The Treatment Intensity of Anticoagulant Therapy for Patients With Sepsis-Induced Disseminated Intravascular Coagulation and Outcomes: A Multicenter Cohort Study

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Abstract

We examined the institutional variations in anticoagulation therapy for sepsis-induced disseminated intravascular coagulation (DIC) and their effects on patient outcomes. This post hoc analysis of a cohort study included 3195 patients with severe sepsis across 42 intensive care units. To evaluate differences in the intensity of anticoagulation therapy, the proportion of patients receiving anticoagulation therapy and the total number of patients with sepsis-induced DIC were compared. Predicted in-hospital mortality for each patient was calculated using logistic regression analysis. To evaluate survival outcomes, the actual/mean predicted in-hospital mortality ratio in each institution was calculated. Thirty-eight institutions with 2897 patients were included. Twenty-five institutions treated 60% to 100% (high-intensity institutions), while the rest treated 0% to 50% (low-intensity institutions) of patients with sepsis-induced DIC having anticoagulant therapy. Every 10-unit increase in the intensity of anticoagulant therapy was associated with lower in-hospital mortality (odds ratio: 0.904). A higher number of high-intensity institutions (compared to low-intensity institutions) had lower in-hospital mortality and fewer bleeding events than predicted. In conclusion, institutional variations existed in the use of anticoagulation therapy in patients with sepsis-induced DIC. High-intensity anticoagulation therapy was associated with better outcomes.

Keywords

anticoagulant therapy, sepsis, disseminated intravascular coagulation

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Introduction

Sepsis, a highly inflammatory condition induced by infection, is associated with high mortality,[1] despite the establishment of guidelines and treatment tools.[2] Around 30% to 50% of all patients with sepsis have sepsis-induced disseminated intravascular coagulation (DIC). Disseminated intravascular coagulation leads to multiple organ dysfunction[3] and high mortality (35%-40%). It is reported that the mortality rate in patients with sepsis having DIC is twice the rate in those without DIC.[4-6] Some observational studies and meta-analyses revealed that anticoagulant therapy has survival benefits in patients with sepsis-induced DIC[7-9]; however, there are no complete randomized controlled trials focusing on such patients. Currently, the effect of anticoagulant therapy on patients with sepsis-induced DIC remains controversial, and there are no established treatment strategies for them.[2]

Institutional variations have been reported in various fields, and many relevant studies have been published recently, especially those on the management of traumatic brain injury,[10-12] successfully resuscitated out-of-hospital cardiac arrest,[13] congenital diaphragmatic hernia and gastroschisis,[14] and prostate cancer.[15] Variable management approaches in different institutions can change clinical outcomes.[10,13-16] Closer monitoring of patient with brain injury[10] or attempting cardiac surgery for single-ventricular lesions in younger children[16] have shown to result in lower mortality. In the management of sepsis-induced DIC, there may be institutional variations in the use of anticoagulant therapy, where such treatment is permitted per medical insurance guidelines, which may impact outcomes. Clarifying the association between institutional variations and survival outcomes will help establish the appropriate strategy for managing patients with sepsis-induced DIC.

The aim of this study was to examine the institutional variations in the use of anticoagulation therapy for patients with sepsis-induced DIC in intensive care units (ICUs) in Japan and to elucidate whether those institutional variations impact outcomes.

Materials and Methods

This post hoc analysis was conducted as part of the Japan Septic Disseminated Intravascular Coagulation (JSEPTIC DIC) study (UMIN000012543 [University Hospital Medical Information Network Clinical Trials Registry]), in which 42 academic or centralized community institutions throughout Japan participated.[4] This study was approved by The Independent Ethics Committee of Hokkaido University Graduate School of Medicine as the primary institution (reference number 013-0246), and all the Institutional Review Boards of the participating institutions (Supplementary Appendix 1). All boards waived the requirement for informed consent because of the retrospective nature of the study, in accordance with Japanese guidelines.[17]

Patient Selection and Data Collection

Patients admitted to ICUs with severe sepsis and septic shock were consecutively enrolled in the JSEPTIC DIC study between January 2011 and December 2013. The definitions used for severe sepsis and septic shock were according to the international guidelines for the management of severe sepsis and septic shock.[18] Patients were excluded if they were <16 years of age and had developed severe sepsis and septic shock after ICU admission.

