Title page

Title

Recombinant human soluble thrombomodulin and mortality in sepsis-induced disseminated intravascular coagulation: a multicentre retrospective study

Short running title

rhTM and mortality in sepsis-induced DIC

Authors and Institutions

Mineji Hayakawa [1)], Kazuma Yamakawa [2)], Shinjiro Saito [3)], Shigehiko Uchino [3)], Daisuke Kudo [4)], Yusuke Iizuka [5) 9)], Masamitsu Sanui [5)], Kohei Takimoto [6)], Toshihiko Mayumi [7)], Kota Ono [8)]

Japan Septic Disseminated Intravascular Coagulation (JSEPTIC DIC) study group

1) Emergency and Critical Care Center, Hokkaido University Hospital
2) Department of Emergency and Critical Care, Osaka General Medical Center
3) Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine
4) Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine
5) Department of Anesthesiology and Critical Care Medicine, Jichi Medical University Saitama Medical Center
6) Department of Anesthesiology and Intensive Care Medicine, Osaka University Graduate School of Medicine
7) Department of Emergency Medicine, University of Occupational and Environmental Health

8) Clinical Research and Medical Innovation Center, Hokkaido University Hospital

9) Department of Critical Care, Shonan Kamakura General Hospital

Corresponding author

Mineji Hayakawa, MD, PhD

Emergency and Critical Care Center, Hokkaido University Hospital

N14W5 Kita-ku, Sapporo 060-8648, Japan

Phone: +81-11-706-7377 Fax: +81-11-706-7378 E-mail: mineji@dream.com

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Abstract

Recombinant human soluble thrombomodulin (rhTM) is a novel class of anticoagulants for treating disseminated intravascular coagulation (DIC). Although rhTM is widely used in clinical settings throughout Japan, there is limited clinical evidence supporting the use of rhTM in patients with sepsis-induced DIC. Furthermore, rhTM is not approved for DIC treatment in other countries. This study aimed to clarify the survival benefits of rhTM administration in critically ill patients. Data from 3,195 consecutive adult patients who were admitted to 42 intensive care units for the treatment of severe sepsis or septic shock between January 2011 and December 2013 were retrospectively analysed, and 1,784 patients were diagnosed with DIC based on the scoring algorithm from the Japanese Association for Acute Medicine DIC (n = 645, rhTM group; n = 1,139, control group). Propensity score matching created 452 matched pairs, and logistic regression analysis revealed a significant association between rhTM administration and lower in-hospital all-cause mortality in the propensity score-matched groups (odds ratio, 0.757; 95% CI, 0.574–0.999, P = 0.049). Inverse probability of treatment weighted and quintile-stratified analyses also revealed significant associations between rhTM administration and lower in-hospital all-cause mortality. Survival time in the propensity score-matched rhTM group was significantly longer than that in the propensity score-matched control group (hazard ratio, 0.781; 95% CI, 0.624–0.977, P = 0.03). Bleeding complications were not more frequent in the rhTM groups. In conclusion, this study demonstrated that rhTM administration is associated with reduced in-hospital all-cause mortality among patients with sepsis-induced DIC.

Key words

Sepsis, disseminated intravascular coagulation, coagulation abnormality, mortality, thrombomodulin

Introduction

Thrombomodulin (TM) is a receptor of thrombin and protein C on the endothelial cell surface and regulates the coagulation and complement system (1). Recombinant human soluble thrombomodulin (rhTM) is a novel class of anticoagulants for the treatment of disseminated intravascular coagulation (DIC). The molecular structure of rhTM consists of the active and extracellular domains of TM on the endothelial cell surface (2). Similar to the function of TM on the endothelial cell surface, rhTM can bind to thrombin and activate protein C (2). In Japan, rhTM (Asahi Kasei Pharma Co., Tokyo, Japan) was approved in 2008 and is widely used for DIC treatment in various clinical settings (2-4). Furthermore, the DIC treatment guidelines from the International and Japanese Society of Thrombosis and Hemostasis recommend the use of rhTM in patients with sepsis-induced DIC (4-6).

However, there is very limited clinical evidence supporting the use of rhTM in patients with sepsis-induced DIC. In a double-blind, randomized, controlled, phase 3 study of Japanese patients with DIC-associated sepsis and haematological malignancy, the improvement in DIC and bleeding symptoms was significantly greater with rhTM treatment than with heparin treatment (2). Furthermore, a retrospective sub-analysis of 80 patients with sepsis-induced DIC in the same study indicated a trend towards better outcomes in the rhTM group, compared to those in the heparin group (7). In the clinical setting, the results of a retrospective observational study indicated that rhTM reduced in-hospital mortality among patients with sepsis-induced DIC (8, 9). However, results from an analysis of a nationwide administrative database indicated no benefit for rhTM administration in patients with sepsis-induced DIC (10, 11). The major limitation of these studies was the lack of laboratory data and clinical severity in the database (10, 11). However, a randomized, controlled, phase 2b study that was conducted in Europe suggested that rhTM was effective among patients with sepsis-associated coagulopathy and severe organ dysfunction (12). Furthermore, in a meta-analysis, rhTM was associated with a trend towards reduced mortality among patients with sepsis-induced DIC (13). Although a phase 3

trial is currently recruiting participants to clarify the effects of rhTM (14), there is limited clinical evidence supporting the use of rhTM in patients with sepsis-induced DIC. Therefore, we conducted the present multicentre retrospective observational study to analyse the effect of rhTM treatment on sepsis-induced DIC using propensity score analysis.

Materials and Methods

This retrospective observational study (Japan Septic Disseminated Intravascular Coagulation [JSEPTIC DIC] study) was conducted in 42 intensive care units (ICUs) from 40 institutions throughout Japan (Supplemental Tables 1 and 2) and was approved by the Institutional Review Board of each hospital. The boards waived the requirement for informed consent, due to the retrospective design.

Patient selection and data collection

We retrospectively reviewed information for consecutive patients who were admitted to the ICUs for the treatment of severe sepsis or septic shock between January 2011 and December 2013. Severe sepsis and septic shock were defined based on the International Sepsis Definitions Conference criteria (15). We excluded patients who were <16 years old, or patients who developed severe sepsis or septic shock after their ICU admission.

