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The prognosis of disseminated intravascular coagulation associated with hematologic malignancy and its response to recombinant human thrombomodulin

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ABSTRACT

Introduction: Disseminated intravascular coagulation (DIC) is a lethal complication in patients with hematologic malignancies (HMs). DIC can be induced by the HM itself, but also by HM-associated secondary infection; however, whether difference of triggering factor impacts the outcome of DIC in HM patients remains unknown. The objective of this study is to clarify the difference between HM-induced DIC and infection-induced DIC in HM patients regarding treatment response and prognosis.

Methods: HM-induced DIC (158 episodes) and infection-induced DIC in HM patients (83 episodes) from a single center were retrospectively analyzed. Recombinant human thrombomodulin (rhTM) was administered in 149 episodes, while the remaining received conventional therapies.

Results: In HM-induced DIC, improvement by day 7 was 46% (95% confidence interval [CI], 38–54), and rhTM enhanced the improvement (hazard ratio [HR], 1.7; 95% CI, 1.1–2.4). In contrast, improvement of infection-induced DIC was significantly worse (29%; 95% CI, 20–39 on day 7), and this was not influenced by rhTM (HR, 1.0; 95% CI, 0.50–2.2). Thirty-day survival in HM-induced DIC and infection-induced DIC was 87% (95% CI, 81–92) and 53% (95% CI, 42–63), respectively, and was not affected by treatment. A DIC score (Japanese Ministry of Health and Welfare criteria) of ≥5 was a predictor of worse survival in both types of DIC (HR, 2.5; 95% CI, 1.5–3.9).

Conclusions: This study showed the inadequacy of current therapeutic strategies for secondary infection-induced DIC, the prognosis of which was significantly worse than HM-induced DIC, and the limited efficacy of rhTM only in the improvement of HM-induced DIC.

1. Introduction

Disseminated intravascular coagulation (DIC) is a potentially lethal complication in patients with hematologic malignancies (HMs). DIC occurs in around 30% of acute myeloid leukemia cases [1,2], and 78% of acute promyelocytic leukemia cases [3]. A major cause of HM-induced DIC is the activation of extrinsic coagulation via tissue factor produced by malignant cells and the associated bleeding symptoms tend to be severe due to fibrinolytic activation and consumption coagulopathy [4]. Furthermore, HM is often associated with severe secondary infection related to the immune deficiency brought on by the HM and its treatment, which can, in turn, provoke DIC. Such infection-induced DIC in HMs, however, has been relatively neglected in the literature and has not been fully characterized, despite the possibility that its prognosis and treatment response could differ from those of infection-induced DIC in non-HM patients or HM-induced DIC without infection. Moreover, the standard therapy for these 2 types of HM-associated DIC has yet to be established.

Recombinant soluble human thrombomodulin (rhTM) has a different anti-DIC activity from conventional DIC treatment agents. rhTM binds to thrombin and activates protein C, prompting anticoagulant activity through protein C activation [5]. This agent has been approved for use in Japan through a phase 3 study that demonstrated a significant improvement in resolution of both infection- and HM-induced DIC,

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compared with heparin therapy [6]. In contrast to the subsequent accumulating evidences of rhTM's efficacy for treating infection-induced DIC [7–10], its efficacy for DIC in HM patients remains unclear because of the lack of evidence [11]; each previous report containing no more than 100 cases of HM-associated DIC treated with rhTM [6,12–14].

In order to clarify the clinical differences between HM-induced DIC and infection-induced DIC in HM patients, we retrospectively analyzed a total of 241 DIC episodes in 215 patients with HMs and compared the outcomes of treatment with rhTM versus conventional agents.

2. Patients and methods

2.1. Patients, study design, and the diagnostic criteria

We retrospectively analyzed 241 DIC episodes that occurred in 215 consecutive adult patients with HMs who were hospitalized between January 2004 and February 2018 in the University of Tsukuba Hospital, Japan. The data were collected from medical records. The episodes for which anticoagulant therapies were started within 2 days of DIC onset were included in the analysis. In all the DIC episodes, the diagnosis was based on the DIC scoring system proposed in the Japanese Ministry of Health and Welfare (JMHW) criteria, in which neither bleeding symptoms nor platelet count was scored [15]. Bleeding tendency was defined as presence of hemorrhagic manifestations described by Kobayashi [15]. DIC improvement was defined as decrease of the DIC score to 2 or less. DIC episodes were categorized based on the triggering factors. HM-induced DIC was defined as DIC induced by HM without infection. Infection-induced DIC was defined as DIC induced by infection secondary to HM, which included cases retrospectively fulfilling the criteria of sepsis according to Sepsis-3 criteria [16], or cases in which DIC was obviously triggered by infection, such as infection during the period of cytopenia after chemotherapy. We excluded patients in which the dominant DIC-triggering factor could not be identified and those with comorbid severe liver dysfunction. The median period of follow-up was 155 days (range, 1–2998). The study protocol was reviewed and approved by the institutional review board of the University of Tsukuba Hospital.

2.2. Treatment

This study includes only DIC episodes treated within the framework of the expert consensus for the treatment for DIC [17] and its addition [18] provided by The Japanese Society of Thrombosis and Hemostasis (JSTH). In 149 episodes treated after 2009, 380 units/kg/day of rhTM was administered intravenously for a median of 6 (range, 1–14) days. rhTM administration was usually continued for 6 days or until improvement of the DIC. Other DIC episodes were treated with either of the following “conventional” anticoagulant therapies for a median of 11 (range, 1–30) days until improvement of the DIC: low molecular weight heparin at 75 units/kg/day, gabexate mesilate at 20–39 mg/kg/day, unfractionated heparin (the therapeutic range for activated partial thromboplastin time [APTT] ratio was 1.5 to 2.0), danaparoid sodium at 2500 units/day, or nafamostat mesilate at 0.06–0.20 mg/kg/h. Concurrent to the anticoagulant therapy, patients also received treatment for the DIC-causing disease. Platelet concentrate, fresh frozen plasma, and anti-thrombin were transfused depending on the respective levels.

