Original Article

Validating plasminogen activator inhibitor-1 as a poor prognostic factor in sepsis

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Aim: Our previous report indicated that plasminogen activator inhibitor-1 (PAI-1) levels of ≥83 ng/mL in patients with sepsis tended to be associated with disseminated intravascular coagulation (DIC), suppressed fibrinolysis, multiple organ dysfunction, and mortality. Therefore, the present study aimed to validate whether 83 ng/mL was a useful cut-off value for using PAI-1 levels to predict a poor prognosis in sepsis.

Methods: Patients with sepsis were included in this single-center retrospective study. The patients were classified as having high or low PAI-1 values (<83 ng/mL versus ≥83 ng/mL), and were compared in terms of their pre-DIC state, intensive care unit-free days, continuous renal replacement therapy-free days, ventilator-free days, catecholamine-free days, and 28-day survival rate.

Results: The high PAI-1 group included 61 patients (54%) and the low PAI-1 group included 52 patients (46%). The high PAI-1 group had significantly higher frequencies of a pre-DIC state within 1 week ($P = 0.009$). There was no significant difference in ventilator-free days. However, the high PAI-1 group had significantly lower values for intensive care unit-free days ($P = 0.01$), continuous renal replacement therapy-free days ($P = 0.02$), and catecholamine-free days ($P = 0.02$). The high PAI-1 group also had a significantly lower 28-day survival rate based on the Kaplan–Meier analysis (log–rank, $P = 0.03$).

Conclusion: Patients with sepsis and PAI-1 levels of ≥83 ng/mL had elevated risks of coagulopathy, organ failure, and mortality. Thus, these results suggest that 83 ng/mL could be a useful cut-off value for prognostication based on PAI-1 levels in this setting.

Key words: Disseminated intravascular coagulation, mortality, organ failure, plasminogen activator inhibitor, sepsis

INTRODUCTION

SEPSIS INVOLVES LIFE -threatening organ dysfunction caused by a dysregulated host response to infection.[1] The global burden of sepsis is difficult to determine, although estimates suggest an annual incidence of >30 million cases and approximately 6 million related deaths.[2] Untreated or inadequately treated cases of sepsis can lead to septic shock, which is associated with high rates of morbidity and mortality. Thus, early diagnosis of sepsis is essential for its successful treatment.

Disseminated intravascular coagulation (DIC) is a serious condition involving widespread and persistent activation of coagulation, in the presence of underlying disease, which causes diffuse microthrombi to form in small blood vessels.[3] This process involves activation of both coagulation and fibrinolysis, although the degree of fibrinolysis activation varies considerably depending on the underlying disease.[4] Suppressed fibrinolytic DIC is typically observed in sepsis cases, which involves strong activation of coagulation with mild activation of fibrinolysis. Furthermore, previous studies have indicated that 20–40% of sepsis cases involve DIC,[5–8] and that sepsis-induced DIC leads to microthrombi development, tissue hypoperfusion, and multiple organ failure. Therefore, sepsis-induced DIC is associated with a high mortality rate.[9]

Endothelial cells and hepatocytes synthesize plasminogen activator inhibitor-1 (PAI-1), which is the main inhibitor of tissue-type plasminogen activator and plays an important role in the regulation of fibrinolysis.[10] In this context, the initiation of fibrinolysis is mediated by plasminogen activators and is regulated by PAI-1,[11] with high PAI-1 levels reportedly reflecting suppressed fibrinolysis and predicting poor sepsis outcomes. Our previous study[12] of patients with sepsis revealed that PAI-1 was the only independent

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predictive marker of 28-day mortality among sepsis biomarkers and coagulation/fibrinolysis markers, with the optimal cut-off value being 83 ng/mL (sensitivity, 75%; specificity, 61%). Furthermore, PAI-1 levels of ≥83 ng/mL in patients with sepsis tend to be associated with DIC development, suppressed fibrinolysis, and multiple organ dysfunction. Thus, PAI-1 is an important predictor of multiple organ failure and mortality in sepsis cases.