The following data were collected: age, sex, body weight, admission route to the ICU, preexisting organ dysfunction, preexisting hemostatic disorder, Acute Physiology and Chronic Health Evaluation (APACHE) II score,[19] Sequential Organ Failure Assessment (SOFA) score[20] upon admission, primary infection site, blood culture findings, microorganisms that caused sepsis, daily results of laboratory tests during the first week after ICU admission, treatment with agents including anticoagulants for anti-DIC, with other anticoagulants not for DIC, or with immunoglobulin and low-dose steroids during the first week after ICU admission, renal replacement therapy (RRT), RRT for nonrenal indications, polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP), plasma exchange, extracorporeal membrane oxygenation (ECMO), and intra-aortic balloon pumping (IABP) during the first week after ICU admission; survival outcome at discharge from the hospital; and bleeding complications requiring any transfusion therapy during the first week after ICU admission. The severity of DIC was assessed using the DIC scoring algorithm of Japanese Association for Acute Medicine (JAAM).[21] Patients with missing values were excluded from the analysis. The following data pertaining to the characteristics of the institutions were also collected: the type of ICU (general or emergency), ICU policy (open or closed), and the number of beds in the ICU. Institutions that enrolled 20 or fewer patients to the JSEPTIC study were excluded.

Definitions and Outcome Measures

To evaluate the intensity of anticoagulant therapy, the ratio of the number of patients with sepsis-induced DIC who received anticoagulant therapy to the total number of patients with sepsis-induced DIC in each institution was calculated. Patients with sepsis-induced DIC were defined as having sepsis and being free of preexisting hemostatic disorders. They had DIC scores ≥4 within 1 week after ICU admission (DIC scores were obtained on days 1, 3, or 7).

Anticoagulant agents comprised antithrombin, recombinant human thrombomodulin (rhTM), protease inhibitors, and heparins, which are frequently administered to patients with sepsis-induced DIC in Japan.[22] Recombinant human-activated protein C is not available in the market in Japan. No predefined protocol for DIC treatment was available at any of the institutions. The attending physicians at each institution decided on the timing and choice of anticoagulants based on personal or institutional preferences. Anticoagulants were

administered according to the medical insurance guidelines in Japan: In patients without severe renal dysfunction, 380 U/kg rhTM was administered for 6 days (130 U/kg/day rhTM for 6 days if the patient had experienced renal dysfunction), along with 20 to 39 mg/kg of gabexate mesylate or 0.06 to 0.20 mg/kg of nafamostat mesylate and 10 000 to 20 000 units of heparin until the resolution of DIC. Patients with antithrombin levels <70% received 1500 IU antithrombin for 3 days. Patients with venous thromboembolim (VTE) or at a risk of VTE, atrial fibrillation, and extracorporeal circulation received heparins in the ICUs. As data used to examine the aim (use of the anticoagulant therapies) were included in the JSEPTIC DIC database, patients were excluded if heparin was administered for reasons other than DIC treatment.

The main outcome of this study was in-hospital, all-cause mortality; secondary outcomes were the incidence of bleeding complications requiring transfusion therapy.

Statistical Analysis

Data are expressed as numbers (%) or medians (interquartile range) as appropriate. To evaluate the outcome in each institution, the predicted mortality for each patient was calculated using logistic regression, where the adjusted covariates were demographics, disease severity, treatments used upon arrival, and the characteristics of the institutions. The explanatory variables were age; sex; body weight; admission route to the ICU; preexisting organ dysfunction; preexisting hemostatic disorder; APACHE II score; SOFA score of the liver, respiratory system, cardiovascular system, central nervous system, and kidneys; primary infection site; blood culture findings; the causative microorganism in sepsis; white blood cell count; platelet count; prothrombin time-international normalized ratio; hemoglobin level; JAAM-DIC score upon admission; administered drugs including anticoagulants for DIC or non-DIC reasons, immunoglobulin, and low-dose steroids during the first week after ICU admission; RRT; RRT for non-renal indications; PMX-DHP; plasma exchange; ECMO; IABP during the first week after ICU admission; the type and policy of the ICU (general or emergency, and open or closed, respectively); the number of beds in the ICU; the intensity of anticoagulant therapy (the ratio of the number of patients with sepsis-induced DIC who received anticoagulant therapy to the total number of patients with sepsis-induced DIC in each institution); and the number of patients enrolled into the JSEPTIC DIC study by each institution. The ratio of actual mortality to mean predicted mortality of patients in each institution was used as the index for survival outcome in each institution. For the secondary outcome, the predicted incidence of bleeding complications was calculated using the same method as that used for predicted mortality. The numbers of institutions with better outcomes than expected were compared between institutions providing high- and low-intensity anticoagulation therapy using Fisher exact test. Data were analyzed using SAS software, version 13.2 (SAS Institute Inc., Cary, North Carolina). All statistical tests were performed with a 2-sided significance of 5%.

