Journal of Critical Care 50 (2019) 23–30

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Epidemiology of disseminated intravascular coagulation in sepsis and validation of scoring systems

Shinjiro Saito [a], Shigehiko Uchino [a,*], Mineji Hayakawa [b], Kazuma Yamakawa [c], Daisuke Kudo [d], Yusuke Iizuka [e], Masamitsu Sanui [e], Kohei Takimoto [f], Toshihiko Mayumi [g], Yusuke Sasabuchi [h], Japan Septic Disseminated Intravascular Coagulation (JSEPTIC DIC) study group

[a] Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine, Japan
[b] Emergency and Critical Care Center, Hokkaido University Hospital, Japan
[c] Division of Trauma and Surgical Critical Care, Osaka General Medical Center, Japan
[d] Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine, Japan
[e] Department of Anesthesiology and Critical Care Medicine, Jichi Medical University Saitama Medical Center, Japan
[f] Department of Anesthesiology and Intensive Care Medicine, Osaka University Graduate School of Medicine, Japan
[g] Department of Emergency Medicine, University of Occupational and Environmental Health, Japan
[h] Department of Health Services Research, Graduate School of Medicine, The University of Tokyo, Japan

ARTICLE INFO

Keywords:
Disseminated intravascular coagulation
Sepsis
Intensive care unit
Mortality

ABSTRACT

Purpose: We investigated the epidemiology and outcome of disseminated intravascular coagulation (DIC) in patients with sepsis.
Materials and methods: We analyzed data from a multicenter observational study (Japan Septic Disseminated Intravascular Coagulation [JSEPTIC-DIC] study) conducted in 42 intensive care units in Japan. DIC scores were calculated using two scoring systems: the International Society on Thrombosis and Haemostasis (ISTH) and Japanese Association for Acute Medicine (JAAM) criteria. We compared demographics and clinical characteristics of patients with and without DIC, and performed multivariable logistic regression analyses to assess the association of diagnosis and scores for DIC with in-hospital mortality.
Results: Of 1895 eligible patients, 1162 (61%) and 554 patients (29%) were diagnosed as having DIC by the JAAM and ISTH criteria, respectively. Patients with DIC had higher in-hospital mortality compared with those without DIC (33% vs. 20% in JAAM and 38% vs. 24% in ISTH). However, in multivariable analysis, the JAAM score (odds ratio 1.026, 95% confidence interval 0.958–1.097; $p = 0.465$) and the ISTH score (odds ratio 1.049, 95% confidence interval 0.969–1.135; $p = 0.238$) did not have an independent association with in-hospital mortality.
Conclusions: Patients with sepsis and DIC have high mortality. However, the DIC are not independently associated with in-hospital mortality.

1. Introduction

Disseminated intravascular coagulation (DIC) is a common complication of sepsis [1-3]. It has been demonstrated that the proportion of DIC in critically ill patients progressively increased from systemic inflammatory response syndrome (SIRS) to sepsis, severe sepsis, and septic shock [3]. DIC associated with sepsis has been considered as a syndrome that should be diagnosed and treated early [2] and several interventions have been studied [4,5]. However, none of such studies have been shown to consistently improve outcomes. One of the reasons why treatment for DIC has not been found might be related to diagnosis of DIC.

In general, to assess whether a specific treatment for a syndrome improves patient outcome, diagnostic criteria meeting following three conditions are considered to be important: they should be readily available and easy to use, have diagnostic accuracy, and display prognostic value [6]. The International Society on Thrombosis and Haemostasis (ISTH) established the first international diagnostic criteria for overt DIC in 2001 [7]. Afterwards, to facilitate the identification of and early

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; AUROC, area under the ROC curve; CI, confidence intervals; DIC, Disseminated intravascular coagulation; FDP, fibrinogen degradation products; ICU, intensive care unit; ISTH, International Society on Thrombosis and Haemostasis; JAAM, Japanese Association for Acute Medicine:; OR, Odds ratios; PT-INR, prothrombin time-international normalized ratio; ROC, receiver operating characteristic; RRT, renal replacement therapy; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; VIF, Variance inflation factor;; WBC, white blood cell.

* Corresponding author at: Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine, 3-19-18, Nishi-Shinbashi, Minato-ku, Tokyo 105-8471, Japan.
E-mail address: s.uchino@mac.com (S. Uchino).

https://doi.org/10.1016/j.jcrc.2018.11.009
0883-9441/

interventions for DIC, the Japanese Association for Acute Medicine (JAAM) proposed new diagnostic criteria in 2006 [8]. Although these two criteria have been validated by several studies, validation of DIC diagnostic criteria is not an easy task because there is no gold standard for the diagnosis [9-11].

One way to validate DIC diagnostic criteria is to evaluate their ability to predict mortality. However, the accuracy for mortality prediction with these two diagnostic criteria has not been sufficiently validated in patients with sepsis. Moreover, only a few studies have investigated the epidemiology of septic patients complicated with DIC. Accordingly, using a large multicenter database, we have two aims in this study: to describe the epidemiology of DIC in patients with sepsis, and to assess the two sets of criteria for their independent association with mortality and their ability to predict mortality.

2. Materials and methods

We conducted this investigation as part of a multicenter retrospective observational study (Japan Septic Disseminated Intravascular Coagulation [JSEPTIC-DIC] study), which was performed in 42 ICUs and 40 institutions in Japan (University Hospital Medical Information Network Individual Clinical Trials Registry (UMIN-CTR) 000012543, http://www.umin.ac.jp/icdr/index-j.html) [12,13]. In short, this study concluded that anticoagulant therapy may be effective in sepsis-induced DIC patients at high risk for death, and that recombinant human soluble thrombomodulin administration and antithrombin supplementation are associated with survival benefits in patients with sepsis-induced DIC [13]. The Institutional Review board of each participating hospital (Additional file) approved the study protocol, and the need for informed consent was waived because of the retrospective design of the study.

2.1. Study patients and data collection

All patients who were admitted to the participating ICUs between January 2011 and December 2013 were screened retrospectively. Patients were eligible for the study if they had a known or suspected infection on the basis of clinical data and met the following criteria at the time of ICU admission: two or more signs of systemic inflammation and at least one sepsis-induced organ dysfunction, and 16 years of age or older. We excluded patients who had pre-existing hemostatic disorder (liver cirrhosis or failure, hematopoietic malignancy, recent irradiation, chemotherapy or anticoagulant therapy), following the exclusion criteria in the previous validation studies [8,14]. We also excluded patients with missing variables necessary to calculate the JAAM and ISTH DIC scores (systemic inflammatory response syndrome (SIRS) score [15], platelet, prothrombin time-international normalized ratio (PT-INR), fibrinogen degradation products (FDP) or D-dimer, and fibrinogen) measured on ICU admission.

