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Perioperative & Critical Care: Short Report

Early Thrombomodulin Improved Disseminated Intravascular Coagulation After Cardiac Surgery

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ABSTRACT

BACKGROUND Disseminated intravascular coagulation (DIC) is a fatal complication in postoperative patients. Recombinant human thrombomodulin (rhTM) has been used to treat DIC in some settings; however, the use of rhTM as a therapy for DIC has not been established in the field of cardiovascular surgery. This study aimed to investigate the efficacy and optimal timing of rhTM treatment in patients with DIC after cardiovascular operation.

METHODS Data were retrospectively collected from patients in whom DIC developed after open cardiac operation and who were treated with rhTM. DIC scores, laboratory data, and major complications were assessed. The end point was the 30-day all-cause mortality. Risk factors influencing mortality were extracted for the survival and nonsurvival groups.

RESULTS A total of 27 patients with postoperative DIC were treated with rhTM. The 30-day mortality rate was 51.9%. Multivariate analysis revealed that rhTM administration ≥5 days after DIC diagnosis was associated with increased mortality. The early administration group (≤4 days after DIC diagnosis) showed significantly improved DIC scores, reduced C-reactive protein levels, and increased number of platelets after rhTM treatment compared with before treatment.

CONCLUSIONS Early administration of rhTM after DIC diagnosis was associated with a decreased 30-day mortality rate in patients after cardiovascular operation.

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The pathophysiologic mechanism of postoperative disseminated intravascular coagulation (DIC) is generally related to surgical invasion, systemic inflammatory response syndrome, and infection. In patients who undergo cardiovascular operation, various factors, such as circulatory insufficiency, coagulation disorder caused by cardiopulmonary bypass use, and activation of the coagulation cascade by the aneurysm or dissected aorta, may induce DIC. This can rapidly lead to organ failure and without intervention has a high mortality rate.

During the past 2 decades, clinical studies have shown the efficacy of recombinant human thrombomodulin (rhTM) for treatment of patients in whom DIC develops as a result of various conditions[1,2]; however, few reports have focused on DIC after cardiovascular operation. Here, we evaluated the efficacy, timing, and

IN SHORT

- In patients in whom disseminated intravascular coagulation (DIC) developed after cardiovascular operation, the initial timing of recombinant human thrombomodulin (rhTM) administration after DIC diagnosis was the only independent risk factor of 30-day mortality. Early administration of rhTM within 4 days decreased the mortality rate.
- Early administration of rhTM showed a significant decrease in fibrinogen and C-reactive protein levels, an increase in platelet count, and an improved DIC score after rhTM treatment.