2.3. Statistical analysis

Comparisons between qualitative variables were carried out using the Mann-Whitney *U* test and the results were expressed as box-whisker plots, in which the rectangles represent the lower and upper limits of the interquartile range (IQR), and the median values are demarcated inside the rectangles. The upper lines represent the third quartile plus 1.5 × IQR, and the lower lines represent the first quartile minus 1.5 × IQR. Outlying values are indicated as circles. Correlation between anti-thrombin and DIC score was analyzed using Spearman rank correlation. Cumulative incidence of DIC improvement and hemorrhagic events were assessed with the Gray test [19], and the competing risk factors contained the following: deaths in the analysis of DIC improvement, and deaths plus discontinuation of anticoagulant therapies due to other causes in the analysis of hemorrhagic events. Survival probabilities were estimated using the Kaplan-Meier method, and differences in survival distributions were evaluated using the log-rank test. The age, pretreatment DIC score, bleeding tendency, diagnoses, and febrile neutropenia were selected as potential biases. To compensate for them, multivariate analyses were performed with the Cox proportional hazard regression model for mortality, and the Fine and Gray proportional hazards regression model for DIC improvement and hemorrhagic events, in which the age and the DIC score were grouped according to the median values. All *P*-values were two-sided with type I error fixed at 0.05. Cases with missing data were excluded from the analysis. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [20], and a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria; Version 3.1.1).

3. Results

3.1. Characteristics of DIC

From a total of 7827 patients, hospitalized at the Department of Hematology, University of Tsukuba Hospital between 2004 and 2018, 315 episodes were extracted in which there was elevated plasma fibrinogen/fibrin degradation product (FDP; above the normal limit) and anti-DIC therapy was performed. Finally, 241 DIC episodes were analyzed after excluding those that did not harbor HM (7 episodes), those which did not fulfil the DIC criteria (16 episodes), those which were treated beyond the guidelines [17,18] (6 episodes), those in which anticoagulant therapy was not started within 2 days of the onset (13 episodes), those with missing data (4 episodes), and those in which either the dominant DIC-triggering factor could not be identified (28 episodes) (flow diagram is shown in Fig. S1). The characteristics of the causes and treatments are summarized in Table 1. There were 158 HM-induced DIC episodes and 83 infection-induced DIC episodes in HM patients. Pretreatment FDP levels and DIC scores of HM-induced DIC were higher than those of infection-induced DIC: FDP, 65 μg/ml (IQR, 32–111) and 30 μg/ml (IQR, 21–64) ($P < 0.001$); DIC score, 4 (3–9) and 4 (range, 3–6) ($P = 0.003$), respectively. Bleeding tendency at diagnosis tended to be more frequent in HM-induced DIC (41%; 95% CI, 33–49) than infection-induced DIC (29%; 95% CI, 10–40) ($P = 0.07$). Median anti-thrombin level of infection-induced DIC was 72% (IQR, 59–85), which was significantly lower than that of HM-induced DIC (92%; IQR, 76–105) ($P < 0.001$). There was a weak correlation between anti-thrombin and DIC score in infection-induced DIC (rs = −0.3, $P = 0.01$), but not in HM-induced DIC (rs = 0, $P = 0.9$).

3.2. The courses of FDP levels and DIC scores

In HM-induced DIC, reduction of FDP levels was rapid (Fig. 1A). The median FDP level on day 7 in HM-induced DIC patients was 21 μg/ml (IQR, 13–71) in the conventional therapy group and 13 μg/ml (IQR, 7–42) in rhTM group ($P = 0.02$). The median FDP on day 9 was 17 μg/ml (IQR, 8–35) and 10 μg/ml (IQR, 6–24), respectively ($P = 0.03$). The difference between the therapy groups was balanced on day 14 in HM-induced DIC patients: 8 μg/ml (IQR, 5–17) and 9 μg/ml (IQR, 5–16), respectively ($P = 0.9$). On the contrary, in HM patients with infection-induced DIC, FDP levels slowly decreased after anticoagulant treatment, despite pretreatment FDP levels being much lower than those of HM-induced DIC. Difference in treatment modality for infection-induced DIC had no impact on FDP levels through the entire courses (Fig. 1B).

Table 1
Patient characteristics.

	Hematologic malignancy-induced DIC			Infection-induced DIC		
	Conventional therapy	rhTM	*P*-value	Conventional therapy	rhTM	*P*-value
No. of DIC episodes	62	96		30	53	
Year, median (range)	2006 (2004–2009)	2013 (2009–2018)		2006 (2004–2010)	2013 (2010–2018)	
Age, median (range)	61 (16–83)	60 (18–85)	0.5	58 (21–82)	62 (17–81)	0.7
Male sex, no. (%)	36 (58)	60 (63)	0.6	17 (57)	27 (51)	0.7
Previous DIC episode, no. (%)	8 (13)	12 (13)	1	1 (3)	5 (9)	0.4
Pre-existing bleeding tendency, no. (%)	29 (47)	36 (38)	0.3	7 (23)	17 (32)	0.5
Pretreatment FDP, median (IQR), μg/ml	63 (33–96)	70 (36–120)	0.3	26 (22–50)	35 (21–66)	0.8
Pretreatment anti-thrombin, median (IQR), %	72 (63–84)	72 (58–85)	0.8	91 (73–124)	92 (79–145)	0.3
Pretreatment CRP, median (IQR), μg/dl	–	–	–	12 (6.9–22)	14 (9.0–22)	0.3
Pretreatment DIC score, median (range)	4 (3–8)	4 (3–9)	0.5	4 (3–6)	4 (3–6)	0.2
SOFA score, median (range)	–	–	–	7 (2–15)	6 (2–18)	0.5
Hematologic malignancy, no. (%)						
AML except for APL	22 (36)	37 (39)	0.1	6 (20)	27 (51)	0.06
APL	14 (23)	21 (22)		0 (0)	1 (2)	
ALL	6 (10)	21 (22)		6 (20)	5 (9)	
Lymphoma	14 (23)	15 (16)		6 (20)	10 (19)	
Myeloma	1 (2)	0 (0)		6 (20)	5 (9)	
MDS	1 (2)	0 (0)		2 (7)	3 (6)	
Others	4 (6)	2 (2)		4 (13)	2 (4)	
Infection focus, no. (%)						
Lung	–	–	–	13 (43)	16 (30)	0.5
Gastrointestinal tract	–	–	–	3 (10)	4 (8)	
Skin/soft tissue	–	–	–	1 (3)	2 (4)	
No obvious focus	–	–	–	11 (37)	29 (55)	
Others	–	–	–	2 (7)	2 (4)	
Febrile neutropenia, no. (%)	–	–	–	18 (60)	35 (66)	0.6
Treatment, no. (%)						
rhTM	0 (0)	96 (100)	< 0.001	0 (0)	53 (100)	< 0.001
Low molecular weight heparin	48 (77)	0 (0)		22 (73)	0 (0)	
Gabexate mesilate	8 (13)	0 (0)		8 (27)	0 (0)	
Unfractionated heparin	3 (5)	0 (0)		0 (0)	0 (0)	
Danaparoid sodium	2 (3)	0 (0)		0 (0)	0 (0)	
Nafamostat mesilate	1 (2)	0 (0)		0 (0)	0 (0)	
Anti-thrombin administration, no. (%)	8 (13)	9 (9.4)	0.6	6 (20)	12 (23)	1.0

DIC, disseminated intravascular coagulation; rhTM, recombinant human thrombomodulin; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome.

