Thrombosis Research 178 (2019) 182–188

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full length article

Role of disseminated intravascular coagulation in severe sepsis

Satoshi Gando[a,*], Atsushi Shiraishi[b], Kazuma Yamakawa[c], Hiroshi Ogura[d], Daizoh Saitoh[e], Seitaro Fujishima[f], Toshihiko Mayumi[g], Shigeki Kushimoto[h], Toshikazu Abe[i], Yasukazu Shiino[j], Taka-aki Nakada[k], Takehiko Tarui[l], Toru Hifumi[m], Yasuhiro Otomo[n], Kohji Okamoto[o], Yutaka Umemura[d], Joji Kotani[p], Yuichiro Sakamoto[q], Junichi Sasaki[r], Shin-ichiro Shiraishi[s], Kiyotsugu Takuma[t], Ryosuke Tsuruta[u], Akiyoshi Hagiwara[v], Tomohiko Masuno[w], Naoshi Takeyama[x], Norio Yamashita[y], Hiroto Ikeda[z], Masashi Ueyama[aa], Satoshi Fujimi[c], for the Japanese Association for Acute Medicine (JAAM) Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis and Trauma (FORECAST) Study Group (Osamu Tasaki[ab], Yasumitsu Mizobata[ac], Hiraku Funakoshi[ad], Toshiro Okuyama[ae], Iwao Yamashita[af], Toshio Kanai[ag], Yasuo Yamada[ah], Mayuki Aibiki[ai], Keiji Sato[aj], Susumu Yamashita[ak], Susumu Yamashita[al], Kenichi Yoshida[am], Shunji Kasaoka[an], Akihide Kon[ao], Hiroshi Rinka[ap], Hiroshi Kato[aq], Hiroshi Okudera[ar], Eichi Narimatsu[as], Toshifumi Fujiwara[at], Manabu Sugita[au], Yasuo Shichinohe[av], Hajime Nakae[aw], Ryouji Iiduka[ax], Yuji Murata[az], Mitsunobu Nakamura[ay], Yoshitake Sato[ba], Hiroyasu Ishikura[bb], Yasuhiro Myojo[bc], Yasuyuki Tsujita[bd], Kosaku Kinoshita[be], Hiroyuki Yamaguchi[bf], Toshihiro Sakurai[bg], Satoru Miyatake[bh], Takao Saotome[bi], Susumu Yasuda[bj], Toshikazu Abe[bk], Hiroshi Ogura[bl], Yutaka Umemura[bl], Atsushi Shiraishi[bm], Shigeki Kushimoto[bn], Daizoh Saitoh[bo], Seitaro Fujishima[bp], Junichi Sasaki[bp], Toshihiko Mayumi[bq], Yasukazu Shiino[br], Taka-aki Nakada[bs], Takehiko Tarui[bt], Toru Hifumi[bu], Yasuhiro Otomo[bv], Joji Kotani[bw], Yuichiro Sakamoto[bx], Shin-ichiro Shiraishi[by], Kiyotsugu Takuma[bz], Ryosuke Tsuruta[ca], Akiyoshi Hagiwara[cb], Kazuma Yamakawa[cc], Naoshi Takeyama[cd], Norio Yamashita[ce], Hiroto Ikeda[cf], Yasuaki Mizushima[cg], Satoshi Gando[ch])

[a] *Department of Anesthesiology and Critical Medicine, Hokkaido University Graduate School of Medicine, Department of Acute and Critical Care Medicine, Sapporo Higashi Tokushukai Hospital, Japan*
[b] *Emergency and Trauma Center, Kameda Medical Center, Japan*
[c] *Division of Trauma and Surgical Critical Care, Osaka General Medical Center, Japan*
[d] *Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, Japan*
[e] *Division of Traumatology, Research Institute, National Defense Medical College, Japan*
[f] *Center for General Medicine Education, Keio University School of Medicine, Japan*
[g] *Department of Emergency Medicine, School of Medicine, University of Occupational and Environmental Health, Japan*
[h] *Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine, Japan*
[i] *Department of General Medicine, Juntendo University, Health Services Research and Development Center, University of Tsukuba, Japan*
[j] *Department of Acute Medicine, Kawasaki Medical School, Japan*
[k] *Department of Emergency and Critical Care Medicine, Chiba University Graduate School of Medicine, Japan*
[l] *Department of Trauma and Critical Care Medicine, Kyorin University School of Medicine, Japan*
[m] *Department of Emergency and Critical Care Medicine, St. Luke's International Hospital, Japan*
[n] *Trauma and Acute Critical Care Center, Medical Hospital, Tokyo Medical and Dental University, Japan*
[o] *Department of Surgery, Center for Gastroenterology and Liver Disease, Kitakyushu City Yahata Hospital, Japan*
[p] *Division of Disaster and Emergency Medicine, Department of Surgery Related, Kobe University Graduate School of Medicine, Japan*
[q] *Emergency and Critical Care Medicine, Saga University Hospital, Japan*
[r] *Department of Emergency and Critical Care Medicine, Keio University School of Medicine, Japan*
[s] *Department of Emergency and Critical Care Medicine, Aizu Chuo Hospital, Japan*

