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Prognostic Impact of Therapeutic Agents for Septic-Associated Disseminated Intravascular Coagulation According to Different Sources of Infection

Makoto Kobayashi[1], Kyohei Sakurai[2], Yoshimatsu Ehama[2]

[1]Director of Surgery and Intensive Care Center, Hakodate Goryoukaku Hospital, Hakodate City, Hokkaido, Japan; [2]Division of Emergency Medicine, Hakodate Goryoukaku Hospital, Hakodate City, Hokkaido, Japan

Correspondence: Makoto Kobayashi, Director of Surgery and Intensive Care Center, Hakodate Goryoukaku Hospital, 38-3 Goryoukaku-cho, Hakodate City, Hokkaido, 040-8611, Japan, Tel +81-138-51-2295, Fax +81-56-2695, Email koba86gg@gmail.com

Purpose: Sepsis can be caused by various infectious sources; however, treatment strategies for secondary disseminated intravascular coagulation (DIC) differ between countries. The Japanese sepsis guidelines recommend the use of two drugs for DIC but do not specify which drugs should be used and under which conditions. No clear reports have compared the outcomes of DIC treatments based on the source of infection. This is the first study to clarify the difference in prognosis by the source of infection and compare the effect of the treatment of choice for DIC on prognosis.

Patients and Methods: This single-center, retrospective, nonrandomized cohort study included 411 patients with a confirmed diagnosis of sepsis-associated DIC who were initiated on DIC therapies. Recombinant thrombomodulin (rTM) preparation and antithrombin (AT) replacement therapy were the DIC therapies used. The patients were divided into five groups determined to be the primary source of infection for treatment: intestine-related, biliary tract, respiratory tract, urinary tract, and catheter-related bloodstream infections (CRBSIs). In addition to differences in DIC treatment, we evaluated the following three covariates that may influence mortality, considering the influence of background interactions at the infection source: serum albumin concentration, APACHE-II score, and blood antithrombin activity. A Cox proportional hazards model was used to assess the association between the covariates and compare their effect on 60-day survival.

Results: Univariate analysis of the DIC drug choice results showed that survival was statistically significantly higher in the rTM arm for biliary tract infections (P = 0.002) and CRBSI (P = 0.021). However, multivariate analysis with other covariates showed that AT replacement therapy was statistically effective for respiratory tract infections (hazard ratio, 0.353; P = 0.027).

Conclusion: Our study showed that the pathogenesis of severe sepsis with DIC differs depending on the source of infection which should be considered when developing treatment strategies. Particularly, the importance of anti-DIC drug selectivity based on the source of infection was confirmed.

Keywords: antithrombin, recombinant thrombomodulin, APACHE-II score, serum albumin, blood antithrombin activity

Introduction

Outcomes in sepsis remain unsatisfactory, and various strategies are being considered worldwide to improve life expectancy.[1] Patient mortality is higher when severe sepsis is complicated by disseminated intravascular coagulation (DIC);[2] however, the approach to the treatment of DIC differs between Japan[3] and other countries.[4] The Japanese guidelines for sepsis treatment recommend initiating treatment for concomitant DIC in addition to treating the underlying disease. These guidelines allow the use of antithrombin (AT) replacement therapy and recombinant thrombomodulin (rTM) preparation but do not specify which agent should be used for which infections. In 2022, we reported a preliminary analysis that showed that different types of anti-DIC drugs yield different outcomes in biliary tract and

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respiratory tract infections.[5] This study aimed to clarify the differences in life expectancy by infected organs and test whether there is organ specificity in the selection of anti-DIC drugs.

Material and Methods

The ethics committee of Hakodate Goryoukaku Hospital approved the study protocol (approval number 2024–021). Because of the retrospective design of the study, the requirement for informed consent was waived. However, patient data remained confidential, and the study was conducted following the Declaration of Helsinki.

Patient Selection

This retrospective cohort study involved patients with sepsis-associated DIC who were admitted to Hakodate Goryoukaku Hospital from May 2008 to March 2023. The hospital's drug database was used to select patients who used AT or rTM. Subsequently, the diagnosis of sepsis was redefined in accordance with the sepsis-3 criteria.[6] DIC was defined as a total score of ≥4 based on the Japanese Association for Acute Medicine (JAAM) DIC scoring system.[7] We excluded patients if they had Child–Pugh C hepatic cirrhosis and hematologic diseases, such as leukemia, end-stage cancer, or abnormal coagulation-fibrinolytic system after massive bleeding. For DIC treatment, the decision of the drug selection was left to the discretion of the attending physician. The specific anti-DIC drugs were as follows: rTM alone (n = 301), AT replacement therapy alone (n = 74), and a combination of rTM and AT (n = 36). These cases were grouped based on the infected organ that was the primary target of the underlying treatment for sepsis, but we excluded cases wherein the source of infection was difficult to identify. They were then categorized into five groups based on the source of infection: intestine-related (n = 95), biliary tract (n = 77), respiratory tract (n = 99), urinary tract (n = 86), and catheter-related bloodstream infection (CRBSI) (n = 54).

Treatment Management

Antibacterial drugs targeting the specific cause of infection were initially administered to all patients when sepsis was diagnosed. Anticoagulant therapy was initiated with AT replacement therapy and/or rTM preparations once DIC was diagnosed by the daily assessment of the JAAM DIC score. For AT replacement therapy, the supplementation dose was 1500 IU/day for 3 days. The rTM preparation was administered at a dose of 380 U/kg, which was reduced to 130 U/kg in patients with impaired renal function requiring hemodialysis. Polymyxin B hemoperfusion was indicated for patients with septic shock unresponsive to standard fluid resuscitation and cardiovascular agents. However, its use was left to the discretion of the attending physician. All patients were treated in the intensive care unit during their critical condition.