The following data were collected: age; sex; body weight; admission route to the ICU; pre-existing organ dysfunction; pre-existing haemostatic disorder; Acute Physiology and Chronic Health Evaluation (APACHE) II score (16); Sequential Organ Failure Assessment (SOFA) score (17) (days 1, 3, and 7); systemic inflammatory response syndrome (SIRS) score (18) (days 1, 3, and 7); primary infection site; blood culture results; microorganisms responsible for the sepsis; daily results from laboratory tests during the first week after ICU admission; lactate levels (days 1, 3, and 7); administration of drugs,

including anti-DIC drugs, other anticoagulants, immunoglobulins, and low-dose steroids, during the first week after ICU admission; transfusion amounts and bleeding complications during the first week after ICU admission; therapeutic interventions, including surgical interventions at the infection site, renal replacement therapy, renal replacement therapy for non-renal indications, polymyxin B direct hemoperfusion, extracorporeal membrane oxygenation, and intra-aortic balloon pumping, during the first week after ICU admission; and outcomes in the hospital.

The DIC score was calculated using the scoring algorithm from the Japanese Association for Acute Medicine (JAAM) DIC criteria (19). Missing values were scored as zero. Patients with DIC were defined as patients without a pre-existing haemostatic disorder and with a single-day DIC score of ≥4 during the first week after ICU admission (on day 1, 3, or 7). Patients were divided into the following two groups: the rhTM group (received rhTM) and the control group (did not receive rhTM). Among the patients with DIC, rhTM was used at the discretion of the attending physician, and there was no predefined protocol regarding rhTM administration. Typically, 380 U/kg·day was intravenously administered to patients with DIC and without severe renal dysfunction. Among patients with DIC and severe renal dysfunction, the dosage of rhTM was maintained at 130 U/kg·day. rhTM administration was usually continued for 6 days or until improvement of the DIC.

Statistical analysis

Data were expressed as number (%), mean ± standard deviation, or median (interquartile range), as appropriate. We performed one-to-one nearest neighbour matching without replacement between the rhTM and control groups, based on estimated propensity scores for each patient. To estimate the propensity score, we fitted a logistic regression model for rhTM administration as a function of patient characteristics, therapeutic interventions, and ICU characteristics: age; sex; body weight; admission route to the ICU; pre-existing organ dysfunction; pre-existing haemostatic disorder; APACHE II score; SOFA

score of each organ (except coagulation) on day 1; SIRS score on day 1; DIC score on day 1; primary infection site; blood culture results; microorganisms responsible for the sepsis; laboratory tests (white blood cell count, platelet count, haemoglobin level, and prothrombin time-international normalized ratio) on day 1; anti-DIC drugs; other anticoagulants; immunoglobulins; low-dose steroids; surgical interventions at the infection site; renal replacement therapy; renal replacement therapy for non-renal indications; polymyxin B direct hemoperfusion; extracorporeal membrane oxygenation; intra-aortic balloon pumping; ICU characteristics; ICU policy; and number of beds in the ICU. Some laboratory tests (fibrinogen, fibrin/fibrinogen degradation products, D-dimer, antithrombin, and lactate) were not used to estimate the propensity score because the proportion of missing data was >10%. In the present analysis, we used the therapeutic interventions to estimate the propensity score because they were usually performed simultaneously with rhTM administration. The calliper width was 0.15 of the standard deviation of the logit of the propensity score. The standardised difference was used to evaluate covariate balance, and an absolute standardised difference of >10% represents meaningful imbalance (20).

For the propensity score matched patients, we performed logistic regression analysis fitted with generalized estimating equations to examine the association between rhTM administration and in-hospital all-cause mortality, after accounting for the matched nature of matched pairs (21). To evaluate the robustness of the results of the propensity score matching analysis, inverse probability of treatment weighted analysis and quintile-stratified propensity score analysis were performed. Cox regression analysis with a sandwich variance estimator (22) was used to assess differences in the in-hospital survival rates between the propensity score-matched rhTM and control groups. In the logistic regression analysis fitted with generalized estimating equations, inverse probability of treatment weighted analysis and Cox regression analysis, we used rhTM administration alone as an independent variable. In the quintile-stratified propensity score analysis, we used rhTM and propensity score strata as independent variables. Intergroup comparisons were performed using the Wilcoxon signed-rank test or McNemar's test

in the propensity score-matched groups.

R software (version 3.1.3) with the “MATCHIT” package was used for the propensity score estimation and matching (23, 24), and SAS® software (version 9.4; SAS Institute Inc., Cary, NC, USA) was used for all other analyses.

Results

The JSEPTIC study included 3,195 consecutive patients with severe sepsis or septic shock, and 1,784 of these patients were diagnosed with DIC (n = 645, rhTM group; n = 1,139, control group).

Propensity score matching created 452 matched pairs (Figure 1). The characteristics of the ICUs, according to the unmatched and propensity score-matched groups, are presented in Table 1, while the characteristics of the patients in the unmatched and propensity score-matched groups are shown in Table 2. Although some patients were missing specific results from the laboratory tests at the ICU admission, the other variables were typically available. The clinical severity and intensity of the therapeutic interventions were imbalanced between the unmatched groups. No patients received recombinant human activated protein C, because it was not approved in Japan during the study period. After propensity score matching, all of the standardised differences, except those for fibrinogen and lactate, were <10% in the matched patients, and the characteristics of the two groups were appropriately balanced.

The odds ratios for in-hospital all-cause mortality with rhTM administration are presented in Figure 2. In all of the propensity score analyses (propensity score matching, inverse probability of treatment weighted, and quintile-stratified analyses), significant associations were observed between rhTM administration and lower in-hospital all-cause mortality. The 28-day mortality rates and odds ratios according to the three propensity score analyses are presented in Table 3. The 28-day mortality rates in

rhTM group were consistently lower than those in the control group, although 453 patients (25.4%) among the 1,784 patients with DIC were not followed for all 28 days, as they were discharged within 28 days after their ICU admission. Survival time analysis revealed a significant difference in the in-hospital survival between the propensity score-matched groups (hazard ratio, 0.781; 95% confidence interval, 0.624–0.977, P = 0.03) (Figure 3). The transfusion amounts and frequencies of bleeding complications were not significantly different between the propensity score-matched groups (Table 4).

