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The Influence of Human Soluble Recombinant Thrombomodulin on In-Hospital Mortality in Patients with Acute Respiratory Distress Syndrome and Disseminated Intravascular Coagulation: A Retrospective Multicenter Study

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Abstract

Background: Patients with acute respiratory distress syndrome (ARDS) often develop disseminated intravascular coagulation (DIC), which can worsen clinical outcomes. Anticoagulant therapy such as human soluble recombinant thrombomodulin (rTM) treatment may help to resolve DIC and improve prognoses. This study analyzes the influence of rTM treatment on in-hospital mortality in patients with both ARDS and DIC.

Methods: In a retrospective cohort study, we examined 75 patients with ARDS and DIC who had been admitted to the intensive care units of 3 university hospitals between March 1, 2008 and February 29, 2016. Data were extracted from clinical records. Subjects were divided into a control group comprising 38 patients who were not administered rTM and an rTM group comprising 37 patients who were administered rTM. Kaplan-Meier survival analysis was performed to produce survival curves and the log-rank test was used to compare survival between the 2 groups. We conducted a Cox proportional hazards regression analysis where the dependent variable was in-hospital mortality and the main independent variable of interest was the use of rTM; the hazard ratio of rTM use was calculated.

Results: The variables of with P values below 0.2 were age (P=0.15), source of sepsis (P=0.17), rTM use (P=0.02) and AT concentrate use (P=0.17) between the survivors and non-survivors. There was no significant difference in the ARDS severity levels between the rTM group and the control group (P=0.71). In-hospital mortality was significantly lower (P=0.02) in the rTM group (37.8%) than in the control group (65.8%). The hazard ratio of rTM use for mortality was 0.49 (95% confidence interval: 0.26-0.95; P=0.03). In addition, the log-rank test showed that the rTM group had significantly better survival than the control group (P=0.04).

Conclusion: Our study indicates that rTM treatment significantly improved prognoses in patients with both ARDS and DIC.

Keywords: Human soluble recombinant thrombomodulin; Acute respiratory distress syndrome; Disseminated intravascular coagulation; In-hospital mortality

Abbreviations: APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: Acute Respiratory Distress Syndrome; DIC: Disseminated Intravascular Coagulation; eGFR: Estimated Glomerular Filtration Rate; HMGB-1: High-Morbidity Group Box-1; HR: Hazard Ratio; ICU: Intensive Care Unit; P/F ratio: PaO_2/Fraction Oxygenation Ratio; rTM: Human Soluble Recombinant Thrombomodulin; SOFA: Sequential Organ Failure Assessment; AT: Antithrombin

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Background

Acute respiratory distress syndrome (ARDS) refers to the development of acute noncardiogenic pulmonary edema due to an increase in pulmonary vascular permeability. It is not uncommon for patients with ARDS to develop disseminated intravascular coagulation (DIC) [1] and patients with DIC also develop ARDS with fairly high frequency [1,2]. The development of DIC in ARDS patients is associated with poorer prognoses, which underlines the need for early treatment [2]. Anticoagulant therapy, including antithrombin therapy and thrombomodulin therapy, has shown to be efficacious in the treatment of acute lung injury in animal experiments [3]. This suggests that anticoagulant therapy may also be effective in the treatment of human patients with ARDS in the clinical setting [3].

Thrombomodulin is a membrane protein that serves as a thrombin receptor on endothelial cells and plays an important role in regulating intravascular coagulation through the thrombomodulin-protein C pathway [4,5]. Human soluble recombinant thrombomodulin (rTM) is composed of the active extracellular domain of thrombomodulin, which forms a reversible complex with thrombin to convert plasma protein C into its activated form. This in turn inactivates coagulation factors and reduces the pro-inflammatory effects of thrombin. In addition, rTM directly binds high-mobility group box 1 (HMGB-1), thereby preventing its interaction with receptors for advanced glycation end-products and suppressing the induction of pro-inflammatory events [6]. A phase III clinical trial of rTM treatment for DIC associated with hematologic malignancies and infection reported that patients treated with rTM had a significantly higher DIC resolution rate when compared with patients treated with unfractionated heparin; however, there was no significant difference in 28-day mortality between the 2 treatment modalities [7]. Previous studies have also observed the anti-inflammatory effects of rTM in mice [6,8]. The use of rTM treatment may therefore improve outcomes in patients with ARDS and DIC by controlling the coagulation system and suppressing inflammation. However, the clinical effects of rTM treatment in these patients have yet to be examined. Here, we conduct a retrospective multicenter cohort study of the influence of rTM treatment on in-hospital mortality in patients with both ARDS and DIC.