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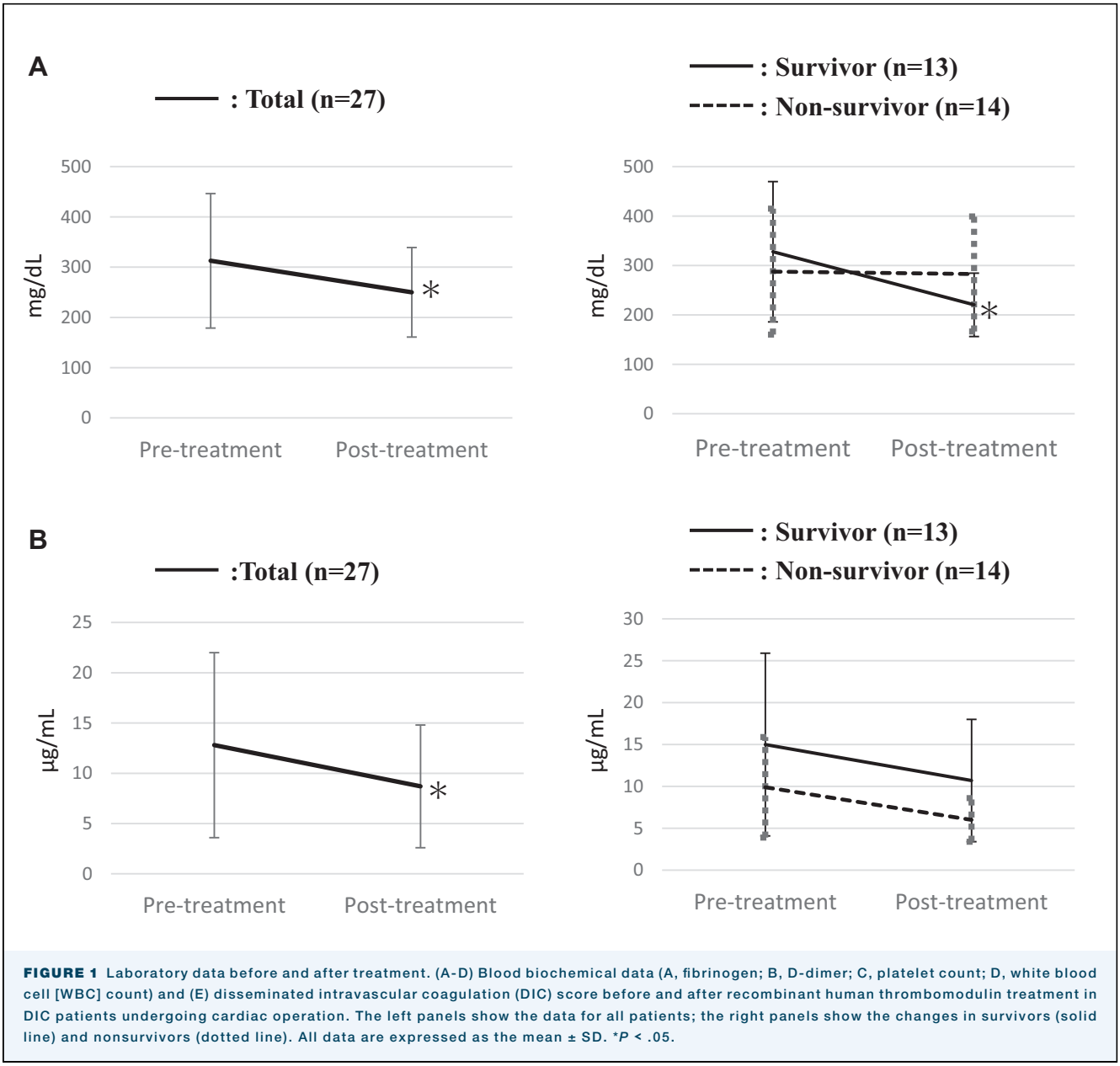

FIGURE 1 Laboratory data before and after treatment. (A-D) Blood biochemical data (A, fibrinogen; B, D-dimer; C, platelet count; D, white blood cell [WBC] count) and (E) disseminated intravascular coagulation (DIC) score before and after recombinant human thrombomodulin treatment in DIC patients undergoing cardiac operation. The left panels show the data for all patients; the right panels show the changes in survivors (solid line) and nonsurvivors (dotted line). All data are expressed as the mean ± SD. *P < .05.

clinical course of rhTM treatment in patients with DIC induced by cardiovascular operation.

PATIENTS AND METHODS

PATIENTS AND STUDY DESIGN. This 2-center (Tohoku University Hospital and Sendai Kousei Hospital, Japan), retrospective, observational study included patients in whom DIC developed after cardiovascular operation and who were subsequently treated with rhTM between January 2011 and December 2015. DIC scores were calculated using the Japanese Association for Acute Medicine DIC criteria (Supplemental Table 1). Patients with active life-threatening bleeding were excluded from this study. This study was approved by the institutional review board of Tohoku University Graduate School of Medicine. Informed consent was obtained from all patients.

Blood samples were collected at the beginning of rhTM administration and 2 days after treatment. Samples were analyzed for white blood cells, platelets, fibrinogen, fibrin degradation products, prothrombin time, activated partial thromboplastin time, D-dimer, antithrombin III, and C-reactive protein (CRP) levels.

