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著者	Daisuke Kudo, Shigeki Kushimoto, Noriko Miyagawa, Tetsuya Sato, Masatsugu Hasegawa, Fumihito Ito, Sathoshi Yamanouchi, Hiroyuki Honda, Kohkichi Andoh, Hajime Furukawa, Yasuo Yamada, Yuta Tsujimoto, Manabu Okuyama
journal or publication title	Journal of Critical Care
volume	45
page range	178-183
year	2018-03-07
URL	http://hdl.handle.net/10097/00125826

doi: 10.1016/j.jcrc.2018.03.011

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The Impact of Organ Dysfunctions on Mortality in Patients with Severe Sepsis: A Multicenter Prospective Observational Study

Authors and Institutions

Daisuke Kudo[a,b], Shigeki Kushimoto[a,b], Noriko Miyagawa[b], Tetsuya Sato[a,b], Masatsugu Hasegawa[c], Fumihito Ito[d], Sathoshi Yamanouchi[e], Hiroyuki Honda[f], Kohkichi Andoh[g], Hajime Furukawa[h], Yasuo Yamada[i], Yuta Tsujimoto[j], Manabu Okuyama[k]

[a]Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan

[b]Department of Emergency and Critical Care Medicine, Tohoku University Hospital, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan

[c]Department of Emergency Center, Hachinohe City Hospital, 1 Bisyamontaira, Ojitamukaiaza, Hachinohe 031-8555, Japan

[d]Department of Emergency and Critical Care Medicine, Ohta General Hospital Foundation, Ohta Nishinouchi Hospital, 2-5-20 Nishinouchi, Koriyama 963-8558, Japan

[e]Department of Emergency and Critical Care Medicine, Osaki Citizen Hospital, 3-8-1 Furukawahonami, Osaki 989-6183, Japan

[f]Department of Advanced Disaster Medicine and Emergency Critical Care Center, Niigata University Medical and Dental Hospital, 1-757 Asahimachi-Dori, Chuo-ku, Niigata, 951-8510, Japan

[g]Emergency and Critical Care Department, Sendai City Hospital, 1-1-1 Asutonagamachi, Taihaku-ku, Sendai 982-8502, Japan

[h]Department of Emergency Medicine, South Miyagi Medical Center, 38-1 Nishi, Ogawara,

Shibata-gun 989-1253, Japan

[i]Department of Emergency Medicine, Sendai Medical Center, 2-8-8 Miyagino, Miyagino-ku, Sendai 983-8520, Japan

[j]Department of Emergency and Critical Care Medicine, Yamagata Prefectural Central Hospital, 1800 Aoyagi, Oaza, Yamagata 990-2292

[k]Department of Critical Care Medicine, Akita University Hospital, 44-2 Hasunuma, Hiroomoteaza, Akita 010-8543, Japan

E-mail addresses

Daisuke Kudo: kudodaisuke@med.tohoku.ac.jp

Shigeki Kushimoto: kussie@emergency-medicine.med.tohoku.ac.jp

Noriko Miyagawa: m-noriko@hosp.tohoku.ac.jp

Tetsuya Sato: t23jor@yahoo.co.jp

Masatsugu Hasegawa: hasegawamasatsugu@gmail.com

Fumito Ito: fleurs_de_cerisier87@yahoo.co.jp

Sathoshi Yamanouchi: y-3104@yc4.so-net.ne.jp

Hiroyuki Honda: h.honda0914@gmail.com

Kokichi Ando: ko.andoh@gmail.com

Hajime Furukawa: fhajime@ac.auone-net.jp

Yasuo Yamada: yamada-y@xa3.so-net.ne.jp

Yuta Tsujimoto: loadandgoyuta22@me.com

Manabu Okuyama: okuyamanabu@med.akita-u.ac.jp

Corresponding author

Daisuke Kudo, M.D., Ph.D.

Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine

1-1 Seiryo-machi Aoba-ku, Sendai 980-8574, Japan

TEL: +81-22-717-7489

FAX: +81-22-717-7492

E-mail: kudodaisuke@med.tohoku.ac.jp

[1]Abbreviations

[1] AECC, American–European Consensus Conference; AKI acute kidney injury; AKIN, Acute Kidney Injury Network; ALI, acute lung injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; CI, confidence interval; DIC, disseminated intravascular coagulations; HR, hazard ratio; ICU, intensive care units; IRB, Institutional Review Board; JAAM, Japanese Association of Acute Medicine; KDIGO, Kidney Disease: Improving Global Outcomes; OR, odds ratio; RRT, renal replacement therapy; RIFLE, Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease; SOFA, Sequential Organ Failure Assessment.

Abstract

Purpose: Disseminated intravascular coagulations (DIC), acute respiratory distress syndrome (ARDS), and acute kidney injury (AKI) are major organ dysfunctions that occur in patients with sepsis. This study aimed to elucidate the impact of these organ dysfunctions on mortality in patients with severe sepsis.