Materials and Method

Study design and data source

We conducted a retrospective analysis of patients with ARDS and DIC who had been admitted to the intensive care units (ICUs) of 3 university hospitals in the Kansai region of Japan between March 1, 2008 and February 29, 2016. All data were extracted from clinical records. This study was approved by the institutional ethics committee of Kansai Medical University Hospital (Approval number: H120721)

Patient selection

We first identified patients who had been diagnosed with both ARDS and DIC during the study period. ARDS was diagnosed according to the Berlin definition [9]. The Japanese Association for Acute Medicine has developed a DIC score for diagnostic purposes and patients with a score of 4 or more were identified as having DIC. Potential subjects were selected according to the following criteria: patients aged 20 years or older who were admitted to the ICUs of the participant hospitals, patients who were diagnosed as having both ARDS and DIC and patients who were administered rTM every day for 6 days after ICU admission. We excluded patients who were diagnosed with diseases other than ARDS and DIC, diagnosed with hepatic failure or hematological malignancy, did not receive rTM treatment from the first day of ICU admission, or had been administered rTM for fewer than 6 days.

The subjects were divided into 2 groups: A control group comprising patients who were not administered rTM and an rTM group comprising patients who were administered rTM. The decision to administer rTM in each patient was made by their attending physician without randomizing. The dose of rTM was set at 380 U/kg for patients with a minimum estimated glomerular filtration rate (eGFR) of 30 mL/min, or 130 U/kg for patients with an eGFR below 30 mL/min. The rTM administration duration was 6 days (or until the patient died, whichever was earlier) and administration was stopped at the discretion of the treating physician.

Patient characteristics

We collected information on the following patient baseline characteristics: Age, sex, source of sepsis (lung, abdomen, others and no sepsis), severity of ARDS using the Berlin definition, Acute Physiology and Chronic Health Evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score and DIC score.

Data were also obtained on the duration of mechanical ventilation, maximum peak inspiratory pressure, minimum PaO_2/fraction of inspiratory oxygen (P/F) ratio, utilization of antithrombin (AT) concentrate and low-dose steroid administration (hydrocortisone sodium phosphate at ≤ 200 mg/day or methylprednisolone at ≤ 2.5 mg/kg/day) in each patient.

Outcome measures

The main outcome measure used in this study was in-hospital mortality. The secondary outcome measures were the platelet count component of the SOFA score, the respiratory component of the SOFA score, the DIC score and the P/F ratio for a week after ICU admission. In the platelet count component of the SOFA score, a coagulation sub-score is given to each patient based on platelet count thresholds. This sub-score ranges from 0 (platelet count: ≥ 150 × 10^3/μl) to 4 (platelet count: <20 × 10^3/μl) and the raw platelet count is not included in the SOFA score.

Statistical Analysis

Continuous variables were calculated as means and standard deviations and categorical variables were calculated as percentages. We used Student's t-test or Welch's t-test following Levene's test to compare continuous variables between the 2

groups. Categorical variables were analyzed using the Chi-square test or Fisher's exact test. The various scores were calculated as median values accompanied by the interquartile range and were analyzed using the Mann-Whitney U test. Univariate analyses were used to identify patient characteristics that were significantly different between the survivors and non-survivors. These factors would then be included as covariates in a Cox proportional hazards regression model with in-hospital mortality as the dependent variable; the main independent variable of interest was the use of rTM. In addition, we also conducted a sensitivity analysis that included other independent variables with P values below 0.2 in the univariate analyses. The sensitivity analysis was conducted for all patients as well as a subgroup comprising only septic patients. The hazard ratios (HRs) for the independent variables were calculated. The Mantel-Haenszel test was used to analyze in-hospital mortality associated with rTM use among the different levels of ARDS severity.

The differences in changes in the DIC score and the platelet count component of the SOFA score between the control group and rTM group were analyzed using two-way repeated measures analysis of variance.

P values lower than 0.05 were regarded as statistically significant. All analyses were performed using SPSS Version 24.0 (IBM Japan, Ltd., Tokyo, Japan).