Definitions

The Sequential Organ Failure Assessment (SOFA)[8] and Acute Physiology and Chronic Health Evaluation II (APACHE-II)[9] scores were evaluated when planning DIC treatment. DIC was considered improved if the JAAM DIC score decreased within 7 days after administration of anti-DIC drug. Based on the J-SSCG 2020 guidelines [3], patients with septic shock can be identified by the clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain a mean blood pressure (mBP) of ≥65 mmHg and a serum lactate level of >2 mmol/l (18 mg/dl) despite adequate volume resuscitation. All patients were followed up for 60 days after sepsis-associated DIC was diagnosed.

Statistical Analysis

We compared the baseline patient characteristics between sources of infection. Continuous variables were presented as means with standard deviations, and analysis of variance (ANOVA) was used to ascertain statistical significance regarding sources of infection. Categorical variables were presented as frequency distributions and percentages, and chi-square tests were used to determine significance. In order to evaluate the difference between the infection sources, three laboratory data points were selected, which were known to be universal indicators of the background factors affecting patient prognosis. These were serum albumin concentration, APACHE-II score, and blood AT activity. Receiver operating characteristic (ROC) curve analysis was performed to assess the ability of these covariates to predict the 30-day mortality. In addition, the Youden index was used to calculate the optimal cut-off value. In a box-and-whisker plot,

the central horizontal bars, columns, and peripheral horizontal bars indicate the median values, the 25th to 75th percentiles, and the 10th to 90th percentiles, respectively.

The estimated survival curves were drawn using the Kaplan–Meier method, and overall survival (OS) was defined as the time from the start of DIC treatment to death within 60 days. Cox regression was used to compare the Kaplan–Meier curves between the two groups for each of the covariates. To assess the influence of the four variables using multivariate analysis, a Cox proportional hazards model was utilized to determine the most significant variables contributing to the 60-day OS. Hazard ratios (HRs) and 95% confidence intervals (CIs) were determined for these variables. Statistical significance was determined at $P < 0.05$. Statistical analysis was performed using IBM SPSS Statistics (Version 21.0, IBM, Armonk, NY, USA) and R (version 4.1.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

This study involved 411 cases, including 210 men and 201 women aged 17–102 years, and all participants were of Japanese origin. Table 1 shows the basic characteristics of each infection source, with the data representing values before initiating treatment for DIC. All of the factors under consideration showed that different sources of infection resulted in statistical differences.

Figure 1 shows the OS curves based on the source of infection. The group-specific survival curves demonstrated statistically significant differences across the different sources of infection, as confirmed by the Kaplan–Meier method and the Log rank test ($P = 0.000$). In the analysis of the effect of different anti-DIC drugs on patient survival (Figure 2), the group of patients with biliary tract infection ($P = 0.002$) and CRBSI ($P = 0.021$) had higher survival rates when treated with rTM preparation. To clarify the difference of variables in each source of infection, patients in each group were divided into two groups based on the optimized cutoff values calculated by ROC analysis. The values for each factor were serum albumin of 2.1g/dL, a score of 20 for APACHE-II, and 56% for blood AT activity. In a univariate analysis of the estimated survival rates, the groups wherein low albumin had a significant adverse effect on survival were biliary tract infection ($P = 0.002$), urinary tract infection ($P = 0.001$) and CRBSI ($P = 0.047$) (Figure 3). The impact of APACHE-II was significant for intestine-related infection ($P = 0.038$), urinary tract infection ($P = 0.005$), and CRBSI ($P = 0.000$) (Figure 4). The urinary tract infection ($P = 0.035$) and CRBSI ($P = 0.047$) groups were significantly affected by the blood AT activity (Figure 5).

The results of examining the impact of covariates on 60-day mortality using the cox proportional hazards model (Table 2) are as follows. In patients with an intestine-related infection, only the albumin concentration significantly influenced mortality. In the biliary tract infection group, only the blood AT activity was statistically significantly affected. In the respiratory tract infection group, APACHE-II and AT replacement therapy significantly influenced mortality. In the urinary tract infection group, both albumin concentration and APACHE-II significantly affected patient mortality. In patients with CRBSI, APACHE-II score significantly influenced mortality. To make it clearer to compare the impacts of different DIC treatments, the HR of the anti-DIC treatment across diverse infection sources was extracted and plotted in a forest plot (Figure 6). AT replacement therapy showed a significant beneficial effect on survival in patients with respiratory tract infections (HR, 0.353, $P = 0.027$).

Discussion

This study aimed to determine whether there is organ specificity in the selection of anti-DIC drugs based on source of infection. We demonstrated that the pathogenesis of severe sepsis with DIC differs depending on the source of infection and confirmed the importance of anti-DIC drug selectivity.