Results

A total of 3195 consecutive patients with severe sepsis, admitted to 42 institutions, were enrolled in the JSEPTIC DIC study. Four institutions with 62 patients were excluded because they enrolled 20 or fewer patients to the JSEPTIC DIC study. Thirty-eight institutions were included in this analysis, including 3133 patients. Of this number, 236 were excluded because they had 1 or more missing values in the JSEPTIC DIC data set. Finally, 38 institutions with 2897 patients were included (Figure 1). Overall, 465 (34.4%) of 1351 patients with sepsis who received anticoagulant therapy and 454 (29.4%) of 1546 patients with sepsis who did not receive such treatment died. Mortality rate in patients with sepsis who also experienced DIC was 436 (36.5%) of 1192 in anticoagulants and 332 (38.4%) of 863 in patients with sepsis who did not receive anticoagulant therapy.

Characteristics of the Institutions and Patients

The characteristics of the institutions are shown in Table 1. Data on demographics, disease severity, and treatments in each institution are shown in Supplemental Tables 1-3. There were institutional variations in terms of the intensity of anticoagulant therapy (Table 1 and Supplemental Figure 1). Twenty-five institutions administered anticoagulant therapy to 60% to 100% of patients with sepsis-induced DIC, while 7 institutions treated 30% to 50%, and 6 institutions treated 0% to 20% of such patients.

Intensity of Anticoagulant Therapy and Survival Outcomes

In the logistic regression model, in which the covariates described in the Methods section were adjusted, the intensity of anticoagulant therapy was associated with lower in-hospital mortality, with an odds ratio of 0.904 (95% confidence interval 0.842-0.970) for every 10-point increase in the intensity of anticoagulant therapy (Table 2).

Data on actual mortality, mean predicted mortality, and actual/mean predicted mortality ratio are shown in Supplementary Table 3. An actual/mean predicted mortality ratio value <1 indicated better outcomes than predicted, whereas a ratio >1 indicated worse outcomes than predicted. The relationship between the actual/mean predicted mortality ratio and the intensity of anticoagulant therapy is shown in Figure 2. Based on the distribution observed in Figure 2 (and Supplemental Figure 1), the institutions were divided into 2 groups according to the intensity of anticoagulant therapy: >60% (high-intensity institutions) or <50% (low-intensity institutions). A higher number of high-intensity institutions had an actual/mean predicted mortality ratio <1 (16 of 25, 64.0%) compared to the low-intensity institutions (3 of 13, 23.1%; P = .0382). The relationship between actual/mean predicted mortality ratio and the intensity of anticoagulant therapy in patients having severe sepsis with or without DIC is shown in Supplementary Figure 2-1.
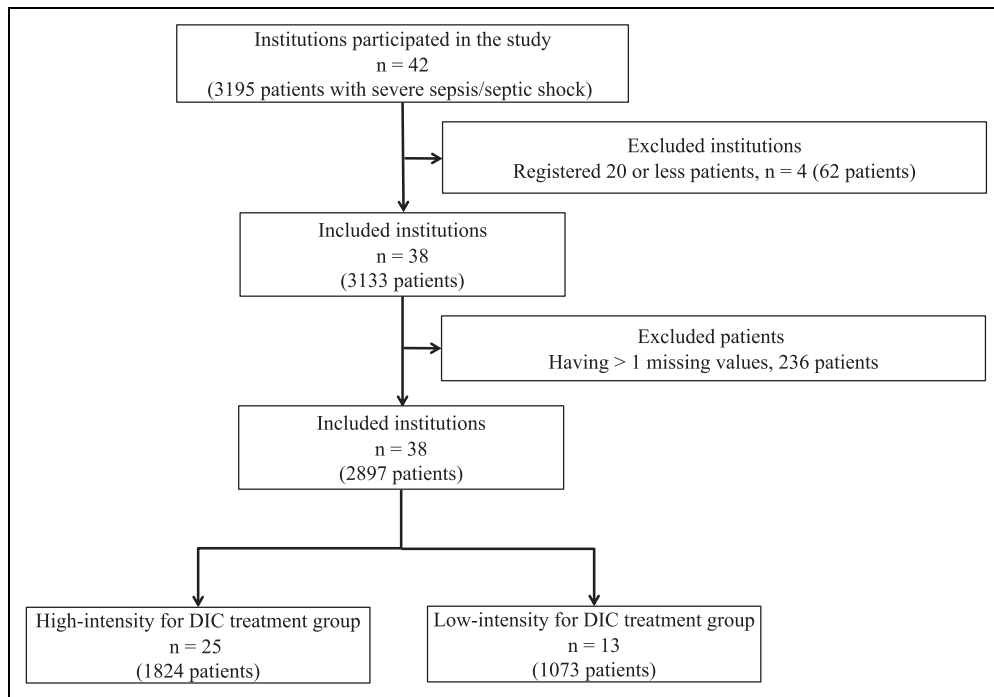
Figure 1. PRISMA flow Chart of Institution and Participant Selection. DIC indicates disseminated intravascular coagulation.