Results

The control group and rTM group comprised 38 patients and 37 patients, respectively **(Table 1)**. There were 36 survivors and 39 non-survivors **(Table 2)**. There were no statistically significant differences in patient characteristics between the control group and rTM group, as well as between the survivors and non-survivors. The variables of with P values below 0.2 were age (P=0.15), source of sepsis (P=0.17), rTM use (P=0.02) and AT concentrate use (P=0.17) between the survivors and non-survivors. The most common level of ARDS severity in the control group and rTM group was moderate ARDS (47.4% and 56.8%, respectively), followed by mild ARDS (31.6% and 27.0%, respectively) and severe ARDS (21.1% and 16.2%, respectively); there was no significant difference among these severity levels (P=0.71). There were also no significant differences in the in-hospital medical care provided to the control group and rTM group, where the minimum P/F ratios within 24 h of ICU admission were 167.4 ± 66.9 mm Hg and 160.4 ± 61.2 mm Hg, respectively (P=0.64).

The clinical outcomes according to rTM use and ARDS severity are presented in **Table 3**. The length of ICU stay was significantly shorter (P=0.05) in the rTM group (15.6 ± 7.2 days) when compared with the control group (20.8 ± 14.4 days). In addition, in-hospital mortality was significantly lower (P=0.02) in the rTM group (37.8%) than in the control group (65.8%). Similarly, cumulative 90 day mortality was significantly lower (P=0.03) in the rTM group (42.8%) than in the control group (76.0%). ARDS severity was not associated with the clinical outcomes. In addition, there were no significant differences in survival among the different levels of ARDS severity **(Figure 1).**

Table 1 Patient characteristics and outcomes in the control and rTM groups (n=75).

Variables	Control (n=38)	rTM (n=37)	*P* value
Number of patients			
Hospital A	21	16	
Hospital B	15	15	
Hospital C	2	6	
Patient characteristics			
Age (years)	69.7 ± 11.5	68.5 ± 17.1	0.72
Male (%)	63.2	81.1	0.08
Source of sepsis (%)			
Lung	57.9	67.6	0.46
Abdomen	28.9	13.5	
Others	7.9	13.5	
No sepsis	5.3	5.4	
ARDS severity (%)			
Mild	31.6	27.0	0.71
Moderate	47.4	56.8	
Severe	21.1	16.2	
APACHE II score	25.8 ± 6.2	27.4 ± 6.1	0.26
SOFA score (IQR)	13.0 (10.0-14.3)	12.0 (11.0-14.0)	0.84
DIC score (%)			
4	31.6	32.4	0.60
5	31.6	21.6	
6	21.1	24.3	
7	2.6	10.8	
8	13.2	10.8	
Year			
2008	12	0	<0.001
2009	11	0	
2010	0	1	
2011	2	3	
2012	1	3	
2013	1	12	
2014	5	11	
2015	5	6	
2016	1	1	
Medical care			
Duration of MV (days)	25.9 ± 27.0	19.7 ± 19.4	0.26
Maximum PIP during MV (cm H_2O)	28.5 ± 6.4	27.2 ± 5.2	0.36
Minimum P/F ratio within 24 h of ICU admission	167.4 ± 66.9	160.4 ± 61.2	0.64
AT concentrate use (%)	71.1	75.7	0.65
Steroid use (%)	39.5	48.6	0.42

Values are presented as mean ± standard deviation for continuous variables and number (percentage) or score (IQR) for categorical variables

APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: Acute Respiratory Distress Syndrome; AT: Antithrombin; DIC: Disseminated Intravascular Coagulation; ICU: Intensive Care Unit; IQR: Interquartile Range; MV: Mechanical Ventilation; P/F: PaO_2/Fraction of Inspiratory Oxygen; PIP: Peak Inspiratory Pressure; rTM: Recombinant Human Soluble Thrombomodulin; SOFA: Sequential Organ Failure Assessment

Table 2 Patient characteristics and outcomes in the survivors and non-survivors (n=75).