This study would be an informative report to highlight the importance of considering differences in infected organs when using DIC treatments in septic DIC. The approach to treating DIC differs between Japan[3] and other countries.[4] The Japanese sepsis treatment guidelines weakly recommend initiating treatment for concomitant DIC in addition to treating the underlying disease. The guidelines allow using AT replacement therapy and rTM preparation but do not specify which treatment should be used for which type of infection. In our study, the univariate survival analysis comparing the efficacy of DIC treatments demonstrated that rTM preparations were statistically effective in improving the prognosis of patients with biliary tract infection and CRBSI. However, multivariate analysis showed that AT replacement therapy was

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Table 1 Characteristics of Patients at Baseline in Each Source of Infection

Factors	Intestine-Related Infection (n = 95)	Biliary Tract Infection (n = 77)	Respiratory Tract Infection (n = 99)	Urinary Tract Infection (n = 86)	CRBSI (n = 54)	P - Value
Age (y.o.), Mean ± SD (Range)	72 ± 12 (37–98)	77 ± 12 (28–102)	74 ± 11 (20–97)	75 ± 11 (41–96)	70 ± 13 (17–89)	0.014*
Male, n (%)	51 (54)	42 (55)	62 (63)	29 (34)	26 (48)	0.002**
SOFA, Mean ± SD (Range)	8.3 ± 3.5 (2–18)	8.1 ± 3.0 (2–14)	9.7 ± 3.1 (3–18)	8.0 ± 3.0 (3–16)	9.0 ± 3.3 (3–16)	0.045*
APACHE-II, Mean ± SD (Range)	20 ± 6.2 (6–37)	16 ± 5.3 (6–29)	22 ± 6.7 (5–33)	16 ± 5.8 (4–31)	20 ± 7.4 (8–43)	0.000*
JAAM DIC, Mean ± SD (Range)	5.2 ± 1.2 (4–8)	6.1 ± 1.1 (4–8)	5.4 ± 1.4 (4–8)	5.9 ± 1.3 (4–7)	6.0 ± 1.6 (4–8)	0.004*
Shock state, n (%)	38 (40)	19 (25)	18 (18)	43 (50)	26 (48)	0.000**
Albumin (g/dl), Mean ± SD (Range)	2.4 ± 0.84 (1.1–4.5)	2.3 ± 0.63 (1.3–3.5)	2.1 ± 0.62 (1.0–3.6)	2.6 ± 0.68 (1.3–3.9)	2.3 ± 0.77 (0.8–4.6)	0.000*
AT activity (%), Mean ± SD (Range)	49 ± 16 (19–94)	49 ± 17 (10–90)	57 ± 18 (26–112)	61 ± 18 (22–127)	50 ± 16 (18–98)	0.001*
Anti-DIC drugs, n (%)						
AT	17 (18)	10 (13)	17 (17)	13 (15)	17 (31)	0.075**
rTM	68 (72)	58 (75)	74 (75)	71 (53)	30 (56)	0.012**
AT & rTM	10 (10)	9 (12)	8 (8)	2 (2)	7 (13)	0.141**
Protease inhibitor	15 (16)	22 (29)	11 (11)	5 (6)	19 (35)	0.000**
Co-administration, n (%)						
Gamma-globulin	43 (45)	17 (22)	32 (32)	13 (15)	22 (41)	0.000**
Steroid pulse	0 (0)	2 (3)	28 (28)	1 (1)	2 (4)	0.000**
Co-therapy, n (%)						
Mechanical ventilation	43 (45)	8 (10)	55 (56)	7 (8)	7 (13)	0.000**
PMX-DHP	25 (26)	4 (5)	13 (13)	7 (8)	11 (20)	0.000**
Surgery	89 (94)	2 (3)	0 (0)	1 (1)	0 (0)	0.000**
Biliary drainage	0 (0)	45 (58)	0 (0)	0 (0)	0 (0)	0.000**
Patient's outcome, n (%)						
DIC improvement	63 (66)	53 (69)	45 (45)	71 (83)	26 (48)	0.000**
30-day mortality	25 (26)	28 (36)	60 (61)	11 (13)	24 (44)	0.000**

Notes: * Analysis of variance, ** Chi-square test.

Abbreviations: CRBSI, catheter related bloodstream infection; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; APACHE-II, Acute Physiology and Chronic Health Evaluation II; JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation; AT, antithrombin; rTM, recombinant thrombomodulin; PMX-DHP, polymyxin B-direct hemoperfusion.

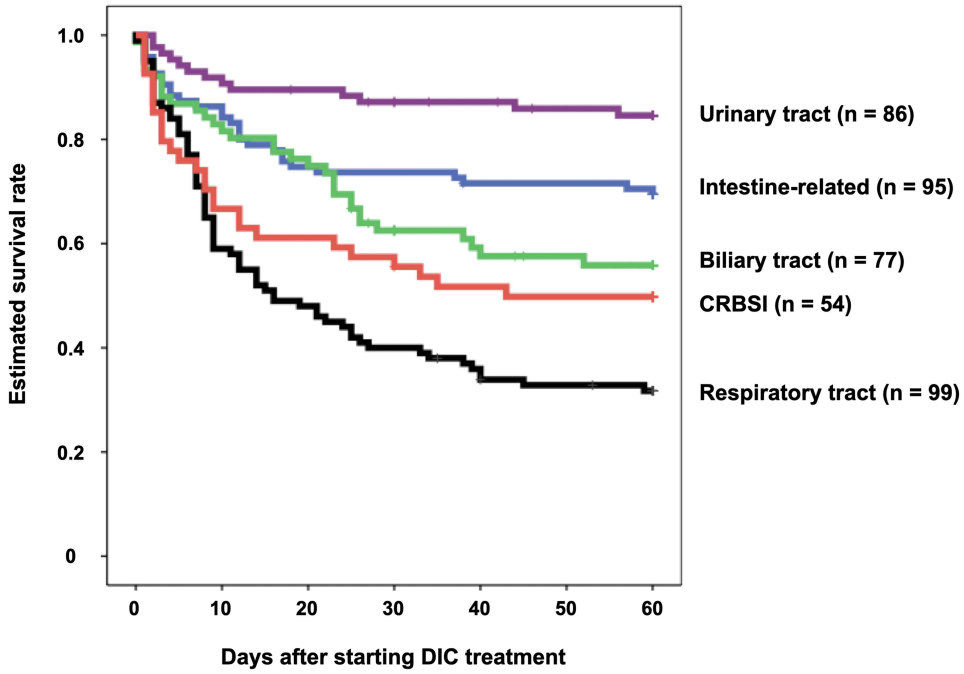

Figure 1 Estimated survival curves in each infection group.
Abbreviations: CRBSI, catheter related bloodstream infection; DIC, disseminated intravascular coagulation.