Recombinant human soluble thrombomodulin (rhsTM) is a novel class of anticoagulants for treating DIC. In 2008, rhsTM was approved for the treatment of sepsis-induced DIC in Japan. Recent clinical studies have shown that treatment with rhsTM can reduce mortality by improving organ dysfunction.[13,14] However, the appropriate indication of rhsTM treatment is unclear.

The present study aimed to validate whether 83 ng/mL was a useful cut-off value for using PAI-1 levels to predict a poor prognosis in sepsis. In addition, we determined whether PAI-1 is a useful marker to decide the appropriate indication for rhsTM treatment.

METHODS

THIS STUDY WAS approved by the ethics committee of Fukuoka University Hospital (No. 19-3-03) and was in compliance with the Helsinki Declaration. This single-center retrospective study evaluated data from sepsis patients (diagnosed according to the Sepsis-3 definition[1]) who were admitted to our intensive care unit (ICU) between October 2015 and September 2018. The exclusion criteria were age of <15 years, cardiopulmonary arrest at admission, malignant disease, liver cirrhosis, and extracorporeal membrane oxygenation support. Eligible patients were classified as having high or low PAI-1 levels (≥83 ng/mL versus <83 ng/mL) on ICU admission.

The two patient groups were then compared in terms of their characteristics, clinical factors, inflammation biomarkers, and coagulation/fibrinolysis markers on ICU admission. The patient characteristics included age and sex. The clinical factors included infection focus, Glasgow Coma Scale score, vital signs, lactate level, and the severity scores. The inflammation biomarkers included white blood cell count (WBC), C-reactive protein (CRP), procalcitonin (PCT), and presepsin (P-SEP). The coagulation/fibrinolysis markers included platelets, prothrombin time – international normalized ratio, activated partial thromboplastin time, fibrinogen, antithrombin, fibrin/fibrinogen degradation products, D-dimer, thrombin–antithrombin complex, plasmin-α2 plasmin inhibitor complex, protein C, thrombomodulin, and soluble fibrin. Relationships between PAI-1 levels and severity scores (DIC and Sequential Organ Failure Assessment [SOFA] scores[15]) were also evaluated. The outcomes of interest were defined as the frequency of a pre-DIC state, ICU-free days, continuous renal replacement therapy (CRRT)-free days, ventilator-free days, catecholamine-free days, and 28-day mortality rate. Kaplan–Meier analysis was used to analyze the 28-day survival rate.

The patients were divided into four groups according to the presence or absence of DIC and those with high or low PAI-1 levels. The SOFA score and 28-day mortality were compared with and without rhsTM treatment in each group to evaluate the differences in rhsTM efficacy.

The diagnosis of DIC was based on the DIC criteria from the Japanese Association for Acute Medicine (JAAM).[16] A pre-DIC state was defined as time spent with the condition (A1 week) before the onset of DIC. The ICU-free days were calculated as days alive and not requiring ICU care in the first 28 days after hospitalization. The days free from CRRT, ventilator support, and catecholamine were calculated based on the days alive and without the related supports during the first 28 days after hospitalization.

Measurement of PAI-1

The PAI-1 level was measured using a STACIA (LSI Medience, Tokyo, Japan). Total PAI-1 including active PAI-1 and tPA-PAI-1 complex was defined as PAI-1 in this study.

Statistical analysis

Continuous variables are presented as median (interquartile range). Comparisons between groups were carried out using the χ^2-test for dichotomous variables and Mann–Whitney *U*-test for continuous variables. Correlations between PAI-1 levels and severity scores were evaluated using Spearman's rank test. A P-value < 0.05 was considered statistically significant. All statistical analyses were undertaken using JMP version 12 (SAS Institute, Cary, NC, USA).

RESULTS

Patient selection

DURING THE STUDY period, 131 patients were admitted to our ICU with sepsis, but 18 patients were excluded (four patients with cardiopulmonary arrest at admission, six patients with malignant disease, three patients with liver cirrhosis, and five patients requiring extracorporeal membrane oxygenation support). The remaining 113 patients were classified into the high PAI-1 group (n = 61; 54%) and the low PAI-1 group (n = 52; 46%).

