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# Association between Sequential Organ Failure Assessment Score and In-hospital Deaths of Surgical, Critically Ill Patients with Sepsis

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## Abstract

**Purpose:** This study was designed to identify factors prognostic of in-hospital deaths of surgical, critically ill patients with sepsis and to evaluate the effects of treatments for sepsis on in-hospital deaths.

**Methods:** This retrospective cohort study involved 103 patients with sepsis who were hospitalized in the surgical intensive care units of 20 hospitals. Clinical, microbiologic, and laboratory factors, as well as treatments, were compared between patients who survived hospitalization and those who died in-hospital.

**Results:** The in-hospital mortality and septic shock rates were 24.3% and 19.4%, respectively. Multivariate logistic regression analysis showed that Sequential Organ Assessment (SOFA) score was the only independent predictor of in-hospital death (P = 0.027). Receiver operating characteristic curve analysis of in-hospital death showed that the optimal SOFA score cutoff at admission to the surgical intensive care unit was 8, with in-hospital death rate being significantly higher in the 22 patients with SOFA score > 8 than in the 81 patients with SOFA score ≤ 8 (P = 0.0039). Cox regression analyses by inverse probability treatment weighting to control for selection bias showed that in-hospital death rates were not significantly altered by treatment with intravenous immunoglobulins, renal replacement therapy, or endotoxin-absorbing therapy using polymyxin B.

**Conclusions:** SOFA score may be prognostic of in-hospital deaths of surgical critically ill patients with sepsis. SOFA score > 8 was associated with a significantly higher in-hospital death rate and should be regarded as a cut-off for intensive treatment in surgical patients with sepsis.

### Keywords

SOFA, Septic shock, Surgical critically ill, Prognostic factors

## Introduction

Sepsis, defined as infection-induced systemic inflammatory response syndrome (SIRS), is the leading cause of death in non-cardiac critically ill patients [1]. In the United States, nearly 200,000 deaths per year are attributed to sepsis [2]. Worldwide, as many as 20 million people may experience sepsis annually, with a mortality rate of about 35% [3]. Sepsis involves multiple mechanisms, including the release of cytokines and the activation of the complement, coagulation and fibrinolytic systems [4].

The first internationally accepted guidelines to improve outcomes in patients with severe sepsis and septic shock were adopted in 2004 [5,6] and updated in 2008 [7] and 2012 [8,9]. Current guidelines recommend a specific anatomical diagnosis of infection as rapidly as possible, with intervention for source control started within the first 12 hours after diagnosis, if feasible [8,9].

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Few studies to date have described the treatment of surgical, critically ill patients with sepsis [10,11,12]. The results of treatments of sepsis in surgical patients requiring other types of treatment, including burn care, catheter drainage of the source of infection and abdominal surgery under general anesthesia, remain unclear. It is therefore of interest to clarify factors prognostic of survival in surgical, critically ill patients with sepsis.

Moreover, although adjunctive therapies, including intravenous immunoglobulins (IVIG) [13,14], renal replacement therapy [15,16], and endotoxin-absorbing therapy using polymyxin B (PMX) [17], have been reported to reduce the risks of death in septic patients, these treatments have not been universally accepted. Inverse probability of treatment weighting (IPTW) was therefore used to balance the underlying distributive covariates among patients who did and did not receive each adjunctive therapy. IPTW weights the samples using propensity score to reduce the confounding that frequently occurs in cohort studies of the effects of treatment on outcome, and enables estimation of marginal or population-average treatment effects [18].

This study was therefore designed to identify factors prognostic of in-hospital deaths in surgical, critically ill patients with sepsis and to evaluate the effects of treatment of sepsis on patient survival.

## Materials and Methods

This retrospective cohort study involved 110 patients who were hospitalized with sepsis in the surgical intensive care units of 20 hospitals affiliated with the Department of Surgery and Medical Science, Graduate School of Medical Sciences, Kyushu University, between January 2012 and December 2013 (Supplemental Table 1). Patients lacking adequate clinical data were excluded.