We collected demographic data (age, sex, body weight); admission route to the ICU; pre-existing organ dysfunction; Acute Physiology and Chronic Health Evaluation (APACHE) II score [16]; Sequential Organ Failure Assessment (SOFA) score [17] and SIRS score on the ICU admission day; primary infection sites (clinically defined by attending physicians); blood culture results; isolated microorganisms; laboratory tests (white blood cell (WBC) counts, platelet counts, hemoglobin, PT-INR, fibrinogen, FDP, D-dimer, antithrombin and lactate level) on the ICU admission day; bleeding complications during the first week after ICU admission; duration of mechanical ventilation, renal replacement therapy (RRT), and vasopressor therapy during the first 28 days after ICU admission; ICU length of stay; and ICU and hospital mortality.

DIC scores were calculated using the two scoring systems on ICU admission: the ISTH and JAAM DIC criteria (Table 1) [7,8]. Patients with DIC score ≥ 5 points in ISTH-DIC criteria and patients with DIC score ≥ 4 points in JAAM-DIC criteria, respectively, were diagnosed as having DIC. The threshold of FDP in the JAAM criteria was used as the fibrin-related marker in the ISTH criteria: no increase, moderate increase, and strong increase of the fibrin-related marker in the ISTH criteria were defined as FDP <10, ≥10 < 25, ≥25 μg/mL, respectively. Event-free days were defined as a number of days without events (mechanical ventilation, RRT and vasopressor therapy) during the first 28 days if a patient survived for at least 28 days or was discharged within 28 days after ICU admission. If a patient died within 28 days after ICU admission, event-free days were defined as a number of days without events while the patient was alive.

Table 1
The scoring systems for DIC.

	The JAAM scoring system	Score	The ISTH scoring system	Score
Platelet count	$<80 \times 10^9$/l or > 50% decrease within 24 h	3	$<50 \times 10^9$/l	2
	$\geq 80 < 120 \times 10^9$/l or > 30% decrease within 24 h	1	$\geq 50 < 100 \times 10^9$/l	1
	$\geq 120 \times 10^9$/l	0	$\geq 100 \times 10^9$/l	0
Prothrombin time	(Value of patient/normal value)		(Prolonged prothrombin time)	
	≥1.2	1	≥6 s	2
	<1.2	0	≥3 < 6 s	1
			<3 s	0
Fibrin-related marker	(Fibrin/fibrinogen degradation products)			
	≥25 mg/l	3	Strong increase	3
	≥10 < 25 mg/l	1	Moderate increase	2
	<10 mg/l	0	No increase	0
SIRS score	≥3	1		
	0 to 2	0		
Fibrinogen level			<100 mg/dl	1
			≥100 mg/dl	0
DIC	≥4 points		≥5 points	

DIC disseminated intravascular Coagulation, *ISTH* International Society on Thrombosis and Haemostasis, *JAAM* Japanese association for acute medicine, *SIRS* systemic inflammatory response syndrome.

2.2. Statistical analysis

We compared variables between patients with DIC (DIC group) and without DIC (Non-DIC group). Quantitative parameters were reported as medians and interquartile ranges (25th to 75th percentile) and were compared using the Mann-Whitney *U* test. Qualitative parameters were expressed as numbers and percentages and were compared using the chi-square test or Fisher's exact test, as appropriate. We performed four multivariable logistic regression analyses with the simultaneous method to assess the impact of DIC diagnosis and DIC scores by the two criteria on in-hospital mortality. Age, sex, body weight, pre-existing organ dysfunction, admission route to the ICU, primary infection site, blood culture result, isolated microorganism, APACHE II score, SOFA score, WBC, hemoglobin, and lactate level on ICU admission were used as explanatory variables. SIRS score, platelet count, PT-INR, Fibrinogen, FDP and D-dimer levels were not used as explanatory variables because they were used to calculate the DIC scores. Antithrombin levels were also not used because the proportion of missing data was high. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated. Variance inflation factor (VIF) was calculated to check for multicollinearity. Pearson's correlation coefficient was used to analyze two-sided correlation between scores. To assess the performance of APACHE II, SOFA and DIC scores to predict the in-hospital mortality, the receiver operating characteristic (ROC) curves were computed and quantified by calculating the area under the ROC curve (AUROC) and 95% CI. A P value of <0.05 was considered statistically significant. A free available software (R 3.3.1,Vienna, Austria) was used for comparison between AUROCs, and a commercially available statistical package (SPSS 19.0, IBM Corp., Armonk, NY, USA) was used for all other statistical analyses.

3. Results

The JSEPTIC-DIC study included 3195 consecutive patients fulfilling inclusion criteria. After excluding 529 patients who had pre-existing hemostatic disorder and 771 patients who had missing variables necessary to calculate the DIC scores, we identified 1895 eligible patients. Table 2 lists demographics and clinical characteristics of these patients. One thousand one hundred and sixty-two patients (61%) and 554 patients (29%) were diagnosed as DIC in the JAAM and the ISTH criteria, respectively, on ICU admission. APACHE II and SOFA scores were higher in the DIC group than the Non-DIC group for the JAAM criteria (APACHE II: 24 vs. 20, $p < 0.001$, SOFA: 10 vs. 8, $p < 0.001$) and the ISTH criteria (APACHE II: 24 vs. 21, $p < 0.001$, SOFA: 12 vs. 8, $p < 0.001$). Comorbidities were similar between DIC and Non-DIC groups for both criteria. Patients in the DIC group had lower platelet counts, higher PT-INR, higher FDP and D-dimer compared with patients in the Non-DIC group for both criteria ($p < 0.001$ for all comparisons). Other laboratory tests except for WBC counts also showed statistically significant differences between DIC and Non-DIC groups for both criteria.

Table 3 lists information regarding infection (primary infection site, blood culture and isolated microorganism). Abdominal infection was present in nearly one-third of both groups in the JAAM criteria (35%) and the ISTH criteria (38%). Lung/thoracic infection was less common in the DIC group than the Non-DIC group (JAAM: 19% vs. 34%, ISTH: 13% vs. 29%). In contrast, urinary tract infection was more common in the DIC group (JAAM: 19% vs. 11%, ISTH: 22% vs. 13%). Patients in the DIC group showed a higher blood culture-positive rate than the Non-DIC group for both criteria (JAAM: 52% vs. 31%, $p < 0.001$, ISTH: 58% vs. 38%, $p < 0.001$). Though gram-negative rods and gram-positive coccus accounted for majority of isolated microorganism in both groups, the proportion of gram-negative rods was higher in the DIC group than the Non-DIC group for both criteria (JAAM: 42% vs. 30%, ISTH: 45% vs. 34%).