The DIC score was improved after treatment in both HM-induced DIC and infection-induced DIC in HM patients (Fig. 2). Improvement was the most rapid in the rhTM-treated HM-induced DIC group. Median DIC score in HM-induced DIC on day 7 was 3 (range, 1–8) in the conventional therapy group and 2 (range, 1–8) in the rhTM group ($P = 0.03$). No difference was seen in the score on day 14 in connection with DIC treatment modality.

3.3. DIC improvement

The cumulative incidences of DIC improvement (decrease of DIC score to 2 or less) are shown in Fig. 3. The rate of DIC improvement on day 7 was 46% (95% confidence of interval [CI], 38–54) in HM-induced DIC ($P < 0.001$), and 29% (95% CI, 20–39) in infection-induced DIC in HM patients. Although the treatment modality did not influence infection-induced DIC improvement ($P = 0.9$), treatment with rhTM significantly ameliorated HM-induced DIC ($P = 0.01$), in which the rate of DIC improvement on day 7 was 32% (95% CI, 21–44) in the conventional therapy group and 55% (95% CI, 45–65) in the rhTM group. The median days of improvement were days 11 and 7, respectively.

Multivariate analyses were performed to take into account the influence of background variables that might affect DIC improvement; factors such as treatment, age, pretreatment DIC score, pre-existing bleeding tendency, diagnosis, and febrile neutropenia (Table 2). The results showed that rhTM was an independent factor that enhances DIC improvement in HM-induced DIC (hazard ratio [HR], 1.7; 95% CI, 1.1–2.4; $P = 0.01$), although no statistical significance was found for the effect of rhTM on infection-induced DIC in HM patients (HR, 1.0; 95% CI, 0.50–2.2; $P = 0.9$). In addition, a DIC score of ≥5 was a factor that deteriorated both infection-induced DIC and HM-induced DIC improvement.

3.4. Survival

Day 30 survival after treatment was 87% (95% CI, 81–92) in HM-induced DIC ($P < 0.001$) and 53% (95% CI, 42–63) in infection-induced DIC in HM patients. rhTM had no significant impact on the survival of both HM-induced DIC ($P = 0.8$) and infection-induced DIC ($P = 1$) (Fig. 4).

Multivariate analyses showed that DIC score (≥5) was the only independent risk factor for the mortality rate in both infection-induced DIC and HM-induced DIC, but not the DIC treatment modality (Table 3). The HR of DIC score (≥5) for the mortality rate was 2.5 (95% CI, 1.5–3.9; $P < 0.001$) among the whole DIC episodes.

3.5. Hemorrhagic events

Cumulative incidence of hemorrhagic events that led to discontinuation of anticoagulant therapy on day 14 was 8.2% (95% CI, 4.6–13) in the HM-induced DIC ($P = 0.2$), and 4.8% (95% CI, 1.6–11) in the infection-induced DIC in HM patients. In HM-induced DIC, discontinuation of therapy due to hemorrhagic events was significantly less with rhTM compared to conventional therapies ($P = 0.005$), but not in infection-induced DIC ($P = 0.7$) (Fig. 5).

After multivariate analysis, rhTM was shown to be a reducing factor of bleeding (HR, 0.23; 95% CI, 0.07–0.78; $P = 0.02$; Table S1), whereas

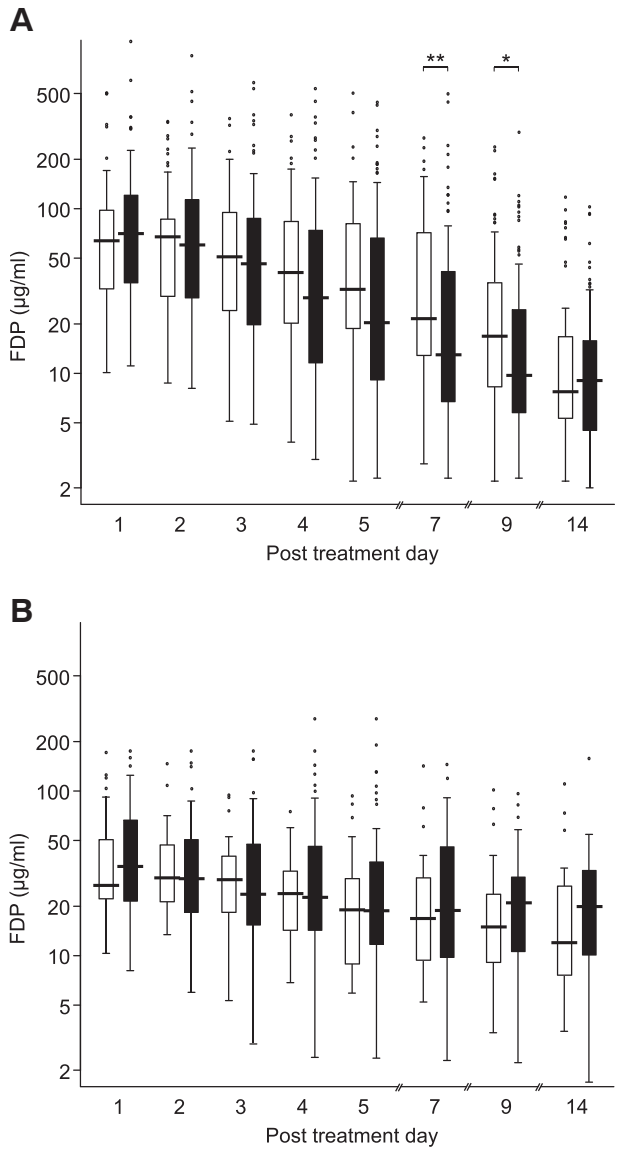

Fig. 1. Fibrinogen/fibrin degradation product (FDP) levels after treatment for hematologic malignancy-induced DIC (A) and infection-induced DIC in hematologic malignancy patients (B).
rhTM (closed column) reduced FDP more promptly than conventional anticoagulant therapy (open column) in hematologic malignancy-induced DIC. The reduction of FDP was slower and no difference was seen between the conventional therapy-treated group and rhTM-treated group in infection-induced DIC. $^{*}P = 0.03$, $^{**}P = 0.02$.

pretreatment DIC score (≥5), and pre-existing bleeding tendency were selected as increasing factors in HM-induced DIC. The frequency of hemorrhagic events in infection-induced DIC was too few to evaluate by multivariate analyses.