RHTM TREATMENT. The initiation of rhTM treatment was determined by a multidisciplinary team on

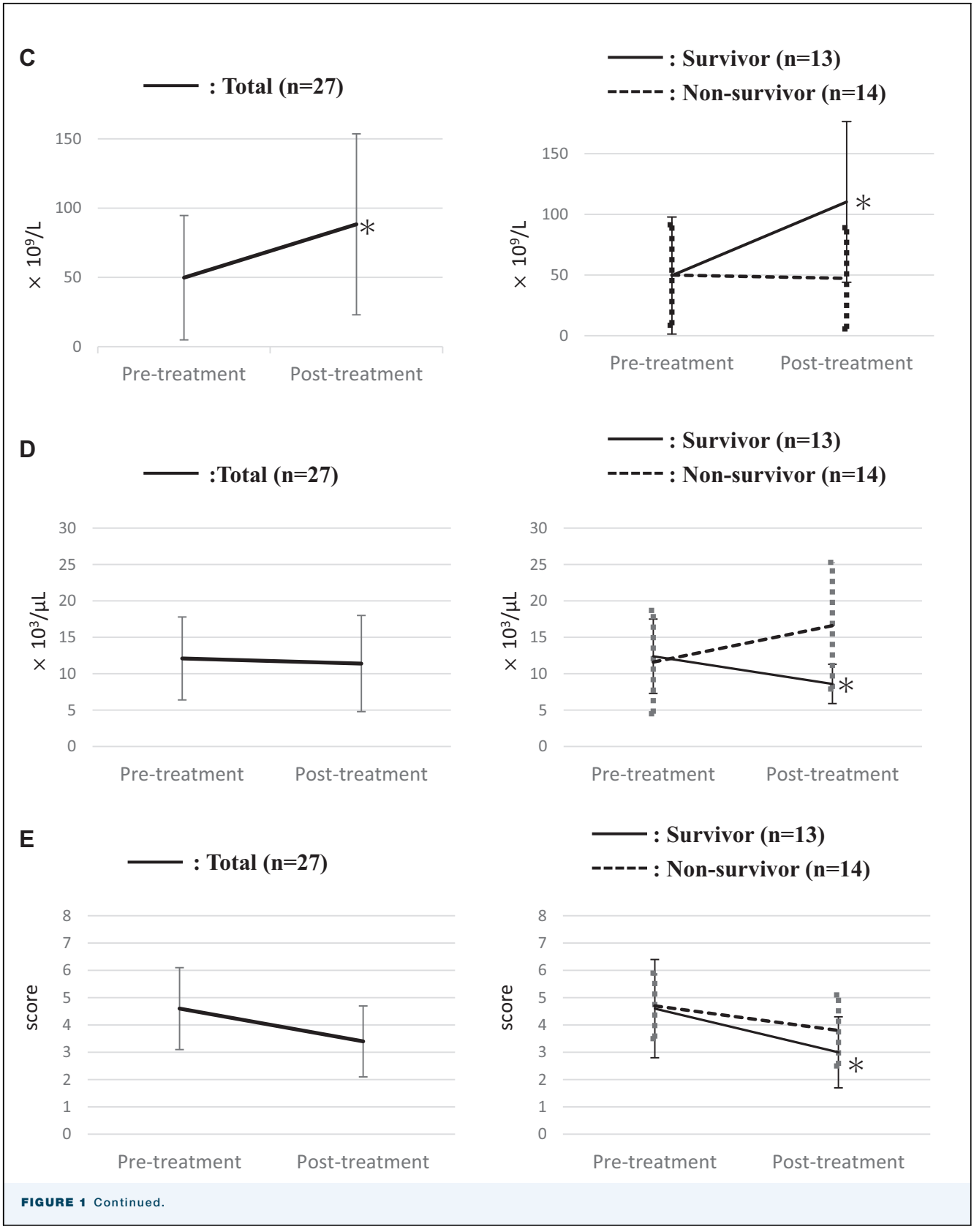

FIGURE 1 Continued.

