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—【Original】——原　著—

Sequential Organ Failure Assessment (SOFA) score as a prognostic factor for disseminated intravascular coagulation patients with infectious disease treated with recombinant human soluble thrombomodulin (rhTM) in clinical practice

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Background: Although recombinant human soluble thrombomodulin (rhTM) is reportedly effective for treating disseminated intravascular coagulation (DIC), the prognosis for DIC patients remains still poor.
Patients and Methods: We retrospectively analyzed 136 DIC patients (infectious group: 103, hematological group: 33) treated with rhTM at a single institution between May 2012 and November 2014.
Results: The resolution rate of DIC was in 57.3% (59/103) and 54.5% (18/33) of patients in the infectious and hematological groups, respectively. The overall survival (OS) rate at 28 days was 73.8% (76/103) and 87.9% (29/33) in the infectious and hematological groups, respectively. Unexpectedly, the DIC scores were resolved in 22.2% (6/27) and 25% (1/4) and the DIC scores were reduced in 63.0% (17/27) and 50.0% (2/4) of non-surviving DIC patients, in the infectious and hematological groups, respectively. Multivariate analysis identified the Sequential Organ Failure Assessment (SOFA) score as a prognostic factor for DIC patients with infectious disease (cut-off point: 10). Moreover, high DIC and SOFA scores at diagnosis were significantly associated with poor OS of DIC patients with infectious disease.
Conclusion: Our study clearly revealed that high SOFA scores (>10) are correlated with poor outcomes for DIC patients with infectious disease. Furthermore, rhTM treatment may improve the abnormal coagulopathy in survivors and in even some populations of non-surviving DIC patients in clinical practice.

Keywords: DIC, rhTM, SOFA score, prognostic factor

Background

Disseminated intravascular coagulation (DIC) is a severe and life-threatening clinical condition secondary to underlying diseases such as sepsis, hematological malignancy, and solid tumors. It is characterized by systemic activation of coagulation pathways that result in multiple organ failure[1)~3)]. Although the mechanism of DIC differs depending on the underlying disease, there is a common process across all cases, characterized by excessive production of thrombi that cause systemic organ damage due to systemic microvascular fibrin generation and deposition[1)~3)]. Furthermore, fibrinolytic activation and over-consumtion of anticoagulation factors can lead to systemic hemorrhage[1)~3)].

Recently, inflammation and coagulation have been closely linked to high mobility group box 1 (HMGB-1), lipopolysaccharide (LPS), neutrophil extracellular traps (NETs), and other inflammatory cytokines[3)~7)]. Regarding the control of inflammation and coagulopathy, re-

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combinant human soluble thrombomodulin (rhTM) may be an appropriate anti-coagulant and anti-inflammatory agent because of its two major effective sites of lectin-like domain and epidermal growth factor (EGF)-like domains[3)~7)]. These sites 1) control inflammation, and 2) bind to thrombin to inactivate coagulation, creating a complex that activates protein C to create activated protein C (APC) for the control of abnormal coagulopathy[3)~7)]. Several retrospective studies, two systemic review/meta-analysis, and major guidelines have reported the efficacy and safety of rhTM for DIC in patients with underlying infectious or hematological diseases in clinical practice[8)~21)].

Previously, we reported that the early administration of rhTM resulted in an increased resolution of DIC among 92 DIC patients (infection: 62 cases, hematology: 30 cases) treated with rhTM at a single institution over 4 years (August 2008 to April 2012)[13)]. However, the rate of resolution of DIC at 28 days was approximately 30% and was still poor prognosis[8)~21)].

To improve the poor outcome of DIC, it is essential to identify the prognostic factors of DIC in clinical practice.

Herein, we analyzed the additional 136 DIC patients treated with rhTM at Miyazaki Prefectural Miyazaki Hospital between May 2012 and November 2014. Furthermore, we focused on the analysis of characteristics between survivors and non-survivors, and the identification of prognostic factors for DIC treatment outcomes in clinical practice.

Patients and Methods

We retrospectively analyzed data from 136 DIC patients (103 with infectious and 33 with hematological diseases) who fulfilled the DIC diagnostic criteria of the Japanese Association for Acute Medicine (JAAM) for infectious diseases (over 4 points) or the DIC diagnostic criteria of the Japanese Ministry of Health and Welfare (JMHW) for hematological diseases (over 3 points) treated between May 2012 and November 2014 at our institution[22)23)].

In 1983, the JMHW criteria were proposed for the diagnosis of DIC with infectious disease including sepsis and hematological disease[23)]. In 2001, the ISTH criteria were proposed for the diagnosis of DIC with infectious disease, including cases of sepsis that had a high specificity of DIC diagnosis[24)]. In 2006, the JAAM criteria were proposed for the diagnosis of DIC with infectious disease, including sepsis harboring a high sensitivity of a DIC diagnosis, to enable further early diagnosis of DIC[23)]. Takemitsu et al. evaluated the prospective evaluation of three different diagnostic criteria for DIC and showed that all three diagnostic criteria were related to poor outcomes[25)]. At present, in Japan, many clinicians have made a diagnosis of DIC with associated infectious disease including sepsis by using the JAAM DIC criteria and have diagnosed DIC with hematological disease by JMHW DIC criteria. In our study between May 2012 and November 2014 before the revision of sepsis by Sepsis-3 in 2016[26)], we made a diagnosis of DIC with infectious disease including sepsis by the JAAM criteria and DIC with hematological disease by the JMHW criteria.

In the DIC patients with infectious disease, DIC was evaluated using the diagnostic criteria of the JAAM[21)]. In the DIC patients with infectious disease, DIC was diagnosed when the DIC score exceeded 4 points. Resolution of DIC was defined as a score of ≤3 points. In the DIC patients with hematological diseases, DIC was evaluated using the diagnostic criteria of the JMHW[23)]. In the DIC patients with hematological disease, DIC was diagnosed when the DIC score exceeded 3 points in the presence of severe thrombocytopenia due to bone marrow failure. Resolution of DIC was defined as a score of ≤2 points.

In DIC with hematological disease, Wada et al. showed that the outcome was poorer with increasing DIC score, suggesting that early diagnosis and early treatment are important[27)]. Although the effectiveness of early treatment for DIC is controversial, according to Wada's report[27)] and our previous report[13)], we immediately administer rhTM for DIC with hematological disease at 3 points of JMHW for DIC with hematological disease because of the aggressive clinical course of DIC with hematological disease. However, all patients with suspected DIC fulfilled the 4 points of JMHW DIC score during the clinical course of rhTM treatment.

The following cases were excluded from the analysis of the DIC resolution rate and the change in the DIC score: cases in which the DIC score did not apply to the diagnosis according to the JAAM and JMHW DIC diagnostic criteria at baseline; and cases in which the DIC score could not be calculated due to missing data, such as laboratory test results at baseline and/or following the day after final treatment. The Japanese pharmaceutical reference about rhTM strongly warned that

patients with active life-threatening bleeding resulting in shock should be contraindicated and excluded. According to the Japanese pharmaceutical reference about rhTM and previous reports[8)13)], the exclusion criteria were as follows: fatal or life-threatening bleeding (intracranial, gastrointestinal, or pulmonary bleeding).

We administered rhTM at a dose of 380 U/kg/day for 6 consecutive days[8)~10)]. For renal insufficiency DIC patients, we administered an adjusted dose of 130 U/kg/day[8)~10)]. For DIC patients with low antithrombin (AT) activity (<70%), we administered AT 1,500 U/day for 3 consecutive days.