Intensity of Anticoagulant Therapy and Bleeding Events

The actual incidence of bleeding events (requiring any transfusion therapy), mean predicted incidence of bleeding events, and the actual/mean predicted incidence of bleeding events' ratio are shown in Supplemental Table 3. An actual/mean predicted incidence of bleeding events ratio <1 indicated better outcomes than predicted, whereas a ratio >1 predicted worse outcomes. The relationship between the actual/mean predicted incidence of bleeding events ratio and the intensity of anticoagulant therapy is shown in Figure 3. A higher number of high-intensity institutions had an actual/mean predicted incidence of bleeding events ratio lower than 1 (15 of 25, 60.0%) than the low-intensity institutions (3 of 13, 23.1%; $P = .0434$). The relationship between actual/mean predicted incidence of bleeding events ratio and the intensity of anticoagulant therapy in patients having severe sepsis with or without DIC is shown in Supplementary Figure 2-2.

Discussion

In this study, we observed institutional variations in the intensity of anticoagulation therapy in patients with sepsis-induced DIC in academic and centralized community institutions in Japan, which impacted outcomes. Institutions providing a higher intensity of anticoagulation therapy for patients with sepsis-induced DIC had lower in-hospital mortality and lower incidence of bleeding events. This study did not focus on a single drug or intervention but on the preference or strategies of the institutions. To our knowledge, this is the first study to examine institutional variations in the use of anticoagulation therapy for patients with sepsis-induced DIC in

intensive care units in Japan and to elucidate their association with outcomes.

In our study, two-third of the institutions provided anticoagulation therapy to >60% of patients with sepsis-induced DIC, while the rest provided anticoagulation therapy to <50% of such patients. In the latest international guidelines on the management of sepsis and septic shock, the use of anticoagulants is not recommended in patients with sepsis, even in the presence of DIC.[2] However, a recent meta-analysis suggested that anticoagulation therapy is beneficial only to patients with sepsis-induced DIC and not the entire population of patients with sepsis.[8] Besides, the Guidance for diagnosis and treatment of DIC by the International Society on Thrombosis and Haemostasis (ISTH) states that therapeutic doses of heparin should be considered in cases of DIC where thrombosis is predominant. The administration of AT, recombinant human TM (rhTM), may even be considered in patients with DIC.[23] The use of anticoagulants is allowed only in patients with DIC per medical insurance guidelines in Japan. In addition, in the Japanese clinical practice guidelines for the management of sepsis and septic shock, anticoagulant therapy recommendations, or suggestions are limited to patients with sepsis-induced DIC.[22] These guidelines suggest the use of antithrombin and recommend against the use of protease inhibitor, heparin, and heparin analogs. The guidelines do not offer clear recommendations on the use of rhTM. In practice, the use of anticoagulants, especially antithrombin and rhTM, in patients with sepsis-induced DIC may depend on the preferences of the physicians or institutions.

