Proposal and Validation of a Clinically Relevant Modification of the Japanese Association for Acute Medicine Disseminated Intravascular Coagulation Diagnostic Criteria for Sepsis

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Abstract

Background Japanese Association for Acute Medicine (JAAM) disseminated intravascular coagulation (DIC) criteria were launched nearly 20 years ago. Following the revised conceptual definition of sepsis and subsequent omission of systemic inflammatory response syndrome (SIRS) score from the latest sepsis diagnostic criteria, we omitted the SIRS score and proposed a modified version of JAAM DIC criteria, the JAAM-2 DIC criteria.

Objectives To validate and compare performance between new JAAM-2 DIC criteria and conventional JAAM DIC criteria for sepsis.

Methods We used three datasets containing adult sepsis patients from a multicenter nationwide Japanese cohort study (J-septic DIC, FORECAST, and SPICE-ICU registries). JAAM-2 DIC criteria omitted the SIRS score and set the cutoff value at $\geq$3 points. Receiver operating characteristic (ROC) analyses were performed between the two DIC

Keywords
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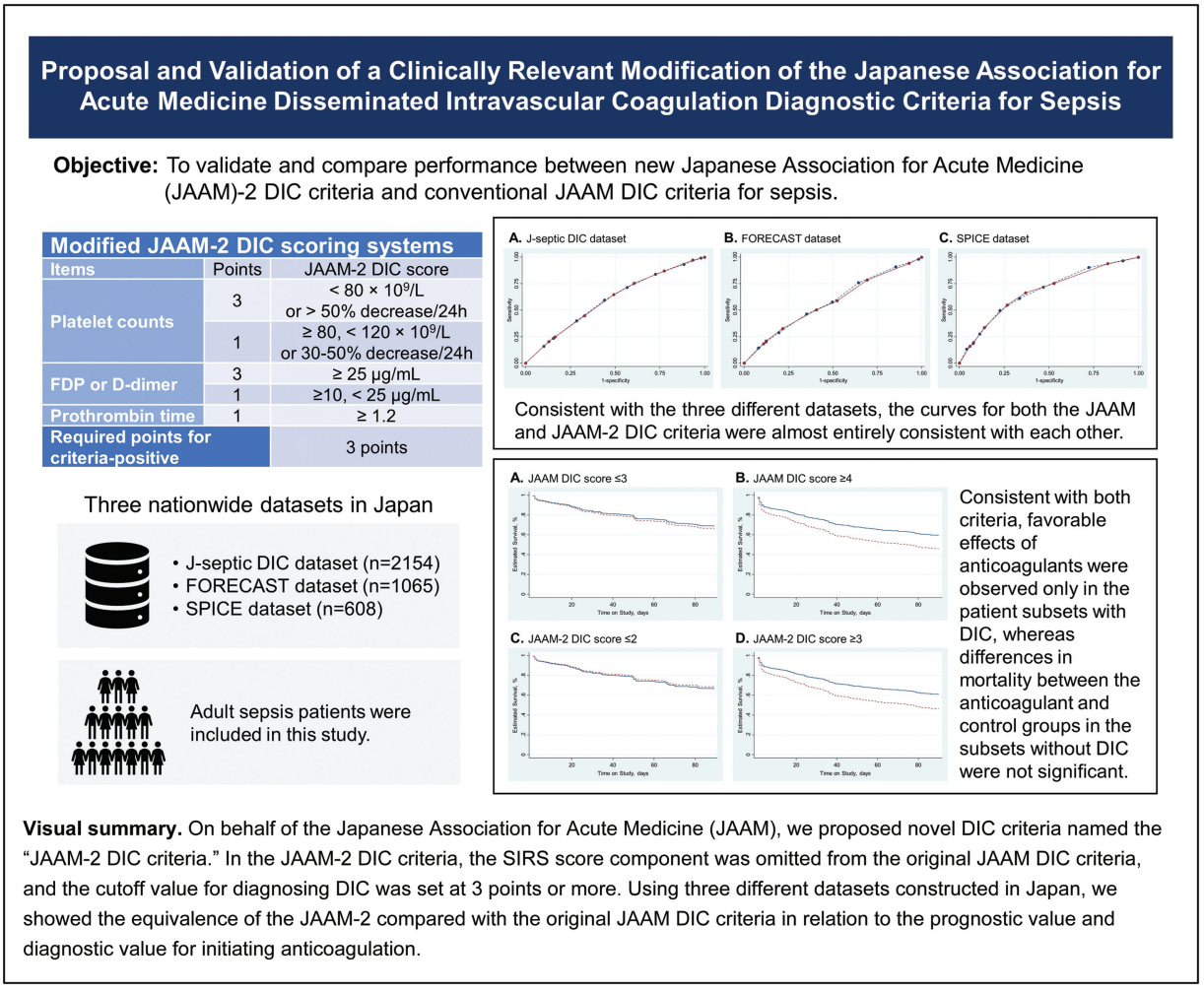

Visual summary. On behalf of the Japanese Association for Acute Medicine (JAAM), we proposed novel DIC criteria named the "JAAM-2 DIC criteria." In the JAAM-2 DIC criteria, the SIRS score component was omitted from the original JAAM DIC criteria, and the cutoff value for diagnosing DIC was set at 3 points or more. Using three different datasets constructed in Japan, we showed the equivalence of the JAAM-2 compared with the original JAAM DIC criteria in relation to the prognostic value and diagnostic value for initiating anticoagulation.

criteria to evaluate prognostic value. Associations between in-hospital mortality and anticoagulant therapy according to DIC status were analyzed using propensity score weighting to compare significance of the criteria in determining introduction of anticoagulants against sepsis.