We retrospectively examined the coagulation markers, DIC score, and Sequential Organ Failure Assessment (SOFA) score, before and after rhTM treatment. Furthermore, we examined the differences in DIC score and SOFA score between survivors and non-survivors. Moreover, we examined overall survival (OS) and adverse effects after rhTM treatment. Subsequently, we analyzed the transfusion rate and dose in 103 DIC patients with infectious disease and 33 DIC patients with hematological disease. In addition, in order to study the relationship between transfusion rate/dose and DIC resolution/DIC treatment outcome, we analyzed the relationship between the transfusion rate/dose and DIC resolution or treatment outcome. We administered red blood cells (RBC), platelet concentrate (PC), and fresh frozen plasma (FFP) for thrombocytopenia, anemia, and hypofibrinogen according to the guidelines of transfusion medicine[28)29)]. In Japan, major points such as proper indications for the use of blood products associated with patient conditions or trigger levels were discussed and were proposed for performing transfusion medicine in clinical practice[28)]. According to Japanese transfusion guidelines and Makino's report[27)28)], an hemogulobin (Hb) concentration <7.0 g/d*l* triggered a RBC transfusion in principle. A platelet concentration $<2.0 \times 10^{10}/l$ is a trigger level for PC transfusion in principle. Fibrinogen level <100 mg/d*l* is also a trigger level for FFP transfusion in principle. Adverse effects were evaluated on the basis of Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE)[30)].

The changes in DIC score and SOFA score were examined using the Wilcoxon signed-rank test. The correlations among parameters such as fibrin/fibrinogen degradation products (FDP), prothrombin time (PT) ratio, platelets, DIC score, and SOFA score in Table 2 were examined by using Spearman's rank correlation coefficient. Thus, there were no statistically significant correlations among variables in Table 2 by using Spearman's rank correlation coefficient. As shown in Table 2, a univariate and a multivariate analysis was performed to identify risk factors associated with the prognosis. To identify the optimal cut-off point of the prognostic factors, we utilized the Youden index, i.e., J = max (sensitivity + sensitivity − 1). As shown in Table 3, a comparison of the rate of transfusion was performed between DIC resolution patients and DIC non-resolution patients by using the Fischer's exact test. The comparison of the rate of transfusion between surviving DIC patients and non-surviving DIC patients was performed by using the Fischer's exact test. The comparison of the dose of transfusion between DIC resolution patients and DIC non-resolution patients was performed by using the Mann-Whitney U test. In Fig. 5A, 5B, and 5C, a Cochran-Armitage test was performed to analyze the statistical differences. Statistical significance was determined with a 2-sided P value (<0.05).

This retrospective study was conducted in compliance with good clinical practices and the ethical principles of the Declaration of Helsinki. We received approval for this study from the appropriate ethics committees and institutional review boards.

Results

The patient characteristics of DIC patients with infectious disease (n=103) are shown in Table 1A. The median age of the infectious disease group was 74 years (range 0-94 years). The etiologies of the underlying disease were sepsis (86), pneumonia (12), meningitis (3), fulminant hepatitis (1), and severe fever with thrombocytopenia syndrome (SFTS) virus (1).

Therefore, our study was performed between May 2012 and November 2014, and the Sepsis-3 definition (2016) was not applied for a diagnosis of sepsis. Instead, sepsis was diagnosed with the Japanese guideline for management of sepsis in 2012 and 2014[20)].

The laboratory data were as follows: median DIC score before rhTM treatment: 6, mean platelet count: $7.5\times10^{10}/l$, median prothrombin time-ratio (PT-ratio): 1.27, median fibrin/fibrinogen degradation products (FDP): 34.3 μg/m*l*, and median fibrinogen: 342 mg/d*l*. We compared DIC scores before and after rhTM treatment (Fig. 1A).

Table 1 Clinical characteristics of DIC patients with infectious (1A) and hematological disease (1B)

Table 1A

parameters	Laboratory findings
Age: median (range)	74 (0-94) IQR: 18
Underlying disease	1. sepsis (86) 2. pneumonia (12) 3. meningitis (3) 4. fulminant hepatitis (1) 5. SFTS (1)
Laboratory findings	
DIC score (before treatment): median (range)	6 (4-9) IQR: 3
DIC score (after treatment): median (range)	3 (0-8) IQR: 3
Plt ($\times 10^{\wedge 10}/l$): median (range)	7.5 (0.4-46.7)
PT-ratio: median (range)	1.27 (0.9-10.7)
FDP (μg/m*l*): median (range)	34.3 (0.7-1,074)
Fibrinogen (mg/d*l*): median (range)	342 (23.3-905.6)
SOFA score (before treatment): median (range)	7 (2-19)
SOFA score (after treatment): median (range)	3.5 (0-18)

Table 1B

parameters	Laboratory findings
Age: median (range)	61 (28-85) IQR: 23.5
Underlying disease	1. AML (16) 2. ML (12) (ATL: 3) 3. ALL (2) 4. MPD (2) 5. MM (1)
Laboratory findings	
DIC score (before treatment): median (range)	4 (3-8) IQR: 3
DIC score (after treatment): median (range)	2 (1-8) IQR: 2
Plt ($\times 10^{\wedge 10}/l$): median (range)	8.1 (0.2-26.8)
PT-ratio: median (range)	1.1 (1.0-1.3)
FDP (μg/m*l*): median (range)	17.6 (5.8-194.5)
Fibrinogen (mg/d*l*): median (range)	236.2 (71.4-693)

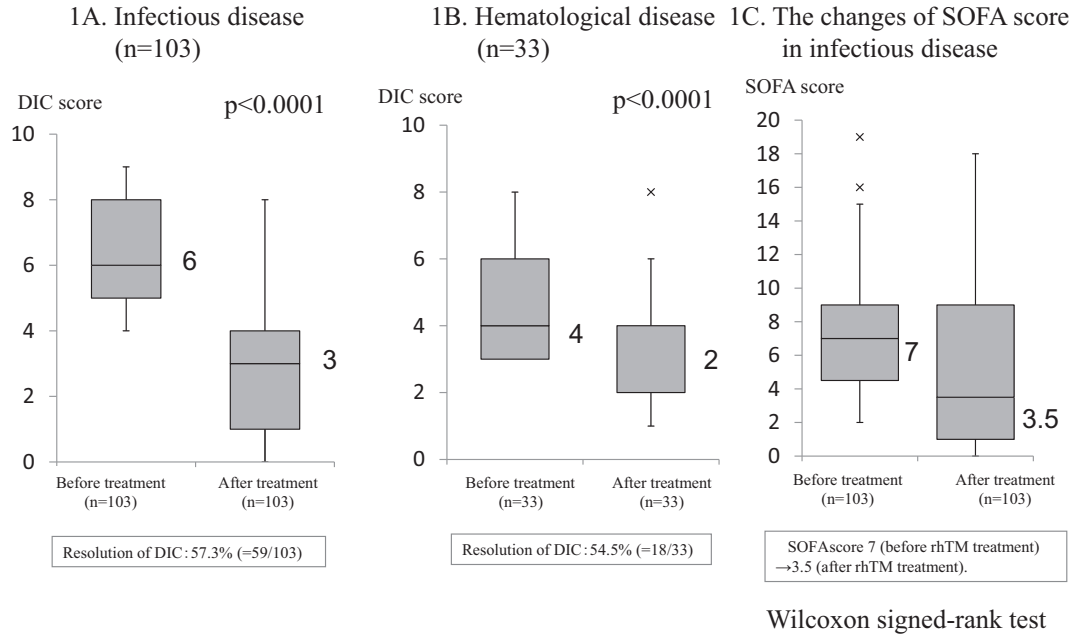


Fig. 1
A and B: DIC resolution among patients with infectious and hematological diseases
C: Changes of SOFA score in DIC patients with infectious disease

Overall, among patients with underlying infectious disease, the median DIC score declined from 6 before rhTM treatment to 3 after rhTM treatment (Fig. 1A). The resolution rate of DIC was 57.3% (59/103) (Fig. 1A). Next, we compared the SOFA score before and after rhTM treatment (Fig. 1C). The median SOFA score declined from 7 before rhTM treatment to 3.5 after rhTM treatment (Fig. 1C). The OS rate of DIC patients with infectious disease at 28 days was 73.8% (76/103) (Fig. 2A).