Discussion

The present multicentre retrospective study used propensity score analysis of clinical information, and the findings indicate that rhTM improved in-hospital all-cause mortality among patients with sepsis-induced DIC, without increasing the frequency of bleeding complications. Furthermore, half of the patients simultaneously received rhTM and other anti-DIC drugs. Therefore, the present results indicate the additional benefits of rhTM when it is coadministered with other anti-DIC drugs, especially antithrombin.

In Japan, rhTM and other anti-DIC drugs are approved and widely used for DIC treatment in various clinical settings. However, some physicians do not administer anti-DIC drugs to patients with DIC because the Surviving Sepsis campaign guidelines do not provide recommendations for the treatment of DIC (25, 26). Therefore, some of the patients with sepsis-induced DIC in the present study did not receive any anti-DIC drugs; as a result, we were able to retrospectively compare the effects of rhTM among patients with sepsis-induced DIC in real clinical settings.

A previous randomized, controlled, phase 2b study that was conducted in Europe did not report survival benefits after rhTM treatment among patients with modified International Society of Thrombosis and Hemostasis (ISTH) overt-DIC, although benefits were observed among patients with sepsis-associated coagulopathy and severe organ dysfunction (12). However, based on the JAAM DIC

criteria (19), the present results suggest that rhTM provides a survival benefit for patients with DIC. Nevertheless, the characteristics of patients with DIC vary according to whether they are diagnosed using the JAAM DIC criteria or ISTH overt-DIC criteria (19, 27), as patients with greater clinical severity are selected using the JAAM DIC scoring system (27). This difference is reflected in the different mortality rates among the control groups from the present study and the phase 2b European study: 25.5% and 21.6%, respectively (12). Furthermore, rhTM administration might only improve mortality among patients with sepsis-induced DIC who have a high risk of death, but not among patients who have a low risk of death (28).

Similar to TM, rhTM binds to thrombin and activates protein C on endothelial cells (2, 29). Activated protein C degrades activated factors V and VIII in the presence of protein S, which results in the attenuation of thrombin generation (30, 31). Therefore, rhTM has two types of anticoagulant action: direct inhibition of thrombin and indirect activation of protein C (29). However, in the clinical setting, the plasma concentration of rhTM does not reach the level that is required to directly inhibit thrombin, as the rhTM concentration that is required for this action is 50× higher than that to activate protein C (2, 29, 32). Therefore, in the clinical setting, the main anticoagulation effects of rhTM are achieved by activating protein C (2, 29, 32). Furthermore, unlike recombinant human-activated protein C, the anti-coagulant effects of rhTM are dependent on thrombin activity in the systemic circulation, as rhTM cannot activate protein C after the attenuation of thrombin generation (2, 29). In addition to its anticoagulant activities, the anti-inflammatory effects of rhTM include the inhibition of leukocyte adhesion to endothelial cells, inhibition of complement pathways, neutralization of lipopolysaccharides, suppression of inflammatory cytokines, and degradation of high-mobility group box 1 protein (33, 34). Thus, rhTM administration could be considered appropriate treatment for patients with sepsis-induced DIC.

Bleeding complications are the greatest concern that is associated with the use of anticoagulants, such as rhTM. In the present study, the transfusion amounts and frequencies of bleeding

requiring transfusion were not higher in the matched rhTM group, despite the co-administration of other anti-DIC drugs. Similarly, previous studies have reported that rhTM, which was administered independent of other anti-DIC drugs, did not increase the frequency of bleeding complications among patients with sepsis (9, 12).

The present study has several limitations that warrant consideration. First, we could not identify the exact timing of the therapeutic interventions. However, the therapeutic interventions and administration of rhTM were usually performed simultaneously at the ICU admission, and the therapeutic interventions were not affected by rhTM administration. Therefore, we considered it acceptable to use the therapeutic interventions to estimate the propensity score. Second, the dose and duration of rhTM administration were not known. However, we assumed that the patients received 380 U/kg of rhTM (or 180 U/kg in patients with severe renal dysfunction) during the first 6 days or until improvement of their DIC. Third, the data set was missing some data, although these missing data were only regarding specific laboratory test results (fibrinogen, fibrin/fibrinogen degradation products, D-dimers, antithrombin, and lactate) at the ICU admission. Fourth, we used a retrospective design, which is more likely to report beneficial effects for an intervention, and this phenomenon has been observed for various drugs, such as activated protein C (Xigris®, Eli Lilly) (35).

Conclusions

Based on propensity score analysis of clinical data, the present multicentre retrospective study revealed that rhTM administration was associated with reduced in-hospital all-cause mortality among patients with sepsis-induced DIC. Furthermore, the transfusion amounts and frequencies of bleeding requiring transfusion did not increase in the rhTM group. Nevertheless, multicentre randomized trials using an appropriate DIC scoring system are needed to determine the true benefits of rhTM.

What is known on this topic?

· Recombinant human soluble thrombomodulin (rhTM) is a novel class of anticoagulants for treating disseminated intravascular coagulation (DIC).

· Similar to TM, rhTM can bind to thrombin and activate protein C on the endothelial cell surface.

· rhTM is widely used among Japanese patients with sepsis-induced DIC.

· There is very limited clinical evidence supporting the use of rhTM among patients with sepsis-induced DIC.

What this paper adds?

· This retrospective study revealed that rhTM treatment was associated with lower in-hospital all-cause mortality rates, which supports the use of rhTM in patients with sepsis-induced DIC.

· The transfusion amounts and frequencies of bleeding complications were not increased by rhTM treatment.

Conflicts of interest

None.