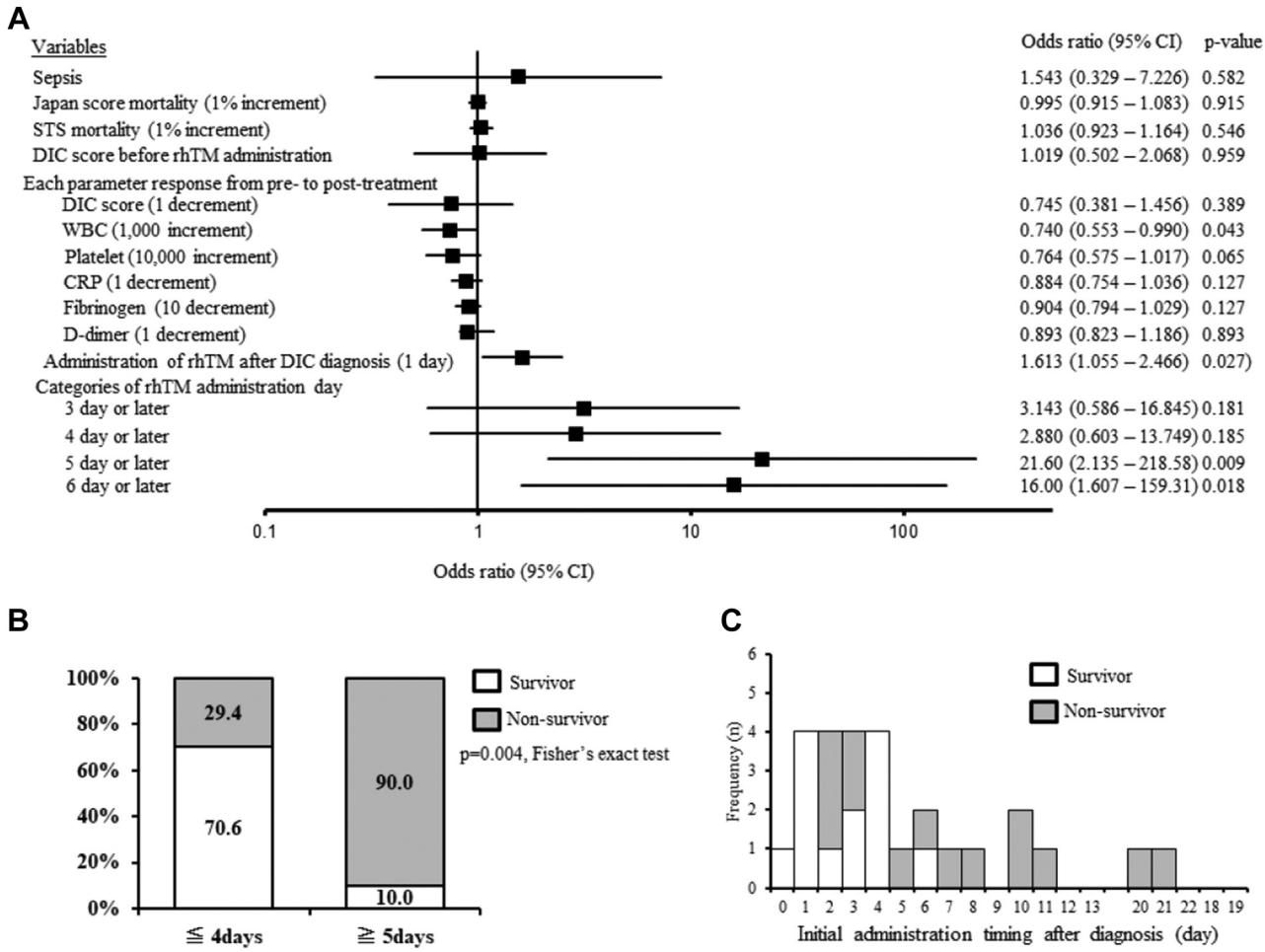

FIGURE 2 Timing of administration after diagnosis of disseminated intravascular coagulation (DIC). (A) Univariate logistic regression analysis showed that an independent risk factor for 30-day mortality was late administration (≥5 days) of recombinant human thrombomodulin (rhTM) after DIC diagnosis. (B) The mortality rate significantly increased in patients treated with rhTM ≥5 days (P = .004) after DIC diagnosis. (C) Distribution of rhTM administration timing after treatment. (CRP, C-reactive protein; STS, The Society of Thoracic Surgeons; WBC, white blood cell.)

the basis of clinical data. rhTM was administered according to the manufacturer's protocol and based on a previous study.[3] The treatment outcomes were evaluated on the basis of the overall survival rate at 30 days, and suspected adverse events were assessed.

STATISTICAL ANALYSIS. Categorical variables are represented as absolute numbers or percentages, and Fisher exact test or the χ^2 test was used for comparison between groups. Intergroup comparison of continuous variables was performed by the Student t-test or Welch t-test; intragroup comparison (pre-treatment vs post-treatment) used a paired t-test. Logistic regression analysis was used to identify the independent risk factors for 30-day mortality. Variables included in the logistic regression models were those considered clinically relevant and those with $P < .05$ in the intergroup or intragroup comparisons. Variables with a $P < .1$ in univariate analysis were used as independent variables in a stepwise logistic regression analysis. Results are expressed as odds ratios and 95% CIs.