Material and Methods: A prospective observational study was performed in 10 ICUs to obtain data from patients with severe sepsis. Multivariate analyses to examine in-hospital mortality were performed.

Results: Data of 573 patients were analyzed. In-hospital mortality rate was 19.4% (111/573). The incidences of DIC, ARDS, and AKI were 58.4%, 18.7%, and 41.7%, while the associated mortality rates were 28.9%, 36.4%, and 31.8%, respectively. In multiple regression model, DIC (odds ratio 2.71, 95% confidence interval [CI] 1.45-5.27) and AKI stage 3 (odds ratio 1.98, 95%CI 1.07-3.63) were significantly associated with higher in-hospital all-cause mortality. DIC (hazard ratio 2.58, 95%CI 1.53-4.55) and AKI stage 3 (hazard ratio 1.73, 95%CI 1.07-2.80) were also significantly associated with longer survival durations. However, severe ARDS was not associated with these outcomes.

Conclusions: DIC and AKI are frequent complications in patients with severe sepsis. In this study, DIC, and AKI stage 3 were independent risk factors of in-hospital mortality.

Key words

Sepsis, acute respiratory distress syndrome, acute kidney injury, disseminated intravascular coagulation, organ dysfunction

Funding

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

Conflicts of interest: none

Introduction

Organ dysfunctions, such as disseminated intravascular coagulations (DIC), acute respiratory distress syndrome (ARDS), and acute kidney injury (AKI) are common complications in patients with sepsis [1]. Although the incidences of these complications varies depending on the clinical criteria, 30-50% of patients with severe sepsis have DIC complications with mortality rates from 35-40%, which was twice as high as compared with patients without DIC [2-6]. Reports have shown that 32.7% of patients with severe sepsis (mortality rate, 41.2%) fulfilled the criteria of ARDS as defined by the American–European Consensus Conference (AECC) in 1994 [7, 8]. However, the rate of sepsis patients with ARDS complications according to the Berlin definition was not reported [9]. A recent report showed that the rates of AKI complications in patients with severe sepsis were 72-88% while the mortality rates were

25-39% [10]. Although the incidences and mortality rates of these organ dysfunctions in patients with sepsis were high, the reported incidences varied, and the differences have not been fully clarified.

Sequential Organ Failure Assessment (SOFA) score is an assessment system for the severity of organ dysfunctions, it creates scores for the respiratory, nervous, and cardiovascular systems, as well as the liver, renal and coagulation functions [11]. SOFA score has a good predictive ability for in-hospital mortality in patients with suspected infections in intensive care units (ICU) [12]. In the updated definition of sepsis (Sepsis-3), organ dysfunction is defined as an acute increase in SOFA score of 2 points or more [13]. Although there are established conceptual and clinical definitions for DIC (including Japanese Association of Acute Medicine (JAAM) criteria for DIC [14] and International Society on Thrombosis and Hemostasis criteria for DIC [15]), ARDS (the Berlin definition for ARDS [9]), and AKI classifications (Acute Kidney Injury Network (AKIN) [16] and Kidney Disease: Improving Global Outcomes (KDIGO) [17]), these differ from their respective SOFA scores. Furthermore, the incidence and outcome of organ dysfunctions complicating sepsis have not been fully elucidated whereas, septic shock, has established definitions and has also been well examined [18].

The aim of the current study was to determine the impact of the individual organ dysfunctions (DIC, ARDS and AKI) on mortality in patients with severe sepsis.

Materials and methods

All data were retrieved from a database named Tohoku Sepsis Registry (UMIN000010297 [University hospital Medical Information Network Clinical Trials Registry]). Data were collected using a prospective observational study design. The study was conducted by 10 institutes, three university hospitals, and seven community hospitals, in Tohoku District, northern part of Japan. The Institutional Review Board (IRB) of each institution approved the study. All IRBs waived the need for informed consent due to the observational study design requiring no treatments beyond the daily clinical practice according to the Japanese guideline (Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labour and Welfare, Japan. Ethical Guidelines for Medical and Health Research Involving Human Subjects. March 2015).

Patient selection and data collection

The Tohoku Sepsis Registry prospectively registered consecutive patients admitted to ICUs with severe sepsis and patients having severe sepsis after admission to ICUs or general wards from January to December 2015. Severe sepsis and septic shock were defined according to the International Sepsis guidelines 2012 [19]. Patients aged < 18 years were excluded from the current analyses. Information were collected from the registry and used in the current analyses. Such information includes age, sex, unit where sepsis was diagnosed, pre-existing diseases, medications before admission, septic shock

or not. Further, information were also collected on Acute Physiology and Chronic Health Evaluation (APACHE) II score [20], SOFA score [11] (upon admission), primary infection site, blood culture findings, time from diagnosis to antimicrobial administration, and interventions for source control. Others were, vital signs, results of laboratory tests on day 1 and 4, and co-existing conditions (DIC, ARDS, and AKI). Treatment information included, treatment for shock, treatment with drugs including anticoagulants for DIC, immunoglobulins, and sivelestat, renal replacement therapy (RRT), RRT for non-renal indications, polymyxin B-immobilized fiber column direct, and hemoperfusion; data on durations of ICU and hospital stays, in-ICU and in-hospital outcomes were also retrieved.

