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Sepsis-related coagulopathy treatment based on the disseminated intravascular coagulation diagnostic criteria: a post-hoc analysis of a prospective multicenter observational study

Takeshi Wada^{1*} , Kazuma Yamakawa², Daijiro Kabata³, Toshikazu Abe^{4,5}, Seitaro Fujishima⁶, Shigeki Kushimoto⁷, Toshihiko Mayumi⁸, Hiroshi Ogura⁹, Daizoh Saitoh¹⁰, Atsushi Shiraishi¹¹, Yasuhiro Otomo¹² and Satoshi Gando^{1,13} on behalf of the JAAM FORECAST Group

Abstract

Background The development of disseminated intravascular coagulation (DIC) in patients with sepsis has been repeatedly confirmed as a factor associated with poor prognosis. Anticoagulant therapy has been expected to improve sepsis patient outcomes, whereas no randomized controlled trials have demonstrated the survival benefit of anticoagulant therapies in non-specific overall sepsis. Patient selection based on the component of “high disease severity” in addition to “sepsis with DIC” has recently proved important in identifying appropriate targets for anticoagulant therapy. The aims of this study were to characterize “severe” sepsis DIC patients and to identify the patient population benefiting from anticoagulant therapy.

Methods This retrospective sub-analysis of a prospective multicenter study included 1,178 adult patients with severe sepsis from 59 intensive care units in Japan from January 2016 to March 2017. We examined the association of patient outcomes, including organ dysfunction and in-hospital mortality, with the DIC score and prothrombin time-international normalized ratio (PT-INR), one of the components of the DIC score, using multivariable regression models including the cross-product term between these indicators. Multivariate Cox proportional hazard regression analysis with non-linear restricted cubic spline including a three-way interaction term (anticoagulant therapy × the DIC score × PT-INR) was also performed. Anticoagulant therapy was defined as the administration of antithrombin, recombinant human thrombomodulin, or their combination.

Results In total, we analyzed 1013 patients. The regression model showed that organ dysfunction and in-hospital mortality deteriorated with higher PT-INR values in the range of < 1.5 and that this trend was more pronounced with higher DIC scores. Three-way interaction analysis demonstrated that anticoagulant therapy was associated with better survival outcome in patients with a high DIC score and high PT-INR. Furthermore, we identified a DIC score ≥ 5 and PT-INR ≥ 1.5 as the clinical threshold for identification of optimal targets for anticoagulant therapy.

*Correspondence:

Takeshi Wada

twada1@med.hokudai.ac.jp

Full list of author information is available at the end of the article



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Conclusions The combined use of the DIC score and PT-INR helps in selecting the optimal patient population for anticoagulant therapy in sepsis-induced DIC. The results obtained from this study will provide valuable information regarding the study design of randomized controlled trials examining the effects of anticoagulant therapy for sepsis.

Trial registration: UMIN-CTR, UMIN000019742. Registered on November 16, 2015.

Keywords Anticoagulant therapy, Disseminated intravascular coagulation, Multiple organ dysfunction syndrome, Prothrombin time, Sepsis

Background

The Analysis for the Global Burden of Disease demonstrated the incidence of sepsis to be 48.9 million and the number of sepsis-related deaths to be 11 million worldwide in 2017 [1]. Thus, 20% of worldwide deaths resulted from sepsis, which is greater than the proportion of deaths from cancer. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) define sepsis as “life-threatening organ dysfunction caused by a dysregulated host response to infection” [2], and disseminated intravascular coagulation (DIC) is one of the most common causes of organ dysfunction associated with sepsis [3]. DIC is characterized by systemic hypercoagulation followed by microcirculatory endothelial dysfunction, leading to the development of organ dysfunction and adversely affecting patient outcomes [3–6]. Two large-scale observational studies have clearly reported significantly higher mortality rate among sepsis patients with DIC than among those without DIC [7, 8]. In addition, a nationwide multicenter observational study suggested that the screening and diagnosis of DIC were associated with a survival benefit in patients with sepsis [9], implying that some interventions for coagulation disorders associated with sepsis may contribute to improved patient outcomes.

However, no large-scale randomized controlled trials (RCTs) have demonstrated the survival benefit of anticoagulant therapies for patients with sepsis. However, a meta-analysis has indicated the important concept regarding anticoagulant therapy for sepsis; the optimal population benefiting from anticoagulant therapy consists of patients with sepsis and DIC, rather than those with sepsis only [10]. In addition, a recent study proposed that patient selection for anticoagulant therapy should be based on disease severity as indicated by the Sequential Organ Failure Assessment (SOFA) or Acute Physiology and Chronic Health Evaluation (APACHE) II scores, in addition to “sepsis with DIC” [11].

The Japanese Association for Acute Medicine (JAAM) DIC diagnostic criteria [12] (see Additional file 1: Table S1) as well as the International Society on Thrombosis and Haemostasis (ISTH) overt DIC diagnostic criteria [4] account for the most widely used diagnostic criteria [13]. The JAAM scoring system has been repeatedly

validated as a highly sensitive and simple diagnostic method [7, 13, 14], consisting of systemic inflammatory response syndrome (SIRS) criteria and global coagulation markers including prothrombin time (PT) ratio, platelet counts, and fibrin/fibrinogen degradation products [12]. The aforementioned SOFA score has also been found to be useful in identifying the optimal patient population benefiting from anticoagulant therapy in patients with sepsis. However, the limitations of this score, including discrepancies with current clinical practices, such as the effect of dopamine in scoring circulatory system, lack of positive end-expiratory pressure in scoring respiratory system, and determination of cut-off values based on expert opinion rather than statistical methods, have been noted [15]. Previous studies have demonstrated that PT values are strongly correlated with SOFA scores [16] and that mortality in patients with sepsis increases with an increase in the PT value [17], further indicating that PT values could serve as an alternative to the SOFA score.

From this perspective, this study aimed to characterize severely septic DIC patients using the DIC score and PT value and to identify the patient population that would best benefit from anticoagulant therapy based on these two indicators.

