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Complete List of Authors:	Hagiwara, Akiyoshi; National Center for Global Health and Medicine, Emergency Medicine and Critical Care Uemura, Tatsuki; National Center for Global Health and Medicine, Emergency Medicine and Critical Care Wataru , Matsuda; National Center for Global Health and Medicine, Emergency Medicine and Critical Care Kimura, Akio; National Center for Global Health and Medicine, Department of Emergency Medicine and Critical Care
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Can recombinant human thrombomodulin increase survival among patients with severe septic-induced disseminated intravascular coagulation: a single-center, open-label, randomized controlled trial

Akiyoshi Hagiwara, MD, PhD; Tatsuki Uemura, MD; Wataru Matsuda, MD; and Akio Kimura, MD, PhD

Department of Emergency Medicine and Critical Care, National Center for Global Health and Medicine,

1-21-1 Toyama, Shinjyuku-ku, Tokyo,

162-8655, Japan

Corresponding author

Akiyoshi Hagiwara, MD, PhD

Department of Emergency Medicine and Critical Care, National Center for Global Health and Medicine

Address; 1-21-1 Toyama, Shinjyuku-ku, Tokyo, 162-8655 Japan

Tel; +81-3-3202-7181, Fax; +81-3-3207-1038

Email: ahagiwar@hosp.ncgm.go.jp

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Abstract

Objective: To determine whether treatment with recombinant human thrombomodulin (rhTM) increases survival among severe septic patients with sepsis-induced disseminated intravascular coagulation (DIC)

Design: Single-center, open-label, randomized controlled trial

Setting: Single tertiary hospital

Participant: 92 severe septic patients with sepsis-induced DIC

Interventions: Patients with DIC scores ≥4, as defined by the Japanese Association of Acute Medicine, were diagnosed with DIC. Randomization was balanced using the envelope method. The treatment group (rhTM group, n=47) was intravenously treated with rhTM within 24 h of admission (day 0), and the control group (n=45) did not receive any anti-coagulants, except in cases of deep venous thrombosis and pulmonary embolism.

Primary and secondary measurements: Data were collected on days 0 (admission), 1, 2, 3, 5, 7, and 10. The primary outcome was survival at 90 days. The secondary endpoints comprised changes in DIC scores; platelet counts; fibrinogen degradation product (FDP), D-dimer, antithrombin III (AT-III), and C-reactive protein (CRP) levels; and Sequential Organ Failure Assessment (SOFA) scores. All analyses were conducted

on an intent-to-treat basis.

Main Results: The 90-day survival rates were 73% and 72% in the control and rhTM groups, respectively (p=0.94, log rank test). Meanwhile, the rates of recovery from DIC (<4) were significantly higher in the rhTM group than in the control group (p=0.001, log rank test). Change rates from baseline (CRBs) of FDP and D-dimer levels were significantly lower in the rhTM group than in the control group, beginning from day 1. CRBs of platelet counts, AT-III and CRP levels, and SOFA values were not significantly different between the groups at any time point.

Conclusion: rhTM treatment decreased FDP and D-dimer levels and facilitated DIC recovery in severe septic patients with sepsis-induced DIC. However, the treatment did not improve survival in this cohort.

Strengths of this study

- This study is the first randomized controlled trial for patients with sepsis who were diagnosed with DIC according to the pre-specified criteria.
- The 90-day survival rates were 73% and 72% in the control and rhTM groups, respectively (p=0.94, log rank test).
- The rates of recovery from DIC (DIC score < 4) were significantly higher in the

rhTM group than in the control group (p=0.001, log rank test).

- Although rhTM treatment facilitated DIC recovery in severe septic patients, the treatment did not improve survival in this cohort.

Limitations

- This study is for an open label RCT, but not a double blind study.
- This study might show a difference in disease severity as compared to other studies.
- The small number of patients in our study may have caused no significant result.

Introduction

Thrombomodulin is a cell membrane protein expressed on vascular endothelium. Although thrombomodulin specifically binds to thrombin and inhibits thrombin activity, resulting in anti-coagulant action, it also has anti-inflammatory effects and regulates high mobility group box 1 (HMGB1) protein activity, a lethal systemic inflammation mediator. [1, 2]

In Japan, a multi-center, prospective, randomized, double-blind, phase III clinical trial [3] of recombinant thrombomodulin (rhTM), an anti-coagulant agent used for disseminated intravascular coagulopathy (DIC), was performed from 2000 to 2005 and included 234 patients with DIC caused by infection or hematologic malignancy. Results showed that although rhTM was associated with a significantly higher DIC resolution rate than heparin, this rate was not significantly different for patients with infection. Further, no difference in 28-day mortality rates of patients with infection or hematologic malignancy was observed. The trial had several weaknesses: 1) the primary outcome was the DIC resolution rate, which is a physiological parameter and 2) the control group included patients with DIC who were treated with heparin, which is not the established and standard treatment for sepsis-induced coagulopathy [4].

In 2011, Aikawa et al. performed a retrospective subanalysis of the phase III

trial including only the patients with sepsis-induced DIC. They reported that 28-day mortality rates were significantly lower for patients in whom DIC was resolved than in those in whom DIC was not resolved; this tendency was more pronounced in the rhTM group than in the heparin treatment group. [5] However, this retrospective subanalysis study did not reveal that rhTM decreased mortality.

In 2011, Yamakawa et al. [6] reported a retrospective historical control study with the mortality rate as the primary outcome. Twenty severe septic patients with sepsis-induced overt DIC (DIC criteria of the International Society on Thrombosis and Haemostasis) who received rhTM between November 2008 and October 2009 were compared with 45 patients who did not receive rhTM between January 2006 and September 2008. The 28-day mortality rate was 25% for the rhTM group versus 47% for the control group. The Sequential Organ Failure Assessment (SOFA) score and C-reactive protein (CRP) and fibrinogen degradation product (FDP) levels were significantly decreased in the rhTM group, whereas the platelet counts were significantly increased. Further, rhTM treatment also improved respiratory function in patients with sepsis-induced DIC. [7]

In 2013, a retrospective cohort study adjusted by the propensity score was performed in patients with Japanese Association for Acute Medicine (JAAM) DIC

scores ≥ 4 who required mechanical ventilation, exhibited multiple organ failure, and presented with platelet counts <80,000/mm^3. Mortality rates were significantly lower in patients treated with rhTM than in those who did not receive the therapy [8]. Although these studies investigated the mortality rate as the primary outcome, they were all retrospective cohort studies, which had certain biases.

In 2013, Vincent et al. reported a phase IIb double-blind randomized controlled trial (RCT) of rhTM, [9] in which patients who fulfilled the DIC criteria of the International Society on Thrombosis and Haemostasis were treated with rhTM or a placebo. Results showed that the 28-day mortality rate tended to be lower in the rhTM group.

It remains unclear whether rhTM is effective in treating severe septic patients with sepsis-induced DIC. Therefore, studies with a high evidence level are required. Our open-label RCT aimed to investigate whether rhTM treatment increases 72-h, 28-day, and 90-day survival rates in patients with severe sepsis and JAAM DIC scores ≥ 4 [10]).

Materials and Methods

This single-center open-label RCT was approved by our institutional ethics committee (NCGM-G-001163-00). Written informed consent was obtained from all participating patients or their legal representatives. Patients aged ≥16 years who were transferred to our hospital with severe sepsis or septic shock were enrolled if their JAAM DIC scores were ≥4 within 24 h of admission (Table 1). The exclusion criteria were 1) refusal to participate; 2) refusal of aggressive intensive treatment, including hemodialysis, mechanical ventilation, and catecholamine administration; 3) emergency surgery within 24 h of admission; 4) intracranial, pulmonary, and/or intestinal hemorrhage; 5) fulminant hepatitis, decompensated liver cirrhosis, or other irreversible severe hepatic disease; 6) past history of hypersensitivity to rhTM; 7) pregnancy or potential pregnancy; and 8) inadequacy for study participation as judged by an attending physician. In the latter case, the attending physician described the reasons for exclusion in the medical record, which was verified by the investigators.

Number of cases and study duration

When our study was planned, the report by Yamakawa et al. [6]) was the only study that investigated rhTM efficacy in severe septic patients with sepsis-induced DIC. Therefore, the required number of patients was calculated based on their report. When

the observation and follow-up periods were set as 2 years and 90 days, respectively, each group required 47 patients to achieve 80% power with α=0.05. At our institute, 53 and 52 patients with severe sepsis or septic shock fulfilled the JAAM DIC criteria and did not undergo emergency surgery within 24 h after admission were admitted in 2010 and 2011, respectively. The number of patients required for the 2-year study was estimated to be 100. The enrollment period was August 2012 to July 2014.

Randomization

Patients who fulfilled the inclusion criteria were randomized into the rhTM or control group using the envelope method. Each opaque envelope enclosed a piece of paper specifying either rhTM or control group assignment. We created 50 envelopes for each group assignment, shuffled them, and placed them in the designated storage box. Pre-registered co-investigators randomly selected envelopes from the box and treated patients according to group assignment. On both the envelope and the enclosed form, the co-investigator's name, date, and other associated information were written by the principal investigator.

Treatment protocol

In both groups, patients were treated under the Surviving Sepsis Campaign 2008 Guideline, [11] in which grade I ("recommendation as strong") denoted mandatory treatment and grade II ("recommendation as weak") required treatment according to the attending physician's judgment. During the initial management period, a staff physician in the emergency department oversaw whether grade I treatment was performed by attending physicians. Before patients were hospitalized, compliance with grade I treatment was confirmed in the morning and evening conference by the chief physician.

The attending physician administered rhTM to patients within 3 h after randomization. rhTM (380 U/kg) was intravenously administered for 30 min.

Treatment was performed for a maximum of 6 days. When the JAAM DIC score was <4, rhTM treatment was terminated. In the control group, no anti-coagulant agent was administered, except in cases of deep venous thrombosis and pulmonary embolism, for which unfractionated heparin was administered. Unfractionated heparin was also administered to patients in the rhTM group with deep venous thrombosis and pulmonary embolism.

Investigated parameters

We obtained the following scores and laboratory data at the time of

randomization: Acute Physiology and Chronic Health Evaluation II (APACHE IIl), SOFA, and JAAM DIC scores; prothrombin time/international normalized ratio (PT-INR); and fibrinogen, fibrin/fibrinogen degradation product (FDP), D-dimer, antithrombin III (AT-III), soluble serum thrombomodulin (TM), and procalcitonin (PCT) levels. We also measured the following scores and data at 24 h, 48 h, 72 h, 5 days, 7 days, and 10 days after admission: SOFA and JAAM DIC scores, PT-INR, and fibrinogen, FDP, D-dimer, and AT-III levels. Other laboratory tests included red blood cell (RBC) and white blood cell (WBC) counts and hemoglobin, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine, electrolyte (Na^+, K^+, and Cl^-), and CRP levels, which were measured at the time of randomization and 24 h, 48 h, 72 h, 5 days, 7 days, and 10 days after admission.

We calculated the change rates from baseline (CRBs) for coagulation and inflammation data and albumin levels using the formula CRB=([measurement day value − day 0 value]/day 0 value). Here we used the modified SOFA score, in which the Glasgow Coma Scale (GCS) for central nervous system evaluation was excluded from the total SOFA score (total SOFA score − SOFA [GCS]). This was done because approximately half of the participating patients were receiving mechanical ventilation,

and verbal responses could not be evaluated because these patients were under sedation at Richmond Agitation–Sedation Scale levels between −2 and −1. CRB of the SOFA score was calculated using the formula CRB=SOFA score at measurement day – SOFA score at day 0.

We also calculated the number of patients who required mechanical ventilation, the duration of mechanical ventilation, and the number of ventilator-free days. The number of ventilator-free days was defined as the number of days without assisted mechanical ventilation through day 28. For patients who died, the value was set as 0 days. Requirement or discontinuance of mechanical ventilation was determined by the stuff physicians in the emergency department. Supplemental table 1 shows the criteria for weaning of mechanical ventilation [12]). We recorded the number of patients who required catecholamine treatment and its duration, which was performed according to the recommendations of the Surviving Sepsis Campaign 2008 Guideline, and recorded blood (concentrated RBCs, fresh frozen plasma [FFP], and platelets) and blood derivative administration amounts at 72 h, 28 days, and 90 days after admission. We investigated hemorrhage-related side effects and the timing of hemorrhage occurrence.

Adverse events

Adverse events were evaluated for the first 90 days after enrollment. Adverse events that were urgently reported were as follows: 1) death during the study, 2) life-threatening hemorrhage (e.g., intracranial, pulmonary, or intestinal tract hemorrhage), 3) extended hospitalization due to hemorrhage, and 4) permanent disability and dysfunction due to hemorrhage. These events were assessed by the institutional ethics committee as well as external experts. Exacerbation of severe sepsis and/or septic shock was not urgently reported.

Endpoints

The primary outcome was 90-day survival. The secondary outcomes included 72-h and 28-day survival rates; number of days until DIC resolution [10]); changes in SOFA scores, CRP levels, platelet counts, and FDP and D-dimer values; blood and blood derivative administration amounts during the first 72 h after diagnosis; and number of mechanical ventilation-free days.

Data Analysis

An intent-to-treat analysis was used according to initial group assignment. The Kolmogorov–Smirnov test was used to verify normality. When the data displayed a

normal distribution, a *t*-test was used to compare the two groups. When the data were not normally distributed, the Mann–Whitney U test was used. Kaplan–Meier analysis was used for outcome analysis, in which 72-h, 28-day, or 90-day survival was set as the event occurrence. The log-rank test was used to compare the two groups. All p values were two-sided, and $p<0.05$ was considered statistically significant. All statistical analyses were performed using R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Study duration and enrolled patients

In total, 74 patients were enrolled through July 2014, which was less than planned. An extension of the patient enrollment period until February 2015 was approved by the institutional ethics committee. During the study period, 232 patients with severe sepsis were admitted to the hospital and provisionally enrolled in this study. Although 105 patients developed DIC within 24 h after admission, five patients were excluded according to the exclusion criteria. Informed consent could not be obtained from eight other patients, including two patients who died. Thus, 92 patients were included in this study (Fig. 1).

Patients' characteristics

Table 2 shows the patient characteristics at baseline. The control and rhTM groups included 45 and 47 patients, respectively. Median patient age was 81 years. Almost all patients were elderly. Approximately 65% patients were male. Median APACHE II score for all patients was 19 points. Median values of soluble serum TM and PCT levels were 5.75 and 9.70 ng/mL, respectively. More patients developed sepsis-induced hypotension and received vasopressors in the control group than in the rhTM group.

Bacteremia was diagnosed in approximately 50% patients. The frequency of bacteremia was slightly higher in the rhTM group. The most frequent infection site was the lungs, comprising approximately 40% of infections, followed by the urinary tract/kidneys, gastrointestinal tract, and skin/tissue. Approximately 64% of the responsible organisms were gram-negative bacilli in both the control and rhTM groups, and 36% were gram-positive cocci. The most frequently used antibiotic was carbapenem. Renal replacement therapy was initiated in six and five patients in the control and rhTM groups, respectively. Mechanical ventilation was used in 26 patients in the control group and 21 in the rhTM group. Approximately 50% patients required

mechanical ventilation. The median [25th percentile, 75th] of rhTM administration duration was 2 days [1, 5 days].

Outcome

The 72-h survival rates were 93% and 91% (p=0.742) and 28-day survival rates were 84% and 83% (p=0.717) in the control and rhTM groups, respectively. Figure 2 shows Kaplan–Meier curves for 90-day survival, illustrating survival rates of 73% and 72% in the control and rhTM groups, respectively (p=0.994).

DIC resolution

Kaplan–Meier analysis was performed to assess DIC resolution rates (Supplemental Figure 1). The log-rank test revealed that the DIC resolution rate was significantly higher in the rhTM group (p<0.001). Figure 3 shows changes in the DIC score over time. The median DIC score was significantly lower in the rhTM group, beginning on day 3 (p<0.01).

Coagulation and inflammation data

Supplemental Table 2 shows data for fibrinogen, AT-III, CRP, D-dimer, and FDP levels, platelet and WBC counts, and PT-INR. CRBs for FDP and D-dimer were significantly lower in the rhTM group than in the control group, starting on day 1. CRB for PT-INR was lower in the rhTM group only on day 7. Additionally, CRBs for fibrinogen, AT-III, CRP, WBC, and platelet counts were not different between the groups at any time point.

SOFA scores (Supplemental Table 3)

SOFA scores of respiratory were significantly lower in the rhTM group than in the control group from days 1 to 10, but CRB for the SOFA scores was significantly lower in the rhTM group only on day 1. CRBs for total SOFA scores were not significantly different between the groups at any time point.

Ventilator-free days, blood transfusion amounts, and albumin and heparin use (Supplemental Table 4)

Although the number of ventilator-free days over the first 28 days was 4.5 days greater in the rhTM group, the difference between the groups was not significant. Although the transfusion amounts of RBCs, FFP, and platelets were not different

between the groups, the number of patients who used albumin was significantly smaller in the rhTM group. Seven patients with deep venous thrombosis in the control group and one in the rhTM group were treated with unfractionated heparin.

Other laboratory findings

Supplemental Table 5 shows albumin, AST, ALT, ALP, LDH, total bilirubin, BUN, creatinine, Na, Cl, hemoglobin, and RBC data for both groups at days 0, 1, 2, 3, 5, 7, and 10. Although serum albumin values tended to be higher in the rhTM group, CRB was not significantly different between the groups. Other laboratory data were not significantly different between the groups.

Adverse events

One patient in the control group and two in the rhTM group experienced adverse events that required either treatment alterations or additional therapies. The patient in the control group developed melena caused by large intestinal diverticulitis and underwent transcatheter arterial embolization. One patient in the rhTM group developed bleeding from an ulcer at the anterior wall of the duodenal bulb (Foster Ib) and received RBC transfusion and endoscopic hemostasis (clipping). Another patient in this group was diagnosed with meningitis and severe sepsis with DIC and was treated

with rhTM. Brain computed tomography (CT) on day 2 revealed a large cerebral infarction, and rhTM administration was discontinued. On day 3, the patient exhibited disturbances in consciousness; brain CT was repeated, revealing a hemorrhagic brain infarction. Following a review, the ethics committee concluded that the causal relationship between hemorrhagic complications and rhTM administration was unclear.

Post-hoc analysis

Survival rate

Survival analyses at 28 and 90 days were performed after dividing patients into two groups according to APACHE II scores of ≥20 (severe) or <20 (moderate status; Supplemental table 6). The moderate and severe groups included 51 and 41 patients, respectively. In the severe group, 90-day survival rates were 52% and 60% in the control and rhTM groups, respectively (p=0.524), with similar findings recorded in the moderate group.

DIC resolution

Differences in 28- and 90-day survival rates were not observed between the control and rhTM groups among patients who achieved DIC resolution within 3 or 7 days of admission (Supplemental table 7). Supplemental Figure 2 shows Kaplan–Meier

curve of the patients with DIC resolution within 3 days in the rhTM group and within 7 days in the control group. The log-rank test identified no significant difference between the groups (p=0.871).

Discussion

Our single-center, open-label RCT found that rhTM treatment did not increase 72-h, 28-day, or 90-day survival rates among severe septic patients with sepsis-induced DIC. The results were different from a series of reports describing the effectiveness of rhTM. [6-8, 13] According to our findings, a sample size of approximately 23,000 would be required to demonstrate a significant difference between the rhTM and control groups within our observation period.

Yoshimura et al. [14] conducted a post-hoc analysis of another study [8] and reported that rhTM significantly reduced mortality in the high-risk subset (APACHE II score=24–29; hazard ratio [HR]=0.281; 95% confidence interval [95%CI]=0.093–0.850; p=0.025), and a trend toward decreased mortality was observed in the extremely high-risk subset (APACHE II score ≥ 30; HR=0.529; 95%CI=0.202–1.387; p=0.195). We divided the study subjects into severe (APACHE II score>20) and mild groups (APACHE II score ≤ 20) by setting "APACHE II score=20" as the cut-off point in the

post-hoc analysis. The results indicated no difference in prognosis between the treatment groups. Our study used a lower cut-off value for APACHE II scores than proposed by Yoshimura et al., [14] which may explain the lack of a significant difference. However, the number of patients in the severe group was 41, which was same as the number of patients in the study by Yoshimura et al. [14]. A significant difference may have not appeared due to a difference in severity level, but a declining trend in mortality risk by rhTM would possibly be observed.

rhTM treatment significantly decreased DIC scores compared with the control group, indicating the drug facilitated DIC resolution. Compared with the control group, rhTM treatment significantly lowered FDP and D-dimer levels, beginning on day 1. Those results matched those of two RCTs [3, 9]. However, platelet counts and prothrombin times were not different between the groups. Thus, declines in the DIC score may only require decreases in FDP values.

We examined patients with DIC resolution within 3 or 7 days, but no significant difference in survival rates was recorded between the rhTM and control groups. Moreover, survival rates were not different between patients in the rhTM group with DIC resolution within 3 days and control group patients with DIC resolution within 7 days. These results indicate that at least prognosis is not changed regardless of rhTM

use if a patient recovers from the DIC within 7 days.

There were no differences in SOFA scores, number of ventilator-free days, and volume of blood transfusion between the rhTM and control groups. Conversely, albumin and heparin use were significantly lower in the rhTM group, although the small number of patients precludes any definitive conclusions. A decline in the DIC score by the rhTM use may not improve the prognosis of severe septic patients with sepsis-induced DIC. Now, we believe that the successful treatment of sepsis-induced DIC by rhTM does not have sufficient evidence on the prognosis from the results of our study. However, the rhTM use has been dramatically increasing in Japan despite a lack of clear evidence of its effectiveness. [15]

Our results unfortunately could not find an effectiveness of rhTM. Yet, we still believe that the ongoing Phase III study (Clinical trials. gov identifier. NCT01598831) could reveal whether our results would be closer to the truth or our study method would be inappropriate.

Study limitations

This study is for an open label RCT, but not a double blind study. Thus, it may possibly include some possible treatment bias. In addition, it requires caution and prudence for interpretation of our results due to a single center study. Our entry criteria

target the patients diagnosed as DIC in accordance with the JAAM DIC criteria. For the ongoing the Phase III study performed in Europe/the US, the entry criteria are set for cardiovascular dysfunction or respiratory failure and severe septic patients with PT-INR > 1.40. Therefore, it is more severe than our entry criteria. Our study might show a difference in disease severity as compared to other studies. The number of patients as being calculated before the study might not possibly be appropriate. The ongoing Phase III study planned that the estimated enrollment was 800 patients. The small number of patients in our study may have caused no significant result.

Conclusion

rhTM treatment decreased FDP and D-dimer values in severe septic patients with sepsis-induced DIC but did not increase survival rates. We do not recommend the routine use of rhTM in these patients. However, further multi-center, double-blind studies could provide additional clarification.

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Data sharing statement: Full data and data analysis files are available on request (hokabe@hosp.ncgm.go.jp. or ahagiwar@hosp.ncgm.go.jp.).

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Figure legends

Figure 1

Patient flow diagram

Figure 2

Kaplan–Meier curve of 90 days survival rate. The log rank test showed that p = 0.944.

Figure 3

Change of DIC score. Mann–Whitney test was performed in the rhTM group vs. control group at days 0, 1, 2, 3, 5, 7, and 10. * p = 0.005, ** p = 0.009, *** p = 0.002, **** p = 0.001, ***** p < 0.001.

Supplemental Figure 1

Histogram of the administration period of rhTM

Supplemental Figure 2

Kaplan–Meier curve of DIC resolution. The log rank test showed that $p < 0.001$.

The vertical axis showed the probability of 1 − DIC resolution rate. For example, on day 0, all patients had DIC. Therefore, the probability was 1.0. Whereas, on day 10, approximately 90% of the patients recovered from DIC in the control group. Therefore, the probability was 0.1.

Supplemental Figure 3

Kaplan–Meier curve of the patients with DIC resolution within 3 days in the rhTM group and within 7 days in the control group. The log rank test showed that $p = 0.871$.