Results Final study cohorts of the datasets included 2,154, 1,065, and 608 sepsis patients, respectively. ROC analysis revealed that curves for both JAAM and JAAM-2 DIC criteria as predictors of in-hospital mortality were almost consistent. Survival curves for the anticoagulant and control groups in the propensity score-weighted prediction model diagnosed using the two criteria were also almost entirely consistent.

Conclusion JAAM-2 DIC criteria were equivalent to JAAM DIC criteria regarding prognostic and diagnostic values for initiating anticoagulation. The newly proposed JAAM-2 DIC criteria could be potentially alternative criteria for sepsis management.

Introduction

Disseminated intravascular coagulation (DIC) is a disorder frequently seen in critically ill patients, especially those with sepsis, that may lead to severe bleeding and organ dysfunction.[1] Because mortality is higher in patients with than without DIC,[2,3] several organizations have put forward DIC scoring systems with the aim of improving the outcome of patients with DIC. The Japanese Ministry of Health and Welfare (JMHW) proposed a criteria for the diagnosis of DIC in 1976.[4] Their criteria involved the evaluation of global coagulation tests, underlying diseases, and clinical

symptoms. Thereafter, the subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) proposed a scoring system for overt and non-overt DIC in 2001.[5] However, patients diagnosed according to the JMHW or ISTH DIC criteria are often at high risk of death at the time of diagnosis because of the delay from the onset of coagulopathy. It has been reported that these patients are missing out on the initiation of interventions in the setting of critical illness.[6,7] Thus, the Japanese Association for Acute Medicine (JAAM) proposed another DIC scoring system that aimed to make early diagnosis of DIC in acute diseases possible.[8,9] Now, both the ISTH overt- and JAAM DIC criteria are widely used in clinical settings.

The JAAM DIC criteria have several unique features compared with other DIC criteria, one of which is the inclusion of the systemic inflammatory response syndrome (SIRS) score. Based on the pathophysiological concept, as sepsis-induced DIC is caused by systemic inflammation and subsequent endothelial injury, inclusion of the SIRS score seemed to be reasonable.[10] The SIRS score was introduced as one of the criteria to diagnose sepsis in 1992.[11] In recent years, however, the prognostic relevance of the SIRS score has been questioned,[12] and SIRS criteria have been omitted from the latest definition of sepsis proposed in 2016[13] and are no longer used in clinical practice. Other concerns with including the SIRS score in the DIC criteria were the clinical burden on physicians and inter-observer variability in scoring. To determine the SIRS score, several vital signs need to be assessed and the score calculated. Because the SIRS criteria are now no longer used to diagnose sepsis, this burden should be eliminated.

Nearly 20 years have passed since the launch of the JAAM DIC criteria. According to the aforementioned concerns, we decided to omit the SIRS score and propose a modified version of the JAAM DIC criteria, the "JAAM-2 DIC" criteria. This proposal will maintain the clinical relevance of DIC criteria to make decisions regarding the application of anticoagulant therapy. Using three multicenter sepsis registry datasets, we validated and compared the performance of our newly proposed JAAM-2 DIC criteria with that of the JAAM DIC criteria for sepsis patients. In this study, we evaluated not only the prognostic value of these criteria but also their utility in terms of patient selection for anticoagulant therapy.

Materials and Methods

Study Population

This investigation was performed using three different datasets extracted from a multicenter nationwide cohort study conducted in Japan. The first dataset, the J-septic DIC dataset, was compiled in 42 intensive care units (ICUs) between January 2011 and December 2013.[2] The second dataset, the FORECAST dataset, was compiled in 59 ICUs between January 2016 and March 2017,[14] and the third dataset, the SPICE dataset, was compiled in 22 ICUs between December 2017 and May 2018.[15] In the first two datasets, patients were eligible for the registry if they were diagnosed as having severe sepsis or septic shock according to the conventional criteria proposed by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus conference in 1991[16] and were 18 years of age or older. In the present analysis, we included as the underlying diseases targeted by the JAAM-2 DIC criteria only those of sepsis patients diagnosed using the Sepsis-3 criteria (i.e., SOFA score of 2 or more points).[13]

The exclusion criteria included the use of warfarin/acetylsalicylic acid/thrombolytic therapy before study entry; a history of fulminant hepatitis, decompensated liver cirrhosis, or other serious liver disorder; a history of hematologic malignant disease; other conditions increasing the risk of bleeding; treatment with any chemotherapy at study entry; treatment with warfarin before or after study entry; and patients with missing data for any hemostatic markers used for calculating JAAM DIC criteria.