Variables	Survivors (n=36)	Non-survivors (n=39)	*P* value
Number of patients			
Hospital A	20	17	0.25
Hospital B	11	19	
Hospital C	5	3	
Patient characteristics			
Age (years)	66.6 ± 17.7	71.4 ± 10.4	0.15
Male (%)	77.8	66.7	0.28
Source of sepsis (%)			
Lung	52.8	71.8	0.17
Abdomen	30.6	12.8	
Others	11.1	10.3	
No sepsis	5.6	5.1	
ARDS severity (%)			
Mild	30.6	28.2	0.26
Moderate	58.3	46.2	
Severe	11.1	25.6	
APACHE II score	26.0 ± 5.2	27.2 ± 6.9	0.39
SOFA score (IQR)	11.5 (9.3-14.8)	13.0 (11.0-14.0)	0.24
DIC score (IQR)	5.0 (4.0-6.0)	5.0 (4.0-6.0)	0.57
Year			
2008	4	8	0.32
2009	6	5	
2010	1	0	
2011	2	3	
2012	1	3	
2013	8	5	
2014	8	8	
2015	5	6	
2016	1	1	
Medical care			
Duration of MV (days)	20.2 ± 23.1	25.3 ± 24.2	0.35
Maximum PIP during MV (cm H_2O)	27.4 ± 4.6	28.2 ± 6.9	0.54
Minimum P/F ratio within 24 h of ICU admission	170.0 ± 57.7	158.4 ± 69.2	0.43
AT concentrate use (%)	80.6	66.7	0.17
Steroid use (%)	47.2	41.0	0.59
rTM use (%)	63.9	35.9	0.02

Values are presented as mean ± standard deviation for continuous variables and number (percentage) or score (IQR) for categorical variables
APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: Acute Respiratory Distress Syndrome; AT: Antithrombin; DIC: Disseminated Intravascular Coagulation; ICU: Intensive Care Unit; IQR: Interquartile Range; MV: Mechanical Ventilation; P/F: PaO_2/Fraction of Inspiratory Oxygen; PIP: Peak Inspiratory Pressure; rTM: Recombinant Human Soluble Thrombomodulin; SOFA: Sequential Organ Failure Assessment

Table 4 shows the in-hospital mortality in the control group and rTM group according to ARDS severity. In all severity levels, the rTM group had lower in-hospital mortality than the control group. Overall, rTM use was significantly associated with in-hospital mortality regardless of ARDS severity (Mantel-Haenszel test: P=0.04).

The Kaplan-Meier curves of both groups are shown in **Figure 2**. The rTM group had significantly better survival than the control group according to the log-rank test (P=0.04). As none of the patient characteristics were significantly associated with mortality, the Cox proportional hazards regression analysis only included the use of rTM as the independent variable. As shown in **Table 5**, rTM use was significantly associated with a reduction in crude in-hospital mortality (HR: 0.49; 95% confidence interval: 0.26-0.95; P=0.03). This association did not lose significance even after the addition of the sources of sepsis, AT concentrate use and age as covariates in the sensitivity analysis of all patients **(Table 5)**. In septic patients, the HR of rTM use was 0.31 (95% confidence interval: 0.10-0.92; P=0.04).

The two-way repeated measures analysis of variance detected significant differences between the 2 groups in changes in the platelet count component of the SOFA score (P<0.001; **Figure 3a**) and the DIC score (P<0.01; **Figure 3b**). The rTM group had a significantly higher platelet count component of the SOFA score on Day 5 (P<0.01) and DIC score on Day 4 (P=0.04); however, no statistical differences were observed in these variables during the other days. Although there was no significant difference in P/F ratio within 24 h of ICU admission between the 2 groups, the P/F ratio was significantly higher throughout the 7-day period after ICU admission in the rTM group (P<0.01; **Table 6**). In particular, the rTM group had a significantly higher P/F ratio on Day 7 (P=0.04). In septic patients, the platelet count component of the SOFA score (P<0.001), the DIC score (P=0.01) and P/F ratio (P<0.001) throughout the 7-day period after ICU admission were also higher in the rTM group relative to the control group (data not shown).

Discussion

This study is, to the best of our knowledge, the first to examine the influence of daily rTM use on in-hospital mortality in patients with both ARDS and DIC. Our results indicate that rTM administration was associated with reductions in in-hospital mortality. The results were similar in the subgroup of patients who had sepsis-induced ARDS.

In an analysis of acute exacerbation of idiopathic pulmonary fibrosis, Isshiki et al. compared outcomes in patients treated with rTM and conventional therapy [10]. That study found that patients treated with rTM had better survival over 90 days. Despite the difference in target diseases between their study subjects and ours, the similar findings are noteworthy. Another study reported that rTM treatment improved lung injury scores and 90 day mortality in patients with sepsis-induced ARDS and DIC [11]. Their findings corroborate those of our sub analysis of similar patients who experienced improvements in oxygenation function and 90-day mortality.

