 doi:10.20944/preprints202210.0002.v1

Article

Therapeutic Approach of Anticoagulants and Acute Blood Purification for Patients with Sepsis-Induced Disseminated Intravascular Coagulation: Post-marketing Surveillance Data of Antithrombin Supplementation

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Abstract: Backgroud. To improve mortality in patients with sepsis and septic shock, anticoagulant and acute blood purification therapies are performed depends on their severity of organ failure including coagulopathy. Therapeutic approach is required in clinical settings. Material and Methods. We evaluated anticoagulant and acute blood purification therapy in 2,007 patients with sepsis-induced disseminated intravascular coagulation (DIC) in a post-marketing survey examining plasma-derived antithrombin (AT) concentrate. Results. The 28-day mortality rate was 24.2%; before AT administration, there was a significant difference in proportion to the severity of the Sequential Organ Failure Assessment (SOFA) score (p<0.001). The median SOFA score was 9. In patients with SOFA scores ≥9, the mortality rate was lower in AT combined therapy with recombinant thrombomodulin (rTM) than in AT monotherapy if their JAAM DIC score was ≥6 (28.5% and 40.0%, respectively; p =0.031). In multiple logistic regression analysis, endotoxin adsorbed polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP) before AT administration was correlated with reduced 28-day mortality (odds ratios: 2.071; 95% confidence intervals 1.374–3.121, p=0.001). Conclusions. To improve mortality in patients with sepsis, if patients with endotoxin-induced septic shock, PMX-DHP would undergo, and further development to DIC, AT concentrate administer, followed by rTM if their SOFA and JAAM DIC scores are ≥9 and 6, respectively. Further prospective study is needed.

Keywords: antithrombin; recombinant thrombomodulin; SOFA score; JAAM DIC score; PMX-DHP

1. Introduction

Although mortality in patients with severe sepsis and septic shock has declined substantially over the past decade [1], it remains high [2]. In 2016, the third consensus definition for sepsis and septic shock defined sepsis as multiple organ failure based on the Sequential Organ Failure Assessment (SOFA) score [3]. In Japan, numerous acute blood purification therapies have been approved for patients with organ failure, such as polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP) for endotoxin-induced septic shock, renal replacement therapy for acute kidney insufficiency, and plasma exchange for acute liver failure. A strategy for sepsis-induced multiple organ failure may affect mortality.

As thrombocytopenia is one of the SOFA score items, the pathological statement of thrombocytopenia following sepsis-induced coagulopathy is considered a treatment target in patients with severe sepsis or septic shock. Coagulative activation generates

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thrombin, mediated by intra-and extra-activation cascades. Antithrombin (AT) and thrombomodulin are important physiological thrombin inhibitors that act as anticoagulants on the endothelial cell surface by binding to glycosaminoglycan and exert anti-inflammatory effects in sepsis [4,5].

Recently, sepsis-induced coagulative activation has been considered to play a role in hemostatic function in localized bacteria formed by thrombosis [6,7]. Based on these theories, the overwhelming inhibition of thrombin can expand local bacteria in general. However, sepsis-induced disseminated intravascular coagulation (DIC) requires sufficient thrombin inhibition.

In Japan, patients with DIC are clinically approved for AT supplementation therapy (30 IU/kg/day × 3 days) with a plasma AT activity ≤70%. Additionally, they are clinically approved to receive other anticoagulants, such as recombinant thrombomodulin (rTM), heparin derivatives, and synthetic protease inhibitors. Several extensive propensity score analyses have indicated that AT supplementation and rTM reduce the mortality rate in patients with sepsis-induced DIC [8,9], whereas combined anticoagulant therapy of AT and rTM or monotherapy is still under consideration [10].

The present study aimed to evaluate the efficacy of anticoagulants, such as AT concentrate monotherapy and combined therapy of AT followed by rTM, and acute blood purification therapy in patients with sepsis-induced DIC.

2. Materials and Methods

Ethics statements

Ethics approval was not applicable for the present study. Our university signed this sponsored research contract with the Japan Blood Products Organization (number: 381-5404). Its survey was conducted following the Declaration of Helsinki, Good Vigilance Practices, and Good Post-marketing Study Practices. Since complete anonymization of personal data was performed during data collection and identifying individual patients was not possible, the ethical committees waived the need to obtain informed consent from patients.