Patient characteristics

The patients' characteristics are presented in Table 1. The high PAI-1 group had significantly lower values for mean blood pressure ($P = 0.01$). Furthermore, the high PAI-1 group had significantly higher values for lactate levels ($P < 0.001$), DIC score ($P = 0.002$), DIC positive rate ($P = 0.01$), and SOFA score ($P < 0.001$). The independent factor of PAI-1 ≥83 ng/mL was identified with multivariate logistic regression analysis using the variables that were significantly different between the high PAI-1 and low PAI-1 groups. According to the multivariate analysis, SOFA score was the only independent factor of PAI-1 ≥83 ng/mL ($P = 0.02$; Table 2).

Table 2. Multivariate analysis of the characteristics of sepsis patients with plasminogen activator inhibitor-1 (PAI-1) ≥ 83 ng/mL

	OR	95% CI	*P*-value
Mean BP	0.993	0.973–1.012	0.45
Lactate	1.007	0.994–1.021	0.26
DIC score	1.211	0.968–1.516	0.09
SOFA score	1.166	1.020–1.332	0.02

BP, blood pressure; CI, confidence interval; DIC, disseminated intravascular coagulation; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

Markers of inflammation, coagulation, and fibrinolysis

Among the inflammation biomarkers, there were no significant intergroup differences in WBC or CRP levels, although the high PAI-1 group had significantly higher PCT and P-SEP levels ($P < 0.001$ and $P = 0.005$, respectively). Among the coagulation and fibrinolysis markers, the high PAI-1 group had significantly higher values for prothrombin time – international normalized ratio ($P < 0.001$), activated partial thromboplastin time ($P < 0.001$), thrombin–antithrombin complex ($P = 0.02$), and thrombomodulin levels ($P = 0.01$). Furthermore, the high PAI-1 group had significantly lower values for platelets ($P < 0.001$), fibrinogen

Table 1. Characteristics of sepsis patients, grouped according to plasminogen activator inhibitor-1 (PAI-1) levels

	PAI-1 ≥ 83 ng/mL *n* = 61	PAI-1 < 83 ng/mL *n* = 52	*P*-value
Age (years)	72 (62–81)	68 (58–76)	0.13
Male, *n* (%)	29 (48)	31 (60)	0.20
Charlson comorbidity index	1 (0–2)	1 (0–2)	0.28
Infection focus			
Lung	19 (31)	23 (44)	0.46
Abdomen	20 (33)	12 (23)	
Urinary tract	9 (15)	4 (8)	
Skin and soft tissue	5 (8)	3 (6)	
Others	3 (5)	5 (10)	
Unknown	5 (8)	5 (10)	
GCS	11 (7–15)	13 (7–15)	0.54
Mean BP (mmHg)	72 (64–93)	89 (70–106)	0.01
HR (b.p.m.)	103 (90–117)	111 (97–129)	0.05
RR (b.p.m.)	22 (19–30)	24 (20–30)	0.31
BT ( )	36.7 (36.1–37.9)	37.3 (36.5–38.4)	0.06
Lactate (mg/dL)	33 (21–66)	16 (10–28)	<0.001
DIC score	5 (3–6)	3 (2–5)	0.002
DIC positive rate, *n* (%)	37 (61)	19 (37)	0.01
SOFA score	11 (10–15)	9 (6–12)	<0.001
APACHE II score	21 (16–27)	19 (12–25)	0.09

Data are presented as median (interquartile range) or number (percentage).
APACHE, Acute Physiology and Chronic Health Evaluation; BP, blood pressure; BT, body temperature; DIC, disseminated intravascular coagulation; GCS, Glasgow Coma Scale; HR, heart rate; RR, respiratory rate; SOFA, Sequential Organ Failure Assessment.