[*] Corresponding author at: Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine, N15W7, Kita-ku, Sapporo 060-8638, Japan.
E-mail address: gandoicoud@icloud.com (S. Gando).

https://doi.org/10.1016/j.thromres.2019.04.025

Available online 26 April 2019

[t] Emergency & Critical Care Center, Kawasaki Municipal Kawasaki Hospital, Japan
[u] Advanced Medical Emergency & Critical Care Center, Yamaguchi University Hospital, Japan
[v] Center Hospital of the National Center for Global Health and Medicine, Japan
[w] Department of Emergency and Critical Care Medicine, Nippon Medical School, Japan
[x] Advanced Critical Care Center, Aichi Medical University Hospital, Japan
[y] Advanced Emergency Medical Service Center Kurume University Hospital, Japan
[z] Department of Emergency Medicine, Teikyo University School of Medicine, Japan
[aa] Department of Trauma, Critical Care Medicine, and Burn Center, Japan Community Healthcare Organization, Chukyo Hospital, Japan
[ab] Nagasaki University Hospital, Japan
[ac] Osaka City University Hospital, Japan
[ad] Tokyobay Urayasu Ichikawa Medical Center, Japan
[ae] Aso Iizuka Hospital, Japan
[af] Tomei Atsugi Hospital, Japan
[ag] Hiratsuka City Hospital, Japan
[ah] National Hospital Organization Sendai Medical Center, Japan
[ai] Ehime University Hospital, Japan
[aj] Okayama University Hospital, Japan
[ak] Tokuyama Central Hospital, Japan
[al] Fukuyama City Hospital, Japan
[am] JA Hiroshima General Hospital, Japan
[an] Kumamoto University Hospital, Japan
[ao] Hachinohe City Hospital, Japan
[ap] Osaka City General Hospital, Japan
[aq] National Hospital Organization Disaster Medical Center, Japan
[ar] University of Toyama, Japan
[as] Sapporo Medical University, Japan
[at] Okayama Saiseikai General Hospital, Japan
[au] Juntendo University Nerima Hospital, Japan
[av] National Hospital Organization Hokkaido Medical Center, Japan
[aw] Akita University Hospital, Japan
[ax] Japanese Red Cross Society Kyoto Daini Hospital, Japan
[ay] Maebashi Red Cross Hospital, Japan
[az] Sendai City Hospital, Japan
[ba] Subaru Health Insurance Society Ota Memorial Hospital, Japan
[bb] Fukuoka University Hospital, Japan
[bc] Ishikawa Prefectural Central Hospital, Japan
[bd] Shiga University of Medical Science, Japan
[be] Nihon University School of Medicine, Japan
[bf] Seirei Yokohama General Hospital, Japan
[bg] National Hospital Organization Kumamoto Medical Center, Japan
[bh] Saiseikai Utsunomiya Hospital, Japan
[bi] National Hospital Organization Higashi-Ohmi General Medical Center, Japan
[bj] National Hospital Organization Mito Medical Center, Japan
[bk] Tsukuba Medical Center Hospital, Japan
[bl] Osaka University Graduate School of Medicine, Japan
[bm] Kameda Medical Center, Japan
[bn] Tohoku University Graduate School of Medicine, Japan
[bo] National Defense Medical College, Japan
[bp] Keio University School of Medicine, Japan
[bq] University of Occupational and Environmental Health, Japan
[br] Kawasaki Medical School, Japan
[bs] Chiba University Graduate School of Medicine, Japan
[bt] Kyorin University School of Medicine, Japan
[bu] Kagawa University Hospital, Japan
[bv] Tokyo Medical and Dental University, Japan
[bw] Hyogo College of Medicine, Japan
[bx] Saga University Hospital, Japan
[by] Aizu Chuo Hospital, Japan
[bz] Kawasaki Municipal Kawasaki Hospital, Japan
[ca] Yamaguchi University Hospital, Japan
[cb] Center Hospital of the National Center for Global Health and Medicine, Japan
[cc] Osaka General Medical Center, Japan
[cd] Aichi Medical University Hospital, Japan
[ce] Kurume University Hospital, Japan
[cf] Teikyo University School of Medicine, Japan
[cg] Rinku General Medical Center, Japan
[ch] Hokkaido University Graduate School of Medicine, Japan

ARTICLE INFO

Keywords:
Disseminated intravascular coagulation (DIC)
Organ dysfunction
Outcome
Sepsis
Septic shock
Severe sepsis

ABSTRACT

Background: Disseminated intravascular coagulation (DIC) associated with multiple organ dysfunction syndrome (MODS) plays pivotal roles in severe sepsis.
Objectives: We performed a multicenter, prospective data collection study and retrospectively analyzed the data to confirm the role of DIC in severe sepsis.
Methods: Eligible patients were ICU patients who met the definitions of severe sepsis, and 1013 patients were included. DIC scores as well as disease severity and the development of MODS on the day of the diagnosis of

severe sepsis (day 0) and at day 3 were evaluated. The primary outcome was hospital mortality, and MODS on days 0 and 3 was the secondary outcomes.