Study design and patient population

The patients with sepsis-induced DIC in the present observational study were derived from a post-marketing surveillance (PMS) analysis examining plasma-derived AT concentrate (Neuart ®; Japan Blood Products Organization, Tokyo, Japan) performed by the Japan Blood Products Organization between April 2013 and April 2016 in a real-world clinical setting. DIC was diagnosed using the Japanese Association and Acute Medicine (JAAM) DIC scoring system [11]. Sepsis was defined as a SOFA score of 2 points or more, a modified form of the American College of Chest Physicians/Society of Critical Care Medicine consensus definition [3]. The exclusion criteria were as follows: age < 15 years, plasma AT level > 70%, insufficient data for a complete analysis, major bleeding, and hypersensitivity to the study agent. The data of patients re-treated with AT concentrate were excluded from the analysis.

AT concentrate was administered by intravenous infusion for 15–30 minutes once a day at a dose of 1,500 IU or 30 IU/kg. The infusion began after DIC diagnosis; however, the start time of AT concentrate administration was not specified, and each physician was free to determine the timing of the initial infusion. No limitation was placed on the duration of AT concentrate administration, which was judged individually by the physician. There were no limitations on the use of other anticoagulants, including rTM, synthetic protease inhibitors, heparin derivatives (heparin, dalteparin, or danaparoid sodium), blood preparations such as fresh frozen plasma (FFP) and platelet concentrate, or acute blood purification before and after AT concentrate administration.

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Data collection

Organ dysfunction was assessed using the SOFA score. Patients were followed up until day 28 after the initial AT administration, and the survival rate was calculated based on the number of patients alive at that time. At the start of AT concentrate administration, information on the following 10 baseline characteristics was collected: age, sex, source of sepsis, JAAM DIC and SOFA scores, plasma AT levels, blood transfusion, other anticoagulants, acute blood purification, and mechanical ventilation. Serum samples were collected at baseline and on days 3 and 6 after the initial administration of AT concentrate. Safety data were coded using the preferred terms from version 20.0 of the Japanese version of the Medical Dictionary for Regulatory Activities [12]. The definitions of adverse events (AEs) and adverse drug reactions (ADRs) were based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines [13]. The safety evaluation included serious bleeding AEs and all ADRs observed until 28 days after the initial AT concentrate administration.

Statistical analyses

In the descriptive analysis of baseline characteristics, numerical data are expressed as mean ± standard deviation (SD) or medians (Q1–Q3; interquartile range). Statistical analysis was performed to compare values between therapies using the chi-square test, Wilcoxon signed-rank test, and Cochran-Armitage test. Differences in the frequency by strata were tested for significance using the chi-square test. Baseline imbalances were detected between AT monotherapy (AT concentrate alone) and combined therapy (AT concentrate followed by rTM). Therefore, an adjusted analysis was performed using the propensity scores [14]. The propensity score for the likelihood of undergoing therapies that the patients received was calculated using a multivariable logistic regression analysis. It included age, sex, the primary source of infection, other coagulants except for rTM, FFP, and platelet concentrate, the JAAM DIC and SOFA scores, plasma AT level before, and acute blood purification before and after AT concentrate administration. Then, the relationship between the 28-day mortality rate and the initial data was examined in multivariate analyses using logistic regression analysis (backward elimination method). The analysis was conducted using outcome (survival, 1; died, 0) as the dependent variable and age, sex, source of sepsis, initial JAAM DIC and SOFA scores, plasma AT level before AT concentrate administration, other anticoagulants, acute blood purification before and after AT concentrate administration, and initial and total amounts of AT concentrate as the independent variables. The results of the logistic regression analysis are reported as odds ratios (ORs), 95% confidence intervals (CIs), and *p*-values. For all reported results, a p-value <0.05, was considered statistically significant. SPSS version 20.0 for MAC OSX (IBM Japan, Tokyo, Japan) was used to perform the statistical analyses and calculations.