Sepsis was defined as an infection with SIRS, defined as the occurrence of at least two of the following criteria: (1) body temperature > 38˚C or < 36˚C, (2) heart rate > 90 beats per minute, (3) respiratory rate > 20 breaths a minute or $PaCO_2$ < 32 mmHg, and (4) white blood cell count > 12,000/ $mm^3$ or < 4000/$mm^3$ or < 10 % immature forms [4]. Blood samples were drawn when patients first fulfilled the criteria for SIRS. Septic shock was defined as sepsis-induced hypotension, consisting of systolic blood pressure below 90 mmHg, which persisted despite adequate fluid resuscitation [8]. Ileus was defined as any impairment, arrest, or reversal of the normal flow of intestinal contents toward the anal canal.

All patients diagnosed with sepsis and admitted to the surgical intensive care unit before and after surgery were enrolled in this study. Demographic and clinical data retrieved from their medical records included sex, age, underlying disease, location of the primary infection, bacterial species, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Assessment (SOFA) score, blood pressure, heart rate, hematocrit, white blood cell (WBC) count, platelet count, C-reactive protein (CRP), total bilirubin, serum creatinine, fibrinogen, prothrombin activity, fibrinogen degradation products (FDP), D-dimer, and type of surgical intervention for sepsis, including removal or drainage of sites of infection.

**Supplemental Table 1:** Hospitals included in this Study

| |
|---|
| National Hospital Organization Kyushu Cancer Center |
| Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers |
| Saiseikai General Hospital |
| Fukuoka City Hospital |
| Fukuoka Higashi Medical Center |
| Social Insurance Nakabaru Hospital |
| Munakata Medical Association Hospital |
| Saiseikai Yahata General Hospital |
| Steel Memorial Yahata Hospital |
| Shinnakama Hospital |
| Aso Iizuka Hospital |
| Tagawa Municipal Hospital |
| Onga Hospital |
| Oita Red Cross Hospital |
| Oita Prefectural Hospital |
| Nakatsu Municipal Hospital |
| Saiseikai Karatsu |
| Imari Arita Kyoritsu Hospital |
| Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital |
| Matsuyama Red Cross Hospital |

Treatment of sepsis, including surgical intervention and antimicrobial therapy, was initiated as soon as possible according to the Surviving Sepsis Campaign guidelines [8,9]. If primary antibiotics were not effective, as determined by WBC count, CRP concentration, and clinical signs such as high fever, IVIG (5 g/kg body weight) was administered for 3 days along with antibiotics [13,14]. Patients with septic shock who experienced acute renal failure, defined as anuria and/or serum creatinine concentration > 4.0 mg/dl, were administered renal replacement therapy, including continuous hemodiafiltration (CHDF) or intermittent hemodialysis, to protect renal function and remove inflammatory cytokines [15,16]. If hemodynamic stability could not be restored by adequate fluid resuscitation and vasopressor therapy, patients were administered PMX [16]. In addition, mechanical ventilation was administered to patients with sepsis-induced acute lung injury (ALI)/acute respiratory distress syndrome (ARDS). Fluid resuscitation and catecholamine were administered to maintain circulation in patients with septic shock, thus preventing the development of a more critical condition that could result in multiple organ failure (MOF) and death [8,9].

## Statistical Analysis

For continuous variables, nonparametric analyses were performed using Wilcoxon rank-sum tests. Categorical variables were compared using chi-squared or Fisher's exact tests. The Kaplan-Meier method was used to construct cumulative survival curves. To identify factors independently predictive of in-hospital death, the factors found to be significant on univariate analysis were assessed by multivariate logistic regression analyses. The SOFA score cut-off value for in-hospital death was calculated using the receiver operator characteristic (ROC) curve method [19].

IPTW analysis was performed to overcome possible biases from differences in distribution among patients who did and did not receive each treatment [18,20]. Propensity scores by IPTW were calculated using a Cox regression model to predict the probability of each patient receiving each treatment on the basis of eight clinical variables: age; sex; APACHE II score; SOFA score; positive (vs. negative) blood culture; and treatment including IVIG, renal replacement therapy, and PMX. Following balancing by IPTW, the between group differences in in-hospital death rates were evaluated by the log-rank test. Statistical analyses were performed using the R statistical programming environment (the Comprehensive R Archive Network, http://cran.md.tsukuba.ac.jp) and JMP 9.0 software (SAS Institute, Cary, NC). Four basic R programming packages were used for IPTW analyses: Rcmdr, survival, RcmdrPlugin, survival, and Epi. Statistical significance was defined as a P value < 0.05.