Results: The overall mortality rate of severe sepsis was 21.5%, and the prevalence of DIC was 50.9% (516/1013). DIC patients were more seriously ill and exhibited a higher prevalence of MODS (32.0% vs. 13.1%) on day 0 and worse mortality rate (24,8% vs. 17.5%) than non-DIC patients. DIC patients also showed a lower survival probability than non-DIC patients (Log rank $p = 0.028$). Logistic regression analyses after propensity score adjustment for potential confounders confirmed a significant association between DIC and MODS and hospital death in the patients with severe sepsis. The new development of DIC and persistent DIC from days 0 to 3 were associated with a high incidence of MODS and low survival probability.

Conclusions: The mortality rate of severe sepsis has been improved; however, DIC is still associated with the poor prognosis of these patients. Evaluating the dynamic changes in the DIC status may improve the prediction capability.

1. Introduction

Innate immune responses consisting of inflammation and immunothrombosis at the site of insults spread into the systemic circulation, which leads to systemic inflammation and disseminated intravascular coagulation (DIC) [1,2]. DIC, defined as dysregulated coagulofibrinolytic responses to insults, is characterized by systemic thrombin generation and endothelial injury, which if sufficiently severe, can induce multiple organ dysfunction syndrome (MODS) [3]. Sepsis has been considered a leading cause of DIC for the past few decades. A prospective study showed that stepwise increases in inflammation from systemic inflammatory response syndrome (SIRS) to sepsis to severe sepsis and septic shock were associated with parallel increases in the prevalence of DIC and organ dysfunctions [4]. Conversely, DIC gives rise to MODS due to microvascular thrombosis and affects the outcome of patients with severe sepsis [1,5].

The incidence of DIC in patients with severe sepsis who were not allocated activated protein C or antithrombin in the retrospective studies of 2 megatrials was 28.9% and 40.7%, and the mortality rates in these patients were 43.0% and 40.9%, respectively [6,7]. A prospective study for the validation of a DIC scoring system showed that the incidence of DIC as diagnosed by International Society on Haemostasis and Thrombosis (ISTH) and Japanese Association for Acute Medicine (JAAM) criteria was 18.1% and 46.8% with mortality rates of 38.1% and 38.4%, respectively [8]. These three studies enrolled patients in the early 2000s and 2010s. However, Levy et al. [9] demonstrated that effective managements of severe sepsis based on the Surviving Sepsis Campaign Guidelines (SSCG) have been associated with marked reduction of hospital mortality.

Therefore, in the present study, we validated the role of DIC in patients with severe sepsis in the era of greatly advanced treatment strategies for this disease.

2. Patients and methods

2.1. Design, setting and ethics approval

This study was prospectively conducted as part of a severe sepsis cohort in the JAAM Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis and Trauma (FORECAST) study [10]. The JAAM FORECAST Sepsis study used consecutive samples from 59 intensive-care units (ICUs) in tertiary hospitals and was conducted from January 2016 to March 2017. The enrolled patients were followed up during their hospital stay. The data collection was performed as a part of routine clinical workup without any interventions, and data management and statistical analyses were processed anonymously. For these reasons, this study was approved by the JAAM and the Ethics Committee of each hospital waiving written informed consent (JAAM, 2014-01; Hokkaido University Graduate School of Medicine, Head institute of the FORECAST group, 014-0306).

2.2. Patients

The JAAM FORECAST Sepsis study recruited adult patients (> 16 years of age) who had been admitted to the ICU when they met the following inclusion criteria of severe sepsis: suspicion of having or a new-onset of infection based on present illness; meeting ≥2 SIRS criteria; and dysfunction of at least one organ, defined by the following criteria: systolic blood pressure < 90 mmHg or mean arterial pressure < 65 mmHg or decreased blood pressure > 40 mmHg from the baseline; serum creatinine > 2.0 mg/dL or diuresis < 0.5 mL/kg/h; total bilirubin > 2.0 mg/dL; platelet count < 100×10^9/L; lactate > 2 mmol/L; prothrombin time International Normalized Ratio (INR) > 1.5; arterial hypoxemia (PaO2/FIO2) < 200 with pneumonia or PaO2/FIO2 < 250 without pneumonia. Patients on end-of-life care or resuscitated from cardiac arrest at the time of the diagnosis of severe sepsis were excluded.