3. Results

Patient demographics and characteristics

A total of 2,007 adult patients with sepsis-induced DIC from 314 institutions were analyzed (Figure 1). The demographic characteristics of the patients are presented in Table 1. The mean age±SD was 72.0±14.1 years. The most frequent underlying disease at the initial AT administration was the abdominal (31.4%), followed by others (30.6%), which were mainly soft tissue and catheter infections. The DIC and SOFA scores and plasma AT levels before AT administration were 5.6±1.3, 9.6±3.9, and 47.9±13.5%, respectively. The duration and dose of AT administration were 3.1±1.8 days and 1,577±439 IU/day, respectively. Before AT administration and overall, other anticoagulants were administered in 740 (36.9%) and 1,592 (79.3%) patients, rTM in 471 (23.5%) and 1214 (60.5%) patients, and acute blood purification treatment in 485 (24.2%) and 825 (41.1%) patients, respectively.

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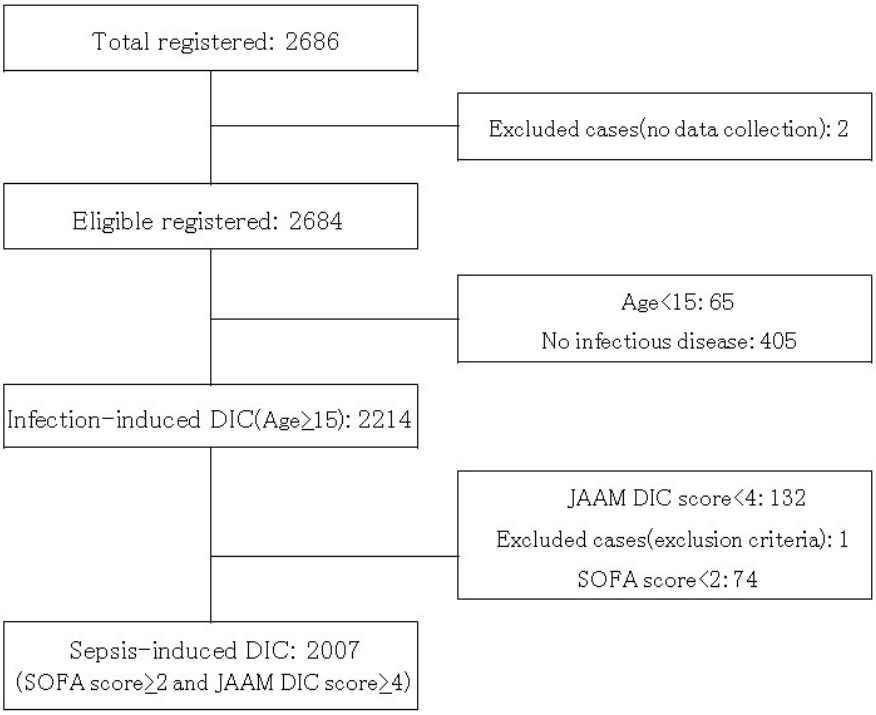

Figure 1. Flow chart of patient selection. DIC, disseminated intravascular coagulation; JAAM, Japanese Association for Acute Medicine; SOFA, Sequential Organ Failure Assessment.

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Table 1. Patient baseline demographics and characteristics. DIC, disseminated intravascular coagulation; JAAM, Japanese Association for Acute Medicine; SOFA, Sequential Organ Failure Assessment; AT, antithrombin; RRT, renal replacement therapy; PMX-DHP, polymyxin B-immobilized fiber column direct hemoperfusion.

Item		Subjects(n)	Rate(%)
Sex	Male	1174	58.5
	Female	833	41.5
Age(years)	15-64	460	22.9
	65-84	1225	61.1
	≥85	321	16.0
Source of sepsis	Lungs	512	25.5
	Abdomen	630	31.4
	Urine	300	15.0
	Focus-unknown	157	7.8
	others	615	30.6
DIC score(JAAM criteria)	4	469	23.4
	5	569	28.4
	6	444	22.1
	7	210	10.5
	8	294	14.7
SOFA score	2-7	561	28.0
	8-10	504	25.1
	11-13	423	21.1
	14≤	294	14.7
AT activity	≤50%	1112	55.8
	50%< ≤70%	837	42.0
		before AT administration/overall	before AT administration/overall
Other anticoagulant treatment		740/1592	36.9/79.3
Heparin derivatives		145/346	7.2/17.2
Synthetic protease inhibitors		195/383	9.7/19.1
Thrombomodulin alfa		471/1214	23.5/60.5
Others		45/93	2.2/4.6
Blood transfusion		478/924	24.4/46.0
Fresh frozen plasma		415/717	20.7/35.7
Platelets concentrate		206/588	10.3/29.3
Acute blood purification		485/825	24.2/41.1
RRT		292/547	14.5/27.2
RRT(Non-Renal indication)		96/173	4.8/8.6
Plasma exchange		8/30	0.4/1.5
PMX-DHP		200/303	10.0/15.1
Others		14/22	0.7/1.1
Mechanical ventilations		762/1007	38.0/50.2