## Results

Of the 110 patients enrolled initially, seven were excluded owing to uncertainties about initial recognition of SIRS. The primary causes of sepsis in the 103 analyzed patients included acute peritonitis (n = 50), acute cholecystitis (n = 17), acute cholangitis (n = 9), ileus (n = 7), gangrene of the lower limbs (n = 4), liver abscess (n = 2), postoperative catheter infection (n = 2), postoperative acute enteritis (n =2), postoperative pneumonitis (n = 2), postoperative urinary tract infection (n = 2), postoperative infectious endocarditis (n = 1), extensive burn (n = 1), abdominal compartment syndrome (n = 1), esophageal perforation (n = 1), postoperative leakage of esophageal anastomosis (n = 1), and postoperative pancreas fistula (n = 1). Table 1 shows the relationships between the primary cause of sepsis and surgical treatment in these patients. Of the 103 patients, 60 (58.3%) underwent surgery under general anesthesia, and 24 (23.3%) underwent surgical drainage under local anesthesia. Adjunctive

**Table 1:** Causes of sepsis and types of treatment in surgical critically ill patients with sepsis

| Cause of sepsis | Patients | Primary therapy | | Adjunctive therapy | | |
|---|---|---|---|---|---|---|
| | | Surgery | Drainage | IVIG | RRT | PMX |
| | (n = 103) | (n = 60) | (n = 24) | (n = 33) | (n = 18) | (n = 21) |
| Acute peritonitis | 50 | 42 | 4 | 19 | 11 | 15 |
| Acute cholecystitis | 17 | 5 | 10 | 4 | 1 | 1 |
| Acute cholangitis | 9 | 0 | 4 | 3 | 1 | 0 |
| Ileus | 7 | 6 | 1 | 1 | 1 | 0 |
| Lower limbs gangrene | 4 | 4 | 0 | 2 | 1 | 1 |
| Liver abscess | 2 | 0 | 2 | 0 | 0 | 0 |
| Postop. catheter infection | 2 | 0 | 2 | 0 | 0 | 0 |
| Postop. acute enteritis | 2 | 0 | 0 | 1 | 1 | 1 |
| Postop. Pneumonitis | 2 | 0 | 0 | 1 | 0 | 1 |
| Postop. UTI | 2 | 0 | 1 | 0 | 0 | 0 |
| Postop. infectious endocarditis | 1 | 0 | 0 | 0 | 0 | 0 |
| Extensive burn | 1 | 1 | 0 | 1 | 1 | 1 |
| Abd. compartment syndrome | 1 | 1 | 0 | 1 | 1 | 1 |
| Esophageal perforation | 1 | 1 | 0 | 0 | 0 | 0 |
| Postop. leakage of esophageal Anastomosis | 1 | 0 | 0 | 0 | 0 | 0 |
| Postoperative pancreas fistula | 1 | 0 | 0 | 0 | 0 | 0 |

**Abbreviations:** IVIG: intravenous immunoglobulins; RRT: renal replacement therapy; PMX: endotoxin-absorbing therapy using polymyxin B; UTI: urinary tract infection; Postop: postoperative; Abd: abdominal.

**Table 2:** Univariate analysis of risk factors for in-hospital deaths among surgical, critically ill patients with sepsis Results reported as mean ± standard error