Table 4 lists outcomes of patients. Patients with DIC in the JAAM criteria had more episodes of bleeding complications requiring transfusion compared with patients without DIC (13% vs. 8%, $p < 0.001$), whereas no significant difference was observed in the ISTH criteria (12% vs. 11%, $p = 0.370$). For both criteria, all categories of 28 day-free days were shorter in the DIC group than the Non-DIC group ($p < 0.001$ for all comparisons). Patients with DIC also demonstrated higher ICU mortality and in-hospital mortality in the JAAM criteria (22% vs. 10%; $P < 0.001$, 33% vs. 20%; $P < 0.001$, respectively) and the ISTH criteria (25% vs. 14%; $P < 0.001$, 38% vs. 24%; $P < 0.001$, respectively).

Fig. 1 shows the relationship between APACHE II score (1A, 1C) / SOFA score (1B, 1D) and the two DIC scores. The APACHE II score and the SOFA score were significantly correlated with the JAAM score ($r = 0.256$; $P < 0.001$, $r = 0.473$; $P < 0.001$, respectively) and the ISTH score ($r = 0.232$; $P < 0.001$, $r = 0.452$; $P < 0.001$, respectively). Fig. 2 shows in-hospital mortality and the distribution of the number of patients for APACHE II score (2A), SOFA score (2B), JAAM DIC score (2C) and ISTH DIC score (2D) on ICU admission. In all scoring systems, higher scores were related to higher mortality. However, the slope of mortality increase was less steep for the two DIC scores than the APACHE II and SOFA scores.

Table 5 lists the results of multivariable logistic regression analysis for in-hospital mortality. The models found that all four DIC related variables (JAAM DIC score, ISTH DIC score, DIC diagnosis defined by the JAAM DIC score ≥ 4 points, DIC diagnosis defined by the ISTH DIC score ≥ 5 points) were not independently associated with an increased risk of in-hospital death. All of the VIF values in these models were <4, which indicates the absence of multicollinearity problems. The AUROC for in-hospital mortality prediction of the JAAM DIC score (0.600; 95%

Table 2
Demographics and clinical characteristics of patients with and without DIC.

	All patients	JAAM			ISTH		
		DIC	Non DIC	*p*	DIC	Non DIC	*p*
Number of patients	1895	1162 (61)	733 (39)		554 (29)	1341 (71)	
Age, year ($n = 1895$)	72 (62–80)	72 (62–80)	71 (61–80)	0.483	72 (61–80)	72 (62–80)	0.775
Male (n = 1895)	1120 (59)	657 (56)	463 (63)	0.004	309 (55)	811 (60)	0.058
Body weight, kg ($n = 1858$)	55 (47–65)	55 (47–65)	55 (48–65)	0.478	55 (46–65)	55 (47–65)	0.339
ICU admission route (n = 1895)				0.220			0.014
Emergency department	860 (45)	509 (43)	351 (47)		231 (41)	629 (46)	
Hospital ward	468 (24)	296 (25)	172 (23)		161 (29)	307 (22)	
Other hospital	567 (29)	357 (30)	210 (28)		162 (29)	405 (30)	
Comorbidity (n = 1895)							
Respiratory failure	73 (3)	42 (3)	31 (4)	0.498	20 (3)	53 (3)	0.725
Heart failure	103 (5)	56 (4)	47 (6)	0.136	30 (5)	73 (5)	0.980
Hemodialysis	151 (7)	100 (8)	51 (6)	0.197	53 (9)	98 (7)	0.099
Immunocompromised	202 (10)	124 (10)	78 (10)	0.984	56 (10)	146 (10)	0.617
APACHE II score ($n = 1894$)	22 (17–28)	24 (18–29)	20 (15–26)	<0.001	24 (19–31)	21 (16–27)	<0.001
SOFA score (n = 1894)	9 (6–12)	10 (8–13)	8 (5–10)	<0.001	12 (9–14)	8 (6–11)	<0.001
SIRS score (n = 1895)	3 (2–4)	3 (3–4)	3 (2–4)	<0.001	3 (3–4)	3 (2–4)	0.004
JAAM DIC score (n = 1895)	4 (3–6)	6 (5–7)	2 (1–3)	<0.001	7 (6–8)	3 (2–5)	<0.001
ISTH DIC score (n = 1895)	4 (2–5)	4 (4–5)	2 (1–3)	<0.001	5 (5–6)	3 (2–4)	<0.001
Laboratory test on ICU admission							
WBC counts, 10^9/L (n = 1895)	11.6 (5.4–18.6)	11.5 (4.6–18.7)	11.9 (7.4–18.6)	0.042	11.2 (4.3–18.2)	11.7 (6.3–18.7)	0.052
Platelet counts, 10^9/L (n = 1895)	126 (70–199)	83 (50–148)	183 (136–246)	<0.001	59 (37–87)	160 (108–228)	<0.001
Hemoglobin, g/dL (n = 1894)	10.9 (9.2–12.7)	10.7 (9–12.6)	11.1 (9.6–12.8)	0.001	10.5 (8.8–12.2)	11.0 (9.4–12.9)	<0.001
PT-INR (n = 1895)	1.3 (1.2–1.5)	1.4 (1.2–1.6)	1.2 (1.1–1.4)	<0.001	1.6 (1.4–1.9)	1.2 (1.1–1.4)	<0.001
Fibrinogen, mg/dL (n = 1895)	400 (274–568)	372 (244–524)	448 (330–617)	<0.001	331 (198–477)	433 (310–591)	<0.001
FDP, μg/mL ($n = 1536$)	20 (11–41)	31 (17–66)	11 (7–16)	<0.001	45 (25–89)	15 (9–24)	<0.001
D-dimer, μg/mL ($n = 1648$)	8.6 (4–20)	15.4 (7.7–30.8)	4.4 (2.4–7.2)	<0.001	20.8 (11.9–40.1)	6.2 (3.2–11.7)	<0.001
Antithrombin, % ($n = 1259$)	57 (45–72)	55 (44–68)	64 (50–79)	<0.001	50 (39–60)	62 (49–76)	<0.001
Lactate, mmol/L ($n = 1747$)	2.9 (1.7–5.5)	3.4 (2–6.7)	2.3 (1.4–4.1)	<0.001	4 (2.3–7.8)	2.5 (1.5–4.8)	<0.001

Quantitative parameters are reported as median (interquartile range; 25th–75th percentile). Qualitative parameters are expressed as number (%).
APACHE II Acute Physiology and Chronic Health Evaluation II, *DIC* disseminated intravascular Coagulation, *FDP* fibrinogen degradation products, *ICU* intensive care unit, *ISTH* International Society on Thrombosis and Haemostasis, *JAAM* Japanese association for acute medicine, *PT-INR* prothrombin time-international normalized ratio, *SIRS* systemic inflammatory response syndrome, *SOFA* Sequential Organ Failure Assessment, *WBC* white blood cell.