4. Discussion

We found a significant difference between HM-induced DIC and infection-induced DIC in HM patients in terms of survival and treatment response. The survival rate of infection-induced DIC was almost half that of HM-induced DIC. Although rhTM promoted early improvement of HM-induced DIC, the novel agent had no significant impact on infection-induced DIC.

DIC is a frequent complication of sepsis, and DIC is associated with increased mortality in these patients [21,22]. Previous studies revealed that the 1-month survival rate of sepsis-induced DIC was 60–80% in the absence of malignancy [7–10], and efficacy of rhTM was shown not only on its control of such DIC, but also on survival [9,10]. However, in our study, 1-month survival of infection-induced DIC associated with HM was no more than 53% and rhTM ameliorated neither infection-induced DIC improvement nor survival. Given that the principle dictating DIC management is the treatment of the underlying cause(s) [23], our findings regarding infection-induced DIC outcome may be attributed to the difficulty of controlling the underlying severe infection in the presence of HM-induced and/or therapy-related immunosuppression. For example, in neutropenic patients admitted to intensive care units, hospital mortality was shown to reach as high as 45% [24] and exceed > 50% when limited to patients who underwent allogeneic stem-cell transplantation [25], although our result might suggest that neutropenia is not the sole factor that deteriorates the clinical outcomes of infection in patients with HM. The mechanisms of rhTM in infection-induced DIC are thought to be an anti-inflammatory effect through the inactivation of high mobility group box 1 protein [26] and an anticoagulation effect through thrombin downregulation and protein C activation [27]; however, the findings of our study suggest that these mechanisms are not sufficient to improve clinical outcomes in the presence of uncontrollable infection related to HMs.

Anti-thrombin is a physiological anticoagulant similar to thrombomodulin. Some studies have suggested that administration of anti-thrombin may be effective not only for shortening the duration of DIC symptoms, but also for improving the outcome of sepsis-induced DIC [28–30]. Combination therapy using anti-thrombin and rhTM may be a treatment option [31,32], although we could not observe a difference in clinical outcomes with anti-thrombin administration in our cohort because of the insufficient number of patients to whom anti-thrombin was given.

The recommendation level of rhTM treatment was not so high according to guidance from the International Society on Thrombosis and Haemostasis [33] and the expert consensus from JSTH [18], because of the insufficiency of evidence. Evidence has been particularly lacking for HM-induced DIC. Some small-scale retrospective studies, such as a study of 17 cases of acute promyelocytic leukemia [12] and that of 47 cases of acute myeloid leukemia [13], have suggested the superior survival of rhTM group compared to the control group, while the subgroup analysis of a phase 3 trial of rhTM could not prove survival benefit [6]. In our study, rhTM rapidly reduced FDP and DIC scores and accordingly contributed to earlier improvement (by 4 days) from HM-induced DIC than conventional therapy. Nevertheless, better DIC improvement did not lead to better survival. Even though the survival benefit was not proved, the prompt DIC recovery brought on by rhTM could be still clinically beneficial. Firstly, Libourel et al. reported that acute myeloid leukemia cases with higher DIC scores developed thrombosis more frequently than those with lower DIC scores [34]. Given that more than half of such thrombosis occurred early (median 8 days after start of the first chemotherapy course) in their study, prompt amelioration of the coagulation abnormality may have contributed to the reduction of thrombotic risks. Secondly, shorter duration of DIC and subsequent earlier discontinuation of the anticoagulant therapy may minimize the risk of bleeding as was shown in the present study. The fewer bleeding events could also be attributed to the wider safety margin of rhTM than other anticoagulants [5].

Although there are no standardized diagnostic criteria for DIC in HM patients, we selected the JMHW criteria because its sensitivity and specificity have been validated for patients with severe thrombocytopenia [1]. In this study, a JMHW DIC Score of ≥5 was the most important predicting factor for failure of DIC improvement and early mortality in both the infection-induced DIC and HM-induced DIC groups, which was consistent with previous reports [35,36]. The patients in whom elevated FDP level (≥40 μg/ml) is the only DIC sign can fulfil the JMHW criteria. Such cases accounted for more than half of participants with a DIC score of 4 in our study, whereas a DIC score of

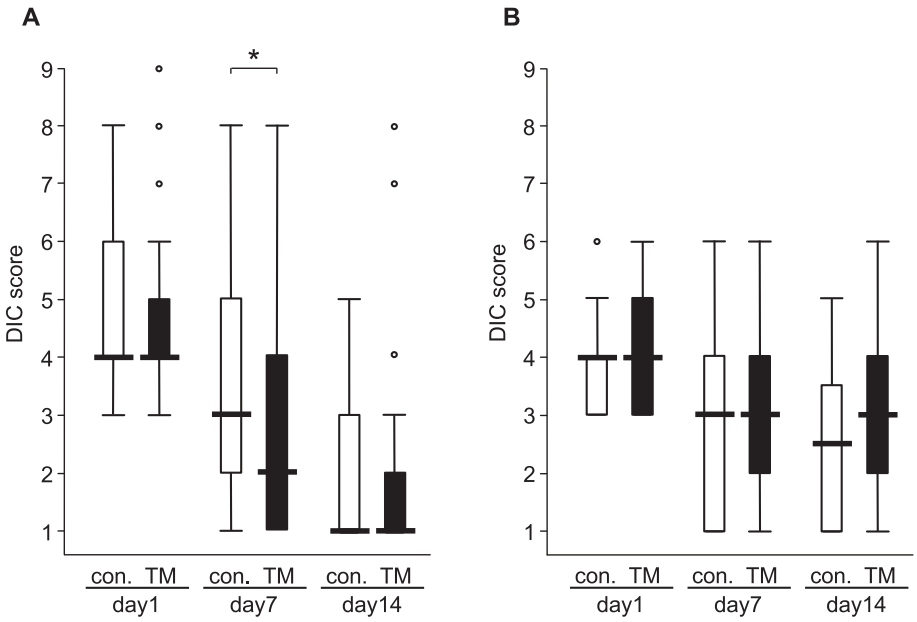

Fig. 2. Japanese Ministry of Health and Welfare (JMHW) DIC scores after the treatment for hematologic malignancy-induced DIC (A) and infection-induced DIC in hematologic malignancy patients (B).
JMHW score of hematologic malignancy-induced DIC on day 7 of the rhTM (TM)-treated group (closed column) was significantly lower than that of the conventional therapy (con.)-treated group (open column). *$P = 0.03$.

