.2–6.6)	6.22
Missing data, n (%)	148 (13.8%)	52 (7.2%)		55 (11.9%)	31 (6.7%)	
Co-administered anti-DIC drug						
Recombinant thrombomodulin	266 (24.9%)	379 (53.0%)	60.23	221 (47.9%)	216 (46.9%)	−2.17
Protease inhibitors	83 (7.8%)	184 (25.7%)	49.58	72 (15.6%)	86 (18.7%)	8.07
Heparinoids	47 (4.4%)	63 (8.8%)	17.85	31 (6.7%)	29 (6.3%)	−1.76
Co-administered anticoagulants not for DIC						
Nafamostat mesilate	294 (27.5%)	311 (43.5%)	33.90	178 (38.6%)	188 (40.8%)	4.43
Heparin	156 (14.6%)	71 (9.9%)	−14.25	50 (10.8%)	48 (10.4%)	−1.41
Warfarin	8 (0.7%)	2 (0.3%)	−6.56	3 (0.7%)	2 (0.4%)	−2.95
Anti-platelet drugs	12 (1.1%)	8 (1.1%)	−0.03	4 (0.9%)	4 (0.9%)	0.00
Others	3 (0.3%)	4 (0.6%)	4.31	3 (0.7%)	2 (0.4%)	−2.95
Other therapeutic intervention						
Surgical intervention	438 (41.0%)	374 (52.3%)	22.87	216 (46.9%)	227 (49.2%)	4.78
Immunoglobulin	230 (21.5%)	379 (53.0%)	68.89	190 (41.2%)	200 (43.4%)	4.39
Low-dose steroid	247 (23.1%)	245 (34.3%)	24.86	150 (32.5%)	159 (34.5%)	4.14
RRT	298 (27.9%)	294 (41.1%)	28.13	166 (36.0%)	176 (38.2%)	4.49
Non-renal indication RRT	69 (6.5%)	108 (15.1%)	28.17	54 (11.7%)	62 (13.4%)	5.23
PMX-DHP	194 (18.1%)	289 (40.4%)	50.48	141 (30.6%)	152 (33.0%)	5.13
Plasma exchange	7 (0.7%)	10 (1.4%)	7.38	6 (1.3%)	3 (0.7%)	−6.62
veno-arterial ECMO	15 (1.4%)	7 (1.0%)	−3.91	5 (1.1%)	5 (1.1%)	0.00
veno-venous ECMO	438 (41.0%)	374 (52.3%)	22.87	216 (46.9%)	227 (49.2%)	4.78
IABP	6 (0.6%)	4 (0.6%)	−0.02	3 (0.7%)	4 (0.9%)	

APACHE indicates Acute Physiology and Chronic Health Evaluation; AT, antithrombin; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation system; FDP, fibrin/fibrinogen degradation products; IABP, intra-aortic balloon pumping system; ICU, intensive care unit; PMX-DHP, Polymixin B-direct hemoperfusion; PT-INR, prothrombin time-international normalized ratio; RRT, renal replacement therapy; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment. Data are expressed as the number (%), mean ± standard deviation, or median (interquartile range).

The odds ratios for in-hospital all-cause mortality with AT supplementation are presented in Figure 2. Analysis of IPTW propensity scores indicated a significant association between AT supplementation and lower in-hospital all-cause mortality (odds ratio [95% confidence intervals]: 0.748 [0.572–0.978], $P = 0.034$). Quintile-stratified propensity score and propensity score matching analyses demonstrated tendencies that were consistent with those of the IPTW propensity score analysis, although statistically significant differences were not observed. Similar results were observed among DIC patients without concomitant heparin use.

Survival curves for the propensity score-matched groups are presented in Figure 3. In the early days after ICU admission, the survival rate in the propensity score-matched AT group was statistically higher than that in the propensity score-matched control group ($P = 0.007$ by the generalized Wilcoxon test). However, in the late days after ICU admission, the survival rates in the matched groups were not different.

Event-free days in the matched groups are presented in Table 3. The number of renal replacement therapy-free days in the matched AT group was significantly greater than that in the control group. Other event-free days were not significantly different between the two groups.