※Duplicate aggregation

Changes in the DIC and SOFA scores

Before and after AT administration, changes in the JAAM DIC and SOFA scores were observed in patients whose scores were calculated on days 3 and 6 (Figure 2). The medians and interquartile ranges of the DIC and SOFA scores before AT administration were 5 (5-7) and 9 (7-12), respectively. The DIC and SOFA scores on days 3 and 6 after AT administration were significantly lower than those before AT administration ($p < 0.001$ and $p < 0.001$, respectively).

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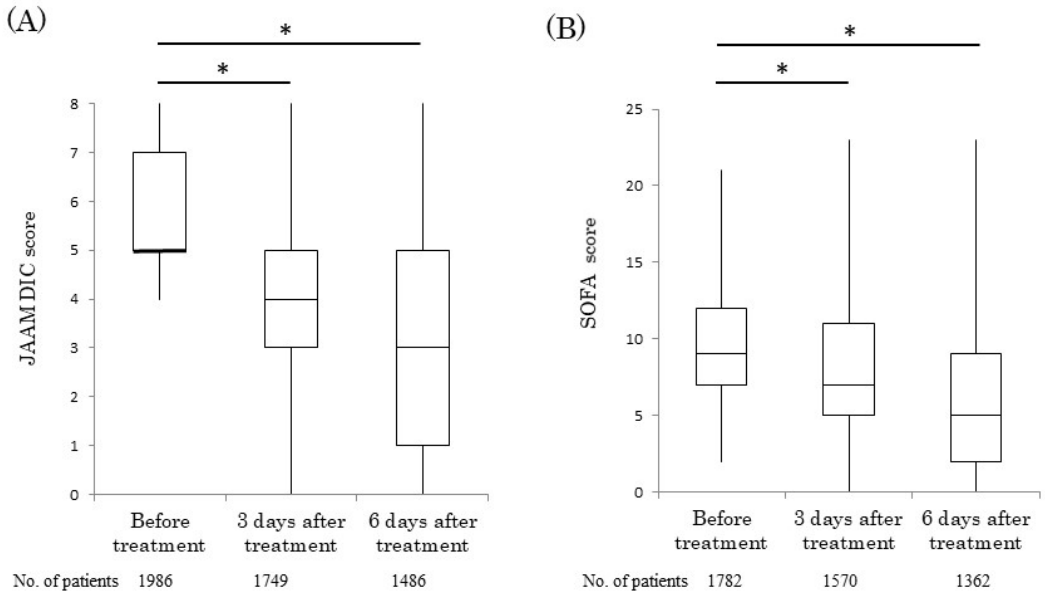

Figure 2. Changes in JAAM DIC (**a**) and SOFA scores (**b**) before and after AT administration. The graphs show the median values at each time point. Error bars indicate the interquartile range. JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation; SOFA, Sequential Organ Failure Assessment; AT, antithrombin. *, $p < 0.01$.

Mortality

Overall, 1,518 of 2,007 patients survived 28 days after AT administration, resulting in an overall mortality rate of 24.2%. Table 2 shows the individual mortality rates before AT administration, stratified by the JAAM DIC and SOFA scores and AT activity. Before AT administration, the mortality rate showed a significant difference in proportion to the severity of the SOFA score and AT activity ($p < 0.001$ and $p < 0.001$, respectively), but not the JAAM DIC score ($p = 0.074$).

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Table 2. Twenty-eight-day mortality rate by JAAM DIC and SOFA scores before AT administration. *p*-values: Cochran-Armitage test. JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation; SOFA, Sequential Organ Failure Assessment; AT, antithrombin.