This study followed the principles of the Declaration of Helsinki. The fundamental study protocol was approved by the Institutional Review Board of Osaka General Medical Center (approval numbers: #25–2050, #30-S11–004, and #S201901009). Due to the anonymous and retrospective nature of this study, the board of each hospital waived the need for informed consent.

Data Collection and Definitions

A case report form was developed for the three datasets used in this study on which the following information was recorded: age, sex, disease severity scores on the day of ICU admission, the source of ICU admission, pre-existing conditions, new organ dysfunction, primary source of infection, and concomitant therapies against sepsis. The severity of illness was evaluated at study entry according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score and SIRS score. The Sequential Organ Failure Assessment (SOFA) score was used to assess organ dysfunction, which was defined as a SOFA subscore $\geq$2 for each organ.[17] The primary outcome measure was all-cause in-hospital mortality.

Newly Proposed Modified JAAM-2 DIC Criteria

We proposed novel DIC criteria named the JAAM-2 DIC criteria that were modified from the original JAAM DIC criteria. The underlying diseases targeted by the JAAM-2 DIC criteria, which comply with those of the original JAAM DIC criteria, are shown in ►**Table 1**.[9] The SIRS score component from the JAAM DIC criteria was omitted, and the cutoff value for diagnosing DIC was set at 3 points or more (►**Table 2**).

Prognostic Value of the Criteria

To identify the differences between the original JAAM and modified JAAM-2 DIC criteria that distinguished nonsurviving from surviving patients with sepsis, receiver operating characteristic (ROC) analyses were performed. The target condition was set as in-hospital mortality.

Validity of the Criteria in Initiating Anticoagulation

We evaluated associations between in-hospital mortality and anticoagulant therapy according to the status of DIC or not to clarify the significance of the two DIC criteria in determining when to introduce anticoagulant therapy against

Table 1 Underlying diseases targeted by the JAAM-2 DIC criteria

1. Sepsis/severe infection (any microorganism)	
2. Trauma/burn/surgery	
3. Vascular abnormalities	
	Large vascular aneurysms
	Giant hemangioma
	Vasculitis
4. Severe toxic or immunological reactions	
	Snakebite
	Recreational drugs
	Transfusion reactions
	Transplant rejection
5. Malignancy (except bone marrow suppression)	
6. Obstetric calamities	
7. Conditions that may be associated with systemic inflammatory response syndrome	
	Organ destruction (e.g., severe pancreatitis)
	Severe hepatic failure
	Ischemia/hypoxia/shock
	Heat stroke/malignant syndrome
	Fat embolism
	Rhabdomyolysis
	Others
8. Others	

Abbreviations: DIC, disseminated intravascular coagulation; JAAM, Japanese Association for Acute Medicine.

sepsis. Participants were categorized into two groups: the anticoagulant group, comprising patients who received any anticoagulant therapy such as antithrombin, recombinant human thrombomodulin, heparin/heparinoid, and serine protease inhibitors, and the control group, comprising patients who received no anticoagulant therapy. Due to the retrospective nature of this analysis, there were baseline imbalances between the two groups; therefore, an adjusted mortality analysis was performed using propensity scoring as described below. The SPICE dataset was not used for this analysis due to the lack of data on anticoagulant therapy.

Statistical Analysis

Descriptive statistics were calculated as medians (interquartile range) or proportions, as appropriate. Univariate differences between the groups were assessed using the Mann–Whitney U test, Kruskal–Wallis test, chi-squared test, or Fisher's exact test. A p-value of <0.05 indicated statistical significance. All statistical analyses were performed using STATA software version 15.0 (Stata Corp, College Station, Texas, United States).

The overall effectiveness of anticoagulant therapy on mortality was assessed using a Cox regression model with inverse probability-of-treatment weighting using the propensity scores. The propensity score for receiving anticoagulant therapy was calculated using multivariate logistic regression and included 25 independent variables for the J-septic DIC cohort and 30 variables for the FORECAST cohort, including age, sex, disease severity, source of ICU admission, past medical history of severe conditions, new organ dysfunctions, ICU characteristics, primary source of infection, causal microorganisms, anticoagulant therapy not for DIC, and other therapeutic interventions (►**Supplementary Table S1** [available in the

Table 2 ISTH overt-DIC, original JAAM DIC, and modified JAAM-2 DIC scoring systems