RESULTS

During the study period, 27 patients with postoperative DIC were treated with rhTM; 13 of these patients survived for 30 days after treatment (51.9% mortality rate). There were no significant differences in the baseline characteristics of the patients between the survivor and nonsurvivor groups, except for the timing of rhTM

TABLE 1 Basic Characteristics (rhTM Administration ≤4 days vs ≥5 Days After Diagnosis)

Characteristic	≤4 Days (n = 17)	≥5 Days (n = 10)	*P* Value
Age, y	66.1 ± 11.2	67.5 ± 10.2	.743
Male	14 (82.4)	8 (80.0)	1.000
Body mass index, kg/m^2	26.3 ± 4.6	25.1 ± 6.0	.578
Severity of illness			
STS mortality, %	8.0 ± 9.9	3.9 ± 2.7	.383
STS complication, %	34.8 ± 24.6	20.4 ± 8.0	.080
Japan score mortality, %	7.9 ± 8.4	15.1 ± 15.2	.129
Japan score complication, %	41.5 ± 13.0	51.4 ± 18.1	.198
Medical history			
Hypertension	12 (70.6)	9 (90.0)	.363
Diabetes	1 (5.9)	2 (20.0)	.535
Chronic renal failure	5 (29.4)	3 (30.0)	1.000
Cerebrovascular disease	1 (5.9)	0 (0)	1.000
Operation			.297
Aorta	9 (52.9)	2 (20.0)	
Valve	2 (11.8)	2 (20.0)	
Coronary artery bypass grafting	0 (0)	1 (10.0)	
Combined above	1 (5.9)	2 (20.0)	
Left ventricular assist device	4 (23.5)	1 (10.0)	
Transplantation	0 (0)	1 (10.0)	
Others	1 (5.9)	1 (10.0)	
Sepsis	10 (58.8)	6 (60.0)	1.000
Bleeding complication	2 (11.8)	1 (10.0)	1.000
30-day survival	12 (70.6)	1 (10.0)	.004
Diagnosis of DIC, POD	24.1 ± 18.5	36.2 ± 48.3	.462
rhTM starting date, POD	26.4 ± 18.5	46.6 ± 47.5	.127
rhTM ending date, POD	32.8 ± 22.1	53.5 ± 49.5	.146
DIC score before rhTM treatment	3.0 ± 1.3	3.8 ± 1.3	.707
Initial administration timing of rhTM, d	2.4 ± 1.3	10.4 ± 5.7	.001
Dosing period of rhTM, d	7.2 ± 5.8	7.3 ± 3.8	.952

Categorical variables are presented as number (percentage). Continuous variables are presented as mean ± SD. DIC, disseminated intravascular coagulation; POD, postoperative day; rhTM, recombinant human thrombomodulin; STS, The Society of Thoracic Surgeons.

administration (Supplemental Table 2). The initial rhTM administration was 2.6 ± 1.8 days after DIC diagnosis in the survivor group and 7.9 ± 6.2 days in the nonsurvivor group (P = .008). During rhTM treatment, 3 of 27 patients (11.1%) had bleeding complications, 2 with gastrointestinal hemorrhage and 1 with subarachnoid hemorrhage.

ANALYSIS OF RHTM TREATMENT EFFECTS. Figure 1 shows the results of the blood analysis. There were significant decreases in fibrinogen (P = .037) and D-dimer (P = .024) and a significant increase in platelet count (P = .012) in all treated patients compared with before treatment. There were significant decreases in fibrinogen (P = .03) and white blood cell counts (P = .047) in the posttreatment survivor group compared with the pretreatment survivor group but not in the nonsurvivor group (P = .87 and P = .07, respectively). The platelet count was significantly increased in the posttreatment survivor group compared with the pretreatment survivor group (P = .002) but not in the nonsurvivor group (P = .90). The DIC score decreased in the posttreatment survivor group compared with the pretreatment survivor group (P = .042). All laboratory data are shown in Supplemental Table 3.