Fig 1 *Patient flow diagram*

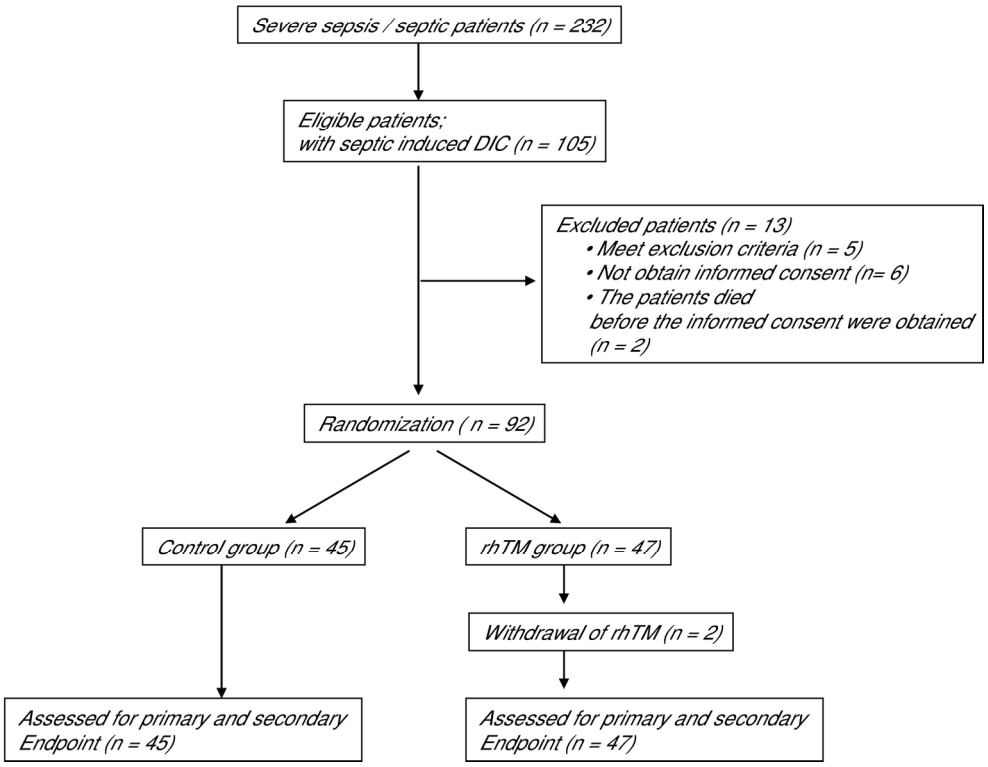

Figure 1

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Figure 2

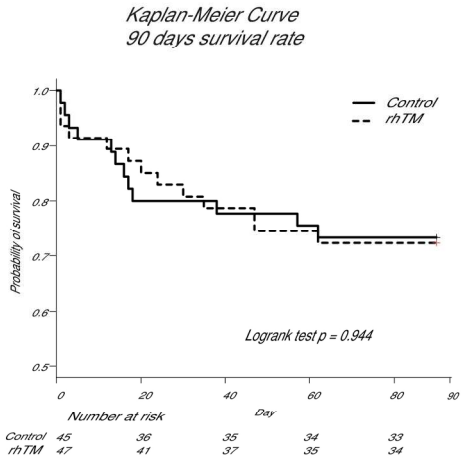

Figure 2

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Figure 3

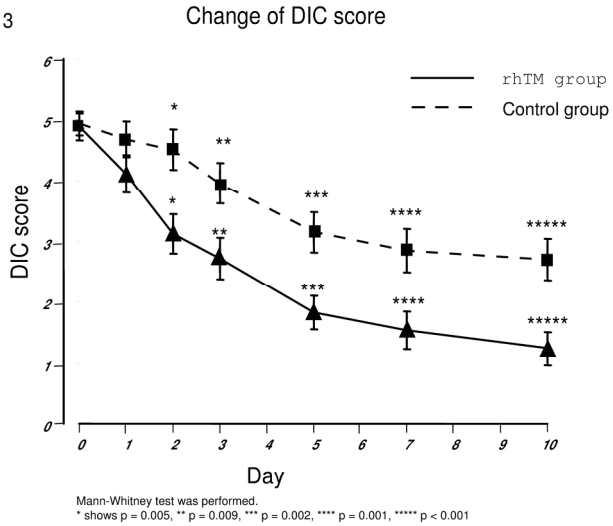


Figure 3

205x116mm (300 x 300 DPI)

Table 1. Japanese Association for Acute Medicine disseminated intravascular coagulation criteria

	Score
Systemic inflammatory response syndrome criteria	
>=3	1
0 – 2	0
platelet count, x 10^9/L	
< 80 or > 50% decrease within 24 h	3
>= 80 and < 120; or 30% decrease within 24 h	1
> 120	0
Prothrombin time	
>= 1.2	1
< 1.2	0
Fibrin/fibrinogen degradation products, $mg \cdot L^{-1}$	
>=25	3
>=10 and < 25	1
<10	0
Diagnosis	
>= 4 points	DIC

JAAM, the Japanese Association for Acute Medicine
DIC, Disseminated intravascular coagulation

Table 2. Baseline patient characteristics

Characteristics	Control (n = 45)	rhTM* (n = 47)	Total (n = 92)	p value
Age	81.0 [43.0, 94.0]	79.0 [23.0, 94.0]	80.5[68.0, 85.0]	0.377
Male, n (%)	28 (62.2)	32 (68.1)	60 (65.2)	0.662
APACHE II	20.0 [8.0, 33.0]	18.0 [8.0, 34.0]	19.0 [14.0, 23.0]	0.101
Soluble TM**(M :2.1–4.1, F: 1.8–3.9 ng/mL)	6.00 [4.70, 6.60]	5.45 [4.38, 8.40]	5.75 [4.40, 7.00]	0.473
PCT (<0.5 ng/mL)	7.21 [1.77, 46.44]	13.77 [1.95, 43.68]	9.70 [1.74, 45.64]	0.718
Sepsis-induced hypotension	26 (57.8)	17 (36.1)	43 (46.7)	0.059
Vasopressor, n	27 (60.0)	16 (34.0)	43 (46.7)	0.013
Norepinephrine, n	23 (51.1)	13 (28.9)	36 (39.1)	
Others, n	4 (8.9)	3 (6.7)	7 (7.6)	
Bacteremia (blood culture positive)	22 (48.9)	29 (61.7)	51 (55.4)	0.294
Site of infection, n (%)				
Lang	17 (37.8)	19 (40.4)	36 (39.1)	0.795
Urinary tract/kidney	18 (40.0)	13 (27.7)	31 (33.7)	
Gastrointestinal	8 (8.8)	5 (10.6)	13 (14.1)	
Skin/soft tissue	3 (6.7)	4 (8.5)	7 (7.6)	
Others	2 (44.4)	3 (6.4)	5 (5.4)	
Responsible organism				
Gram-negative rod	27 (60.0)	32 (68.0)	59 (64.1)	0.515
Gram-positive coccus	18 (40.0)	15 (31.9)	33 (35.9)	
Antibiotic				
Carbapenem	26 (57.8)	31 (66.0)	57 (62.0)	0.530
Cephalosporin	18 (40.0)	14 (29.8)	32 (34.8)	
Other	1 (2.2)	2 (4.3)	3 (3.3)	
Renal replacement therapy, n	6 (13.3)	5 (10.6)	11 (12.0)	0.756
Duration, day	9.0 [8.3, 13.5]	3.0 [2.0, 6.0]	8.0 [3.0, 10.5]	0.081

Mechanical ventilation, n	26 (57.8)	21 (44.7)	47 (51.0)	0.220

*rhTM, recombinant thrombomodulin. **In the rhTM group, the values were measured before the infusion of rhTM. Median [25th percentile, 75th percentile]

Supplement Table 1. Criteria for discontinuing mechanical ventilation

Criteria	Description
Objective measurements	Adequate oxygenation ($P_{O_2} \geq 60$ mm Hg on $F_{IO_2} \leq 0.4$; PEEP ≤ 5–10 cm H_2O; $P_{O_2}/F_{IO_2} \geq 150–300$);
	Stable cardiovascular system ([HR ≤ 140; stable BP; no (or minimal) pressure)
	Afebrile (temperature < 38°C)
	No significant respiratory acidosis
	Adequate hemoglobin (Hb ≥ 8–10 g/dL)
	Adequate mentation (arousable, GCS ≥ 13, no continuous sedative infusions)
	Stable metabolic status (acceptable electrolytes)
Subjective clinical assessments	Resolution of the disease' acute phase, physician believes that discontinuation is possible, adequate cough

from reference [12]

Supplemental Table 2. Coagulation and inflammation data

		Control	rhTM			Control	rhTM	
		Measurement value		p value		Rate of change		p value
D-dimer	day 0	22.2 [12.7, 41.2]	18.6 [11.8, 28.7]	0.524				
(μg/mL)	day 1	16.2 [9.3, 35.2]	11.7 [5.5, 18.7]	0.06	delta 1	−0.22 [−0.49, 0.22]	−0.36 [−0.60, −0.18]	0.037
	day 2	14.5 [8.6, 23.1]	5.0 [3.2, 11.3]	0.001	delta 2	−0.31 [−0.69, 0.10]	−0.73 [−0.82, −0.38]	0.014
	day 3	13.2 [7.1, 21.3]	5.5 [3.5, 11.1]	0.001	delta 3	−0.41 [−0.70, 0.26]	−0.69 [−0.81, −0.23]	0.027
	day 5	11.9 [8.2, 23.6]	5.5 [3.8, 10.3]	<0.001	delta 5	−0.40 [−0.67, 0.35]	−0.71 [−0.81, −0.44]	0.007
	day 7	14.8 [6.5, 21.0]	5.8 [2.9, 9.7]	0.001	delta 7	−0.34 [−0.73, 0.22]	−0.73 [−0.81, −0.33]	0.015
	day	9.0 [5.5, 28.4]	4.4 [2.3, 9.4]	<0.001	delta 10	−0.58 [−0.79, 0.43]	−0.75 [−0.82, −0.60]	0.006
FDP	day 0	36.0 [25.0, 84.1]	33.0 [21.3, 62.7]	0.361				
(μg/mL)	day 1	29.7 [15.6, 60.7]	20.3 [11.3, 33.2]	0.037	delta 1	−0.24 [−0.46, 0.14]	−0.38 [−0.55, −0.16]	0.046
	day 2	27.3 [12.7, 46.9]	10.6 [7.2, 17.6]	0.001	delta 2	−0.46 [−0.65, 0.08]	−0.58 [−0.78, −0.26]	0.046

	day 3	21.1 [13.1, 40.7]	9.4 [6.7, 18.7]	<0.001	delta 3	−0.45 [−0.73, 0.13]	−0.68 [−0.78, −0.29]	0.045
	day 5	18.3 [13.6, 37.2]	8.75 [7.1, 15.5]	<0.001	delta 5	−0.48 [−0.64, 0.15]	−0.72 [−0.81, −0.37]	0.007
	day 7	20.6 [12.2, 30.2]	8.6 [5.3, 16.0]	<0.001	delta 7	−0.47 [−0.74, 0.02]	−0.70 [−0.84, −0.39]	0.028
	day 10	14.4 [9.3, 40.4]	7.1 [4.5, 13.7]	<0.001	delta 10	−0.54 [−0.79, 0.00]	−0.73 [−0.85, −0.55]	0.011
Platelet ($\times 10^4$ /μL)	day 0	9.9 [3.5, 36.1]	10.7 [1.7, 33.2]	0.819				
	day 1	9.2 [2.4, 20.9]	8.9 [2.6, 24.7]	0.951	delta 1	−0.18 [−0.66, 1.93]	−0.15 [−0.71, 3.06]	0.661
	day 2	8.8 [2.2, 21.0]	8.8 [2.5, 25.4]	0.976	delta 2	−0.24 [−0.72, 1.23]	−0.21 [−0.78, 1.76]	0.775
	day 3	9.1 [1.3, 21.5]	9.3 [1.2, 28.3]	0.65	delta 3	−0.25 [−0.83, 1.17]	−0.13 [−0.84, 2.00]	0.289
	day 5	11.4 [2.3, 31.4]	11.45 [2.2, 37.6]	0.403	delta 5	−0.01 [−0.81, 2.27]	0.07 [−0.71, 2.35]	0.214
	day 7	17.2 [1.4, 46.7]	20.6 [2.5, 48.5]	0.082	delta 7	0.41 [−0.90, 3.93]	0.58 [−0.67, 11.71]	0.199
	day 10	21.0 [2.9, 56.6]	27.8 [2.3, 74.3]	0.055	delta 10	0.62 [−0.67, 8.43]	0.86 [−0.70, 11.71]	0.313
PT-INR	day 0	1.25 [0.98, 2.03]	1.29 [0.96, 3.81]	0.418				
	day 1	1.31 [1.06, 1.75]	1.31 [1.00, 2.58]	0.775	delta 1	0.02 [−0.27,	−0.00 [−0.51,	0.384

						0.30]	0.36]	
	day 2	1.22 [0.98, 2.02]	1.23 [0.95, 1.92]	0.931	delta 2	−0.01 [−0.35, 0.53]	−0.06 [−0.58, 0.25]	0.066
	day 3	1.17 [0.95, 2.04]	1.14 [0.97, 2.09]	0.454	delta 3	−0.05 [−0.35, 0.48]	−0.11 [−0.63, 0.12]	0.052
	day 5	1.19 [0.98, 1.78]	1.17 [1.00, 1.89]	0.328	delta 5	−0.04 [−0.41, 0.82]	−0.10 [−0.65, 0.12]	0.089
	day 7	1.23 [0.97, 3.80]	1.15 [0.94, 2.13]	0.216	delta 7	−0.05 [−0.34, 1.70]	−0.11 [−0.66, 0.31]	0.030
	day 10	1.22 [0.96, 2.79]	1.15 [0.95, 2.22]	0.654	delta 10	−0.06 [−0.33, 0.98]	−0.12 [−0.66, 0.78]	0.354
Fib	day 0	470.0 [123.9, 896.4]	412.0 [93.8, 1104.0]	0.331				
(mg/dL)	day 1	443.5 [135.7, 759.4]	375.4 [71.1, 976.0]	0.589	delta 1	−0.03 [−0.48, 0.67]	0.00 [−0.42, 1.39]	0.655
	day 2	487.7 [154.6, 726.4]	438.8 [117.2, 1014.4]	0.899	delta 2	−0.03 [−0.55, 0.95]	0.07 [−0.52, 2.03]	0.299
	day 3	422.0 [47.2, 966.0]	440.6 [142.5, 1128.0]	0.958	delta 3	−0.04 [−0.90, 1.31]	−0.01 [−0.56, 2.35]	0.319
	day 5	349.7 [76.7, 1112.0]	427.0 [153.1, 885.0]	0.861	delta 5	−0.17 [−0.76, 1.28]	−0.02 [−0.77, 2.00]	0.223
	day 7	388.4 [90.5, 950.0]	404.8 [88.2, 579.6]	0.600	delta 7	−0.21 [−0.75, 1.50]	−0.10 [−0.83, 2.41]	0.319

	day 10	291.7 [155.0, 705.4]	412.7 [88.2, 746.0]	0.025	delta 10	−0.28 [−0.74, 1.68]	−0.14 [−0.89, 3.12]	0.065
ATIII	day 0	58.8 [48.8, 71.2]	62.6 [53.1, 70.8]	0.458				
(%)	day 1	46.2 [38.6, 59.8]	59.2 [46.3, 65.0]	0.064	delta 1	−0.14 [−0.32, −0.04]	−0.10 [−0.23, 0.00]	0.198
	day 2	52.7 [37.3, 61.6]	56.9 [48.5, 66.5]	0.117	delta 2	−0.16 [−0.33, 0.00]	−0.06 [−0.20, 0.04]	0.229
	day 3	57.1 [40.5, 64.9]	62.9 [51.4, 74.3]	0.074	delta 3	−0.07 [−0.24, 0.07]	−0.01 [−0.10, 0.17]	0.052
	day 5	61.7 [47.5, 72.2]	68.9 [58.1, 79.5]	0.054	delta 5	−0.02 [−0.16, 0.15]	0.13 [−0.06, 0.33]	0.061
	day 7	65.3 [48.5, 80.9]	74.1 [61.6, 88.3]	0.079	delta 7	0.09 [−0.14, 0.32]	0.18 [−0.02, 0.41]	0.238
	day 10	70.0 [47.6, 75.8]	77.5 [65.5, 98.6]	0.024	delta 10	0.13 [0.01, 0.29]	0.29 [0.13, 0.53]	0.089
CRP	day 0	15.6 [10.0, 29.8]	14.2 [5.2, 26.1]	0.279				
(mg/dL)	day 1	18.9 [11.6, 28.4]	15.5 [9.9, 28.0]	0.407	delta 1	0.04 [−0.13, 0.54]	0.03 [−0.18, 0.54]	0.809
	day 2	18.8 [10.9, 24.8]	14.0 [8.8, 22.9]	0.131	delta 2	0.02 [−0.19, 0.76]	−0.10 [−0.39, 0.29]	0.162
	day 3	15.0 [9.1, 20.8]	9.0 [5.3, 15.0]	0.018	delta 3	−0.12 [−0.46, 0.35]	−0.37 [−0.61, −0.12]	0.058
	day 5	9.7 [4.2, 15.6]	4.9 [2.6, 8.4]	0.035	delta 5	−0.46 [−0.69,	−0.59 [−0.75,	0.260

						−0.09]	−0.25]	
	day 7	6.6 [2.3, 12.8]	2.4 [1.5, 7.2]	0.024	delta 7	−0.58 [−0.78, −0.27]	−0.73 [−0.86, −0.55]	0.088
	day 10	3.9 [1.7, 9.1]	2.6 [0.8, 4.9]	0.047	delta 10	−0.78 [−0.90, −0.44]	−0.81 [−0.90, −0.59]	0.325
WBC	day 0	10.82 [7.35, 16.24]	13.92 [7.79, 18.77]	0.435				
(×10^2/μL)	day 1	10.58 [6.39, 17.72]	13.83 [9.49, 17.73]	0.293	delta 1	−0.06 [−0.22, 0.14]	0.01 [−0.19, 0.26]	0.387
	day 2	10.19 [6.89, 15.18]	10.62 [7.59, 15.21]	0.499	delta 2	−0.10 [−0.26, 0.29]	−0.14 [−0.39, 0.25]	0.450
	day 3	9.62 [6.24, 12.12]	9.64 [7.02, 12.88]	0.699	delta 3	−0.26 [−0.44, 0.24]	−0.19 [−0.52, 0.14]	0.699
	day 5	9.16 [6.33, 11.12]	9.39 [7.37, 12.91]	0.508	delta 5	−0.17 [−0.53, 0.41]	−0.27 [−0.52, 0.08]	0.657
	day 7	8.93 [6.80, 13.93]	9.61 [7.54, 12.96]	0.996	delta 7	−0.16 [−0.52, 0.52]	−0.23 [−0.54, 0.01]	0.292
	day 10	11.16 [8.62, 12.92]	9.24 [7.33, 11.13]	0.064	delta 10	−0.14 [−0.43, 0.34]	−0.28 [−0.51, −0.07]	0.180

Median [25th percentile, 75th percentile]

FDP, fibrin/fibrinogen degradation products; PT-INR, prothrombin time–international normalized ratio;

Fib, fibrinogen; AT III, antithrombin III; CRP, C-reactive protein; WBC, white blood cell

Rate of change means changes from baseline (= vale at day X minus value at day 0) divided by value at day 0.

Supplemental Table 3. Sequential Organ Failure Assessment score (SOFA score)

		Control	rhTM	p value		Control	rhTM	p value
		Scores				Rate of change		
SOFA(R)	day 0	2 [0, 4]	1 [0, 4]	0.299				
(points)	day 1	2 [0, 4]	1 [0, 3]	0.004	delta 1	0 [–2, 3]	0 [–3, 2]	0.021
	day 2	2 [0, 4]	0.5 [0.0, 3.0]	0.009	delta 2	0 [–2, 3]	–1 [–3, 2]	0.131
	day 3	2 [0, 4]	0 [0, 3.]	0.012	delta 3	–1 [–4, 2]	–1 [–3, 1]	0.280
	day 5	1 [0, 4]	0 [0, 3]	0.028	delta 5	–1 [–4, 2]	–1 [–3, 0]	0.521
	day 7	1 [0, 4]	0 [0, 3]	0.047	delta 7	–1 [–4, 3]	–1 [–3, 0]	0.377
	day 10	0 [0, 3]	0 [0, 3]	0.033	delta 10	–1 [–4, 2]	–1 [–4, 1]	0.903
SOFA	day 0	7 [2, 14]	5 [0, 15]	0.121				
(Total)	day 1	5 [0, 13]	5 [0, 16]	0.061	delta 1	0 [–5, 4]	–1 [–6, 5]	0.210
minus	day 2	5 [0, 13]	3 [0, 14]	0.099	delta 2	–1 [–5, 4]	–1 [–8, 5]	0.594
SOFA	day 3	5 [0, 13]	3 [0, 14]	0.185	delta 3	–1 [–7, 4]	–2 [–9, 2]	0.926
(Glasgow	day 5	3 [0, 13]	2 [0, 13]	0.124	delta 5	–3 [–9, 3]	–2.5 [–9.0, 0.0]	0.651
Coma	day 7	2 [0, 16]	1 [0, 14]	0.048	delta 7	–3 [–10, 4.]	–3 [–11, 0]	0.918
Scale)	day 10	1.5 [0.0, 14.0]	0 [0, 16.]	0.074	delta 10	–4 [–10, 2]	–4 [–11, 1]	0.487

SOFA (R), SOFA scores of respiratory

Supplemental Table 4. **Ventilator-free days, blood transfusion, and albumin and heparin use**

Characteristics		Control (n = 45)	rhTM* (n = 47)	p value
Ventilator free day at day 28		17.5 [0, 23.3]	22 [0, 25.0]	0.213
Blood transfusion (within 72 h)				
RBC (U)		8.0 [2.0, 10.0], n = 11	3.0 [2.0, 8.0], n = 10	0.089
FFP (U)		10.0 [8.0, 20.0], n = 5	5.0 [4.0, 24.0], n = 7	0.100
PC (U)		30.0 [10.0, 70.0], n = 6	20.0 [10.0, 90.0], n = 5	0.710
Albumin use, n (within 72 h)		16 (35.6)	4 (8.5)	0.002
Albumin preparation (mg)	n = 16, 4	50.0 [34.4, 65.6]	37.5 [12.5, 84.4]	0.632
*Heparin use, n		7 (15.6)	1 (2.2)	0.029

Heparin was used on diagnosis of deep venous thrombosis

Ventilator free day at day 28 was defined as the number of days a patient had breathed without mechanical ventilation for at least 48 h continuously during a 28-day period. Patients who did not survive till 28 days were assigned 0 ventilator free days.