Factor		Total subjects (*n*)	Mortality rate		
Item	Score		Subjects (*n*)	Rate (%)	*p* value*
JAAM DIC score before AT administration	Total	1,986	438	22.0	-
	4	469	83	17.7	
	5	569	131	23.0	
	6	444	110	24.8	0.074
	7	210	44	20.9	
	8	294	70	23.8	
SOFA score before AT administration	Total	1,782	393	22.0	-
	0–7	561	59	10.5	
	8–10	504	91	18.1	< 0.001
	11–13	423	104	24.6	
	≥ 14	294	139	47.3	
AT activity before AT administration	Total	1994	441	22.1	-
	≤30	207	80	38.7	
	30-40	371	107	28.8	
	40-50	534	111	20.8	< 0.001
	50-60	514	90	17.5	
	60-70	323	46	14.2	

Propensity score analyses

In the PMS study, baseline imbalances were detected between AT monotherapy and combined therapy. Therefore, an adjusted analysis was performed using propensity scores. The numbers of patients with AT monotherapy and combined therapy were 590. The 28-day mortality between the two groups did not show a significant difference (23.2% and 24.4%, respectively; $p = 0.406$), and further propensity score analyses were performed (Figure 3). Patients were assigned to disease severity based on a SOFA score ≤ 8 or ≥ 9, because the overall SOFA median score was 9. We further categorized patients with a JAAM DIC score of 4–5 or ≥ 6. In patients with a JAAM DIC score of 4 or 5, we found that the mortality of the patients with AT monotherapy was significantly lower, with both a SOFA score ≤8 and ≥9 (10.1% versus (vs.) 18.5%, $p = 0.036$ and 24.3% vs. 37.0%, $p = 0.031$, respectively). However, in patients with a JAAM DIC score ≥ 6, mortality was higher in patients with AT monotherapy than in those with combined therapy, with a SOFA score ≥9 (40.0% vs. 28.5%, $p = 0.031$) (Figure 4).

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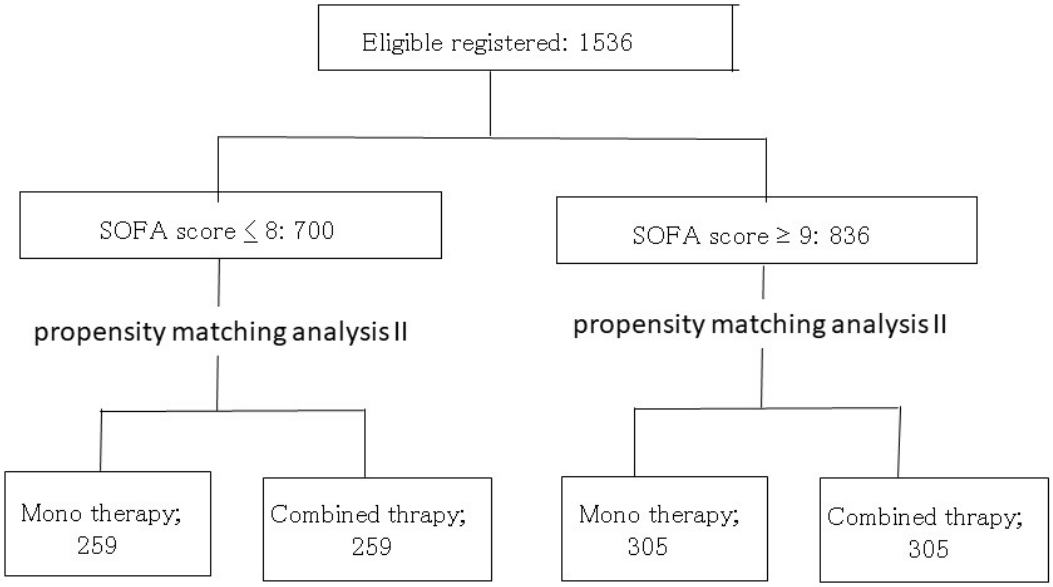

Figure 3. Flow chart of patient selection for propensity score analysis II. SOFA, Sequential Organ Failure Assessment.