Institutional variations in disease management have been shown in various fields[10-16] and are associated with survival

Table 1. Patient Characteristics and Outcomes per Institution.

| Institution | No. of Patients, n | No. of Beds in ICU, n | ICU Type | ICU policy | Admission Route to ICU | | | Intensity of ACT for SI-DIC,[a] % | In-Hospital Mortality, n (%) | Bleeding Events, n (%) |
					ED, n (%)	Other, n (%)	Ward, n (%)			
1	62	6	Emergency	Open	47 (72.6)	17 (27.4)	0	0/31 (0)	19 (30.6)	3 (4.8)
2	54	7	Emergency	Closed	18 (33.3)	25 (46.3)	11 (20.4)	44/50 (88.0)	12 (22.2)	3 (5.6)
3	94	8	General	Closed	19 (10.6)	37 (39.4)	47 (50.0)	46/72 (63.9)	38 (40.4)	6 (6.4)
4	114	6	General	Open	86 (75.4)	9 (7.9)	19 (16.7)	62/91 (68.1)	42 (36.8)	4 (3.5)
5	39	8	Emergency	Closed	11 (28.2)	22 (56.4)	6 (15.4)	24/37 (64.9)	15 (38.5)	3 (7.7)
6	62	6	Emergency	Open	29 (46.8)	17 (27.4)	16 (25.8)	33/44 (75.0)	23 (37.1)	3 (4.8)
7	23	6	General	Open	19 (82.6)	4 (17.3)	0	17/18 (94.4)	13 (56.5)	6 (26.1)
8	80	12	General	Closed	17 (21.3)	6 (7.5)	57 (71.3)	55/63 (87.3)	23 (28.8)	13 (16.3)
9	58	19	Emergency	Open	23 (39.7)	35 (60.3)	0	3/47 (6.4)	18 (31.0)	12 (20.7)
10	127	12	General	Closed	84 (66.1)	12 (9.4)	31 (24.4)	36/93 (38.7)	35 (27.6)	15 (11.8)
11	40	14	General	Open	3 (7.5)	32 (80.0)	5 (12.5)	23/25 (92.0)	5 (12.5)	3 (7.5)
12	43	6	Emergency	Other	12 (28.0)	31 (72.1)	0	37/39 (94.9)	7 (16.3)	8 (18.6)
13	117	12	Emergency	Closed	6 (5.1)	45 (38.5)	66 (56.4)	67/103 (65.0)	46 (39.3)	3 (2.6)
14	21	11	General	Closed	7 (33.3)	11 (52.4)	3 (14.9)	12/15 (80.0)	6 (28.6)	3 (14.3)
15	140	7	Emergency	Closed	63 (45.0)	34 (24.3)	43 (30.7)	71/116 (0.612)	51 (36.4)	15 (10.7)
16	76	10	General	Open	26 (34.2)	15 (19.7)	35 (46.1)	38/51 (74.5)	18 (23.7)	12 (15.8)
17	99	18	Emergency	Closed	37 (37.4)	60 (60.1)	2 (2.0)	28/75 (37.3)	25 (25.3)	11 (11.1)
18	186	20	General	Closed	66 (35.5)	9 (4.8)	111 (59.7)	4/124 (3.2)	80 (43.0)	9 (4.8)
19	23	15	Emergency	Open	5 (21.7)	17 (73.9)	1 (4.3)	11/17 (64.7)	3 (13.0)	2 (8.7)
20	99	20	Emergency	Other	31 (31.3)	62 (62.6)	6 (6.1)	45/70 (64.3)	20 (20.2)	11 (11.1)
21	136	10	Emergency	Closed	51 (37.5)	83 (61.0)	2 (1.5)	55/88 (62.5)	40 (29.4)	19 (14.0)
22	123	12	General	Other	55 (44.7)	22 (17.9)	46 (37.4)	64/71 (90.1)	35 (28.5)	31 (25.2)
23	45	20	Emergency	Other	8 (17.8)	35 (77.8)	2 (4.4)	23/24 (95.8)	6 (13.3)	11 (24.4)
24	87	20	Emergency	Closed	53 (60.9)	34 (39.1)	0	40/63 (63.5)	35 (40.2)	0
25	31	10	General	Open	19 (61.3)	3 (9.7)	9 (29.0)	23/27 (85.2)	8 (25.8)	5 (16.1)
26	27	4	General	Open	12 (44.4)	0	15 (55.6)	20/24 (83.3)	12 (44.4)	17 (63.0)
27	50	8	General	Other	9 (18.0)	7 (14.0)	34 (68.0)	39/43 (90.7)	29 (58.0)	9 (18.0)
28	21	10	General	Open	9 (42.9)	0	12 (57.1)	7/15 (46.7)	10 (47.6)	2 (9.5)
29	45	12	General	Closed	13 (28.9)	5 (11.1)	27 (60.0)	3/30 (10.0)	19 (42.2)	7 (15.6)
30	113	10	General	Closed	34 (30.1)	17 (15.0)	62 (54.9)	63/85 (74.1)	31 (27.4)	19 (16.8)
31	26	8	General	Open	20 (76.9)	5 (19.2)	1 (3.8)	7/16 (43.8)	11 (42.4)	3 (11.5)
32	150	30	Emergency	Closed	136 (90.1)	3 (2.0)	11 (7.3)	40/86 (46.5)	33 (22.0)	24 (16.0)
33	123	18	General	Open	95 (77.2)	8 (6.5)	20 (16.3)	14/73 (19.2)	43 (35.0)	5 (4.1)
34	79	16	General	Other	45 (57.0)	20 (25.3)	14 (17.7)	42/54 (77.8)	18 (22.8)	18 (22.8)
35	23	14	General	Closed	0	0	23 (100)	1/14 (7.1)	9 (39.1)	1 (4.3)
36	127	10	Emergency	Open	102 (80.3)	12 (9.4)	13 (10.2)	20/66 (30.3)	41 (32.3)	5 (3.9)
37	26	12	General	Open	20 (76.9)	2 (7.7)	4 (15.4)	5/11 (45.5)	10 (38.5)	1 (3.8)
38	108	20	Emergency	Open	43 (39.8)	29 (26.9)	36 (33.3)	70/86 (81.4)	30 (27.8)	13 (12.0)