≥5 requires at least one of the following signs: organ dysfunction, decreased fibrinogen, or elongation of prothrombin time. In other words, participants with a DIC of ≥5 necessarily have secondary impacts of activated blood coagulation. Accordingly, there may be pathophysiological discrepancy between the patients with DIC scores of 4 and those of ≥5, which, in this study, was observed as difference of DIC improvement and survival. Recently, a novel DIC scoring system was proposed, in which a patient with FDP elevation alone does not fulfil the criteria [37]. Therefore, results could change depending on the scoring system.

Some limitations of our study are its retrospective nature and modest sample size; thus, we could not exclude potential selection bias. Accordingly, multivariate analyses were performed to adjust for the differences in patient characteristics between the groups; however, there may have been some uncompensated biases that influenced the outcomes. There was variation in terms of the proportion of background diseases, and long-term survival can vary according to each disease. Short-term survival (up to 60 days after the onset of DIC), however, did not differ in our cohort, and its influence on our conclusion was thought to be minimal. Although the statistical difference of survival was not observed in the rhTM/conventional therapy groups, the sample size was insufficient to determine equality. So, further investigation with a larger sample size is needed. The difference of time period between the treatment groups (rhTM versus conventional therapies) was another limitation. Since 2009, the conventional anticoagulant therapies for DIC were gradually replaced with rhTM at our hospital. Therefore the updated sepsis care bundles [38] and some new agents for DIC-triggering diseases (such as antifungals and agents for myeloma) could have influenced the outcome, although the number of DIC cases that benefited from these new agents was small. In order to ensure external validity, we extracted data from all the patients hospitalized in the hematologic ward. However, the applicability is limited in the population in which the triggering factor could not be identified due to coexistence of infection and active HM, because such cases were excluded from this study.

5. Conclusions

This retrospective study shows that rhTM prompts early improvement of HM-induced DIC (but not infection-induced DIC in HM patients) without exacerbating bleeding tendency. It also revealed that the outcome of HM-associated infection-induced DIC is poor compared to HM-induced DIC or infection-induced DIC in the absence of HMs. Improvements in treatment for DIC-triggering infection or HMs, as well as for DIC itself, are needed for better treatment outcomes in cases of HM-associated DIC.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2018.11.014.

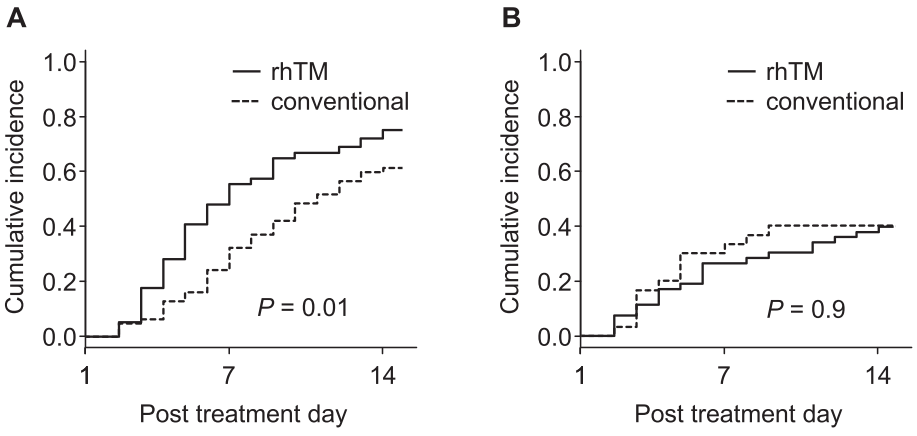

Fig. 3. Cumulative incidence of improvement of hematologic malignancy-induced DIC (A) and infection-induced DIC in hematologic malignancy patients (B).
rhTM enhanced the improvement significantly in hematologic malignancy-induced DIC ($P = 0.01$). The treatment modality did not influence the improvement of infection-induced DIC ($P = 0.9$).

Table 2
Multivariate analysis of DIC improvement.

Factors	Level	Hematologic malignancy-induced DIC		Infection-induced DIC	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Treatment	Without rhTM	1	–	1	–
	With rhTM	1.7 (1.1–2.4)	0.01	1.0 (0.50–2.2)	0.9
Age	< 60	1	–	1	–
	≥60	0.85 (0.59–1.2)	0.4	1.7 (0.76–3.6)	0.2
Pretreatment DIC score	< 5	1	–	1	–
	≥5	0.61 (0.42–0.89)	0.01	0.31 (0.11–0.86)	0.02
Pre-existing bleeding tendency	No	1	–	1	–
	Yes	0.61 (0.41–0.90)	0.01	1.3 (0.59–3.0)	0.5
Diagnosis	AL except for APL	1	–	1	–
	APL	1.9 (1.2–2.9)	0.006	–	–
	Lymphoma	0.63 (0.37–1.1)	0.09	0.81 (0.32–2.1)	0.7
	Others	1.1 (0.22–5.7)	0.9	1.1 (0.42–2.6)	0.9
Febrile neutropenia	No	–	–	1	–
	Yes	–	–	1.3 (0.62–2.8)	0.5

DIC, disseminated intravascular coagulation; rhTM, recombinant human thrombomodulin; AL, acute leukemia; APL, acute promyelocytic leukemia.

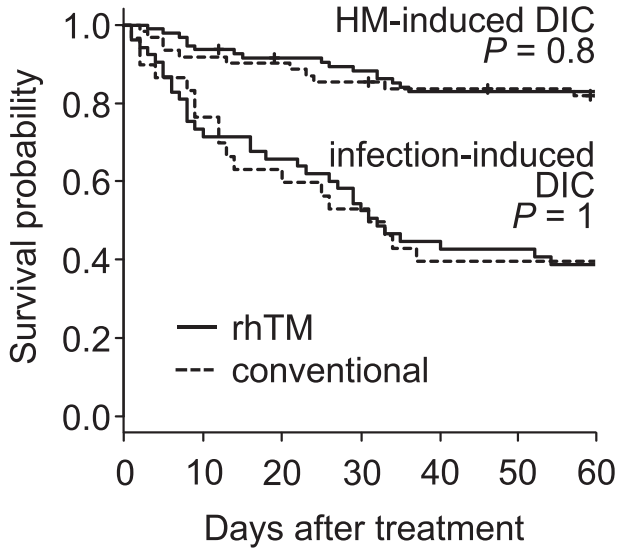

Fig. 4. Survival plot.
The treatment modality did not influence the improvement of both hematologic malignancy (HM)-induced DIC ($P = 0.8$) and infection-induced DIC in HM patients ($P = 1$).