RBC, red blood cell; FFP, fresh freeze plasma; PC, platelet

Supplemental Table 5. Other laboratory findings

		Control	rhTM	p value
	n	45	47	
Alb (g/dL)	day 0	2.60 [2.20, 3.20]	2.95 [2.40, 3.40]	0.09
	day 1	2.10 [1.90, 2.30]	2.30 [2.00, 2.58]	0.01
	day2	2.00 [1.90, 2.20]	2.15 [1.90, 2.42]	0.193
	day 3	2.00 [1.80, 2.30]	2.25 [1.98, 2.50]	0.077
	day 5	2.05 [1.80, 2.20]	2.30 [2.00, 2.55]	0.027
	day 7	2.00 [1.80, 2.32]	2.30 [1.85, 2.50]	0.107
	day 10	2.20 [1.80, 2.38]	2.50 [1.90, 2.77]	0.044
Delta Alb	delta 1	–0.21 [–0.32, –0.14]	–0.24 [–0.29, –0.05]	0.749
	delta 2	–0.28 [–0.34, –0.13]	–0.25 [–0.35, –0.09]	0.787
	delta 3	–0.26 [–0.34, –0.10]	–0.29 [–0.36, –0.07]	0.847
	delta 5	–0.22 [–0.32, –0.11]	–0.24 [–0.38, –0.05]	0.925
	delta 7	–0.25 [–0.32, –0.11]	–0.28 [–0.36, –0.03]	0.768
	delta 10	–0.23 [–0.36, –0.10]	–0.21 [–0.36, –0.02]	0.69
ALP (IU/L)	day 0	230.00 [167.00, 361.00]	261.00 [223.50, 382.50]	0.278
	day 1	208.00 [159.00, 265.75]	220.00 [176.00, 316.00]	0.227
	day2	190.00 [152.00, 250.00]	254.00 [187.00, 311.00]	0.023
	day 3	230.50 [164.00, 274.25]	241.00 [194.00, 302.00]	0.257
	day 5	215.00 [190.25, 336.50]	249.00 [184.00, 309.50]	0.511
	day 7	243.50 [195.75, 334.25]	243.50 [198.25, 367.75]	0.798
	day 10	297.00 [219.00, 412.75]	254.00 [205.25, 368.50]	0.75
AST (IU/L)	day 0	24.00 [14.75, 72.25]	37.00 [24.00, 107.00]	0.03
	day 1	27.00 [15.50, 66.50]	43.00 [24.25, 151.75]	0.037
	day2	28.00 [16.00, 51.00]	40.00 [25.00, 106.25]	0.071
	day 3	29.00 [17.00, 76.00]	47.00 [24.00, 150.00]	0.075
	day 5	44.00 [29.00, 71.00]	46.00 [24.00, 119.00]	0.822
	day 7	44.00 [24.50, 73.00]	47.00 [21.75, 91.25]	0.939
	day 10	47.50 [27.25, 72.50]	36.00 [24.00, 72.00]	0.337
ALT (IU/L)	day 0	49.00 [33.00, 114.00]	60.00 [32.50, 219.00]	0.22
	day 1	56.00 [29.00, 157.00]	75.50 [45.25, 244.50]	0.126
	day2	48.50 [28.50, 105.75]	68.00 [38.00, 189.50]	0.106
	day 3	46.00 [31.00, 78.50]	69.00 [29.50, 156.50]	0.316
	day 5	47.00 [35.00, 72.00]	51.50 [28.00, 141.50]	0.653

	day 7	43.00 [28.50, 60.50]	41.00 [31.00, 63.00]	0.878
	day 10	36.00 [27.00, 61.00]	31.00 [25.00, 60.75]	0.34
Bil	day 0	0.90 [0.60, 1.30]	1.30 [0.80, 2.20]	0.042
(mg/dL)	day 1	0.70 [0.60, 1.00]	0.90 [0.60, 1.80]	0.068
	day2	0.60 [0.50, 0.97]	0.80 [0.50, 1.50]	0.095
	day 3	0.70 [0.50, 1.00]	0.80 [0.60, 1.37]	0.143
	day 5	0.60 [0.40, 1.05]	0.70 [0.50, 1.40]	0.183
	day 7	0.70 [0.45, 0.90]	0.70 [0.50, 1.20]	0.343
	day 10	0.60 [0.40, 0.90]	0.75 [0.50, 1.30]	0.192
BUN	day 0	31.50 [22.10, 47.20]	35.10 [19.85, 51.65]	0.722
(mg/dL)	day 1	33.70 [20.50, 46.30]	31.75 [16.02, 53.52]	0.997
	day2	28.20 [17.77, 40.48]	26.00 [13.70, 46.35]	0.676
	day 3	24.50 [14.77, 34.18]	19.60 [12.55, 37.65]	0.294
	day 5	20.30 [12.50, 32.00]	16.60 [10.80, 24.08]	0.219
	day 7	20.10 [11.55, 33.10]	15.90 [13.10, 22.10]	0.348
	day 10	22.30 [14.10, 40.10]	17.70 [11.38, 24.90]	0.284
Cr	day 0	1.45 [0.89, 2.39]	1.58 [0.98, 2.18]	0.648
(mg/dL)	day 1	0.94 [0.74, 2.33]	1.27 [0.82, 1.92]	0.614
	day2	0.87 [0.64, 1.84]	1.01 [0.64, 1.32]	0.836
	day 3	0.89 [0.63, 1.69]	0.94 [0.64, 1.14]	0.885
	day 5	0.79 [0.50, 1.89]	0.83 [0.56, 1.09]	0.959
	day 7	0.74 [0.54, 1.55]	0.85 [0.60, 1.10]	0.855
	day 10	0.75 [0.49, 1.28]	0.82 [0.57, 1.18]	0.637
Hb	day 0	11.70 [10.50, 13.30]	13.20 [10.80, 15.50]	0.189
(g/dL)	day 1	10.40 [9.50, 11.80]	11.15 [9.62, 12.47]	0.385
	day2	10.45 [9.35, 11.40]	10.80 [9.20, 11.45]	0.715
	day 3	10.45 [9.15, 11.28]	11.00 [9.25, 12.10]	0.253
	day 5	10.30 [9.70, 11.35]	11.00 [9.12, 12.78]	0.277
	day 7	10.30 [9.00, 11.40]	11.00 [8.80, 12.70]	0.298
	day 10	10.25 [9.17, 11.55]	10.70 [8.77, 12.52]	0.358
RBC	day 0	3.76 [3.43, 4.48]	4.15 [3.38, 4.92]	0.306
($\times 10^6$ /uL)	day 1	3.44 [3.09, 3.76]	3.56 [2.96, 4.02]	0.953
	day2	3.33 [3.04, 3.77]	3.39 [2.92, 3.77]	0.951
	day 3	3.37 [3.00, 3.64]	3.50 [2.84, 3.90]	0.394
	day 5	3.47 [3.24, 3.84]	3.60 [2.90, 4.07]	0.719
	day 7	3.40 [3.13, 3.73]	3.60 [2.82, 3.96]	0.61

	day 10	3.39 [3.05, 3.83]	3.28 [2.65, 3.95]	0.762
LDH	day 0	325.00 [247.00, 491.75]	367.00 [285.50, 575.50]	0.28
(IU/L)	day 1	307.00 [239.00, 469.00]	321.50 [230.25, 519.25]	0.594
	day2	258.00 [209.00, 371.00]	284.00 [229.00, 486.00]	0.325
	day 3	285.00 [236.00, 372.50]	290.00 [235.50, 418.50]	0.5
	day 5	296.50 [224.75, 364.75]	318.00 [244.00, 406.00]	0.305
	day 7	286.50 [212.50, 344.00]	294.00 [252.00, 400.00]	0.45
	day 10	273.00 [225.00, 334.50]	280.50 [206.75, 346.00]	0.982
Na	day 0	140.00 [137.00, 143.00]	141.00 [134.00, 144.00]	0.848
(mEq/L)	day 1	142.00 [138.00, 145.00]	141.00 [138.00, 144.00]	0.426
	day2	141.00 [139.00, 143.75]	140.00 [137.00, 145.00]	0.489
	day 3	140.00 [137.50, 144.75]	140.00 [137.00, 143.50]	0.514
	day 5	141.00 [138.50, 144.00]	140.00 [137.25, 142.75]	0.142
	day 7	141.00 [138.00, 144.50]	140.00 [137.00, 143.00]	0.454
	day 10	140.00 [136.00, 144.00]	140.00 [137.00, 143.00]	0.987
Cl	day 0	105.00 [101.00, 109.50]	102.00 [99.25, 107.75]	0.283
(mEq/L)	day 1	108.00 [106.00, 111.50]	107.50 [104.00, 111.25]	0.498
	day2	109.00 [105.00, 111.00]	108.00 [105.00, 112.25]	0.739
	day 3	108.00 [105.00, 112.00]	106.00 [104.75, 109.00]	0.274
	day 5	107.00 [105.00, 110.00]	108.00 [105.00, 110.00]	0.938
	day 7	106.00 [104.00, 110.00]	107.00 [105.00, 110.00]	0.46
	day 10	106.00 [103.00, 111.00]	107.00 [103.00, 109.00]	0.902

Median [25 percentile, 75percentile]

ALB, albumin; Bil, bilirubin; Cr, creatinine

These measurements were planned in the study protocol.

Supplemental Table 6. Kaplan–Meier analysis of the severe and moderate groups

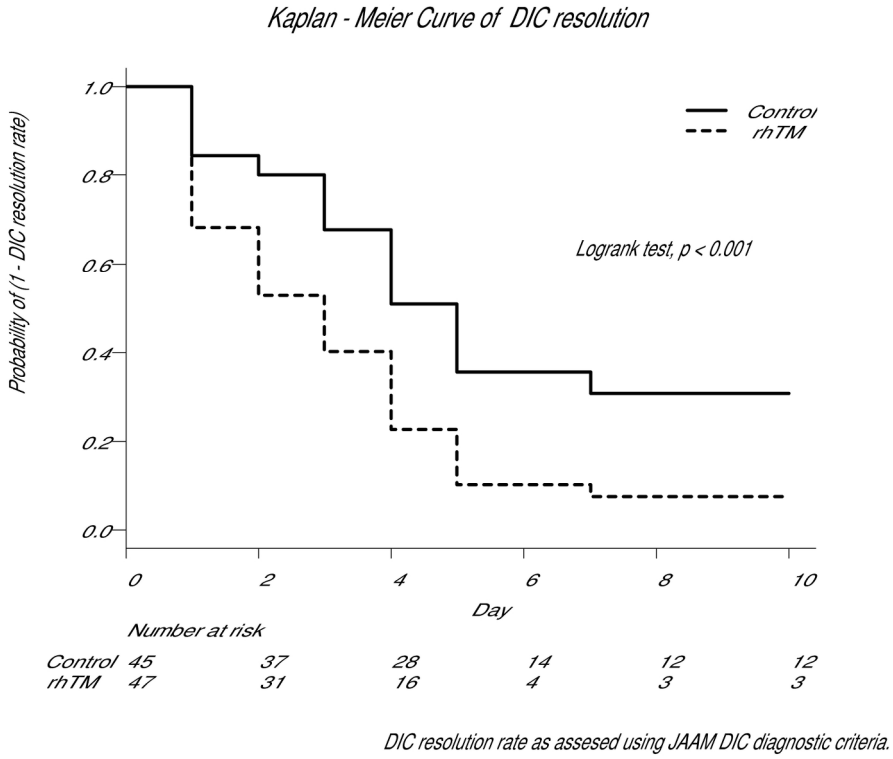
Moderate group (n = 51)				
		Survival	Non-survival	Log rank test p
28 days	Control (n = 24)	24 (100%)	0	
	rhTM (n= 27)	25 (93%)	2 (7%)	0.178
90 days	Control (n = 24)	22 (92%)	2 (8%)	
	rhTM (n = 27)	22 (81%)	5 (19%)	0.278
Severe group (n = 41)				
		Survival	Non-survival	Log rank test p
28 days	Control (n = 21)	12 (57%)	9 (43%)	
	rhTM (n = 20)	14 (70%)	6 (30%)	0.376
90 days	Control (n = 21)	11 (52%)	10 (48%)	
	rhTM (n = 20)	12 (60%)	8 (40%)	0.524

Moderate group comprises patients with APACHE II score < 20 points.
Severe group comprises patients with APACHE II score ≤ 20 points.

Supplemental Table 7. Kaplan–Meier analysis of patients who experienced disseminated intravascular coagulation resolution

		Within 3 days		
		Survival	Non-survival	Log rank test p
28 days	Control	13	4	
	rhTM	27	4	0.358
90 days	Control	11	6	
	rhTM	25	6	0.231
		Within 7 days		
		Survival	Non-survival	Log rank test p
28 days	Control	28	5	
	rhTM	39	5	0.676
90 days	Control	26	7	
	rhTM	34	10	0.901

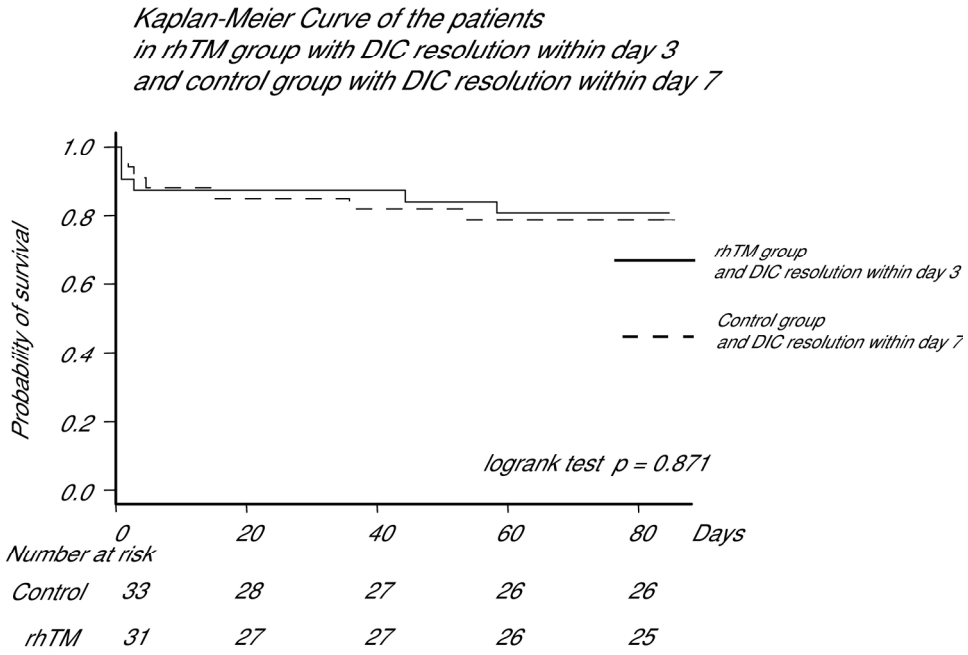
Supplement figure 1



Suppl. Figure 1

196x164mm (300 x 300 DPI)

Supplemental Figure 3



Suppl. Figure 2

194x135mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1 page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3 page
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5 page
	2b	Specific objectives or hypotheses	7 page
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8 page
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	14 page
Participants	4a	Eligibility criteria for participants	8 page
	4b	Settings and locations where the data were collected	10 page
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10 page
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	13 page
	6b	Any changes to trial outcomes after the trial commenced, with reasons	none
Sample size	7a	How sample size was determined	8 page
	7b	When applicable, explanation of any interim analyses and stopping guidelines	none
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9 page
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9 page
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9 page
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9 page
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	none

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	none
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13 page
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	14 page
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	14 page
	13b	For each group, losses and exclusions after randomisation, together with reasons	14 page
Recruitment	14a	Dates defining the periods of recruitment and follow-up	14 page
	14b	Why the trial ended or was stopped	none
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	15 page
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	15 page
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	16 page
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	16 page
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	19 page
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	18 page
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	22 page
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	22 page
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	2 page
Protocol	24	Where the full trial protocol can be accessed, if available	2 page
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2 page

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Can recombinant human thrombomodulin increase survival among patients with severe septic-induced disseminated intravascular coagulation: a single-center, open-label, randomized controlled trial

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Can recombinant human thrombomodulin increase survival among patients with severe septic-induced disseminated intravascular coagulation: a single-center, open-label, randomized controlled trial

Akiyoshi Hagiwara, MD, PhD. 1); Noriko Tanaka, M.H.S, Ph.D. 2); Tatsuki Uemura, MD. 1); Wataru Matsuda, MD. 1); and Akio Kimura, MD, PhD. 1)

1) Department of Emergency Medicine and Critical Care, National Center for Global Health and Medicine,

1-21-1 Toyama, Shinjyuku-ku, Tokyo,

162-8655, Japan

2) Biostatistics Section, Department of Data Science Clinical Science Center, National Center for Global Health and Medicine,

1-21-1 Toyama, Shinjyuku-ku, Tokyo,

162-8655, Japan

Corresponding author

Akiyoshi Hagiwara, MD, PhD

Department of Emergency Medicine and Critical Care, National Center for Global Health and Medicine

Address; 1-21-1 Toyama, Shinjyuku-ku, Tokyo, 162-8655 Japan

Tel; +81-3-3202-7181, Fax; +81-3-3207-1038

Email: ahagiwar@hosp.ncgm.go.jp

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Word count: 3539

Abstract

Objective: To determine whether treatment with recombinant human thrombomodulin (rhTM) increases survival among severe septic patients with sepsis-induced disseminated intravascular coagulation (DIC)

Design: Single-center, open-label, randomized controlled trial

Setting: Single tertiary hospital

Participant: 92 severe septic patients with sepsis-induced DIC

Interventions: Patients with DIC scores ≥4, as defined by the Japanese Association of Acute Medicine, were diagnosed with DIC. The envelope method was used for randomization. The treatment group (rhTM group, n = 47) was intravenously treated with rhTM within 24 h of admission (day 0), and the control group (n = 45) did not receive any anti-coagulants, except in cases of deep venous thrombosis and pulmonary embolism.

Primary and secondary measurements: Data were collected on days 0 (admission), 1, 2, 3, 5, 7, and 10. The primary outcome was survival at 28 and 90 days. The secondary endpoints comprised changes in DIC scores, platelet counts, D-dimer, antithrombin III (ATIII), and C-reactive protein (CRP) levels, and Sequential Organ Failure Assessment (SOFA) scores. All analyses were conducted on an intent-to-treat basis.

Main Results: The 28-day survival rates were 84 and 83% in the control and rhTM groups, respectively (p = 0.745, log rank test). The 90-day survival rates were 73% and 72% in the control and rhTM groups, respectively (p = 0.94, log rank test). Meanwhile, the rates of recovery from DIC (<4) were significantly

higher in the rhTM group than in the control group (p = 0.001, log rank test). Relative change from baseline of D-dimer levels were significantly lower in the rhTM group than in the control group, on day 3 and 5.

Conclusion: rhTM treatment decreased D-dimer levels and facilitated DIC recovery in severe septic patients with sepsis-induced DIC. However, the treatment did not improve survival in this cohort.

Strengths of this study

- This study is the first randomized controlled trial to evaluate the efficacy of recombinant thrombomodulin (rhTM) for patients with severe sepsis.
- rhTM was administered to patients with severe sepsis and DIC, which was defined by the Japanese Association of Acute Medicine criteria.
- In the control group, no anti-coagulant agent was administered.
- The primary outcomes were the 28- and 90-day survival rates.

Limitations

- This study was not a double-blind study.
- This study might have presented a difference in the disease severity compared with other studies.

Introduction

Thrombomodulin is a cell membrane protein expressed on vascular endothelium. Although thrombomodulin specifically binds to thrombin and inhibits thrombin activity, resulting in anti-coagulant action, it also has anti-inflammatory effects and regulates high mobility group box 1 (HMGB1) protein activity, a systemic inflammation mediator. [1, 2]

In Japan, a multi-center, prospective, randomized, double-blind, phase III clinical trial [3] of recombinant thrombomodulin (rhTM), an anti-coagulant agent used for disseminated intravascular coagulopathy (DIC), was performed from 2000 to 2005 and included 234 patients with DIC caused by infection or hematologic malignancy. Results showed that although rhTM was associated with a significantly higher DIC resolution rate than heparin, this rate was not significantly different for patients with infection. Further, no difference in 28-day mortality rates of patients with infection or hematologic malignancy was observed. The trial had several weaknesses: 1) the primary outcome was the DIC resolution rate, which is a physiological parameter and 2) the control group included patients with DIC who were treated with heparin, which is not the established and standard treatment for sepsis-induced coagulopathy [4].

In 2011, Yamakawa et al. [5] reported a retrospective historical control study with the mortality rate as the primary outcome. Twenty severe septic patients with sepsis-induced overt DIC (DIC criteria of the International Society on Thrombosis and Haemostasis) who received rhTM between November 2008 and October 2009 were compared with 45 patients who did not receive rhTM between January 2006 and

September 2008. The 28-day mortality rate was 25% for the rhTM group versus 47% for the control group. The Sequential Organ Failure Assessment (SOFA) score and C-reactive protein (CRP) and fibrinogen degradation product (FDP) levels were significantly decreased in the rhTM group, whereas the platelet counts were significantly increased. Further, rhTM treatment also improved respiratory function in patients with sepsis-induced DIC. [6]

In 2013, a retrospective cohort study adjusted by the propensity score was performed in patients with Japanese Association for Acute Medicine (JAAM) DIC scores ≥ 4 who required mechanical ventilation, exhibited multiple organ failure, and presented with platelet counts <80,000/mm^3. Mortality rates were significantly lower in patients treated with rhTM than in those who did not receive the therapy [7]. Although these studies investigated the mortality rate as the primary outcome, they were all retrospective cohort studies, which had certain biases.

In 2013, Vincent et al. reported a phase IIb double-blind randomized controlled trial (RCT) of rhTM, [8] in which patients who fulfilled the DIC criteria of the International Society on Thrombosis and Haemostasis were treated with rhTM or a placebo. Results showed that the 28-day mortality rate tended to be lower in the rhTM group.

It remains unclear whether rhTM is effective in treating severe septic patients with sepsis-induced DIC. Therefore, studies with a high evidence level are required. Our open-label RCT aimed to investigate whether rhTM treatment increases 28-day and 90-day survival rates in patients with severe sepsis and JAAM DIC scores ≥ 4 [9]).

Materials and Methods

This single-center open-label RCT was approved by our institutional ethics committee (NCGM-G-001163-00). Written informed consent was obtained from all participating patients or their legal representatives. Patients aged ≥16 years who were transferred to our hospital with severe sepsis were enrolled if their JAAM DIC scores were ≥4 within 24 h of admission (Table 1) [9].

Table 1. Japanese Association for Acute Medicine disseminated intravascular coagulation criteria

	Score
Systemic inflammatory response syndrome criteria	
>=3	1
0 – 2	0
platelet count, x 10^9/L	
< 80 or > 50% decrease within 24 h	3
>= 80 and < 120; or 30% decrease within 24 h	1
> 120	0
Prothrombin time	
>= 1.2	1
< 1.2	0
Fibrin/fibrinogen degradation products, $mg \cdot L^{-1}$	
>=25	3
>=10 and < 25	1
<10	0
Diagnosis	
>= 4 points	DIC

JAAM, the Japanese Association for Acute Medicine
DIC, Disseminated intravascular coagulation

The exclusion criteria were 1) refusal to participate; 2) refusal of aggressive intensive treatment,

including hemodialysis, mechanical ventilation, and catecholamine administration; 3) emergency surgery within 24 h of admission; 4) intracranial, pulmonary, and/or intestinal hemorrhage; 5) fulminant hepatitis, decompensated liver cirrhosis, or other irreversible severe hepatic disease; 6) past history of hypersensitivity to rhTM, and 7) pregnancy or potential pregnancy.

Number of cases and study duration

When our study was planned, the report by Yamakawa et al. [5] was the only study that investigated the efficacy of rhTM in patients with severe sepsis and sepsis-induced DIC. Therefore, the required number of patients was calculated on the basis of their report. When the observation and follow-up periods were set as 2 years and 90 days, respectively, each group required 47 patients to achieve over 80% power with $\alpha = 0.05$ on a log-rank test. At our institute, 53 and 52 patients with severe sepsis or septic shock who fulfilled the JAAM DIC criteria and who did not undergo emergency surgery within 24 h after admission were admitted in 2010 and 2011, respectively. The number of patients required for the 2-year study was estimated to be 100. The enrollment period was August 2012 to July 2014.

Randomization

Patients who fulfilled the inclusion criteria were randomized into the rhTM or control group using the envelope method. Each opaque envelope enclosed a piece of paper specifying either rhTM or control group assignment. We created 50 envelopes for each group assignment, shuffled them, and placed them in the designated storage box. Pre-registered co-investigators randomly selected envelopes from the box and

treated patients according to group assignment.

Treatment protocol

In both groups, patients were treated under the Surviving Sepsis Campaign 2008 Guideline, [10] in which grade I ("recommendation as strong") denoted mandatory treatment and grade II ("recommendation as weak") required treatment according to the attending physician's judgment.

The attending physician administered rhTM to patients within 3 h after randomization. rhTM (380 U/kg) was intravenously administered for 30 min.

Treatment was performed for a maximum of 6 days. When the JAAM DIC score was <4, rhTM treatment was terminated. In the control group, no anti-coagulant agent was administered, except in cases of deep venous thrombosis and pulmonary embolism, for which unfractionated heparin was administered. Unfractionated heparin was also administered to patients in the rhTM group with deep venous thrombosis and pulmonary embolism.

Investigated parameters

We obtained the following scores and laboratory data at the time of randomization: Acute Physiology and Chronic Health Evaluation II (APACHE IIl), SOFA, and JAAM DIC scores; prothrombin time/international normalized ratio (PTINR); and fibrinogen, D-dimer, antithrombin III (ATIII), soluble serum thrombomodulin (TM), and procalcitonin (PCT) levels. We also measured the following scores and data at 24 h, 48 h, 72 h, 5 days, 7 days, and 10 days after admission: SOFA and JAAM DIC scores, PTINR,

and fibrinogen, D-dimer, and ATIII levels. Other laboratory tests included red blood cell (RBC) and white blood cell (WBC) counts and hemoglobin, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine, electrolyte (Na^+, K^+, and Cl^-), and CRP levels, which were measured at the time of randomization and 24 h, 48 h, 72 h, 5 days, 7 days, and 10 days after admission.

We calculated the relative change from baseline for coagulation and inflammation data and albumin levels using the formula relative change from baseline = ([measurement day value − day 0 value]/day 0 value). The relative change from baseline of the SOFA score was calculated using the formula (SOFA score at measurement day – SOFA score at day 0).