Abbreviations: ED, emergency department; Other, other hospital; ward, hospital ward; ACT, anticoagulant therapy; SI-DIC, sepsis-induced disseminated intravascular coagulation; ICU, intensive care unit.
[a]Intensity of anticoagulant therapy for sepsis-induced DIC indicates the ratio of the number of patients with sepsis-induced-DIC who received anticoagulant therapy to the number of patients with sepsis-induced DIC.

outcomes in some cases. Trauma centers providing high-intensity ICP monitoring of patients with severe traumatic brain injury,[10] and institutions with a higher presence of cardiologists (as admitting consultants) in the treatment of successfully resuscitated out-of-hospital patients with cardiac arrest were associated with better survival outcomes.[13] In addition, Yamakawa et al recently showed that screening patients with severe sepsis for DIC impacted survival outcomes.[24] To diagnose patients with severe sepsis as having sepsis-induced DIC, several blood values are required,[21,25] but about 30% of the patients in the database lacked 1 or more of these values for DIC diagnosis. Patients without missing values had decreased

in-hospital mortality. Interestingly, the provision of ICP monitoring, presence of a cardiologist (as a consultant), and screening for diagnosis (despite not being regarded as treatment measures) were associated with better survival outcomes. In the current study, not all patients with sepsis-induced DIC (60%-90%) received anticoagulation therapy in high-intensity institutions. However, institutions providing a higher intensity of therapy had better survival outcomes. The results of the aforementioned studies suggest that treatment preference or strategy impacts clinical outcomes.[10,13,24]

The presence of an association between institutional volume and treatment-associated complications has been reported in

the field of percutaneous coronary intervention,[26] abdominal aortic aneurysm treatment,[27] nephrectomy,[28] hypospadias surgery,[29] gastrectomy,[30] and spine surgery.[31] In our study, the volume of patients with severe sepsis or sepsis-induced DIC who received anticoagulation therapy was not associated with the incidence of bleeding events (Supplemental Figure 3). However, the intensity of the treatment (the ratio of the number of patients who received anticoagulant therapy to those with sepsis-induced DIC) was associated with a lower number of bleeding events. These results suggest that the presence of experienced physicians and/or institutional characteristics lowers complication incidence rates.