Among patients included in the JAAM FORECAST Sepsis study, the present study further excluded the patients with too many missing values (the threshold for the numbers of missing value was estimated by a 1-sample robust regression with an M estimator) and the patients lacking DIC scores on the day of inclusion.

2.3. Definitions

SIRS, sepsis, severe sepsis and septic shock were defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus conference (Sepsis-1) and its revised version (Sepsis-2) published in 2003 [11,12]. The disease severity of the patients was evaluated according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score. Organ dysfunction was assessed according to the Sequential Organ Failure Assessment (SOFA) score [13]. APACHE II and SOFA scores were evaluated at the time of inclusion. MODS was defined as a SOFA score ≥12 [13]. The Charlson index was used for the assessment of comorbidities and was classified as low (0), medium (1–2), high (3–4) and very high (≥5) [14]. A DIC diagnosis was made by the JAAM DIC diagnostic criteria using prothrombin time INR as a substitute for prothrombin time ratio (Supplementary Table 1) [15]. Overt DIC scores based on the ISTH scoring system were also calculated [3]. The fibrin/fibrinogen degradation product (FDP) was used as the fibrin-related marker for the ISTH criteria. No increase, moderate increase and strong increase were defined as having FDP values of < 10, 10 to < 25, and ≥25 mg/L, respectively.

2.4. Outcomes

The primary outcome was hospital all-cause mortality. The development of MODS on days 0 and 3 was assessed as the secondary outcomes. ICU-free days, ventilator-free days and duration of hospital stay were also recorded as secondary outcomes.

2.5. Data collection

In addition to the collected data for the JAAM FORECAST Sepsis data base, platelet counts as well as coagulation and fibrinolysis variables to establish the DIC diagnosis were prospectively obtained. APACHE II, SOFA, SIRS and DIC scores were assessed on the day of enrollment (day 0). The SOFA, SIRS and DIC scores on day 3 were also recorded.

2.6. Statistical analyses

All measurements are expressed as the median with the 25th–75th interquartile range. Comparisons between two groups were made with Mann-Whitney U-test for continuous variables and either the chi-square test or Fisher's exact test for nominal variables were used when required. To compare multiple groups, the Kruskal-Wallis test and multiple chi-square test with Bonferroni correction were applied. Survival curves were derived according to the Kaplan-Meier method and compared using the Log rank test. The curves were drawn for 60 days, which showed that approximately 80% of patients were discharged.

The relationships between DIC and outcomes were analyzed using a logistic regression analysis with propensity score adjustment for potential confounders. Potential confounders were identified *a priori* to be associated with the prognosis of severe sepsis (age, sex, septic shock, positive blood culture and existence of comorbidity [Charlson score > 1]). Individual organ SOFA scores (central nervous system, cardiovascular, respiration, hepatic and renal systems) except coagulation system were also identified as potential confounders.

Differences with a p value of < 0.05 was considered statistically significant. The IBM SPSS 25.0 for MAC OSX software program(IBM Japan, Tokyo, Japan)was used for the statistical analyses and calculations.

3. Results

3.1. Demographics and patient characteristics

A total of 1,184 patients were registered during the study period. Six registered patients who had missing values exceeding the threshold (> 170) detected by a 1-sample robust regression with M estimator were excluded. In addition, 165 patients were excluded due to missing data on the day 0 DIC score. The other missing data were used as-is without any imputation. The final cohort of 1013 patients were analyzed in the present study. Of these patients, 516 (50.9%) were diagnosed with DIC.

DIC patients were frequently associated with SIRS (989/1013, 97.6%) and showed higher incidences of septic shock and positive blood culture than non-DIC patients. Significant differences in SOFA scores and the prevalence of MODS between the two groups were also observed (Table 1). These serious conditions in DIC patients were associated with a higher hospital mortality rate than in non-DIC patients (24.8% vs. 17.5%, $p = 0.008$). Antithrombin concentrate or recombinant human thrombomodulin was administered to 337 DIC patients. Platelet counts and variables on coagulation and fibrinolysis are presented as Supplementary Table 2.

3.2. Relationships between DIC and MODS and hospital mortality

Kaplan-Meier curves confirmed a lower survival probability in DIC patients than in non-DIC patients (Log Rank $p = 0.028$) (Fig. 1). Table 2 shows that changes in the DIC status from days 0 to 3 (non-DIC, improvement, new development, and continuation of DIC) significantly affected the incidence of MODS and hospital mortality. The new development and continuation of DIC were associated with a high prevalence of MODS on days 0 and 3 and a poor outcome. Fig. 2 supports the results of Table 2, showing that persistent DIC and newly developed DIC conditions during an early phase of severe sepsis markedly reduced the survival probability of the patients (Log Rank $p = 0.000$).

Table 1
Demographics and outcomes of the patients.