Authors' contributions

S. Chiba directed the study and all authors acquired the data. N. Kurita analyzed data and wrote the first draft of the manuscript. All authors were responsible for data analysis and interpretation, manuscript writing, and final approval of the manuscript, and are accountable for all aspects of the work.

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Table 3
Multivariate analysis of mortality after DIC.

Factors	Level	Hematologic malignancy-induced DIC		Infection-induced DIC	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Treatment	Without rhTM	1	–	1	–
	With rhTM	0.92 (0.42–2.0)	0.9	1.0 (0.57–1.9)	0.9
Age	< 60	1	–	1	–
	≥60	1.1 (0.49–2.4)	0.9	0.88 (0.45–1.7)	0.7
Pretreatment DIC score	< 5	1	–	1	–
	≥5	3.3 (1.4–7.8)	0.007	2.0 (1.1–3.6)	0.02
Pre-existing bleeding tendency	No	1	–	1	–
	Yes	1.6 (0.69–3.5)	0.3	1.3 (0.70–2.5)	0.4
Diagnosis	AL except for APL	1	–	1	–
	APL	0.42 (0.13–1.3)	0.1	–	–
	Lymphoma	1.5 (0.61–3.8)	0.4	1.4 (0.69–3.1)	0.3
	Others	2.5 (0.29–21)	0.4	1.2 (0.55–2.7)	0.6
Febrile neutropenia	No	–	–	1	–
	Yes	–	–	0.58 (0.26–1.3)	0.2

DIC, disseminated intravascular coagulation; rhTM, recombinant human thrombomodulin; AL, acute leukemia; APL, acute promyelocytic leukemia.

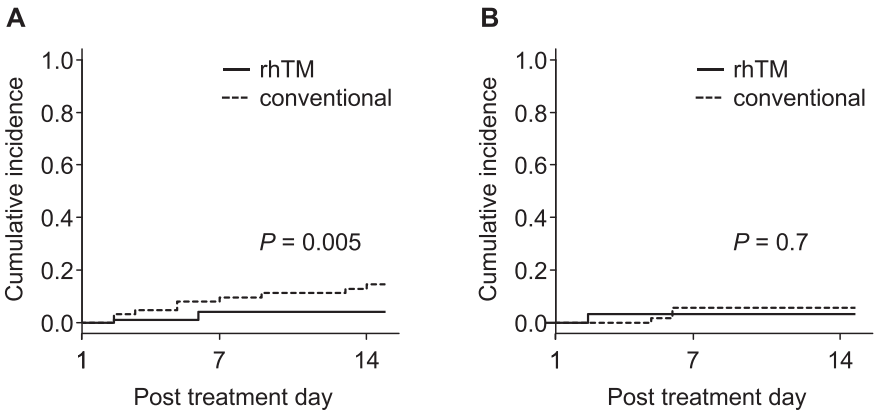

Fig. 5. Hemorrhagic events that led to discontinuation of anticoagulant therapy of hematologic malignancy-induced DIC (A) and infection-induced DIC in hematologic malignancy patients (B).
A higher rate of deterioration of bleeding tendency was seen in the conventional therapy-treated group than in the rhTM-treated group in hematologic malignancy-induced DIC ($P = 0.005$), but not in infection-induced DIC ($P = 0.7$).

References

[1] M. Yanada, T. Matsushita, M. Suzuki, H. Kiyoi, K. Yamamoto, T. Kinoshita, T. Kojima, H. Saito, T. Naoe, Disseminated intravascular coagulation in acute leukemia: clinical and laboratory features at presentation, Eur. J. Haematol. 77 (2006) 282–287, https://doi.org/10.1111/j.1600-0609.2006.00711.x.

[2] T. Uchiumi, A. Fotovati, T. Sasaguri, K. Shibahara, T. Shimada, T. Fukuda, T. Nakamura, H. Izumi, T. Tsuzuki, M. Kuwano, K. Kohno, YB-1 is important for an early stage embryonic development: neural tube formation and cell proliferation, J. Biol. Chem. 281 (2006) 40440–40449, https://doi.org/10.1074/jbc.M605948200.

[3] H. Chang, M.C. Kuo, L.Y. Shih, P. Dunn, P.N. Wang, J.H. Wu, T.L. Lin, Y.S. Hung, T.C. Tang, Clinical bleeding events and laboratory coagulation profiles in acute promyelocytic leukemia, Eur. J. Haematol. 88 (2012) 321–328, https://doi.org/10.1111/j.1600-0609.2011.01747.x.

[4] H. Asakura, Classifying types of disseminated intravascular coagulation: clinical and animal models, J. Intensive Care 2 (2014) 20, https://doi.org/10.1186/2052-0492-2-20.

[5] M. Mohri, E. Sugimoto, M. Sata, T. Asano, The inhibitory effect of recombinant human soluble thrombomodulin on initiation and extension of coagulation—a comparison with other anticoagulants, Thromb. Haemost. 82 (1999) 1687–1693.

[6] H. Saito, I. Maruyama, S. Shimazaki, Y. Yamamoto, N. Aikawa, R. Ohno, A. Hirayama, T. Matsuda, H. Asakura, M. Nakashima, N. Aoki, Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial, J. Thromb. Haemost. 5 (2007) 31–41, https://doi.org/10.1111/j.1538-7836.2006.02267.x.

[7] N. Aikawa, S. Shimazaki, Y. Yamamoto, H. Saito, I. Maruyama, R. Ohno, A. Hirayama, Y. Aoki, N. Aoki, Thrombomodulin alfa in the treatment of infectious patients complicated by disseminated intravascular coagulation: subanalysis from the phase 3 trial, Shock 35 (2011) 349–354, https://doi.org/10.1097/SHK.0b013e318204c019.

[8] K. Yamakawa, S. Fujimi, T. Mohri, H. Matsuda, Y. Nakamori, T. Hirose, O. Tasaki, H. Ogura, Y. Kuwagata, T. Hamasaki, T. Shimazu, Treatment effects of recombinant human soluble thrombomodulin in patients with severe sepsis: a historical control study, Crit. Care 15 (2011) R123, https://doi.org/10.1186/cc10228.

[9] K. Yamakawa, Y. Umemura, M. Hayakawa, D. Kudo, M. Sanui, H. Takahashi, Y. Yoshikawa, T. Hamasaki, S. Fujimi, group JSDICJ-SDs, Benefit profile of anticoagulant therapy in sepsis: a nationwide multicentre registry in Japan, Crit. Care 20 (2016) 229, https://doi.org/10.1186/s13054-016-1415-1.