Methods

Study design, setting, and ethical approval

This study was a retrospective sub-analysis of a cohort of patients with sepsis in the JAAM Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma (FORECAST) database. The main investigation in this cohort had evaluated the characteristics, management, and outcomes among patients with severe sepsis in Japan [18]. The JAAM FORECAST study was a multicenter prospective study of acutely ill patients, including those with acute respiratory distress syndrome, sepsis, and trauma, that collected consecutive samples from 59 intensive care units in Japan from January 2016 to March 2017. This manuscript was written in accordance with the STROBE reporting guidelines (<https://www.strobe-statement.org/>).

This study was approved by the JAAM and the Ethics Committee of all participating hospitals, waiving written

informed consent (JAAM, 2014-01, Hokkaido University Graduate School of Medicine, Head institute of the FORECAST group, 014-0307) since these were already previously obtained from each patient or their next of kin. Furthermore, the study was performed in accordance with the tenets underlying the Declaration of Helsinki.

Participants

The sepsis sub-cohort of the JAAM FORECAST study included adult patients aged ≥ 16 years with severe sepsis and septic shock according to the Sepsis-2 criteria [19] who had been admitted to the intensive care unit. The exclusion criteria were as follows: end-of-life care or resuscitated status after cardiac arrest at the time of sepsis diagnosis. The current study also excluded patients with substantial missing data, such as DIC scores at study enrollment. The size of the study population was dependent on the study period. All patients were followed up until discharge.

Participants were divided into four groups according to a PT-international normalized ratio (INR) ≤ 1.2 , $1.2 < \text{PT-INR} \leq 1.4$, $1.4 < \text{PT-INR} \leq 1.6$, and $1.6 < \text{PT-INR}$, based on existing diagnostic scoring systems of sepsis-related coagulopathies [12, 17, 20].

Definitions

SIRS, sepsis, severe sepsis, and septic shock were defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus conference (Sepsis-1) [21] and its revised version (Sepsis-2) [19]. Moreover, disease severity was assessed based on the APACHE II score [22], and organ dysfunction was evaluated based on the SOFA score [23]. Multiple organ dysfunction syndrome (MODS) was defined as a SOFA score of ≥ 12 based on a previous study [23]. Baseline comorbidities were assessed by the Charlson Comorbidity Index (CCI) [24]. Additionally, DIC was diagnosed based on the JAAM DIC scoring system using PT-INR as a substitute for the PT ratio [12]. Anticoagulant therapy was defined as the administration of antithrombin, rhTM, or their combination based on the J-SSCG 2020 [25]. Serine protease inhibitors mentioned in this guideline were not included in anticoagulant therapy based on the results of a previous study reporting that their administration as treatment for sepsis-induced DIC had decreased over the years in Japan [26]. Heparin was also excluded from the anticoagulant therapy since no corresponding data for sepsis were present in the JAAM FORECAST sepsis database. There were no pre-determined, definitive indications for anticoagulant therapy, and anticoagulants were administered at the discretion of the attending physicians based on the treatment policies of each hospital. The standard dosage and administration of antithrombin

for sepsis-induced DIC in Japan is 1500 U/day or 30 U/kg/day for 3–5 days, whereas that of rhTM is 380 U/kg for 6 days.

Data collection

Data were collected from the electronic data capture system, which was compiled by the FORECAST investigators. Patient information included baseline characteristics, various comorbidities, activity of daily living (ADL), suspected sites of infection, indicators of severity associated with sepsis, and therapeutic interventions. The primary outcome was in-hospital all-cause mortality. The SOFA scores and MODS prevalence at 72 h after admission were recorded as secondary outcomes.

Statistical analyses

Descriptive statistics used numbers for categorical variables and median values (interquartile range) for continuous variables. Categorical variables were compared using Chi-squared tests or Fisher's exact test, as appropriate. The Mann–Whitney U and Chi-squared tests were used to determine the differences between two groups. To compare results among multiple groups, Kruskal–Wallis one-way analysis was adopted. We examined the association of prognosis with the DIC score and PT-INR value, which were assessed at the time of admission, using multivariable regression models including the cross-product term between the DIC score and PT-INR value.

To estimate the occurrence of MODS at 72 h after admission, we used multivariable logistic regression models with adjustment for age, sex, CCI, and ADL at the time of admission. We allowed the non-linear association of PT-INR with the outcome variable through a restricted-cubic-spline with knot three. Furthermore, we estimated the correlation of the SOFA score at 72 h after admission with the time to in-hospital mortality within 90 days of admission using a multivariable non-linear regression model and multivariable Cox proportional hazard regression model, respectively. In these models, the consideration of the non-linear association of PT-INR values and adjustment for the covariates were conducted similarly to the logistic regression model described above. Furthermore, to illustrate the effect of the anticoagulant therapy according to the DIC score and PT-INR value, we performed similar analyses as described above, including three- and two-way cross-product terms between the presence or absence of anticoagulant therapy, DIC scores, and PT-INR values. In the regression models, all missing values were imputed using multiple imputation methods with the predictive mean matching approach with five repetitions. We compared disease severity using the SOFA score at 0 h and APACHE II score, as well as in-hospital mortality between the groups with and without

anticoagulant therapy using several DIC score and PT-INR value combinations as a sensitive analysis.

All statistical hypothesis tests were performed with a two-sided 5% significance level using SPSS version 26 (IBM Japan, Tokyo, Japan) and R version 4.1.1 (<https://cran.r-project.org/>).