	Points	ISTH overt-DIC	JAAM DIC	JAAM-2 DIC
Platelet counts	3	–	$<80\times10^9$/L or >50% decrease/24 hours	$<80\times10^9$/L or >50% decrease/24 hours
	2	$<50\times10^9$/L	–	–
	1	≥50, $<100\times10^9$/L	≥80, $<120\times10^9$/L or 30–50% decrease/24 hours	≥80, $<120\times10^9$/L or 30–50% decrease/24 hours
FDP or D-dimer	3	Strong increase	≥25 μg/mL	≥25 μg/mL
	2	Moderate increase	–	–
	1	–	≥10, <25 μg/mL	≥10, <25 μg/mL
Prothrombin time	2	≥6 seconds	–	–
	1	≥3, <6 seconds	≥1.2	≥1.2
Fibrinogen	1	<100 g/mL	–	–
SIRS score	1	–	≥3	–
Required points for criteria-positive		5 points	4 points	3 points

Abbreviations: DIC, disseminated intravascular coagulation; FDP, fibrin degradation products; ISTH, International Society on Thrombosis and Haemostasis; JAAM, Japanese Association for Acute Medicine; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

online version]). Hazard ratio and estimated 95% confidence interval were calculated along with estimated survival curves.

Results

Patient Characteristics

The patient flow diagram is shown in ►**Fig. 1**. During the study period, 3,195 consecutive patients fulfilling the inclusion criteria were registered in the J-Septic DIC registry database. After excluding 1,040 patients who met at least one exclusion criterion, we analyzed 2,154 patients in the final study cohort. The anticoagulant group comprised 1,089 patients, and the control group comprised 1,065 patients. Similarly, we enrolled 817 patients from the FORECAST registry and 608 patients from the SPICE-ICU registry in the final study cohort.

Baseline characteristics of the study population are shown in ►**Table 3**, ►**Supplementary Table S2** and **S3** (available in the online version). Patient characteristics such as age and sex were similar between the three datasets. After applying an inverse probability of treatment weighting with propensity score, patient characteristics, such as illness severity, as indicated by SOFA, APACHE II, and DIC scores and the rate of new organ dysfunction, were well matched between the anticoagulant and control groups.

Prognostic Value of the Criteria

ROC curves for the original JAAM and modified JAAM-2 DIC criteria as predictors of in-hospital mortality are shown in ►**Fig. 2**. Consistent with the three different datasets, the curves for both the JAAM and JAAM-2 DIC criteria were almost entirely consistent with each other. These data suggested that in predicting short-term mortality, use of the JAAM DIC and JAAM-2 DIC criteria was considered to be equivalent.

Validity of the Criteria in Initiating Anticoagulation

Survival curves for the anticoagulant and control groups in the propensity score-weighted prediction model according to DIC status diagnosed using the two criteria are shown in ►**Fig. 3** (J-septic DIC dataset) and ►**Fig. 4** (FORECAST dataset). Consistent with both criteria and both datasets, favorable effects of anticoagulant therapy were observed only in the patient subsets with DIC, whereas differences in mortality between the anticoagulant and control groups in the subsets without DIC were not significant. These findings were consistent between the two datasets and suggested that to determine the optimal target of anticoagulant therapy for sepsis, use of the JAAM DIC and JAAM-2 DIC criteria for diagnosing DIC was considered to be equivalent.

Discussion

Principal Findings

On the basis of the study results, we proposed modified JAAM DIC criteria that omitted the SIRS criteria but included platelet count, fibrin degradation products (or D-dimer), and prothrombin time, and the cutoff value for diagnosing DIC was set at 3 points or more. We named these new DIC criteria the JAAM-2 DIC criteria.

Using three different datasets constructed in Japan, we verified the prognostic value and diagnostic value of the JAAM-2 compared with the original JAAM DIC criteria for initiating anticoagulation. Consequently, ROC analysis revealed that curves for both the original JAAM and JAAM-2 DIC criteria were almost consistent with each other. Survival analysis revealed that the curves of the anticoagulant and control groups for both the original JAAM and JAAM-2 DIC criteria were also almost entirely consistent with each other. Thus, the newly proposed JAAM-2 DIC criteria could potentially be used as an alternative to the original JAAM DIC criteria in clinical practice.

Clinical Application of the Findings

Several different clinical practice guidelines for DIC have been developed by societies in Britain,[18] Japan,[19] and Italy,[20] along with the harmonized guidance by the ISTH.[21] Some distinct discrepancies in the appraisal of diagnostic criteria