	Non-DIC (n = 497)	DIC (n = 516)	p-Value
Age (year)	72(63–81)	72(64–82)	0.960
Male n(%)	318(64.0)	304(58.9)	0.107
Charlson index	1(0–2)	1(0–2)	0.998
Charlson class n			
Low (0)	164	169	
Medium (1–2)	227	236	
High (3–4)	79	80	
Very high (≥5)	27	31	0.981
APACHE II score	21(16–28)	24(18–30)	0.000
SIRS score	3(2–4)	3(3–4)	0.008
SOFA score	7(5–10)	10(7–13)	0.000
MODS day 0 n(%)	65(13.1)	165(32.0)	0.000
MODS day 3 n(%)	49(9.9)	110(21.3)	0.000
DIC score day 0	3(2–4)	5(4–7)	0.000
DIC score day 3	2(1–4)	5(3–6)	0.000
Septic shock n(%)	272(54.7)	362(70.2)	0.000
Positive blood culture n(%)	243(48.9)	343(66.5)	0.000
Lactate (mmol/L)	2.6(1.6–4.7)	3.5(2.2–6.1)	0.000
Duration of hospital stay (days)	22(12–43)	25(13–47)	0.189
ICU-free days	20(11–24)	17(8–23)	0.000
Ventilator-free days	22(4–28)	20(0–28)	0.007
Hospital mortality n(%)	87(17.5)	128(24.8)	0.008

APACHE, Acute Physiology and Chronic Health Evaluation; DIC, disseminated intravascular coagulation; MODS, multiple organ dysfunction syndrome; n, number; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment. Missing data of MODS and DIC score on day 3 (non-DIC and DIC) are (165, 128) and (161, 116), respectively. Measurements are expressed as the median with the 25th–75th interquartile range.

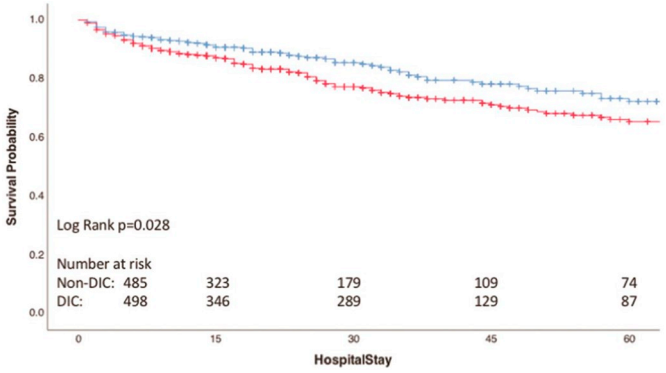

Fig. 1. Kaplan-Meier curves during the first 60 days for the cumulative survival of the patients according to the diagnosis of DIC. Blue line, non-DIC; red line, DIC.

Table 2
Multiple organ dysfunction syndrome, and hospital mortality based on an disseminated intravascular coagulation diagnosis from days 0 to 3.

Changes in DIC	−/−	+/−	−/+	+/+	p-Value
n	266	198	70	201	
MODS day 0 n(%)	24(9.0)	39(19.7)	20(28.6)	76(37.8)	0.000
MODS day 3 n(%)	14(5.3)	14(7.1)	28(40.0)	86(42.8)	0.000
Mortality n(%)	32(12.0)	18(9.1)	22(31.4)	67(33.3)	0.000

DIC, disseminated intravascular coagulation; MODS, multiple organ dysfunction syndrome; n, number; SOFA, sequential organ failure assessment score. −/−, non-DIC both on days 0 and 3; +/−, improvement of DIC on day 3; −/+, new onset of DIC on day 3; +/+, persistent DIC both on days 0 and 3. p-Values are calculated by the Kruskal-Wallis test.

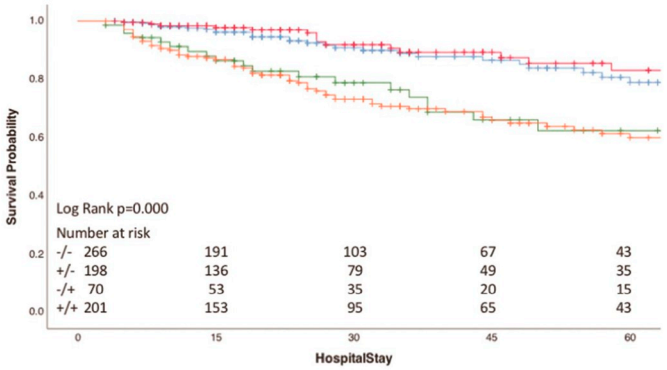

Fig. 2. Kaplan-Meier curves during the first 60 days for cumulative survival. Blue line (–/–), non-DIC patients; red line (+/–), patients whose DIC was improved; green line (–/+), patients who have newly developed DIC; yellow line (+/+), patients whose DIC continued from days 0 to 3.