Table 3
Information for infection in patients with and without DIC.

	All patients	JAAM			ISTH		
		DIC	Non DIC	*p*	DIC	Non DIC	*p*
Number of patients	1895	1162 (61)	733 (39)		554 (29)	1341 (71)	
Primary infection site				<0.001			<0.001
Lung/thoracic	472 (24)	221 (19)	251 (34)		75 (13)	397 (29)	
Abdomen	631 (33)	416 (35)	215 (29)		215 (38)	416 (31)	
Urinary tract	310 (16)	228 (19)	82 (11)		127 (22)	183 (13)	
Bone/soft tissue	242 (12)	130 (11)	112 (15)		54 (9)	188 (14)	
Cardiovascular	42 (2)	32 (2)	10 (1)		18 (3)	24 (1)	
Central nervous system	49 (2)	35 (3)	14 (1)		19 (3)	30 (2)	
Catheter-related	20 (1)	14 (1)	6 (0)		4 (0)	16 (1)	
Others	37 (1)	22 (1)	15 (2)		10 (1)	27 (2)	
Unknown	92 (4)	64 (5)	28 (3)		32 (5)	60 (4)	
Blood culture				<0.001			<0.001
Negative	965 (50)	513 (44)	452 (61)		223 (40)	742 (55)	
Positive	834 (44)	606 (52)	228 (31)		313 (56)	521 (38)	
Not taken	96 (5)	43 (3)	53 (7)		18 (3)	78 (5)	
Isolated microorganism				<0.001			0.001
Gram-negative rods	716 (37)	492 (42)	224 (30)		250 (45)	466 (34)	
Gram-positive-coccus	461 (24)	271 (23)	190 (25)		122 (22)	339 (25)	
Fungus	30 (1)	15 (1)	15 (2)		3 (0)	27 (2)	
Virus	16 (0)	8 (0)	8 (1)		3 (0)	13 (0)	
Mixed infection	242 (12)	132 (11)	110 (15)		58 (10)	184 (13)	
Others	30 (1)	22 (1)	8 (1)		7 (1)	23 (1)	
Unknown	400 (21)	222 (19)	178 (24)		111 (20)	289 (21)	

Qualitative parameters are expressed as number (%).
DIC disseminated intravascular Coagulation, *ISTH* International Society on Thrombosis and Haemostasis, *JAAM* Japanese association for acute medicine.

CI, 0.572–0.627) and the ISTH DIC score (0.602; 95% CI, 0.575–0.630) were significantly lower than that of APACHE II score and SOFA score (All P < 0.001). AUROCs of the APACHE II score (0.712; 95% CI, 0.687–0.737) and SOFA score (0.708; 95% CI, 0.682–0.734) were not significantly different (P = 0.739) (Fig. 3).

3.1. Supplemental analysis

As supplemental analysis, we repeated all analyses presented above by including patients who had missing variables to calculate the JAAM and ISTH DIC scores (SIRS, platelet, INR, FDP or D-dimer, and fibrinogen) and assigning zero for missing variables. 2666 patients were included for this analysis. Results of the analysis were essentially similar to the main findings (Additional file: Tables S1 to S4 and Figs. S1 to S3).

4. Discussion

4.1. Key findings

We have observed that 61% and 29% of eligible patients with sepsis were diagnosed as having DIC on ICU admission by the JAAM and ISTH criteria, respectively. There were significant differences in demographics and clinical characteristics of patients between patients with and without DIC. Patients with DIC diagnosed by the two criteria had higher severity and in-hospital mortality than patients without DIC. The two DIC scores showed positive correlations with the APACHE II and SOFA scores. However, on multivariable regression analysis, the DIC scores and DIC diagnosed by two criteria were not statistically associated with in-hospital mortality. Moreover, on ROC curve analysis, the

Table 4
Outcome of patients with and without DIC.

	All patients	JAAM			ISTH		
		DIC	Non DIC	*p*	DIC	Non DIC	*p*
Number of patients	1895	1162 (61)	733 (39)		554 (29)	1341 (71)	
Bleeding complications							
Transfusion required	220 (11)	157 (13)	63 (8)	0.001	70 (12)	150 (11)	0.370
Intervention required	28 (1)	21 (1)	7 (0)	0.134	10 (1)	18 (1)	0.448
Intracranial hemorrhage	11 (0)	9 (0)	2 (0)	0.161	3 (0)	8 (0)	0.886
Bleeding to death	2 (0)	2 (0)	0 (0)	0.261	2 (0)	0 (0)	0.028
ICU length of stay, days	7 (4–14)	7 (4–14)	7 (4–14)	0.852	7 (3−13)	8 (4–15)	0.002
Mechanical ventilation	1384 (73)	858 (73)	526 (71)	0.321	411 (74)	973 (72)	0.467
Renal replacement therapy	707 (37)	512 (44)	195 (26)	<0.001	284 (51)	423 (31)	<0.001
Vasopressor	1453 (76)	957 (82)	496 (67)	<0.001	479 (86)	974 (72)	<0.001
28 day-free days							
ICU-free days	18 (0−23)	16 (0−22)	19 (8–23)	<0.001	15 (0–22)	18 (3−23)	<0.001
Ventilator-free days	21 (6–27)	20 (2–27)	23 (14–28)	<0.001	19 (1–26)	22 (9–28)	<0.001
RRT-free days	28 (16–28)	26 (9–28)	28 (24–28)	<0.001	24 (4–28)	28 (21–28)	<0.001
Vasopressor-free days	24 (16–27)	23 (11–26)	25 (21–28)	<0.001	22 (3–26)	25 (19–27)	<0.001
ICU mortality	340 (17)	261 (22)	79 (10)	<0.001	143 (25)	197 (14)	<0.001
In-hospital mortality	541 (28)	394 (33)	147 (20)	<0.001	213 (38)	328 (24)	<0.001

Quantitative parameters are reported as median (interquartile range; 25th–75th percentile). Qualitative parameters are expressed as number (%).
DIC disseminated intravascular coagulation, *ICU* intensive care unit, *ISTH* International Society on Thrombosis and Haemostasis, *JAAM* Japanese association for acute medicine, *RRT* renal replacement therapy.