The characteristics of DIC patients with hematological disease (n=33) are shown in Table 1B. The median age of the hematological group was 61 years (range 28-85 years). The etiologies of the underlying disease were acute myelogenous leukemia (AML) (16), including acute promyelocytic leukemia (APL) (3); malignant lymphoma (12), including adult T-cell leukemia/lymphoma (ATL) (3); acute lymphocytic leukemia (ALL) (2); myeloproliferative disorder (MPD) (2); and multiple myeloma (MM) (1). The laboratory findings were as follows: median DIC score before rhTM treatment: 4, median platelet count: $8.1\times10^{10}/l$, median PT-ratio: 1.1, median FDP: 17.6 μg/m*l*, and median fibrinogen: 236.2 mg/d*l*.

Among patients with underlying hematological dis-

2A. Survival rate of DIC patients with infectious disease　2B. Survival rate of DIC patients with hematological disease

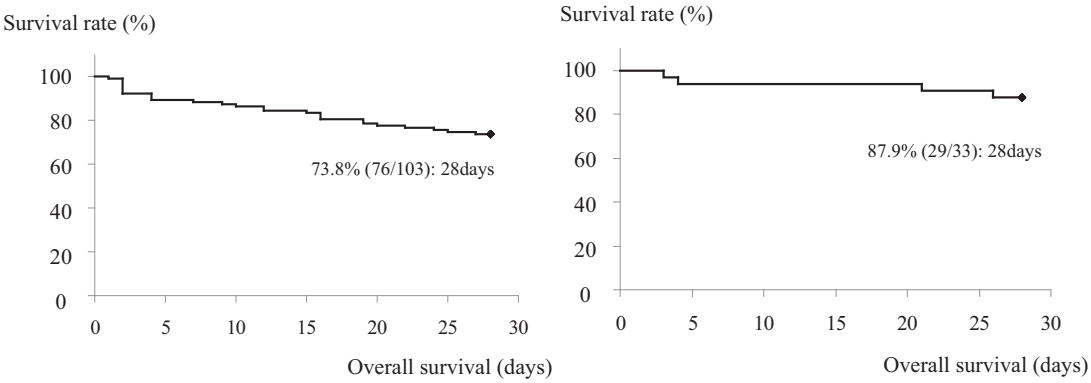


Fig. 2　Survival rate of DIC patients with infectious (2A) and hematological diseases (2B)

ease, the median DIC score of 4 before rhTM treatment declined to a DIC score 2 after rhTM treatment (Fig. 1B). The resolution rate of DIC was 54.5% (18/33) (Fig. 1B). The OS rate of DIC patients with hematological disease at 28 days was 87.9% (29/33) (Fig. 2B). In summary, of all 136 DIC patients, the resolution rate of DIC was 56.6% (77/136). The OS rate of the 136 DIC patients at 28 days was 77.2% (105/136).

Next, we compared DIC scores before and after rhTM treatment between survivors (n=76) and non-survivors (n=27) in DIC patients with infectious disease (Fig. 3A). In survivors, the median DIC score of 6 before rhTM treatment declined to a median DIC score of 2.5 after rhTM treatment. The resolution rate of DIC was 69.7% (53/76) (Fig. 3A). In non-survivors, the median DIC score of 7 before rhTM treatment declined to a median DIC score of 5 after rhTM treatment. The resolution rate of DIC among non-survivors was 22.2% (6/27). Unexpectedly, 63.0% of patients experienced a reduction in DIC score among non-survivors (17/27) (Fig. 3A).

Similarly, we compared the SOFA score before and after rhTM treatment between survivors (n=76) and non-survivors (n=27) in DIC patients with infectious disease (Fig. 3B). In survivors, a SOFA score of 6 before rhTM treatment declined to a SOFA score of 2 after rhTM treatment. However, in non-survivors, a SOFA score of 8 before rhTM treatment increased to a SOFA score of 9.5 after rhTM treatment (Fig. 3B).

We also compared DIC scores before and after rhTM treatment between survivors (n=29) and non-survivors (n=4) among DIC patients with hematological disease (Fig. 3C). In survivors, the median DIC score of 4 before rhTM treatment declined to a median DIC score of 2 after rhTM treatment (Fig. 3C). The resolution rate of DIC was 58.6% (17/29) (Fig. 3C). In non-survivors, the median DIC score of 5.5 before rhTM treatment declined to a median DIC score of 4.5 after rhTM treatment. The resolution of DIC was 25.0% (1/4). Unexpectedly, 50.0% of patients experienced a reduction in DIC score among non-survivors (=2/4) (Fig. 3C).

In DIC patients with low AT activity (<70%) (n=35), we administered AT 1,500 U/day for 3 consecutive days (infectious disease, n=29; hematological disease, n=6). We examined the effect of AT administration on DIC resolution and OS. In DIC patients with infectious disease who were administered AT (n=29), the rate of DIC resolution was not superior (45%) compared to the rate of DIC resolution in patients who were not administered AT (62%, 46/74) (Fig. 4A). Regarding the OS of DIC patients, the OS of DIC patients with infectious disease who were administered AT tended to be superior to the OS of DIC patients who were not administered AT (Fig. 4B).

In DIC patients with infectious disease who did not survive (n=27), the cumulative mortality rate was 50% at day 11 and 75% at day 17. Mortality tended to occur within 2 weeks of DIC onset. In DIC patients with hematological disease who did not survive (n=4), the cumulative mortality rate was 50% at day 4 and 75% at day 17. Mortality tended to occur within a week of DIC onset.

The causes of mortality among non-surviving DIC patients with infectious disease were sepsis (19), pneumonia (6), fulminant hepatitis (1), and SFTS (1). The causes of mortality among non-surviving DIC patients