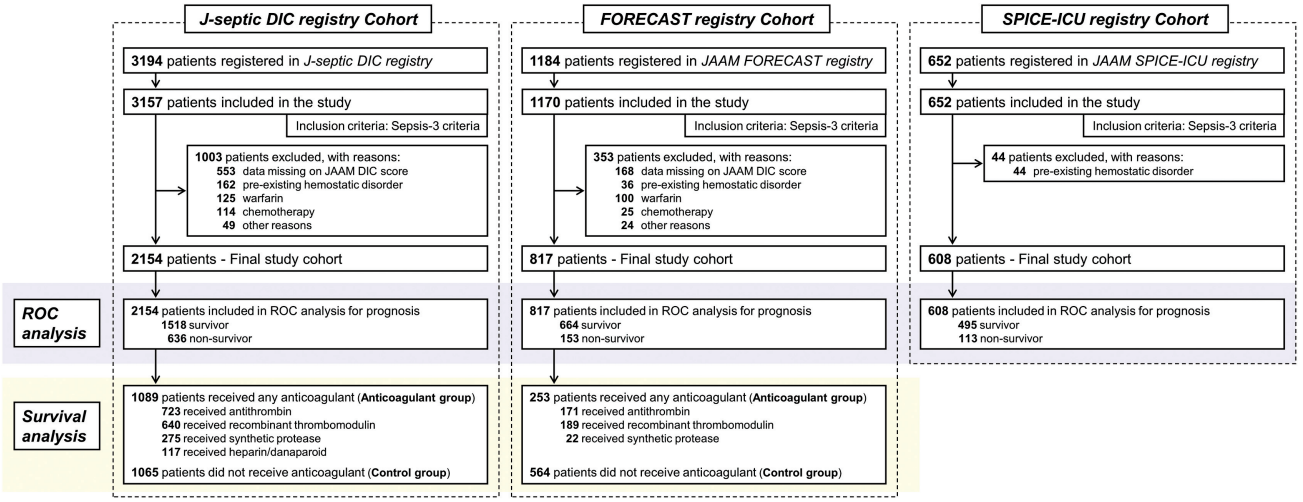

Fig. 1 Patient flow for the three datasets used in this study. DIC, disseminated intravascular coagulation; JAAM, Japanese Association for Acute Medicine; ROC, receiver operating characteristic.

Table 3 Baseline characteristics of included sepsis patients in the three datasets

Characteristics	J-septic DIC dataset ($n = 2,154$)	FORECAST dataset ($n = 817$)	SPICE dataset ($n = 608$)
Age in years	72 (62–80)	72 (63–82)	72 (60–82)
Male sex	1,270 (59%)	496 (61%)	350 (58%)
Illness severity			
SIRS score	3 (2–4)	3 (2–4)	3 (2–3)
SOFA score	9 (7–12)	9 (6–11)	7 (4.5–10)
APACHE II score	22 (17–28)	22 (17–29)	20 (14–27)
ISTH overt-DIC score	4 (2–5)	3 (2–4)	2 (0–3)
JAAM DIC score	4 (3–6)	4 (2–5)	3 (2–5)
Source of ICU admission			
Emergency department	1,018 (47%)	465 (57%)	350 (58%)
Ward	515 (24%)	352 (43%)	258 (42%)
Other hospital	621 (29%)		
Pre-existing condition			
Liver insufficiency	16 (1%)	26 (3%)	26 (4%)
Chronic heart failure	116 (5%)	104 (13%)	57 (9%)
Chronic respiratory disorder	85 (4%)	58 (7%)	52 (9%)
Chronic hemodialysis	167 (8%)	52 (6%)	52 (9%)
Immunocompromised	228 (11%)	96 (12%)	38 (6%)
New organ dysfunction (SOFA subscores ≥ 2)			
Respiratory	1,489 (69%)	575 (70%)	370 (61%)
Cardiovascular	1,416 (66%)	461 (56%)	254 (42%)
Renal	1,071 (50%)	413 (51%)	268 (44%)
Hepatic	383 (18%)	127 (16%)	84 (14%)
Coagulation	816 (38%)	233 (29%)	127 (21%)
Primary source of infection			
Abdomen	696 (32%)	212 (26%)	120 (20%)
Lung	556 (26%)	259 (32%)	203 (33%)
Urinary tract	385 (18%)	159 (19%)	102 (17%)
Bone/soft tissue	250 (12%)	111 (14%)	90 (15%)
Central nervous system	50 (2%)	15 (2%)	15 (2%)
Other/unknown	217 (10%)	61 (7%)	78 (13%)
Other therapeutic interventions			
Immunoglobulin	685 (32%)	158 (19%)	
Low-dose steroids	539 (25%)	241 (30%)	
Renal replacement therapy	599 (28%)	231 (28%)	
PMX-DHP	465 (22%)	78 (10%)	
Surgical intervention	906 (42%)	145 (18%)	

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; DIC, disseminated intravascular coagulation; ICU, intensive care unit; ISTH, International Society on Thrombosis and Hemostasis; JAAM, Japanese Association for Acute Medicine; PMX-DHP, polymyxin B direct hemoperfusion; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.
Note: Data are expressed as group medians (interquartile range) or number (percent).

for DIC exist between these guidelines. The Japanese and Italian clinical practice guidelines recommend the use of either the JMHW, ISTH, or the JAAM criteria, whereas the British guideline recommends the use of the ISTH criteria. The guidelines do not offer consistent recommendations on diagnosing DIC, and thus, there is currently no definitive agreement as to which of these criteria is superior to the other. The present study does not aim to discuss the