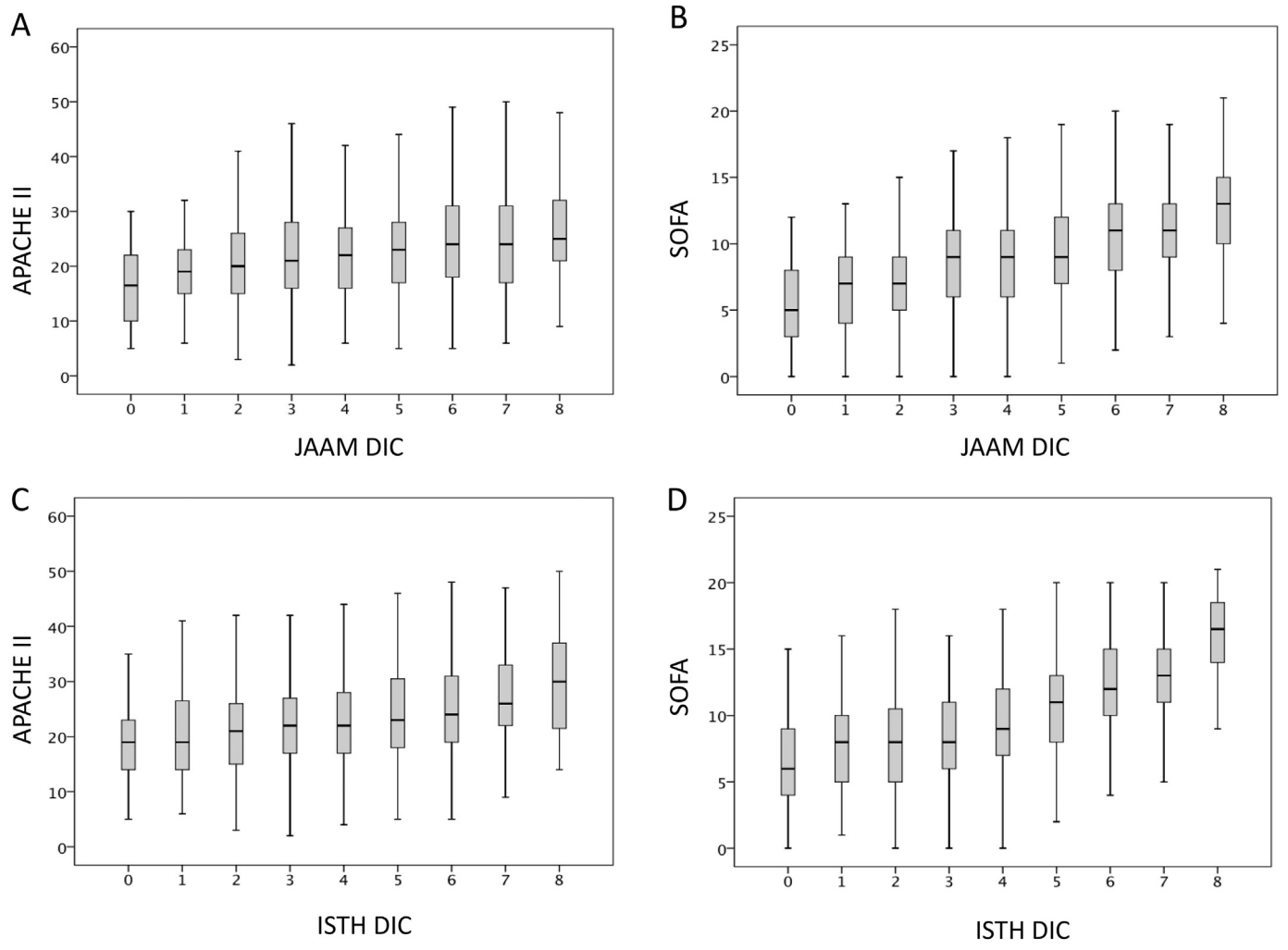

Fig. 1. Relationship between APACHE II score (A and C) / SOFA score (B and D) and the JAAM (A and B) and ISTH (C and D) DIC scores on ICU admission. *APACHE II* Acute Physiology and Chronic Health Evaluation II, *DIC* Disseminated Intravascular Coagulation, *ICU* Intensive Care Unit, *ISTH* International Society on Thrombosis and Haemostasis, *JAAM* Japanese Association for Acute Medicine, *SOFA* Sequential Organ Failure Assessment.

discrimination ability of the two DIC scores to predict in-hospital mortality was significantly lower than APACHE II and SOFA scores.

4.2. Epidemiology of DIC in sepsis

DIC has been considered as a frequent complication of sepsis [1-3]. Several studies have reported the epidemiology of DIC in sepsis using established DIC criteria. However, studies to date have been mostly restricted to specific patients, e.g., with low platelet counts [10,14]. Angstwurm et al. reported the prevalence of 13% for overt DIC diagnosed by the ISTH criteria in 232 patients admitted to a single ICU [18]. In a large randomized trial of 1690 patients with severe sepsis, 29% had overt DIC diagnosed by the ISTH criteria at study entry, with higher in-hospital mortality of 37% compared with 25% in septic patients without DIC [19]. Using the JAAM criteria, Ogura et al. studied the prevalence of DIC in patients with severe sepsis [20]. This study reported that 292 out of 634 (46.8%) patients with severe sepsis had DIC, also with higher in-hospital mortality of 38% compared with 22% in septic patients without DIC [11]. Our study results confirm the previous findings that, using consensus criteria, DIC is a common condition coexisting in sepsis, with high associated mortality.

4.3. Significance of DIC scores in sepsis

Several prior studies have shown that the DIC score was an important predictor of sepsis outcome. For example, a multicenter survey of severe sepsis in Japan showed that the JAAM DIC score was an independent predictor of 28-day mortality though the severity of patients was not included as an adjustment variable [11]. We assessed the difference of prognostic impact between the DIC scores and general severity of patients, and found that the two DIC scores were significantly correlated with the APACHE II and SOFA scores (Fig. 1) and related to higher mortality (Fig. 2). However, the slope of mortality increase was less steep for the two DIC scores than the APACHE II and SOFA scores (Fig. 2). Furthermore, the AUROC of the two DIC scores was nearly 0.6, lower than the APACHE II and SOFA scores (Fig. 3). These results, as well as the lack of independent association with in-hospital mortality on multivariable regression analysis, including severity scores, imply that the prognostic value of the DIC scores might be small and mainly dependent on the general illness severity of patients (represented by the APACHE II and SOFA scores). The reason why our findings are in contradiction with other previous studies might be that most of the previous studies did not include general severity scores in their multivariable analysis, except one small retrospective study [21]. Thrombocytopenia in patients with severe sepsis are not only caused by DIC but also by various