The frequency of bleeding events that required transfusion was significantly higher in the propensity score-matched AT group than in the propensity score-matched control group (Table 4). However, severe bleeding complications were not significantly different

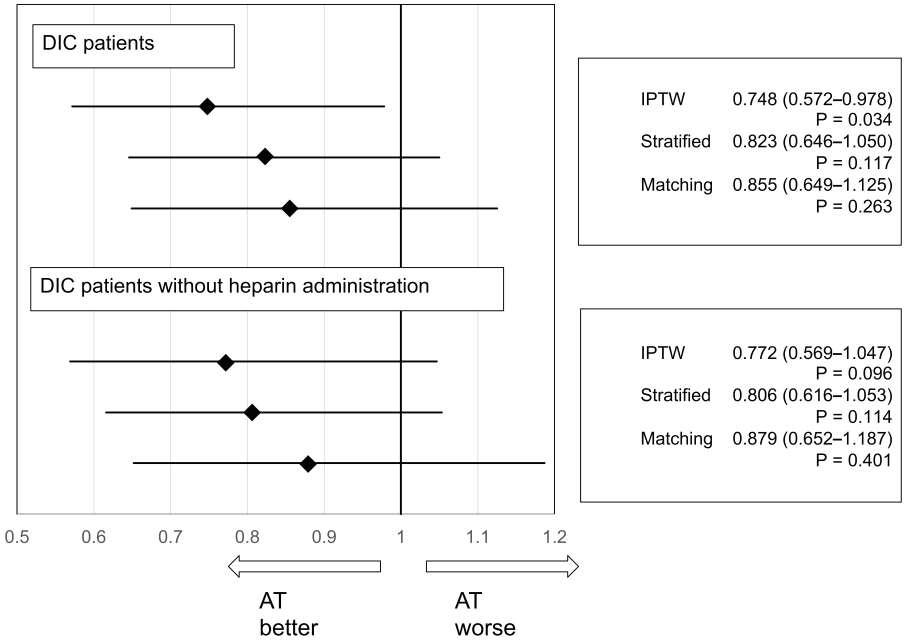

Fig. 2. **Odds ratios for in-hospital all-cause mortality for R-antithrombin supplementation.** Odds ratios (black squares) and 95% confidence intervals (bars). AT indicates antithrombin; DIC, disseminated intravascular coagulation; IPTW, inverse probability of treatment-weighted.

between the two groups. Moreover, the number of transfusions needed was significantly greater in the propensity score-matched AT group than in the propensity score-matched control group (Table 5). Among DIC patients without concomitant heparin use, similar results were observed (Tables 4 and 5).

DISCUSSION

In the present multicenter retrospective observational study, propensity score analyses (IPTW, stratified, and matching) indicated consistent tendencies toward reduced all-cause mortality in patients with sepsis-induced DIC who received AT supplementation. However, the statistical robustness of this trend was not strong. Furthermore, the number of renal replacement therapy-free days was higher in the AT group. In addition, although the number of transfusions needed increased in patients who received AT supplementation, severe bleeding complications did not increase.

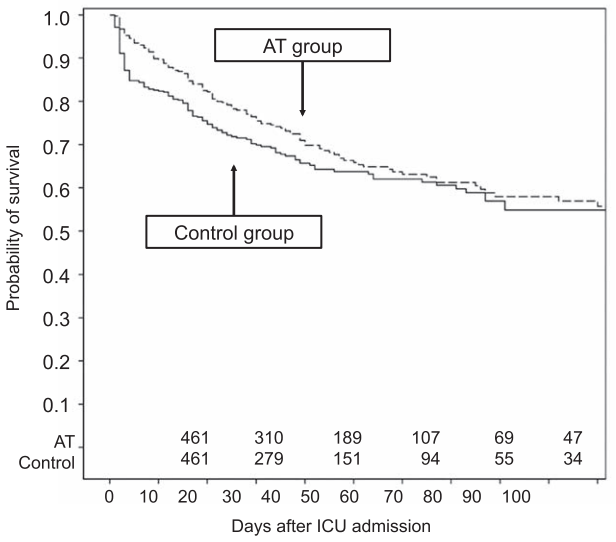

Fig. 3. **Survival plots for patients in the propensity score-matched control and AT groups.** In the early days after ICU admission, the survival rate in the propensity score-matched AT group was significantly higher than that in the propensity score-matched control group ($P = 0.007$ by the generalized Wilcoxon test). However, in the late days after ICU admission, the survival rates in the matched groups were not different. AT indicates antithrombin; ICU, intensive care unit.