Collaborators

Takeo Azuhata (Division of Emergency and Critical Care Medicine, Department of Acute Medicine,

Nihon University School of Medicine), Fumihito Ito (Department of Emergency & Critical Care Medicine, Ohta General Hospital Foundation Ohta Nishinouchi Hospital), Shodai Yoshihiro (Pharmaceutical Department, JA Hiroshima General Hospital), Hayakawa Katsura (Department of Emergency and Critical Care Medicine, Saitama Red Cross Hospital), Tsuyoshi Nakashima (Department of Emergency and Critical Care Medicine, Wakayama Medical University), Takayuki Ogura (Department of Emergency Medicine and Critical Care Medicine, Advanced Medical Emergency Department and Critical Care Center, Japan Red Cross Maebashi Hospital), Eiichiro Noda (Emergency and Critical Care Center, Kyushu University Hospital), Yoshihiko Nakamura (Department of Emergency and Critical Care Medicine, Fukuoka University Hospital), Ryosuke Sekine (Emergency Department, Ibaraki Prefectural Central Hospital), Yoshiaki Yoshikawa (Department of Emergency and Critical Care, Osaka General Medical Center), Motohiro Sekino (Division of Intensive Care, Nagasaki University Hospital), Keiko Ueno (Department of Emergency and Critical Care Medicine, Tokyo Medical University, Hachioji Medical Center), Yuko Okuda (Anesthesiology, Kyoto First Red-cross hospital), Masayuki Watanabe (Intensive Care Unit, Saiseikai Yokohamasi Tobu Hospital), Akihito Tampo (Department of Emergency Medicine, Asahikawa Medical University), Nobuyuki Saito (Shock and Trauma Center, Nippon Medical School Chiba Hokusoh Hospital), Yuya Kitai (Emergency Medicine, Kameda Medical Center), Hiroki Takahashi (Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine), Iwao Kobayashi (Emergency and Critical Care Medicine, Asahikawa Red Cross Hospital), Yutaka Kondo (Department of Emergency and Critical Care Medicine, Graduate School of Medicine, University of the Ryukyus), Wataru Matsunaga (Department of Anesthesia and Critical Care Medicine, Saitama Medical Center Jichi Medical University), Sho Nachi (Advanced Critical Care Center, Gifu University Hospital), Toru Miike (Emergency and Critical Care Center, Saga University Hospital), Hiroshi Takahashi (Division of Cardiovascular Disease, Steel Memorial Muroran Hospital), Shuhei Takauji (Department of Emergency Medicine and Critical Care, Sapporo City General Hospital), Kensuke

Umakoshi (Division of Emergency Medicine, Ehime University Hospital), Takafumi Todaka (Intensive Care Unit, Tomishiro Central Hospital), Hiroshi Kodaira (Department of Emergency Medicine, Akashi City Hospital), Kohkichi Andoh (Critical Care Department, Sendai City Hospital), Takehiko Kasai (Emergency Department, Hakodate Municipal Hospital), Yoshiaki Iwashita (Emergency and Critical Care Center, Mie University Hospital), Hideaki Arai (Department of Emergency Medicine, University of Occupational and Environmental Health Hospital), Masato Murata (Department of Emergency Medicine, Gunma University), Masahiro Yamane (Department of Anesthesia and Intensive Care, KKR Sapporo Medical Center), Kazuhiro Shiga (Emergency and Critical Care Center, Seirei Mikatahara General Hospital), Naoto Hori (Intensive Care Unit, Hyogo College of Medicine)

Contributions of Authors and Collaborators

Hayakawa M, Saito S, Uchino S, Yamakawa K, Kudo D, Iizuka Y, Sanui M, Takimoto K and Mayumi T designed the study and checked the data set. Hayakawa M interpreted the data and drafted the manuscript. Ono K performed the statistical analysis. Hayakawa M, Saito S, Kudo D, Iizuka Y, Takimoto K, Azuhata T, Ito F, Yoshihiro S, Hayakawa K, Nakashima T, Ogura T, Noda E, Nakamura Y, Sekine R, Yoshikawa Y, Sekino M, Ueno K, Okuda Y, Watanabe M, Tampo A, Saito N, Kitai Y, Takahashi Hiroki, Kobayashi I, Kondo Y, Matsunaga W, Nachi S, Miike T, Takahashi Hiroshi, Takauji S, Umakoshi K, Todaka T, Kodaira H, Andoh K, Kasai T, Iwashita Y, Arai H, Murata M, Yamane M, Shiga K and Hori N collected and assessed the data at each institution. All authors read and approved the final manuscript.

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Figure legends

Figure 1 Patient selection for evaluation of recombinant human soluble thrombomodulin treatment

DIC, disseminated intravascular coagulation; rhTM, recombinant human soluble thrombomodulin

Figure 2 Odds ratios for in-hospital all-cause mortality after recombinant human soluble thrombomodulin administration

In all of the propensity score analyses, significant associations were observed between rhTM administration and lower in-hospital all-cause mortality.

Odds ratios (black squares) and 95% confidence intervals (bars)

IPTW, inverse probability of treatment weighted; rhTM, recombinant human soluble thrombomodulin

Figure 3 Survival plots for patients in the propensity score-matched control and rhTM groups

The survival rate was higher in the rhTM group, compared to that in the control group.

rhTM, recombinant human soluble thrombomodulin

Table 1 Characteristics of the intensive care units according to the unmatched and propensity-matched groups of patients with disseminated intravascular coagulation

	Unmatched group		Unmatched standardized difference (%)	Matched group		Matched standardized difference (%)
	Control n = 1139	rhTM n = 645		Control n = 452	rhTM n = 452	
ICU characteristics						
General ICU	560 (49.2)	324 (50.2)	–2.13	211 (46.7)	225 (49.8)	–6.2
Emergency ICU	579 (50.8)	321 (49.8)		241 (53.3)	227 (50.2)	
ICU policy						
Closed policy	587 (51.5)	339 (52.6)	2.05	242 (53.5)	231 (51.1)	–4.87
Open policy	427 (37.5)	169 (26.2)	–24.41	140 (31.0)	140 (31.0)	0
Other	125 (11.0)	137 (21.2)	28.2	70 (15.5)	81 (17.9)	6.53
Number of beds	12 (8–19)	12 (8–16)	–18.67	10 (8–18)	12 (8–16)	–2.02

rhTM, recombinant human soluble thrombomodulin; ICU, intensive care unit

Data are presented as median (interquartile range) or n (%).