3.3. Prediction of MODS and the outcome

Logistic regression analyses for MODS or mortality in severe sepsis showed that an established DIC diagnosis in severe sepsis was independently associated with the development of MODS on days 0 and 3 and hospital mortality. The association between the increment in DIC and MODS on days 0 and 3 and death remained significant in a sensitivity analysis with propensity score adjustments which balanced for age, sex, development of septic shock, coexistence of comorbidity (Charlson comorbidity index ≥1), positive blood culture and individual organs SOFA scores except coagulation. Although a DIC diagnosis on day 0 did not independently predicted a patient's death, DIC on day 3 was associated with a poor outcome in patients with severe sepsis (Table 3).

3.4. ISTH overt DIC and severe sepsis

A total of 179 patients (17.7%) with severe sepsis simultaneously met the criteria of the JAAM and ISTH overt DIC on the day of the inclusion. The ISTH overt DIC patients showed a higher incidence of MODS (47.5%) and hospital mortality (30.7%) than non-DIC patients and those who only met the JAAM DIC criteria. The adjusted odds ratio for prediction of hospital death was 1.74 (95% confidence interval 1.158–2.599, $p = 0.008$), which indicated that the simultaneous diagnosis of DIC by both the JAAM and the ISTH overt DIC on the day of the development severe sepsis (day 0) was significantly associated with death of the patients. The results are shown in Supplementary Tables 3 and 4, and Supplementary Fig. 1.

Table 3
Logistic regression analyses for prediction of hospital mortality and multiple organ dysfunction on days 0 and 3.

	Odds ratio	95% confidence interval	*p*-Value
Hospital mortality			
Unadjusted			
DIC day 0	1.26	0.895–1.775	0.185
DIC day 3	3.61	2.367–5.519	0.000
Adjusted			
DIC day 0	1.22	0.876–1.702	0.239
DIC day 3	3.45	2.279–5.227	0.000
MODS day 0			
Unadjusted			
DIC day 0	4.04	2.008–8.131	0.000
Adjusted			
DIC day 0	1.75	1.193–2.553	0.004
MODS day 3			
Unadjusted			
DIC day 0	1.84	1.204–2.822	0.005
DIC day 3	9.72	5.833–16.204	0.000
Adjusted			
DIC day 0	1.67	1.118–2.491	0.012
DIC day 3	7.76	4.840–12.439	0.000

DIC, disseminated intravascular coagulation; MODS, multiple organ dysfunction syndrome. Potential confounders used for propensity score adjustments are described in the Statistical analyses section.

4. Discussion

The overall hospital mortality of severe sepsis in the present study was 21.1%. Although the inclusion criteria differed among the studies, this figure was markedly lower than that in the severe sepsis cohort of 2 previous studies (41.9% and 55.2%) conducted without interventions in the early 2000s [16,17]. Furthermore, the mortality rate was lower than that of our previous severe sepsis study (29.5%) conducted from 2010 to 2011, which used the same inclusion criteria and the patients were treated under SSCG 2008 [18]. This reduction in hospital mortality is considered due to the high compliance rate of the newly proposed 3-hr bundle under SSCG 2012 in our FORECAST study, which suggest the advancement in treatment strategies for severe sepsis between our two severe sepsis cohorts [10,18]. The mortality of DIC patients (24.8%) in the present study was also decreased compared with previous studies [6,7,8,18]. The present study, however, shows that DIC patients are associated with an increased prevalence of MODS and that the mortality rate of the DIC patients is still significantly higher than that of non-DIC patients.

The differences in the incidence of MODS and mortality rate between DIC and non-DIC patients suggest that DIC is a predictor of MODS and death in severe sepsis patients. To confirm this hypothesis, we first constructed Kaplan-Meier curves, which clearly showed a lower survival probability in DIC patients than in non-DIC patients. The relationships between the DIC status and MODS as well as patient's death in the early stage of severe sepsis were then investigated. As shown in Table 2, we confirmed that the new onset of DIC after a diagnosis of severe sepsis and persistent DIC status for 4 days correlated with the development of MODS and a high mortality rate. The results of the Kaplan-Meier analyses shown in Fig. 2 support our findings that dynamic changes in the DIC status, namely new-onset and persistent DIC, predict the marked reduction in the survival probability of severe sepsis.

To validate the association of DIC and the development of MODS and hospital mortality in patients with severe sepsis, logistic regression analyses with propensity score adjustments were applied. Based on the results of these analyses, a DIC diagnosis on the day of the diagnosis of severe sepsis was associated with the development of MODS in patients with severe sepsis. While a DIC diagnosis on day 0 did not predict patient's death, DIC on day 3 was associated with hospital death in patients with severe sepsis, which supports the importance of the repeated evaluation of the DIC status during the early phase of severe sepsis. Given that both DIC and severe sepsis are dynamic conditions, these findings underscore the need for the series assessment of DIC scores [3,8].