Recent guidelines for the management of DIC (26) and severe sepsis (10) have provided different recommendations for AT administration. These differences are the result of differences in valuation from the KyberSept trial and its *post hoc* analyses (8, 11, 12). Although the KyberSept trial reported on the effects of high-dose AT administration in patients with severe sepsis (8), recent investigations have indicated that AT treatment is most appropriate in cases of sepsis-induced DIC (13, 27). In Japan, AT supplemental treatment is frequently performed in patients with sepsis-induced DIC, not sepsis, for the last three decades. Various studies by Tagami et al. (14, 15) have reported on the benefits of AT supplementation in patients with DIC induced by pneumonia and perforation of the lower intestinal tract. In those studies, 30% of patients with sepsis-induced DIC received therapy with recombinant thrombomodulin (14, 15). However, in the present study, 50% of the patients with sepsis-induced DIC in matched groups received therapy with recombinant thrombomodulin (Table 2). Therefore, the benefits of AT supplementation might diminish when comparing AT and control groups.

Recently, propensity score analyses have been increasingly used in critical care medicine (28). In the present study, we applied three methods of propensity score analyses, namely IPTW, quintile-stratified, and matching analyses, to confirm statistical robustness. Three propensity score analyses indicated consistent tendencies toward reduced all-cause mortality in patients with sepsis-induced DIC who received AT supplementation. However, this relationship was only statistically significant according to the

Table 3. **Event-free days over 28 days in the propensity score-matched groups**

DIC patients	Control n = 461	AT n = 461	*P* value
ICU-free days	15 (0–22)	17 (0–22)	0.372
Ventilator-free days, days	19 (1–26)	20 (3–26)	0.520
RRT-free days, days	25 (5–28)	26 (16–28)	0.006
Vasopressor-free days, days	22 (10–26)	23 (15–26)	0.075
DIC patients without heparin administration	n = 379	n = 379	
ICU-free days	15 (0–22)	17 (0–22)	0.557
Ventilator-free days, days	20 (1–26)	20 (2–26)	0.912
RRT-free days, days	25 (3–28)	26 (12–28)	0.009
Vasopressor-free days, days	23 (8–26)	23 (12–26)	0.382

AT indicates antithrombin; DIC, disseminated intravascular coagulation; ICU, intensive care unit; RRT, renal replacement therapy. Data are presented as the median (interquartile range).

Table 4. **Bleeding complications in the propensity score-matched groups**

DIC patients	Control n = 461	AT n = 461	*P* value
Bleeding needed transfusion	53 (11.5%)	82 (17.8%)	0.007
Bleeding needed therapeutic intervention	5 (1.1%)	11 (2.4%)	0.210
Intracranial hemorrhage	1 (0.2%)	2 (0.4%)	1.000
Bleeding to death	2 (0.4%)	1 (0.2%)	1.000
DIC patients without heparin administration	n = 379	n = 379	
Bleeding needed transfusion	38 (10.0%)	68 (17.9%)	0.002
Bleeding needed therapeutic intervention	5 (1.3%)	10 (2.6%)	0.267
Intracranial hemorrhage	2 (0.5%)	3 (0.8%)	1.000
Bleeding to death	2 (0.5%)	0 (0.0%)	NA

AT indicates antithrombin; DIC, disseminated intravascular coagulation; NA, not available. Data are presented as the median (interquartile range) or number (%).

Table 5. **Transfusion amounts in the propensity score-matched groups**

DIC patients	Control n = 461	AT n = 461	*P* value
Red blood cell concentration, units	0 (0–4)	2 (0–6)	0.020
Fresh frozen plasma, units	0 (0–5)	0 (0–10)	0.002
Platelet concentration, units	0 (0–10)	0 (0–20)	0.003
DIC patients without heparin administration	n = 379	n = 379	
Red blood cell concentration, units	0 (0–4)	2 (0–6)	0.005
Fresh frozen plasma, units	0 (0–6)	0 (0–10)	0.006
Platelet concentration, units	0 (0–10)	0 (0–20)	0.003

AT indicates antithrombin; DIC, disseminated intravascular coagulation. Data are presented as the median (interquartile range) or number (%).

IPTW propensity score analysis; quintile-stratified propensity score analysis and propensity score matching analysis did not find a statistically significant relationship between these variables. Among these types of propensity score analyses, propensity score matching is the most comprehensive type of analysis. However, the statistical power is reduced with this method because the number of analyzed patients is reduced in matched groups. On the other hand, IPTW analysis provides better precision with minimal bias compared with quintile-stratified and matching analyses (29). Therefore, we concluded that AT supplementation may be associated with reduced in-hospital all-cause mortality in patients with sepsis-induced DIC.