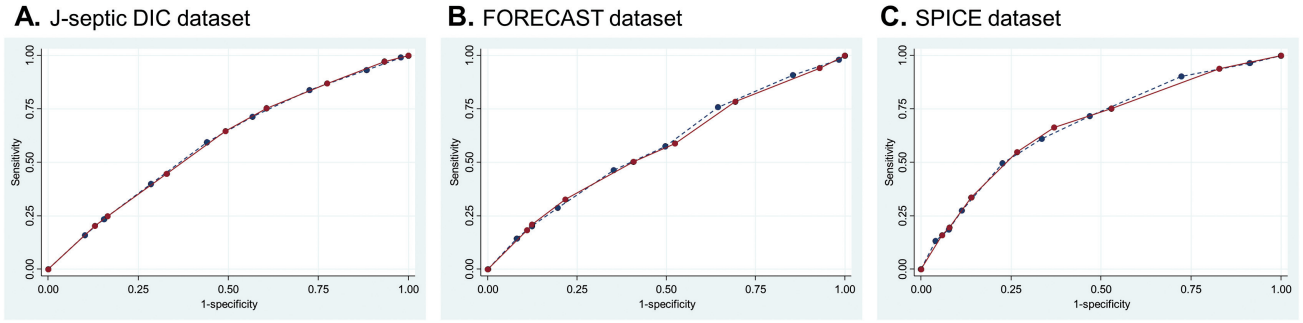

Fig. 2 Receiver operating characteristic curves for original JAAM and modified JAAM-2 DIC criteria as predictors of in-hospital mortality. The solid line represents curves for JAAM-2, and the dotted line represents curves for original JAAM. (**A**) J-Septic DIC dataset, (**B**) FORECAST dataset, (**C**) SPICE dataset. DIC, disseminated intravascular coagulation; JAAM, Japanese Association for Acute Medicine.

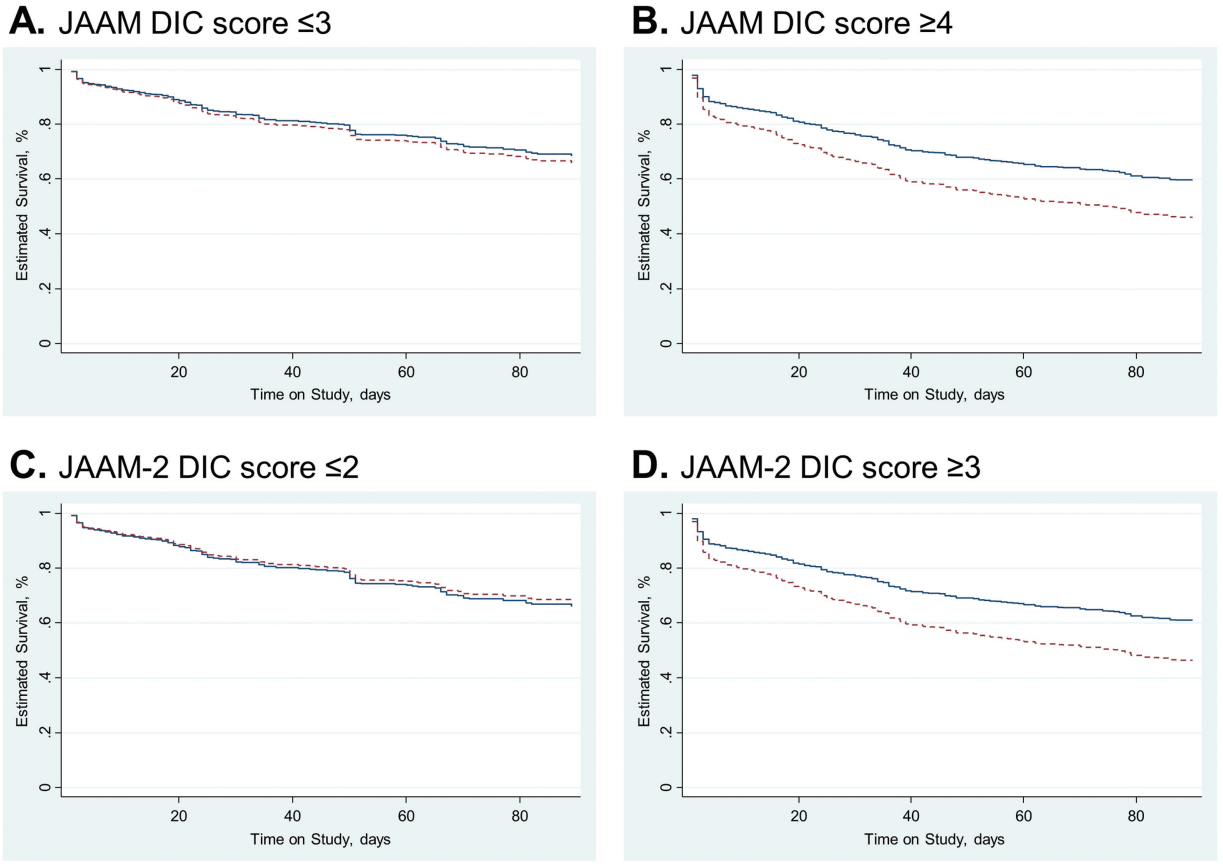

Fig. 3 Adjusted estimated survival curves according to the original JAAM and modified JAAM-2 DIC status using the J-septic DIC dataset. (**A**) JAAM DIC score $\leq$ 3, (**B**) JAAM DIC score $\geq$ 4, (**C**) JAAM-2 DIC score $\leq$ 2, and (**D**) JAAM-2 DIC score $\geq$ 3. The solid line represents patients in the anticoagulant group, and the dotted line represents patients in the control group. DIC, disseminated intravascular coagulation; JAAM, Japanese Association for Acute Medicine.

