Epidemiology of severe sepsis in critically ill surgical patients in ten university hospitals in China*

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Objectives: **To determine the occurrence rate, outcomes, and the characteristics of severe sepsis in surgical intensive care units in multiple medical centers within China and to assess the cost and resource use of severe sepsis in China.**

Design and Setting: **Prospective, observational study of surgical intensive care unit patients at ten university hospitals in six provinces in China.**

Patients: **All adult admissions in studied intensive care units from December 1, 2004, to November 30, 2005.**

Interventions: **None.**

Measurements and Main Results: **The criteria of severe sepsis were based on the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definition. Analysis of data from 3,665 intensive care unit admissions identified 318 (8.68%) cases of severe sepsis, 64.8% of which were men. The median age (interquartile range) of patients with severe sepsis was 64 (47–74) yrs. Microbes had been isolated from 228 (71.7%) patients, including 171 (53.8%) with Gram-negative bacteria and 146 (45.9%) with Gram-positive bacteria. A total of 90 (22.0%) patients had invasive fungal infection, 20 (6.3%) of which had fungemia. The abdomen was the most common site of infections (72.3%), followed by lung (52.8%). The overall hospital mortality of severe sepsis was 48.7%. Risk factors for hospital mortality included age, chronic comorbidity of malignant neoplasm, Gram-positive bacterial infection, invasive fungal infection, admission Acute Physiology Score, and admission Sequential Organ Failure Assessment score of respiratory dysfunction and cardiovascular dysfunction. The median Therapeutic Intervention Scoring System-28 score was 43 (38–49). The mean hospital cost was $11,390 per patient and $502 per patient per day.**

Conclusions: **Severe sepsis is a common, expensive, and frequently fatal syndrome in critically ill surgical patients in China. Other than the microbiological patterns, the incidence, mortality, and major characteristics of severe sepsis in Chinese surgical intensive care units are close to those documented in developed countries. (Crit Care Med 2007; 35:2538–2546)**

KEY WORDS: epidemiology; severe sepsis; critically ill surgical patients; multicenter study

Sepsis is an infection-initiated, inflammation-induced syndrome. It is considered severe when associated with acute organ dysfunction (1, 2). Severe sepsis has become a leading cause of morbidity and mortality in critical illness and a major public health burden throughout the world (3–17). Accurate data on severe sepsis would be helpful to advance the mission of practicing intensive care unit (ICU) physicians and scientific researchers, to understand the epidemiology of sepsis, and to evaluate the efficiency of therapeutic trials in severe sepsis. Meanwhile, it would be invaluable for establishing healthcare policy and for determining healthcare resource allocation. In recent years, several multicenter studies have presented the epidemiologic data regarding prevalence, mortality, associated risk factors, and even costs of severe sepsis in many other countries (3–17). Most studies have reported an occurrence rate of severe sepsis ranging between 6% and 14% among critical care admissions, with a hospital mortality rate from 27% to 59% (3–17). Angus et al. (3) estimated that 751,000 cases of severe sepsis occurred annually in the United States, with a hospital mortality rate of 34.1% and an average cost per case of $22,100. More recently, a large European study, Sepsis Occurrence in Acutely Ill Patients (SOAP), reported that severe sepsis accounted for 30% of critical care admissions and was associated with an ICU mortality rate of 32.2%, with a considerable variation in the

***See also p. 2646.**

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The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/01.CCM.0000284492.30800.00

Table 1. Participating university hospitals

Hospital (n = 10)	Total Hospital Beds	Total Hospital Admissions per Year	Surgical ICU Beds	Surgical ICU Admissions[a] (n = 6,548)	Included Patients (n = 3.665)	Severe Sepsis Patients (n = 318)	Period Incidence of Severe Sepsis, %
The First Affiliated Hospital of Beijing University, Beijing	1,368	Around 23,000	10	845	451	34	7.54
Union Hospital, Affiliated Hospital of Huazhong University of Science and Technology, Wuhan	1,300	Around 35,000	8	291	163	19	11.66
Zhongnan Hospital, Affiliated Hospital of Wuhan University, Wuhan	1,200	Around 28,000	12	441	263	24	9.13
Xiangya Hospital, Affiliated Hospital of Center South University, Changsha	1,500	Around 40,000	13	755	445	30	6.74
South Hospital, Affiliated Hospital of South Medical University, Guangdong	1,800	Around 32,000	11	317	150	17	11.33
The Affiliated Hospital of Qingdao University, Qingdao	1,200	Around 32,000	7	342	184	15	8.15
The First Affiliated Hospital of Zhejiang University, Hangzhou	1,400	Around 30,000	31	1,039	580	58	10.00
Sir Run Run Shaw Hospital, Affiliated Hospital of Zhejiang University, Hangzhou	800	Around 25,000	28	1,152	641	58	9.05
Lihuili Hospital, Affiliated Hospital of Ningbo University, Ningbo	780	Around 11,000	15	667	402	32	7.96
The First Affiliated Hospital of Wenzhou Medical College, Wenzhou	1,432	Around 34,000	20	699	381	31	8.14

ICU, intensive care unit.
[a]ICU admissions from December 1, 2004, to November 30, 2005.

frequency of sepsis and the mortality rates among European countries (4).