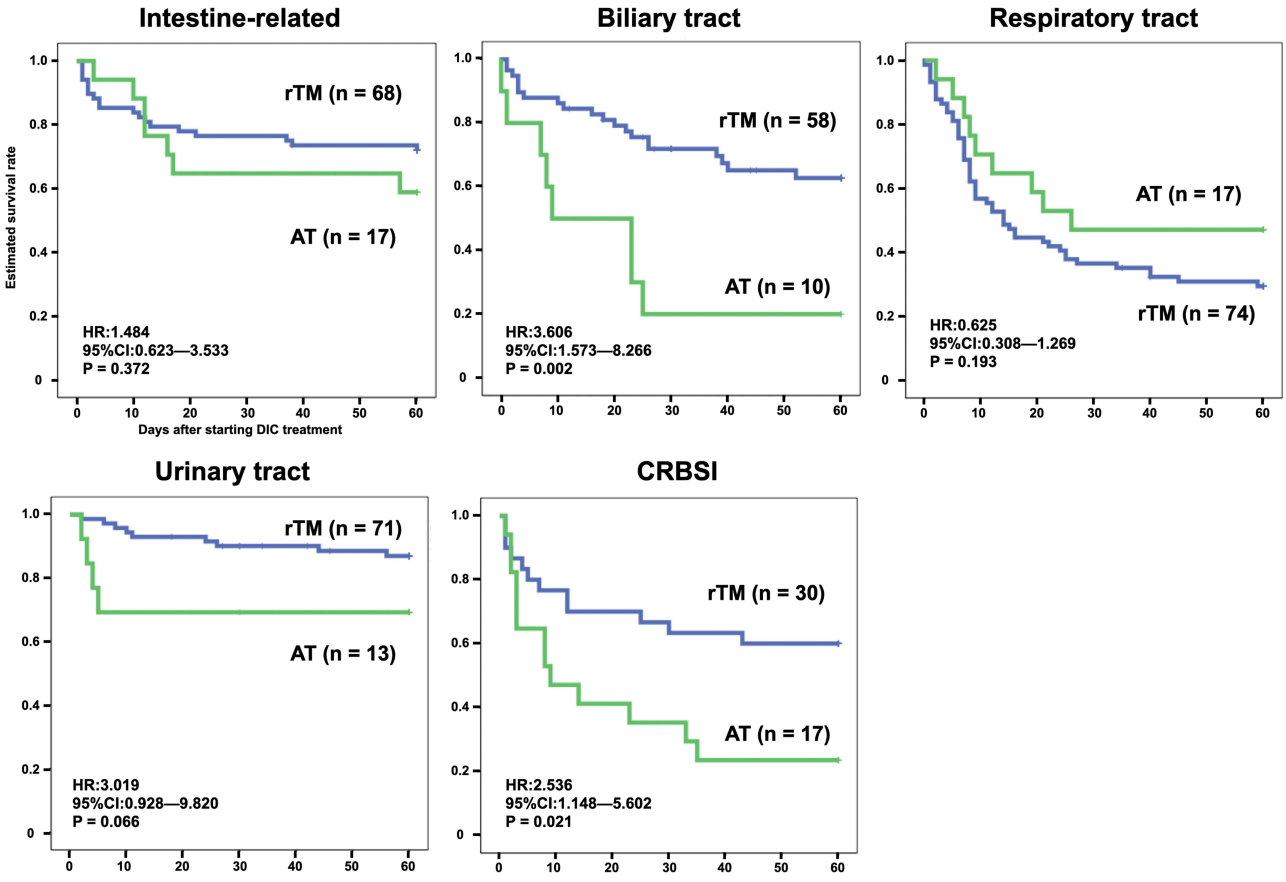

Figure 2 Comparison of survival between AT replacement therapy and rTM preparation in each source of infection.
Abbreviations: AT, antithrombin replacement therapy; rTM, recombinant thrombomodulin preparation; CRBSI, catheter related bloodstream infection; HR, Hazard ratio; CI, 95% confidence interval.