Table 2 Characteristics of the patients with disseminated intravascular coagulation in the unmatched and propensity-matched groups

	Unmatched group		Unmatched standardized difference (%)	Matched group		Matched standardized difference (%)
	Control n = 1,139	rhTM n = 645		Control n = 452	rhTM n = 452	
Age, years	70 ± 15	70 ± 14	–2.24	70 ± 14	70 ± 14	–4.13
Male sex	657 (57.7)	356 (55.2)	5.02	253 (56.0)	252 (55.8)	0.45
Body weight, kg	55.7 ± 14.0	55.8 ± 13.6	2.53	56.1 ± 13.6	55.8 ± 13.7	–2.66
Admission route to the ICU						
Emergency department	558 (49.0)	252 (39.1)	–20.08	195 (43.1)	191 (42.3)	–1.79
Other hospital	281 (24.7)	235 (36.4)	25.75	149 (33.0)	152 (33.6)	1.41
Hospital ward	300 (26.3)	158 (24.5)	–4.23	108 (23.9)	109 (24.1)	0.52
Pre-existing organ dysfunction						
Liver insufficiency	9 (0.8)	8 (1.2)	4.49	5 (1.1)	6 (1.3)	2.02
Chronic respiratory disorder	50 (4.4)	14 (2.2)	–12.48	11 (2.4)	10 (2.2)	–1.47
Chronic heart failure	61 (5.4)	28 (4.3)	–4.72	20 (4.4)	23 (5.1)	3.12
Chronic haemodialysis	118 (10.4)	38 (5.9)	–16.41	28 (6.2)	31 (6.9)	2.69
Immunocompromised	109 (9.6)	81 (12.6)	9.54	51 (11.3)	51 (11.3)	0
Severity						
APACHE II score	23 (17–29)	24 (18–29)	2.72	24 (17–30)	24 (18–29)	–1.50
SOFA score total	10 (7–13)	11 (8–13)	24.95	11 (8–13)	11 (8–13)	–1.03

Respiratory	2 (1–3)	2 (1–3)	–0.09	2 (1–3)	2 (1–3)	–5.74
Renal	2 (0–3)	2 (1–3)	10.31	2 (1–3)	2 (1–3)	–0.93
Liver	0 (0–1)	0 (0–1)	10.07	0 (0–1)	0 (0–1)	4.18
Cardiovascular	3 (1–4)	3 (2–4)	25.20	3 (1–4)	3 (2–4)	–1.62
Coagulation	1 (0–2)	2 (1–3)	31.18	2 (1–2)	2 (1–2)	7.61
Central nervous	1 (0–3)	1 (0–3)	–4.08	1 (1–3)	1 (0–3)	–4.25
SIRS score	3 (3–4)	3 (2–4)	–3.82	3 (3–4)	3 (2–4)	–5.53
DIC score	5 (4–6)	5 (4–7)	31.11	5 (4–7)	5 (4–6)	–4.21
Primary infection site						
Abdomen	429 (37.7)	224 (34.7)	–6.11	156 (34.5)	161 (35.6)	2.32
Lung/thoracic	249 (21.9)	126 (19.5)	–5.74	94 (20.8)	87 (19.2)	–3.87
Urinary tract	185 (16.2)	140 (21.7)	13.97	93 (20.6)	87 (19.2)	–3.32
Bone/soft tissue	118 (10.4)	76 (11.8)	4.54	51 (11.3)	61 (13.5)	6.72
Cardiovascular	28 (2.5)	16 (2.5)	0.14	15 (3.3)	15 (3.3)	0
Central nervous system	29 (2.5)	15 (2.3)	–1.43	8 (1.8)	7 (1.5)	–1.73
Catheter-related	13 (1.1)	8 (1.2)	0.91	7 (1.5)	6 (1.3)	–1.86
Others	21 (1.8)	11 (1.7)	–1.05	9 (2.0)	8 (1.8)	–1.63
Unknown	67 (5.9)	29 (4.5)	–6.25	19 (4.2)	20 (4.4)	1.09
Blood culture						
Positive	542 (47.6)	345 (53.5)	11.83	254 (56.2)	237 (52.4)	–7.56
Negative	525 (46.1)	283 (43.9)	–4.46	186 (41.2)	201 (44.5)	6.71

Not taken	72 (6.3)	17 (2.6)	–17.89	12 (2.7)	14 (3.1)	2.65
Microorganisms that caused the sepsis						
Gram-negative rods	428 (37.6)	298 (46.2)	17.55	202 (44.7)	201 (44.5)	–0.45
Gram-positive cocci	251 (22.0)	170 (26.4)	10.1	120 (26.5)	121 (26.8)	0.5
Fungus	18 (1.6)	6 (0.9)	–5.84	4 (0.9)	5 (1.1)	2.23
Virus	11 (1.0)	2 (0.3)	–8.24	0 (0.0)	2 (0.4)	9.43
Mixed infection	163 (14.3)	64 (9.9)	–13.48	53 (11.7)	46 (10.2)	–4.96
Others	22 (1.9)	5 (0.8)	–10.02	5 (1.1)	5 (1.1)	0
Unknown	246 (21.6)	100 (15.5)	–15.73	68 (15.0)	72 (15.9)	2.45
Laboratory tests at ICU admission						
White blood cell count, 10^9/L	11.3 (4.8–18.0)	11.2 (3.8–18.3)	2.53	11.5 (3.9–18.7)	11.5 (4.0–18.9)	0.12
Missing data, n (%)	0 (0.0)	1 (0.2)		0 (0.0)	0 (0.0)	
Platelet count, 10^9/L	109 (61–176)	81 (41–139)	–29.33	90 (55–148)	90 (50–144)	–2.22
Missing data, n (%)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Haemoglobin, g/L	10.7 (8.9–12.5)	10.8 (9.2–12.5)	2.94	10.8 (9.1–12.6)	10.8 (9.2–12.6)	–2.57
Missing data, n (%)	1 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
PT-INR	1.35 (1.19–1.61)	1.38 (1.20–1.61)	2.68	1.38 (1.22–1.67)	1.37 (1.20–1.59)	1.53
Missing data, n (%)	37 (3.2)	14 (2.2)		0 (0.0)	0 (0.0)	
Fibrinogen, g/L	3.79 (2.48–5.30)	3.84 (2.49–5.47)	6.19	3.67 (2.21–5.24)	3.94 (2.49–5.60)	12.96
Missing data, n (%)	242 (21.2)	80 (12.4)		58 (12.8)	49 (10.8)	
FDP, mg/L	23.9 (13.0–49.9)	30.3 (15.4–67.0)	11.38	25.6 (13.4–51.0)	27.2 (13.7–59.7)	7.10
Missing data, n (%)	339 (29.8)	149 (23.1)		99 (21.9)	107 (23.7)	