We also calculated the number of patients who required mechanical ventilation and the number of ventilator-free days. The number of ventilator-free days was defined as the number of days without assisted mechanical ventilation through day 28. For patients who did not survive to 28 days, the value was set as 0 days. Requirement or discontinuance of mechanical ventilation was determined by the stuff physicians in the emergency department. Supplemental table 1 shows the criteria for weaning of mechanical ventilation [11]. We recorded the number of patients who required catecholamine treatment and its duration, which was performed according to the recommendations of the Surviving Sepsis Campaign 2008 Guideline, and recorded blood (concentrated RBCs, fresh frozen plasma [FFP], and platelets) and blood derivative administration amounts at 72 h, 28 days, and 90 days after admission. We investigated hemorrhage-related side effects and the timing of hemorrhage occurrence.

Adverse events

Adverse events were monitored prospectively via the daily evening conference. When adverse events occurred, one principle investigator (A.H.) reported them to our institutional ethics committee.

Adverse events were evaluated for the first 90 days after enrollment. Adverse events that were urgently reported were as follows: 1) death during the study, 2) life-threatening hemorrhage (e.g., intracranial, pulmonary, or intestinal tract hemorrhage), 3) extended hospitalization due to hemorrhage, and 4) permanent disability and dysfunction due to hemorrhage. These events were assessed by the institutional ethics committee as well as external experts.

Endpoints

The primary outcomes were the 28- and 90-day survival rates. The secondary outcomes included 72-h survival rates; number of days until DIC resolution [9]; changes in SOFA scores, platelet counts, D-dimer values, and CRP levels; blood and blood derivative administration amounts during the first 72 h after diagnosis; and number of mechanical ventilation-free days.

Data Analysis

An intent-to-treat analysis was used according to initial group assignment. When the basic assumptions of Student's *t*-test were not satisfied, a logarithmic transformation of the variables or the Mann–Whitney test was performed. For repeated comparisons, Bonferroni's correction was used. As our longitudinal data have comparisons with six hypotheses between the two groups, $p < 0.01$ (0.05/6) was

considered statistically significant. Kaplan–Meier analysis was used for outcome analysis, in which 72-h, 28-day, or 90-day survival was set as the event occurrence. The log-rank test was used to compare the two groups. All p values were two-sided, and $p < 0.05$ or $p < 0.01$ was considered statistically significant.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan),[12] which is a graphical user interface for R v3.1.1 (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Study duration and enrolled patients

In total, 74 patients were enrolled through July 2014, which was less than planned. An extension of the patient enrollment period until February 2015 was approved by the institutional ethics committee. During the study period, 232 patients with severe sepsis were admitted to the hospital and provisionally enrolled in this study. Although 105 patients developed DIC within 24 h after admission, five patients were excluded according to the exclusion criteria. Informed consent could not be obtained from eight other patients, including two patients who died. The two patients were solitary individuals, and we could not contact their legal representatives within 24 h after admission. Thus, 92 patients were included in this study (Fig. 1).

Baseline variables

Table 2 shows the patient baseline variables. The control and rhTM groups included 45 and 47

patients, respectively. The mean patient ages in the two groups were 77.2 and 74.7 years, respectively. Almost all patients were elderly. Approximately 65% of patients were male. The mean APACHE II score in the control group was 19.7 points, compared to 17.8 points in the rhTM group. The mean soluble serum TM values were 6.3 ng/mL in the control group and 8.0 ng/mL in the rhTM group. The mean PCT levels were 36.8 ng/mL in the control group and 39.3 ng/mL in the rhTM group.

Table 2. Baseline patient characteristics

Characteristics	Control (n = 45)	rhTM* (n = 47)
Age	77.2 (73.6, 80.7)	74.7 (70.6,78.8)
Male, n (%)	28 (62.2%)	32 (68.1%)
APACHE II	19.7 (18.0, 21.5)	17.8 (16.2, 19.4)
Soluble TM** (M: 2.1–4.1, F: 1.8–3.9 ng/mL)	6.3 (5.5, 7.0)	8.0 (5.7, 10.2)
PCT (<0.5 ng/mL)	36.8 (17.6, 56.1)	39.3 (19.0, 59.7)

*rhTM, recombinant thrombomodulin. The rhTM values were measured before the infusion of rhTM. The continuous variables were the mean (95% confidence interval).

Follow up variables

Table 3 shows the patient follow-up variables. More patients developed sepsis-induced hypotension and received vasopressors in the control group than in the rhTM group. Bacteremia was diagnosed in approximately 50% patients. The frequency of bacteremia was slightly higher in the rhTM group. The most frequent infection site was the lungs, comprising approximately 40% of infections, followed by the urinary tract/kidneys, gastrointestinal tract, and skin/tissue. Approximately 64% of the responsible organisms were gram-negative bacilli in both the control and rhTM groups, and 36% were gram-positive cocci. The most frequently used antibiotic was carbapenem. Renal replacement therapy was initiated in six and five patients in the control and rhTM groups, respectively. Mechanical ventilation was used in 26 patients in the control

group and 21 in the rhTM group. Approximately 50% patients required mechanical ventilation. The median [25th percentile, 75th] of rhTM administration duration was 2 days [1, 5 days].

Table 3. Follow-up variables

Characteristics	Control (n = 45)	rhTM* (n = 47)	Odds ratio (95% CI)	p value
Sepsis-induced hypotension[#], n (%)	26 (57.8)	17 (36.1)	0.42 (0.96 – 6.09)	0.059*
Vasopressor, n (%)	27 (60.0)	16 (34.0)	0.35 (0.13 – 0.87)	0.021*
Norepinephrine, n (%)	23 (51.1)	13 (28.9)		
Dopamin, n (%)	1 (2.2)	1 (2.2)		
Dobutamin, n (%)	1 (2.2)	1 (2.2)		
Epinephrine, n (%)	2 (4.45)	1 (2.2)		
Bacteremia (blood culture positive)	22 (48.9)	29 (61.7)	1.67 (0.68 – 4.19)	0.294*
Site of infection, n (%)				0.795**
Lang	17 (37.8)	19 (40.4)		
Urinary tract/kidney	18 (40.0)	13 (27.7)		
Gastrointestinal	8 (8.8)	5 (10.6)		
Skin/soft tissue	3 (6.7)	4 (8.5)		
Others	2 (44.4)	3 (6.4)		
Responsible organism				
Gram-negative rod	27 (60.0)	32 (68.0)	1.42 (0.56 – 3.66)	0.515*
Gram-positive coccus	18 (40.0)	15 (31.9)		
Antibiotic				
Carbapenem	26 (57.8)	31 (66.0)		0.530**
Cephalosporin	18 (40.0)	14 (29.8)		
Other	1 (2.2)	2 (4.3)		
Renal replacement therapy, n	6 (13.3)	5 (10.6)	0.78 (0.17 – 3.33)	0.756*
Duration, day	9.0 [8.3, 13.5][$]	3.0 [2.0, 6.0][$]	NA	0.099[$$]
Mechanical ventilation, n (%)	26 (57.8)	21(44.7)	0.59 (0.24 – 1.46)	0.220*

*Fisher's exact test was performed. ** chi-squared test was performed.

$ The data were shown median and 25 and 75 percentiles; [25, 75perventile].
$$ Mann-Whitney test was performed.
NA: none available
Sepsis-induced hypotension was defined as follows; despite adequate fluid resuscitation, vasopressors required to maintain MAP ≥65 mm Hg.

Outcome

The 72-h survival rates were 93% and 91% (Fisher's exact test, p = 0.742) and 28-day survival rates were 84% and 83% (Fisher's exact test, p = 0.717) in the control and rhTM groups, respectively. Supplemental Table 2 shows the results of Kaplan–Meier analysis, and Figure 2 shows Kaplan–Meier curves for 90-day survival, illustrating survival rates of 73% and 72% in the control and rhTM groups, respectively (log-rank test, p = 0.994).

DIC resolution

The number of patients in whom DIC was resolved within 72 h in the rhTM and control groups were 56 (27/48) and 40% (17/42), respectively (odds ratio = 2.45, 95% confidence interval = 0.95–6.52, p = 0.0516, Fisher's exact test). The number of patients in whom DIC resolved within 7 days in the rhTM and control groups were 91 (39/43) and 61% (27/41), respectively (odds ratio = 4.96, 95% confidence interval = 1.36–22.97, p = 0.0075, Fisher's exact test). Figure 3 shows the changes in the DIC score through 10 days. The mean DIC score was significantly lower in the rhTM group, beginning on day 5 (p < 0.01).

Coagulation data

Supplemental Table 3 shows data for D-dimer, platelet, PTINR, fibrinogen, and ATIII. The relative changes from baseline in the levels of D-dimer were significantly lower in the rhTM group than in the control group, on days 3 and 5. The relative changes from baseline for platelet counts, PTINR, fibrinogen, and ATIII were

not different between the groups at any time point.

Inflammation data (Supplement Table 3)

WBC and CRP counts were not different between the groups at any time point.

SOFA scores (Supplemental Table 4)

The relative changes from baseline for respiratory SOFA scores and total SOFA scores were not significantly different between the groups at any time point.

Ventilator-free days, blood transfusion amounts, and albumin and heparin use (Supplemental Table 5)

The mean numbers of ventilator-free days in the rhTM and control groups were 15.5 (10.7–20.2) and 17.5 days (9.2–17.7), respectively. The difference of 2.0 days (−4.4–8.4) between the groups was not significant (p = 0.530). The transfusion amounts of RBCs, FFP, and platelets were not different between the groups. Four patients (8.5%, 4/47) were administered albumin in the rhTM group compared to 16 patients (35.6%, 16/45) in the control group. Seven patients with deep venous thrombosis in the control group and one in the rhTM group were treated with unfractionated heparin.

Other laboratory findings

Supplemental Table 6 shows albumin, ALP, ALT, AST, LDH, total bilirubin, BUN, creatinine, Na, Cl, RBC, and hemoglobin data for both groups at days 0, 1, 2, 3, 5, 7, and 10. Although serum albumin values were significantly higher in the rhTM group only on day 1, the relative change from baseline was not significantly different between the groups. Other laboratory data were not significantly different between the groups.

Adverse events

One patient in the control group and two in the rhTM group experienced adverse events that required either treatment alterations or additional therapies. The patient in the control group developed melena caused by large intestinal diverticulitis and underwent transcatheter arterial embolization. One patient in the rhTM group developed bleeding from an ulcer at the anterior wall of the duodenal bulb (Foster Ib) and received RBC transfusion and endoscopic hemostasis (clipping). Another patient in this group was diagnosed with meningitis and severe sepsis with DIC and was treated with rhTM. Brain computed tomography (CT) on day 2 revealed a large cerebral infarction, and rhTM administration was discontinued. On day 3, the patient exhibited disturbances in consciousness; brain CT was repeated, revealing a hemorrhagic brain infarction. Following a review, the ethics committee concluded that the causal relationship between hemorrhagic complications and rhTM administration was unclear.

Post-hoc analysis

Survival rate

We selected the patients with mechanical ventilation from the study population and performed a survival analysis at 28 and 90 days for the rhTM and control groups. The 28-day survival rates in the treatment and control groups were 71 (15/21) and 69% (18/26) (odds ratio = 1.1, 95% CI = 0.27–4.8, p = 1.0, Fisher's exact test), respectively. The 90-day survival rates in the treatment and control groups were 62 (13/21) and 62% (16/26) (odds ratio = 1.0, 95% CI = 0.27–3.9, p = 1, Fisher's exact test), respectively.

APACHE II scores of ≥20 (severe) or <20 (moderate status; Supplemental table 7). The moderate

and severe groups included 51 and 41 patients, respectively. In the severe group, 90-day survival rates were 52% and 60% in the control and rhTM groups, respectively (Log-rank test p = 0.524), with similar findings recorded in the moderate group.

DIC resolution

The 28-day mortality rate among patients in whom DIC was resolved within 7 days was 2.6% (1/39) in the rhTM group compared to 50.0% (4/8) among those in whom DIC was not resolved (odds ratio = 0.03, 95% CI = 0.0–0.4, p = 0.0018, Fisher's exact test). In the control group, the 28-day mortality rate among patients in whom DIC was resolved within 7 days was 0% (0/27); conversely, the rate for those in whom DIC was not resolved was 50% (9/18) (odds ratio = 0, 95% CI = 0.0–0.2, p < 0.001, Fisher's exact test). The mortality rate was significantly lower among patients in whom DIC was resolved.

However, differences in the 28- and 90-day survival rates were not observed between the control and rhTM groups among patients who experienced DIC resolution within 3 or 7 days of admission (Supplemental Table 8). Differences in the 28- and 90-survival rates were not observed between patients who experienced DIC resolution within 3 days in the rhTM group and those who experienced resolution within 7 days in the control group. Supplemental Figure 1 shows the Kaplan–Meier curve.

Discussion

Our single-center, open-label RCT found that rhTM treatment did not increase 72-h, 28-day, or 90-day survival rates among severe septic patients with sepsis-induced DIC. The results were different from a series of reports describing the effectiveness of rhTM. [5-7, 13] According to our findings, a sample size of

approximately 23,000 would be required to demonstrate a significant difference between the rhTM and control groups within our observation period.

Through 2015, five retrospective studies reported the efficacy of rhTM in patients with sepsis and DIC [5-7, 13, 14]. These studies reported mortality rates of 8.3–40% in the rhTM group and 33–57% in the control group. These mortality rates were higher than our values. This may be explained by differences in disease severity. In four of the studies, patients with sepsis who required mechanical ventilation were included. [5-7, 14]. In contrast, one phase IIb study [8] and another retrospective subanalysis [15] of a phase III clinical trial [3] reported mortality rates of 17.8 and 21.4%, respectively, in the rhTM group and 21.6 and 31.6%, respectively, in the control group. The former study diagnosed DIC according to the ISTH criteria, and the latter study diagnosed DIC according to the JAAM DIC criteria. As we also administered rhTM to patients with sepsis according to the JAAM DIC criteria, our mortality rates may be lower than those of the retrospective studies. However, our mortality rates were similar to those of the two prospective studies. We believe that our results provide real-world evidence of the efficacy of rhTM in Japan.

rhTM treatment significantly decreased DIC scores compared with the control group, indicating the drug facilitated DIC resolution. Compared with the control group, rhTM treatment significantly lowered D-dimer levels on day 3 and 5. Those results almost matched those of two RCTs [3, 8]. However, platelet counts and prothrombin times were not different between the groups. Thus, decreases in FDP values may induce declines in the DIC score (the changes in the FDP values are shown in Supplemental Table 2).

Aikawa et al. [15] stated that “the 28-day mortality rate among patients in whom the DIC resolved was 3.7% (1/27) in rhTM group, the rate for those in whom the DIC did not resolve was 46.2% (6/13) (p =

0.0026, Fisher's exact test). In the heparin treatment group, the 28-day mortality rate among patients in whom the DIC resolved was 15% (3/20); the rate for those in whom the DIC did not resolve was 43.8% (7/16) (p = 0.0732, Fisher's exact test)." They reported that "the 28-day mortality rates were significantly lower for patients in whom the JAAM DIC was resolved within 7 days than in those in whom the JAAM DIC was not resolved." Our results were similar to theirs.

We examined patients who experienced DIC resolution within 3 or 7 days, but no difference in survival rates was recorded between the rhTM and control groups. Moreover, survival rates were not different between patients in the rhTM group who experienced DIC resolution within 3 days and those in the control group who experienced DIC resolution within 7 days. These results illustrated that the 28-day mortality rates were lower for patients in whom JAAM DIC was resolved within 7 days, but the outcome did not change after the use of rhTM if patients recovered from DIC within 7 days.

There were no differences in SOFA scores, number of ventilator-free days, and volume of blood transfusion between the rhTM and control groups. Conversely, albumin and heparin use were lower in the rhTM group, although the small number of patients precludes any definitive conclusions. A decline in the DIC score by the rhTM use may not improve the outcome of severe septic patients with sepsis-induced DIC compared to the control group. Our study did not uncover sufficient evidence of the effects of treatment with rhTM for sepsis-induced DIC on patient outcome. However, rhTM use has been drastically increasing in Japan despite a lack of clear evidence of its effectiveness [16].

Our results unfortunately could not find an effectiveness of rhTM. Yet, we believe that the ongoing Phase III study (Clinical trials. gov identifier. NCT01598831) could reveal whether our results would be

closer to the truth or our study method would be inappropriate.

Study limitations

This study was an RCT opposed to a double-blind study. Thus, the study may have been affected by treatment bias. In addition, it requires caution and prudence for interpretation of our results due to a single center study. Our entry criteria target the patients diagnosed as DIC in accordance with the JAAM DIC criteria. For the ongoing the Phase III study performed in Europe/the US, the entry criteria are set for cardiovascular dysfunction or respiratory failure and severe septic patients with PTINR > 1.40. Therefore, it is more severe than our entry criteria. Our study might show a difference in disease severity as compared to other studies. The number of patients as being calculated before the study might not possibly be appropriate. The ongoing Phase III study planned that the estimated enrollment was 800 patients. The small number of patients in our study may have caused no significant result.

Conclusion

rhTM treatment decreased D-dimer values in severe septic patients with sepsis-induced DIC but did not increase survival rates. We do not recommend the routine use of rhTM in these patients.

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Contributors: MW, TU, and AH performed the acquisition of the data. TU, AH, and NT revised the manuscript and approved the final version. AK and AH contributed to the conception of the work and approved the final version. NT and AH performed the statistical analysis. In addition, all authors had agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data sharing statement: Full data and data analysis files are available on request (hokabe@hosp.ncgm.go.jp or ahagiwar@hosp.ncgm.go.jp).

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Figure legends

Figure 1

Patient flow diagram

Figure 2

Kaplan–Meier curve of 90 days survival rate. The log rank test showed that p = 0.944.

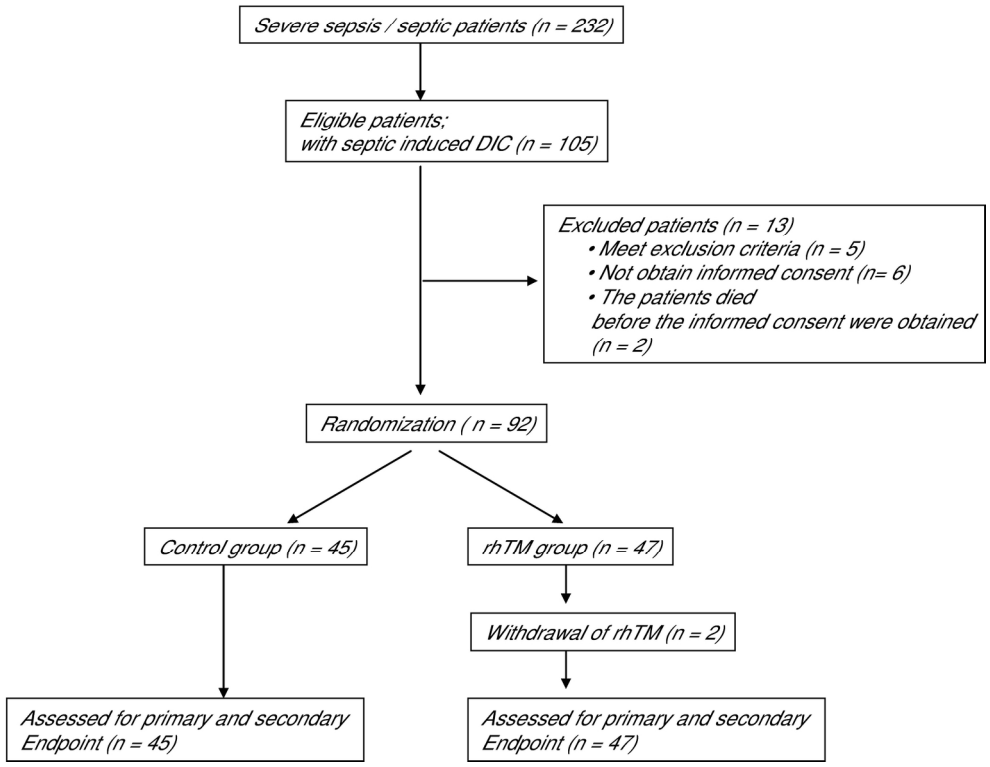
Figure 3

Change of DIC score. Unpaired t test with Bonferroni correction was performed in the rhTM group vs. control group at days 0, 1, 2, 3, 5, 7, and 10. P < 0.001 (0.05/6) was considered statistically significant.

Supplemental Figure 1

Kaplan–Meier curve of the patients with DIC resolution within 3 days in the rhTM group and within 7 days in the control group. The log rank test showed that p = 0.871.

Fig 1 *Patient flow diagram*



177x149mm (300 x 300 DPI)

Figure 2

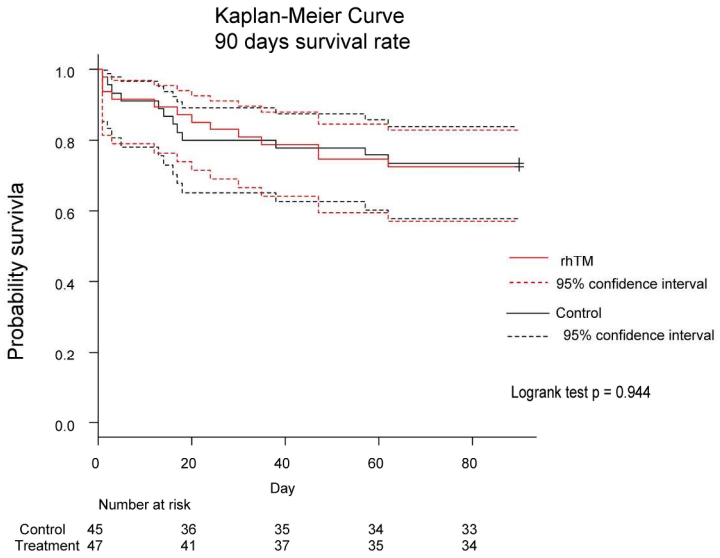


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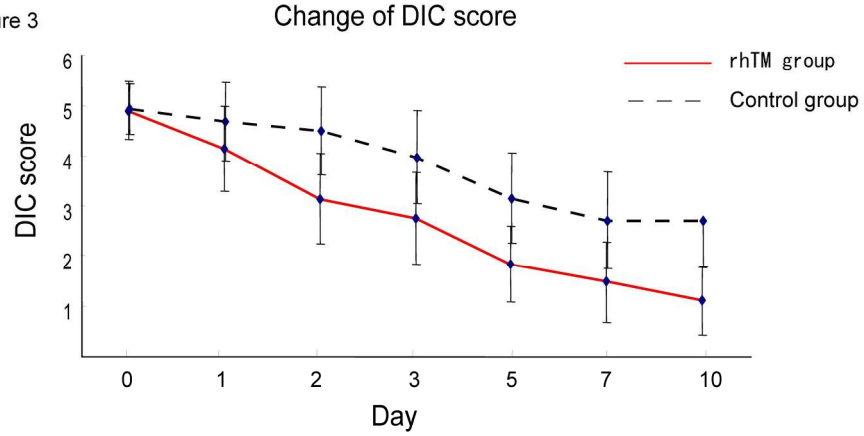
Figure 3



The dots show the mean.
The erro bars show the 99% confidence interval.