Definitions and measurements

The severity of DIC was assessed using the JAAM scoring algorithm for DIC [14]. Based on the JAAM criteria (JAAM-DIC), patients were considered as having DIC if they had scores ≥ 4 on day 1 and/or day 4. ARDS was diagnosed on day 1 and/or day 4 by the Berlin definitions [9]. AKI was diagnosed using the AKIN criteria from day 1 through day 3 (AKIN criteria required, at the maximum, creatinine levels in three consecutive days, or 24h urine output) [16]. The numbers of ICU- and hospital-free days within a 28- and 90-day period were calculated by subtracting the duration of the ICU- or hospital-stay from 28 and 90 days, respectively. If a patient died before discharge from the ICU or hospital, the ICU- or hospital- free days were calculated as

zero.

The main outcome measurement was all-cause in-hospital mortality.

Statistical analysis

Categorical and continuous variables were expressed as counts (%), or median (interquartile range). Missing values were excluded from each analysis. Values were compared using Pearson's chi-square test for the categorical variables, the Mann-Whitney U test for the continuous variables between two groups and the Kruskal-Wallis test among three groups. Independent factors associated with in-hospital mortality rate and survival duration were examined using multivariate logistic regression analysis and Cox hazard regression model, respectively. In the regression models, the following confounders were adjusted for: age, gender, and several factors that showed significant differences between survivors and non-survivors at univariate analysis. Data were analyzed using JMP® Pro Version 11.0 software (SAS Institute Japan Ltd., Tokyo, Japan). All statistical tests were two-sided and $P < 0.05$ was considered as having a significant difference.

Results

Six hundred and sixteen patients were enrolled in the Tohoku Sepsis Registry. Forty-three patients withdrew from the aggressive treatment within 4 days of the diagnosis of sepsis and were thus excluded. The data for 573 patients were analyzed in

the current study (Figure 1).

Demographics, severity and mortality of the patients

The median age was 74 (64-83) years and 62% of the patients were male. Median APACHE II and SOFA scores were 20 (15-26) and 8 (5-11), respectively. The comparison of demographics and severity of sepsis in survivors and non-survivors are shown in Table 1. The proportion of non-survivor patients diagnosed as severe sepsis in the general wards and ICUs was higher than the emergency department. The proportions of survivors and non-survivors with pre-existing diseases were similar. The proportion of patients who took steroids and immunosuppressant drugs as daily medications before admission was higher in non-survivors than survivors. The scores of APACHE II, SOFA, and JAAM-DIC were higher in non-survivors than survivors. The non-survivors were more likely to have had septic shock. Overall, patients' 28-day mortality was 12.4% (71/573) while the in-hospital all-cause mortality was 19.4% (111/573) (Table 2). The data on infection management, circulation management (for resuscitation), anticoagulant therapies, and other additional therapies are shown in supplemental Tables 1, 2 and 3, respectively.

Organ dysfunctions

The incidences of DIC, ARDS, and AKI in patients with severe sepsis were 225/385 (58.4%, 188 cases were missing the values for both fibrin degradation products

and D-dimer required for calculating JAAM-DIC score), 107/573 (18.7%), and 239/573 (41.7%), respectively (Table 1). The non-survivors were more likely to have had organ dysfunctions (DIC, ARDS and AKI), compared with the survivors. In-hospital mortality rates of patients complicated with DIC, ARDS, and AKI were 28.9%, 36.4%, and 31.8%, respectively (Table 2). The patients with these organ dysfunctions had two- to three-fold higher mortality rates than those without complications ($P < 0.05$ for DIC, ARDS, and AKI). Patients with more severe stages of complications or organ dysfunctions had higher mortality rates, 51.4% in patients with severe ARDS and 37.9% in patients with AKI stage 3 (there were no statistically significant differences between severity levels with either ARDS or AKI).

Impact of organ dysfunctions on in-hospital mortality

In addition to age and gender, nine factors and covariates which showed significant differences between the survivors and non-survivors in univariate analysis were included in the multiple and Cox hazard regression models for in-hospital mortality. Among the organ dysfunctions (including their severity levels), in the multiple regression model, JAAM-DIC (odds ratio [OR] 2.71, 95% confidence interval [CI] 1.45 – 5.27) and AKI stage 3 (OR 1.98, 95% CI 1.07 – 3.63) were significantly associated with higher in-hospital all-cause mortality, while severe ARDS was not (Table 3). In Cox hazard regression model, JAAM-DIC (hazard ratio [HR] 2.58, 95% CI 1.53 – 4.55) and AKI stage 3 (HR 1.73, 95% CI 1.07 – 2.80) were also significantly associated with

shorter survival duration, while severe ARDS was not (Table 4). When all ARDS patients (mild, moderate, and severe ARDS) was included as an explanatory variable instead of severe ARDS patients, the odds ratio of ARDS with in-hospital mortality was not statistically significant, neither in the logistic regression model (OR 1.13, 95%CI 0.58-2.15) nor the Cox hazard regression model (HR 0.94, 95%CI 0.57-1.53). Figure 2 shows the survival curves comparing the patients with and without DIC, severe ARDS, and AKI stage 3 (P<0.001, <0.001, and <0.001 respectively, by log-rank test).