The main finding of the present study is that DIC showed a significant association with the development of MODS and a poor prognosis of severe sepsis after adjusting for individual organ SOFA scores. These results suggest that DIC rather than individual organ dysfunction is correlated with MODS and associated with a poor outcome among patients with severe sepsis. Our previous study [18] showed that, in addition to DIC, the patient age, septic shock, cardiovascular SOFA, and comorbidity were associated with hospital death in severe sepsis patients. In the present study, however, the significant odds ratio of DIC after adjusting for the propensity score using these variables as potential confounders indicated that DIC is the most important predictor of a poor outcome among these confounders in patients with severe sepsis. Furthermore, the results presented in Table 3 and Fig. 2 suggest that

persistent DIC is more important predictor of mortality than DIC at the time of diagnosis in patients with severe sepsis.

Similar to non-overt DIC, the JAAM DIC definition used in the present study has been used to diagnose DIC that is not yet at the stage of severe decompensation [15]. In contrast, the ISTH overt-DIC scoring system diagnoses full-blown DIC with decompensation [3,15]. As a result, the current study showed a higher mortality rate in patients who met the criteria for ISTH DIC than in those who met the JAAM DIC criteria. In addition, the diagnosis of overt DIC on the day of the diagnosis of severe sepsis was associated with patient death (Odds ratio, 1.74; $p = 0.008$) in those with severe sepsis. These results suggest that the application of both diagnostic criteria for the patients with severe sepsis may be useful for identifying patients who need more careful management of DIC.

Several limitations associated with the present study warrant mention. First, this was a retrospective analysis of prospective data collection. Second, missing data on day 3 may have resulted in selection and immortal time biases. Third, during study period, a new definition and diagnostic criteria for sepsis (Sepsis-3) were announced [19]. Recent study suggests that this new definition and diagnostic criteria of sepsis may select more serious sepsis patients than those diagnosed using the previous criteria, Sepsis-1 and Sepsis-2, used in the present study [20]. Therefore, the role of DIC in the sepsis patients diagnosed by the new Sepsis-3 may be different from the role of DIC diagnosed with the Sepsis-1 and Sepsis-2. Therefore, validating the roles of DIC in sepsis diagnosed with the new Sepsis-3 criteria will be mandatory.

Despite these limitations, our study suggests that DIC remains a condition that must be treated in order to further improve the prognosis of severe sepsis patients [21].

5. Conclusions

The present study demonstrated that although the outcome of the patients with severe sepsis has been greatly improved over the past two decades, DIC is still associated with the development of MODS and hospital death of these patients. In addition to having a DIC diagnosis on the day of the diagnosis of severe sepsis, dynamic changes in the DIC condition may improve the prediction capability.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.04.025.

Declaration of interest

None.

Authorship contribution statement

S. Gando analyzed the data, interpreted the results, drafted the figures and tables and wrote the manuscript. A. Shiraishi checked the statistics, interpreted the results, and critically inspected the manuscript. K. Yamakawa gave advice on the analytical methods, interpreted the results and critically inspected the manuscript. A. Shiraishi, H. Ogura, D. Saitoh, S. Fujishima. T. Mayumi, S. Kushimoto and T. Abe designed the study and organized the data collection and critically inspected the manuscript. The other authors contributed to the design of the study, organization of data collection, drafting of database charts and scientific discussion of all of the processes of the study as well as reviewed the manuscript and registered the patients. All authors approved the final version of the manuscript.

Financial support

This work was supported by the JAAM.

Disclosure of conflict of interests

The authors state that they have no conflict interest regarding this manuscript.

Acknowledgements

The JAAM FORECST Study Group thanks to Shuta Fukuda for his special assistance in completing the study. The JAAM FORECST Study Group also thanks Professor Toshiaki Iba for his valuable advice on this project.

Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
DIC	disseminated intravascular coagulation
FDP	fibrin fibrinogen degradation products
ISTH	International Society on Thrombosis and Haemostasis
JAAM	Japanese Association for Acute Medicine
MODS	multiple organ dysfunction syndrome
SIRS	systemic inflammatory response syndrome
SOFA	sequential organ failure assessment
SSCG	Surviving Sepsis Campaign Guidelines