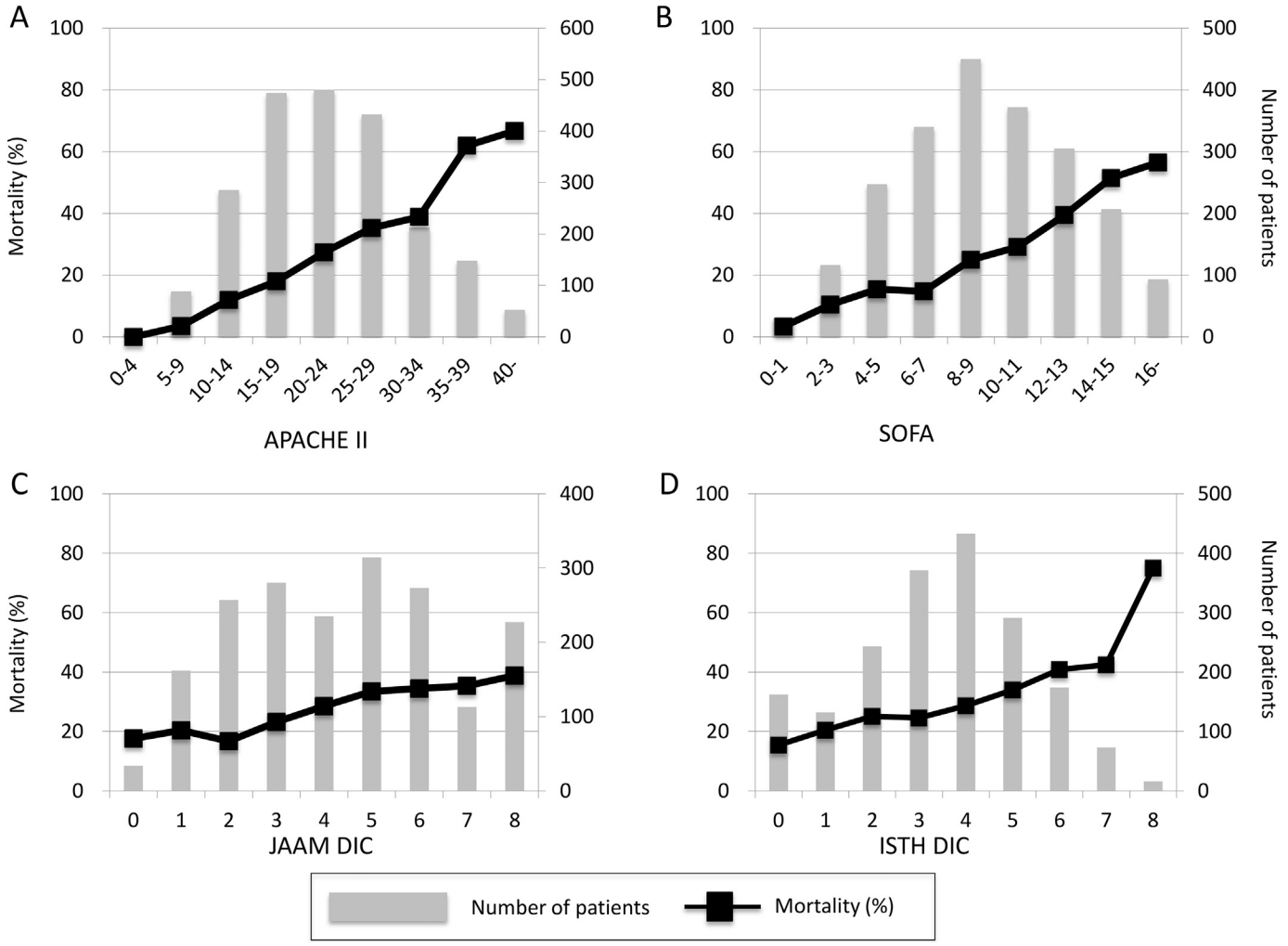

Fig. 2. In-hospital mortality and distribution of the number of patients for APACHE II score (A), SOFA score (B), JAAM DIC score (C) and ISTH DIC score (D) on ICU admission. *APACHE II* Acute Physiology and Chronic Health Evaluation II, *DIC* Disseminated Intravascular Coagulation, *ICU* Intensive Care Unit, *ISTH* International Society on Thrombosis and Haemostasis, *JAAM* Japanese Association for Acute Medicine, *SOFA* Sequential Organ Failure Assessment.

Table 5
Multivariable logistic regression analyses for in-hospital mortality.

	Odds ratio (95%CI)	*p*-value
Model 1		
APACHE II score	1.030 (1.011–1.051)	0.002
SOFA score	1.153 (1.101–1.208)	<0.001
JAAM DIC score	1.032 (0.963–1.106)	0.369
Model 2		
APACHE II score	1.031 (1.011–1.051)	0.002
SOFA score	1.149 (1.099–1.202)	<0.001
DIC diagnosed by JAAM	1.331 (0.995–1.781)	0.054
Model 3		
APACHE II score	1.033 (1.013–1.053)	0.001
SOFA score	1.149 (1.098–1.203)	<0.001
ISTH DIC score	1.050 (0.969–1.137)	0.232
Model 4		
APACHE II score	1.032 (1.012–1.053)	0.001
SOFA score	1.153 (1.102–1.207)	<0.001
DIC diagnosed by ISTH	1.125 (0.838–1.511)	0.432

APACHE II Acute Physiology and Chronic Health Evaluation II, *CI* confidential interval, *DIC* disseminated intravascular coagulation, *ISTH* International Society on Thrombosis and Haemostasis, *JAAM* Japanese association for acute medicine, *SOFA* Sequential Organ Failure Assessment. Other explanatory variables: age, sex, body weight, pre-existing organ dysfunction, admission route to the ICU, primary infection site, blood culture result, isolated microorganism, white blood cell, hemoglobin, and lactate level on ICU admission.

conditions [22]. Many patients with severe thrombocytopenia and sepsis do not fulfill the criteria for overt DIC [23]. Therefore, thrombocytopenia not due to true DIC may distort the relation between the DIC score and prognosis.

The JAAM criteria include the SIRS score. However, many studies have shown that the presence of SIRS is nearly ubiquitous in hospitalized patients and occurs in many benign conditions, and is not specific for inflammation [24-26]. The new sepsis definition (SEPSIS 3) published recently no longer includes SIRS criteria [27]. In addition, although both the JAAM and ISTH criteria have each cutoff point for DIC diagnosis (JAAM ≥4, ISTH ≥5, respectively), the mortality in our present study seems to increase linearly with each additional point from 0 to 8 without any thresholds to distinguish patient outcome (Fig. 2). This finding is similar to SIRS criteria for sepsis, which did not define any specific transition point for mortality [24].