Discussion

In the present study, we determined the incidences of DIC, AKI, ARDS and associated mortality rates in patients with severe sepsis. The incidences of DIC and AKI were high while that of ARDS was low (58.4%, 41.7%, and 18.7%, respectively); the associated mortality rates were high (28.9 %, 31.8% and 36.4%, respectively) In addition, DIC and AKI stage 3 were significantly associated with worse in-hospital mortality and survival duration. To the best of our knowledge, this is the first report comparing the incidences and effects on mortality rate of organ dysfunctions in patients with sepsis in the same cohort.

In the current study, the incidence of DIC was 58.4%. This was slightly higher than that reported previously (30-50%) [2-6]. The mortality rate in patients with DIC was 28.9%, and was more than twice as high as those without DIC (11.9%) in the present

study. However, the mortality rate in patients with DIC in the present study was lower than that reported previously (35-40%) [2-6]. In the current cohort, 186/573 (32.5%) of patients took anticoagulant therapy including thrombomodulin, antithrombin, protease inhibitors, or the combination of these anticoagulants.

Incidences (42-78%) and mortality rates (30-70%) in septic patients with AKI varied in previous reports [20-24]. One reason for this might be the severity of sepsis in subjects in each study. Some studies focused on patients with sepsis based on the definition by the International Sepsis Definitions Conference in 2001 [25] which included sepsis without organ dysfunction, while other studies focused only on patients with septic shock. Another reason might be the definitions and classifications of AKI. In previous reports [20-24], the Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease (RIFLE) criteria [26] or original criteria other than RIFLE, AKIN, and KDIGO were used. Recently, the incidence and mortality rates in patients with severe sepsis complicating AKI classified by RIFLE, KDIGO, and AKIN were compared [10]. The incidences showed slight differences (73-88%) between the classifications, while the mortality rates were similar among the classifications (35-38%). According to Pereira et al., the incidence in patients classified using AKIN was 72.8% while the mortality rate was 38.3% [10]. Our study focused on patients with severe sepsis, and AKI was classified using AKIN. Our findings were based on the same classification as in the study by Pereira et al [10]. However, in our study, the incidence (41.7%) was much lower, while our mortality rate (31.8%) was similar

compared to those reported by Pereira et al [10]. Therefore, further cohort study is needed to determine the exact incidence of AKI complicating severe sepsis using the same definition and classification of sepsis and AKI.

Fujishima et al. [8] reported the incidence and mortality rate of the acute lung injury (ALI) and ARDS defined by the AECC in 1994 [7]. In this report, incidences of ALI and ARDS were 40.2% and 32.7% while the mortality rates were 38.6% and 41.2%, respectively. In the current study, ARDS was defined using an updated definition (the Berlin definition) [9], and the incidence of ARDS (including mild to severe ARDS) was 18.7% while the mortality rate was 36.4%. The incidence of ARDS was much lower in the current study than that reported by Fujishima et al. [8], although the definition of ARDS was not so much different, while the mortality was similar in both studies.

Currently, organ dysfunction is much emphasized in the updated definition of sepsis, and SOFA score is applied in the diagnostic criteria of sepsis [13]. However, the effect of each organ dysfunction on mortality has not been fully considered. The present study provided the novel aspect of organ dysfunctions on the outcomes in patients with sepsis. JAAM-DIC and AKI stage 3 were independent risk factors of higher in-hospital mortality and were also associated with shorter survival durations, while severe ARDS was not, in the current study. The statistical power may not have been strong enough to reach the significance level because of the small sample size of only 37 patients complicated with severe ARDS in the current cohort. Further cohort study is needed to

clarify the impact of ARDS, especially severe ARDS, on patients with sepsis.

Based on the findings in our study, DIC and AKI stage 3 are possible risk factors for in-hospital mortality in patients with sepsis. However, preventions and early specific treatments targeting these organ dysfunctions other than the general management of patients with sepsis have not been established. Anticoagulation therapies may have survival benefit for patients with sepsis-induced DIC according to a meta-analysis, however, this has not yet been established [27, 28]. For the prevention of AKI, hydroxyethyl starch should be avoided in fluid therapy [29]. There is no high level evidence for pharmacological and blood purified therapies for AKI [30]. It is therefore necessary to develop effective preventions and specific treatments for these organ dysfunctions.