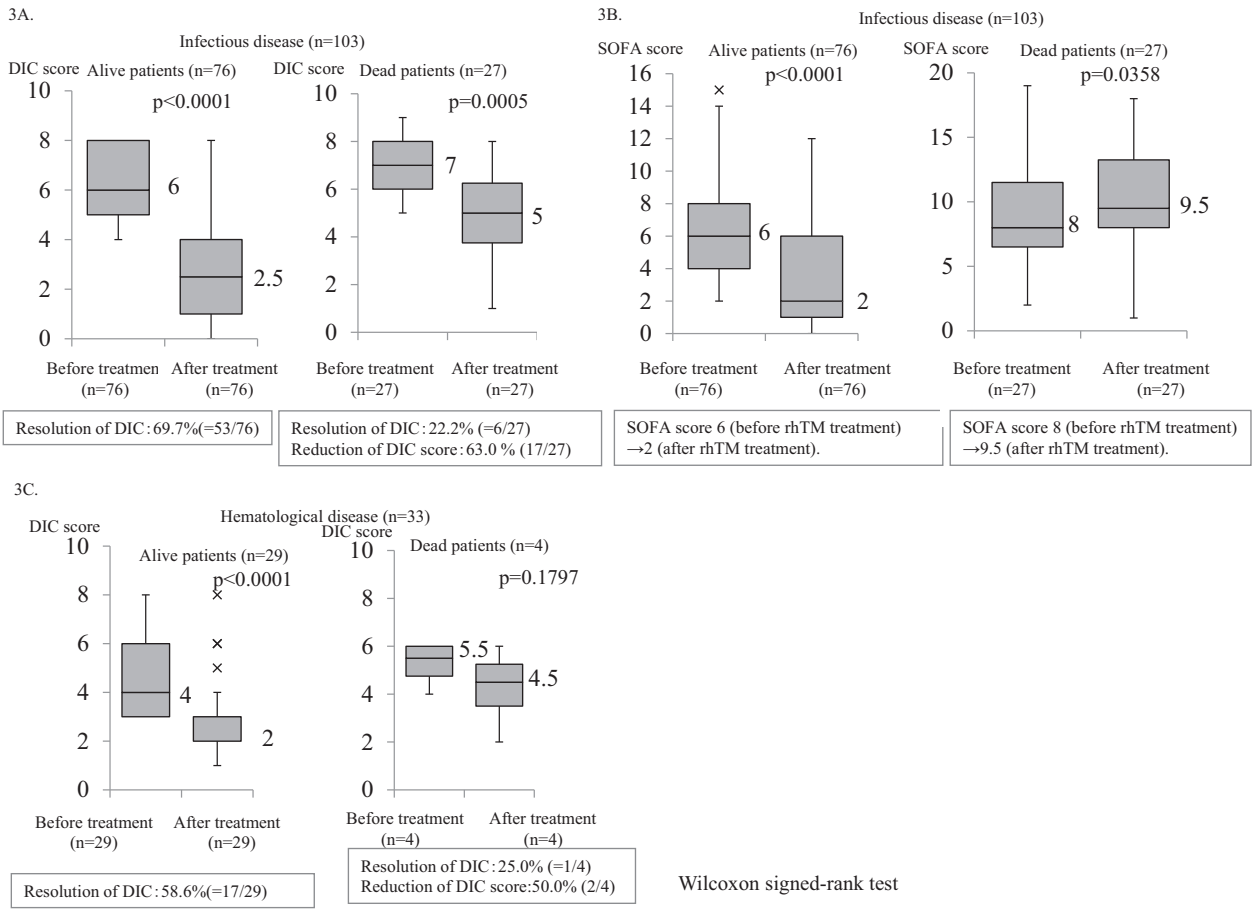


Fig. 3

A: DIC resolution and DIC score reduction in surviving and non-surviving DIC patients with infectious disease
B: The changes of SOFA score in surviving and non-surviving DIC patients with infectious disease
C: DIC resolution and DIC score reduction of hematological disease in surviving and non-surviving DIC patients

with hematological disease were AML (2), ATL (1), and MM (1).

Next, to evaluate prognostic factors associated with outcomes of DIC patients with infectious disease, we performed univariate analysis of the laboratory findings at diagnosis (Table 2A). The univariate analysis revealed that PT-ratio, DIC score, and SOFA score were significantly associated with poor treatment outcomes (HR=1.217, 95% confidence interval [CI] 1.021-1.449, P=0.028; HR= 1.389, 95% CI 1.045-1.846, P=0.024; HR=1.213, 95% CI 1.107-1.329), P<0.001, respectively (Table 2A). The multivariate analysis revealed that SOFA score was the only statistically significant factor associated with poor treatment outcomes of DIC among patients with infectious disease (HR=1.167, 95% CI 1.022-1.333, P=0.023) (Table 2A).

Furthermore, we analyzed the cut-off values of the SOFA score to predict the treatment outcomes of DIC with infectious disease. The ROC curve for the logistic regression model for SOFA is shown in Fig. 5. The model including SOFA achieved an AUC of 0.72. The optimal cut-off was 10, and the sensitivity and specificity were 0.481 and 0.88, respectively, by the Youden index method. Thus, we clearly showed that the optimal cut-off point was 10 as determined by the Youden index.

Similarly, in DIC patients with hematological disease, we performed univariate analysis of the laboratory findings at diagnosis (Table 2B). The univariate and multivariate analysis did not reveal any factors significantly associated with the outcomes (Table 2B). However, in univariate analysis, platelet count tended to be near the statistical significance threshold (HR=0.639, 95% CI 0.376-1.086, P=0.098). Additional research with a larger population of DIC patients is needed to clarify the prognostic factors associated with outcomes in DIC patients with hematological disease.

Based on our findings of the prognostic factors asso-

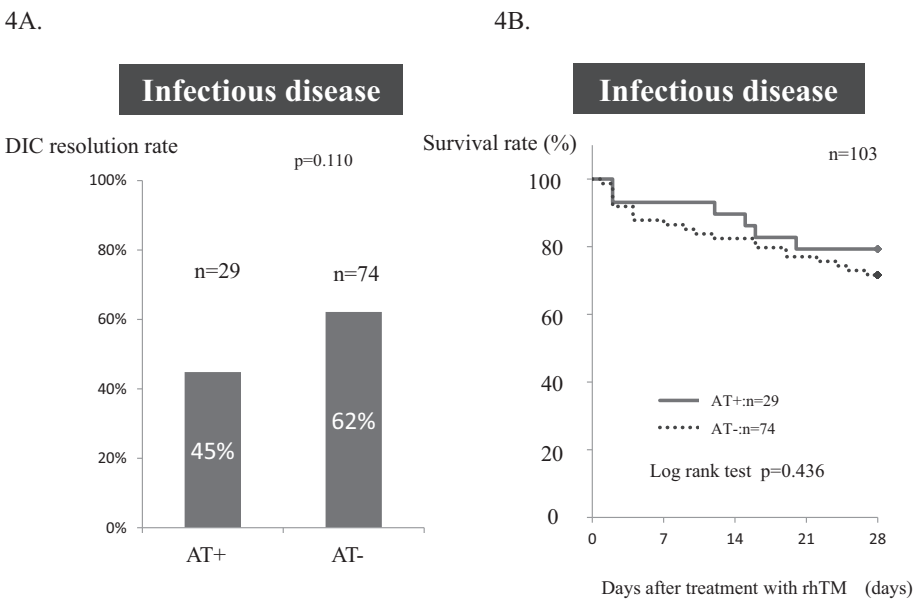


Fig. 4
A: Effect of AT administration on DIC resolution in infectious disease
B: Effect of AT administration on treatment outcomes in infectious disease

Table 2　Prognostic factors associated with poor treatment outcomes in DIC patients with infectious (2A) and hematological disease (2B)

Table 2A

	Univariate analysis			Multivariate analysis		
	Hazard ratio (95%CI)		P value	Hazard ratio (95%CI)		P value
FDP μg/m*l*	1.002	(1.000-1.003)	0.076	1.007	(0.995-1.019)	0.285
PT-ratio	1.217	(1.021-1.449)	*0.028*	1.155	(0.781-1.706)	0.471
Fibrinogen mg/d*l*	1.000	(0.997-1.002)	0.638	1.000	(0.997-1.002)	0.866
PLT $\times 10^{10}/l$	0.968	(0.902-1.039)	0.370	0.981	(0.906-1.063)	0.644
SIRS score	1.596	(0.747-3.409)	0.228	2.251	(0.924-5.481)	0.074
DIC score	1.389	(1.045-1.846)	*0.024*	0.948	(0.627-1.433)	0.798
SOFA score	1.213	(1.107-1.329)	*＜0.001*	1.167	(1.022-1.333)	*0.023*