($P = 0.001$), antithrombin III ($P < 0.001$), plasmin-α2 plasmin inhibitor complex ($P = 0.006$), and protein C levels ($P < 0.001$; Table 3).

Correlations between PAI-1 levels and severity scores

Table S1 shows the correlations between PAI-1 levels and the various severity scores. The results indicate that PAI-1 levels were significantly and positively correlated with the DIC score ($r = 0.31$; $P < 0.001$) and the SOFA score ($r = 0.47$; $P < 0.001$). Furthermore, the DIC score was positively correlated with the SOFA score ($r = 0.37$; $P < 0.001$).

Relationships between PAI-1 levels and outcomes

Table 4 shows the relationships between PAI-1 levels and outcomes. The high PAI-1 group had a significantly higher frequency of the pre-DIC state within 1 week (63% [15/24] versus 39% [13/33], $P = 0.009$). There was no significant intergroup difference in ventilator-free days (21 [4–26] versus 22 [17–25], $P = 0.25$). The high PAI-1 group had significantly lower values for ICU-free days (18 [10–22] versus 20 [16–25], $P = 0.01$), CRRT-free days (28 [17–28] versus 28 [27–28], $P = 0.02$), and catecholamine-free days (23 [7–27] versus 26 [21–28], $P = 0.02$). The Kaplan–Meier analysis confirmed that the high PAI-1 group had a significantly lower 28-day survival rate (log–rank, $P = 0.03$; Fig. 1).

Patient characteristics according to PAI-1 levels and DIC status

Patient characteristics were compared according to DIC status between the high PAI-1 and low PAI-1 groups (Table 5). Patients with high PAI-1 and DIC had significantly higher SOFA score than patients with high PAI-1 but without DIC. In addition, patients with low PAI-1 and DIC had significantly higher APACHE II score than patients with low PAI-1 but without DIC.

Evaluation of rhsTM efficacy

Figure 2 shows the difference in SOFA score between patients with and without rhsTM treatment in the four groups. There were no significant differences in SOFA score

Table 3. Comparison of inflammation biomarkers and coagulation/fibrinolysis markers in patients with sepsis, grouped according to plasminogen activator inhibitor-1 (PAI-1) levels

		PAI-1 ≥ 83 ng/mL *n* = 61	PAI-1 < 83 ng/mL *n* = 52	*P*-value
Inflammation biomarkers	WBC (10^3/μL)	10 (5–18)	12 (7–17)	0.380
	CRP (mg/dL)	10 (6–21)	12 (4–21)	0.740
	PCT (ng/mL)	15.6 (3.1–60.9)	1.2 (0.2–8.2)	<0.001
	P-SEP (pg/mL)	1034 (570–2007)	584 (295–1316)	0.005
Coagulation/fibrinolysis markers	Platelets (10^4/μL)	13 (7–21)	21 (14–25)	<0.001
	PT-INR	1.4 (1.3–1.7)	1.2 (1.1–1.4)	<0.001
	APTT (s)	41 (34–49)	34 (27–42)	<0.001
	Fbg (mg/dL)	431 (272–614)	608 (392–838)	0.001
	AT (%)	63 (56–77)	82 (68–95)	<0.001
	FDP (μg/mL)	16 (9–45)	14 (9–29)	0.530
	D-dimer (μg/mL)	6 (3–19)	5 (3–11)	0.320
	TAT (ng/mL)	10 (5–33)	7 (4–14)	0.020
	PIC (μg/mL)	1,5 (0.9–2..8)	2.4 (1.5–4.1)	0.006
	Protein C (%)	43 (32–56)	63 (46–84)	<0.001
	TM (U/mL)	33 (23–47)	21 (15–38)	0.010
	SF (μg/mL)	18 (9–54)	12 (7–26)	0.150

Data are presented as median (interquartile range)
APTT, activated partial thromboplastin time; AT, antithrombin; CRP, C-reactive protein; Fbg, fibrinogen; FDP, fibrinogen/fibrin degradation product; PCT, procalcitonin; PIC, plasmin-α2 plasmin inhibitor complex; P-SEP, presepsin; PT-INR, prothrombin time – international normalized ratio; SF, soluble fibrin; TAT, thrombin–antithrombin complex; TM, thrombomodulin; WBC, white blood count.