Results

Patient demographics and baseline characteristics

A total of 1,184 consecutive patients with severe sepsis fulfilling the inclusion criteria were included in the JAAM FORECAST sepsis study. As shown in Additional file 2: Fig. S1, six patients with missing values exceeding the threshold (>170) detected by a one-sample robust regression with M estimator were excluded. In addition, 165 patients were excluded as shown in Table 1 and Additional file 1: Tables S2 and S3 due to missing information regarding the DIC score or PT-INR value at day 0. In total, 1013 patients were analyzed in this study. Table 1 shows baseline clinical and demographic characteristics of the patients divided into four groups according to the PT-INR value. No significant differences were observed in patient characteristics, including age, sex, and preexisting conditions such as CCI and ADL, among the groups. The SOFA and DIC scores at 0 h increased with higher PT-INR values, then plateaued at PT-INR values >1.4 . The most common site of infection was the lungs (31.3%), followed by the abdomen (26.8%), urinary tract (18.6%), and skin/soft tissues (9.7%). In addition, the proportion of patients receiving various therapeutic interventions generally tended to increase with increasing PT-INR values up to 1.6. The proportion of patients with PT-INR values >1.6 receiving AT or rhTM was lower than that of patients with PT-INR values between 1.4 and 1.6. A comparison of platelet counts, global markers of coagulation and fibrinolysis, and clinical outcomes are shown in Additional file 1: Tables S2 and S3.

Figure 1a shows the results of a multivariable Cox proportional hazard regression model including the cross-product term between the DIC score and PT-INR. For PT-INR values approximately <1.5 , the hazard of in-hospital mortality markedly increased with increasing PT-INR values, and the changes were more pronounced with higher DIC scores. In addition, similar results were found regarding the development of MODS in patients with DIC (DIC score ≥ 4) according to a multivariate logistic regression analysis (Fig. 1b). A multivariable nonlinear regression model indicated that the SOFA scores at 72 h after admission increased with higher PT-INR values, and this trend was more prominent with higher DIC scores within the range of less than approximately 1.5 (Fig. 1c).

Efficacy of anticoagulant therapy according to the DIC score and PT-INR value

The median doses within 24 and 72 h after admission for patients who received AT were 1500 U (interquartile range, 1500–1500) and 4500 U (interquartile range, 1500–4500), respectively, whereas those of patients who received rhTM were 12,800 U (interquartile range, 6400–19,200) and 30,720 U (interquartile range, 17,160–55,680), respectively. Regardless of the DIC score within the range of ≥ 4 , the hazard of in-hospital mortality was equivalent in patients with and without anticoagulant therapy at a PT-INR value of 1.4 (Fig. 2a). A survival benefit from anticoagulant therapy was confirmed in patients with a higher DIC score and PT-INR value (Fig. 2b) (a 3D digital figure that can trace the coordinates and be rotated is shown in Additional file 2: Fig. S2). Notably, anticoagulant therapy in patients with both lower DIC scores and PT-INR values increased the hazard of in-hospital mortality. Based on this result, we compared the disease severity according to the SOFA and APACHE II scores at hospital admission, as well as the in-hospital mortality between patients with and without anticoagulant therapy, to determine the clinical threshold for this treatment. Patients with a DIC score ≥ 5 and PT-INR ≥ 1.5 showed similar disease severity regardless of anticoagulant therapy, while in-hospital mortality was 30.6% and 46.9% ($P=0.067$) in those with and without anticoagulant therapy, respectively. For factors associated with severe coagulation disorder, such as DIC score ≥ 6 and PT ≥ 1.5 or DIC score ≥ 6 and PT ≥ 1.6 , anticoagulant therapy was significantly associated with better survival outcomes ($P=0.010$ and $P=0.014$, respectively) (Table 2).

We then performed the same abovementioned analysis for the cohort of patients with PT-INR values ≤ 2.2 to exclude the effect of an extremely high PT-INR, which could have been due to the prescribed anticoagulants. The survival benefit of anticoagulant therapy was found to be more strongly associated with increased DIC scores and PT-INR values (Fig. 3; Additional file 2: Fig. S3: 3D digital figure).

Discussion

Our previous study found that anticoagulant therapy was associated with better outcomes according to both DIC and disease severity. Based on these findings, this study assessed the association of in-hospital mortality and organ dysfunction with JAAM DIC score, which is sensitive, simple, and available worldwide, and the PT-INR, a specific surrogate marker of disease severity. We then evaluated the interaction between these two indicators and the impact of anticoagulant therapy on

Table 1 Baseline characteristics in sepsis patients according to the PT-INR value