Limitations

There are some limitations of the current study. First, the definition of sepsis was not according to the new definition presented in 2016 [13], since the current study was conducted earlier (2015). The results may differ if the new definition of sepsis is applied for the inclusion criteria. Second, the number of patients in the current cohort was not large enough to conclude about the incidences of complications (organ dysfunctions) of sepsis, especially, the incidence of ARDS. Due to the small number of patients, fewer explanatory variables were applied in the multivariate analysis. Third, using KDIGO for

the definition of AKI complicated with sepsis has not been confirmed in any guidelines or consensus meeting. Although Bellomo et al. recommended the use of KDIGO for the definition of AKI in patients with sepsis [30], not KDIGO, but AKIN was used in the current study because the current study was commenced before the KDIGO criteria announcement [31]. Moreover, the creatinine levels in 7 consecutive days are necessary to diagnose AKI by KDIGO criteria; however, creatinine levels on days 5 to 7 were not collected in the current study. Therefore, we could not apply the KDIGO criteria to our subjects. Pereira et al. showed that the incidence of AKI in patients with sepsis according to KDIGO was higher than that according to AKIN (87.5% vs. 72.8%), while in-hospital mortality for AKI was not different between KDIGO and AKIN in sepsis patients (35.8% vs. 38.3% in any category and 48.3% vs. 56.6% in stage 3) [10]. Therefore, further cohort study, collecting data from a greater number of patients and using KDIGO criteria to diagnose AKI, is needed to conclude on the impact of organ dysfunctions on sepsis.

Conclusions

In this study, the incidence of DIC and AKI was high and that of ARDS was low in patients with severe sepsis. In addition, DIC and AKI stage 3 were observed to be the independent risk factors of in-hospital mortality in patients with sepsis. Based on these findings, it is therefore necessary to establish effective early prevention and specific therapeutic strategies for these organ dysfunctions in the management of patients with sepsis.

Acknowledgements

The other Tohoku Sepsis Registry investigators also contributed to the collection and assessment of the data at each institution. The authors are grateful to S. Osaki for data management and administrative support and T. Ishigaki (Tohoku University Graduate School of Economics and Management) for advising on the statistical analyses. This manuscript was edited by a native English speaker associated with Editage, Tokyo, Japan.

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Figure Legends

Figure 1. Study flow

Diagnosis at the ED: The patients were transferred to the emergency department (ED) either as outpatients or from the other hospitals and were diagnosed as severe sepsis at the ED. Diagnosis at the general wards: The patients were diagnosed as severe sepsis following admission to the general wards for diagnosis other than severe sepsis. Diagnosis at ICU: The patients were diagnosed as severe sepsis after admission to the intensive care unit (ICU) for diagnosis other than severe sepsis.

ED, emergency department; ICU, intensive care unit

Figure 2. Survival curves

JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; HR, hazard ratio; CI, confidence interval

Table 1 Patients demographics, severity, and organ dysfunctions in survivors and non-survivors

	Survivors N=462	Non-survivors N=111	P value
Age, years, median (IQR)	75 (65-83)	73 (64-82)	0.2878
Male, n (%)	277 (60.0)	78 (70.3)	0.0445
Diagnosed at, n (%)			0.0004
Emergency department	378 (84.0)	72 (16.0)	
General wards	61 (70.1)	26 (29.9)	
ICU	23 (63.9)	13 (36.1)	
Pre-existing disease, n (%)			
Cardiovascular disease	75 (16.2)	21 (18.9)	0.5000
Stroke	64 (13.6)	15 (13.5)	0.9258
COPD	17 (3.7)	2 (1.8)	0.3211
Autoimmune disease	22 (4.8)	8 (7.2)	0.2990
Chronic liver disease	15 (3.3)	3 (2.7)	0.7679
DM	141 (30.5)	29 (26.1)	0.8280
Chronic kidney disease	41 (8.9)	16 (14.4)	0.0799
Malignancy	48 (10.4)	18 (16.2)	0.0842
Medications before admission, n (%)			

Steroids	46 (10.0)	23 (20.7)	0.0019
Immunosuppressant Drugs	14 (3.0)	8 (7.2)	0.0408
Statin	68 (14.8)	13 (11.7)	0.4052
Anti-platelets	76 (16.5)	22 (19.8)	0.4082
β-blocker	48 (10.4)	15 (13.5)	0.3528
Severity			
Septic shock, n (%)	226 (49.0)	84 (75.7)	< 0.0001
APACHE II score (day 1), median (IQR)	18 (14–24)	26 (20–32)	< 0.0001
SOFA score (day 1), median (IQR)	7 (5–10)	10 (7–14)	< 0.0001
Complicating organs dysfunction			
JAAM-DIC score (day 1), median (IQR)	2 (1–4)	4 (2–5)	< 0.0001
JAAM-DIC (day 1 and/or day 4), n (%)	160/301 (53.2)	65/84 (77.4)	< 0.0001
ARDS (day 1 and/or day 4), n (%)	68 (14.7)	39 (35.1)	< 0.0001
Severity of ARDS			< 0.0001
Mild	12 (2.6)	6 (5.4)	
Moderate	38 (8.2)	14 (12.6)	
Severe	18 (3.9)	19 (17.1)	
AKI (day 1 through day 3), n (%)	163 (35.3)	76 (68.5)	< 0.0001
Stage (AKIN Criteria), n (%)			< 0.0001
1	46 (10.0%)	14 (12.6%)	
2	40 (8.7%)	15 (13.5%)	

3		77 (16.7%)	47 (24.0%)

IQR, interquartile range; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; AKIN, acute kidney injury network.