Table 2. Logistic Regression Analysis of in-Hospital Mortality.

	Odds ratio (95% CI)
Intensity of anticoagulant therapy for sepsis-induced DIC[a] (for every 10-point increase)	0.904 (0.842-970)
Age (in each 10 years)	1.28 (1.17 -1.38)
Sex, female	0.746 (0.60-0.924)
Body weight	0.990 (0.981-0.998)
APACHE II score	1.037 (1.019 -1.055)
JAAM DIC score	1.135 (1.069 -1.04)
Pre-existing liver insufficiency	2.326 (1.083-4.975)
Preexisting chronic heart failure	2.146 (1.418-3.236)
Preexisting chronic hemodialysis	1.481 (1.004-2.183)
Preexisting immunocompromised status	1.426 (1.076 -1.988)
Preexisting hematologic malignancy	1.905 (1.067-3.401)
Hemoglobin level on admission	0.924 (0.886-0.964)
Blood culture positive (vs negative)	1.305 (1.021 -1.667)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; DIC, disseminated intravascular coagulation; JAAM, Japanese Association for Acute Medicine.

[a]Intensity of anticoagulant therapy for sepsis-induced DIC indicates the ratio of the number of patients with sepsis-induced-DIC who received anticoagulant therapy to the number of patients with sepsis-induced DIC.

Limitations

There were some limitations to the current study, including those pertaining to its retrospective design. First, the exact timing of the administration of anticoagulant agents to the patients in each institution was not known. However, anticoagulant therapies and other therapeutic interventions are usually administered within a few hours after admission. We regarded that it is acceptable for anticoagulant therapies and therapeutic interventions to be used as explanatory variables in the logistic regression model for calculating the predicted mortality and incidence of bleeding events because the use of anticoagulant therapies did not influence the use of other interventional therapies. The results of laboratory testing after the initiation of anticoagulant therapy were not used as explanatory variables. Second, data on the exact dose and treatment duration of anticoagulant agents were not recorded in the database, so we were unable to identify whether all patients in all institutions received the same medication dose. However, anticoagulant agents were administered according to the medical insurance guidelines in Japan as described in detail under the subheading *Definitions and outcome measures* in Material and Methods section. Therefore, the dose and treatment duration did not vary between different institutions. Third, we only used the DIC scoring algorithm of JAAM to diagnose DIC in this study. Previous studies have reported varied outcomes depending on the scoring algorithms used.[5,32] Thus, our results might also change if another scoring algorithm, such as ISTH system, was used to diagnose DIC. The sensitivity of JAAM scoring algorithm for mortality was reportedly higher in DIC.[5,32] Therefore, we applied this scoring algorithm in this study. Finally, there may have been unknown confounders that we did not include as explanatory variables, which might have affected the results.
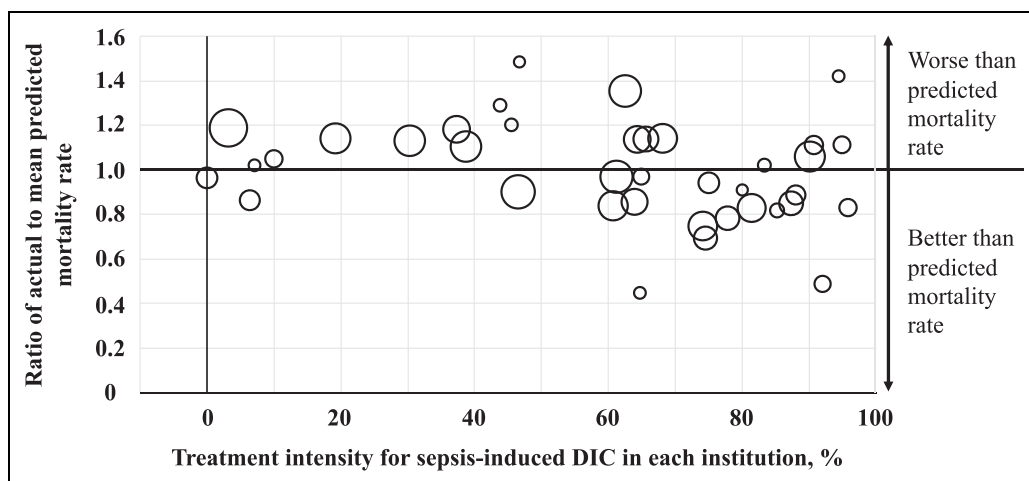