Day	0	1	2	3	4	5	7	10
p value		0.835	0.185	0.04	0.011	0.003	0.008	<0.001

Unpaired t tests were performed with Bounferroni correction (p = 0.01)
The mrean values were significalntly difference on day 5, 7, and 10

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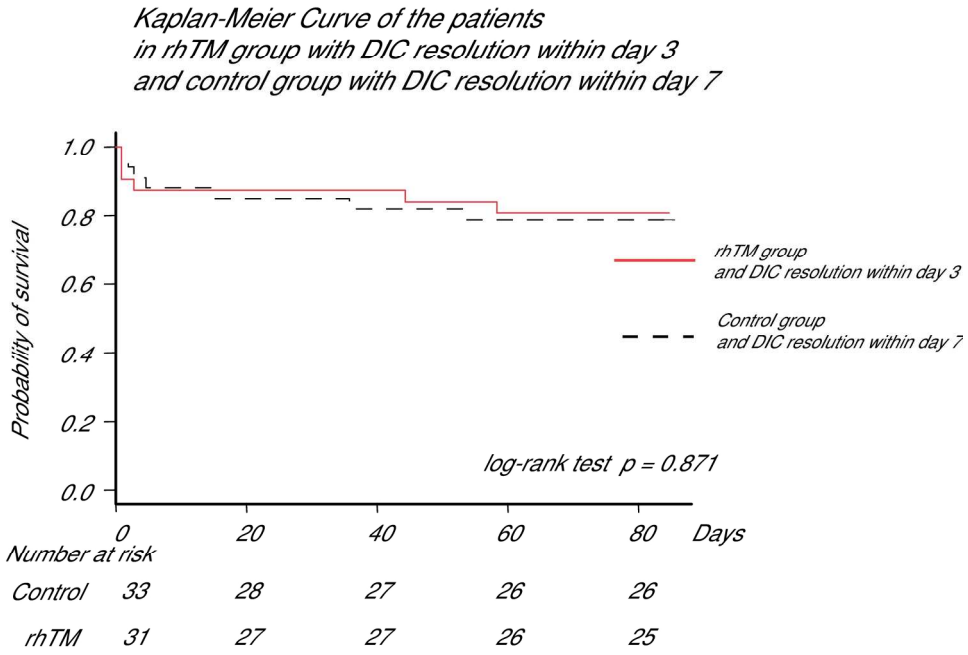
Supplemental Figure 1



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Supplement Table 1. Criteria for discontinuing mechanical ventilation

Criteria	Description
Objective measurements	Adequate oxygenation ($P_{O_2} \geq 60$ mm Hg on $F_{IO_2} \leq 0.4$; PEEP ≤ 5–10 cm H_2O; $P_{O_2}/F_{IO_2} \geq 150–300$);
	Stable cardiovascular system ([HR ≤ 140; stable BP; no (or minimal) pressure)
	Afebrile (temperature < 38°C)
	No significant respiratory acidosis
	Adequate hemoglobin (Hb ≥ 8–10 g/dL)
	Adequate mentation (arousable, GCS ≥ 13, no continuous sedative infusions)
	Stable metabolic status (acceptable electrolytes)
Subjective clinical assessments	Resolution of the disease' acute phase, physician believes that discontinuation is possible, adequate cough

from reference [11]

Supplement table 2
Results of Kaplan–Meier analysis

Control group

Time	n. risk	n. event	survival	std.err	lower 95% CI	upper 95% CI
1	45	1	0.978	0.0220	0.853	0.997
2	44	1	0.956	0.0307	0.834	0.989
3	43	1	0.933	0.0372	0.807	0.978
5	42	1	0.911	0.0424	0.780	0.966
13	41	1	0.889	0.0468	0.753	0.952
14	40	1	0.867	0.0507	0.727	0.938
16	39	1	0.844	0.0540	0.701	0.923
17	38	1	0.822	0.0570	0.676	0.907
18	37	1	0.800	0.0596	0.651	0.891
38	36	1	0.778	0.0620	0.626	0.874
57	35	1	0.756	0.0641	0.602	0.856
62	34	1	0.733	0.0659	0.578	0.839

rhTM group

time	n. risk	n. event	survival	std.err	lower 95% CI	upper 95% CI
1	47	3	0.936	0.0357	0.815	0.979
3	44	1	0.915	0.0407	0.789	0.967
12	43	1	0.894	0.0450	0.763	0.954
17	42	1	0.872	0.0487	0.738	0.941
20	41	1	0.851	0.0519	0.713	0.926
24	40	1	0.830	0.0548	0.688	0.911
30	39	1	0.809	0.0574	0.664	0.895
35	38	1	0.787	0.0597	0.641	0.879
47	37	2	0.745	0.0636	0.594	0.846
62	35	1	0.723	0.0652	0.572	0.829

n.: number, std: standard, CI: confidence interval

Supplemental Table 3. Coagulation and inflammation data

Coagulation data

		Measurement value					Relative change from baseline			
		Control	rhTM	Difference (95% CI)	p value		Control	rhTM	Difference (95% CI)	p value
D-dimer	day 0	39.5 (21.9, 57.0)	30.2 (13.0, 47.3)	-9.3 (-33.8, 15.2)	0.320					
(μg/mL)	day 1	27.4 (17.3, 37.7)	18.3 (8.3, 28.3)	-9.2(-23.4, 5.1)	0.094	delta 1	-0.13 (-0.32, 0.05)	-0.29 (-0.46, -1.09)	-0.15 (-0.41, 0.10)	0.112
	day 2	17.7 (10.4, 25.0)	12.8 (5.5, 20.0)	-4.9(-15.2, 5.4)	0.214	delta 2	-0.17 (-0.42, 0.06)	-0.49 (-0.73, -0.25)	-0.31 (-0.65, 0.03)	0.017
	day 3	16.9 (11.4, 22.5)	9.6 (4.1, 15.0)	-7.4 (-15.1, 0.4)	0.014	delta 3	-0.11 (-0.39, 0.17)	-0.51 (-0.78, -0.24)	-0.40 (-0.79, -0.01)	0.008*
	day 5	18.5 (12.9, 24.1)	8.0 (2.6, 13.5)	-10.5 (-18.2, -2.7)	0.001*	delta 5	-0.01 (-0.37, 0.35)	-0.52 (-0.87, -0.18)	-0.52 (-1.02, -0.02)	0.008*
	day 7	20.6 (12.1, 29.2)	8.0 (-0.4, 16.5)	-12.6 (-24.6, -0.6)	0.007*	delta 7	0.23 (-0.41, 0.86)	-0.55 (-1.17, 0.07)	-0.78 (-1.66, 0.11)	0.024
	day	19.7 (13.2, 26.2)	7.0 (0.6, 13.5)	-12.7 (-21.8, -3.5)	<0.001*	delta 10	0.35 (-0.74, 1.39)	-0.43 (-1.48, 0.62)	-0.76 (-2.25, 0.74)	0.185
FDP	day 0	78.3 (35.5, 121.1)	62.3 (20.4, 104.1)	-16.0 (-75.9, 43.9)	0.483					
(μg/mL)	day 1	55.3 (32.7, 77.9)	32.0 (10.1, 53.8)	-23.4 (-54.8, 8.1)	0.053	delta 1	-0.01 (-0.26, 0.12)	-0.29 (-0.48, -0.10)	-0.22 (-0.49, 0.05)	0.035
	day 2	32.7 (18.2, 47.2)	25.3 (11.0, 39.6)	-7.4 (-27.8, 13.0)	0.339	delta 2	-0.20 (-0.44, 0.03)	-0.47 (-0.70, -0.24)	-0.27 (-0.59, 0.06)	0.036

	day 3	32.6 (21.2, 43.9)	18.9 (7.7, 30.1)	-13.7 (-29.6, 2.2)	0.026	delta 3	-0.09 (-0.38, 0.21)	-0.48 (-0.78, -0.19)	-0.40 (-0.81, 0.0)	0.014
	day 5	32.9 (20.9, 44.9)	14.5 (2.9, 26.1)	-18.4 (-35.1, -1.7)	0.005*	delta 5	-0.13 (-0.41, 0.15)	-0.57 (-0.84, -0.30)	-0.43 (-0.82, -0.05)	0.004*
	day 7	32.2 (20.0, 44.3)	13.3 (1.3, 25.3)	-18.9 (-36.0, -1.8)	0.005*	delta 7	-0.04 (-0.43, 0.35)	-0.58 (-0.96, -0.20)	-0.54 (-1.09, 0.01)	0.011
	day 10	30.7 (19.7, 41.6)	11.4 (0.4, 22.3)	-19.3 (-34.8, -3.8)	0.002*	delta 10	-0.20 (-0.48, 0.08)	-0.66 (-0.94, -0.38)	-0.46 (-0.85, -0.06)	0.003*
Platelet ($\times 10^4$ /μL)	day 0	13.3 (10.4, 16.3)	13.5 (10.6, 16.3)	0.11 (-4.0, 4.2)	0.946					
	day 1	10.5 (8.2, 12.8)	10.7 (8.5, 13.0)	0.27 (-2.9, 3.5)	0.824	delta 1	-0.12 (-0.31, 0.07)	-0.10 (-0.29, 0.08)	0.02 (-0.25, 0.28)	0.863
	day 2	9.3 (7.1, 11.5)	10.6 (8.4, 12.8)	1.3 (-1.8, 4.4)	0.276	delta 2	-0.17 (-0.34, -0.01)	-0.12 (-0.29, 0.04)	0.05 (-0.18, 0.28)	0.573
	day 3	9.4 (7.0, 11.8)	11.4 (9.1, 13.8)	2.1 (-1.3, 5.4)	0.108	delta 3	-0.17 (-0.36, 0.03)	-0.02 (-0.21, 0.17)	0.15 (-0.12, 0.42)	0.156
	day 5	12.2 (8.7, 15.8)	16.0 (12.5, 19.4)	3.7 (-1.2, 8.6)	0.051	delta 5	0.11 (-0.22, 0.44)	0.41 (0.09, 0.73)	0.30 (-0.16, 0.76)	0.086
	day 7	16.9 (12.7, 21.1)	22.2 (18.0, 26.3)	5.3 (-0.7, 11.2)	0.021	delta 7	0.57 (-0.14, 1.27)	1.30 (0.61, 1.99)	0.73 (-0.26, 1.72)	0.054
	day 10	22.1 (16.8, 27.5)	28.3 (23.1, 33.4)	6.2 (-1.3, 13.6)	0.032	delta 10	1.14 (0.22, 2.06)	1.93 (1.04, 2.81)	0.79 (-0.48, 2.06)	0.11
PT-INR	day 0	1.31 (1.14, 1.48)	1.42 (1.25, 1.58)	0.11 (-0.13, 0.34)	0.244					
	day 1	1.33 (1.23, 1.43)	1.35 (1.25, 1.45)	0.02 (-0.11, 0.16)	0.654	delta 1	0.02 (-0.04, 0.07)	-0.01 (-0.06, 0.05)	-0.03 (-0.10, 0.05)	0.376
	day 2	1.27 (1.17, 1.36)	1.24 (1.15, 1.34)	-0.02 (-0.15, 0.11)	0.655	delta 2	-0.02 (-0.09, 0.05)	-0.09 (-0.16, -0.03)	0.07 (-0.17, 0.02)	0.053
	day 3	1.23 (1.14, 1.32)	1.20 (1.12, 1.29)	-0.02 (-0.15, 0.10)	0.635	delta 3	-0.05 (-0.11, 0.01)	-0.12 (-0.18, -0.06)	-0.07 (-0.16, 0.02)	0.042

	day 5	1.25 (1.17, 1.32)	1.19 (1.12, 1.27)	-0.05 (-0.16, 0.05)	0.196	delta 5	-0.03 (-0.11, 0.05)	-0.12 (-0.20, -0.04)	-0.09 (0.20, 0.02)	0.040
	day 7	1.29 (1.15, 1.44)	1.20 (1.06, 1.34)	-0.09 (-0.25, 0.11)	0.226	delta 7	-0.01 (-0.11, 0.10)	-0.12 (-0.22, -0.016)	-0.11 (-0.26, 0.04)	0.050
	day 10	1.23 (1.11, 1.35)	1.23 (1.11, 1.34)	-0.004 (-0.17, 0.16)	0.951	delta 10	-0.05 (-0.15, 0.04)	-0.10 (-0.19, -0.01)	-0.05 (-0.18, 0.09	0.374
Fib	day 0	457.1 (376.0, 538.2)	456.4 (376.2, 536.6)	-0.73 (-114.8, 113.3)	0.99					
(mg/dL)	day 1	445.0 (370.1, 519.4)	436.4 (364.5, 508.3)	-8.61 (-112.1, 94.9)	0.827	delta 1	-0.03 (-0.14, 0.09)	0.02 (-0.09, 0.13)	0.05 (-0.11,0.21)	0.433
	day 2	455.7 (381.3, 530.1)	473.0 (401.25, 544.8)	17.3 (-86.1, 120.7)	0.660	delta 2	0.06 (-0.12, 0.25)	0.18 (-0.01, 0.36)	0.11 (-0.15, 0.37)	0.299
	day 3	434.0 (353.7, 514.3)	457.3 (379.9, 534.8)	23.3 (-88.2, 134.)	0.583	delta 3	0.03 (-0.20, 0.25)	0.17 (-0.05, 0.38)	0.14 (-0.17, 0.45)	0.247
	day 5	414.6 (332.7, 496.6)	424.5 (346.6, 502.3)	9.8 (-103.2, 122.9)	0.819	delta 5	-0.04 (-0.29, 0.20)	0.15 (-0.08, 0.39)	0.19 (-0.14, 0.53)	0.134
	day 7	389.3 (318.4, 460.0)	391.5 (323.4, 459.6)	2.3 (-95.9, 100.5)	0.952	delta 7	-0.11 (-0.36, 0.14)	0.12 (-0.13, 0.37)	0.23 (-0.13, 0.58)	0.094
	day 10	335.8 (264.0, 407.6)	423.4 (354.5, 492.2)	87.6 (-11.916, 187.071)	0.025	delta 10	-0.17 (-0.48, 0.14)	0.19 (-0.11, 0.49)	0.36 (-0.07, 0.79)	0.028
ATIII	day 0	58.8 (50.7, 97.0)	62.8 (54.8, 70.7)	3.93 (-7.5, 15.3)	0.367					
(%)	day 1	48.9 (42.1, 55.7)	54.8 (48.2, 61.3)	5.85 (-3.6, 15.3)	0.106	delta 1	-1.62 (-0.25, -0.08)	-0.12 (-0.20, -0.03)	0.05 (-0.07, 0.16)	0.265
	day 2	51.3 (43.7, 58.8)	57.1 (49.8, 64.4)	5.85 (-4.6, 16.3)	0.144	delta 2	-0.14 (-0.23, -0.05)	-0.09 (-0.17, -0.003)	0.05 (-0.07, 0.17)	0.257
	day 3	55.0 (47.0, 63.0)	62.6 (54.7, 70.4)	7.60 (-3.6, 18.8)	0.078	delta 3	-0.08 (-0.18, 0.02)	0.02 (-0.07, 0.12)	0.10 (-0.03, 0.24)	0.049
	day 5	60.6 (52.4, 68.9)	69.7 (61.6, 77.7)	9.02 (-2.5, 20.6)	0.042	delta 5	0.02 (-0.11, 0.15)	0.17 (0.04, 0.30)	0.15 (-0.03, 0.33)	0.032

	day 7	64.5 (54.9, 74.1)	74.1 (64.9, 83.3)	9.58 (-3.7, 22.9)	0.061	delta 7	0.10 (-0.03, 0.23	0.20 (0.07, 0.32)	0.10 (-0.09, 0.28)	0.171
	day 10	66.5 (55.9, 77.1)	80.0 (69.8, 90.1)	13.4 (-1.3, 28.1)	0.018	delta 10	0.16 (0.02, 0.31)	0.28 (0.14, 0.41)	0.12 (-0.08, 0.31)	0.120

Inflammation data

		Measurement value					Relative change from baseline			
		Control	rhTM	Difference (95% CI)	p value		Control	rhTM	Difference (95% CI)	p value
CRP	day 0	20.5 (16.0, 25.0)	18.5 (14.0, 23.0)	-2.0 (-8.4, 4.4)	0.409					
(mg/dL)	day 1	19.2 (14.9, 23.5)	15.7 (11.5, 19.9)	-3.5 (-9.5, 2.5)	0.130	delta 1	1.7 (0.14, 3.27)	1.4 (-0.12, 2.98)	-0.28 (-2.48, 1.92)	0.740
	day 2	14.9 (11.5, 18.3)	10.8 (7.5, 14.1)	-4.1 (-8.8, 0.7)	0.027	delta 2	8.0 (-4.21, 20.25)	1.7 (-10.22, 13.67)	-6.3 (-23.39, 10.796)	0.334
	day 3	10.7 (7.2, 14.2)	7.7 (4.3, 11.0)	-3.0 (-7.8, 1.8)	0.104	delta 3	5.1 (-3.36, 13.48)	0.9 (-7.26, 8.98)	-4.2 (-15.90, 7.50)	0.347
	day 5	8.2 (5.6, 10.8)	5.2 (2.7, 7.7)	-3.0 (-6.6, 0.6)	0.031	delta 5	3.5 (-2.64, 9.63)	0.4 (-5.34, 6.18)	-3.1 (-11.50, 5.34)	0.337
	day 7	5.8 (3.7, 7.9)	4.0 (1.9, 6.0)	-1.8 (-4.7, 1.1)	0.100	delta 7	2.9 (-2.48, 8.20)	-0.04 (-5.11, 5.03)	-2.90 (-10.26, 4.46)	0.302
	day 10	8.5 (2.9, 14.1)	4.0 (-1.5, 9.4)	-4.5 (-12.3, 3.3)	0.131	delta 10	1.4 (-6.25, 9.14)	3.0 (-4.35, 10.41)	1.9(-9.08, 12.25)	0.695
WBC	day 0	12.63 (9.24, 16.02)	14.35 (11.03, 17.67)	1.7 (-3.02, 6.46)	0.343					
($\times 10^2/\mu L$)	day 1	14.55 (10.38, 18.72)	15.01 (10.89, 19.14)	0.4 (-5.40, 6.33)	0.836	delta 1	0.6 (-0.11, 1.37)	0.4 (-0.36, 1.11)	-0.2 (-1.30, 0.80)	0.532
	day 2	12.31 (9.14, 15.48)	12.98 (9.84, 16.11)	0.7 (-3.79, 5.12)	0.695	delta 2	0.6 (-0.12, 1.25)	0.2 (-0.43, 0.93)	-0.3 (-1.29, 0.64)	0.383

	day 3	11.13 (8.42, 13.84)	10.97 (8.29, 13.65)	-0.2 (-3.98, 3.65)	0.909	delta 3	0.7 (-0.13, 1.61)	0.04 (-0.81, 0.90)	-0.7 (-1.92, 0.53)	0.137
	day 5	10.34 (7.64, 13.04)	11.24 (8.64, 13.84)	0.9 (-2.84, 4.64)	0.528	delta 5	0.6 (-0.36, 1.55)	0.2 (-0.69, 1.15)	-0.4 (-1.7, 0.9)	0.465
	day 7	10.88 (8.42, 13.34)	10.84 (8.44, 13.23)	-0.05 (-3.47, 3.39)	0.975	delta 7	0.7 (-0.26, 1.62)	0.1 (-0.83, 0.99)	-0.6 (-1.91, 0.71)	0.230
	day 10	11.25 (9.48, 13.04)	9.49 (7.76, 11.22)	-1.8 (-4.24, 0.71)	0.064	delta 10	0.5 (-0.38, 1.40)	0.02 (-0.85, 0.89)	-0.5 (-1.73, 0.75)	0.298

mean (95% confidence interval)

PTINR, prothrombin time–international normalized ratio;

Fib, fibrinogen; AT III, antithrombin III; CRP, C-reactive protein; WBC, white blood cell

Relative change rate from baseline = ([measurement day value − day 0 value]/day 0 value).

This table includes fibrin/fibrinogen degradation products (FDP) value. This information was not noted in the main manuscript to avoid redundancy.

Supplemental Table 4. Sequential Organ Failure Assessment score (SOFA score)

		Measurement value					Relative change from baseline			
		Control	rhTM	Difference (95% CI)	p value		Control	rhTM	Difference (95% CI)	p value
SOFA(R)	day 0	2.0 (1.4, 2.6)	1.7 (1.1, 2.2)	-0.3 (-1.1, 0.5)	0.334					
(points)	day 1	2.0 (1.5, 2.5)	1.2 (0.7, 1.7)	-0.8 (-1.5, -0.1)	0.004*	delta 1	0.05 (-0.3, 0.4)	-0.4 (-0.7, -0.1)	-0.5 (-0.9, 0.02)	0.013
	day 2	1.6 (1.1, 2.1)	0.9 (0.4, 1.3)	-0.7 (-1.4, -0.1)	0.004*	delta 2	-0.3 (-0.7, 0.2)	-0.7 (-1.1, -0.2)	-0.4 (-1.0, 0.2)	0.088
	day 3	1.4 (0.9, 1.8)	0.7 (0.3, 1.2)	-0.6 (-1.3, 0.02)	0.012	delta 3	-0.5 (-1.0, -0.03)	-0.8 (-1.3, -0.3)	-0.3 (-0.9, 0.4)	0.247
	day 5	1.2 (0.7, 1.7)	0.6 (0.2, 1.1)	-2.2 (-1.3, 0.11)	0.029	delta 5	-0.7 (-1.2, -0.2)	-0.9 (-1.4, -0.4)	-0.2 (-0.9, 0.4)	0.343
	day 7	1.2 (0.7, 1.7)	0.6 (0.1, 1.1)	-0.6 (-1.3, 0.1)	0.021	delta 7	-0.7 (-1.2, -0.2)	-1.0 (-1.5, -0.5)	-0.3 (-1.1, 0.4)	0.225
	day 10	0.9 (0.5, 1.3)	0.4 (0.0, 0.8)	-0.5 (-1.1, 0.1)	0.031	delta 10	-1.1 (-1.7, -0.5)	-1.2 (-1.8, -0.6)	-0.1 -0.9, 0.7	0.737
	day 0	8.1 (7.1, 9.1)	7.3 (6.4, 8.3)	-0.7 (-2.1, 0.6)	0.367					
	day 1	8.0 (6.3, 9.7)	6.5 (4.8, 8.1)	-1.5 (-3.9, 0.8)	0.091	delta 1	0.02 (-0.9, 0.)	-0.8 (-1.7, 0.1)	-0.8 (-2.0, 0.5)	0.121
Total	day 2	6.9 (5.9, 7.9)	5.3 (4.2, 6.3)	-1.6 (-3.1, -0.1)	0.071	delta 2	-1.0 (-2.0, -0.01)	-1.8 (-2.8, -0.9)	-0.8 (-2.2, 0.6)	0.118
SOFA	day 3	6.0 (4.3, 7.6)	4.6 (2.9, 6.2)	-1.4 (-3.7, 0.9)	0.120	delta 3	-1.9 (-3.1, -0.8)	-2.6 (-3.7, -1.4)	-0.6 (-2.3, 1.0)	0.308
(points)	day 5	4.9 (3.2, 6.6)	3.5 (1.8, 5.1)	-1.4 (-3.8, 0.9)	0.113	delta 5	-3.2 (-4.6, -1.9)	-3.7 (-5.0, -2.4)	-0.5 (-2.3, 1.4)	0.490
	day 7	4.3 (2.6, 6.0)	2.6 (1.0, 4.3)	-1.6 (-4.0, 0.8)	0.075	delta 7	-3.8 (-5.3, -2.4)	-4.6 (-6.0, -3.2)	-0.7 (-2.8, 1.2)	0.317
	day 10	3.6 (2.0, 5.2)	2.4 (0.8, 4.0)	-1.2 (-3.5, 1.1)	0.159	delta 10	-4.8 (-6.2, -3.3)	-4.7 (-6.1, -3.3)	0.1 (-1.9, 2.1)	0.924

SOFA (R), SOFA scores of respiratory

Change rate from baseline = SOFA score of measurement day − SOFA score of day 0.

* shows statistically significance ($p < 0.01$).

Supplemental Table 5. Ventilator-free days, blood transfusion, and albumin and heparin use

Characteristics	Control (n = 45)	rhTM* (n = 47)	p value
Ventilator free day at day 28	15.5 (10.7, 20.2)*	17.5 (9.2, 17.7)*	0.530**
Blood transfusion (within 72 h)			
RBC (U)	8.0 [2.0, 10.0]$, n = 11	3.0 [2.0, 8.0], n = 10	0.089$$
FFP (U)	10.0 [8.0, 20.0], n = 5	5.0 [4.0, 24.0], n = 7	0.100$$
PC (U)	30.0 [10.0, 70.0], n = 6	20.0 [10.0, 90.0], n = 5	0.710$$
Albumin use, n (within 72 h)	16 (35.6)	4 (8.5)	0.002$$
Albumin preparation (mg),n = 16, 4	50.0 [34.4, 65.6]	37.5 [12.5, 84.4]	0.632$$
*Heparin use, n (%)	7 (15.6)	1 (2.2)	NA

Heparin was used on diagnosis of deep venous thrombosis

Ventilator free day at day 28 was defined as the number of days a patient had breathed without mechanical ventilation for at least 48 h continuously during a 28-day period. Patients who did not survive till 28 days were assigned 0 ventilator free days.

RBC, red blood cell; FFP, fresh freeze plasma; PC, platelet

* mean (95% confidence interval), ** An unpaired t test was performed.

$ median [25percentile, 75percentile], $$ Mann-Whitney test was performed.

NA: none available.