diagnostic value of the several DIC criteria because we have no gold standard for DIC diagnosis. No meta-analysis has been conducted so far to compare the prognostic performance among the several available DIC criteria. Nonetheless, we showed that the clinical usefulness of the proposed JAAM-2 DIC criteria was nearly equivalent to that of the traditional JAAM DIC criteria. While a discussion on superiority would be worthless, we showed that the performance of the JAAM-2 scoring system is almost identical to that of the JAAM criteria in terms of mortality prediction and determining treatment timing.

Modification of the JAAM DIC criteria has been discussed in several studies so far. Umemura et al[22] proposed unified DIC criteria involving several hemostatic endothelial molecular markers based on the JAAM DIC criteria and showed that the addition of protein C activity and plasminogen activator inhibitor 1 to the original JAAM DIC criteria resulted in greater prognostic value than the original criteria. Iba et al[23] proposed replacing the SIRS score with antithrombin activity in the JAAM DIC criteria. They validated the proposed criteria using a dataset of 819 sepsis patients and found that using AT-based DIC criteria makes it possible to discriminate

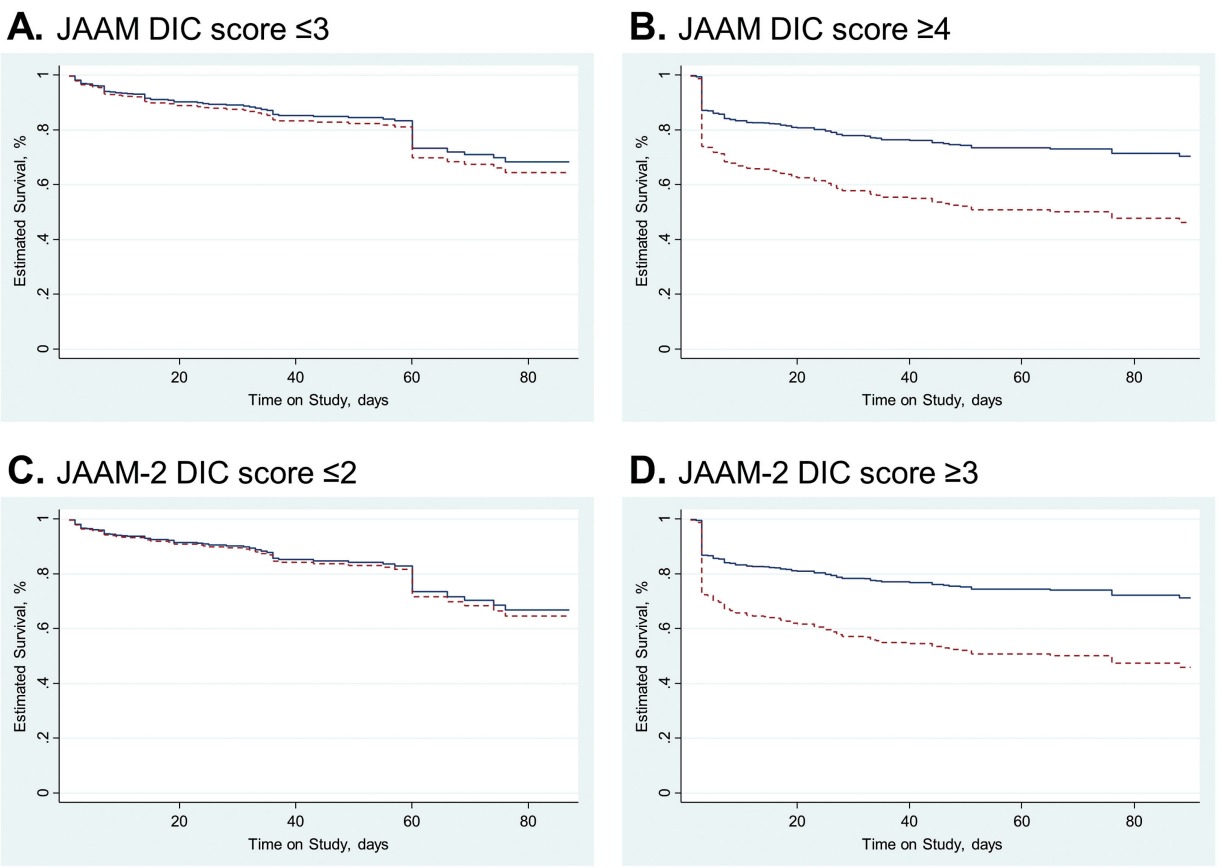

Fig. 4 Adjusted estimated survival curves according to the original JAAM and modified JAAM-2 DIC status using the FORECAST dataset. (**A**) JAAM DIC score ≤ 3, (**B**) JAAM DIC score ≥ 4, (**C**) JAAM-2 DIC score ≤ 2, and (**D**) JAAM-2 DIC score ≥ 3. The solid line represents patients in the anticoagulant group, and the dotted line represents patients in the control group. DIC, disseminated intravascular coagulation; JAAM, Japanese Association for Acute Medicine.