	Overall (N = 1,013)	PT-INR ≤ 1.2 (N = 505)	1.2 < PT-INR ≤ 1.4 (N = 265)	1.4 < PT-INR ≤ 1.6 (N = 106)	1.6 < PT-INR (N = 137)	P-value
Patient characteristics						
Age, years	72 (63–81)	74 (64–82)	70 (63–79)	72 (62–82)	72 (62–79)	0.182
Sex (female/male)	391/622	198/307	100/165	38/68	55/82	0.887
Preexisting conditions						
Charlson Comorbidity Index	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–3)	2 (0–3)	0.070
ADL dependent/independent	223/779	119/386	63/201	17/89	34/103	0.403
Disease severity						
APACHE II score	22 (17–29)	21 (16–28)	24 (17–31) ^a	24 (18–33) ^a	28 (18–33) ^{a,b}	<0.001
SOFA score	9 (6–11)	8 (5–10)	9 (6–12) ^a	11 (7–13) ^{a,b}	11 (7–13) ^{a,b}	<0.001
SIRS score	3 (2–4)	3 (2–4)	3 (3–4)	3 (3–4)	3 (2–3)	0.081
DIC score	4 (2–5)	3 (2–5)	4 (3–6) ^a	5 (3–6) ^{a,b}	5 (2–6) ^a	<0.001
DIC, % (freq.)	50.9 (516)	40.4 (204)	59.2 (157) ^a	70.8 (75) ^{a,b}	58.4 (80) ^a	<0.001
Septic shock, % (freq.)	62.6 (634)	55.2 (279)	64.9 (172) ^a	78.3 (83) ^{a,b}	73.0 (100) ^a	<0.001
Blood culture (positive), % (freq.)	58.2 (586)	55.0 (275)	61.9 (164)	61.0 (64)	60.6 (83)	0.223
Primary site of infection, % (freq.)						
Lung	31.3 (317)	35.0 (177)	31.7 (84)	21.7 (23)	24.1 (33)	<0.001
Abdomen	26.8 (271)	22.8 (115)	28.7 (76)	43.4 (46)	24.8 (34)	<0.001
Urinary tract	18.6 (188)	20.6 (104)	14.0 (37)	16.0 (17)	21.9 (30)	<0.001
Skin/soft tissue	7.7 (98)	8.5 (43)	14.0 (37)	5.7 (6)	8.8 (12)	<0.001
Intravenous catheter	1.7 (17)	2.0 (10)	0.8 (2)	2.8 (3)	1.5 (2)	<0.001
Bone/joint	1.7 (17)	1.8 (9)	0.8 (2)	0.9 (1)	3.6 (5)	<0.001
CNS	1.9 (19)	2.4 (12)	2.3 (6)	0.9 (1)	0 (0)	<0.001
Endocardium	1.4 (14)	1.6 (8)	0.8 (2)	0.9 (1)	2.2 (3)	<0.001
Implant device	0.6 (6)	0.6 (3)	0 (0)	0.9 (1)	1.5 (2)	<0.001
Wound	1.2 (12)	1.2 (6)	1.5 (4)	0.9 (1)	0.7 (1)	<0.001
Others	5.3 (54)	3.6 (18)	5.7 (15)	5.7 (6)	10.9 (15)	<0.001
Therapeutic interventions						
Mechanical ventilation, % (freq.)	42.4 (422)	38.4 (191)	45.8 (120)	54.9 (56) ^a	40.7 (55)	0.026
PMX-DHP, % (freq.)	9.1 (89)	7.4 (37)	8.3 (21) ^a	15.6 (15) ^{a,b}	12.0 (16)	<0.001
IVIg, % (freq.)	20.5 (201)	13.5 (67)	26.1 (66) ^a	30.5 (29) ^a	29.3 (39) ^a	<0.001
Antithrombin, % (freq.)	22.2 (218)	14.3 (71)	25.3 (64) ^a	38.9 (37) ^{a,b}	32.6 (43) ^a	<0.001
rTM, % (freq.)	30.4 (228)	21.1 (87)	38.3 (70) ^a	61.0 (36) ^{a,b}	36.8 (35) ^a	<0.001
Protease inhibitor, % (freq.)	8.1 (79)	7.2 (36)	8.7 (22) ^a	11.6 (11) ^a	7.5 (10) ^a	0.001
CRRT, % (freq.)	27.7 (271)	22.3 (111)	26.6 (67) ^a	41.7 (40) ^{a,b}	39.8 (53) ^a	<0.001
Corticosteroids, % (freq.)	28.9 (296)	24.3 (121)	30.8 (78) ^a	40.0 (38) ^{a,b}	45.0 (59) ^a	<0.001
Noradrenaline, % (freq.)	66.1 (649)	58.7 (294)	70.8 (179) ^a	78.1 (75) ^a	76.5 (101) ^a	<0.001
Enteral nutrition, % (freq.)	49.4 (482)	45.5 (235)	52.2 (131) ^a	45.3 (43) ^a	55.3 (73) ^c	<0.001

The P-values shown in this table were obtained by comparing variables among four groups (PT-INR ≤ 1.2, 1.2 < PT-INR ≤ 1.4, 1.4 < PT-INR ≤ 1.6, and 1.6 < PT-INR) using the Kruskal–Wallis one-way analysis

SOFA, SIRS, and DIC scores in this table represent those at the time of admission

ADL, activities of daily living; APACHE, Acute Physiology and Chronic Health Evaluation; CNS, central nerve system; CRRT, continuous renal replacement therapy; DIC, disseminated intravascular coagulation; IVIg, intravenous immunoglobulin; JAAM, Japanese Association for Acute Medicine; PMX-DHP, polymyxin B direct hemoperfusion; PT-INR, prothrombin time-international normalized ratio; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment

^a P < 0.05 vs. PT-INR ≤ 1.2

^b P < 0.05 vs. 1.2 < PT-INR ≤ 1.4

^c P < 0.05 vs. 1.4 < PT-INR ≤ 1.6 using the Mann–Whitney U test

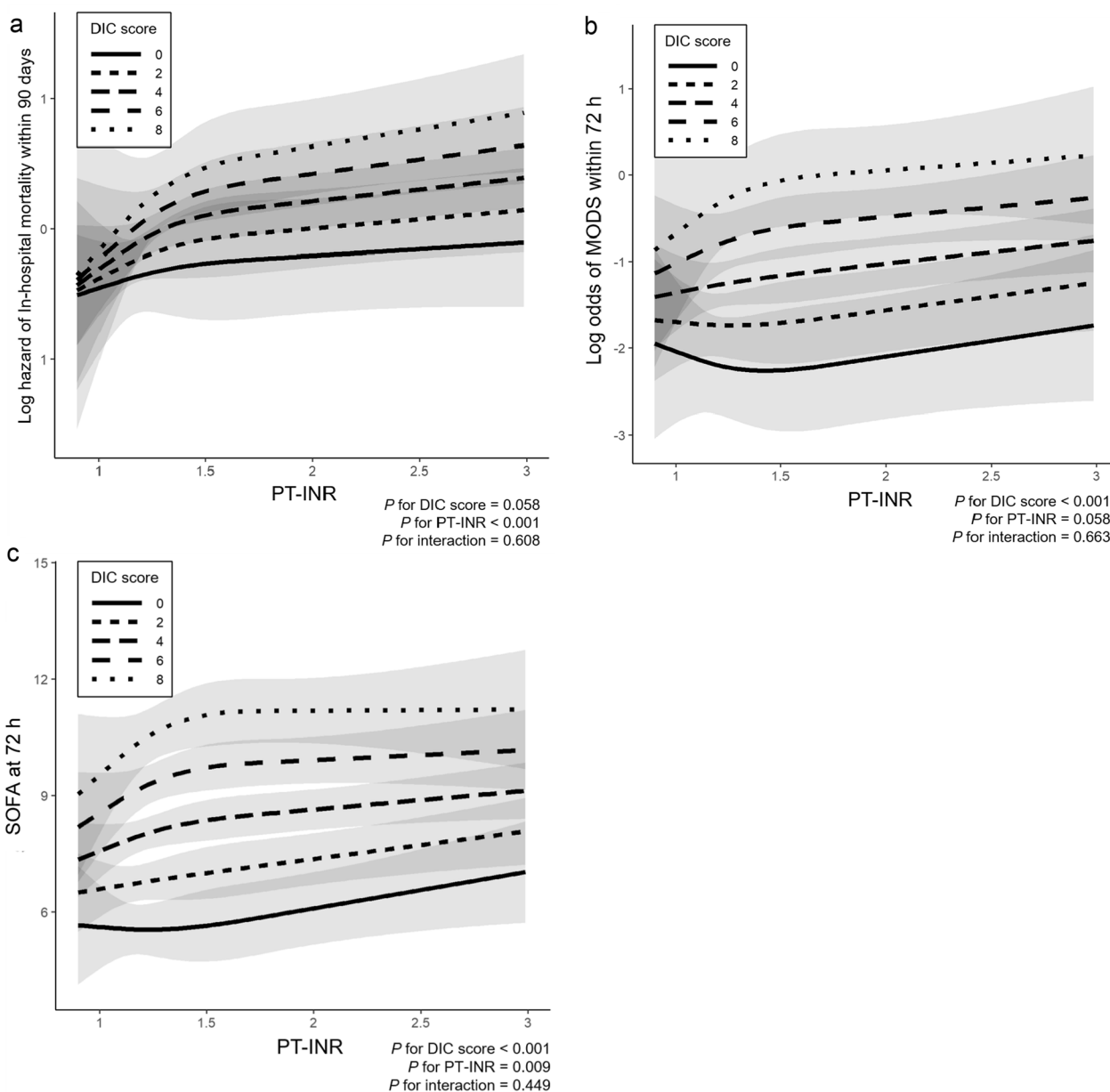


Fig. 1 In-hospital mortality within 90 days after admission and organ dysfunction within 72 h after admission. **a** Regression lines of in-hospital mortality estimated by multivariable Cox proportional hazard regression model including the cross-product term between the DIC score and PT-INR value. In-hospital mortality increased with higher values of PT-INR, and this trend was more prominent with higher DIC scores. **b** Regression lines of the development of MODS estimated by multivariate logistic regression analysis. The odds of the development of MODS in patients with DIC increased with higher PT-INR values and DIC scores. **c** Regression lines of the SOFA scores at 72 h after admission estimated by a multivariable linear regression model. The SOFA score was higher with higher PT-INR values, and this trend was more prominent with higher DIC scores. Solid and dashed lines indicate the estimated log-transformed hazard, and shaded areas represent 95% confidence intervals. *DIC*, disseminated intravascular coagulation; *PT-INR*, prothrombin time-international normalized ratio; *MODS*, multiple organ dysfunction syndrome; *SOFA*, Sequential Organ Failure Assessment

in-hospital mortality. Then, we established a threshold to identify the patient population that would best benefit from this therapy. The degree of organ dysfunction became more severe and in-hospital mortality increased

with increasing PT-INR. This trend was more prominent with higher DIC scores. Although patients with anticoagulant therapy in the lower range of DIC scores and PT-INR values had a higher risk of in-hospital mortality,

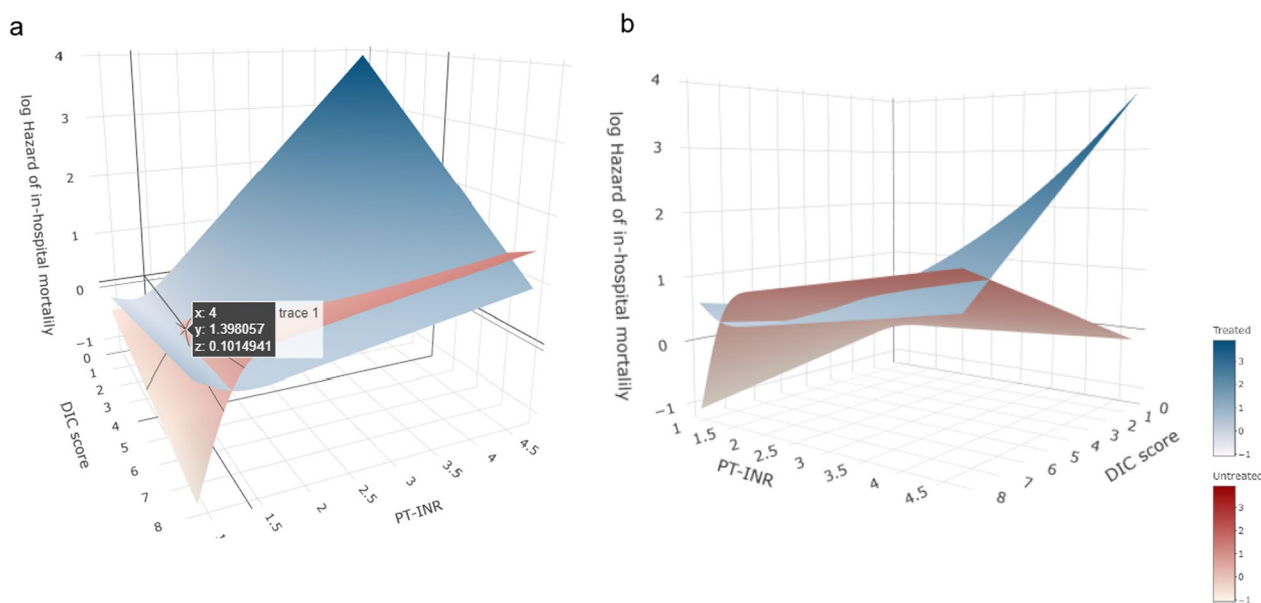


Fig. 2 The hazard of in-hospital mortality by PT-INR value and DIC score. **a** When the DIC score is ≥ 4 , the hazard of in-hospital mortality is equivalent in patients with and without anticoagulant therapy when the PT-INR value = 1.4. **b** The survival benefit of anticoagulant therapy was confirmed in the patient population with higher DIC scores and PT-INR values. **a, b** Are originally similar, shown at different viewing angles to demonstrate the results. The plates represent the estimated log-transformed relative hazard. The blue plate indicates patients who received anticoagulant therapy, and the red plate indicates those who did not. DIC, disseminated intravascular coagulation; PT-INR, prothrombin time-international normalized ratio

anticoagulant therapy was associated with better survival outcomes in patients with higher DIC scores and PT-INR values. Among those with a DIC score ≥ 5 and PT-INR ≥ 1.5 , patients receiving anticoagulant therapy had a lower risk of in-hospital mortality compared with those without anticoagulant therapy.