The number of event free-days is an important outcome in critically ill patients. In previous studies of AT administration in severe sepsis patients, only two reports discussed this topic, and these studies only reported that AT supplementation improved the number of ventilator-free days in patients with severe pneumonia and abdominal sepsis; other types of event-free days were not evaluated (14, 15). In the present study, the number of renal replacement therapy-free days improved with AT supplementation, although the number of other event free-days did not. Because AT has anticoagulant as well as anti-inflammatory properties (30), AT supplementation may improve organ dysfunction, which is often induced by

inflammation and microcirculatory impairment resulting from sepsis-induced DIC (2, 4). In patients with severe sepsis, acute kidney injury requiring renal replacement therapy is an independent predictor of mortality and poor outcomes (31). Therefore, it is an important finding that the number of renal replacement therapy-free days improved with AT supplementation.

In the KyberSept trial, increased bleeding complications, which were caused by excessive AT administration, were associated with worse outcomes in severe sepsis patients who received high doses of AT (8). Bleeding complications are the most serious side effect of DIC treatments such as AT supplementation. Among the DIC patients in this study, the number of transfusions needed in the propensity score-matched AT group was greater than that in the propensity score-matched control group. Furthermore, among the DIC patients who did not receive concomitant heparin, similar results were observed. These adverse results might be explained by the combined effect of AT and other anti-DIC drugs, especially recombinant thrombomodulin, in the 50% of patients in the matched AT group.

In Japan, AT supplementation was approved as a treatment for DIC patients with AT levels $\leq$70%, and it is frequently used to treat DIC in clinical settings. However, some physicians do not administer AT to patients with DIC because the ''Surviving Sepsis Campaign'' guidelines recommend against AT administration for the treatment of severe sepsis and septic shock (10). Therefore, in the present study, some DIC patients did not receive AT supplementation and were included in the control group. Furthermore, physicians who do not administer AT to DIC patients do not routinely measure AT levels in their DIC patients (AT levels were not measured in 50% of the DIC patients in the control group [545/1,069 patients]). Therefore, in the present study, we believe that the evaluation of AT supplementation in DIC patients both with and without measurements of AT levels is more accurate than evaluation in only DIC patients with measurements of AT levels. Although the AT levels were not balanced in the propensity score-matched groups, other important measures of severity were completely balanced. In addition, recent studies have indicated that the benefits of AT supplementation are greater in DIC patients with AT levels $\leq$40% compared with DIC patients with AT levels $\leq$70% (32, 33). However, in the present study, there were only 188 DIC patients with AT levels $\leq$40% on Day 1. Therefore, we could not fully evaluate the effects of AT supplementation in DIC patients with AT levels $\leq$40%.

In Japan, the Japanese Association for Acute Medicine DIC score is used more frequently than the ISTH DIC score in clinical settings. Furthermore, several previous studies reported that the Japanese Association for Acute Medicine DIC score was better than the ISTH DIC score in diagnosing DIC and predicting prognosis (3, 34). Therefore, we used the Japanese Association for Acute Medicine DIC criteria in the present study.

The present study has some limitations, including its retrospective design. First, we could not identify the exact timing of the therapeutic interventions that were administered. However, therapeutic interventions and AT supplementation were usually performed simultaneously upon ICU admission, and other therapeutic interventions were not affected by AT supplementation. Therefore, we determined that it was acceptable to incorporate the use of therapeutic interventions to estimate the propensity score. Second, the dose and duration of AT supplementation were not known for all patients. However, we assumed that nearly all patients received typical supplemental doses of AT during their first 3 days of ICU admission. Third, some data were missing from the data set, particularly AT levels. However, the characteristics of the DIC patients were appropriately evaluated and balanced by using other variables.

In conclusion, propensity score analyses indicated that AT supplementation may be associated with reduced in-hospital all-cause mortality in patients with sepsis-induced DIC in the present multicenter retrospective observational study. However, the statistical robustness of this association was not strong. Although the number of transfusions needed in patients who received AT supplementation increased, the incidence of severe bleeding complications did not. To determine the true benefits of AT supplementation, there is a need for future multicenter randomized trials that specifically include DIC patients with decreased AT levels.

ACKNOWLEDGMENT

The authors thank Editage (www.editage.jp) for English language editing.

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