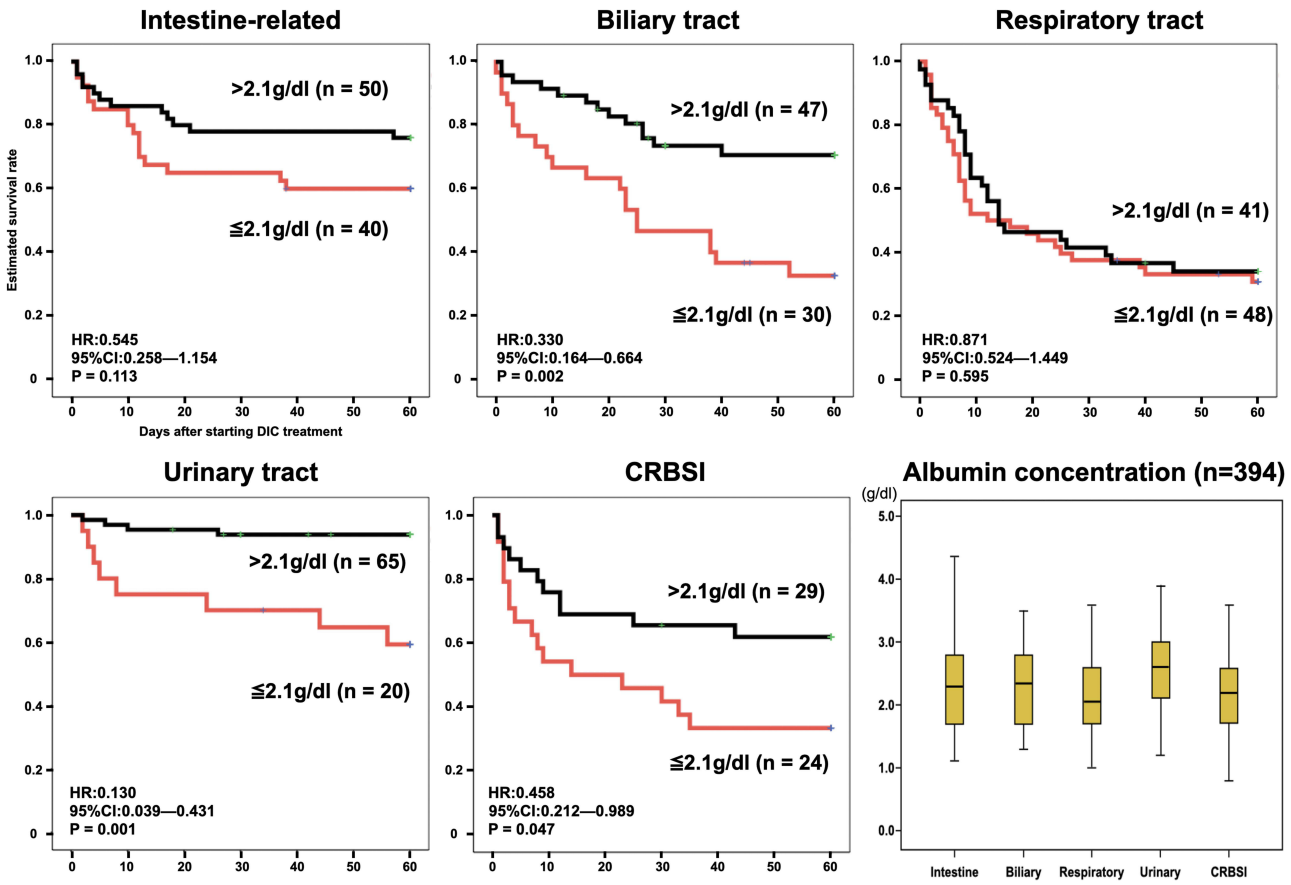

Figure 3 Comparison of survival according to serum albumin concentration and the box-and-whisker plot for the albumin level in each infection group.
Notes: In a box-and-whisker plot, the central horizontal bars, columns, and peripheral horizontal bars indicate the median values, the 25th to 75th percentiles, and the 10th to 90th percentiles, respectively.
Abbreviations: CRBSI, catheter related bloodstream infection; HR, Hazard ratio; CI, confidence interval.

significantly associated with a reduced risk of respiratory tract infections. Reports using data from the Japanese National Database on the efficacy of two DIC treatments in patients with severe pneumonia[10,11] suggest that AT replacement therapy was superior to rTM preparation, which supports our study results. One of the reasons for the high efficacy of AT treatment in respiratory tract infection may be that the average AT activity level in this disease group was originally high (57%), making the benefits of additional AT replacement therapy easier to obtain. However, the reasons underlying the ineffectiveness of rTM in respiratory tract infections remain unclear. A meta-analysis of the amount of endogenous thrombomodulin leaking into the blood due to damage to the lung tissue from acute respiratory distress syndrome found that blood thrombomodulin levels were significantly increased in patients who died,[12] indicating that the loss of endogenous thrombomodulin on the inner surface of pulmonary vessels impaired by neutrophil elastase may be greater than expected, resulting in the insufficient function of tTM preparations at the prescribed volume. Dose issues have been also noted with AT replacement therapy. Iba et al demonstrated a favorable trend for AT supplement at a dosage of 3000 IU/day over 1500 IU/day for the treatment of sepsis-associated DIC.[13] In the treatment of Septic DIC, it may be necessary to adjust the optimal dose, taking into account not only the difference in source of infection, but also the severity of the patient's illness and the status of coagulation-fibrinolytic disruption.

To clarify the differences in the background of the source of infection, this study was simultaneously validated using three covariates in addition to the different DIC treatments. The selected covariates were serum albumin level, APACHE-II score, and blood AT activity. Each of these factors strongly influence the prognosis of sepsis and have been reported as universal covariates for patient mortality. We applied these variables because complex background differences should be incorporated by source of infection into the multivariate analysis to accurately assess the selectivity of DIC treatment.