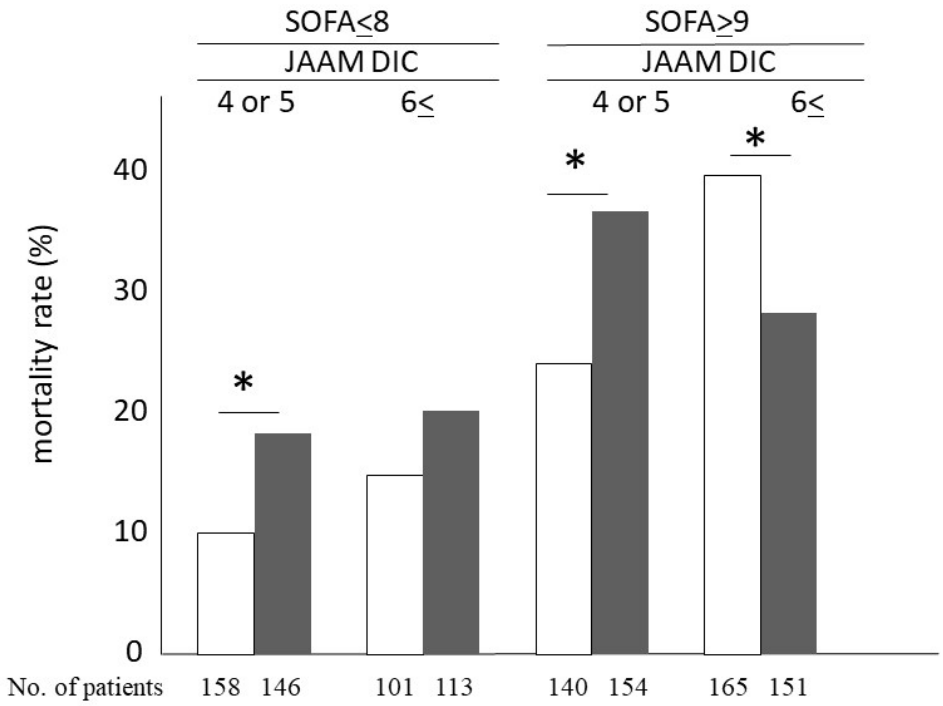

Figure 4. Twenty-eight-day mortality by JAAM DIC and SOFA scores. JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation; SOFA, Sequential Organ Failure Assessment. *, $p < 0.05$.

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Multiple logistic regression analysis

The source of sepsis in the urinary tract, AT activity, and PMX-DHP procedure before AT administration were associated with reduced 28-day mortality, whereas age, source of sepsis in the lungs and focus unknown, SOFA score, treatment with danaparoid sodium, RRT and PE procedures after AT administration resulted in increased 28-day mortality (Figure 5). This result suggests that mortality in patients with sepsis-induced DIC further depends on the source of sepsis and the intervention of acute blood purification.