4.4. Comparison of two DIC criteria

We found remarkable difference in the incidence rate between the two criteria (29% by ISTH and 61% by JAAM). Several previous studies, although smaller than ours, have also compared ISTH and JAAM DIC criteria. For example, Singh et al. studied 148 blood samples from 42 patients with platelet count of $<150 \times 10^9$/L [10]. They found that JAAM was positive in 119 samples (80.4%) and ISTH was positive in 54 samples (36.5%). Takemitsu et al. studied 413 patients with different

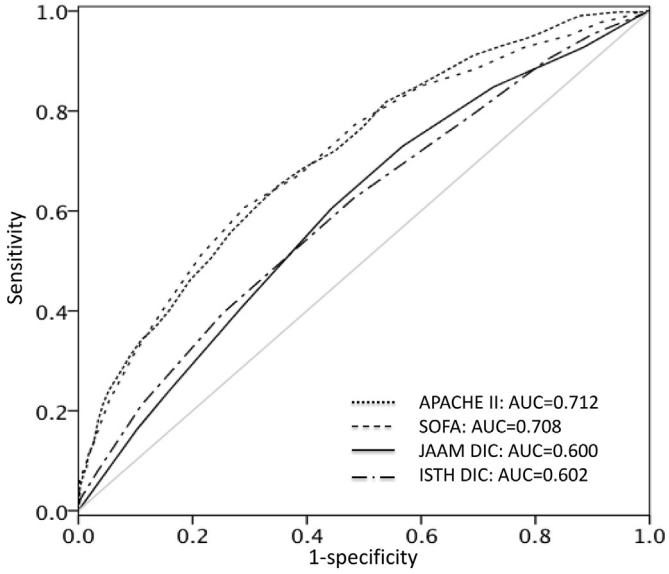

Fig. 3. Receiver-operating characteristics curves of scoring systems on ICU admission for in-hospital mortality. *APACHE II* Acute Physiology and Chronic Health Evaluation II, *AUROC* Area Under the Receiver-Operating Characteristics Curve, *DIC* Disseminated Intravascular Coagulation, *ICU* Intensive Care Unit, *ISTH* International Society on Thrombosis and Haemostasis, *JAAM* Japanese Association for Acute Medicine, *SOFA* Sequential Organ Failure Assessment.

underlying diseases, and found that 143 (34.6%) and 291 (70.5%) had DIC according to the ISTH and JAAM criteria [28]. Gando et al. studied 166 septic patients with sepsis-related DIC according to the JAAM DIC criteria [9]. Among the study patients, only 67 patients met the ISTH DIC criteria (40.3%). Therefore, all these studies, including ours, found that the incidence rate of DIC diagnosed with the JAAM criteria is more than double of that with the ISTH criteria.

Since the criteria of the two scores are similar (both use platelet count, prothrombin time and fibrin/fibrinogen degradation products) but different (JAAM includes SIRS, ISTH includes fibrinogen), it is difficult to explore why these two criteria show such remarkable difference in the incidence rate of DIC [29]. Nonetheless, such difference will make conducting clinical research difficult (e.g., patient inclusion for randomized studies, comparisons for results of various studies) and might become a barrier for future studies.

4.5. Implications for future research

Our findings suggest that current DIC diagnosis criteria need further modification to meet the condition of displaying prognostic values. Recently several studies have suggested that new biomarkers might be useful for early assessment of sepsis-induced DIC [30,31]. These new biomarkers may be important keys to revise DIC diagnostic criteria in future. Recently, modification of the JAAM DIC score (replacing SIRS with antithrombin levels <70%) have been suggested [32]. Further studies are needed to more properly identify patients with true sepsis-induced DIC.

4.6. Study strengths and limitations

The present study has several strengths. It has the largest sample size among studies reporting the epidemiology of DIC in patients with sepsis so far. We focused on patients without diseases or conditions that might mimic DIC diagnosis to exactly assess the association and predictive value of sepsis-induced DIC. In addition, this is the first study to demonstrate that the prognostic impact of DIC scores on outcome is weak when prediction is adjusted according to established illness severity scores.

There are also several limitations in the present study. First, this study is retrospective in design. We could not control for all confounding factors when evaluating the prognostic accuracy of the DIC scores. However, we entered clinical characteristics of patients including infection details and severity of illness. Second, this study may have some selection biases because we excluded patients who had missing variables necessary to calculate the DIC scores. Thus, we performed a supplementary analysis including patients with missing variables and found similar results. Third, anti-DIC drugs such as recombinant human soluble thrombomodulin and antithrombin are approved and widely used as DIC treatment in Japan [12,13]. Although there is limited clinical evidence supporting the use of these drugs for DIC, they might have influenced the results of the present study [12,33]. Forth, the new definition for sepsis (SEPSIS-3) has been published after data collection of our study finished [27]. However, we do not have information for the baseline SOFA score to define sepsis using SEPSIS-3. Assuming the baseline of zero, 98.5% of the study patients had the SOFA score of two or more, suggesting that the study results would be quite similar even if we used the different definition for sepsis.

5. Conclusions

We have conducted a multicenter retrospective observational study with a large sample size to investigate the epidemiology of DIC in patients with sepsis. We found that patients with DIC diagnosed by the two consensus criteria had higher severity and in-hospital mortality than patients without DIC. However, the two DIC scores did not have an independent association with in-hospital mortality on multivariable analysis and did not predict outcome after adjustment for illness severity. Although we confirmed that patients with DIC have distinct biological characteristics and high mortality, two current established diagnostic criteria for DIC may not have ability to independently identify patients with poor outcome.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgement

We wish to thank Dr. Rinaldo Bellomo, Intensive Care Unit, Austin Hospital, Melbourne, Australia, for the preparation of this manuscript and all of the J-Septic DIC study contributors: Takeo Azuhata (Nihon university school of medicine), Fumihito Ito (Ohta General Hospital Foundation Ohta Nishinouchi Hospital), Shodai Yoshihiro (JA Hiroshima General Hospital), Katsura Hayakawa (Saitama Red Cross Hospital), Tsuyoshi Nakashima (Wakayama Medical University), Takayuki Ogura (Japan Red Cross Maebashi Hospital), Eiichiro Noda (Kyushu University Hospital), Yoshihiko Nakamura (Fukuoka University Hospital), Ryosuke Sekine (Ibaraki Prefectural Central Hospital), Yoshiaki Yoshikawa (Osaka General Medical Center), Motohiro Sekino (Nagasaki University Hospital), Keiko Ueno (Tokyo Medical University, Hachioji Medical Center), Yuko Okuda (Japan Red Cross Kyoto Daiichi Hospital), Masayuki Watanabe (Saiseikai Yokohamasi Tobu Hospital), Akihito Tampo (Asahikawa Medical University), Nobuyuki Saito (Nippon Medical School Chiba Hokusoh Hospital), Yuya Kitai (Kameda Medical Center), Hiroki Takahashi (Osaka University Graduate School of Medicine), Iwao Kobayashi (Asahikawa Red Cross Hospital), Yutaka Kondo (University of the Ryukyu), Wataru Matsunaga (Jichi medical university Saitama medical center), Sho Nachi (Gifu University Hospital), Toru Miike (Saga University Hospital), Hiroshi Takahashi (Steel Memorial Muroran

Hospital), Shuhei Takauji (Sapporo City General Hospital), Kensuke Umakoshi (Ehime University Hospital), Takafumi Todaka (Tomishiro Central Hospital), Hiroshi Kodaira (Akashi City Hospital), Kohkichi Andoh (Sendai City Hospital), Takehiko Kasai (Hakodate Municipal Hospital), Yoshiaki Iwashita (Mie University Hospital), Hideaki Arai (University of Occupational and Environmental Health), Masato Murata (Gunma university), Masahiro Yamane (KKR Sapporo Medical Center), Kazuhiro Shiga (Seirei Mikatahara general hospital), Naoto Hori (Hyogo College of Medicine).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.11.009.