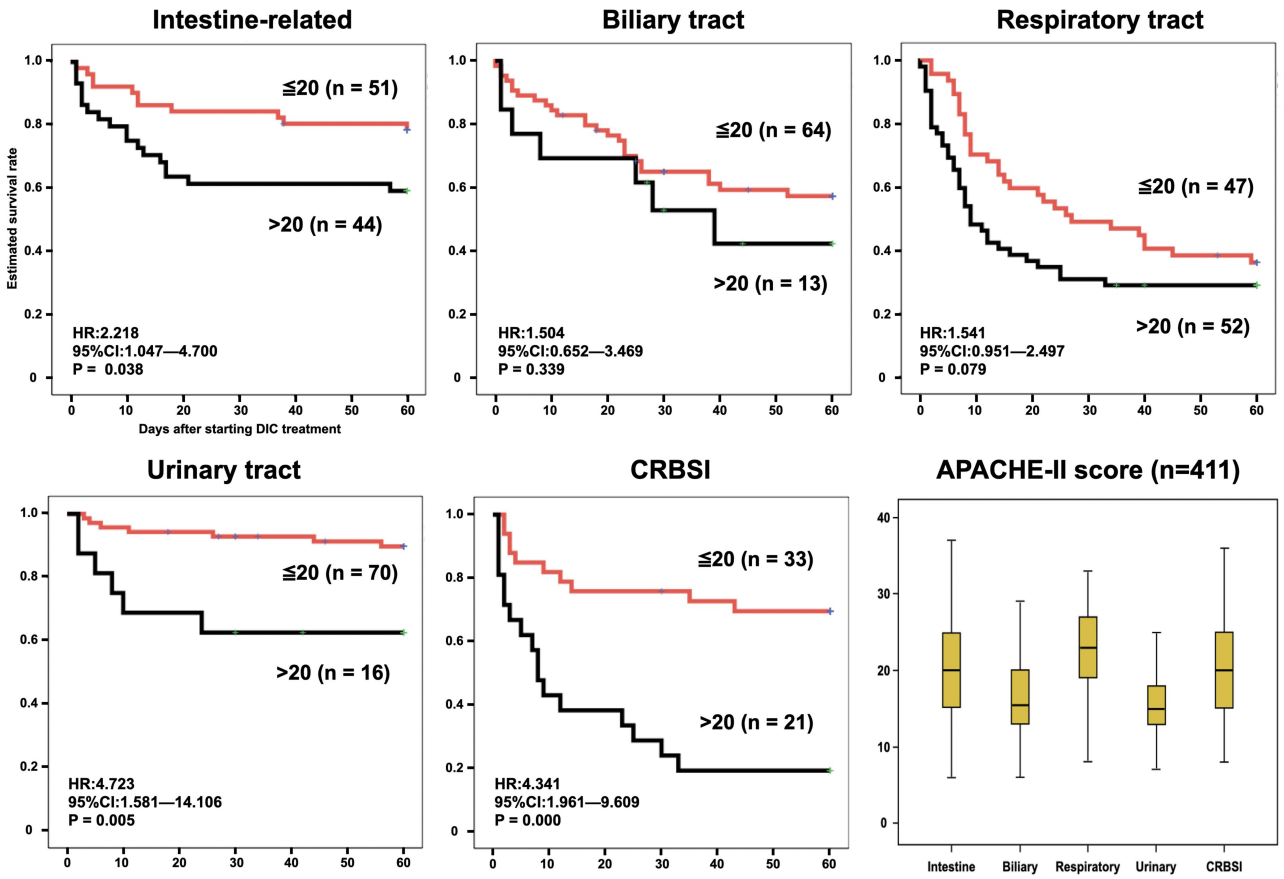

Figure 4 Comparison of survival according to APACHE-II score and the box-and-whisker plot for the score in each infection group.
Notes: In a box-and-whisker plot, the central horizontal bars, columns, and peripheral horizontal bars indicate the median values, the 25th to 75th percentiles, and the 10th to 90th percentiles, respectively.
Abbreviations: CRBSI, catheter related bloodstream infection; HR, Hazard ratio; CI, confidence interval; APACHE-II, Acute Physiology and Chronic Health Evaluation II.

Albumin is mainly produced in the liver and is considered a strong indicator of health and nutritional status. Critically ill patients have low albumin level, which is associated with poor prognosis and prolonged treatment in the ICU.[14] The albumin value was excluded among the endpoints of the SOFA or APACHE-II scoring systems. Consequently, there is no risk of introducing confounding, then it could be used as an independent covariate with APACHE-II for multivariate analysis. A review of 90 previous cohort studies has shown that hypoalbuminemia (albumin <3 g/dL) in acutely ill patients was strongly associated with poor clinical outcomes.[15] To the best of our knowledge, no previous study has examined whether the source of infection alters the prognostic impact of albumin levels in the septic state.

The SOFA and APACE-II are widely accepted as objective comparative measures of a patient's clinical status. The SOFA score consists of six items, whereas the APACHE-II score is a more detailed and complex assessment that includes 12 clinical items as well as age, acute or chronic severe comorbidities, and emergency surgery. Our results of the ANOVA comparing covariates between sources of infection (Table 1) demonstrated that the F-statistic for APACHE-II and SOFA was 12.265 (P = 0.000) and 2.456 (P = 0.045), respectively, indicating that the APACHE-II score is a more sensitive assessment of clinical severity by organ than the SOFA. We concluded that the APACHE-II score was a more useful overall assessment for our analysis comparing patient's severity according to source of infection.

When blood coagulation abnormalities occur in vivo, the levels of AT activity in the blood change, and survival rates significantly decrease in patients with DIC where blood AT activity levels decreased <50%.[16] Reduced AT activity in septic DIC may be caused by the following mechanisms: the consumption of AT caused by activated coagulation,[17] decreased production due to a disorder of hepatic synthesis,[18] and leakage of circulating AT from the intravascular space.[19] In our series, the biliary tract and intestine-related infection groups showed the lowest level of AT activity.