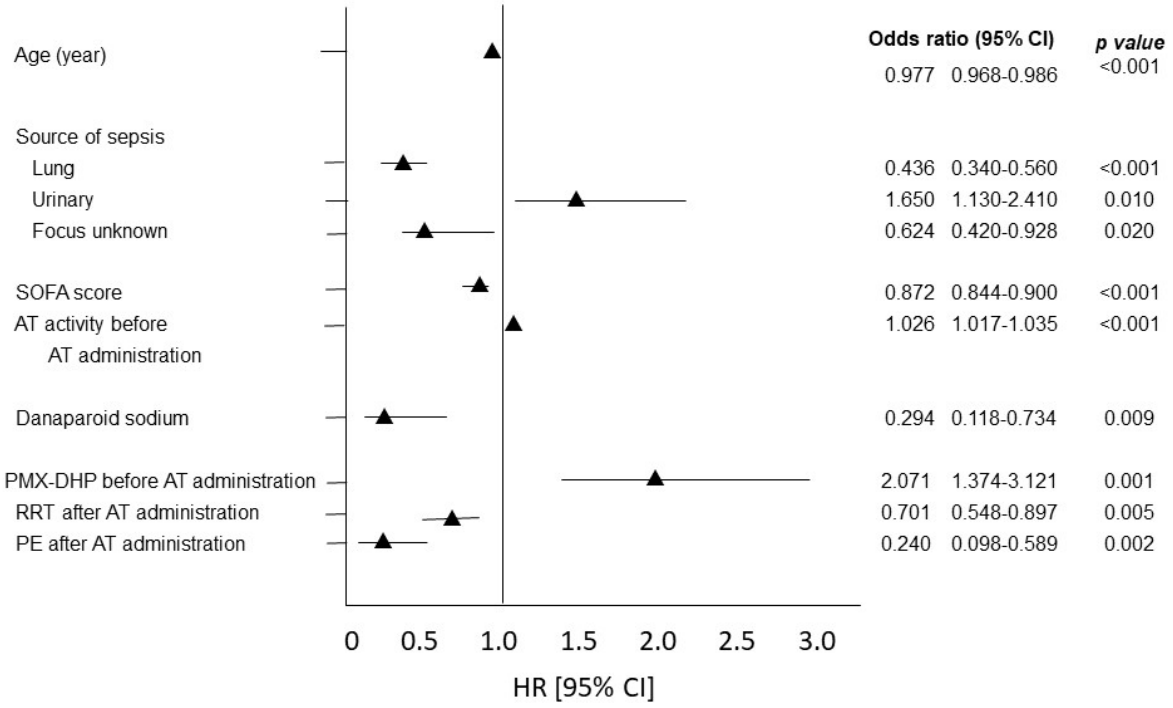

Figure 5. Results of multivariate logistic regression analysis of the 28-day survival rate. SOFA, Sequential Organ Failure Assessment; AT, antithrombin; PMX-DHP, polymyxin B-immobilized fiber column direct hemoperfusion; PE, plasma exchange; RRT, renal replacement therapy; HR, hazard ratio; CI, confidence interval.

Safety

ADRs were observed in 57 cases (2.84%), while bleeding ADRs and serious bleeding AEs were observed in 21 (1.05%) and 130 (6.48%) cases, respectively (Table 3). The overall ADR and serious bleeding AEs did not differ between the groups. Bleeding AEs occurred mainly in the gastrointestinal tract and intra-abdominal cavity, followed by the urinary tract. However, none of the patients with bleeding AEs died after the 28-day AT administration.

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Table 3. Incidences of ADRs and AEs. ADRs and AEs were analyzed according to the Medical Dictionary for Regulatory Activities. ADRs, adverse drug reactions; AEs, adverse events; rTM, recombinant thrombomodulin.

	ADR (Bleeding)		AE (Serious bleeding)	
	Cases/Total	Incidence (%)	Cases/Total	Incidence (%)
overall	21/2007	1.05	130/2007	6.48
AT	2/590	0.34	34/590	5.76
AT+rTM	8/590	1.36	46/590	7.79
SOFA≤8				
AT	2/259	0.77	13/259	5.02
AT+rTM	1/259	0.39	17/259	6.56
SOFA≥9				
AT	1/305	0.33	19/305	6.23
AT+rTM	5/305	1.64	26/305	8.52

4. Discussion

In the present study of patients from a PMS analysis, in which AT concentrate was administered according to the JAAM DIC criteria in patients with sepsis, the 28-day mortality was 24.2%, which was significantly related to the SOFA score. The mortality rates in patients with SOFA and JAAM DIC scores $\geq$ 9 and 6 were 28.5% in the combined therapy group and 40.0% in the AT monotherapy group. This difference was statistically significant. These findings suggest that combined therapy should be performed in patients with severe coagulopathy and multiple organ failure, as calculated using the JAAM DIC and SOFA scores.

In Japan, the Japanese Ministry of Health, Labour and Welfare (JMHLW) permits its use as a DIC treatment for anticoagulants such as AT concentrate, serine proteases, and rTM, and the choice of which combination depends on the individual case. Recently, a nationwide Japanese registry study indicated that AT concentrate and rTM may have comparable efficacy in reducing mortality in patients with sepsis [15]. However, concomitant therapy appears to offer no additional survival benefit [10]. Judging by our propensity score-adjusted analysis, the overall mortality rate in patients receiving combined therapy with AT concentrate followed by rTM was not differ in those receiving AT monotherapy, however, mortality was higher based on their SOFA score ($\leq$ 8) and their JAAM DIC score (< 6) (Figures 3 and 4). Regarding the mechanism, it has been suggested that excessive inhibition of coagulopathy blocks the development of immunothrombosis and immunohemostasis [6,7]. These findings suggest that the choice of anticoagulants and their combination would be considered based on the severity of the septic state calculated using both the JAAM DIC and SOFA scores.