[10] M. Hayakawa, K. Yamakawa, S. Saito, S. Uchino, D. Kudo, Y. Iizuka, M. Sanui, K. Takimoto, T. Mayumi, K. Ono, group JSDICJDs, Recombinant human soluble thrombomodulin and mortality in sepsis-induced disseminated intravascular coagulation. A multicentre retrospective study, Thromb. Haemost. 115 (2016) 1157–1166, https://doi.org/10.1160/TH15-12-0987.

[11] A.J. Martí-Carvajal, V. Anand, I. Solà, Treatment for disseminated intravascular coagulation in patients with acute and chronic leukemia, Cochrane Database Syst. Rev. (2015) CD008562, , https://doi.org/10.1002/14651858.CD008562.pub3.

[12] T. Ikezoe, A. Takeuchi, M. Isaka, Y. Arakawa, N. Iwabu, T. Kin, K. Anabuki, M. Sakai, A. Taniguchi, K. Togitani, A. Yokoyama, Recombinant human soluble thrombomodulin safely and effectively rescues acute promyelocytic leukemia patients from disseminated intravascular coagulation, Leuk. Res. 36 (2012) 1398–1402, https://doi.org/10.1016/j.leukres.2012.08.012.

[13] N. Takezako, N. Sekiguchi, A. Nagata, C. Homma, Y. Takezako, S. Noto, K. Natori, A. Miwa, Recombinant human thrombomodulin in the treatment of acute myeloid leukemia patients complicated by disseminated intravascular coagulation: retrospective analysis of outcomes between patients treated with heparin and recombinant human thrombomodulin therapy, Thromb. Res. 136 (2015) 20–23, https://doi.org/10.1016/j.thromres.2015.03.029.

[14] H. Yokoyama, N. Takahashi, Y. Katsuoka, M. Inomata, T. Ito, K. Meguro, Y. Kameoka, R. Tsumanuma, K. Murai, H. Noji, K. Ishizawa, S. Ito, Y. Onishi, H. Harigae, T.H. Forum, Evaluation of the safety and efficacy of recombinant soluble thrombomodulin for patients with disseminated intravascular coagulation associated with acute leukemia: multicenter prospective study by the Tohoku Hematology Forum, Int. J. Hematol. 105 (2017) 606–613, https://doi.org/10.1007/s12185-017-2190-8.

[15] N. Kobayashi, T. Maekawa, M. Takada, H. Tanaka, H. Gonmori, Criteria for diagnosis of DIC based on the analysis of clinical and laboratory findings in 345 DIC patients collected by the Research Committee on DIC in Japan, Bibl. Haematol. (1983) 265–275.

[16] M. Singer, C.S. Deutschman, C.W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, R. Bellomo, G.R. Bernard, J.D. Chiche, C.M. Coopersmith, R.S. Hotchkiss, M.M. Levy, J.C. Marshall, G.S. Martin, S.M. Opal, G.D. Rubenfeld, T. van der Poll, J.L. Vincent, D.C. Angus, The third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA 315 (2016) 801–810, https://doi.org/10.1001/jama.2016.0287.

[17] H. Wada, H. Asakura, K. Okamoto, T. Iba, T. Uchiyama, K. Kawasugi, S. Koga, T. Mayumi, K. Koike, S. Gando, S. Kushimoto, Y. Seki, S. Madoiwa, I. Maruyama, A. Yoshioka, subcommittee JSoTHD, Expert consensus for the treatment of disseminated intravascular coagulation in Japan, Thromb. Res. 125 (2010) 6–11, https://doi.org/10.1016/j.thromres.2009.08.017.

[18] H. Wada, K. Okamoto, T. Iba, S. Kushimoto, K. Kawasugi, S. Gando, S. Madoiwa, T. Uchiyama, T. Mayumi, Y. Seki, subcommittee JSoTHD, Addition of recommendations for the use of recombinant human thrombomodulin to the “Expert consensus for the treatment of disseminated intravascular coagulation in Japan”, Thromb. Res. 134 (2014) 924–925, https://doi.org/10.1016/j.thromres.2014.07.033.

[19] D.Y. Lin, Non-parametric inference for cumulative incidence functions in competing risks studies, Stat. Med. 16 (1997) 901–910.

[20] Y. Kanda, Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics, Bone Marrow Transplant. 48 (2013) 452–458, https://doi.org/10.1038/bmt.2012.244.

[21] F. Fourrier, C. Chopin, J. Goudemand, S. Hendrycx, C. Caron, A. Rime, A. Marey, P. Lestavel, Septic shock, multiple organ failure, and disseminated intravascular coagulation. Compared patterns of antithrombin III, protein C, and protein S deficiencies, Chest 101 (1992) 816–823.

[22] K. Bakhtiari, J.C. Meijers, E. de Jonge, M. Levi, Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation, Crit. Care Med. 32 (2004) 2416–2421.

[23] J. Thachil, Disseminated intravascular coagulation - new pathophysiological concepts and impact on management, Expert. Rev. Hematol. 9 (2016) 803–814, https://doi.org/10.1080/17474086.2016.1203250.

[24] D. Mokart, M. Darmon, M. Resche-Rigon, V. Lemiale, F. Pène, J. Mayaux, A. Rabbat, A. Kouatchet, F. Vincent, M. Nyunga, F. Bruneel, C. Lebert, P. Perez, A. Renault, R. Hamidfar, M. Jourdain, A.P. Meert, D. Benoit, S. Chevret, E. Azoulay, Prognosis of neutropenic patients admitted to the intensive care unit, Intensive Care Med. 41 (2015) 296–303, https://doi.org/10.1007/s00134-014-3615-y.

[25] E. Azoulay, D. Mokart, F. Pène, J. Lambert, A. Kouatchet, J. Mayaux, F. Vincent, M. Nyunga, F. Bruneel, L.M. Laisne, A. Rabbat, C. Lebert, P. Perez, M. Chaize, A. Renault, A.P. Meert, D. Benoit, R. Hamidfar, M. Jourdain, M. Darmon, B. Schlemmer, S. Chevret, V. Lemiale, Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium—a groupe de recherche respiratoire en réanimation onco-hématologique study, J. Clin. Oncol. 31 (2013) 2810–2818, https://doi.org/10.1200/JCO.2012.47.2365.

[26] C. Herzog, A. Lorenz, H.J. Gillmann, A. Chowdhury, J. Larmann, T. Harendza, F. Echtermeyer, M. Müller, M. Schmitz, J. Stypmann, D.G. Seidler, M. Damm, S.N. Stehr, T. Koch, K.C. Wollert, E.M. Conway, G. Theilmeier, Thrombomodulin's lectin-like domain reduces myocardial damage by interfering with HMGB1-mediated TLR2 signalling, Cardiovasc. Res. 101 (2014) 400–410, https://doi.org/10.1093/cvr/cvt275.