D-dimer, mg/L	11.5 (5.6–25.0)	14.17 (6.1–30.8)	–0.29	12.0 (5.7–24.7)	13.3 (6.0–28.2)	–5.91
Missing data, n (%)	267 (23.4)	109 (16.9)		92 (20.4)	80 (17.7)	
Antithrombin, %	57 (44–71)	54 (42–66)	–14.82	56 (43–69)	54 (43–67)	–5.35
Missing data, n (%)	552 (48.5)	199 (30.9)		172 (38.1)	156 (34.5)	
Lactate, mmol/L	3.28 (1.75–6.30)	3.50 (2.11–6.60)	–2.29	3.75 (2.00–7.00)	3.66 (2.11–6.70)	–10.54
Missing data, n (%)	152 (13.3)	48 (7.4)		46 (10.2)	35 (7.7)	
Co-administered anti-DIC drugs						
Antithrombin	336 (29.5)	379 (58.8)	61.67	213 (47.1)	228 (50.4)	6.64
Protease inhibitors	172 (15.1)	95 (14.7)	–1.05	72 (15.9)	76 (16.8)	2.39
Heparinoids	77 (6.8)	33 (5.1)	–6.96	28 (6.2)	27 (6.0)	–0.93
Co-administered anticoagulants not for DIC						
Nafamostat mesilate	316 (27.7)	289 (44.8)	36.06	181 (40.0)	186 (41.2)	2.25
Heparin	167 (14.7)	60 (9.3)	–16.56	53 (11.7)	46 (10.2)	–4.96
Warfarin	8 (0.7)	2 (0.3)	–5.53	1 (0.2)	2 (0.4)	3.85
Anti-platelet drugs	14 (1.2)	6 (0.9)	–2.89	4 (0.9)	4 (0.9)	0
Others	5 (0.4)	2 (0.3)	–2.11	1 (0.2)	2 (0.4)	3.85
Other therapeutic interventions						
Surgical intervention	500 (43.9)	312 (48.4)	8.98	216 (47.8)	218 (48.2)	0.89
Immunoglobulin	277 (24.3)	332 (51.5)	58.3	191 (42.3)	198 (43.8)	3.13
Low-dose steroid	249 (21.9)	243 (37.7)	35.11	145 (32.1)	149 (33.0)	1.89
RRT	309 (27.1)	283 (43.9)	35.55	166 (36.7)	177 (39.2)	5.02

Non-renal indication RRT	87 (7.6)	90 (14.0)	20.46	50 (11.1)	55 (12.2)	3.45
PMX-DHP	256 (22.5)	227 (35.2)	28.36	133 (29.4)	143 (31.6)	4.81
Plasma exchange	4 (0.4)	13 (2.0)	15.44	4 (0.9)	8 (1.8)	7.74
Veno-arterial ECMO	18 (1.6)	4 (0.6)	–9.21	4 (0.9)	3 (0.7)	–2.52
Veno-venous ECMO	13 (1.1)	9 (1.4)	2.27	6 (1.3)	5 (1.1)	–2.02
IABP	9 (0.8)	1 (0.2)	–9.27	1 (0.2)	1 (0.2)	0

rhTM, recombinant human soluble thrombomodulin; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; SIRS, systemic inflammatory response syndrome; DIC, disseminated intravascular coagulation; PT-INR, prothrombin time-international normalized ratio; FDP, fibrin/fibrinogen degradation products; RRT, renal replacement therapy; PMX-DHP, Polymyxin B-direct hemoperfusion; ECMO, extracorporeal membrane oxygenation system; IABP, intra-aortic balloon pumping system

Data are presented as n (%), mean ± standard deviation, or median (interquartile range).

Table 3 The 28-day mortality rate among the patients with disseminated intravascular coagulation

	Control	rhTM	Odds ratio (95% CI)	P-value
IPTW analysis	460/1,746 (26.3)	385/1,691 (22.7)	0.786 (0.557–1.111)	0.1724
Stratified analysis	276/1,072 (25.7)	141/628 (22.5)	0.769 (0.579–1.021)	0.07
Matching analysis	116/452 (25.7)	102/452 (22.6)	0.794 (0.574–1.098)	0.163

rhTM, recombinant human soluble thrombomodulin; CI, confidence interval; IPTW, inverse probability of treatment weighted.

Data are presented as n (%) or odds ratio (95% confidence interval)

Table 4 Transfusion and bleeding complications in the propensity-matched groups of patients with disseminated intravascular coagulation

	Control n = 452	rhTM n = 452	P-value
Transfusion during 7 days after ICU admission			
Red blood cell concentration, units	1 (0–6)	2 (0–6)	0.335
Fresh frozen plasma, units	0 (0–10)	0 (0–10)	0.478
Platelet concentration, units	0 (0–10)	0 (0–20)	0.326
Bleeding complications during 7 days after ICU admission			
Bleeding requiring transfusion	62 (13.7)	64 (14.2)	1.000
Bleeding requiring a therapeutic intervention	6 (1.3)	9 (2.0)	0.607
Intracranial haemorrhage	2 (0.4)	3 (0.7)	0.923
Bleeding to death	0 (0.0)	1 (0.2)	NA

rhTM, recombinant human soluble thrombomodulin; NA, not available

P-values were calculated using the Wilcoxon signed rank test and McNemar's test.

Data are presented as median (interquartile range) or n (%).