Figure 2. Actual to mean predicted mortality ratio and intensity of anticoagulant therapy for sepsis-induced DIC in each institution. The intensity of anticoagulant therapy for sepsis-induced DIC indicates the ratio of the number of patients who received anticoagulant therapy to the number of patients with sepsis-induced DIC in each institution. The size of the circle indicates the volume of patients with sepsis-induced DIC in each institution. DIC indicates disseminated intravascular coagulation.
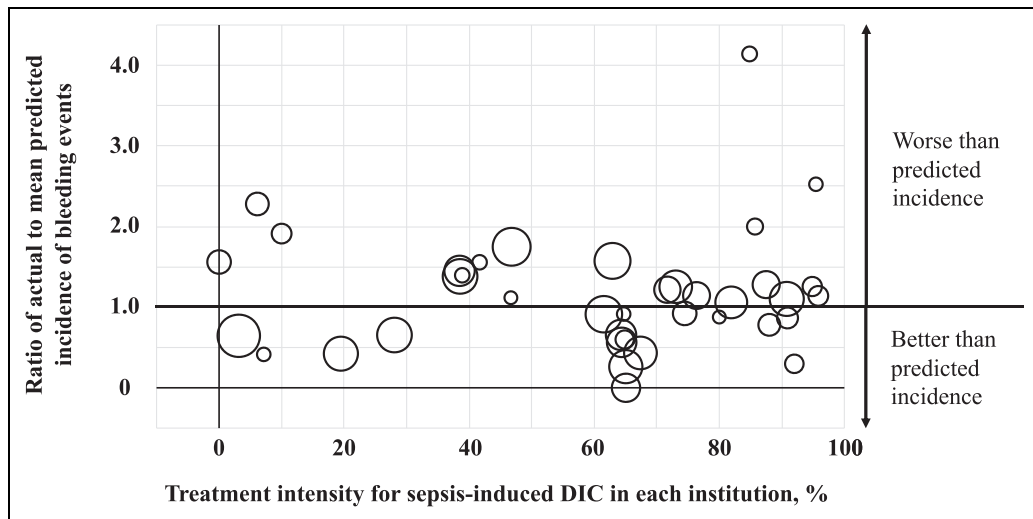
Figure 3. Ratio of actual to mean predicted incidence of bleeding events and intensity of anticoagulant therapy for sepsis-induced DIC in each institution. Bleeding events indicate the presence of events requiring any transfusion therapy. The intensity of anticoagulant therapy for sepsis-induced DIC indicates the ratio of the number of patients who received anticoagulant therapy to the number of patients with sepsis-induced DIC in each institution. The size of the circle indicates the volume of patients with sepsis-induced DIC in each institution. DIC indicates disseminated intravascular coagulation.

Conclusions

The current study elucidated that there were institutional variations in the use of anticoagulation therapy in patients with sepsis-induced DIC in academic and centralized community institutions in Japan. It also indicated that institutions providing high-intensity anticoagulation therapy had better survival outcomes and lower rate of adverse events. These results suggest that the preference or strategy used for anticoagulation therapy for patients with sepsis-induced DIC impacts their outcomes, which may help in developing appropriate strategies and policies. To generalize these results, a further observational study with a higher number of institutions providing both high- and low-intensity anticoagulation therapy across various regions and countries is needed.

Authors' Note

The data sets generated and analyzed during the current study are available in the University Hospital Medical Information Network Individual Case Data Repository (UMIN000012543, http://www.umin.ac.jp/icdr/index-j.html).

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Supplemental Material

Supplemental material for this article is available online.

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