| Variables | Hospital Survivors | Hospital Non-survivors | *P-value* |
|---|---|---|---|
| | (n = 78) | (n = 25) | |
| Age (years) | 72.5 ± 1.4 | 71.7 ± 2.3 | 0.869 |
| Gender (Male) | 47 (60.3%) | 18 (72.0%) | 0.347 |
| Body weight (kg) | 52.1 ± 1.3 | 57.0 ± 3.6 | 0.299 |
| Comorbidities | | | |
| Diabetes mellitus | 11 (14.1%) | 4 (16.0%) | 0.755 |
| Hypertension | 18 (23.1%) | 3 (12.0%) | 0.271 |
| Heart failure | 4 (5.1%) | 5 (20.0%) | 0.036 |
| Chronic renal failure | 9 (11.5%) | 0 (0.0%) | 0.109 |
| Neoplasm | 21 (26.9%) | 9 (36.0%) | 0.450 |
| Positive blood culture | 30 (38.5%) | 7 (28.0%) | 0.473 |
| Localization of infection | | | |
| Respiratory | 2 (2.6%) | 0 (0.0%) | 1.000 |
| Heart | 1 (1.3%) | 0 (0.0%) | 1.000 |
| Upper digestive tract | 11 (14.1%) | 2 (8.0%) | 0.730 |
| Hepatobiliary-pancreas | 25 (32.0%) | 8 (32.0%) | 1.000 |
| Lower digestive tract | 32 (41.0%) | 13 (52.0%) | 0.362 |
| Urinary tract | 1 (1.3%) | 1 (4.0%) | 0.428 |
| Soft tissue | 6 (7.7%) | 1 (4.0%) | 1.000 |
| APACHE II score (points) | 14.0 ± 0.8 | 20.4 ± 2.0 | 0.002 |
| SOFA score (points) | 5.0 ± 0.4 | 8.8 ± 0.8 | < 0.0001 |
| Body temperature (centigrade) | 37.6 ± 0.2 | 37.0 ± 0.3 | 0.145 |
| Heart rate (/minute) | 101.8 ± 2.0 | 106.6 ± 4.9 | 0.508 |
| Hematocrit (%) | 33.6 ± 0.8 | 35.1 ± 1.6 | 0.263 |
| White blood cell count (/mm$^3$) | 13920 ± 1184 | 15296 ± 9968 | 0.661 |
| Platelet (×10$^4$/mm$^3$) | 20.4 ± 1.3 | 17.2 ± 2.4 | 0.162 |
| C-reactive protein (mg/dl) | 16.2 ± 1.3 | 14.4 ± 3.2 | 0.222 |
| Total bilirubin (mg/dl) | 1.3 ± 0.1 | 2.3 ± 0.8 | 0.205 |
| Serum creatinine (mg/dl) | 1.7 ± 0.2 | 1.9 ± 0.3 | 0.147 |
| Fibrinogen (mg/dl) | 476.9 ± 30.9 | 351.0 ± 72.2 | 0.054 |
| Prothrombin activity (%) | 66.6 ± 2.7 | 55.2 ± 3.4 | 0.006 |
| FDP (μg/ml) | 24.9 ± 3.7 | 62.2 ± 34.0 | 0.983 |
| D-dimer (μg/ml) | 10.6 ± 1.5 | 17.4 ± 7.5 | 0.480 |
| Surgical intervention | 66 (84.6%) | 18 (72.0%) | 0.234 |

**Abbreviations:** APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; FDP: fibrinogen degradation products

treatments included IVIG therapy in 33 patients (32.0%), renal replacement therapy in 18 (17.5%), and PMX in 21 (20.4%).

The mean age of the 103 patients (65 men and 38 women) was 72.3 ± 1.2 years (range, 37-99 years). Twenty-five (24.3 %) patients died in-hospital and 20 (19.4 %) experienced septic shock. The mean hospital stay was 36.7 ± 2.5 days (range, 2-100 days). The mean APACHE II and SOFA scores at admission were 15.5 ± 0.8 and 5.9 ± 0.4, respectively.

**Table 3:** Multivariate analysis of risk factors for in-hospital deaths among surgical, critically ill patients with sepsis

| Variables | Multiple logistic regression analysis | | |
|---|---|---|---|
| | Odds ratio | 95% Confidence Interval | P-value |
| Heart failure | 1.71 | 0.25-11.9 | 0.575 |
| APACHE II score (points) | 1.02 | 0.94-1.11 | 0.617 |
| SOFA score (points) | 1.24 | 1.03-1.52 | 0.023 |
| Prothrombin activity (%) | 0.99 | 0.96-1.02 | 0.521 |

**Abbreviations:** APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment

Univariate analysis identified four variables as risk factors for in-hospital deaths in these patients: heart failure as a comorbidity (P = 0.036), APACHE II score (P = 0.002), SOFA score (P < 0.0001), and prothrombin activity (P = 0.006). Of the 78 in-hospital survivors, nine had chronic renal failure, including two on hemodialysis, with no differences in rates of chronic renal failure between survivors and non-survivors (P = 0.109). Multivariate logistic regression analysis showed that SOFA score was the only independent predictor of in-hospital death (P = 0.027, odds ratio 1.24; 95% confidence interval 1.03-1.52, Table 2 and Table 3).