References

[1] Gando S, Levi M, Toh CH. Disseminated intravascular coagulation. Nat Rev. Dis Prim 2016; 2:1–16.
[2] B. Engelmann, S. Massberg, Thrombosis as an intravascular effector of innate immunity, Nat Rev. Immunol 13 (2013) 34–45.
[3] F.B.J. Taylor, C.H. Toh, W.K. Hoots, H. Wada, M. Levi, Toward definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation, Thromb Haemost 86 (2001) 1327–1330.
[4] M.S. Rangel-Frausto, D. Pittet, M. Costigan, T. Hwang, C.S. Davis, R.P. Wenzel, The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study, JAMA 273 (1995) 117–123.
[5] N. Semeraro, C.T. Ammollo, F. Semeraro, M. Colluci, Sepsis, thrombosis and organ dysfunction, Thromb Res 129 (2012) 290–295.
[6] J.F. Dhainaut, S.B. Yan, D.E. Joyce, V. Pettiiä, B. Basson, J.T. Brandt, D.P. Sundin, M. Levi, Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation, J Thromb Haemost 2 (2004) 1924–1933.
[7] J. Kienast, M. Juers, C.J. Wiedermann, J.N. Hoffmann, H. Ostermann, R. Strauss, H.O. Keinecke, B.L. Warren, Opal SM for the Kybersept investigators, Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation, J Thromb Haemost 4 (2006) 90–97.
[8] Gando S, Saitoh D, Ogura H, Fujishima S, Mayumi T, Araki T, Ikeda H, Kotani J, Kushimoto S, Miki Y, Shiraishi S, Suzuki K, Suzuki Y, Takeyama N, Takuma K, Tsuruta R, Yamaguchi Y, Yamashita N, Aikawa N, Japanese Association for Acute Medicine Sepsis Registry (JAAMSR) 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.
[9] M.M. Levy, A. Rhodes, G.S. Phillips, S.R. Townsend, C.A. Schorr, R. Beale, T. Osborn, S. Lemeshow, J.D. Chiche, A. Artigas, R.P. Dellinger, Surviving sepsis campaign: Association between performance metrics and outcomes in a 7.5-year study, Crit Care Med 43 (2015) 3–12.
[10] T. Abe, H. Ogura, A. Shiraishi, S. Kushimoto, D. Saitoh, S. Fujishima, T. Mayumi, Y. Shiino, T. Nakada, T. Tarui, T. Hifumi, Y. Otomo, K. Okamoto, Y. Umemura, J. Kotani, Y. Sakamoto, J. Sasaki, S. Shiraishi, K. Takuma, R. Tsuruta, et al., Characteristics, patterns of care, and in-hospital mortality for patients with severe sepsis in ICUs in Japan: The FORECAST study, Crit Care 22 (2018) 322.
[11] Members of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference committee: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definition for sepsis and organ failure and guidelines for the use innovative therapies in sepsis. Crit Care Med 1992; 20:864–74.
[12] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal S, Vincent JL, Ramsey G for the International Sepsis Definition Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31:1250–6.
[13] F.L. Ferreira, D.P. Bota, A. Bross, C. Mélot, J.L. Vincent, Serial evaluation of the SOFA score to predict outcome in critically ill patients, JAMA 286 (2001) 1754–1758.
[14] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J Chronic Dis 40 (1987) 373–383.

[15] Gando S, Saitoh D, Ogura H, Mayumi T, Koseki K, Ikeda T, Ishikura H, Iba T, Ueyama M, Eguchi Y, Otomo Y, Okamoto K, Kushimoto S, Endo S, Shimazaki S; Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) Study Group. Natural history of disseminated intravascular coagulation diagnosed based on the newly established diagnostic criteria for critically ill patients: Results of a multicenter, prospective survey. Crit Care Med 2008; 36:145–50.

[16] C. Brun-Buison, P. Meshaka, P. Pinton, B. Vallet, EPISEPSIS Study Group, EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units, Intensive Care Med 30 (2004) 580–588.

[17] C. Engel, F.M. Brunkhorst, H.G. Bone, R. Brunkhorst, H. Gerlach, S. Grond, M. Gruendling, G. Huhle, U. Jaschinski, S. John, K. Mayer, M. Oppert, D. Olthoff, M. Quintel, M. Ragaller, R. Rossaint, F. Stuber, N. Weber, T. Welte, H. Bogatsch, et al., Epidemiology of sepsis in Germany: results from a national prospective multicenter study, Intensive Care Med 33 (2007) 606–618.

[18] Ogura H, Gando S, Saitoh D, Takeyama N, Kushimoto S, Fujishima S, Mayumi T, Araki T, Ikeda H, Kotani J, Miki Y, Shiraishi S, Suzuki K, Suzuki Y, Takuma K, Tsuruta R, Yamaguchi Y, Yamashita N, Aikawa N; 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.

[19] M. Singer, C.S. Deutschman, C.W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, R. Bellomo, G.R. Bernard, J.D. Chiche, C.M. Coopersmith, R.S. Hotchkiss, M.M. Levy, J.C. Marshall, G.S. Martin, S.M. Opal, G.D. Rubenfeld, T. van der Poll, J.L. Vincent, D.C. Angus, The third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA 315 (2016) 801–810.

[20] S.M. Fernand, A. Tran, M. Taljaard, Y. Cheng, B. Rochwerg, A.J.E. Seely, J.J. Perry, Prognostic accuracy of the quick sequential organ failure assessment for mortality in patients with suspected infection. A systematic review and meta-analysis, Ann Intern Med 168 (2018) 266–275.

[21] M. Levi, M. Scully, How I treat disseminated intravascular coagulation, Blood 131 (2018) 845–854.