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Original article

Epidemiology of severe sepsis in Japanese intensive care units: A prospective multicenter study

Hiroshi Ogura, MD [a,*], Satoshi Gando, MD, FCCM [b], Daizoh Saitoh, MD [c], Naoshi Takeyama, MD [d], Shigeki Kushimoto, MD [e], Seitaro Fujishima, MD [f], Toshihiko Mayumi, MD [g], Tsunetoshi Araki, MD [h], Hiroto Ikeda, MD [i], Joji Kotani, MD [j], Yasuo Miki, MD [k], Shin-ichiro Shiraishi, MD [l], Koichiro Suzuki, MD [m], Yasushi Suzuki, MD [n], Kiyotsugu Takuma, MD [o], Ryosuke Tsuruta, MD [p], Yoshihiro Yamaguchi, MD [q], Norio Yamashita, MD [r], Naoki Aikawa, MD, FACS [s], the Japanese Association for Acute Medicine Sepsis Registry (JAAMSR) Study Group

[a] *Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, 2-15 Yamadaoka, Suita, Osaka 565-0871, Japan*
[b] *Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine, Kita 2 jou Nishi 5, Kitaku, Sapporo, Hokkaido 060-8638, Japan*
[c] *Division of Traumatology, Research Institute, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan*
[d] *Department of Emergency and Acute Intensive Care Medicine, Fujita Health University, Dengakugakubo 1-98, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan*
[e] *Division of Emergency Medicine, Tohoku University Graduate School of Medicine, Seiryoumachi 2-1, Aobaku, Sendai, Miyagi 980-8575, Japan*
[f] *Department of Emergency & Critical Care Medicine, School of Medicine, Keio University, Shinanomachi 35, Shinjuku-ku, Tokyo 160-8582, Japan*
[g] *Emergency Center, Department of Emergency and Critical Care Medicine, Ichinomiya Municipal Hospital, Bunkyo 2-2-22, Ichinomiya, Aichi 491-8558, Japan*
[h] *Department of Emergency & Critical Care Medicine, Trauma Center St. Mary's Hospital, Tsubukuhonmachi 422, Kurume, Fukuoka 830-8543, Japan*
[i] *Department of Emergency Medicine, Trauma and Resuscitation Center, Teikyo University School of Medicine, Kaga 2-11-1, Itabashi-ku, Tokyo 173-8606, Japan*
[j] *Department of Emergency, Critical Care and Disaster Medicine, Hyogo College of Medicine, Mukogawa 1-1, Nishinomiya, Hyogo 663-8501, Japan*
[k] *Advanced Critical Care Center, Aichi Medical University Hospital, Yazakokarimata 1-1, Nagakute, Aichi 480-1195, Japan*
[l] *Department of Emergency and Critical Care Medicine, Nippon Medical School, Sendagi 1-1-5, Bunkyou-ku, Tokyo 113-8603, Japan*
[m] *Department of Acute Medicine, Kawasaki Medical School, Matsushima 577, Kurashiki, Okayama 701-0114, Japan*
[n] *Department of Critical Care Medicine, Iwate Medical University, Uchimaru 19-1, Morioka, Iwate 020-8505, Japan*
[o] *Emergency & Critical Care Center, Kawasaki Municipal Hospital, Shinkawadori 12-1, Kawasaki-ku, Kawasaki, Kanagawa 210-0013, Japan*
[p] *Advanced Medical Emergency & Critical Care Center, Yamaguchi University Hospital, Minamikogushi 1-1-1, Ube, Yamaguchi 755-8505, Japan*
[q] *Department of Trauma & Critical Care Medicine, Kyorin University, School of Medicine, Shinkawa 6-20-2, Mitaka, Tokyo 181-8611, Japan*
[r] *Department of Emergency & Critical Care Medicine, School of Medicine, Kurume University, Asahimachi 67, Kurume, Fukuoka 830-0011, Japan*
[s] *Department of Emergency & Critical Care Medicine, School of Medicine, Keio University, Shinanomachi 35, Shinjuku-ku, Tokyo 160-8582, Japan*

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ABSTRACT

Severe sepsis is a leading cause of morbidity and mortality in the intensive care unit (ICU). We conducted a prospective multicenter study to evaluate epidemiology and outcome of severe sepsis in Japanese ICUs. The patients were registered at 15 general critical care centers in Japanese tertiary care hospitals when diagnosed as having severe sepsis. Of 14,417 patients, 624 (4.3%) were diagnosed with severe sepsis. Demographic and clinical characteristics at enrollment (Day 1), physiologic and blood variables on Days 1 and 4, and mortality were evaluated. Mean age was 69.0 years, and initial mean Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were 23.4 and 8.6, respectively. The 28-day mortality was 23.1%, and overall hospital mortality was 29.5%. SOFA score and disseminated intravascular coagulation (DIC) score were consistently higher in nonsurvivors than survivors on Days 1 and 4. SOFA score, DIC score on Days 1 and 4, and hospital mortality were higher in patients with than without septic shock. SOFA score on Days 1 and 4 and hospital mortality were higher in patients with than without DIC. Logistic regression analyses showed age, presence of septic shock, DIC, and cardiovascular dysfunction at enrollment to be

* Corresponding author. Tel.: +81 6 6879 5707; fax: +81 6 6879 5720.
E-mail address: ogura@hp-emerg.med.osaka-u.ac.jp (H. Ogura).