Cox proportional hazards model

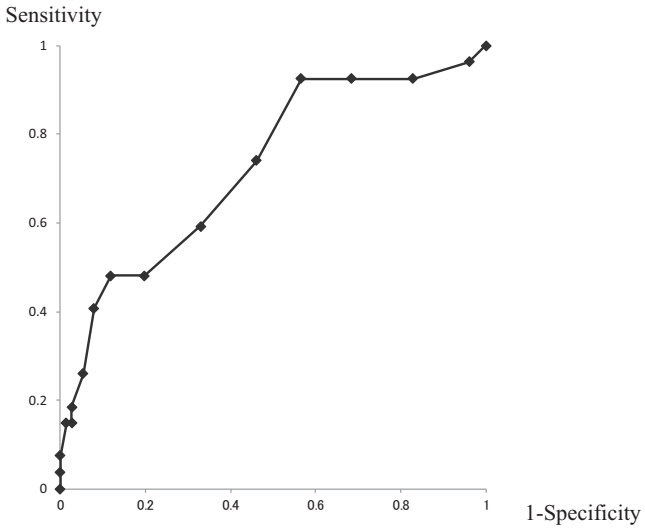
Table 2B

	Univariate analysis			Multivariate analysis		
	Hazard ration (95%CI)		P value	Hazard ration (95%CI)		P value
FDP μg/m*l*	1.003	(0.987-1.020)	0.700	1.033	(0.959-1.113)	0.387
PT-ratio	2.307	(＜0.001-＞1,000)	0.866	788.095	(＜0.001-＞1,000)	0.659
Fibrinogen mg/d*l*	0.999	(0.994-1.005)	0.818	0.974	(0.929-1.021)	0.268
PLT $\times 10^{10}/l$	0.639	(0.376-1.086)	0.098	0.370	(0.100-1.381)	0.139
SIRS score	3.530	(0.402-30.986)	0.255	1,158.693	(0.010-＞1,000)	0.239
DIC score	1.347	(0.861-2.109)	0.192	0.018	(0.0001-5.52)	0.169

Cox proportional hazards model

ciated with DIC outcomes, including higher DIC score (univariate analysis), and higher SOFA score (multivariate analysis) (cut-off point: 10) at diagnosis in DIC patients with infectious disease, and the lower platelet count in DIC patients with hematological diseases, we examined the relationship between OS, DIC, and SOFA score in patients with infectious disease, and OS and platelet count in patients with hematological disease.

Higher DIC score at diagnosis was significantly associated with poorer OS in DIC patients with infectious disease (P=0.028) (Fig. 6A), lower platelet count at diagnosis was significantly associated with poorer OS in



SOFA	2 (min)	4 (Q1)	7 (median)	9 (Q3)	19 (max)
Sensitivity	1.000	0.926	0.741	0.481	0.037
Specificity	0	0.171	0.539	0.803	1.000
Odds ratio	-	2.579	3.347	3.776	-

Fig. 5 ROC curve of SOFA score in DIC patients with infectious disease. The ROC curve for the logistic regression model for SOFA is shown. The model including SOFA achieved an AUC of 0.72. The optimal cut-off was 10, and the sensitivity and specificity were 0.481 and 0.88 respectively, by the Youden index method.

DIC patients with hematological diseases (P=0.031) (Fig. 6B), and higher SOFA score at diagnosis was significantly related to worse OS in DIC patients with infectious disease (P<0.001) (Fig. 6C).

Finally, we analyzed the transfusion rate and dose in 103 DIC patients with infectious disease and 33 DIC patients with hematological disease (Table 3). In 103 DIC patients with infectious disease, we analyzed the transfusion rate and dose between DIC resolution patients and DIC non-resolution patients (Table 3A). The transfusion rate (RBC, PC, and FFP) in DIC resolution patients was statistically lower than that in DIC non-resolution patients. The transfusion dose (RBC, PC, and FFP) in DIC resolution patients was statistically lower than that in DIC non-resolution patients. These results clearly showed that rhTM treatment may affect the transfusion rate and dose in DIC resolution patients with infectious disease.

Furthermore, we analyzed the transfusion rate and dose between surviving DIC patients and non-surviving DIC patients (Table 3B). The transfusion rate (RBC, PC, and FFP) in surviving DIC patients was statistically lower than that in non-surviving DIC patients. The transfusion dose (RBC, PC, and FFP) in surviving DIC patients was statistically lower than that in non-surviving DIC patients. These results clearly showed that rhTM treatment may affect the transfusion rate and dose in surviving DIC patients with infectious disease.

In 33 DIC patients with hematological disease, we analyzed the transfusion rate and dose between DIC resolution patients and DIC non-resolution patients (Table 4A). Only the FFP transfusion rate in DIC resolution patients was statistically inferior to that in DIC non-resolution patients. Only the FFP transfusion dose in DIC resolution patients was also statistically inferior to that in DIC non-resolution patients. Moreover, we analyzed the transfusion rate and dose between surviving DIC patients and non-surviving DIC patients (Table 4B). Only the PC transfusion dose in surviving DIC patients was statistically inferior to that in non-surviving DIC patients. These results clearly revealed that rhTM treatment may affect the FFP transfusion rate and dose in surviving DIC patients with hematological disease.

The adverse effects of treatment with rhTM were tolerable except for two occurrences of grade 2 bleeding, cerebral hemorrhage (1), and bleeding at the opera-