Supplemental Table 6. Other Laboratory findings

		Control	rhTM	P value
	n	45	47	
Alb (g/dL)	day 0	2.65 (0.72)	2.94 (0.63)	0.051
	day 1	2.07 (0.38)	2.33 (0.40)	0.004*
	day 2	2.05 (0.41)	2.18 (0.42)	0.166
	day 3	2.08 (0.39)	2.23 (0.43)	0.111
	day 5	2.06 (0.42)	2.28 (0.48)	0.041
	day 7	2.11 (0.46)	2.26 (0.49)	0.177
	day 10	2.11 (0.44)	2.36 (0.53)	0.038
Delta Alb		-0.21 (0.15)	-0.17 (0.18)	0.342
		-0.24 (0.16)	-0.22 (0.19)	0.656
		-0.22 (0.17)	-0.21 (0.22)	0.801
		-0.22 (0.19)	-0.19 (0.21)	0.633
		-0.21 (0.21)	-0.20 (0.25)	0.919
		-0.19 (0.22)	-0.15 (0.28)	0.476
ALP (IU/L)	day 0	327.72 (290.90)	362.71 (357.99)	0.674
	day 1	255.81 (194.08)	283.22 (186.25)	0.54
	day 2	252.77 (214.62)	330.24 (330.80)	0.279
	day 3	270.18 (184.96)	323.81 (308.08)	0.382
	day 5	276.21 (166.61)	369.69 (466.70)	0.317
	day 7	296.57 (145.90)	382.18 (341.37)	0.207
	day 10	326.86 (162.12)	418.10 (417.71)	0.284
ALT (IU/L)	day 0	62.84 (89.26)	115.30 (209.89)	0.129
	day 1	78.07 (127.98)	135.07 (233.97)	0.162
	day 2	90.37 (168.76)	115.47 (198.39)	0.537
	day 3	106.90 (224.77)	122.61 (227.07)	0.754
	day 5	94.65 (153.06)	101.85 (171.84)	0.846
	day 7	65.15 (63.89)	79.34 (103.25)	0.469
	day 10	68.19 (68.87)	63.49 (75.34)	0.781
AST (IU/L)	day 0	114.02 (147.40)	229.47 (430.63)	0.092
	day 1	135.29 (188.04)	274.35 (522.03)	0.096

	day 2	153.38 (341.98)	180.19 (246.58)	0.679
	day 3	192.90 (549.88)	159.44 (255.87)	0.719
	day 5	120.82 (305.89)	103.17 (117.07)	0.729
	day 7	61.21 (67.53)	68.68 (100.29)	0.698
	day 10	74.95 (160.93)	44.42 (30.49)	0.255
LDH	day 0	407.14 (207.25)	556.49 (679.65)	0.166
(IU/L)	day 1	368.42 (215.27)	495.57 (548.45)	0.159
	day 2	344.37 (235.32)	381.98 (215.62)	0.447
	day 3	365.35 (308.27)	391.23 (279.30)	0.689
	day 5	351.24 (235.63)	355.95 (155.61)	0.916
	day 7	316.47 (157.25)	332.00 (131.56)	0.635
	day 10	300.60 (146.05)	284.13 (81.80)	0.55
Bil	day 0	1.15 (0.86)	1.67 (1.24)	0.023
(mg/dL)	day 1	0.98 (0.77)	1.69 (3.10)	0.139
	day 2	0.94 (0.88)	1.26 (1.12)	0.141
	day 3	1.02 (1.21)	1.23 (1.08)	0.396
	day 5	1.28 (2.29)	1.64 (3.14)	0.562
	day 7	1.32 (2.66)	1.30 (1.90)	0.972
	day 10	1.33 (3.41)	1.53 (2.74)	0.778
BUN	day 0	39.89 (26.37)	45.96 (36.80)	0.367
(mg/dL)	day 1	39.05 (27.09)	40.15 (28.01)	0.849
	day 2	35.19 (26.29)	133.08 (652.19)	0.334
	day 3	31.43 (24.80)	33.27 (41.88)	0.807
	day 5	26.11 (20.12)	25.73 (28.18)	0.945
	day 7	26.54 (19.53)	22.68 (18.80)	0.371
	day 10	31.60 (34.35)	28.26 (39.51)	0.697
Cr	day 0	2.21 (2.14)	2.30 (2.44)	0.841
(mg/dL)	day 1	1.95 (2.06)	4.77 (20.44)	0.361
	day 2	1.63 (1.98)	1.48 (1.50)	0.693
	day 3	1.50 (1.75)	1.31 (1.39)	0.574
	day 5	1.47 (1.59)	1.15 (1.17)	0.299
	day 7	1.39 (1.60)	1.18 (1.24)	0.505
	day 10	57.95 (344.70)	1.78 (3.31)	0.318
Na	day 0	140.62 (7.94)	139.64 (6.89)	0.527

(mEq/L)	day 1	142.49 (7.64)	140.89 (6.82)	0.308
	day 2	142.33 (6.85)	141.19 (6.91)	0.444
	day 3	140.71 (8.02)	140.53 (6.15)	0.908
	day 5	141.72 (4.51)	140.38 (5.32)	0.228
	day 7	140.92 (5.58)	140.27 (4.52)	0.565
	day 10	140.05 (5.26)	139.92 (3.77)	0.9
Cl	day 0	102.53 (19.24)	103.16 (7.29)	0.852
(mEq/L)	day 1	106.83 (18.63)	105.34 (18.37)	0.721
	day 2	103.79 (25.81)	108.45 (7.03)	0.276
	day 3	108.95 (6.47)	107.70 (6.66)	0.408
	day 5	102.80 (23.65)	107.13 (6.22)	0.275
	day 7	104.00 (18.53)	107.19 (4.32)	0.312
	day 10	100.58 (25.74)	103.46 (17.81)	0.592
RBC	day 0	3.93 (0.84)	4.05 (0.98)	0.504
(x 10^6/uL)	day 1	9.77 (42.12)	3.50 (0.68)	0.315
	day 2	3.37 (0.55)	3.35 (0.67)	0.9
	day 3	3.35 (0.49)	4.17 (4.97)	0.291
	day 5	3.53 (0.75)	3.74 (1.94)	0.526
	day 7	3.39 (0.57)	53.42 (319.13)	0.331
	day 10	4.31 (5.76)	3.34 (0.76)	0.308
Hb	day 0	12.72 (4.73)	12.86 (2.87)	0.855
(g/dL)	day 1	11.20 (3.90)	11.03 (1.95)	0.792
	day 2	10.45 (1.74)	10.55 (1.88)	0.797
	day 3	10.37 (1.39)	10.79 (1.98)	0.267
	day 5	10.40 (1.88)	10.89 (2.15)	0.283
	day 7	10.37 (1.83)	12.42 (10.62)	0.238
	day 10	10.27 (1.85)	12.71 (13.06)	0.271

Mean (standard deviation)

Alb: albumin, Bil: bilirubin, Cr: creatinine

* shows statistically significance ($p < 0.01$).

Supplemental Table 7. Kaplan–Meier analysis of the severe and moderate groups

Moderate group (n = 51)				
		Survival	Non-survival	Lo- rank test p
28 days	Control (n = 24)	24 (100%)	0	
	rhTM (n= 27)	25 (93%)	2 (7%)	0.178
90 days	Control (n = 24)	22 (92%)	2 (8%)	
	rhTM (n = 27)	22 (81%)	5 (19%)	0.278
Severe group (n = 41)				
		Survival	Non-survival	Log-rank test p
28 days	Control (n = 21)	12 (57%)	9 (43%)	
	rhTM (n = 20)	14 (70%)	6 (30%)	0.376
90 days	Control (n = 21)	11 (52%)	10 (48%)	
	rhTM (n = 20)	12 (60%)	8 (40%)	0.524

Moderate group comprises patients with APACHE II score < 20 points.
Severe group comprises patients with APACHE II score ≤ 20 points.

Supplemental Table 8. Kaplan–Meier analysis of patients who experienced disseminated intravascular coagulation resolution

		Within 3 days		
		Survival	Non-survival	Log-rank test p
28 days	Control	13	4	
	rhTM	27	4	0.358
90 days	Control	11	6	
	rhTM	25	6	0.231
		Within 7 days		
		Survival	Non-survival	Log-rank test p
28 days	Control	28	5	
	rhTM	39	5	0.676
90 days	Control	26	7	
	rhTM	34	10	0.901

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Can recombinant human thrombomodulin increase survival among patients with severe septic-induced disseminated intravascular coagulation: a single-center, open-label, randomized controlled trial

Akiyoshi Hagiwara, MD, PhD. 1); Noriko Tanaka, M.H.S, Ph.D. 2); Tatsuki Uemura, MD. 1); Wataru Matsuda, MD. 1); and Akio Kimura, MD, PhD. 1)

1) Department of Emergency Medicine and Critical Care, National Center for Global Health and Medicine,

1-21-1 Toyama, Shinjyuku-ku, Tokyo,

162-8655, Japan

2) Biostatistics Section, Department of Data Science Clinical Science Center, National Center for Global Health and Medicine,

1-21-1 Toyama, Shinjyuku-ku, Tokyo,

162-8655, Japan

Corresponding author

Akiyoshi Hagiwara, MD, PhD

Department of Emergency Medicine and Critical Care, National Center for Global Health and Medicine

Address; 1-21-1 Toyama, Shinjyuku-ku, Tokyo, 162-8655 Japan

Tel; +81-3-3202-7181, Fax; +81-3-3207-1038

Email: ahagiwar@hosp.ncgm.go.jp

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Abstract

Objective: To determine whether treatment with recombinant human thrombomodulin (rhTM) increases survival among severe septic patients with sepsis-induced disseminated intravascular coagulation (DIC)

Design: Single-center, open-label, randomized controlled trial

Setting: Single tertiary hospital

Participant: 92 severe septic patients with sepsis-induced DIC

Interventions: Patients with DIC scores ≥4, as defined by the Japanese Association of Acute Medicine, were diagnosed with DIC. The envelope method was used for randomization. The treatment group (rhTM group, n = 47) was intravenously treated with rhTM within 24 h of admission (day 0), and the control group (n = 45) did not receive any anti-coagulants, except in cases of deep venous thrombosis and pulmonary embolism.

Primary and secondary measurements: Data were collected on days 0 (admission), 1, 2, 3, 5, 7, and 10. The primary outcome was survival at 28 and 90 days. The secondary endpoints comprised changes in DIC scores, platelet counts, D-dimer, antithrombin III (ATIII), and C-reactive protein (CRP) levels, and Sequential Organ Failure Assessment (SOFA) scores. All analyses were conducted on an intent-to-treat basis.

Main Results: The 28-day survival rates were 84 and 83% in the control and rhTM groups, respectively (p = 0.745, log rank test). The 90-day survival rates were 73% and 72% in the control and rhTM groups, respectively (p = 0.94, log rank test). Meanwhile, the rates of recovery from DIC (<4) were significantly

higher in the rhTM group than in the control group (p = 0.001, log rank test). Relative change from baseline of D-dimer levels were significantly lower in the rhTM group than in the control group, on day 3 and 5.

Conclusion: rhTM treatment decreased D-dimer levels and facilitated DIC recovery in severe septic patients with sepsis-induced DIC. However, the treatment did not improve survival in this cohort.

Strengths of this study

- This study is the first randomized controlled trial to evaluate the efficacy of recombinant thrombomodulin (rhTM) for patients with severe sepsis.
- rhTM was administered to patients with severe sepsis and DIC, which was defined by the Japanese Association of Acute Medicine criteria.
- In the control group, no anti-coagulant agent was administered.
- The primary outcomes were the 28- and 90-day survival rates.

Limitations

- This study was not a double-blind study.
- This study might have presented a difference in the disease severity compared with other studies.

Introduction

Thrombomodulin is a cell membrane protein expressed on vascular endothelium. Although thrombomodulin specifically binds to thrombin and inhibits thrombin activity, resulting in anti-coagulant action, it also has anti-inflammatory effects and regulates high mobility group box 1 (HMGB1) protein activity, a systemic inflammation mediator. [1, 2]

In Japan, a multi-center, prospective, randomized, double-blind, phase III clinical trial [3] of recombinant thrombomodulin (rhTM), an anti-coagulant agent used for disseminated intravascular coagulopathy (DIC), was performed from 2000 to 2005 and included 234 patients with DIC caused by infection or hematologic malignancy. Results showed that although rhTM was associated with a significantly higher DIC resolution rate than heparin, this rate was not significantly different for patients with infection. Further, no difference in 28-day mortality rates of patients with infection or hematologic malignancy was observed. The trial had several weaknesses: 1) the primary outcome was the DIC resolution rate, which is a physiological parameter and 2) the control group included patients with DIC who were treated with heparin, which is not the established and standard treatment for sepsis-induced coagulopathy [4].

In 2011, Yamakawa et al. [5] reported a retrospective historical control study with the mortality rate as the primary outcome. Twenty severe septic patients with sepsis-induced overt DIC (DIC criteria of the International Society on Thrombosis and Haemostasis) who received rhTM between November 2008 and October 2009 were compared with 45 patients who did not receive rhTM between January 2006 and

September 2008. The 28-day mortality rate was 25% for the rhTM group versus 47% for the control group. The Sequential Organ Failure Assessment (SOFA) score and C-reactive protein (CRP) and fibrinogen degradation product (FDP) levels were significantly decreased in the rhTM group, whereas the platelet counts were significantly increased. Further, rhTM treatment also improved respiratory function in patients with sepsis-induced DIC. [6]

In 2013, a retrospective cohort study adjusted by the propensity score was performed in patients with Japanese Association for Acute Medicine (JAAM) DIC scores ≥ 4 who required mechanical ventilation, exhibited multiple organ failure, and presented with platelet counts <80,000/mm^3. Mortality rates were significantly lower in patients treated with rhTM than in those who did not receive the therapy [7]. Although these studies investigated the mortality rate as the primary outcome, they were all retrospective cohort studies, which had certain biases.

In 2013, Vincent et al. reported a phase IIb double-blind randomized controlled trial (RCT) of rhTM, [8] in which patients who fulfilled the DIC criteria of the International Society on Thrombosis and Haemostasis were treated with rhTM or a placebo. Results showed that the 28-day mortality rate tended to be lower in the rhTM group.

It remains unclear whether rhTM is effective in treating severe septic patients with sepsis-induced DIC. Therefore, studies with a high evidence level are required. Our open-label RCT aimed to investigate whether rhTM treatment increases 28-day and 90-day survival rates in patients with severe sepsis and JAAM DIC scores ≥ 4 [9]).

Materials and Methods

This single-center open-label RCT was approved by our institutional ethics committee (NCGM-G-001163-00). Written informed consent was obtained from all participating patients or their legal representatives. Patients aged ≥16 years who were transferred to our hospital with severe sepsis were enrolled if their JAAM DIC scores were ≥4 within 24 h of admission (Table 1) [9].

Table 1. Japanese Association for Acute Medicine disseminated intravascular coagulation criteria

	Score
Systemic inflammatory response syndrome criteria	
>=3	1
0 – 2	0
platelet count, x 10^9/L	
< 80 or > 50% decrease within 24 h	3
>= 80 and < 120; or 30% decrease within 24 h	1
> 120	0
Prothrombin time	
>= 1.2	1
< 1.2	0
Fibrin/fibrinogen degradation products, $mg \cdot L^{-1}$	
>=25	3
>=10 and < 25	1
<10	0
Diagnosis	
>= 4 points	DIC

JAAM, the Japanese Association for Acute Medicine
DIC, Disseminated intravascular coagulation

The exclusion criteria were 1) refusal to participate; 2) refusal of aggressive intensive treatment,

including hemodialysis, mechanical ventilation, and catecholamine administration; 3) emergency surgery within 24 h of admission; 4) intracranial, pulmonary, and/or intestinal hemorrhage; 5) fulminant hepatitis, decompensated liver cirrhosis, or other irreversible severe hepatic disease; 6) past history of hypersensitivity to rhTM, and 7) pregnancy or potential pregnancy.

Number of cases and study duration

When our study was planned, the report by Yamakawa et al. [5] was the only study that investigated the efficacy of rhTM in patients with severe sepsis and sepsis-induced DIC. Therefore, the required number of patients was calculated on the basis of their report. When the observation and follow-up periods were set as 2 years and 90 days, respectively, each group required 47 patients to achieve over 80% power with $\alpha = 0.05$ on a log-rank test. At our institute, 53 and 52 patients with severe sepsis or septic shock who fulfilled the JAAM DIC criteria and who did not undergo emergency surgery within 24 h after admission were admitted in 2010 and 2011, respectively. The number of patients required for the 2-year study was estimated to be 100. The enrollment period was August 2012 to July 2014.

Randomization

Patients who fulfilled the inclusion criteria were randomized into the rhTM or control group using the envelope method. Each opaque envelope enclosed a piece of paper specifying either rhTM or control group assignment. We created 50 envelopes for each group assignment, shuffled them, and placed them in the designated storage box. Pre-registered co-investigators randomly selected envelopes from the box and

treated patients according to group assignment.

Treatment protocol

In both groups, patients were treated under the Surviving Sepsis Campaign 2008 Guideline, [10] in which grade I ("recommendation as strong") denoted mandatory treatment and grade II ("recommendation as weak") required treatment according to the attending physician's judgment.

The attending physician administered rhTM to patients within 3 h after randomization. rhTM (380 U/kg) was intravenously administered for 30 min.

Treatment was performed for a maximum of 6 days. When the JAAM DIC score was <4, rhTM treatment was terminated. In the control group, no anti-coagulant agent was administered, except in cases of deep venous thrombosis and pulmonary embolism, for which unfractionated heparin was administered. Unfractionated heparin was also administered to patients in the rhTM group with deep venous thrombosis and pulmonary embolism.

Investigated parameters

The baseline data were collected after randomization. We obtained the following scores and laboratory data at the time of randomization: Acute Physiology and Chronic Health Evaluation II (APACHE III), SOFA, and JAAM DIC scores; prothrombin time/international normalized ratio (PTINR); and fibrinogen, D-dimer, antithrombin III (ATIII), soluble serum thrombomodulin (TM), and procalcitonin (PCT) levels. We also measured the following scores and data at 24 h, 48 h, 72 h, 5 days, 7 days, and 10 days after

admission: SOFA and JAAM DIC scores, PTINR, and fibrinogen, D-dimer, and ATIII levels. Other laboratory tests included red blood cell (RBC) and white blood cell (WBC) counts and hemoglobin, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine, electrolyte (Na^+, K^+, and Cl^-), and CRP levels, which were measured at the time of randomization and 24 h, 48 h, 72 h, 5 days, 7 days, and 10 days after admission.

We calculated the relative change from baseline for coagulation and inflammation data and albumin levels using the formula relative change from baseline = ([measurement day value − day 0 value]/day 0 value). The relative change from baseline of the SOFA score was calculated using the formula (SOFA score at measurement day – SOFA score at day 0).

We also calculated the number of patients who required mechanical ventilation and the number of ventilator-free days. The number of ventilator-free days was defined as the number of days without assisted mechanical ventilation through day 28. For patients who did not survive to 28 days, the value was set as 0 days. Requirement or discontinuance of mechanical ventilation was decided by the stuff physicians in the emergency department. Supplemental table 1 shows the criteria for weaning of mechanical ventilation [11]. We recorded the number of patients who required catecholamine treatment and its duration, which was performed according to the recommendations of the Surviving Sepsis Campaign 2008 Guideline, and recorded blood (concentrated RBCs, fresh frozen plasma [FFP], and platelets) and blood derivative administration amounts at 72 h, 28 days, and 90 days after admission. We investigated hemorrhage-related side effects and the timing of hemorrhage occurrence.

Adverse events

Adverse events were monitored prospectively via the daily evening conference. When adverse events occurred, one principle investigator (A.H.) reported them to our institutional ethics committee.

Adverse events were evaluated for the first 90 days after enrollment. Adverse events that were urgently reported were as follows: 1) death during the study, 2) life-threatening hemorrhage (e.g., intracranial, pulmonary, or intestinal tract hemorrhage), 3) extended hospitalization due to hemorrhage, and 4) permanent disability and dysfunction due to hemorrhage. These events were assessed by the institutional ethics committee as well as external experts.

Endpoints

The primary outcomes were the 28- and 90-day survival rates. The secondary outcomes included 72-h survival rates; number of days until DIC resolution [9]; changes in SOFA scores, platelet counts, D-dimer values, and CRP levels; blood and blood derivative administration amounts during the first 72 h after diagnosis; and number of mechanical ventilation-free days.

Data Analysis

An intent-to-treat analysis was used according to initial group assignment. When the basic assumptions of Student's *t*-test were not satisfied, a logarithmic transformation of the variables or the Mann–Whitney test was performed. For repeated comparisons, Bonferroni's correction was used. As our

longitudinal data have comparisons with six hypotheses between the two groups, $p < 0.01$ (0.05/6) was considered statistically significant. Kaplan–Meier analysis was used for outcome analysis, in which 72-h, 28-day, or 90-day survival was set as the event occurrence. The log-rank test was used to compare the two groups. All p values were two-sided, and $p < 0.05$ or $p < 0.01$ was considered statistically significant.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan),[12] which is a graphical user interface for R v3.1.1 (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Study duration and enrolled patients

In total, 74 patients were enrolled through July 2014, which was less than planned. An extension of the patient enrollment period until February 2015 was approved by the institutional ethics committee. During the study period, 232 patients with severe sepsis were admitted to the hospital and provisionally enrolled in this study. Although 105 patients developed DIC within 24 h after admission, five patients were excluded according to the exclusion criteria. Informed consent could not be obtained from eight other patients, including two patients who died. The two patients were solitary individuals, and we could not contact their legal representatives within 24 h after admission. Thus, 92 patients were included in this study (Fig. 1).

Baseline variables

Table 2 shows the patient baseline variables. The control and rhTM groups included 45 and 47 patients, respectively. The mean patient ages in the two groups were 77.2 and 74.7 years, respectively. Almost all patients were elderly. Approximately 65% of patients were male. The mean APACHE II score in the control group was 19.7 points, compared to 17.8 points in the rhTM group. The mean soluble serum TM values were 6.3 ng/mL in the control group and 8.0 ng/mL in the rhTM group. The mean PCT levels were 36.8 ng/mL in the control group and 39.3 ng/mL in the rhTM group.

Table 2. Baseline patient characteristics

Characteristics	Control (n = 45)	rhTM* (n = 47)
Age	77.2 (73.6, 80.7)	74.7 (70.6,78.8)
Male, n (%)	28 (62.2%)	32 (68.1%)
APACHE II	19.7 (18.0, 21.5)	17.8 (16.2, 19.4)
Soluble TM** (M: 2.1–4.1, F: 1.8–3.9 ng/mL)	6.3 (5.5, 7.0)	8.0 (5.7, 10.2)
PCT (<0.5 ng/mL)	36.8 (17.6, 56.1)	39.3 (19.0, 59.7)

*rhTM, recombinant thrombomodulin. The rhTM values were measured before the infusion of rhTM. The continuous variables were the mean (95% confidence interval).

Follow up variables

Table 3 shows the patient follow-up variables. More patients developed sepsis-induced hypotension and received vasopressors in the control group than in the rhTM group. Bacteremia was diagnosed in approximately 50% patients. The frequency of bacteremia was slightly higher in the rhTM group. The most frequent infection site was the lungs, comprising approximately 40% of infections, followed by the urinary tract/kidneys, gastrointestinal tract, and skin/tissue. Approximately 64% of the responsible organisms were gram-negative bacilli in both the control and rhTM groups, and 36% were gram-positive cocci. The most frequently used antibiotic was carbapenem. Renal replacement therapy was initiated in six and five patients

in the control and rhTM groups, respectively. Mechanical ventilation was used in 26 patients in the control group and 21 in the rhTM group. Approximately 50% patients required mechanical ventilation. The median [25th percentile, 75th] of rhTM administration duration was 2 days [1, 5 days].

Table 3. Follow-up variables

Characteristics	Control (n = 45)	rhTM* (n = 47)	Odds ratio (95% CI)	p value
Sepsis-induced hypotension[#], n (%)	26 (57.8)	17 (36.1)	0.42 (0.96 – 6.09)	0.059*
Vasopressor, n (%)	27 (60.0)	16 (34.0)	0.35 (0.13 – 0.87)	0.021*
Norepinephrine, n (%)	23 (51.1)	13 (28.9)		
Dopamin, n (%)	1 (2.2)	1 (2.2)		
Dobutamin, n (%)	1 (2.2)	1 (2.2)		
Epinephrine, n (%)	2 (4.45)	1 (2.2)		
Bacteremia (blood culture positive)	22 (48.9)	29 (61.7)	1.67 (0.68 – 4.19)	0.294*
Site of infection, n (%)				0.795**
Lang	17 (37.8)	19 (40.4)		
Urinary tract/kidney	18 (40.0)	13 (27.7)		
Gastrointestinal	8 (8.8)	5 (10.6)		
Skin/soft tissue	3 (6.7)	4 (8.5)		
Others	2 (44.4)	3 (6.4)		
Responsible organism				
Gram-negative rod	27 (60.0)	32 (68.0)	1.42 (0.56 – 3.66)	0.515*
Gram-positive coccus	18 (40.0)	15 (31.9)		
Antibiotic				
Carbapenem	26 (57.8)	31 (66.0)		0.530**
Cephalosporin	18 (40.0)	14 (29.8)		
Other	1 (2.2)	2 (4.3)		
Renal replacement therapy, n	6 (13.3)	5 (10.6)	0.78 (0.17 – 3.33)	0.756*
Duration, day	9.0 [8.3, 13.5][$]	3.0 [2.0, 6.0][$]	NA	0.099[$$]
Mechanical ventilation, n (%)	26 (57.8)	21(44.7)	0.59 (0.24 – 1.46)	0.220*

*Fisher's exact test was performed. ** chi-squared test was performed.