References

[1] Levi M, ten Cate H, van der Poll T, van Deventer SJ. Pathogenesis of disseminated intravascular coagulation in sepsis. JAMA 1993;270:975–9.
[2] Zeerleder S, Hack CE, Wuillemin WA. Disseminated intravascular coagulation in sepsis. Chest 2005;128:2864–75.
[3] Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA 1995;273:117–23.
[4] Warren BL, Eid A, Singer P, Pillay SS, Carl P, Novak I, et al. KyberSept Trial Study Group. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 2001;286:1869–78.
[5] Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, et al. PROWESS-SHOCK Study Group. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med 2012;366:2055–64.
[6] Gando S, Meziani F, Levi M. What's new in the diagnostic criteria of disseminated intravascular coagulation? Intensive Care Med 2016;42:1062–4.
[7] Taylor Jr FB, Toh CH, Hoots WK, Wada H, Levi M. Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001;86:1327–30.
[8] Gando S, Iba T, Eguchi Y, Ohtomo Y, Okamoto K, Koseki K, et al. Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) study Group. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. Crit Care Med 2006;34:625–31.
[9] Gando S, Saitoh D, Ogura H, Mayumi T, Koseki K, Ikeda T, et al. Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) study Group. Disseminated intravascular coagulation (DIC) diagnosed based on the Japanese Association for Acute Medicine criteria is a dependent continuum to overt DIC in patients with sepsis. Thromb Res 2009;123:715–8.
[10] Singh RK, Baronia AK, Sahoo JN, Sharma S, Naval R, Pandey CM, et al. Prospective comparison of new Japanese Association for Acute Medicine (JAAM) DIC and International Society of Thrombosis and Hemostasis (ISTH) DIC score in critically ill septic patients. Thromb Res 2012;129:e119–25.
[11] Gando S, Saitoh D, Ogura H, Fujishima S, Mayumi T, Araki T, et al. Japanese Association for Acute Medicine Sepsis Registry Study Group. A multicenter, prospective validation study of the Japanese Association for Acute Medicine disseminated intravascular coagulation scoring system in patients with severe sepsis. Crit Care 2013;17:R111.
[12] Hayakawa M, Yamakawa K, Saito S, Uchino S, Kudo D, Iizuka Y, et al. Japan Septic Disseminated Intravascular Coagulation (JSEPTIC DIC) study group. Recombinant human soluble thrombomodulin and mortality in sepsis-induced disseminated intravascular coagulation. A multicentre retrospective study. Thromb Haemost 2016;115:1157–66.
[13] Hayakawa M, Ono K. A summary of the Japan septic disseminated intravascular coagulation study. Acute Med Surg 2018;5:123–8.
[14] Bakhtiari K, Meijers JC, de Jonge E, Levi M. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. Crit Care Med 2004;32:2416–21.
[15] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644–55.
[16] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–29.
[17] Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study: Working group on sepsis-related problems of the European Society of Intensive Care Medicine. Crit Care Med 1998;26:1793–800.
[18] Angstwurm MW, Dempfle CE, Spannagl M. New disseminated intravascular coagulation score: a useful tool to predict mortality in comparison with Acute Physiology and Chronic Health Evaluation II and Logistic Organ Dysfunction scores. Crit Care Med 2006;34:314–20.
[19] Dhainaut JF, Yan SB, Joyce DE, Pettila V, Basson B, Brandt JT, et al. Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. J Thromb Haemost 2004;2:1924–33.
[20] Ogura H, Gando S, Saitoh D, Takeyama N, Kushimoto S, Fujishima S, et al. Japanese Association for Acute Medicine Sepsis Registry (JAAMSR) study Group. Epidemiology of severe sepsis in Japanese intensive care units: a prospective multicenter study. J Infect Chemother 2014;20:157–62.
[21] Ha SO, Park SH, Hong SB, Jang S. Performance Evaluation of five Different Disseminated Intravascular Coagulation (DIC) Diagnostic Criteria for predicting Mortality in patients with Complicated Sepsis. J Korean Med Sci 2016;31:1838–45.
[22] Thiele T, Selleng K, Selleng S, Greinacher A, Bakchoul T. Thrombocytopenia in the intensive care unit-diagnostic approach and management. Semin Hematol 2013;50:239–50.
[23] Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. Br J Haematol 2009;145:24–33.
[24] Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med 2015;372:1629–38.
[25] Vincent JL, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: time for change. Lancet 2013;381:774–5.
[26] Churpek MM, Zadravecz FJ, Winslow C, Howell MD, Edelson DP. Incidence and prognostic value of the systemic inflammatory response syndrome and organ dysfunctions in ward patients. Am J Respir Crit Care Med 2015;192:958–64.
[27] Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Sepsis definitions task force. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:775–87.
[28] Takemitsu T, Wada H, Hatada T, Ohmori Y, Ishikura K, Takeda T, et al. Prospective evaluation of three different diagnostic criteria for disseminated intravascular coagulation. Thromb Haemost 2011;105:40–4.
[29] Dempfle CE. Comparing DIC scores: not an easy task indeed. Thromb Res 2009;124:651–2.
[30] Delabranche X, Boisrame-Helms J, Asfar P, Berger A, Mootien Y, Lavigne T, et al. Microparticles are new biomarkers of septic shock-induced disseminated intravascular coagulopathy. Intensive Care Med 2013;39:1695–703.
[31] Ishikura H, Nishida T, Murai A, Nakamura Y, Irie Y, Tanaka J, et al. New diagnostic strategy for sepsis-induced disseminated intravascular coagulation: a prospective single-center observational study. Crit Care 2014;18:R19.
[32] Iba T, Di Nisio M, Thachil J, Wada H, Asakura H, Sato K, et al. Revision of the Japanese Association for Acute Medicine (JAAM) disseminated intravascular coagulation (DIC) diagnostic criteria using antithrombin activity. Crit Care 2016;20:287.
[33] Yamakawa K, Umemura Y, Hayakawa M, Kudo D, Sanui M, Takahashi H, et al. Japan Septic Disseminated Intravascular Coagulation (J-Septic DIC) study group. Benefit profile of anticoagulant therapy in sepsis: a nationwide multicentre registry in Japan. Crit Care 2016;20:229.