A previous retrospective analysis found that patients with ARDS and DIC experienced improved P/F ratios after 7 days of rTM administration [12]. Similarly, Ogawa et al. showed that rTM administration improved respiratory function (using the lung injury score and the respiratory component of the SOFA score) in Japanese patients with sepsis [11]. However, our study is

Table 3 Clinical outcomes according to rTM use and ARDS severity (n=75).

Variables	rTM use		*P* value	ARDS severity			*P* value
	Control (n=38)	rTM (n=37)		Mild (n=22)	Moderate (n=39)	Severe (n=14)	
ICU stay (days)	20.8 ± 14.4	15.6 ± 7.2	0.05	21.2 ± 11.7	16.6 ± 8.5	18.1 ± 17.6	0.16
Hospital stay (days)	54.0 ± 59.6	68.0 ± 72.1	0.36	50.2 ± 36.6	73.2 ± 82.9	43.4 ± 39.9	0.19
In-hospital mortality (%)	65.8	37.8	0.02	50.0	46.2	71.4	0.26
Cumulative 90 day mortality (%)	76.0	42.8	0.03	60.8	62.1	71.4	0.20

Values are presented as mean ± standard deviation for continuous variables and percentage for categorical variables
ARDS: Acute Respiratory Distress Syndrome; ICU: Intensive Care Unit; rTM: Recombinant Human Soluble Thrombomodulin

Table 4 Association between rTM use and in-hospital mortality stratified by ARDS severity (n=75).

ARDS severity	rTM use	In-hospital mortality (%)	*P* value
Mild (n=22)	Control	75.0	0.04
	rTM	20.0	
Moderate (n=39)	Control	55.6	
	rTM	38.1	
Severe (n=14)	Control	75.0	
	rTM	66.7	

ARDS: Acute Respiratory Distress Syndrome; rTM: Recombinant Human Soluble Thrombomodulin

Table 5 Results of Cox hazard regression analyses of in-hospital mortality (n=75).

Variables	Hazard ratio	95% CI	*P* value
Independent variables: rTM use, source of sepsis, AT concentrate use and age in all patients (n=75)			
rTM use	0.23	0.08-0.66	<0.01
Source of sepsis (Ref: No sepsis)			0.15
Lung	2.20	0.27-18.2	0.46
Abdomen	0.45	0.04-4.70	0.51
Others	2.14	0.16-28.85	0.57
AT concentrate use	0.56	0.17-1.83	0.34
Age	1.03	0.99-1.07	0.15
Independent variables: rTM use, source of sepsis, AT concentrate use and age in septic patients (n=70)			
rTM use	0.31	0.10-0.92	0.04
Source of sepsis (Ref: Lung)			0.12
Abdomen	0.24	0.06-0.96	0.04
Others	1.05	0.19-5.75	0.95
AT concentrate use	0.38	0.10-1.35	0.13
Age	1.04	0.99-1.08	0.10

AT: Antithrombin; CI: Confidence Intervals; rTM: Recombinant Human Soluble Thrombomodulin

Table 6 P/F ratios throughout the 7-day period after ICU admission (n=75).

Variables	Control (n=38)	rTM (n=37)	*P* value
P/F ratio			
Day 1	167.4 ± 66.9	160.4 ± 61.2	0.01
Day 2	215.0 ± 90.8	232.3 ± 92.3	
Day 3	240.3 ± 96.0	263.1 ± 111.9	
Day 4	249.9 ± 97.6	284.2 ± 104.1	
Day 5	264.5 ± 122.1	294.3 ± 110.7	
Day 6	250.3 ± 104.0	286.3 ± 114.9	
Day 7	248.2 ± 110.1	304.9 ± 106.2	

Values are presented as mean ± standard deviation
P/F: PaO_2/Fraction of Inspiratory Oxygen; rTM: Recombinant Human Soluble Thrombomodulin

the first to continuously monitor P/F ratios for 7 days after ICU admission in patients with ARDS and DIC. Although the patients in Isshiki et al. had substantially higher P/F ratios [10] than our subjects, both studies observed similar improvements after rTM treatment. Furthermore, previous studies have indicated that higher oxygenation is associated with improved prognoses [13,14]. As shown in **Table 6**, the rTM group in our study generally experienced higher levels of oxygenation within 7 days of starting rTM treatment. Additionally, our analysis did not detect any improvements in DIC score and the platelet count component of the SOFA score. It is therefore possible that the improvement in oxygenation function contributed to the improvement in clinical outcomes. However, it is unclear if the improvements are due to increased oxygenation function following the inhibition of microthrombi formation or if they are attributable to other mechanisms that are presently unknown. The mechanisms should be examined in future studies.