$ The data were shown median and 25 and 75 percentiles; [25, 75perventile].
$$ Mann-Whitney test was performed.
NA: none available
Sepsis-induced hypotension was defined as follows; despite adequate fluid resuscitation, vasopressors required to maintain MAP ≥65 mm Hg.

Outcome

The 72-h survival rates were 93% and 91% (Fisher's exact test, p = 0.742) and 28-day survival rates were 84% and 83% (Fisher's exact test, p = 0.717) in the control and rhTM groups, respectively. Supplemental Table 2 shows the results of Kaplan–Meier analysis, and Figure 2 shows Kaplan–Meier curves for 90-day survival, illustrating survival rates of 73% and 72% in the control and rhTM groups, respectively (log-rank test, p = 0.994).

DIC resolution

The number of patients in whom DIC was resolved within 72 h in the rhTM and control groups were 56 (27/48) and 40% (17/42), respectively (odds ratio = 2.45, 95% confidence interval = 0.95–6.52, p = 0.0516, Fisher's exact test). The number of patients in whom DIC resolved within 7 days in the rhTM and control groups were 91 (39/43) and 61% (27/41), respectively (odds ratio = 4.96, 95% confidence interval = 1.36–22.97, p = 0.0075, Fisher's exact test). Figure 3 shows the changes in the DIC score through 10 days. The mean DIC score was significantly lower in the rhTM group, beginning on day 5 (p < 0.01).

Coagulation data

Supplemental Table 3 shows data for D-dimer, platelet, PTINR, fibrinogen, and ATIII. The relative changes from baseline in the levels of D-dimer were significantly lower in the rhTM group than in the control group, on days 3 and 5. The relative changes from baseline for platelet counts, PTINR, fibrinogen,

and ATIII were not different between the groups at any time point.

Inflammation data (Supplement Table 3)

WBC and CRP counts were not different between the groups at any time point.

SOFA scores (Supplemental Table 4)

The relative changes from baseline for respiratory SOFA scores and total SOFA scores were not significantly different between the groups at any time point.

Ventilator-free days, blood transfusion amounts, and albumin and heparin use (Supplemental Table 5)

The mean numbers of ventilator-free days in the rhTM and control groups were 15.5 (10.7–20.2) and 17.5 days (9.2–17.7), respectively. The difference of 2.0 days (−4.4–8.4) between the groups was not significant (p = 0.530). The transfusion amounts of RBCs, FFP, and platelets were not different between the groups. Four patients (8.5%, 4/47) were administered albumin in the rhTM group compared to 16 patients (35.6%, 16/45) in the control group. Seven patients with deep venous thrombosis in the control group and one in the rhTM group were treated with unfractionated heparin.

Other laboratory findings

Supplemental Table 6 shows albumin, ALP, ALT, AST, LDH, total bilirubin, BUN, creatinine, Na, Cl, RBC, and hemoglobin data for both groups at days 0, 1, 2, 3, 5, 7, and 10. Although serum albumin values were significantly higher in the rhTM group only on day 1, the relative change from baseline was not significantly different between the groups. Other laboratory data were not significantly different between the groups.

Adverse events

One patient in the control group and two in the rhTM group experienced adverse events that required either treatment alterations or additional therapies. The patient in the control group developed melena caused by large intestinal diverticulitis and underwent transcatheter arterial embolization. One patient in the rhTM group developed bleeding from an ulcer at the anterior wall of the duodenal bulb (Foster Ib) and received RBC transfusion and endoscopic hemostasis (clipping). Another patient in this group was diagnosed with meningitis and severe sepsis with DIC and was treated with rhTM. Brain computed tomography (CT) on day 2 revealed a large cerebral infarction, and rhTM administration was discontinued. On day 3, the patient exhibited disturbances in consciousness; brain CT was repeated, revealing a hemorrhagic brain infarction. Following a review, the ethics committee concluded that the causal relationship between hemorrhagic complications and rhTM administration was unclear.

Post-hoc analysis

Survival rate

We selected the patients with mechanical ventilation from the study population and performed a survival analysis at 28 and 90 days for the rhTM and control groups. The 28-day survival rates in the treatment and control groups were 71 (15/21) and 69% (18/26) (odds ratio = 1.1, 95% CI = 0.27–4.8, p = 1.0, Fisher's exact test), respectively. The 90-day survival rates in the treatment and control groups were 62 (13/21) and 62% (16/26) (odds ratio = 1.0, 95% CI = 0.27–3.9, p = 1, Fisher's exact test), respectively.

APACHE II scores of ≥20 (severe) or <20 (moderate status; Supplemental table 7). The moderate

and severe groups included 51 and 41 patients, respectively. In the severe group, 90-day survival rates were 52% and 60% in the control and rhTM groups, respectively (Log-rank test p = 0.524), with similar findings recorded in the moderate group.

DIC resolution

The 28-day mortality rate among patients in whom DIC was resolved within 7 days was 2.6% (1/39) in the rhTM group compared to 50.0% (4/8) among those in whom DIC was not resolved (odds ratio = 0.03, 95% CI = 0.0–0.4, p = 0.0018, Fisher's exact test). In the control group, the 28-day mortality rate among patients in whom DIC was resolved within 7 days was 0% (0/27); conversely, the rate for those in whom DIC was not resolved was 50% (9/18) (odds ratio = 0, 95% CI = 0.0–0.2, p < 0.001, Fisher's exact test). The mortality rate was significantly lower among patients in whom DIC was resolved.

However, differences in the 28- and 90-day survival rates were not observed between the control and rhTM groups among patients who experienced DIC resolution within 3 or 7 days of admission (Supplemental Table 8). Differences in the 28- and 90-survival rates were not observed between patients who experienced DIC resolution within 3 days in the rhTM group and those who experienced resolution within 7 days in the control group. Supplemental Figure 1 shows the Kaplan–Meier curve.

Discussion

Our single-center, open-label RCT found that rhTM treatment did not increase 72-h, 28-day, or 90-day survival rates among severe septic patients with sepsis-induced DIC. The results were different from a series of reports describing the effectiveness of rhTM. [5-7, 13] According to our findings, a sample size of

approximately 23,000 would be required to demonstrate a significant difference between the rhTM and control groups within our observation period.

Through 2015, five retrospective studies reported the efficacy of rhTM in patients with sepsis and DIC [5-7, 13, 14]. These studies reported mortality rates of 8.3–40% in the rhTM group and 33–57% in the control group. These mortality rates were higher than our values. This may be explained by differences in disease severity. In four of the studies, patients with sepsis who required mechanical ventilation were included. [5-7, 14]. In contrast, one phase IIb study [8] and another retrospective subanalysis [15] of a phase III clinical trial [3] reported mortality rates of 17.8 in the rhTM group and 21.4% in the control group, respectively, and 21.6 in the rhTM group and 31.6% in the control group, respectively. The former study diagnosed DIC according to the ISTH criteria, and the latter study diagnosed DIC according to the JAAM DIC criteria. As we also administered rhTM to patients with sepsis according to the JAAM DIC criteria, our mortality rates may be lower than those of the retrospective studies. However, our mortality rates were similar to those of the two prospective studies. We believe that our results provide real-world evidence of the efficacy of rhTM in Japan.

rhTM treatment significantly decreased DIC scores compared with the control group, indicating the drug facilitated DIC resolution. Compared with the control group, rhTM treatment significantly lowered D-dimer levels on day 3 and 5. Those results almost matched those of two RCTs [3, 8]. However, platelet counts and prothrombin times were not different between the groups. Thus, decreases in FDP values may induce declines in the DIC score (the changes in the FDP values are shown in Supplemental Table 2).

Aikawa et al. [15] stated that “the 28-day mortality rate among patients in whom the DIC resolved

was 3.7% (1/27) in rhTM group, the rate for those in whom the DIC did not resolve was 46.2% (6/13) (p = 0.0026, Fisher's exact test). In the heparin treatment group, the 28-day mortality rate among patients in whom the DIC resolved was 15% (3/20); the rate for those in whom the DIC did not resolve was 43.8% (7/16) (p = 0.0732, Fisher's exact test)." They reported that "the 28-day mortality rates were significantly lower for patients in whom the JAAM DIC was resolved within 7 days than in those in whom the JAAM DIC was not resolved." Our results were similar to theirs.

We examined patients who experienced DIC resolution within 3 or 7 days, but no difference in survival rates was recorded between the rhTM and control groups. Moreover, survival rates were not different between patients in the rhTM group who experienced DIC resolution within 3 days and those in the control group who experienced DIC resolution within 7 days. These results illustrated that the 28-day mortality rates were lower for patients in whom JAAM DIC was resolved within 7 days, but the outcome did not change after the use of rhTM if patients recovered from DIC within 7 days.

There were no differences in SOFA scores, number of ventilator-free days, and volume of blood transfusion between the rhTM and control groups. Conversely, albumin and heparin use were lower in the rhTM group, although the small number of patients precludes any definitive conclusions. A decline in the DIC score by the rhTM use may not improve the outcome of severe septic patients with sepsis-induced DIC compared to the control group. Our study did not uncover sufficient evidence of the effects of treatment with rhTM for sepsis-induced DIC on patient outcome. However, rhTM use has been drastically increasing in Japan despite a lack of clear evidence of its effectiveness [16].

Our results unfortunately could not find an effectiveness of rhTM. Yet, we believe that the ongoing

Phase III study (Clinical trials. gov identifier. NCT01598831) could reveal whether our results would be closer to the truth or our study method would be inappropriate.

Study limitations

As this study was the open label RCT, this may have differences in the behavior of patients and/or study staff. In addition, it requires caution and prudence for interpretation of our results due to a single center study. Our entry criteria target the patients diagnosed as DIC in accordance with the JAAM DIC criteria. For the ongoing the Phase III study performed in Europe/the US, the entry criteria are set for cardiovascular dysfunction or respiratory failure and severe septic patients with PTINR > 1.40. Therefore, it is more severe than our entry criteria. Our study might show a difference in disease severity as compared to other studies. The number of patients as being calculated before the study might not possibly be appropriate. The ongoing Phase III study planned that the estimated enrollment was 800 patients. The small number of patients in our study may have caused no significant result.

Conclusion

rhTM treatment decreased D-dimer values in severe septic patients with sepsis-induced DIC but did not increase survival rates. We do not recommend the routine use of rhTM in these patients.

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Contributors: MW, TU, and AH performed the acquisition of the data. TU, AH, and NT revised the manuscript and approved the final version. AK and AH contributed to the conception of the work and approved the final version. NT and AH performed the statistical analysis. In addition, all authors had agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data sharing statement: Full data and data analysis files are available on request (hokabe@hosp.ncgm.go.jp or ahagiwar@hosp.ncgm.go.jp).

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Figure legends

Figure 1

Patient flow diagram

Figure 2

Kaplan–Meier curve of 90 days survival rate. The log rank test showed that p = 0.944.

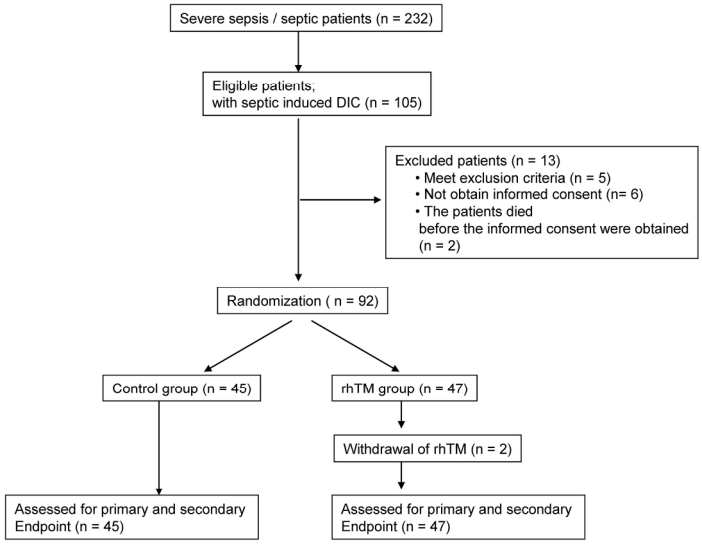
Figure 3

Change of DIC score. Unpaired t test with Bonferroni correction was performed in the rhTM group vs. control group at days 0, 1, 2, 3, 5, 7, and 10. P < 0.001 (0.05/6) was considered statistically significant.

Supplemental Figure 1

Kaplan–Meier curve of the patients with DIC resolution within 3 days in the rhTM group and within 7 days in the control group. The log rank test showed that p = 0.871.

Fig 1 Patient flow diagram



209x148mm (300 x 300 DPI)

Figure 2

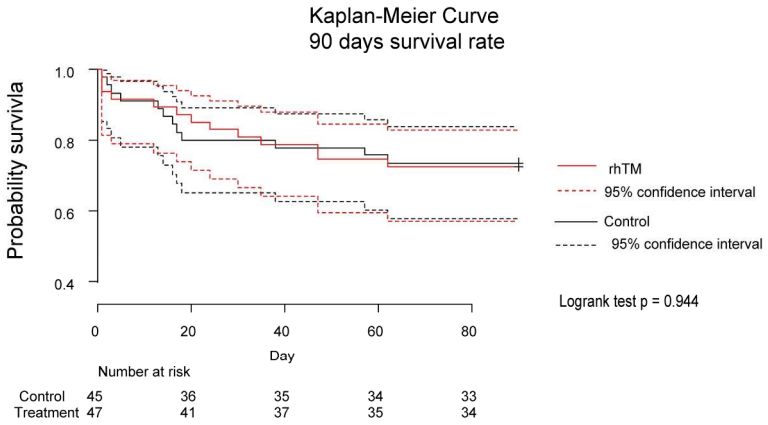


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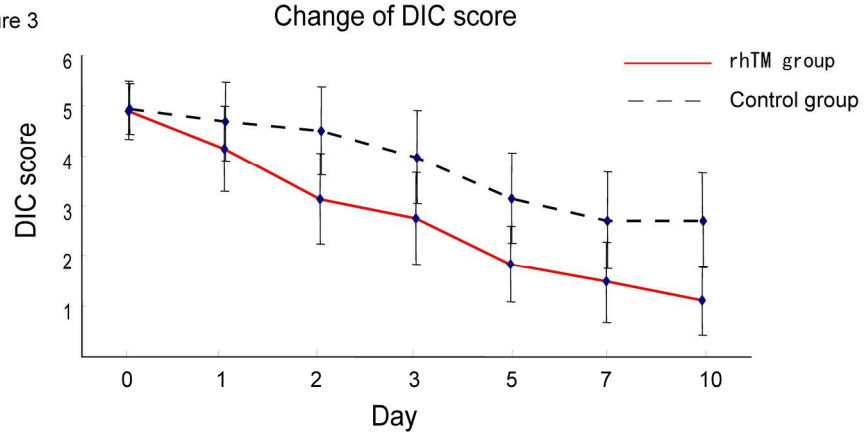
Figure 3



The dots show the mean.
The erro bars show the 99% confidence interval.

Day	0	1	2	3	4	5	7	10
p value		0.835	0.185	0.04	0.011	0.003	0.008	<0.001

Unpaired t tests were performed with Bounferroni correction (p = 0.01)
The mrean values were significalntly difference on day 5, 7, and 10

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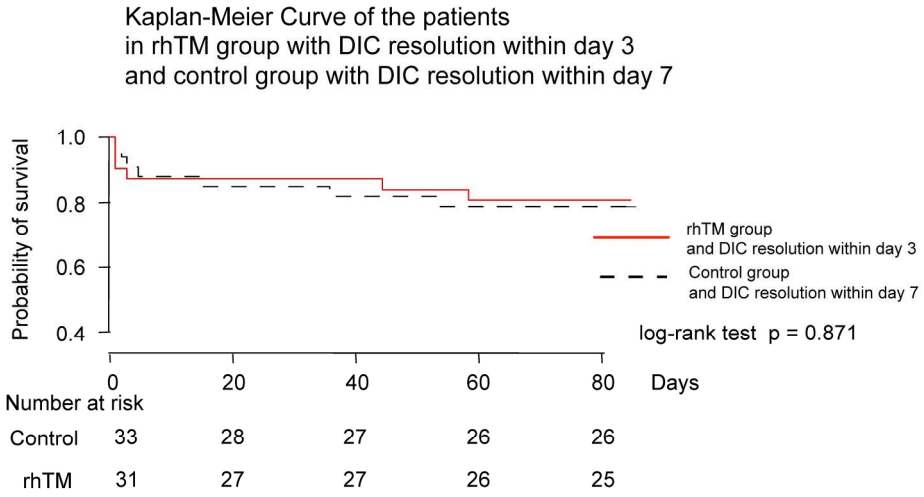
Supplemental Figure 1



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Supplement Table 1. Criteria for discontinuing mechanical ventilation

Criteria	Description
Objective measurements	Adequate oxygenation ($P_{O_2} \geq 60$ mm Hg on $F_{IO_2} \leq 0.4$; PEEP ≤ 5–10 cm H_2O; $P_{O_2}/F_{IO_2} \geq 150–300$);
	Stable cardiovascular system ([HR ≤ 140; stable BP; no (or minimal) pressure)
	Afebrile (temperature < 38°C)
	No significant respiratory acidosis
	Adequate hemoglobin (Hb ≥ 8–10 g/dL)
	Adequate mentation (arousable, GCS ≥ 13, no continuous sedative infusions)
	Stable metabolic status (acceptable electrolytes)
Subjective clinical assessments	Resolution of the disease' acute phase, physician believes that discontinuation is possible, adequate cough

from reference [11]

Supplement table 2
Results of Kaplan–Meier analysis

Control group

Time	n. risk	n. event	survival	std.err	lower 95% CI	upper 95% CI
1	45	1	0.978	0.0220	0.853	0.997
2	44	1	0.956	0.0307	0.834	0.989
3	43	1	0.933	0.0372	0.807	0.978
5	42	1	0.911	0.0424	0.780	0.966
13	41	1	0.889	0.0468	0.753	0.952
14	40	1	0.867	0.0507	0.727	0.938
16	39	1	0.844	0.0540	0.701	0.923
17	38	1	0.822	0.0570	0.676	0.907
18	37	1	0.800	0.0596	0.651	0.891
38	36	1	0.778	0.0620	0.626	0.874
57	35	1	0.756	0.0641	0.602	0.856
62	34	1	0.733	0.0659	0.578	0.839

rhTM group

time	n. risk	n. event	survival	std.err	lower 95% CI	upper 95% CI
1	47	3	0.936	0.0357	0.815	0.979
3	44	1	0.915	0.0407	0.789	0.967
12	43	1	0.894	0.0450	0.763	0.954
17	42	1	0.872	0.0487	0.738	0.941
20	41	1	0.851	0.0519	0.713	0.926
24	40	1	0.830	0.0548	0.688	0.911
30	39	1	0.809	0.0574	0.664	0.895
35	38	1	0.787	0.0597	0.641	0.879
47	37	2	0.745	0.0636	0.594	0.846
62	35	1	0.723	0.0652	0.572	0.829

n.: number, std: standard, CI: confidence interval

Supplemental Table 3. Coagulation and inflammation data

Coagulation data

		Measurement value					Relative change from baseline			
		Control	rhTM	Difference (95% CI)	p value		Control	rhTM	Difference (95% CI)	p value
D-dimer	day 0	39.5 (21.9, 57.0)	30.2 (13.0, 47.3)	-9.3 (-33.8, 15.2)	0.320					
(μg/mL)	day 1	27.4 (17.3, 37.7)	18.3 (8.3, 28.3)	-9.2(-23.4, 5.1)	0.094	delta 1	-0.13 (-0.32, 0.05)	-0.29 (-0.46, -1.09)	-0.15 (-0.41, 0.10)	0.112
	day 2	17.7 (10.4, 25.0)	12.8 (5.5, 20.0)	-4.9(-15.2, 5.4)	0.214	delta 2	-0.17 (-0.42, 0.06)	-0.49 (-0.73, -0.25)	-0.31 (-0.65, 0.03)	0.017
	day 3	16.9 (11.4, 22.5)	9.6 (4.1, 15.0)	-7.4 (-15.1, 0.4)	0.014	delta 3	-0.11 (-0.39, 0.17)	-0.51 (-0.78, -0.24)	-0.40 (-0.79, -0.01)	0.008*
	day 5	18.5 (12.9, 24.1)	8.0 (2.6, 13.5)	-10.5 (-18.2, -2.7)	0.001*	delta 5	-0.01 (-0.37, 0.35)	-0.52 (-0.87, -0.18)	-0.52 (-1.02, -0.02)	0.008*
	day 7	20.6 (12.1, 29.2)	8.0 (-0.4, 16.5)	-12.6 (-24.6, -0.6)	0.007*	delta 7	0.23 (-0.41, 0.86)	-0.55 (-1.17, 0.07)	-0.78 (-1.66, 0.11)	0.024
	day	19.7 (13.2, 26.2)	7.0 (0.6, 13.5)	-12.7 (-21.8, -3.5)	<0.001*	delta 10	0.35 (-0.74, 1.39)	-0.43 (-1.48, 0.62)	-0.76 (-2.25, 0.74)	0.185
FDP	day 0	78.3 (35.5, 121.1)	62.3 (20.4, 104.1)	-16.0 (-75.9, 43.9)	0.483					
(μg/mL)	day 1	55.3 (32.7, 77.9)	32.0 (10.1, 53.8)	-23.4 (-54.8, 8.1)	0.053	delta 1	-0.01 (-0.26, 0.12)	-0.29 (-0.48, -0.10)	-0.22 (-0.49, 0.05)	0.035
	day 2	32.7 (18.2, 47.2)	25.3 (11.0, 39.6)	-7.4 (-27.8, 13.0)	0.339	delta 2	-0.20 (-0.44, 0.03)	-0.47 (-0.70, -0.24)	-0.27 (-0.59, 0.06)	0.036