ROC curve analysis and determination of the area under the ROC curve (AUC) showed that SOFA score was effective in distinguishing surgical, critically ill patients with sepsis who did and did not survive in-hospital. The AUC of SOFA score was 0.76. ROC curve analysis for in-hospital deaths showed that the optimal SOFA score cutoff at admission to the surgical intensive care unit was 8 (sensitivity; 0.64, 1-specificity; 0.25, Figure 1). The in-hospital death rate was significantly higher in the 22 patients with SOFA score > 8 than in the 81 patients with SOFA score ≤ 8 (P = 0.0039, Figure 2).

The microorganisms isolated from these patients are shown in table 4. Gram-positive microorganisms were cultured from 37.9 % of these patients; Gram-negative organisms from 34.0 %; and Candida species from 2.9%. In-hospital deaths were not associated with either Gram-positive or Gram-negative organisms. Escherichia coli was associated with the main source of infection in patients with septic shock (P = 0.021), but not with in-hospital deaths. None of the other microorganisms was associated with either septic shock or in-hospital death rate. Antimicrobial treatment was administered to all patients. Only six patients (7.8%) received inadequate antimicrobial treatment, but this was not related to in-hospital mortality (P = 0.620). Of these six patients, three were infected with methicillin-resistant

**Table 4:** Microorganisms associated with in-hospital deaths among surgical, critically ill patients with sepsis

| Variables | Hospital Survivors (n = 78) | Hospital Non-survivors (n = 25) | P-value | Septic shock (n = 20) | P-value |
|---|---|---|---|---|---|
| Gram positive | 31 | 8 | 0.344 | 5 | 0.211 |
| Enterococcus species | 10 | 3 | 1 | 1 | 0.454 |
| Staphylococcus aureus | 10 | 2 | 0.726 | 1 | 0.453 |
| Streptococcus species | 7 | 1 | 0.676 | 2 | 0.651 |
| Clostridium species | 2 | 1 | 0.57 | 1 | 0.481 |
| Staphylococcus epidermidis | 1 | 0 | 1 | 1 | 0.454 |
| Bacillus species | 1 | 0 | 1 | 0 | 1 |
| Corynebacterium species | 0 | 1 | 1 | 0 | 1 |
| Gram negative | 25 | 10 | 0.476 | 10 | 0.116 |
| Escherichia coli | 11 | 6 | 0.352 | 7 | 0.021 |
| Bacteroides species | 6 | 1 | 1 | 1 | 0.454 |
| Klebsiella pneumoniae | 2 | 2 | 1 | 1 | 1 |
| Pseudomonas aeruginosa | 2 | 1 | 0.57 | 1 | 0.481 |
| Enterobacter cloacae | 2 | 0 | 1 | 0 | 1 |
| Citrobacter freundii | 1 | 0 | 1 | 0 | 1 |
| Proteus vulgaris | 1 | 0 | 1 | 0 | 1 |
| Candida species | 2 | 1 | 0.57 | 0 | 1 |
| Unknown | 20 | 6 | - | 5 | - |