RISK FACTORS OF 30-DAY MORTALITY. All variables were entered into the logistic regression analysis. Univariate logistic regression analysis showed that an independent incremental risk factor for 30-day mortality was late administration of rhTM (≥5 days) after DIC diagnosis (Figure 2a). Receiver operating characteristic analysis identified the cutoff day of rhTM administration for survival as 4.5 days (area under the curve, 0.802; sensitivity, 64.3%; specificity, 92.3%).

EARLY (≤4 DAYS) VS LATE (≥5 DAYS) RHTM ADMINISTRATION. There were no significant differences in patient characteristics and preoperative risk factors

TABLE 2 Efficacy of rhTM Treatment (Pre- and Post-Treatment Values in the Early and Late Administration Groups)

	All		Administration at ≤4 Days Early Administration Group: E		Administration at ≥5 days Late Administration Group: L		E Pre vs Post	L Pre vs Post	Pre E vs L	Post E vs L
Variable	Pre	Post	Pre	Post	Pre	Post	*P*	*P*	*P*	*P*
DIC score	4.6 ± 1.5	3.4 ± 1.3	4.5 ± 1.7	3.0 ± 1.3	4.8 ± 1.5	3.8 ± 1.3	.048	.229	.707	.264
FDP, μg/mL	24.9 ± 19.2	18.5 ± 10.4	23.6 ± 11.6	19.4 ± 8.6	26.7 ± 27.6	17.3 ± 13.2	.441	.194	.774	.718
D-dimer, μg/mL	12.8 ± 9.2	8.7 ± 6.1	11.9 ± 5.1	8.2 ± 5.3	13.9 ± 13.4	9.4 ± 7.5	.115	.157	.704	.727
PT-INR	1.32 ± 0.56	1.39 ± 0.56	1.21 ± 0.46	1.28 ± 0.53	1.47 ± 0.68	1.56 ± 0.60	0.761	0.505	0.373	0.326
Fibrinogen, mg/dL	312.7 ± 133.8	243.9 ± 89.1	304.3 ± 131.9	214.0 ± 66.8	326.7 ± 148.3	293.7 ± 105.0	.042	.539	.758	.083
Platelets, $\times 10^9$/L	49.8 ± 44.9	88.3 ± 65.3	53.2 ± 47.0	103.8 ± 68.6	43.4 ± 43.4	59.3 ± 50.9	.007	.572	.656	.150
ATIII, %	63.3 ± 12.9	61.9 ± 16.8	66.6 ± 13.5	65.1 ± 20.1	58.3 ± 11.2	57.0 ± 9.5	.860	.865	.240	.316
APTT, s	64.3 ± 27.3	59.4 ± 28.7	57.2 ± 26.6	49.3 ± 15.9	74.9 ± 27.0	74.7 ± 37.9	.405	.981	.232	.170
WBCs, $\times 10^3/\mu$L	12.1 ± 5.7	11.4 ± 6.6	11.6 ± 4.2	10.04.9	13.1 ± 8.1	14.0 ± 8.9	.386	.794	.667	.206

Values are reported as mean ± SD. APTT, activated partial thromboplastin time; ATIII, antithrombin III; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; FDP, fibrin/fibrinogen degradation products; PT-INR, prothrombin time–international normalized ratio; WBCs, white blood cells.

between the early and late administration groups (Table 1). In addition, there were no significant differences in DIC scores or pretreatment laboratory data between these 2 groups (Table 2). The mortality rate was significantly increased in patients treated with rhTM ≥5 days after DIC diagnosis compared with those treated early ($P = .004$; Figure 2b). The distribution of the timing of rhTM administration is shown in Figure 2c.

COMMENT

This study demonstrated that rhTM treatment significantly increased platelet count and decreased D-dimer and fibrinogen in all patients. The survivor group significantly improved DIC scores. Among the factors composing the DIC score, only the number of platelets was improved by treatment. Platelet count was not significantly increased in the nonsurvivor group; hence, an increased platelet count might be an important factor in DIC treatment. rhTM directly inactivates the coagulant activity of thrombin and indirectly activates protein C,[1] thus inhibiting aggregation and preserving consumption of platelets. Platelets also participate in the response to infection by interacting with the vascular endothelium or stimulating intravascular immune cells.[4] An increased number of platelets may enhance the innate immune system in sepsis-induced DIC.