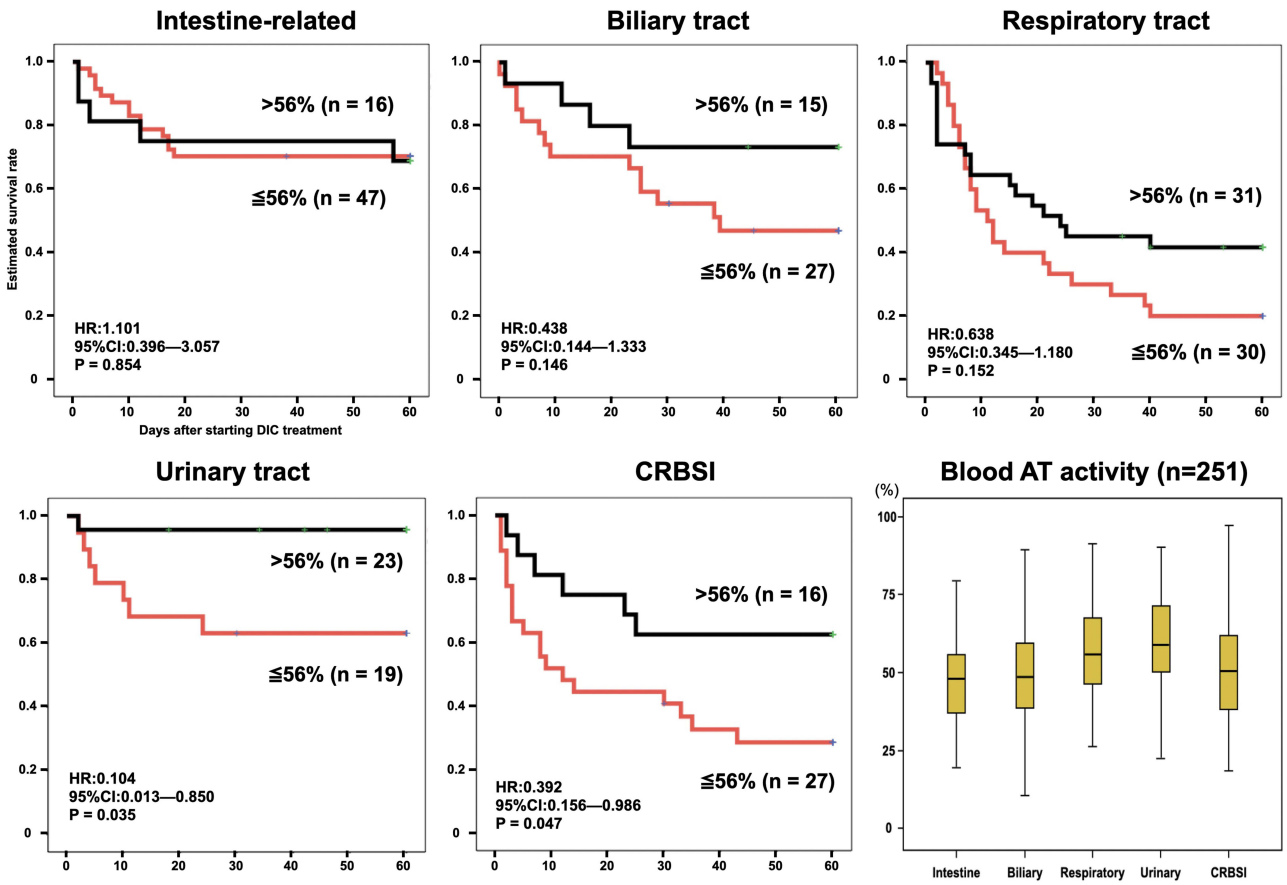

Figure 5 Comparison of survival according to blood antithrombin activity level and the box-and-whisker plot for the score in each infection group.
Notes: In a box-and-whisker plot, the central horizontal bars, columns, and peripheral horizontal bars indicate the median values, the 25th to 75th percentiles, and the 10th to 90th percentiles, respectively.
Abbreviations: CRBSI, catheter related bloodstream infection; HR, Hazard ratio; CI, confidence interval; AT, antithrombin.

Multivariate analysis showed that the AT activity significantly affected survival in the biliary tract infection group (P = 0.019). Our study is the first to demonstrate that blood AT activity varies based on the source of infection in septic DIC and that the impact of this variation on survival also differs based on the source of infection.

Table 2 Results of Cox Proportional Hazard Model Between the Outcome (60-Day Survival) and Four Variables in Each Source of Infection

Variables	Intestine-Related Infection	Biliary Tract Infection	Respiratory Tract Infection	Urinary Tract Infection	CRBSI
Serum Alb concentration	0.367	0.551	0.949	0.179	0.702
	(0.152–0.885)	(0.167–1.813)	(0.558–1.615)	(0.032–0.991)	(0.349–1.409)
	P = 0.026	P = 0.327	P = 0.949	P = 0.049	P = 0.319
APACHE-II	1.082	1.069	1.069	1.229	1.088
	(0.979–1.197)	(0.949–1.203)	(1.000–1.143)	(1.085–1.392)	(1.019–1.163)
	P = 0.123	P = 0.274	P = 0.049	P = 0.001	P = 0.012

(*Continued*)

Table 2 (Continued).