Table 4. Relationships between plasminogen activator inhibitor-1 (PAI-1) PAI-1 levels and outcomes in sepsis patients

	PAI-1 ≥ 83 ng/mL	PAI-1 < 83 ng/mL	*P*-value
Pre-DIC	63% (15/24)	39% (13/33)	0.009
ICU-free days	18 (10–22)	20 (16–25)	0.010
CRRT-free days	28 (17–28)	28 (27–28)	0.020
Ventilator-free days	21 (4–26)	22 (17–25)	0.250
Catecholamine-free days	23 (7–27)	26 (21–28)	0.020
28-day mortality	23% (14/61)	8% (4/52)	0.020

Data are presented as median (interquartile range) or number (percentage).
CRRT, continuous renal replacement therapy; DIC, disseminated intravascular coagulation; ICU, intensive care unit.

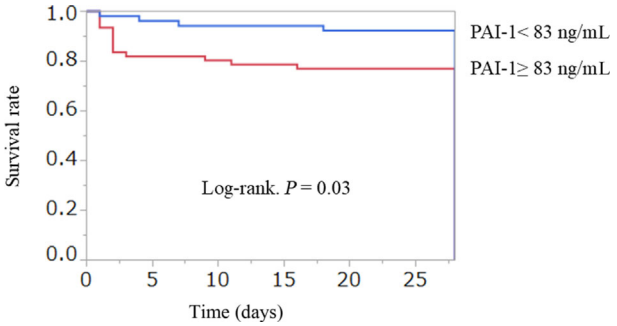

Fig. 1. Kaplan–Meier analysis between the high plasminogen activator inhibitor-1 (PAI-1) group and the low PAI-1 group of sepsis patients. The survival rate in 28 days is significantly higher in the high PAI-1 group (≥83 ng/mL; $n = 61$) than in the low PAI-1 group (<83 ng/mL; $n = 52$) (log–rank test, $P = 0.03$).

between patients with and without rhsTM treatment in each group. In the group with DIC and high PAI-1 levels, the 28-day survival rate was significantly higher with rhsTM treatment than without (log–rank, $P < 0.001$). However, there were no significant differences between with and without rhsTM treatment in other groups (Fig. 3).

DISCUSSION

THIS STUDY AIMED to validate 83 ng/mL as a prognostic cut-off value for PAI-1 levels in patients with sepsis, based on our previous report.[12] The present study revealed that, relative to the low PAI-1 group, the high PAI-1 group had significantly greater sepsis severity based on mean blood pressure, lactate level, DIC, and organ failure. Moreover, the Kaplan–Meier analysis confirmed that the high PAI-1 group had a significantly lower 28-day survival rate. These results suggest that 83 ng/mL is an appropriate cut-off value for using PAI-1 levels to predict prognosis in patients with sepsis.

Recent studies have indicated that PCT and P-SEP are useful biomarkers that can help guide therapeutic decision-making in sepsis cases, as these factors were associated with sepsis severity and prognosis.[17–19] However, elevated values for WBC and CRP levels do not appear to predict mortality.[17,18] Similarly, the present study revealed that the high PAI-1 group had elevated PCT and P-SEP levels, but not elevated values for WBC and CRP levels. These results could be related to the greater sepsis severity and poorer patient characteristics in the high PAI-1 group.

Based on a cut-off value of 83 ng/mL, high PAI-1 levels were significantly associated with an increased frequency of the pre-DIC state. In this context, DIC occurred within 1 week for approximately two-thirds of patients with PAI-1 levels of >83 ng/mL at ICU admission. Moreover, the high PAI-1 group had significantly lower values for ICU-free days, CRRT-free days, and catecholamine-free days, as well as an increased 28-day mortality rate. Thus, PAI-1 levels of ≥83 ng/mL appear to be associated with clinical outcomes, disease progression, and mortality in sepsis cases.