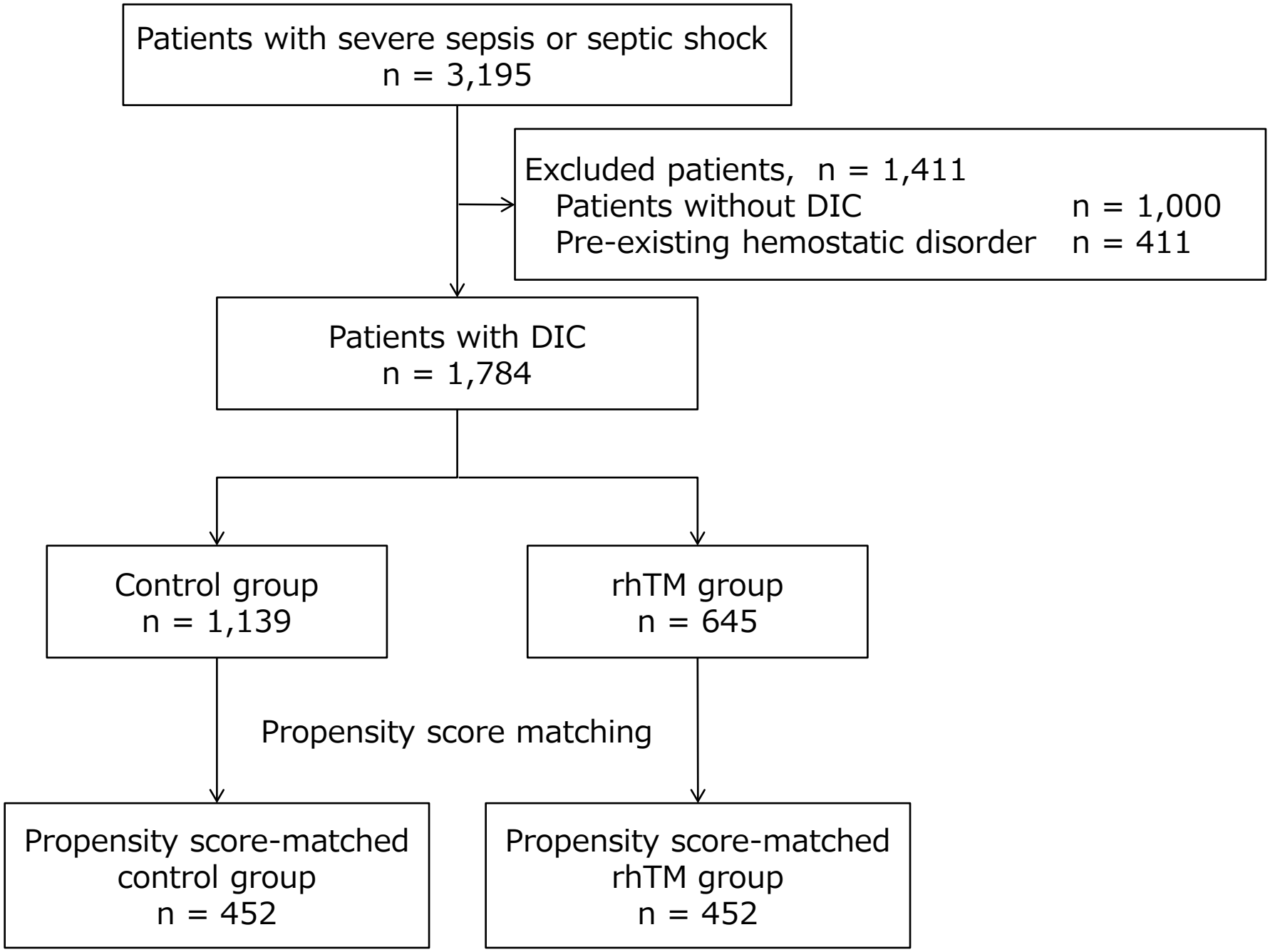
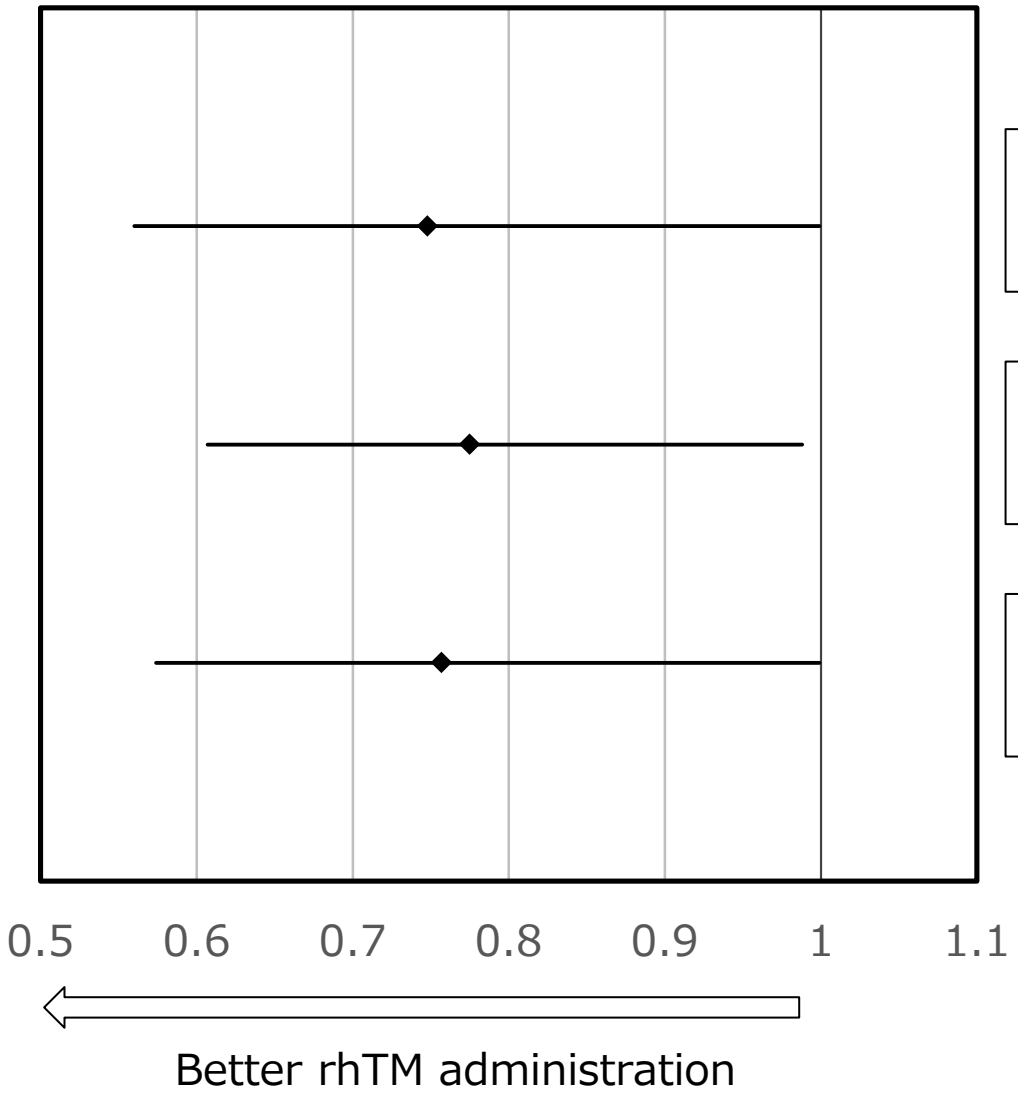