Table 2

Outcomes in patients with and without DIC, ARDS, and acute kidney injury complications

	In-hospital mortality	ICU-free days	Hospital-free days
All patients	111/573 (19.4)	21 (12-25)	56 (0-75)
JAAM-DIC (day 1 and/or day 4)			
No, n (%)	19/160 (11.9)	21 (13-24)	49 (2-73)
Yes, n (%)	65/225 (28.9)*	19 (8-23)*	32 (0-70)*
ARDS (day 1 and/or day 4)			
ARDS (-), n (%)	72/466 (15.5)	22 (16-25)	65 (16-77)
ARDS (+), n (%)	39/107 (36.4)*	12 (0-19)*	0 (0-42)*
Mild	6/18 (33.3)	19 (2-23)	17 (0-46)

Moderate	14/52 (26.9)	12 (6-20)	17 (0-44)
Severe	19/37 (51.4)	12 (0-19)	0 (0-39)
AKI (day 1 through day 4)			
AKI (-), n (%)	35/334 (10.5)	23 (17-25)	68 (33-77)
AKI (+), n (%)	76/239 (31.8)*	17 (5-23)*	18 (0-66)*
Stage 1	14/60 (23.3)	20 (7-24)	29 (0-70)
Stage 2	15/55 (27.3)	17 (12-24)	52 (0-73)
Stage 3	47/124 (37.9)	14 (1-22)	0 (0-64)

AKI and its stages were diagnosed according to the Acute Kidney Injury Network Criteria.

* P <0.05 when patients with and without complications (organ dysfunctions) were compared. Any mortality and free-days were not statistically different among the different severity levels in ARDS and AKI.

JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; AKI, Acute kidney injury.

Table 3 Logistic regression model for in-hospital mortality

	Odds ratio	95% confidential interval
JAAM-DIC (day 1 and/or day 4)	2.71	1.45 – 5.27
Acute kidney injury Stage 3 (day 1 through day 4)	1.98	1.07 – 3.63
Severe ARDS (day 1 and/or day 4)	2.02	0.82 – 4.90
Respiratory tract infections	1.98	1.05 – 3.74
Septic shock	1.34	0.68 – 2.79
Gram-positive cocci positive on blood culture	2.37	1.23 – 4.52
APACHE II day 1	1.05	1.01 – 1.09
Sepsis diagnosed at ICU (vs. ED)	2.78	1.03 – 7.40
Medication steroid	1.64	0.78 – 3.36
Age	1.00	0.98 – 1.02
Gender male	1.17	0.64 – 2.16

JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation; ARDS, acute respiratory distress syndrome; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; ED, emergency department.

Table 4 Cox hazard regression model for in-hospital mortality

	Hazard ratio	95% confidential interval
JAAM-DIC (day 1 and/or day 4)	2.58	1.53-4.55
Acute kidney injury Stage 3 (day 1 through day 4)	1.73	1.07-2.80
Severe ARDS (day 1 and/or day 4)	1.40	0.72-2.59
Respiratory tract infections	1.69	1.02-2.77
Septic shock	1.16	0.66-2.16
Gram-positive cocci positive on blood culture	1.78	1.07-2.86
APACHE II day 1	1.04	1.01-1.08
Sepsis diagnosed at ICU (vs. ED)	0.99	0.45-1.99
Medication steroid	1.17	0.65-2.02
Age	1.00	1.01-1.08
Gender male	0.92	0.56-1.54

JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation; ARDS, acute respiratory distress syndrome; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; ED, emergency department.