The patients with lung and focus unknown derived sepsis were associated with reduced mortality. AT supplementation therapy has been approved by the JMHLW in patients with DIC derived from medical diseases and patients that have been limited to the dosage of 30 IU/kg/day within 3 days. A prospective multicenter survey showed that a dose of 3,000 IU/day of AT concentrate is a substantial factor for improving survival in patients with septic DIC [16]. Recently, supplementation with recombinant AT (Acoalan

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®, Kyowa Kirin Co., Tokyo, Japan) has been considered more effective than plasma-derived AT [17], and a maximum dose of 72 IU/kg/day of recombinant AT has been permitted by the JMHLW for administration in patients with sepsis-induced DIC, including their infection sources derived from medical diseases. Taken together, recombinant AT could reduce mortality in patients with sepsis-induced DIC, even in those with lung and focus unknown derived sepsis.

In clinical settings, multidisciplinary therapy, including acute blood purification, is performed in patients with sepsis-induced shock and acute renal failure. PMX-DHP adsorbs both endotoxins and neutrophils [18], and is widely used in Japan for patients with septic shock. In our multiple logistic regression analysis, the PMX-DHP procedure prior to the administration of AT concentrate was substantially associated with 28-day mortality. Recent a propensity-matched cohort study showed that PMX-DHP reduces all-caused hospital mortality in patients with septic shock-induced DIC [19]. These findings suggest that intervention using PMX-DHP before DIC development would improve outcomes in patient with septic shock followed by DIC.

DIC diagnosis calculated using the JAAM DIC criteria in patients with sepsis seems to be useful for improving outcomes [20]. However, the severity of the JAAM DIC score was not related to mortality (Table 2), and this phenomenon has been previously reported in the PMS data of rTM [21]. Recently, the Japanese Society of Thrombosis and Hemostasis (JSTH) developed novel DIC criteria, including plasma AT activity [22]. Based on our propensity analysis, plasma AT activity before AT administration is a prognostic ameliorative factor; therefore, the JSTH DIC score would be superior to the JAAM DIC score in patients with sepsis-induced coagulopathy.

Anticoagulant administration is considered to be associated with bleeding complications. According to a meta-analysis of randomized controlled trials, anticoagulant therapy is associated with bleeding complications in overall sepsis population [23], whereas, bleeding complications were not more frequent in the rTM therapy [24]. Recent study also showed that the administration of high-dose AT alone or concomitantly with rTM was not associated with an elevated risk of bleeding complications, however, sustained DIC lasting more than one week was with an increased risk of bleeding in patients with sepsis-induced DIC [25]. In a previous PMS sub-population analysis of rTM, the rate of serious bleeding events was 6.8% [20], and was almost the same as that in our PMS study. Survival was not affected in the PMS analysis of rTM [21], and also in this study, as all patients with serious bleeding events survived during the observation period. Taking an overall view of this coagulopathy, it seems that serious bleeding may partially depend on the severity of DIC rather than on the administration of anticoagulant or the particular anticoagulant used.

5. Limitations

There are limitations to the current study. First, data from a post-marketing survey were used, and all patients were treated with an AT concentrate. Second, the study examined a single arm with no comparison arms. Third, it was performed under daily clinical practice conditions, with no restrictions on treating underlying diseases.

6. Conclusion

In patients with sepsis, AT supplementation was administered when they were diagnosed with DIC, and their overall 28-day mortality rate was 24.2% that was associated with SOFA score. The mortality of these patients would be beneficially affected by the performance of PMX-DHP prior to the administration of AT concentrate, and combined therapy with AT concentrate followed by rTM with both severe DIC and MOF, as calculated by JAAM DIC and SOFA scores $\geq$ 6 and 9, respectively. Further studies are needed to confirm this therapeutic approach.

Author Contributions: This work was performed as a post-marketing surveillance by the Japanese Blood Products Organization, which participated in the study design and data collection. Y.E. wrote

the initial draft of the manuscript. H.N. and T.I. contributed to the analysis and interpretation of the data and assisted in the preparation of the manuscript. All authors have revised and approved the final version of the manuscript.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Ethics approval and consent to participate: The need for informed consent was waived, and ethics approval was not applicable for the present study. Our university signed this sponsored research contract with the Japan Blood Products Organization (number: 381-5404).

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

Acknowledgments: The authors would like to thank all participating physicians, registered patients, and families who participated in this post-marketing surveillance study. This study was supported by the Japan Blood Products Organization. The authors would like to thank Editage (www.editage.com) for English language editing.

Conflicts of Interest: The authors declare that there is no conflict of interest

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