Recent studies have shown that anticoagulant therapy should be given to patients with a combination of sepsis, DIC, and high disease severity, rather than to those with sepsis only, which has been the target population in most previous large-scale RCTs [27–32]. The SCARLET trial [33], the most recent RCT that evaluated the efficacy of rhTM, adopted sepsis-associated coagulopathy characterized by PT-INR > 1.4 , platelet count of $30\text{--}150 \times 10^9/\text{L}$, or a decrease in platelet count $> 30\%$ within 24 h, as inclusion criteria. The disease severity in the patient population defined by sepsis-associated coagulopathy was likely to be milder than that defined by DIC, and it was suggested that the enrollment criteria should be modified [34]. In fact, post hoc, sub-analysis of the SCARLET trial showed that patients receiving rhTM with higher levels of thrombin generation biomarkers, including prothrombin fragment 1 + 2 and thrombin antithrombin complex, had lower mortality rates compared with those receiving a placebo [35]. Importantly, this study demonstrated the harmful effects of anticoagulant therapy on sepsis patients without DIC or with lower PT-INR values. This

result is supported by the concept of immunothrombosis, a physiological process characterized by the coagulofibrinolytic responses against sepsis, which is not an indication for targets of anticoagulant therapy [3, 36].

Our previous study indicated that anticoagulant therapy can be more effective when based on the level of aggravation of DIC and disease severity as evaluated by the ISTH overt DIC diagnostic criteria and APACHE II score, respectively [37]. As shown in Fig. 2, the issues investigated in the previous study can be evaluated using the DIC score and PT-INR value. Based on these results, we have identified a DIC score ≥ 5 and PT-INR value ≥ 1.5 as the threshold for identifying the optimal target population for anticoagulant therapy. It is important to note that the proportion of patients with PT-INR values > 1.6 receiving AT or rhTM was lower than that of patients with PT-INR values between 1.4 and 1.6, which may be owing to hesitation regarding anticoagulant therapy with AT or rhTM because of concerns about bleeding complications. This study supports a major purpose of diagnostic criteria: to diagnose diseases to improve patient outcomes by intervening with specific treatments [38].

This study had some limitations. First, although the data set was prospectively collected, we were unable to define causal relationships due to the retrospective study design. Second, this study did not assess the efficacy of

Table 2 SOFA score, APACHE II score, and in-hospital mortality in patients groups categorized by values of the DIC score and PT-INR

	Overall	Untreated	Treated	P-value
DIC score ≥ 4 and PT-INR ≥ 1.3	<i>n</i> = 295	<i>n</i> = 139	<i>n</i> = 156	
SOFA score 0 h	11 (8–13)	11 (7–12)	11 (8–13)	0.078
APACHE II score	25 (19–32)	23 (17–29)	27 (20–34)	0.003
In-hospital mortality, % (freq.)	28.5% (84)	26.6% (37)	29.7% (47)	0.505
DIC score ≥ 4 and PT-INR ≥ 1.4	<i>n</i> = 215	<i>n</i> = 99	<i>n</i> = 116	
SOFA score 0 h	11 (8–13)	11 (7–12)	11 (8–13)	0.219
APACHE II score	26 (20–33)	26 (17–29)	27 (21–34)	0.108
In-hospital mortality, % (freq.)	32.6% (70)	31.3% (31)	33.6% (39)	0.719
DIC score ≥ 4 and PT-INR ≥ 1.5	<i>n</i> = 143	<i>n</i> = 62	<i>n</i> = 81	
SOFA score 0 h	12 (9–14)	12 (10–14)	11 (7–13)	0.829
APACHE II score	26 (20–33)	26 (19–31)	25 (19–33)	0.961
In-hospital mortality, % (freq.)	35.7% (51)	41.9% (26)	30.9% (25)	0.171
DIC score ≥ 4 and PT-INR ≥ 1.6	<i>n</i> = 109	<i>n</i> = 49	<i>n</i> = 60	
SOFA score 0 h	12 (9–14)	12 (9–13)	11 (8–14)	0.904
APACHE II score	26 (20–33)	26 (18–30)	27 (21–33)	0.943
In-hospital mortality, % (freq.)	42.2% (46)	46.9% (23)	38.3% (23)	0.366
DIC score ≥ 5 and PT-INR ≥ 1.3	<i>n</i> = 233	<i>n</i> = 102	<i>n</i> = 131	
SOFA score 0 h	11 (8–13)	11 (7–13)	11 (8–13)	0.581
APACHE II score	26 (19–33)	26 (17–29)	26 (20–34)	0.136
In-hospital mortality, % (freq.)	31.3% (73)	31.4% (32)	31.3% (41)	0.990
DIC score ≥ 5 and PT-INR ≥ 1.4	<i>n</i> = 177	<i>n</i> = 76	<i>n</i> = 101	
SOFA score 0 h	11 (9–14)	11 (7–12)	11 (8–13)	0.667
APACHE II score	26 (20–33)	26 (17–29)	27 (21–34)	0.431
In-hospital mortality, % (freq.)	35.0% (62)	35.5% (27)	34.5% (35)	0.904
DIC score ≥ 5 and PT-INR ≥ 1.5	<i>n</i> = 121	<i>n</i> = 49	<i>n</i> = 72	
SOFA score 0 h	12 (9–14)	12 (11–14)	11 (8–13)	0.480
APACHE II score	26 (21–33)	28 (21–33)	26 (20–33)	0.616
In-hospital mortality, % (freq.)	37.2% (45)	46.9% (23)	30.6% (22)	0.067
DIC score ≥ 5 and PT-INR ≥ 1.6	<i>n</i> = 92	<i>n</i> = 38	<i>n</i> = 54	
SOFA score 0 h	12 (9–14)	12 (9–14)	11 (10–13)	0.533
APACHE II score	27 (22–33)	26 (18–32)	28 (22–33)	0.474
In-hospital mortality, % (freq.)	43.5% (40)	52.6% (20)	37.0% (20)	0.137
DIC score ≥ 6 and PT-INR ≥ 1.3	<i>n</i> = 140	<i>n</i> = 58	<i>n</i> = 82	
SOFA score 0 h	12 (9–14)	11 (7–14)	12 (9–14)	0.970
APACHE II score	28 (20–34)	25 (17–31)	29 (22–35)	0.239
In-hospital mortality, % (freq.)	31.4% (44)	34.5% (20)	29.3% (24)	0.513
DIC score ≥ 6 and PT-INR ≥ 1.4	<i>n</i> = 109	<i>n</i> = 45	<i>n</i> = 64	
SOFA score 0 h	12 (9–14)	10 (7–14)	12 (9–14)	0.712
APACHE II score	27 (20–33)	21 (15–30)	29 (23–34)	0.332
In-hospital mortality, % (freq.)	32.1% (35)	37.8% (17)	28.1% (18)	0.288
DIC score ≥ 6 and PT-INR ≥ 1.5	<i>n</i> = 76	<i>n</i> = 30	<i>n</i> = 46	
SOFA score 0 h	13 (10–14)	13 (10–14)	12 (10–14)	0.239
APACHE II score	28 (22–33)	29 (20–33)	29 (22–33)	0.601
In-hospital mortality, % (freq.)	32.9% (25)	50.0% (15)	21.7% (10)	0.010
DIC score ≥ 6 and PT-INR ≥ 1.6	<i>n</i> = 61	<i>n</i> = 25	<i>n</i> = 36	
SOFA score 0 h	12 (9–14)	11 (9–14)	12 (9–14)	0.195
APACHE II score	28 (22–33)	28 (18–32)	27 (21–33)	0.154
In-hospital mortality, % (freq.)	41.0% (25)	56.0% (14)	25.0% (9)	0.014