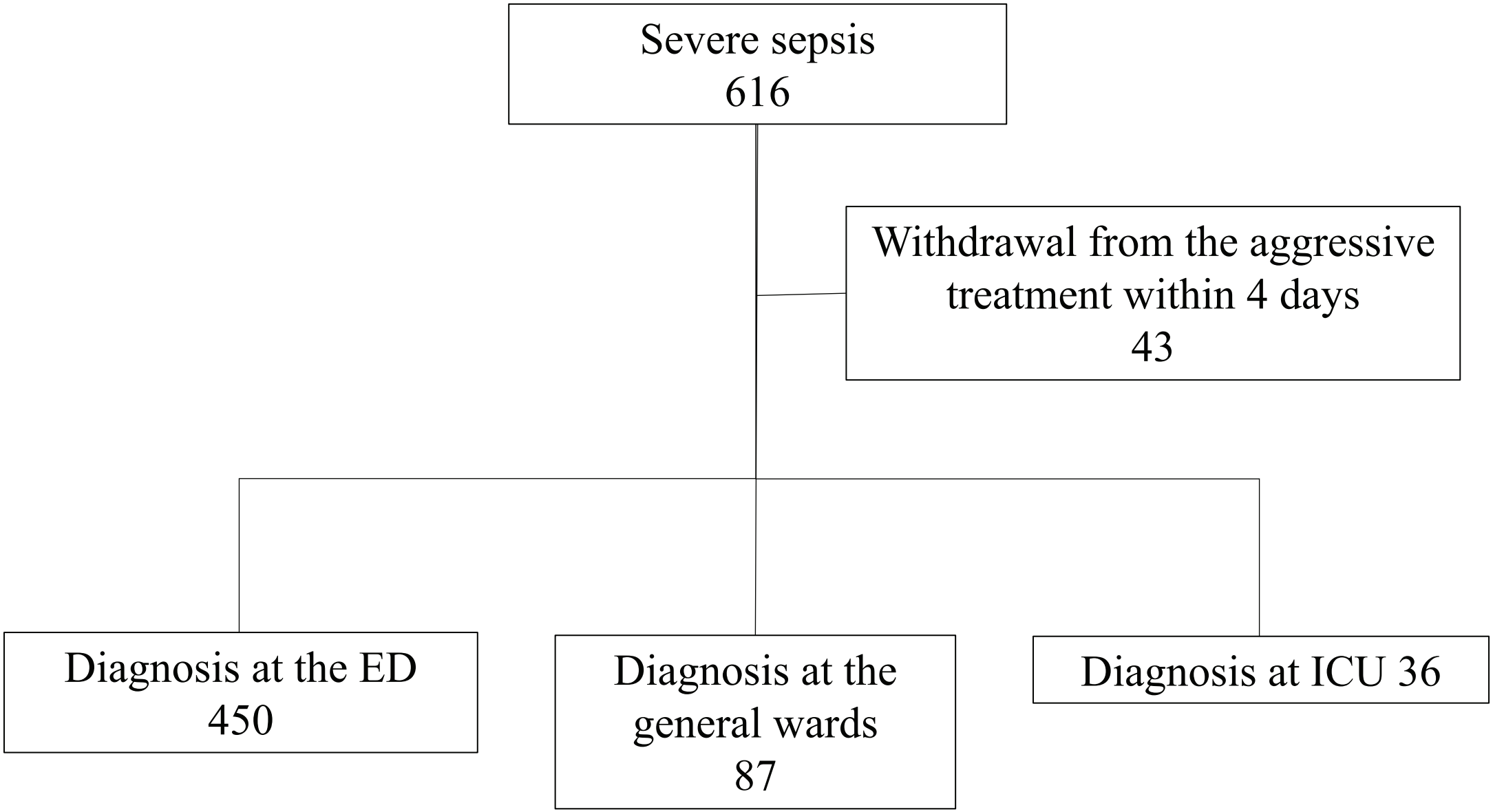
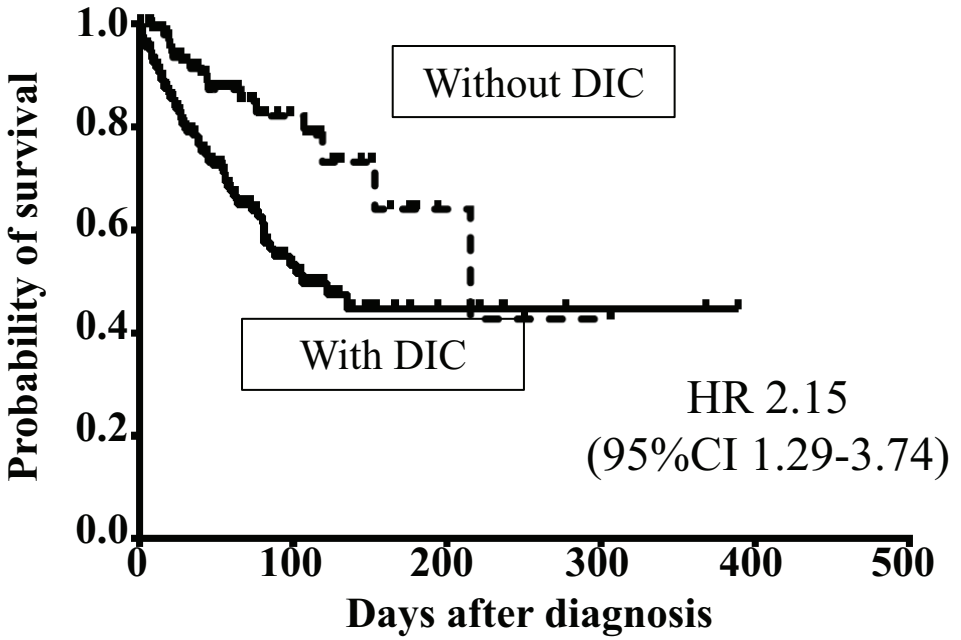
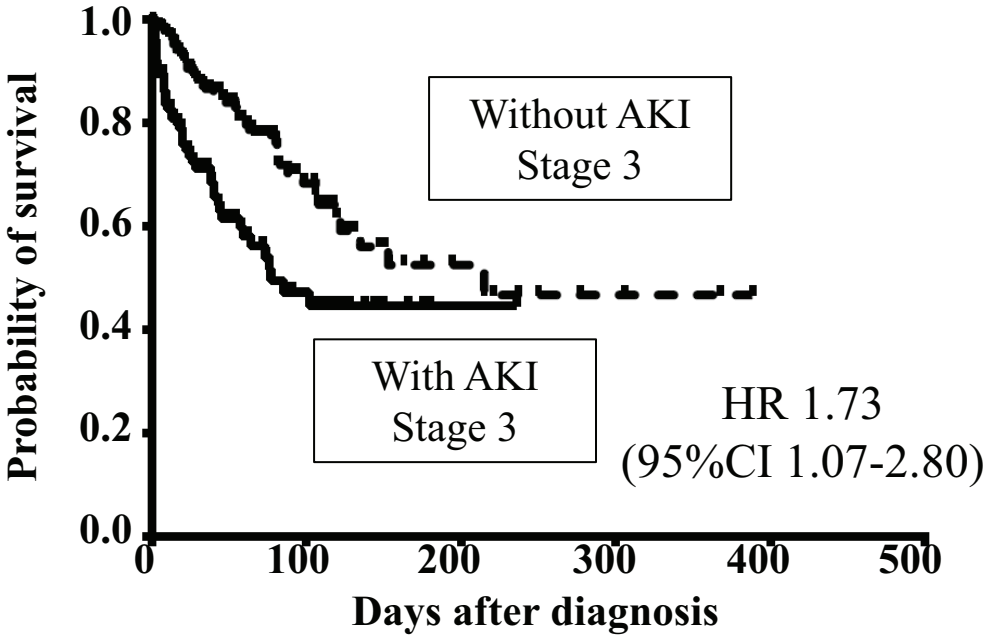