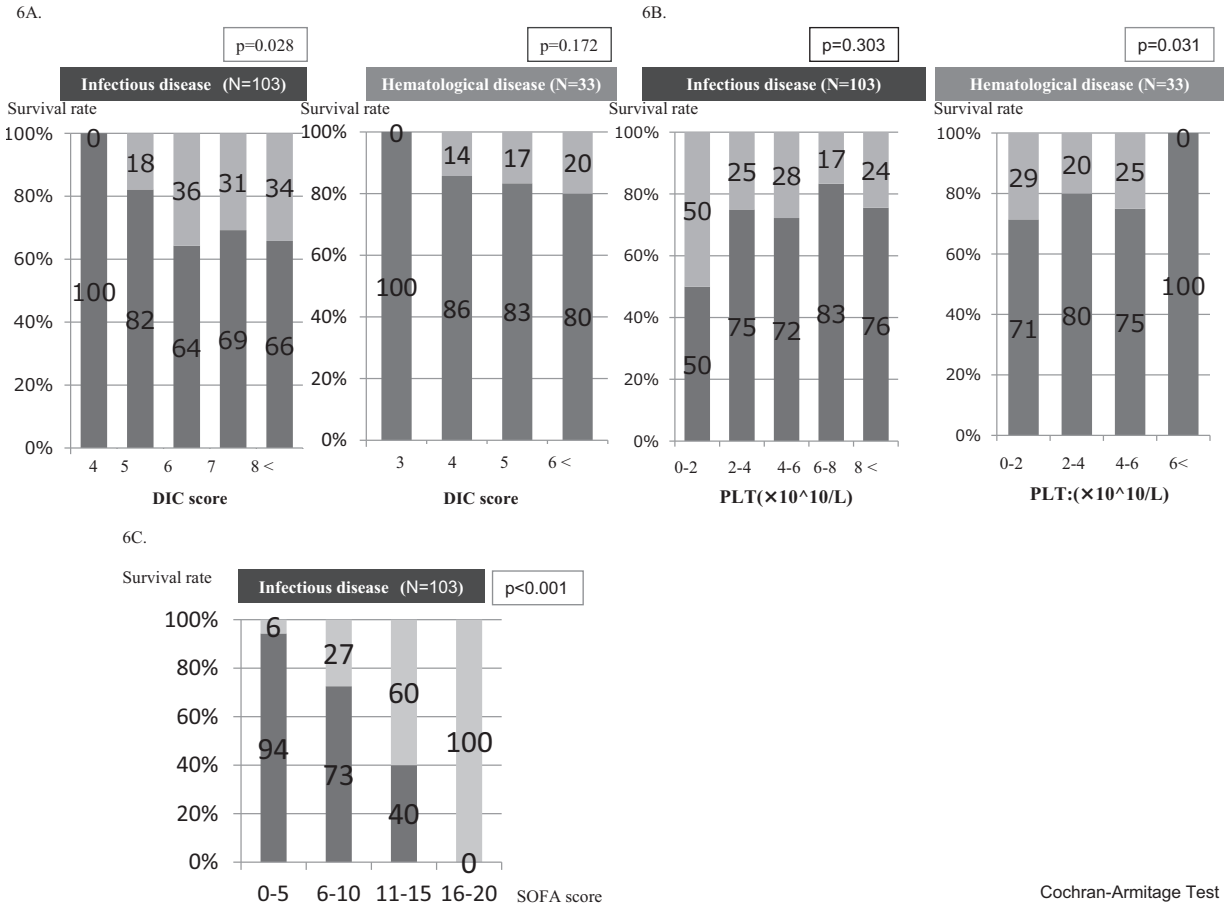


Fig. 6

A: Survival rate according to DIC score in patients with infectious and hematological diseases

B: Survival rate according to platelet count in patients with infectious and hematological diseases

C: Survival rate according to SOFA score among DIC patients with infectious disease

Table 3A　The comparison between transfusion rate and dose in DIC resolution patients and DIC non-resolution patients with infectious disease

	Transfusion rate				Transfusion dose (median)		
	total	RBC	PC	FFP	RBC	PC	FFP
Transfusion (+)/DIC resolution patients	40.6% (=24/59)	32.2% (=19/59)	22.0% (=13/59)	6.8% (=4/59)	4 (0-38)	10 (0-460)	0 (0-24)
Transfusion (+)/DIC non-resolution patients	72.7% (=32/44)	52.3% (=23/44)	52.3% (=23/44)	40.9% (=18/44)	6 (0-62)	25 (0-240)	6 (0-302)
	p=0.001	p=0.018	p=0.000	p=0.045	p=0.049	p=0.002	p=0.002
		Fischer's exact test			Mann-Whitney U test		

Table 3B　The comparison between transfusion rate and dose of surviving DIC patients and non-surviving DIC patients with infectious disease

	Transfusion rate				Transfusion dose (median)		
	Total	RBC	PC	FFP	RBC	PC	FFP
Transfusion (+)/surviving DIC patients	48.7% (=37/76)	34.2% (=26/76)	28.9% (=22/76)	14.5% (=11/76)	0 (0-38)	0 (0-460)	0 (0-24)
Transfusion (+)/non-surviving DIC patients	70.3% (=19/27)	59.3% (=16/27)	51.9% (=14/27)	40.7% (=11/27)	4 (0-62)	10 (0-240)	4 (0-302)
	p=0.0071	p=0.039	p=0.037	p=0.006	p=0.014	p=0.036	p=0.004
		Fischer's exact test			Mann-Whitney U test		

Table 4A The comparison between transfusion rate and dose of DIC resolution patients and DIC non-resolution patients with hematological disease

	Transfusion rate (median)				Transfusion dose (median)		
	total	RBC	PC	FFP	RBC	PC	FFP
Transfusion (+)/DIC resolution patients	73.7% (=14/19)	57.9% (=11/19)	68.4% (=13/19)	26.3% (=5/19)	7 (0-20)	75 (0-190)	2 (0-44)
Transfusion (+)/DIC non-resolution patients	100% (=14/14) p=0.057	78.6% (=11/14) p=0.278	92.9% (=13/14) p=0.195	78.6% (=11/14) p=0.004	9 (0-26) p=0.101	95 (0-410) p=0.115	12 (0-60) p=0.003
		Fischer's exact test			Mann-Whitney U test		

Table 4B The comparison between transfusion rate and dose of surviving DIC patients and non-surviving DIC patients with hematological disease

	Transfusion rate (median)				Transfusion dose (median)		
	total	RBC	PC	FFP	RCC	PC	FFP
Transfusion (+)/surviving DIC patients	82.8% (=24/29)	70.0% (=20/29)	79.3% (=23/29)	48.3% (=14/29)	7 (0-20)	75 (0-190)	2 (0-44)
Transfusion (+)/non-surviving DIC patients	100% (=4/4)	50% (=2/4)	75% (=3/4)	50% (=2/4)	9 (0-26)	95 (0-410)	12 (0-60)
	p=1.00	p=0.586	p=1.000	p=1.000	p=0.357	p=0.036	p=0.102
		Fischer's exact test			Mann-Whitney U test		

tion site (1). The overall incidence of adverse effects was 8.8% (12/136). The incidence of bleeding adverse effects was 5.9% (8/136) and included subcutaneous hemorrhage (6), cerebral hemorrhage (1), and bleeding at the operative site (1). Grade 2 bleeding adverse effects included cerebral hemorrhage (1) and bleeding at the operative site (1). Our case with cerebral hemorrhage after rhTM treatment gradually recovered with conservative therapy without requiring surgery.

Discussion

Recently, several retrospective clinical reports, two systemic reviews/meta-analyses, and major guidelines revealed the efficacy and safety of rhTM for DIC patients with infectious or hematological diseases in clinical practice (Table 5)[3)9)~13)]. Yamakawa's systemic review/meta-analysis including 12 studies (838 patients included in 3 randomized controlled trials [RCTs]; 571 patients in 9 observational studies) revealed a statistically significant effect on OS at 28 days after rhTM treatment for DIC patients[14)]. In contrast, Zhang's systemic review/meta-analysis including 10 observational studies and 2 RCTs involving 18,288 patients did not reveal a statistically significant effect on OS at 28 days following rhTM treatment for DIC patients[15)]. Thus, the effect of rhTM on DIC treatment outcome is still controversial. Consequently, the predicted survival rate of DIC after 28 days treated with rhTM was approximately 30% and was still poor prognosis[8)~21)]. Thus, to improve the poor outcome of DIC, it is essential to identify the prognostic factors of DIC. Furthermore, we analyzed the clinical effect of DIC resolution, the OS of DIC patients, the adverse effects on DIC patients, the transfusion rate, and transfusion dose for DIC patients during rhTM treatment in clinical practice.

In our retrospective study,

(i) We identified a prognostic factor, SOFA (>10 points) for DIC patients with infectious disease.

(ii) rhTM treatment may have an effect on reduction of the abnormal coagulopathy (DIC score) in DIC patients with infectious disease and hematological disease.

(iii) rhTM treatment may reduce the transfusion rate and dose (RBC, PC, and FFP) in DIC resolution patients and surviving DIC patients with infectious disease. Moreover, rhTM treatment may reduce the transfusion rate and dose (FFP) in DIC resolution patients and the transfusion dose (PC) in surviving DIC patients with hematological disease.

(iv) Our analysis also found that the reduction of DIC, OS, and adverse effects of DIC patients with infectious disease and hematological disease were consistent with previous reports[8)~21)].