Several studies have evaluated the usefulness of PAI-1 levels in patients with sepsis, which were associated with sepsis severity and prognosis.[20–23] Moreover, a systematic review revealed that high PAI-1 levels were significantly correlated with mortality in sepsis cases.[20] Madoiwa *et al.*[21] also examined 117 patients with sepsis-induced DIC, which revealed that PAI-1 levels of >90 ng/mL were associated with a 23-fold higher risk of 28-day mortality. Their PAI-1 cut-off value is similar to the value from the present study (90 ng/mL versus 83 ng/mL).

Marked activation of coagulation is a major pathogenic factor in all types of DIC, although other pathological factors (especially the degree of fibrinolytic activation) differ considerably depending on the underlying disease. In this context, PAI regulates the degree of fibrinolytic activation and is an important factor in characterizing DIC.[8] Suppressed fibrinolytic-type DIC is typically observed in sepsis

Table 5. Characteristics of sepsis patients, grouped according to plasminogen activator inhibitor-1 (PAI-1) levels and presence or absence of disseminated intravascular coagulation (DIC)

	PAI-1 ≥ 83 ng/mL		*P*-value	PAI-1 < 83 ng/mL		*P*-value
	DIC+ (*n* = 37)	DIC− (*n* = 24)		DIC+ (*n* = 19)	DIC− (*n* = 33)	
Age (years)	72 (65–78)	77 (55–78)	0.530	73 (66–78)	67 (51–78)	0.310
Male sex	17 (46)	12 (50)	0.760	10 (53)	21 (64)	0.440
Charlson comorbidity index	1 (0lso	1 (0lso	0.260	0 (0lso	1 (0lso	0.390
Infection focus						
Lung	8 (22)	11 (46)	0.250	6 (11)	17 (52)	0.200
Abdomen	12 (32)	8 (33)		7 (37)	5 (15)	
Urinary tract	7 (19)	2 (8)		2 (11)	2 (6)	
Skin and soft tissue	4 (11)	1 (4)		0 (0)	3 (9)	
Others	3 (8)	0 (0)		1 (5)	4 (12)	
Unknown	3 (8)	2 (8)		3 (16)	2 (6)	
GCS	11 (7)nd	12 (6)nd	0.740	10 (6–14)	14 (9–14)	0.130
Mean BP (mmHg)	72 (54–91)	76 (67–99)	0.220	84 (62–107)	90 (75–508)	0.360
HR (b.p.m.)	100 (87g)sof	106 (93g)sof	0.540	113 (96g)sof	110 (98g)sof	0.860
RR (b.p.m.)	24 (198g)s	22 (198g)s	0.340	24 (208g)s	24 (208g)s	0.730
BT (20	36.6 (36.0oft ti	37.2 (36.2–38.3)	0.290	37.5 (36.4–38.3)	37.2 (36.5–38.3)	0.480
Lactate (mg/dL)	40 (22e (m	31 (19e (m	0.190	18 (13e (m	14 (10e (m	0.290
DIC score	6 (5sco	3 (2sco	<0.001	5 (4sco	2 (2sco	<0.001
DIC positive rate, *n* (%)	37 (100)	0 (0)	<0.001	19 (100)	0 (0)	<0.001
SOFA score	13 (10core	11 (70cor	0.040	9 (670co	8 (670co	0.150
APACHE II score	22 (17core	20 (14core	0.160	21 (16core	16 (11core	0.030

Data are presented as median (interquartile range) or number (percentage).
APACHE, Acute Physiology and Chronic Health Evaluation; BP, blood pressure; BT, body temperature; GCS, Glasgow Coma Scale; HR, heart rate; RR, respiratory rate; SOFA, Sequential Organ Failure Assessment.

cases, and involves severe coagulation activation with relatively mild fibrinolytic activation. In cases with markedly increased PAI-1 levels, fibrinolysis is strongly suppressed and the dissolution of microthrombi is more difficult, which can lead to microcirculatory impairment and severe organ dysfunction.[8] The present study revealed that PAI-1 levels were significantly correlated with the DIC score, and that high PAI-1 levels were associated with significantly higher values for the DIC score, the frequency of DIC, and the SOFA score. Therefore, it appears that high PAI-1 levels could reflect DIC with suppressed fibrinolysis and organ failure, and that they can be used to predict prognosis in sepsis cases.