[27] D. Hoppensteadt, K. Tsuruta, J. Cunanan, J. Hirman, I. Kaul, Y. Osawa, J. Fareed, Thrombin generation mediators and markers in sepsis-associated coagulopathy and their modulation by recombinant thrombomodulin, Clin. Appl. Thromb. Hemost. 20 (2014) 129–135, https://doi.org/10.1177/1076029613492875.

[28] J. Kienast, M. Juers, C.J. Wiedermann, J.N. Hoffmann, H. Ostermann, R. Strauss, H.O. Keinecke, B.L. Warren, S.M. Opal, investigators K, Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation, J. Thromb. Haemost. 4 (2006) 90–97, https://doi.org/10.1111/j.1538-7836.2005.01697.x.

[29] Y. Umemura, K. Yamakawa, H. Ogura, H. Yuhara, S. Fujimi, Efficacy and safety of anticoagulant therapy in three specific populations with sepsis: a meta-analysis of randomized controlled trials, J. Thromb. Haemost. 14 (2016) 518–530, https://doi.org/10.1111/jth.13230.

[30] M. Hayakawa, D. Kudo, S. Saito, S. Uchino, K. Yamakawa, Y. Iizuka, M. Sanui, K. Takimoto, T. Mayumi, K. Ono, T. Azuhata, F. Ito, S. Yoshihiro, K. Hayakawa, T. Nakashima, T. Ogura, E. Noda, Y. Nakamura, R. Sekine, Y. Yoshikawa, M. Sekino, K. Ueno, Y. Okuda, M. Watanabe, A. Tampo, N. Saito, Y. Kitai, H. Takahashi, I. Kobayashi, Y. Kondo, W. Matsunaga, S. Nachi, T. Miike, S. Takauji, K. Umakoshi, T. Todaka, H. Kodaira, K. Andoh, T. Kasai, Y. Iwashita, H. Arai, M. Murata, M. Yamane, K. Shiga, N. Hori, Antithrombin supplementation and mortality in sepsis-induced disseminated intravascular coagulation: a multicenter retrospective observational study, Shock 46 (2016) 623–631, https://doi.org/10.1097/SHK.0000000000000727.

[31] N. Yasuda, K. Goto, Y. Ohchi, T. Abe, H. Koga, T. Kitano, The efficacy and safety of antithrombin and recombinant human thrombomodulin combination therapy in patients with severe sepsis and disseminated intravascular coagulation, J. Crit. Care 36 (2016) 29–34, https://doi.org/10.1016/j.jcrc.2016.06.008.

[32] T. Iba, A. Hagiwara, D. Saitoh, H. Anan, Y. Ueki, K. Sato, S. Gando, Effects of combination therapy using antithrombin and thrombomodulin for sepsis-associated disseminated intravascular coagulation, Ann. Intensive Care 7 (110) (2017), https://doi.org/10.1186/s13613-017-0332-z.

[33] H. Wada, J. Thachil, M. Di Nisio, P. Mathew, S. Kurosawa, S. Gando, H.K. Kim, J.D. Nielsen, C.E. Dempfle, M. Levi, C.H. Toh, Haemostasis TSSCoDotISoT, Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines, J. Thromb. Haemost. (2013), https://doi.org/10.1111/jth.12155.

[34] E.J. Libourel, C.P.W. Klerk, Y. van Norden, M.P.M. de Maat, M.J. Kruip, P. Sonneveld, B. Löwenberg, F.W.G. Leebeek, Disseminated intravascular coagulation at diagnosis is a strong predictor for thrombosis in acute myeloid leukemia, Blood 128 (2016) 1854–1861, https://doi.org/10.1182/blood-2016-02-701094.

[35] H. Wada, Y. Wakita, T. Nakase, M. Shimura, K. Hiyoyama, S. Nagaya, Y. Mori, H. Shiku, Outcome of disseminated intravascular coagulation in relation to the score when treatment was begun. Mie DIC Study Group, Thromb. Haemost. 74 (1995) 848–852.

[36] T. Aota, H. Wada, N. Fujimoto, K. Sugimoto, Y. Yamashita, T. Matsumoto, K. Ohishi, K. Suzuki, H. Imai, K. Kawasugi, S. Madoiwa, H. Asakura, N. Katayama, The valuable diagnosis of DIC and pre-DIC and prediction of a poor outcome by the evaluation of diagnostic criteria for DIC in patients with hematopoietic injury established by the Japanese Society of Thrombosis and Hemostasis, Thromb. Res. 147 (2016) 80–84, https://doi.org/10.1016/j.thromres.2016.09.028.

[37] T. Iba, M. Di Nisio, J. Thachil, H. Wada, H. Asakura, K. Sato, D. Saitoh, A proposal of the modification of Japanese Society on Thrombosis and Hemostasis (JSTH) disseminated intravascular coagulation (DIC) diagnostic criteria for sepsis-associated DIC, Clin. Appl. Thromb. Hemost. (2017) 1076029617720069, , https://doi.org/10.1177/1076029617720069.

[38] A. Rhodes, L.E. Evans, W. Alhazzani, M.M. Levy, M. Antonelli, R. Ferrer, A. Kumar, J.E. Sevransky, C.L. Sprung, M.E. Nunnally, B. Rochwerg, G.D. Rubenfeld, D.C. Angus, D. Annane, R.J. Beale, G.J. Bellinghan, G.R. Bernard, J.D. Chiche, C. Coopersmith, D.P. De Backer, C.J. French, S. Fujishima, H. Gerlach, J.L. Hidalgo, S.M. Hollenberg, A.E. Jones, D.R. Karnad, R.M. Kleinpell, Y. Koh, T.C. Lisboa, F.R. Machado, J.J. Marini, J.C. Marshall, J.E. Mazuski, L.A. McIntyre, A.S. McLean, S. Mehta, R.P. Moreno, J. Myburgh, P. Navalesi, O. Nishida, T.M. Osborn, A. Perner, C.M. Plunkett, M. Ranieri, C.A. Schorr, M.A. Seckel, C.W. Seymour, L. Shieh, K.A. Shukri, S.Q. Simpson, M. Singer, B.T. Thompson, S.R. Townsend, T. Van der Poll, J.L. Vincent, W.J. Wiersinga, J.L. Zimmerman, R.P. Dellinger, Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016, Intensive Care Med. 43 (2017) 304–377, https://doi.org/10.1007/s00134-017-4683-6.