The *P*-values shown in this table were obtained by comparing variables between two groups (treated and untreated) using the Mann–Whitney U test

APACHE, Acute Physiology and Chronic Health Evaluation; DIC, disseminated intravascular coagulation; PT-INR, prothrombin time-international normalized ratio; SOFA, Sequential Organ Failure Assessment

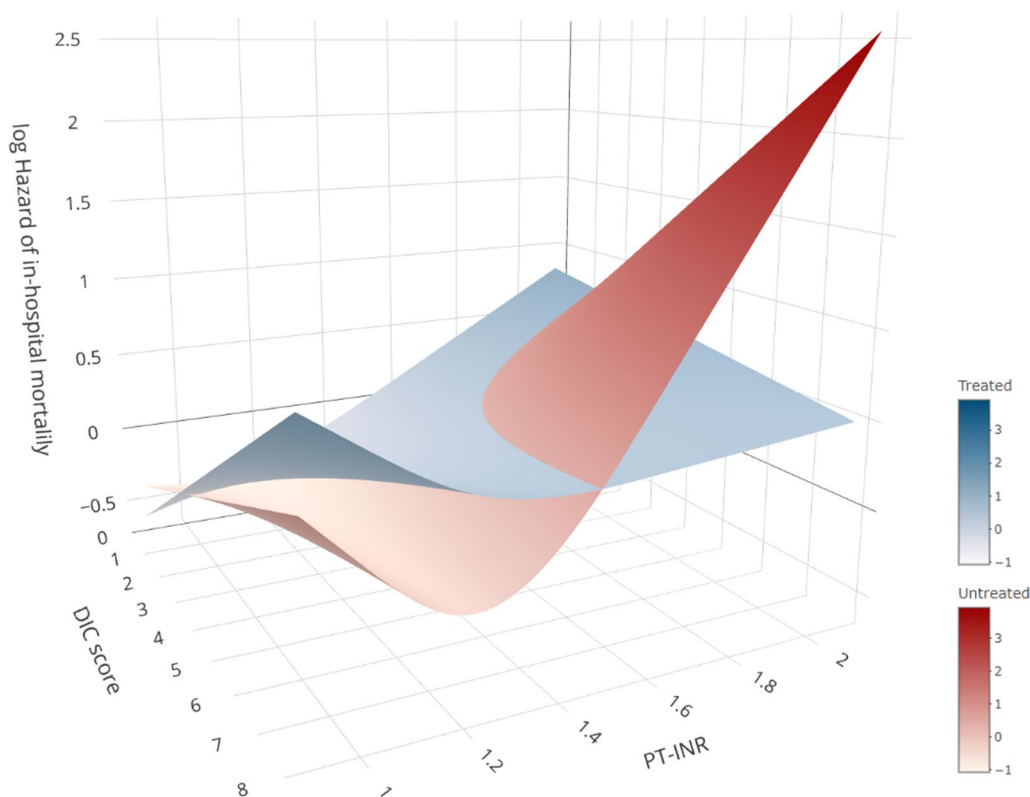


Fig. 3 The hazard of in-hospital mortality by PT-INR value and DIC score in patients with PT-INR ≤ 2.2 . The survival benefit of anticoagulant therapy was found to be more pronounced with increasing DIC score and PT-INR value. The plates represent the estimated log-transformed relative hazard. The blue plate indicates patients who received anticoagulant therapies, and the red plate indicates those who did not. *DIC*, disseminated intravascular coagulation; *PT-INR*, prothrombin time-international normalized ratio