Our study clearly revealed that higher SOFA score (>10) was associated with a poor outcome in DIC patients with infectious disease. Furthermore, rhTM treatment demonstrated an improvement in abnormal coagulopathy in survivors and even some populations

Table 5　Previous reports regarding DIC patients treated with rhTM and our study

Retrospective studies	n	Underlying disease	Resolution of DIC (%)	Improvement of DIC score despite of the exacerbation of the underlying disease	Survival rate (%)	Improvement of overall survival	Side effect (%): Overall (%) Bleeding (%)
Infection (post-marketing surveillance) Eguchi et al.	n = 1,787	Infection	58.3%	Not described	64.1%	Not described	Overall = 7.0% Bleeding = 5.4%
Hematology (post-marketing surveillance) Asakura et al.	n = 1,032	Hematological disease	55.9%	+	70.7%	Not described	Overall = 6.3% Bleeding = 4.6%
JSEPTIC study Hayakawa et al.	rhTM = 452 control = 452	Infection	Not described	Not described	Improvement of OS at 100 days.	+	Bleeding requiring the blood tansfusion rhTM = 14.2% control = 13.7%
Yamakawa et al.	rhTM = 68 control = 94	Infection	Improvement at 3days and 7days after treatment	Not described	Death rate in hospital rhTM = 40% control = 57%	+	Bleeding rhTM = 8.8% control = 11.7%
Tagami et al.	rhTM = 1,280 Control = 5,062	Severe pneumonia with sepsis-associated DIC	Not described	Not described	Little association between rhTM and control of mortality	Not described	Not described
In our study Kawano et al.	n = 136	Infection: 103 cases, Hematological disease: 33 cases	Infection: 57%, Hematological disease: 55%	Infection +, Hematology +	Infection: 77%, Hematology: 87%	Not described	Overall: 8.8% (= 12/136). Bleeding: 5.9% (= 8/136)
Systemic meta-anaylsis							
Yamakawa et al.	12 studies 868 patients among 3 RCTs 571 patients among 9 observational study	Sepsis induced DIC	Not described	(1) 1RCT Improvement of DIC resolution (2) 8Observational studies Improvement of DIC resolution	A trend in reduction of 28 mortality by rhTM	+	no significant differences in the serious bleeding risk between rhTM and control groups
Zhang et al.	12 studies: 18,288 patients 2 RCTs 10 Observational study	Infection patients complicated with DIC	Not described	Not described	No significant differences in treatment outcome between rhTM group and control group	−	no significant differences in the bleeding risk between the rhTM group and the control group

of non-survivors in clinical practice.

We discussed (i) the SOFA score as a prognostic factor for DIC patients, (ii) the improvement of abnormal coagulopathy in some populations of non-survivors of DIC by rhTM treatment, (iii) the reduction of transfusion rate and dose of DIC patients by rhTM treatment, and (iv) the clinical effect of DIC resolution, OS of DIC, and adverse effects due to rhTM treatment of DIC.

In our study, we focused on the identification of prognostic factors for DIC patients to improve the poor outcome of DIC. First, regarding prognostic factors associated with treatment outcome, SOFA score (multivariate analysis) (cut-off point: 10) at diagnosis in DIC patients with infectious disease was identified. In previous DIC studies without rhTM treatment, various markers such as AT, SF, high-mobility group box 1 (HMGB-1), TM, acute DIC score, or SOFA score were reported as prognostic factors for DIC patients[31)～36)] (Table 6). Among these markers, in a previous DIC study without rhTM treatment, Seki et al. reported that the outcomes of 77 septic patients with DIC primarily depended on the SOFA score and the resolution of DIC, which are related to organ failure[36)] (Table 6). At present, in previous DIC studies with rhTM treatment, sex[9)], duration of DIC before rhTM[9)], fibrinogen[9)], SOFA[9)], and ADAMTS 13 activity[37)] were reported as prognostic factors for DIC treatment outcome[9)37)] (Table 6). Eguchi et al. reported that sex, the duration of DIC before rhTM, fibrinogen, and SOFA score were identified as significant independent factors affecting

Table 6 Previous reports regarding prognostic factors for DIC treatment outcomes and our study

(1) Previous DIC reports without rhTM treatment
AT (ref 31), SF (ref 32), HMGB-1 (ref 33), TM (ref 34), Acute DIC score (ref 35), SOFA score (ref 36).
(2) Previous DIC reports with rhTM treatment
Sex (ref 9), duration of DIC before rhTM (ref 9), Fibrinogen (ref 9), SOFA (ref 9), ADAMTS 13 activity (ref 36)
(3) Our present study
SOFA score (optimal cut-off points: 10)

the survival rate among 1,787 sepsis-induced DIC patients in post-marketing surveillance[9]. Ohshiro et al. reported that low ADAMTS 13 activity (<65%) may worsen DIC and organ failure by promoting vascular endothelial damage in 30 DIC patients with hematological malignancies[37]. Although various markers were reported, these markers are not easily measured or promptly available in clinical practice.

In our study with rhTM treatment for DIC, the SOFA score was identified as the most important predictor of the treatment outcome of DIC with infectious disease (cut off point: 10). These results are consistent with the previous reports regarding SOFA[9)36)]. However, these previous reports[9)36)] did not examine and discuss the cut-off point of SOFA for the treatment outcome. In our study, the optimal cut-off of SOFA for affecting the treatment outcome was 10, and the sensitivity and specificity were 0.481 and 0.88, respectively, by the Youden index method. As for the relationship between SOFA score and mortality, Vincent et al. reported that a higher SOFA score was associated with an increased probability of mortality in 1,449 patients admitted to 40 ICUs in 16 countries[38]. In this report, for a total SOFA score of >10, the mortality rate was approximately 40%[38]. Furthermore, for a total SOFA score of >15, the mortality rate was approximately 90%[38]. In survivors, the peak of maximum SOFA score was distributed in scores 3-4[38]. In non-survivors, the peak of maximum SOFA score was distributed in scores 10-11[38]. Our results revealing the prognostic factor as SOFA score (>10) were consistent with Vincent's report[38] of a total score of >10 (approximate mortality rate 40%) and maximum SOFA score distribution (10-11) in non-survivors. Thus, the evaluation of SOFA score at DIC diagnosis may be essential to improve the poor outcome of DIC patients with infectious disease. As for the relationship between SOFA score and anti-coagulant therapy for DIC patients with sepsis, Yamakawa et al. reported that anti-coagulant therapy may be effective for sepsis-DIC patients with a higher SOFA score (SOFA score: 13-17) in a nationwide study including 2,663 patients (anticoagulant group: 1,247 patients consisting of 818 received AT, 717 received rhTM, 323 received synthetic protease inhibitor, 144 received heparin/danaparoid, versus the control, 1,416 patients)[39]. Moreover, in February 2016, Sepsis-3 emphasized the evaluation of SOFA score at diagnosis and sequential SOFA score in sepsis to improve the poor outcome[26]. Consistent with the importance of the SOFA score in Yamakawa's report[39] and Sepsis-3[26], an early diagnosis using the diagnostic criteria of DIC with early evaluation multi-organ status using the SOFA score led to the subsequent successful rhTM treatment for DIC patients with infectious disease in clinical practice. However, in non-surviving DIC patients with infectious disease, the SOFA score increased after rhTM treatment (8→9.5). Thus, rhTM treatment did not have an ameliorative effect for reduction of the SOFA score in non-surviving DIC patients. Furthermore, our study revealed that a higher DIC score and higher SOFA score at diagnosis of DIC were significantly associated with lower OS for DIC in patients with infectious disease. Thus, before the progression of systemic organ damage due to cross talk of inflammation and coagulation mechanisms, prompt rhTM treatment for DIC, based on early diagnosis of DIC patients with lower SOFA score, and subsequent rapid rhTM treatment, may improve the poor outcome of DIC patients with infectious disease in clinical practice.