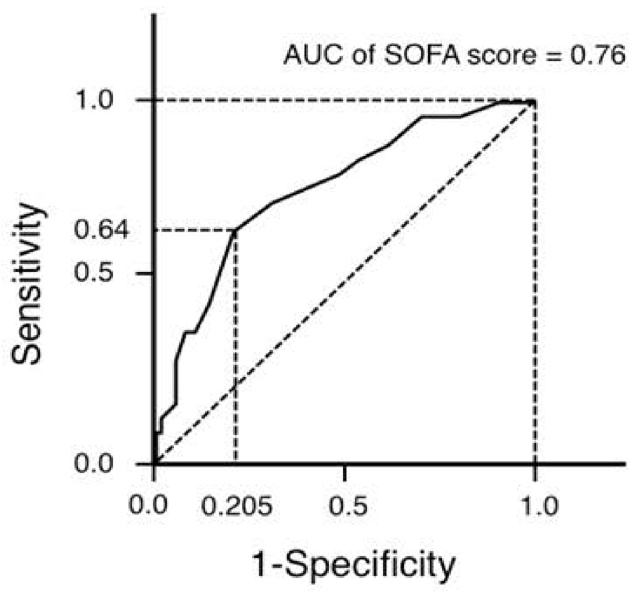


**Figure 1:** Receiver operating characteristic (ROC) curve analysis of SOFA score distinguishing in-hospital survivors and non-survivors among surgical, critically ill patients with sepsis. The area under the ROC curve (AUC) was 0.76.

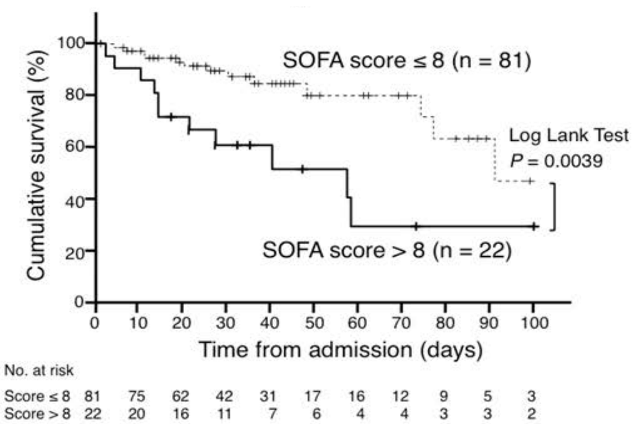


**Figure 2:** Kaplan-Meier survival curves of surgical, critically ill patients with sepsis having SOFA scores ≤ 8 and > 8. The 22 patients with SOFA score > 8 had a significantly higher in-hospital death rate than the 81 patients with SOFA score ≤ 8 (*P* = 0.0039).

**Table 5:** Analyses of the effects of adjunctive treatments of surgical, critically ill patients with sepsis by inverse probability of treatment weighting

| Treatments | Multiple Cox regression analyses for in-hospital death | | | |
|---|---|---|---|---|
| | n | Adjusted HR | 95% CI | P-value |
| Intravenous immunoglobulins | 33 | 2.834 | 1.085-7.404 | 0.059 |
| Renal replacement therapy | 18 | 0.855 | 0.361-2.025 | 0.733 |
| PMX | 21 | 2.356 | 0.872-6.371 | 0.229 |

**Abbreviations:** HR: hazard ratio; CI: confidence interval; PMX: endotoxin-absorbing therapy using polymyxin B.

Staphylococcus aureus (MRSA), two with Candida glabrata, and one with Enterococcus faecium; four (67%) of these patients received empirical treatment with carbapenems.

We also assessed the effects of adjunctive treatment with IVIG, renal replacement therapy, and PMX in patients with sepsis. Following IPTW using eight variables: age, sex, positive blood culture, APACHE score, SOFA score, and treatment with IVIG, renal replacement therapy, and PMX, we found that the weighted in-hospital death rates were similar in patients who did and did not receive each treatment (Table 5).

## Discussion

Sepsis is the leading cause of death of surgical patients pre- and postoperatively [21-23]. Once the sources of infection are identified, surgical intervention plus antibiotics are recommended as treatment [8,9]. However, the in-hospital death rate remains high, even following these guidelines [8,9]. The mortality rate in surgical patients with sepsis was reported to be 25.5%, similar to the rate in our study (24.3%) [22]. However, the effectiveness of adjunctive treatments, such as IVIG, renal replacement therapy, and PMX, remains unclear. Moreover, few reports have assessed surgical treatments associated with sepsis, risk factors associated with mortality of surgical, critically ill patients, and microbes associated with sepsis [23]. Although epidemiology and outcomes before and after admission to the surgical intensive care unit have been analyzed [10,11], prognostic factors and treatment results in septic surgical patients remain unclear. The duration of SIRS has been reported to be significantly prognostic of sepsis in medical and surgical units (P = 0.015) [22]. Our study showed that SOFA score may be potentially prognostic of in-hospital deaths in surgical, critically ill patients with sepsis. These results are in accordance with a study that found an association between SOFA score and outcomes in patients admitted to the intensive care unit [24]. Serial measurements of SOFA score during the first week were very useful in predicting the outcome of sepsis, whereas APACHE II scores on the day of admission were not reliable in predicting mortality [25].