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predictors of 28-day mortality and presence of comorbidity to be an additional predictor of hospital mortality. Presence of septic shock or DIC resulted in approximately twice the mortality of patients without each factor, whereas the presence of comorbidity may be a significant predictor of delayed mortality in severe sepsis.

1. Introduction

Severe sepsis is a leading cause of morbidity and high mortality in the intensive care unit (ICU) [1,2]. It has been reported that 72% of patients with sepsis develop severe sepsis, and 17% evolve to septic shock [3]. The incidence of severe sepsis has increased significantly over time [4,5]. Despite the availability of potent antibiotics and refined supportive care, the mortality of severe sepsis remains high, with overall estimates of approximately 30%–50% that increase to over 50% when sepsis is associated with shock [6].

Several multicenter studies have presented recent epidemiologic data on sepsis [7–14]. In a large European study, Sepsis Occurrence in Acutely Ill Patients (SOAP), sepsis accounted for 37% of critical care admissions and was associated with a hospital mortality rate of 36%, with considerable variation in the frequency of sepsis and mortality rates among European countries [13]. The Promoting Global Excellence in Severe Sepsis (PROGRESS) international sepsis registry demonstrated a global hospital mortality rate in 12,881 patients in 37 countries of 50% (ranging from 33% to 66% in the 8 majority countries) [12]. These results showed that there is a significant difference between countries in the outcome of patients with sepsis.

Epidemiological studies on sepsis are important to increase our knowledge of the frequency and outcome of sepsis in different countries and health care systems and to improve patient care and prognosis [15]. In Japan, there is limited epidemiologic information on the demographics and outcomes of severe sepsis. In the present study, the Japanese Association for Acute Medicine Sepsis Registry (JAAMSR) Study Group therefore conducted a prospective multicenter study to evaluate the patient characteristics, outcome, and prognostic factors of severe sepsis in Japan.

2. Patients and methods

This study was prospectively conducted as a multicenter survey of the epidemiology of severe sepsis in Japan by the JAAMSR Study Group. Both the JAAM and the Ethics Committee of each participating hospital approved the study protocol. Data collection was performed as a part of the routine clinical workup without any interventions, and data management and statistical analyses were processed anonymously. On the basis of these reasons, written informed consent was waived by both the JAAM and the Ethics Committee of each hospital. The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR ID: UMIN000008195).

2.1. Patients

The patients for this prospective survey were registered at 15 critical care centers in tertiary care hospitals from June 1, 2010, to May 31, 2011. All patients admitted to the ICU were enrolled without exclusion when they were diagnosed as having severe sepsis.

2.2. Definitions

Systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock were defined according to the definitions of the American College of Chest Physicians/Society of Critical Care Medicine consensus conference and its revised version in 2003 [16,17]. Severity of illness of the patients was evaluated according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score at the time of enrollment [18], and organ dysfunction was assessed by the Sequential Organ Failure Assessment (SOFA) score [19]. Organ dysfunction was defined as a SOFA score $\geq$2 for each organ system in question. Multiple organ dysfunction syndrome (MODS) was defined as a SOFA score $\geq$12 [19]. The diagnosis of disseminated intravascular coagulation (DIC) was made on the basis of the JAAM DIC diagnostic criteria [20,21], with a total score of $\geq$4 establishing a diagnosis of DIC. Comorbidities were defined as the presence of one or more disorders in addition to severe sepsis documented in medical records. The following were considered comorbidities: diabetes, cerebrovascular disorder, cancer or hematologic malignancy, acute or chronic heart failure, chronic renal failure, chronic hepatic disease, autoimmune disease, ischemic heart disease, chronic respiratory disease, peripheral circulatory disturbance, metastatic cancer, peptic ulcer, and acquired immune deficiency syndrome [22].

2.3. Data sampling

Prospective blood samplings were performed on admission to the ICU and daily thereafter as part of the routine clinical and laboratory workup using established standard laboratory techniques. APACHE II, SOFA, SIRS, and DIC scores were assessed on the day of enrollment (Day 1). Platelet counts, prothrombin time ratio, and fibrin/fibrinogen degradation products were measured, and the SIRS criteria met by the patients were determined for DIC scoring. Age, sex, admission category (underlying diseases), source of the severe sepsis diagnosed, comorbidities, presence of septic shock, positive blood culture, and cultured bacteria and antibiotics used were recorded. The evaluation of SOFA, SIRS, and DIC scores on Day 4 was also mandatory. Outcome measures were 28-day and hospital all-cause mortality. Length of hospital stay was also evaluated.

2.4. Statistical analysis

If not otherwise noted, data are reported as the mean $\pm$ standard deviation (SD). Parametric data were analyzed with the unpaired Student *t*-test, and the Mann–Whitney *U* test was applied for two-group unpaired and paired comparisons. Proportions were compared with the chi-square test or Fisher's exact test when necessary. Relations between outcome and various factors were analyzed by stepwise logistic regression analysis (backward elimination method based on likelihood ratio). The stepwise method used outcome (dead, 1; survived, 0) as a criterion variate and used age, sex (male, 1; female, 0), admission category (medical, 1; trauma/surgery/burns/others, 0), comorbidity (present, 1; absent, 0), blood culture (positive, 1; negative, 0), septic shock (present, 1; absent, 0), DIC (present, 1; absent, 0), respiratory SOFA score ($\geq$2, 1; <2, 0), cardiovascular SOFA score ($\geq$2, 1; <2, 0), liver SOFA score ($\geq$2, 1; <2, 0), and renal SOFA score ($\geq$2, 1; <2, 0) as explanatory variables. Results