Reports have revealed that the lectin-like domain of thrombomodulin suppresses inflammation independent of coagulant activity.[5] This domain has an inhibitory effect on high-mobility group box 1 (HMGB1), which is a procoagulant and proinflammatory mediator (Supplemental Figure), and may also interfere with leukocyte adhesion, complement activation, and cytokine production. In this report, there was a significant decrease in the number of white blood cells, and CRP levels were considerably lower after treatment in the survivor group. These data indicate that rhTM may have anti-inflammatory effects in DIC patients. Cardiovascular operation may cause postoperative DIC through activation of coagulation, cytokine inflammation, and fibrinolytic pathways during cardiopulmonary bypass. rhTM should therefore have anticoagulant and anti-inflammatory effects in this setting.

Logistic regression analysis demonstrated that the initial timing of rhTM administration was the only independent risk factor of 30-day mortality. The early administration group (≤4 days) after DIC diagnosis had significantly decreased fibrinogen and CRP levels, increased platelets, and improved DIC score after treatment. The precise mechanism of the therapeutic time window has not been elucidated. HMGB1 is considered an essential facilitator in acute inflammatory diseases and may be involved very early after inflammatory onset. In ischemic mice, systemic HMGB1 levels increased in a time-dependent manner.[6] In mice treated with endotoxin, tumor necrosis factor and interleukin 1β reach toxic levels within a few hours, followed by HMGB1 release and the onset of lethality.[7] Serum HMGB1 levels were significantly increased in critically septic patients, and HMGB1 levels were significantly higher in patients who did not survive than in survivors.[8] This suggests that inhibition of HMGB1 by earlier intervention might limit the subsequent inflammatory responses. This study indicated a therapeutic window of 4 days for patients with sepsis.

The safety of rhTM should be investigated in further large-scale studies. The 3 patients with bleeding complications in this study were all left ventricular assist device patients who needed anticoagulant therapy. A

few reports have combined rhTM and anticoagulant therapy for DIC[9]; however, the risks and benefits of concomitant therapy remain controversial. Nonetheless, the efficacy of early rhTM treatment of patients with DIC after cardiovascular operation was indicated. This report demonstrated that early diagnosis and treatment within 4 days after diagnosis is critical for improving the prognosis of DIC.

The Supplemental Material can be viewed in the online version of this article [http://doi.org/10.1016/j.atssr.2023.02.012] on http://www.annalsthoracicsurgery.org.

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DISCLOSURES

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REFERENCES

1. Kato T, Sakai T, Kato M, et al. Recombinant human soluble thrombomodulin administration improves sepsis-induced disseminated intravascular coagulation and mortality: a retrospective cohort study. *Thromb J*. 2013;11:3.

2. Vincent JL, Francois B, Zabolotskikh I, et al. Effect of a recombinant human soluble thrombomodulin on mortality in patients with sepsis-associated coagulopathy: the SCARLET randomized clinical trial. *JAMA*. 2019;321:1993-2002.

3. Saito H, Maruyama I, Shimazaki S, et al. 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*. 2007;5:31-41.

4. Deppermann C, Kubes P. Platelets and infection. *Semin Immunol*. 2016;28:536-545.

5. Li YH, Kuo CH, Shi GY, Wu HL. The role of thrombomodulin lectin-like domain in inflammation. *J Biomed Sci*. 2012;19:34.

6. Nakano T, Nakamura Y, Matsuyama K, et al. Long-term treatment with thrombomodulin improves functional outcomes after cerebral ischemia even if administration is delayed. *Thromb Haemost*. 2019;119:467-478.

7. Wang H, Bloom O, Zhang M, et al. HMG-1 as a late mediator of endotoxin lethality in mice. *Science*. 1999;285:248-251.

8. Wang H, Yang H, Czura CJ, Sama AE, Tracey KJ. HMGB1 as a late mediator of lethal systemic inflammation. *Am J Respir Crit Care Med*. 2001;164:1768-1773.

9. Umemura Y, Yamakawa K, Hayakawa M, Kudo D, Fujimi S. Concomitant versus individual administration of antithrombin and thrombomodulin for sepsis-induced disseminated intravascular coagulation: a nationwide Japanese registry study. *Clin Appl Thromb Hemost*. 2018;24:734-740.