Treatment with rhsTM could reduce the risk of mortality by improving organ dysfunction in patients with sepsis.[7,14,24–27] However, in the SCARLET study,[28] which was undertaken as a randomized, double-blind, placebo-controlled, multinational phase III clinical study to assess the safety and efficacy of rhsTM in 800 patients with sepsis and coagulopathy, the 28-day all-cause mortality rate was not significantly different between the rhsTM group and the placebo group (26.8% [106/395] versus 29.4% [119/405], $P = 0.32$). The intended indication, sepsis with coagulopathy, differed from the approved indication for rhsTM in Japan, which is DIC. As some patients with mild coagulopathy might be included, a significant difference was not observed.

The present study used a DIC definition that was based on the JAAM DIC score, which is known to provide high sensitivity and moderate specificity for diagnosing DIC.[9] Furthermore, the JAAM DIC scoring system is able to diagnose DIC earlier than the other DIC scoring systems.[29] As early treatment with rhsTM is effective,[30] using the rhsTM strategy in combination with the JAAM DIC score is logical. However, unaffected patients are likely included if only the JAAM DIC score is used. According to our study, although there was no significant difference in the 28-day survival rates between patients with and without rhsTM treatment in those with DIC and low PAI-1 levels, the 28-day survival rate with rhsTM treatment was significantly higher than without rhsTM treatment in patients with DIC and high PAI-1 level. As patients with DIC and high PAI-1 levels are

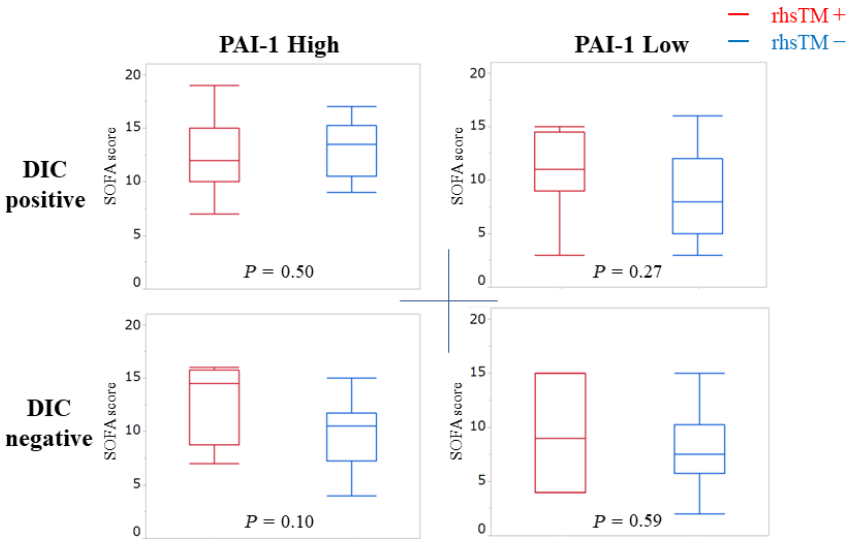

Fig. 2. Analysis of Sequential Organ Failure Assessment (SOFA) scores between sepsis patients with and without recombinant human soluble thrombomodulin (rhsTM) treatment. Data are shown as median (interquartile range). The patients were divided into four groups according to the presence or absence of disseminated intravascular coagulation (DIC) and high or low plasminogen activator inhibitor-1 (PAI-1) levels. There were no significant differences in SOFA scores between patients who received or did not receive rhsTM treatment in each group. The rhsTM+ : rhsTM− ratios were: 27:10 in patients with DIC and high PAI-1 levels; 9:10 in patients with DIC and low PAI-1 levels; 4:20 in patients without DIC and with high PAI-1 levels; and 3:30 in patients without DIC and with low PAI-1 levels.