Although our study did not examine how rTM administration

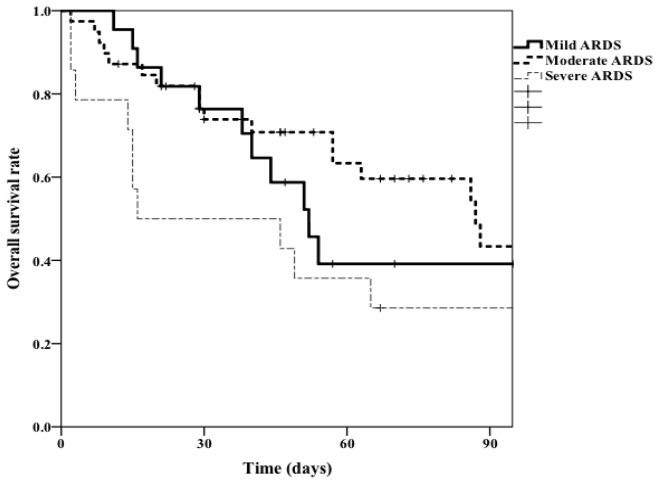

Figure 1 Kaplan-Meier in-hospital survival curves according to ARDS severity. There were no significant differences in survival among the different levels of ARDS severity (Log-rank test: P=0.20).

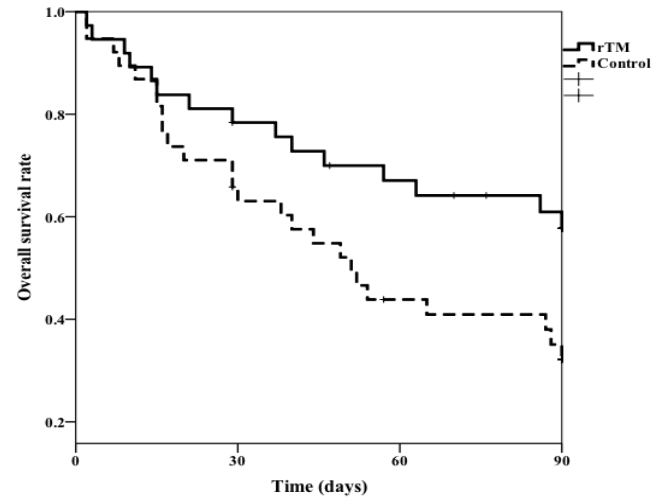

Figure 2 Kaplan-Meier in-hospital survival curves in the control and rTM groups. Patients in the rTM group had significantly better survival than patients in the control group (Log-rank test: P=0.04).

improves prognoses in patients with ARDS and DIC, a possible mechanism is the lowering of HMGB-1 levels. A previous study reported that HMGB-1 levels in the lungs of ARDS mice were higher than in non-ARDS mice and that rTM administration prolonged survival time and halted the exacerbation of ARDS [15]. In addition, rTM treatment has been reported to prevent lipopolysaccharide-induced pulmonary vascular injury through protein C activation in rats [16,17], as well as increase HMGB-1 concentrations in patients with acute lung injury [18]. In ARDS patients who were administered rTM, survivors had significantly lower HMGB-1 levels than non-survivors after 7 days of treatment [19]. While our study did not measure HMGB-1 concentrations, our findings that rTM treatment improves prognoses in ARDS patients do not contradict the results of these previous studies.