Severe sepsis
616
Withdrawal from the aggressive treatment within 4 days
43
Diagnosis at the ED
450
Diagnosis at the general wards
87
Diagnosis at ICU 36

Figure 1


1.0
0.8
0.6
0.4
0.2
0.0
Probability of survival
Without DIC
With DIC
HR 2.15
(95%CI 1.29-3.74)
0
100
200
300
400
500
Days after diagnosis


1.0
0.8
0.6
0.4
0.2
0.0
Probability of survival
Without AKI
Stage 3
With AKI
Stage 3
HR 1.73
(95%CI 1.07-2.80)
0
100
200
300
400
500
Days after diagnosis

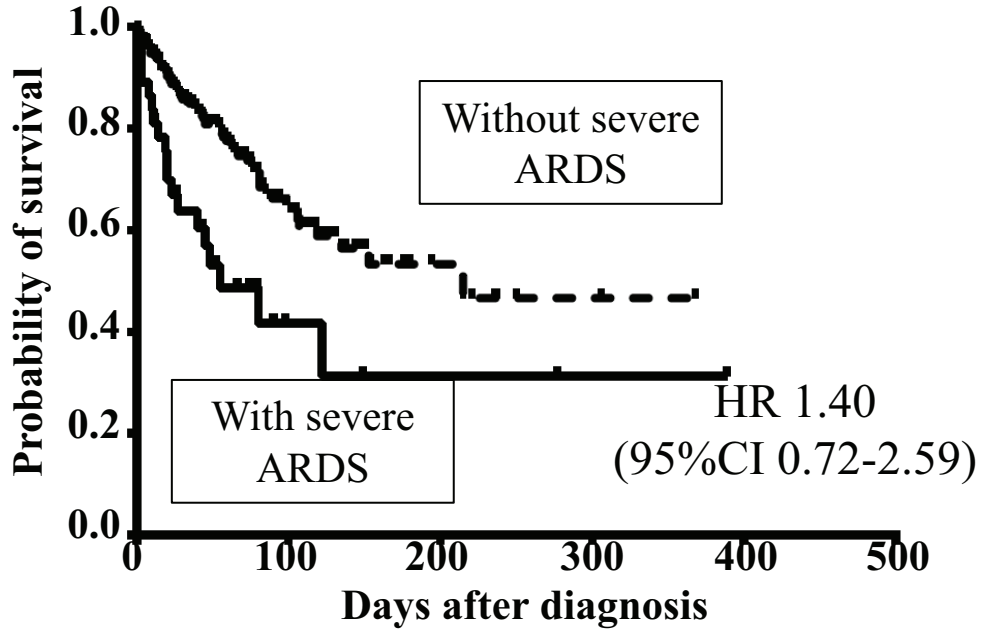

1.0
0.8
0.6
0.4
0.2
0.0
Probability of survival
Without severe
ARDS
With severe
ARDS
HR 1.40
(95%CI 0.72-2.59)
0
100
200
300
400
500
Days after diagnosis

Figure 2