individual anticoagulant drugs or concomitant therapy because we defined anticoagulant therapy as the administration of rhTM, antithrombin, or their combination. In addition, this study was unable to evaluate the duration and dosage of anticoagulant agents. Third, the efficacy of anticoagulant therapy might not have been evaluated correctly because we did not exclude patients with prescribed anticoagulants as with our previous studies [8, 37, 39]. However, sensitivity analysis of a cohort of patients with a PT-INR value ≤ 2.2 to exclude the effect of patients with an extremely high PT-INR (possibly due to the prescribed anticoagulants) confirmed the robustness of the results regarding the interaction between anticoagulant therapy and in-hospital mortality. Fourth, the data set used in this study did not include several important variables, such as adverse events associated with anticoagulant therapies, including bleeding complications, or the administration of heparin, which is widely used for the prevention of venous thromboembolism, and the administration of coagulation factors corrected prior to ICU admission. Fifth, we estimated regression curves using restricted-cubic-splines, a reasonable choice for assessing the non-linear association between a predictor and

an outcome. However, restricted-cubic-spline linearly fits for both ends of the distribution, which do not always provide well-fitted estimates of the actual observations on these regions. Therefore, we should carefully interpret the estimates among the end of the distributions of the predictors. Sixth, data required to control potential confounders might have resulted in biased estimates of the effects. Finally, the study being conducted in a single country may limit the generalizability of the obtained results.

Conclusion

Organ dysfunction associated with sepsis and in-hospital mortality worsened with higher PT-INR values, and this trend was more prominent with higher DIC scores. Anticoagulant therapy was associated with better survival outcomes based on increases in the DIC scores and PT-INR values, while it should be noted that anticoagulant therapy would be harmful to patients with extremely high PT-INR values, probably caused by the prescribed anticoagulants. Moreover, among patients with a DIC score ≥ 5 and PT-INR value ≥ 1.5 , those receiving anticoagulant therapy had lower in-hospital mortality compared with

those without anticoagulant therapy. The effects of anti-coagulant drugs must be properly assessed in RCTs with robust study designs to further benefit more patients with sepsis. The current results will provide important evidence for designing future RCTs evaluating the effects of anticoagulant therapies for sepsis.

Abbreviations

ADL	Activities of daily living
APACHE	Acute Physiology and Chronic Health Evaluation
CCI	Charlson Comorbidity Index
DIC	Disseminated Intravascular Coagulation
FDP	Fibrin/fibrinogen degradation products
FORECAST	Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma
ICUs	Intensive care units
ISTH	International Society on Thrombosis and Haemostasis
JAAM	Japanese Association for Acute Medicine
J-SSCG 2020	Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020
MODS	Multiple organ dysfunction syndrome
PT	Prothrombin time
PT-INR	Prothrombin time-international normalized ratio
qSOFA	Quick Sequential Organ Failure Assessment
RCTs	Randomized controlled trials
rhTM	Recombinant human thrombomodulin
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment
SSCG	Survival Sepsis Campaign Guidelines for Management of Sepsis and Septic Shock

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s40560-023-00656-5>.

Additional file 1: Table S1. Scoring system for DIC according to the JAAM. **Table S2.** Platelet counts, global markers of coagulation, and fibrinolysis at hospital arrival in sepsis patients according to PT-INR value. **Table S3.** Clinical outcomes and PT-INR at hospital arrival.

Additional file 2: Figure S1. Flowchart of the study population. **Figure S2.** Original three-dimensional representation shown in Fig. 2. **Figure S3.** Original three-dimensional representation shown in Fig. 3.

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Author contributions

TW conceived and designed this study; contributed to the analysis and interpretation of the data; and was responsible for drafting, editing, and submitting the manuscript. KY contributed to the acquisition of data, interpreted the data, and revised the manuscript for important intellectual content. DK played a significant role in data analysis and helped in drafting the manuscript. TA, SF, SK, TM, HO, DS, AS, and YO contributed to the design of the study, organization of data collection, drafting of database charts, and scientific discussion of all processes of the study as well as reviewed the manuscript and registered the patients. SG had a significant influence on data interpretation and the critical appraisal of the manuscript. All authors read and approved the final version of the manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the authors upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the JAAM and the Ethics Committee of all participating hospitals waiving written informed consent (JAAM, 2014-01, Hokkaido University Graduate School of Medicine, Head institute of the FORECAST group, 014-0307) since these were already previously obtained from each patient or their next of kin.

Consent for publication

Not applicable.

Competing interests

None of the authors declare any conflicts of interests in connection with the submitted article. TW reported receiving research funding from Takeda Science Foundation and personal fees from Asahi Kasei Pharma America Inc. and Asahi Kasei Pharma Japan Inc. outside the submitted work. AS reported receiving personal fees from CSL Behring outside the submitted work. All other authors have no conflicts of interest to declare.

Author details

¹Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Faculty of Medicine, N15, W7, Kita-Ku, Sapporo, Japan. ²Department of Emergency Medicine, Osaka Medical and Pharmaceutical University, Takatsuki, Japan. ³Department of Medical Statistics, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan. ⁴Department of Emergency and Critical Care Medicine, Tsukuba Memorial Hospital, Tsukuba, Japan. ⁵Health Services Research and Development Center, University of Tsukuba, Tsukuba, Japan. ⁶Center for General Medicine Education, Keio University School of Medicine, Tokyo, Japan. ⁷Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan. ⁸Department of Trauma, Critical Care Medicine and Burn Center, Community Healthcare Organization, Chukyo Hospital, Nagoya, Japan. ⁹Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, Suita, Japan. ¹⁰Division of Traumatology,

Research Institute, National Defense Medical College, Tokorozawa, Japan.
¹¹Emergency and Trauma Center, Kameda Medical Center, Kamogawa, Japan.
¹²Trauma and Acute Critical Care Center, Medical Hospital, Tokyo Medical and Dental University, Tokyo, Japan. ¹³Department of Acute and Critical Care Medicine, Sapporo Higashi Tokushukai Hospital, Sapporo, Japan.

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