Variables	Intestine-Related Infection	Biliary Tract Infection	Respiratory Tract Infection	Urinary Tract Infection	CRBSI
Blood AT activity	1.010	0.947	0.982	0.995	0.983
	(0.982–1.039)	(0.903–0.993)	(0.960–1.005)	(0.920–1.077)	(0.948–1.019)
	P = 0.588	P = 0.024	P = 0.127	P = 0.907	P = 0.356
Anti-DIC treatment (AT or rTM)	1.768	3.115	0.353	1.062	0.983
	(0.654–4.778)	(0.830–11.689)	(0.140–0.889)	(0.180–6.274)	(0.482–2.912)
	P = 0.261	P = 0.092	P = 0.027	P = 0.947	P = 0.712

Notes: Results are presented as HR, (95% CI), P - value.
Abbreviations: CRBSI, catheter related bloodstream infection; Alb, albumin; HR, hazard ratio; CI, confidential interval; APACHE-II, Acute Physiology and Chronic Health Evaluation II; DIC, disseminated intravascular coagulation; AT, antithrombin; rTM, recombinant thrombomodulin.

We found that different infection sources causing septic DIC had a different impact on several covariates considered to be significantly associated with patient prognosis. In actual medical practice, it has also become clear that there are various differences in medical interventions when different organs are targeted for treatment. Besides the influence of background factors, an important point in the clinical treatment of sepsis is whether the cause of infection can be reliably eliminated. The treatment strategy is based on the complete eradication of the cause of infection in addition to the use of appropriate antimicrobial agents. However, the feasibility of this approach varies from organ to organ. Some groups are capable of fairly complete therapeutic intervention, such as resection and drainage of the necrotic bowel for intestine-related infections, biliary drainage for biliary tract infections, ureteral stenting for urinary tract infections, and catheter removal for CRBSI. Although mechanical ventilators can assist with air exchange for respiratory tract infections, early

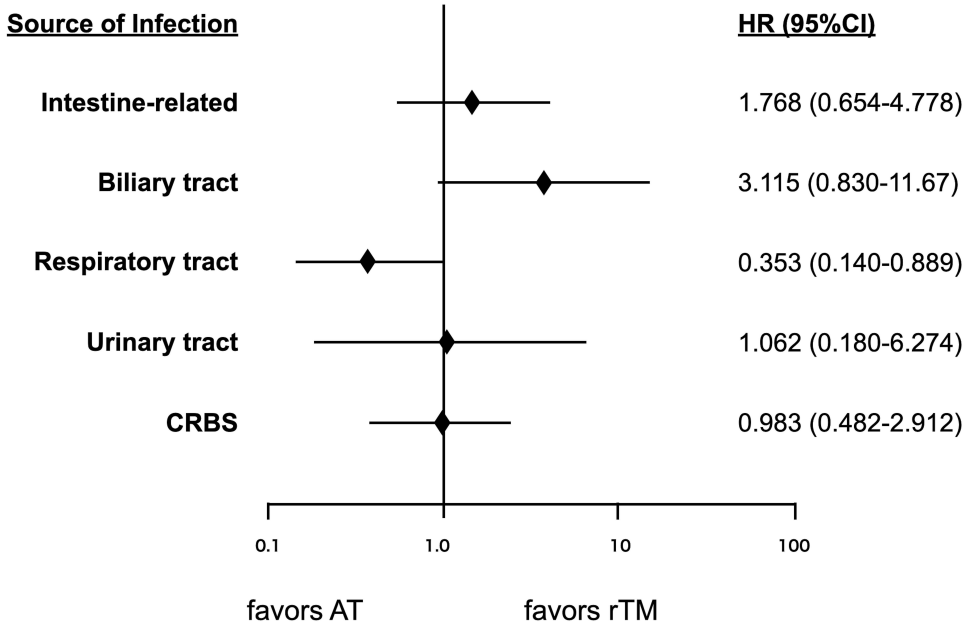

Figure 6 Forest plot from results of influence of anti-DIC treatment by Cox proportional hazard model.
Abbreviations: CRBS, catheter related bloodstream; HR, Hazard ratio; CI, confidence; AT, antithrombin replacement therapy; rTM, recombinant thrombomodulin preparation.

resolution of the cause of infection within the lung tissue is relatively difficult. These issues likely contribute to the difficulty in the basic treatment of respiratory tract infections and their associated poor prognosis.

Limitations

This study has several limitations. First, this was a retrospective analysis of data collected from a single center. Our data were enrolled over 14 years, so the prolonged sample collection period might be a concern. The variable effect of the year significantly influenced treatment outcomes (HR, 0.953; 95% CI, 0.909–0.998), but no difference was observed between the groups. Second, only 61% of the total cases had measured blood AT activity values, which may reduce the accuracy of the multivariate analysis that incorporated this variable. Third, in our institution, there were no clear guidelines for the selection of DIC treatments, and the choice of anti-DIC drugs was left to the discretion of the treating physician. There is a concern about the risk of errors in the analysis due to drug selection bias. Lastly, the date of the initiate of DIC treatment has been used as the starting point for the assessment of patient severity, and our survival analysis was performed with the subsequent course of the disease. Therefore, it is possible that the influence of treatment history from the time of admission to the start of DIC treatment is not fully reflected in the analysis results.

Conclusion

This study showed that despite the same diagnosis of septic DIC, the prognosis of patients differed based on the chosen drug for the DIC treatment. Therefore, we believe that treatment strategies for sepsis with DIC should consider the differences in the underlying diseases. Caution should also be taken during the analysis of sepsis data, as results may be skewed if patients with different sources of infection are examined collectively.

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Disclosure

The authors report no conflicts of interest in this work.

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