	day 3	32.6 (21.2, 43.9)	18.9 (7.7, 30.1)	-13.7 (-29.6, 2.2)	0.026	delta 3	-0.09 (-0.38, 0.21)	-0.48 (-0.78, -0.19)	-0.40 (-0.81, 0.0)	0.014
	day 5	32.9 (20.9, 44.9)	14.5 (2.9, 26.1)	-18.4 (-35.1, -1.7)	0.005*	delta 5	-0.13 (-0.41, 0.15)	-0.57 (-0.84, -0.30)	-0.43 (-0.82, -0.05)	0.004*
	day 7	32.2 (20.0, 44.3)	13.3 (1.3, 25.3)	-18.9 (-36.0, -1.8)	0.005*	delta 7	-0.04 (-0.43, 0.35)	-0.58 (-0.96, -0.20)	-0.54 (-1.09, 0.01)	0.011
	day 10	30.7 (19.7, 41.6)	11.4 (0.4, 22.3)	-19.3 (-34.8, -3.8)	0.002*	delta 10	-0.20 (-0.48, 0.08)	-0.66 (-0.94, -0.38)	-0.46 (-0.85, -0.06)	0.003*
Platelet ($\times 10^4$ /μL)	day 0	13.3 (10.4, 16.3)	13.5 (10.6, 16.3)	0.11 (-4.0, 4.2)	0.946					
	day 1	10.5 (8.2, 12.8)	10.7 (8.5, 13.0)	0.27 (-2.9, 3.5)	0.824	delta 1	-0.12 (-0.31, 0.07)	-0.10 (-0.29, 0.08)	0.02 (-0.25, 0.28)	0.863
	day 2	9.3 (7.1, 11.5)	10.6 (8.4, 12.8)	1.3 (-1.8, 4.4)	0.276	delta 2	-0.17 (-0.34, -0.01)	-0.12 (-0.29, 0.04)	0.05 (-0.18, 0.28)	0.573
	day 3	9.4 (7.0, 11.8)	11.4 (9.1, 13.8)	2.1 (-1.3, 5.4)	0.108	delta 3	-0.17 (-0.36, 0.03)	-0.02 (-0.21, 0.17)	0.15 (-0.12, 0.42)	0.156
	day 5	12.2 (8.7, 15.8)	16.0 (12.5, 19.4)	3.7 (-1.2, 8.6)	0.051	delta 5	0.11 (-0.22, 0.44)	0.41 (0.09, 0.73)	0.30 (-0.16, 0.76)	0.086
	day 7	16.9 (12.7, 21.1)	22.2 (18.0, 26.3)	5.3 (-0.7, 11.2)	0.021	delta 7	0.57 (-0.14, 1.27)	1.30 (0.61, 1.99)	0.73 (-0.26, 1.72)	0.054
	day 10	22.1 (16.8, 27.5)	28.3 (23.1, 33.4)	6.2 (-1.3, 13.6)	0.032	delta 10	1.14 (0.22, 2.06)	1.93 (1.04, 2.81)	0.79 (-0.48, 2.06)	0.11
PT-INR	day 0	1.31 (1.14, 1.48)	1.42 (1.25, 1.58)	0.11 (-0.13, 0.34)	0.244					
	day 1	1.33 (1.23, 1.43)	1.35 (1.25, 1.45)	0.02 (-0.11, 0.16)	0.654	delta 1	0.02 (-0.04, 0.07)	-0.01 (-0.06, 0.05)	-0.03 (-0.10, 0.05)	0.376
	day 2	1.27 (1.17, 1.36)	1.24 (1.15, 1.34)	-0.02 (-0.15, 0.11)	0.655	delta 2	-0.02 (-0.09, 0.05)	-0.09 (-0.16, -0.03)	0.07 (-0.17, 0.02)	0.053
	day 3	1.23 (1.14, 1.32)	1.20 (1.12, 1.29)	-0.02 (-0.15, 0.10)	0.635	delta 3	-0.05 (-0.11, 0.01)	-0.12 (-0.18, -0.06)	-0.07 (-0.16, 0.02)	0.042

	day 5	1.25 (1.17, 1.32)	1.19 (1.12, 1.27)	-0.05 (-0.16, 0.05)	0.196	delta 5	-0.03 (-0.11, 0.05)	-0.12 (-0.20, -0.04)	-0.09 (0.20, 0.02)	0.040
	day 7	1.29 (1.15, 1.44)	1.20 (1.06, 1.34)	-0.09 (-0.25, 0.11)	0.226	delta 7	-0.01 (-0.11, 0.10)	-0.12 (-0.22, -0.016)	-0.11 (-0.26, 0.04)	0.050
	day 10	1.23 (1.11, 1.35)	1.23 (1.11, 1.34)	-0.004 (-0.17, 0.16)	0.951	delta 10	-0.05 (-0.15, 0.04)	-0.10 (-0.19, -0.01)	-0.05 (-0.18, 0.09	0.374
Fib	day 0	457.1 (376.0, 538.2)	456.4 (376.2, 536.6)	-0.73 (-114.8, 113.3)	0.99					
(mg/dL)	day 1	445.0 (370.1, 519.4)	436.4 (364.5, 508.3)	-8.61 (-112.1, 94.9)	0.827	delta 1	-0.03 (-0.14, 0.09)	0.02 (-0.09, 0.13)	0.05 (-0.11,0.21)	0.433
	day 2	455.7 (381.3, 530.1)	473.0 (401.25, 544.8)	17.3 (-86.1, 120.7)	0.660	delta 2	0.06 (-0.12, 0.25)	0.18 (-0.01, 0.36)	0.11 (-0.15, 0.37)	0.299
	day 3	434.0 (353.7, 514.3)	457.3 (379.9, 534.8)	23.3 (-88.2, 134.)	0.583	delta 3	0.03 (-0.20, 0.25)	0.17 (-0.05, 0.38)	0.14 (-0.17, 0.45)	0.247
	day 5	414.6 (332.7, 496.6)	424.5 (346.6, 502.3)	9.8 (-103.2, 122.9)	0.819	delta 5	-0.04 (-0.29, 0.20)	0.15 (-0.08, 0.39)	0.19 (-0.14, 0.53)	0.134
	day 7	389.3 (318.4, 460.0)	391.5 (323.4, 459.6)	2.3 (-95.9, 100.5)	0.952	delta 7	-0.11 (-0.36, 0.14)	0.12 (-0.13, 0.37)	0.23 (-0.13, 0.58)	0.094
	day 10	335.8 (264.0, 407.6)	423.4 (354.5, 492.2)	87.6 (-11.916, 187.071)	0.025	delta 10	-0.17 (-0.48, 0.14)	0.19 (-0.11, 0.49)	0.36 (-0.07, 0.79)	0.028
ATIII	day 0	58.8 (50.7, 97.0)	62.8 (54.8, 70.7)	3.93 (-7.5, 15.3)	0.367					
(%)	day 1	48.9 (42.1, 55.7)	54.8 (48.2, 61.3)	5.85 (-3.6, 15.3)	0.106	delta 1	-1.62 (-0.25, -0.08)	-0.12 (-0.20, -0.03)	0.05 (-0.07, 0.16)	0.265
	day 2	51.3 (43.7, 58.8)	57.1 (49.8, 64.4)	5.85 (-4.6, 16.3)	0.144	delta 2	-0.14 (-0.23, -0.05)	-0.09 (-0.17, -0.003)	0.05 (-0.07, 0.17)	0.257
	day 3	55.0 (47.0, 63.0)	62.6 (54.7, 70.4)	7.60 (-3.6, 18.8)	0.078	delta 3	-0.08 (-0.18, 0.02)	0.02 (-0.07, 0.12)	0.10 (-0.03, 0.24)	0.049
	day 5	60.6 (52.4, 68.9)	69.7 (61.6, 77.7)	9.02 (-2.5, 20.6)	0.042	delta 5	0.02 (-0.11, 0.15)	0.17 (0.04, 0.30)	0.15 (-0.03, 0.33)	0.032

	day 7	64.5 (54.9, 74.1)	74.1 (64.9, 83.3)	9.58 (-3.7, 22.9)	0.061	delta 7	0.10 (-0.03, 0.23	0.20 (0.07, 0.32)	0.10 (-0.09, 0.28)	0.171
	day 10	66.5 (55.9, 77.1)	80.0 (69.8, 90.1)	13.4 (-1.3, 28.1)	0.018	delta 10	0.16 (0.02, 0.31)	0.28 (0.14, 0.41)	0.12 (-0.08, 0.31)	0.120

Inflammation data

		Measurement value					Relative change from baseline			
		Control	rhTM	Difference (95% CI)	p value		Control	rhTM	Difference (95% CI)	p value
CRP	day 0	20.5 (16.0, 25.0)	18.5 (14.0, 23.0)	-2.0 (-8.4, 4.4)	0.409					
(mg/dL)	day 1	19.2 (14.9, 23.5)	15.7 (11.5, 19.9)	-3.5 (-9.5, 2.5)	0.130	delta 1	1.7 (0.14, 3.27)	1.4 (-0.12, 2.98)	-0.28 (-2.48, 1.92)	0.740
	day 2	14.9 (11.5, 18.3)	10.8 (7.5, 14.1)	-4.1 (-8.8, 0.7)	0.027	delta 2	8.0 (-4.21, 20.25)	1.7 (-10.22, 13.67)	-6.3 (-23.39, 10.796)	0.334
	day 3	10.7 (7.2, 14.2)	7.7 (4.3, 11.0)	-3.0 (-7.8, 1.8)	0.104	delta 3	5.1 (-3.36, 13.48)	0.9 (-7.26, 8.98)	-4.2 (-15.90, 7.50)	0.347
	day 5	8.2 (5.6, 10.8)	5.2 (2.7, 7.7)	-3.0 (-6.6, 0.6)	0.031	delta 5	3.5 (-2.64, 9.63)	0.4 (-5.34, 6.18)	-3.1 (-11.50, 5.34)	0.337
	day 7	5.8 (3.7, 7.9)	4.0 (1.9, 6.0)	-1.8 (-4.7, 1.1)	0.100	delta 7	2.9 (-2.48, 8.20)	-0.04 (-5.11, 5.03)	-2.90 (-10.26, 4.46)	0.302
	day 10	8.5 (2.9, 14.1)	4.0 (-1.5, 9.4)	-4.5 (-12.3, 3.3)	0.131	delta 10	1.4 (-6.25, 9.14)	3.0 (-4.35, 10.41)	1.9(-9.08, 12.25)	0.695
WBC	day 0	12.63 (9.24, 16.02)	14.35 (11.03, 17.67)	1.7 (-3.02, 6.46)	0.343					
($\times 10^2/\mu L$)	day 1	14.55 (10.38, 18.72)	15.01 (10.89, 19.14)	0.4 (-5.40, 6.33)	0.836	delta 1	0.6 (-0.11, 1.37)	0.4 (-0.36, 1.11)	-0.2 (-1.30, 0.80)	0.532
	day 2	12.31 (9.14, 15.48)	12.98 (9.84, 16.11)	0.7 (-3.79, 5.12)	0.695	delta 2	0.6 (-0.12, 1.25)	0.2 (-0.43, 0.93)	-0.3 (-1.29, 0.64)	0.383

	day 3	11.13 (8.42, 13.84)	10.97 (8.29, 13.65)	-0.2 (-3.98, 3.65)	0.909	delta 3	0.7 (-0.13, 1.61)	0.04 (-0.81, 0.90)	-0.7 (-1.92, 0.53)	0.137
	day 5	10.34 (7.64, 13.04)	11.24 (8.64, 13.84)	0.9 (-2.84, 4.64)	0.528	delta 5	0.6 (-0.36, 1.55)	0.2 (-0.69, 1.15)	-0.4 (-1.7, 0.9)	0.465
	day 7	10.88 (8.42, 13.34)	10.84 (8.44, 13.23)	-0.05 (-3.47, 3.39)	0.975	delta 7	0.7 (-0.26, 1.62)	0.1 (-0.83, 0.99)	-0.6 (-1.91, 0.71)	0.230
	day 10	11.25 (9.48, 13.04)	9.49 (7.76, 11.22)	-1.8 (-4.24, 0.71)	0.064	delta 10	0.5 (-0.38, 1.40)	0.02 (-0.85, 0.89)	-0.5 (-1.73, 0.75)	0.298

mean (95% confidence interval)

PTINR, prothrombin time–international normalized ratio;

Fib, fibrinogen; AT III, antithrombin III; CRP, C-reactive protein; WBC, white blood cell

Relative change rate from baseline = ([measurement day value − day 0 value]/day 0 value).

This table includes fibrin/fibrinogen degradation products (FDP) value. This information was not noted in the main manuscript to avoid redundancy.

Supplemental Table 4. Sequential Organ Failure Assessment score (SOFA score)

		Measurement value					Relative change from baseline			
		Control	rhTM	Difference (95% CI)	p value		Control	rhTM	Difference (95% CI)	p value
SOFA(R)	day 0	2.0 (1.4, 2.6)	1.7 (1.1, 2.2)	-0.3 (-1.1, 0.5)	0.334					
(points)	day 1	2.0 (1.5, 2.5)	1.2 (0.7, 1.7)	-0.8 (-1.5, -0.1)	0.004*	delta 1	0.05 (-0.3, 0.4)	-0.4 (-0.7, -0.1)	-0.5 (-0.9, 0.02)	0.013
	day 2	1.6 (1.1, 2.1)	0.9 (0.4, 1.3)	-0.7 (-1.4, -0.1)	0.004*	delta 2	-0.3 (-0.7, 0.2)	-0.7 (-1.1, -0.2)	-0.4 (-1.0, 0.2)	0.088
	day 3	1.4 (0.9, 1.8)	0.7 (0.3, 1.2)	-0.6 (-1.3, 0.02)	0.012	delta 3	-0.5 (-1.0, -0.03)	-0.8 (-1.3, -0.3)	-0.3 (-0.9, 0.4)	0.247
	day 5	1.2 (0.7, 1.7)	0.6 (0.2, 1.1)	-2.2 (-1.3, 0.11)	0.029	delta 5	-0.7 (-1.2, -0.2)	-0.9 (-1.4, -0.4)	-0.2 (-0.9, 0.4)	0.343
	day 7	1.2 (0.7, 1.7)	0.6 (0.1, 1.1)	-0.6 (-1.3, 0.1)	0.021	delta 7	-0.7 (-1.2, -0.2)	-1.0 (-1.5, -0.5)	-0.3 (-1.1, 0.4)	0.225
	day 10	0.9 (0.5, 1.3)	0.4 (0.0, 0.8)	-0.5 (-1.1, 0.1)	0.031	delta 10	-1.1 (-1.7, -0.5)	-1.2 (-1.8, -0.6)	-0.1 -0.9, 0.7	0.737
	day 0	8.1 (7.1, 9.1)	7.3 (6.4, 8.3)	-0.7 (-2.1, 0.6)	0.367					
	day 1	8.0 (6.3, 9.7)	6.5 (4.8, 8.1)	-1.5 (-3.9, 0.8)	0.091	delta 1	0.02 (-0.9, 0.)	-0.8 (-1.7, 0.1)	-0.8 (-2.0, 0.5)	0.121
Total	day 2	6.9 (5.9, 7.9)	5.3 (4.2, 6.3)	-1.6 (-3.1, -0.1)	0.071	delta 2	-1.0 (-2.0, -0.01)	-1.8 (-2.8, -0.9)	-0.8 (-2.2, 0.6)	0.118
SOFA	day 3	6.0 (4.3, 7.6)	4.6 (2.9, 6.2)	-1.4 (-3.7, 0.9)	0.120	delta 3	-1.9 (-3.1, -0.8)	-2.6 (-3.7, -1.4)	-0.6 (-2.3, 1.0)	0.308
(points)	day 5	4.9 (3.2, 6.6)	3.5 (1.8, 5.1)	-1.4 (-3.8, 0.9)	0.113	delta 5	-3.2 (-4.6, -1.9)	-3.7 (-5.0, -2.4)	-0.5 (-2.3, 1.4)	0.490
	day 7	4.3 (2.6, 6.0)	2.6 (1.0, 4.3)	-1.6 (-4.0, 0.8)	0.075	delta 7	-3.8 (-5.3, -2.4)	-4.6 (-6.0, -3.2)	-0.7 (-2.8, 1.2)	0.317
	day 10	3.6 (2.0, 5.2)	2.4 (0.8, 4.0)	-1.2 (-3.5, 1.1)	0.159	delta 10	-4.8 (-6.2, -3.3)	-4.7 (-6.1, -3.3)	0.1 (-1.9, 2.1)	0.924

SOFA (R), SOFA scores of respiratory

Change rate from baseline = SOFA score of measurement day − SOFA score of day 0.

* shows statistically significance ($p < 0.01$).

Supplemental Table 5. Ventilator-free days, blood transfusion, and albumin and heparin use

Characteristics	Control (n = 45)	rhTM* (n = 47)	p value
Ventilator free day at day 28	15.5 (10.7, 20.2)*	17.5 (9.2, 17.7)*	0.530**
Blood transfusion (within 72 h)			
RBC (U)	8.0 [2.0, 10.0]$, n = 11	3.0 [2.0, 8.0], n = 10	0.089$$
FFP (U)	10.0 [8.0, 20.0], n = 5	5.0 [4.0, 24.0], n = 7	0.100$$
PC (U)	30.0 [10.0, 70.0], n = 6	20.0 [10.0, 90.0], n = 5	0.710$$
Albumin use, n (within 72 h)	16 (35.6)	4 (8.5)	0.002$$
Albumin preparation (mg),n = 16, 4	50.0 [34.4, 65.6]	37.5 [12.5, 84.4]	0.632$$
*Heparin use, n (%)	7 (15.6)	1 (2.2)	NA

Heparin was used on diagnosis of deep venous thrombosis

Ventilator free day at day 28 was defined as the number of days a patient had breathed without mechanical ventilation for at least 48 h continuously during a 28-day period. Patients who did not survive till 28 days were assigned 0 ventilator free days.

RBC, red blood cell; FFP, fresh freeze plasma; PC, platelet

* mean (95% confidence interval), ** An unpaired t test was performed.

$ median [25percentile, 75percentile], $$ Mann-Whitney test was performed.

NA: none available.

Supplemental Table 6. Other Laboratory findings

		Control	rhTM	P value
	n	45	47	
Alb (g/dL)	day 0	2.65 (0.72)	2.94 (0.63)	0.051
	day 1	2.07 (0.38)	2.33 (0.40)	0.004*
	day 2	2.05 (0.41)	2.18 (0.42)	0.166
	day 3	2.08 (0.39)	2.23 (0.43)	0.111
	day 5	2.06 (0.42)	2.28 (0.48)	0.041
	day 7	2.11 (0.46)	2.26 (0.49)	0.177
	day 10	2.11 (0.44)	2.36 (0.53)	0.038
Delta Alb		-0.21 (0.15)	-0.17 (0.18)	0.342
		-0.24 (0.16)	-0.22 (0.19)	0.656
		-0.22 (0.17)	-0.21 (0.22)	0.801
		-0.22 (0.19)	-0.19 (0.21)	0.633
		-0.21 (0.21)	-0.20 (0.25)	0.919
		-0.19 (0.22)	-0.15 (0.28)	0.476
ALP (IU/L)	day 0	327.72 (290.90)	362.71 (357.99)	0.674
	day 1	255.81 (194.08)	283.22 (186.25)	0.54
	day 2	252.77 (214.62)	330.24 (330.80)	0.279
	day 3	270.18 (184.96)	323.81 (308.08)	0.382
	day 5	276.21 (166.61)	369.69 (466.70)	0.317
	day 7	296.57 (145.90)	382.18 (341.37)	0.207
	day 10	326.86 (162.12)	418.10 (417.71)	0.284
ALT (IU/L)	day 0	62.84 (89.26)	115.30 (209.89)	0.129
	day 1	78.07 (127.98)	135.07 (233.97)	0.162
	day 2	90.37 (168.76)	115.47 (198.39)	0.537
	day 3	106.90 (224.77)	122.61 (227.07)	0.754
	day 5	94.65 (153.06)	101.85 (171.84)	0.846
	day 7	65.15 (63.89)	79.34 (103.25)	0.469
	day 10	68.19 (68.87)	63.49 (75.34)	0.781
AST (IU/L)	day 0	114.02 (147.40)	229.47 (430.63)	0.092
	day 1	135.29 (188.04)	274.35 (522.03)	0.096

	day 2	153.38 (341.98)	180.19 (246.58)	0.679
	day 3	192.90 (549.88)	159.44 (255.87)	0.719
	day 5	120.82 (305.89)	103.17 (117.07)	0.729
	day 7	61.21 (67.53)	68.68 (100.29)	0.698
	day 10	74.95 (160.93)	44.42 (30.49)	0.255
LDH	day 0	407.14 (207.25)	556.49 (679.65)	0.166
(IU/L)	day 1	368.42 (215.27)	495.57 (548.45)	0.159
	day 2	344.37 (235.32)	381.98 (215.62)	0.447
	day 3	365.35 (308.27)	391.23 (279.30)	0.689
	day 5	351.24 (235.63)	355.95 (155.61)	0.916
	day 7	316.47 (157.25)	332.00 (131.56)	0.635
	day 10	300.60 (146.05)	284.13 (81.80)	0.55
Bil	day 0	1.15 (0.86)	1.67 (1.24)	0.023
(mg/dL)	day 1	0.98 (0.77)	1.69 (3.10)	0.139
	day 2	0.94 (0.88)	1.26 (1.12)	0.141
	day 3	1.02 (1.21)	1.23 (1.08)	0.396
	day 5	1.28 (2.29)	1.64 (3.14)	0.562
	day 7	1.32 (2.66)	1.30 (1.90)	0.972
	day 10	1.33 (3.41)	1.53 (2.74)	0.778
BUN	day 0	39.89 (26.37)	45.96 (36.80)	0.367
(mg/dL)	day 1	39.05 (27.09)	40.15 (28.01)	0.849
	day 2	35.19 (26.29)	133.08 (652.19)	0.334
	day 3	31.43 (24.80)	33.27 (41.88)	0.807
	day 5	26.11 (20.12)	25.73 (28.18)	0.945
	day 7	26.54 (19.53)	22.68 (18.80)	0.371
	day 10	31.60 (34.35)	28.26 (39.51)	0.697
Cr	day 0	2.21 (2.14)	2.30 (2.44)	0.841
(mg/dL)	day 1	1.95 (2.06)	4.77 (20.44)	0.361
	day 2	1.63 (1.98)	1.48 (1.50)	0.693
	day 3	1.50 (1.75)	1.31 (1.39)	0.574
	day 5	1.47 (1.59)	1.15 (1.17)	0.299
	day 7	1.39 (1.60)	1.18 (1.24)	0.505
	day 10	57.95 (344.70)	1.78 (3.31)	0.318
Na	day 0	140.62 (7.94)	139.64 (6.89)	0.527

(mEq/L)	day 1	142.49 (7.64)	140.89 (6.82)	0.308
	day 2	142.33 (6.85)	141.19 (6.91)	0.444
	day 3	140.71 (8.02)	140.53 (6.15)	0.908
	day 5	141.72 (4.51)	140.38 (5.32)	0.228
	day 7	140.92 (5.58)	140.27 (4.52)	0.565
	day 10	140.05 (5.26)	139.92 (3.77)	0.9
Cl	day 0	102.53 (19.24)	103.16 (7.29)	0.852
(mEq/L)	day 1	106.83 (18.63)	105.34 (18.37)	0.721
	day 2	103.79 (25.81)	108.45 (7.03)	0.276
	day 3	108.95 (6.47)	107.70 (6.66)	0.408
	day 5	102.80 (23.65)	107.13 (6.22)	0.275
	day 7	104.00 (18.53)	107.19 (4.32)	0.312
	day 10	100.58 (25.74)	103.46 (17.81)	0.592
RBC	day 0	3.93 (0.84)	4.05 (0.98)	0.504
(x 10^6/uL)	day 1	9.77 (42.12)	3.50 (0.68)	0.315
	day 2	3.37 (0.55)	3.35 (0.67)	0.9
	day 3	3.35 (0.49)	4.17 (4.97)	0.291
	day 5	3.53 (0.75)	3.74 (1.94)	0.526
	day 7	3.39 (0.57)	53.42 (319.13)	0.331
	day 10	4.31 (5.76)	3.34 (0.76)	0.308
Hb	day 0	12.72 (4.73)	12.86 (2.87)	0.855
(g/dL)	day 1	11.20 (3.90)	11.03 (1.95)	0.792
	day 2	10.45 (1.74)	10.55 (1.88)	0.797
	day 3	10.37 (1.39)	10.79 (1.98)	0.267
	day 5	10.40 (1.88)	10.89 (2.15)	0.283
	day 7	10.37 (1.83)	12.42 (10.62)	0.238
	day 10	10.27 (1.85)	12.71 (13.06)	0.271

Mean (standard deviation)

Alb: albumin, Bil: bilirubin, Cr: creatinine

* shows statistically significance ($p < 0.01$).

Supplemental Table 7. Kaplan–Meier analysis of the severe and moderate groups

Moderate group (n = 51)				
		Survival	Non-survival	Lo- rank test p
28 days	Control (n = 24)	24 (100%)	0	
	rhTM (n= 27)	25 (93%)	2 (7%)	0.178
90 days	Control (n = 24)	22 (92%)	2 (8%)	
	rhTM (n = 27)	22 (81%)	5 (19%)	0.278
Severe group (n = 41)				
		Survival	Non-survival	Log-rank test p
28 days	Control (n = 21)	12 (57%)	9 (43%)	
	rhTM (n = 20)	14 (70%)	6 (30%)	0.376
90 days	Control (n = 21)	11 (52%)	10 (48%)	
	rhTM (n = 20)	12 (60%)	8 (40%)	0.524

Moderate group comprises patients with APACHE II score < 20 points.
Severe group comprises patients with APACHE II score ≤ 20 points.

Supplemental Table 8. Kaplan–Meier analysis of patients who experienced disseminated intravascular coagulation resolution

		Within 3 days		
		Survival	Non-survival	Log-rank test p
28 days	Control	13	4	
	rhTM	27	4	0.358
90 days	Control	11	6	
	rhTM	25	6	0.231
		Within 7 days		
		Survival	Non-survival	Log-rank test p
28 days	Control	28	5	
	rhTM	39	5	0.676
90 days	Control	26	7	
	rhTM	34	10	0.901

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	12
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the 8random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11 - 12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	15
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	13
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	15
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	17
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	17
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	21
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	22
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.