a more coagulation disorder-specific population. All of these previous attempts were in addition to or replacements of the other variables instead of the SIRS score, and thus, the burden on clinicians still remained. In the present study, we simply omitted the SIRS score, so this modification of the JAAM DIC criteria should allow a totally clinical-friendly approach.

We intended to evaluate the severity of sepsis by adding "SIRS score ≥ 3"; however, the present study showed the prognosis to be not different without this item included. Therefore, we think it is reasonable to omit the SIRS item from the JAAM criteria. In the present analysis, as the JAAM-2 DIC criteria have been shown to increase clinical simplicity without diminishing any diagnostic performance, the educational activities led by our academic society will aid in the replacement of original JAAM with JAAM-2 DIC criteria in Japan. Furthermore, it will be necessary to verify coherence with the sepsis-induced coagulopathy criteria[24] proposed by the ISTH in the future.

Strengths and Limitations

This comprehensive analysis was undertaken using different large-scale registry datasets that include patients with all categories of sepsis along with patients with and without DIC. These datasets also include substantial variables indicative of hemostatic abnormality, which enabled us to evaluate the nature of the coagulopathy or DIC in depth. Additionally, almost half of the included population received anticoagulant therapy against sepsis, which is a unique treatment option applied only in Japan. Thus, the treatment effect of anticoagulation can be estimated based on the sub-groups of DIC status.

We acknowledge several limitations of this study. First, due to its retrospective nature, the anticoagulant intervention was not standardized. The indications for the intervention being examined were dependent on the treatment principles of each hospital or each attending physician. Thus, we used propensity scoring to handle the nonrandomization. Second, this study used sub-group analysis, which might have accidentally generated both false-positive and false-negative results. Finally, this article focused only on patients with sepsis among various underlying diseases of DIC. The original JAAM DIC criteria have been reported to be useful in a variety of underlying diseases.[25–28] Further validation studies of these novel JAAM-2 DIC criteria targeting other underlying diseases such as trauma, postcardiac arrest, and pancreatitis should be conducted in the future.

Conclusion

We validated the JAAM-2 DIC criteria and showed that they may be valuable in detecting appropriate candidates for

anticoagulant therapy to treat sepsis. The JAAM-2 DIC criteria may be potentially useful as an alternative tool to the conventional JAAM DIC criteria for coagulopathy in sepsis in terms of their validity and simplicity.

What is known about this topic?

- The Japanese Association for Acute Medicine (JAAM) disseminated intravascular coagulation (DIC) criteria were launched 20 years ago.
- Based on the pathophysiological concept, as sepsis-induced DIC is caused by systemic inflammation, the SIRS score was included as one of the items to diagnose DIC in JAAM criteria.
- SIRS score has been omitted from the latest definition of sepsis proposed in 2016.

What does this paper add?

- We proposed novel DIC criteria named "JAAM-2 DIC" criteria in which the SIRS score component was omitted and the cutoff value for diagnosing DIC was set at $\geq$3 points.
- Using three different Japanese datasets, we showed equivalence of the JAAM-2 with original JAAM DIC criteria for prognostic and diagnostic values to initiate anticoagulation.
- The newly proposed JAAM-2 DIC criteria could potentially be used as an alternative to the conventional JAAM DIC criteria for sepsis management.

Ethical Approval statement

The study protocol was approved by the Institutional Review Board of the Osaka General Medical Center (approval numbers: #25–2050, #30-S11–004, and #S201901009). Informed consent was waived due to the nature of the registries.

Authors' Contribution

K.Y. and T.I. conceived and designed this study. K.Y. contributed to acquisition, analysis, and interpretation of the data and was responsible for drafting, editing, and submission of the manuscript. Y.U. contributed to acquisition, analysis, interpretation of the data, and drafting of the manuscript. K.M., T.M., T.W., and M.H. played a significant role in the analysis of the data and helped to draft the manuscript. T.I., Y.O., K.O., T.M., T.I., H.I., H.O., S.K., D.S., and S.G. had a significant influence on the interpretation of the data and critical appraisal of the manuscript. All of the authors contributed to the acquisition of data and reviewed, discussed, and approved the final manuscript.

Conflict of Interest

K.Y. reported receiving grants from Asahi Kasei Pharma and Japan Blood Products Organization. T.I. participated on advisory boards of Japan Blood Products Organization, Asahi Kasei Pharmaceuticals, and Toray Medical. None of the other authors have any potential conflicts of interest to disclose.

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