SOFA score is simple and objective, allowing the calculation of the number of dysfunctional organ systems and their severity among six organ systems (respiratory, coagulatory, liver, cardiovascular, renal, and neurologic) [26]. Moreover, SOFA score can measure dysfunction of individual and aggregate organs [27]. SOFA score has been used to evaluate patients with multiple organ dysfunction syndromes (MODS) and their survival [26]. Organ failure may worsen outcomes in surgical critically ill patients with sepsis. Indeed, we found that in-hospital death rates were significantly higher in patients with SOFA scores > 8 than ≤ 8 at admission. SOFA score at admission may therefore suggest the type of primary treatment, including adjunctive therapy. In surgical patients, organ dysfunction at sites other than that of surgery may be more strongly associated with death than transient vital signs and serum chemistry included in the APACHE II score on admission [28].

Although our univariate analysis found that APACHE II score was prognostic of in-hospital deaths, this finding was not observed on from multivariate analyses. APACHE II score is used in intensive care units to assess disease severity. However, SOFA score may be superior to APACHE II score in predicting in-hospital deaths of surgical, critically ill patients with sepsis, because SOFA score, which includes platelet count, may objectively evaluate failure of individual and aggregate organs [26]. Coagulopathy, such as low platelet count, has been associated with sepsis-induced disseminated intravascular coagulation (DIC) [29] and may lead to a severe disease condition or in-hospital death. A prospective survey in Japan also demonstrated that SOFA and DIC scores were consistently higher in nonsurvivors than survivors on the day of admission and 3 days later [23].

Microbial assessment found that E. coli infection was frequently associated with septic shock, including in patients with community-acquired bloodstream infection [30]. Because none of the other microorganisms assayed was associated with septic shock or in-hospital death and only 7.8% of patients received inadequate antimicrobial treatment, surgical, critically ill patients with sepsis should be treated with a broad empirical antimicrobial agent such as a carbapenem. Infections with MRSA and Candida species are of particular concern. The frequency of invasive fungal infections in developed countries has increased because of advances in medical management [31]. Although invasive Candidiasis is frequently intraabdominal in critically ill surgical patients, prompt antifungal therapy and adequate source control may yield good outcomes [32]. Resistance to azoles, particularly fluconazole, should be considered when starting an empirical treatment [32].

Although we attempted to assess the effects of adjunctive treatment, including IVIG, renal replacement therapy, and PMX, in patients with sepsis by IPTW analysis, we found that none had a significantly positive effect on this patient population. However, our study had several limitations. First, relatively few patients received each type of adjunctive treatment. Second, this was a retrospective cohort study assessing the causes of sepsis in Japanese patients. Thus, the results were not externally validated and were limited to patients of Japanese ethnicity. Third, we could not plan a prospective study to clarify the effectiveness of each adjunctive therapy in surgical critically ill patients with sepsis. However, well-designed randomized controlled studies and/or meta-analyses may result in external validity, as well as assessing these adjunctive treatments in patients of varying ethnicity.

In conclusion, this study found that SOFA score may be prognostic of in-hospital deaths of surgical, critically ill patients with sepsis. SOFA > 8 was associated with significantly higher in-hospital death rate and may be a cut-off for the necessity of intensive treatment in these patients.

## Conflict of Interest

All authors declare no conflicts of interest.

## Compliance with Ethical Requirements

The study protocol was approved by the ethics committees of all participating hospitals, and study information was disclosed to the patients or their survivors by members of the Department of Surgery and Medical Science, Graduate School of Medical Sciences, Kyushu University.

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