Patients with severe sepsis or septic shock
n = 3,195
Excluded patients, n = 1,411
Patients without DIC n = 1,000
Pre-existing hemostatic disorder n = 411
Patients with DIC
n = 1,784
Control group
n = 1,139
rhTM group
n = 645
Propensity score matching
Propensity score-matched
control group
n = 452
Propensity score-matched
rhTM group
n = 452

Figure 1



IPTW	0.748 (0.560–0.999)	p = 0.049
Stratified	0.775 (0.607–0.988)	p = 0.040
Matching	0.757 (0.574–0.999)	p = 0.049

Figure 2

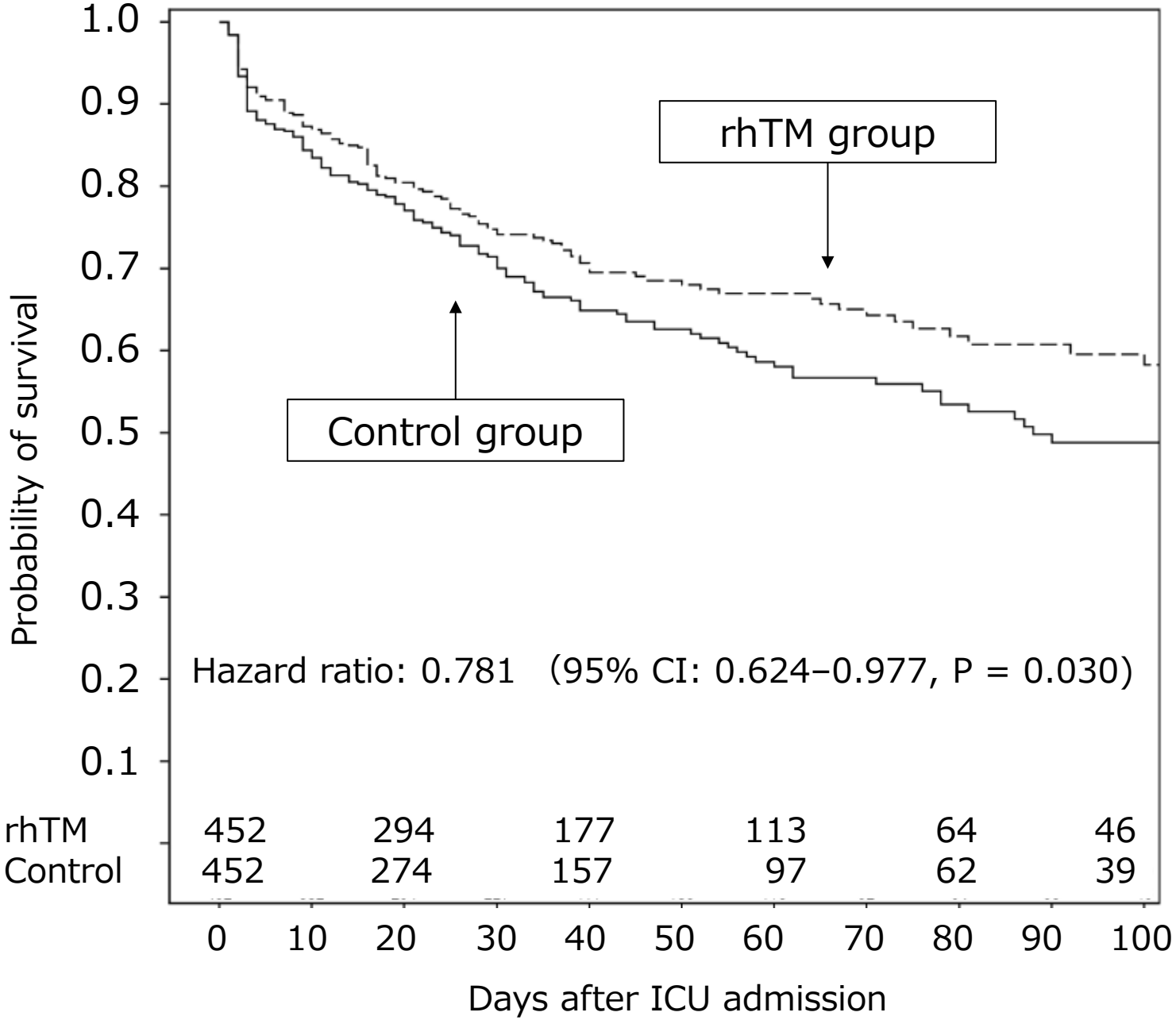

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
Probability of survival
rhTM group
Control group
Hazard ratio: 0.781 (95% CI: 0.624–0.977, P = 0.030)
rhTM 452 294 177 113 64 46
Control 452 274 157 97 62 39
0 10 20 30 40 50 60 70 80 90 100
Days after ICU admission

Figure 3