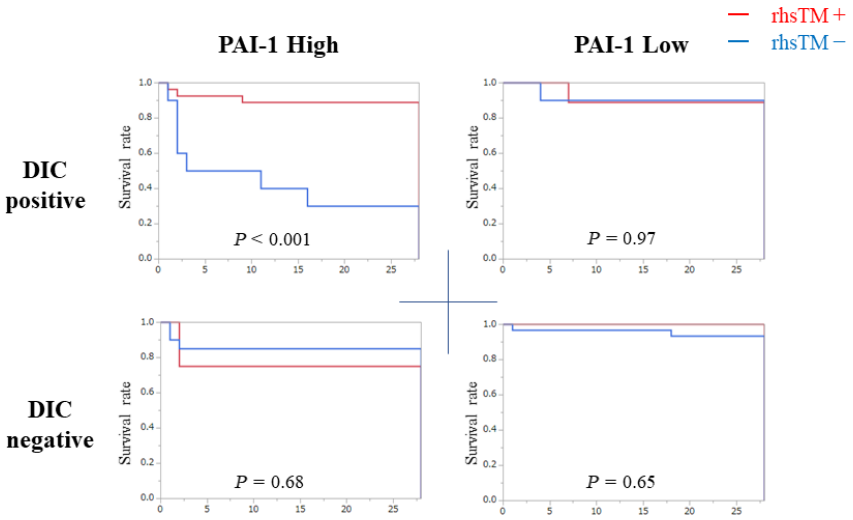

Fig. 3. Kaplan–Meier analysis between sepsis patients who received or did not receive recombinant human soluble thrombomodulin (rhsTM) treatment. The patients were divided into four groups according to the presence or absence of disseminated intravascular coagulation (DIC) and high or low plasminogen activator inhibitor-1 (PAI-1) levels. In each group, 28-day survival rates were compared with and without rhsTM treatment. The 28-day survival rate was significantly higher with rhsTM treatment than without in the group with DIC and high PAI-1 level ($P < 0.001$). The rhsTM+ : rhsTM− ratios were: 27:10 in patients with DIC and high PAI-1 levels; 9:10 in patients with DIC and low PAI-1 levels; 4:20 in patients without DIC and with high PAI-1 levels and 3:30 in patients without DIC and with low PAI-1 levels.

at risk of severe organ failure, rhsTM treatment was effective in these patients. The prognosis could be improved by rhsTM treatment in patients selected based on severity. Therefore, guiding treatment of sepsis-induced DIC based on the JAAM DIC score and the PAI-1 level might be a cost-effective way of improving the prognosis. Plasminogen activator inhibitor-1 is a useful marker not only to predict the prognosis but also to determine the appropriate indication for rhsTM treatment.

The present study has several limitations. The single-center retrospective design is associated with risks of bias, and multicenter studies are needed to validate the prognostic value of PAI-1 in this setting. Additionally, there are several methods for measuring PAI-1 levels, and our findings might have been influenced by the measurement method that we used. Thus, it will be necessary to determine whether our findings are replicated in studies that use different measurement methods.

CONCLUSION

PATIENTS WITH SEPSIS and PAI-1 levels of ≥83 ng/mL had elevated risks of coagulopathy, organ failure, and mortality. Moreover, these patients tended to develop DIC within 1 week after the diagnosis of sepsis. Treatment with rhsTM could be effective in selected patients with DIC and high PAI-1 level. Thus, our findings suggest that the PAI-1 level of 83 ng/mL is a useful cut-off value in sepsis.

DISCLOSURE

Approval of the research protocol: This study was approved by the ethics committee of Fukuoka University Hospital.
Informed consent: The requirement for informed consent of patients was waived.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Correlations between PAI-1 levels and the severity scores.