The findings of this study should be considered in the context of several limitations. Firstly, this was a retrospective study with a relatively small sample size. Secondly, there may be therapeutic biases that affected the results of the time course of DIC score and the platelet count component of the SOFA core. Thirdly, there may be confounding factors that were not included in analysis. For example, the analysis did not account for differences in underlying disease. Severe diseases such as chronic obstructive pulmonary disease or chronic kidney failure would affect patient prognosis. In addition, as the management of ARDS may have improved over time, it is possible that this and other unidentified confounding factors had influenced in-

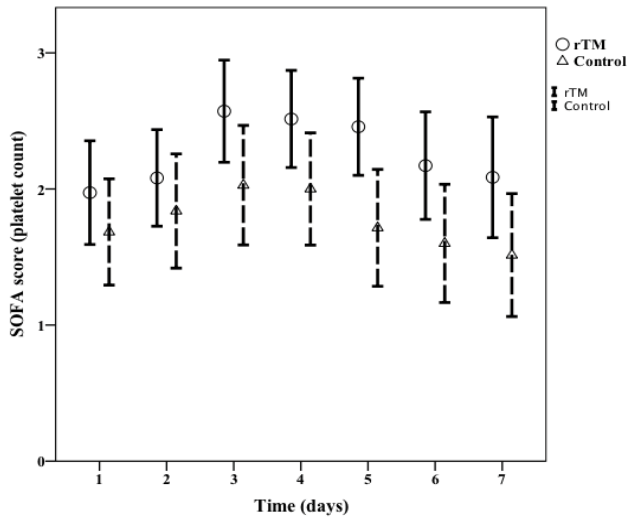

Figure 3a Seven-day changes in the platelet count component of the sequential organ failure assessment (SOFA) score in the control and rTM groups. (Between subjects: P<0.001)

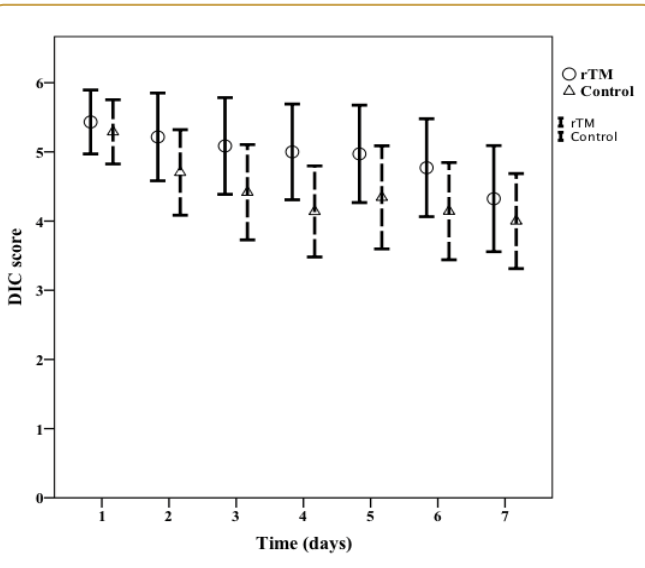

Figure 3b Seven-day changes in the Japanese Association for Acute Medicine disseminated intravascular coagulation (DIC) score in the control and rTM groups (between subjects: P<0.01).

hospital mortality during the relatively long study period. For example, the determination of ARDS severity was based on the P/F ratio and the initial positive end-expiratory pressure setting for mechanical ventilation may vary among the hospitals and physicians. The imprecise identification of moderate ARDS cases as mild ARDS cases may have resulted in disproportionately high in-hospital and cumulative 90-day mortality rates in patients with mild ARDS, thereby causing a lack of significant associations between these outcomes and ARDS severity. Fourthly, we did not collect raw data on platelet count and C-reactive protein levels in the initial protocol of this study. As these variables are useful for understanding the clinical course of ARDS and DIC, they should also be included in downstream analyses. Finally, we calculated that the detection of an in-hospital mortality reduction of 10% would indicate a statistical power of 0.36; similarly, the detection of an in-hospital mortality reduction of 20% would indicate a statistical power of 0.09. There would therefore need to be at least 120 cases in each group to detect a reduction of 10% in in-hospital mortality. Accordingly, there is a need to further increase the number of cases to compare mortality rates.

Conclusion

Our study indicates that rTM treatment was able to significantly improve prognoses in patients with both ARDS and DIC. However, there is a need to confirm these findings in large-scale prospective studies, including randomized control trials. Our analysis suggests that rTM treatment improved oxygenation function relatively quickly after administration and this mechanism warrants further examination.

Acknowledgement

We thank the patients and their families for their participation in the study.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the internal ethics review board of Kansai Medical University Hospital (Approval Number: H120721).

Consent for publication

Informed consent was obtained from all enrolled patients or their relatives.

Availability of data and material

The dataset supporting the conclusions of this article is available upon request. Please contact the corresponding author (Takeshi Umegaki) for data requests.

Competing interests

The authors declare that they have no competing interests.

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