Second, rhTM, as a powerful anti-coagulant and anti-inflammatory agent, may improve abnormal coagulopathy in some populations of non-surviving DIC patients with infectious and hematological diseases. In a previous DIC study without rhTM treatment, Seki et al. reported the importance of the resolution of DIC for treatment outcomes of DIC with infection[36]. Moreover, in post-marketing surveillance of DIC patients with hematological diseases (n=1,032), Asakura et al. reported that abnormal coagulation tests were significantly im-

proved after rhTM treatment even in subjects whose clinical course of underlying disease was assessed as unchanged or exacerbated[10]. Thus, our clinical retrospective study revealed that rhTM treatment may have an ameliorative effect for resolution or reduction of the DIC score in even some populations of non-surviving DIC patients. These results may be explained by the mechanism of anti-coagulant effects by APC activation and anti-inflammatory effects by the lectin like-domain because of the inflammation-coagulopathy cross-talk mechanism[3)~8)].

Third, rhTM treatment may reduce the transfusion rate and dose (RBC, PC, FFP) in DIC resolution patients and surviving DIC patients with infectious disease. Moreover, rhTM treatment may reduce the transfusion dose of PC and FFP in DIC resolution and surviving DIC patients with hematological disease. In a previous report regarding the relationship between rhTM treatment and transfusion treatment, Murata et al. reported that a retrospective large nationwide DPC (Diagnosis Procedure Combination)-based study (7,535 DIC patients with infectious disease in 886 hospitals) revealed that the use of rhTM treatment group (n=3,934) significantly decreased the length of stay and medical costs during hospitalization of patients with DIC in contrast to the AT treatment group (n=3,601)[40]. In this study, the transfusion rate of PC and FFP in the rhTM treatment group was significant lower than in the AT treatment group[40]. Consistent with Murata's report[40], our results showed that in DIC patients with infectious diseases, the transfusion rate and dose (RBC, PC, and FFP) in DIC resolution patients and surviving DIC patients was significantly lower than in DIC non-resolution patients and non-surviving DIC patients, respectively. Moreover, our results showed that in DIC patients with hematological diseases, the transfusion dose of PC and FFP in DIC resolution patients and surviving DIC patients were significantly lower than in DIC non-resolution patients and non-surviving DIC patients, respectively. Thus, these findings of our study clearly showed that early administration of rhTM after immediate diagnosis of DIC may result in the reduction of the transfusion rate and dose in patients who are expected to experience DIC resolution and survive. In 2017, the Japanese society of transfusion and cell therapy proposed a guideline for the use of RBC, PC, and FFP based on scientific evidence[41)~43)]. In these guidelines[41)~43)], the trigger levels of RBC, PC, and FFP in DIC patients with infectious and hematological disease were not described because of the variation in the underlying diseases. Further analysis was essential to elucidate the appropriate trigger level of transfusion. Consequently, rhTM treatment may ameliorate the reduction in the transfusion rate and dose (RBC, PC, and FFP) of DIC patients with infectious disease and the transfusion dose of PC and FFP in patients expected to experience DIC resolution and survival with hematological diseases.

Finally, our analysis also revealed that the reduction of DIC, OS, and adverse effects of DIC patients with infectious disease and hematological disease were consistent with previous reports[9)~21)]. The adverse effects of rhTM treatment in DIC patients were tolerable; the incidence of adverse effects and the incidence and grade of bleeding were consistent with previous reports[9)~21)]. Our cerebral hemorrhage case after rhTM gradually recovered with conservative therapy and without surgery. In the prediction of hemorrhagic events during and following rhTM treatment, Chinen et al. reported that low ADAMTS-13 activity at diagnosis of DIC may predict a higher risk of hemorrhagic events[44]. In our case, ADAMTS-13 activity was not measured at diagnosis of DIC. Thus, cerebral hemorrhage should be watched for during and after rhTM treatment for DIC patients in clinical practice.

Wada reviewed the differences among the recommendations provided by the five guidelines (BSCH, JSTH, SISET, ISTH, and J-SSCG 2016)[17)~21)45)46)]. Among the five guidelines[17)~21)45)46)], the Japanese expert consensus for the treatment of DIC recommends the use of rhTM for DIC patients in 2014 (recommendation: B1-C)[18]. The ISTH/SSC guideline suggested the use of rhTM for DIC patients in 2013[19]. Furthermore, Japanese guidelines for the treatment of sepsis from the sepsis registry committee of the Japanese Society of Intensive Care Medicine recommended rhTM for DIC patients with sepsis in 2014 (recommendation: 2C)[20]. However, in 2016, Japanese clinical practice guidelines for management sepsis and septic shock 2016, J-SSCG 2016, did not mention rhTM for DIC[21]. Thus, unifying the recommendations of these five guidelines may be required to perform appropriate treatment for DIC patients in clinical practice worldwide[17].

At present, a phase III clinical trial evaluating the efficacy of rhTM in severely septic patients with abnormal coagulopathy is now enrolling patients and is being

conducted in the USA, South America, Asia, Australia, the European Union, and other countries[3]. This study is expected to clarify whether rhTM may be the standard treatment for severe sepsis with abnormal coagulopathy worldwide.

In conclusion, our study clearly revealed that SOFA at diagnosis may be an independent prognostic factor for DIC patients with infectious disease treated with rhTM in clinical practice. Furthermore, rhTM treatment even for some populations of non-surviving DIC patients with infectious and hematological diseases demonstrated resolution and reduction of the DIC score. Thus, rhTM treatment may be a powerful anticoagulant and anti-inflammatory agent that improves abnormal coagulopathy even in some populations of non-surviving DIC patients. A higher SOFA score (>10) was related to poor outcomes of DIC associated with infectious disease, and thus, early diagnosis of DIC with evaluation of SOFA, and subsequent rhTM treatment may improve the resolution and poor outcomes of DIC in clinical practice. In the future, a larger population of DIC patients treated with rhTM is needed to further research and clarify the clinical effect of rhTM on DIC patients in clinical practice.

Conflict of Interest Statement

All authors have no conflict of interest.

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当院の播種性血管内凝固症候群（DIC）治療に対する遺伝子組換えトロンボモジュリンの効果―136 例（感染症 103 例と血液疾患 33 例）の解析―
―感染症に合併した DIC の転帰に影響を及ぼす予後不良因子として SOFA score を同定―

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要旨：

（背景）遺伝子組み換えヒト可溶性トロンボモジュリン（rhTM）の DIC に対する有効性の報告はあるが依然として DIC は予後不良である．そのため，DIC の予後不良因子の同定は必須である．

（患者と方法）2012 年 5 月～2014 年 11 月に当院の 136 症例の rhTM 加療の DIC 患者（感染症：103 症例，血液疾患：33 症例）を後方視的に検討した．

（結果）感染症合併/血液疾患合併 DIC の DIC 離脱率は 57.3%（59/103）・54.5%（18/33）であった．28 日生存率は，感染症/血液疾患合併 DIC で，73.8%（76/103）・87.9%（29/33）であった．死亡例の感染症合併 DIC/血液疾患合併 DIC で，DIC 離脱率 22.2%（6/27）/25.0%（1/4），DIC スコア低下 63.0%（17/27）/50.0%（2/4）であった．多変量解析で感染症合併 DIC の SOFA score を予後不良因子として同定した（cut-off：10）．

（結論）感染症合併 DIC の診断時の高 SOFA score（＞10）は予後不良因子であった．さらに，rhTM 治療により，一部の死亡例においても，凝固マーカー改善を認めた．

キーワード：
DIC，rhTM，SOFA score，prognostic factor

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