China is the most populous country in the world, but epidemiology of severe sepsis within this country is still not well understood, which might be partly due to the lack of a nationwide database of healthcare information. Up to now, there have been only a few studies confined to either a single center or single district (18, 19). The present study was conducted as a multicenter, nationwide, epidemiologic survey of severe sepsis in surgical ICU patients. The objective of this study was to determine the occurrence rate and outcomes of severe sepsis in surgical ICU patients in multiple medical centers located in different provinces of China; to characterize differences in demographics, chronic comorbidity, infection, and illness severity and to determine the relationship of these differences with patient outcomes; and to assess the cost and workload of severe sepsis in China.

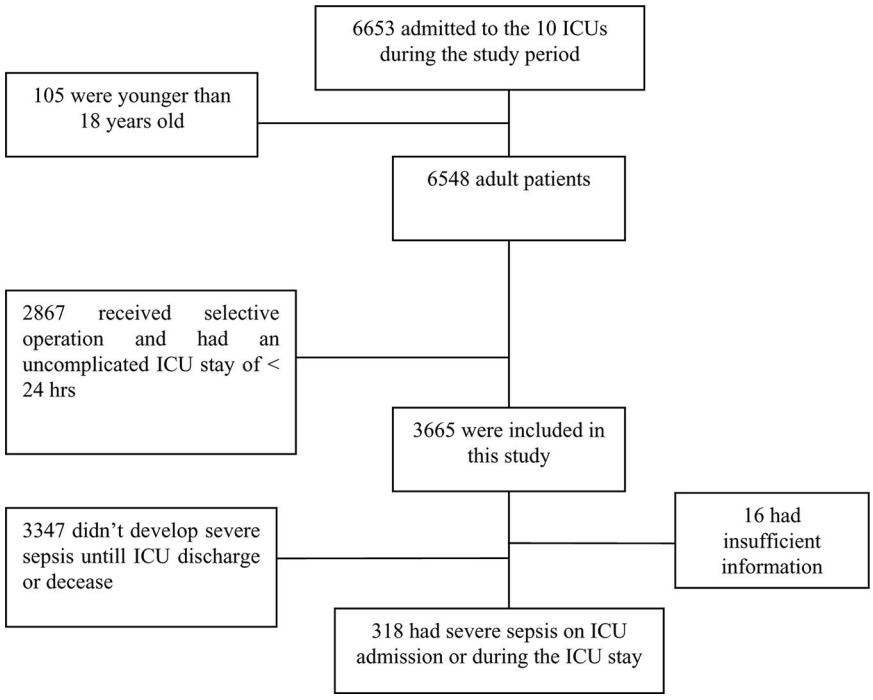

Figure 1. Flow diagram of the enrolled patients. Of the 6,653 patients admitted during the study period, excluding 16 cases with incomplete and irretrievable data, 3,665 patients were hospitalized for >24 hrs and 318 patients met the criteria for severe sepsis. *ICU*, intensive care unit.

MATERIALS AND METHODS

The present study was conducted in surgical ICUs of ten university hospitals in six major provinces, which covered 27.98% of the population of China, from December 1, 2004, to November 30, 2005. Each participating hospital is one of the largest comprehensive university hospitals either regionally or nationally, with >800 beds (participating centers are listed at Table 1). These centers were selected for their geographic representation, good data management, and consensus on the definition and management of severe sepsis. The study protocol was reviewed by the ethical committees at each participating center. Informed consent was waived by the ethical committees of these centers because the nature of this observational study.

Study Population. All adult patients (age of ≥18 yrs) admitted to surgical ICUs in the participating centers during the observational period were included, whereas those who

stayed in the ICU for <24 hrs for routine postoperative surveillance were excluded. Those who were readmitted and had been included at their first admission were not included for a second time. The flow diagram of this study is shown in Figure 1.

Definitions. Infection was defined as the presence of a pathogenic microorganism in a sterile milieu (such as blood, abscess fluid, cerebrospinal fluid, or ascitic fluid) or as clinically suspected infection, plus the administration of antibiotics (1, 2). Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions by infection plus two systemic inflammatory response syndrome criteria (1, 2). Severe sepsis was defined by sepsis plus sepsis-induced acute organ dysfunction (at least occurred in one organ) (1, 2). Acute organ dysfunction was defined as a Sequential Organ Failure Assessment (SOFA) score of ≥2 for the organ in question (20, 21). The causal relationship between sepsis and organ dysfunction was confirmed based on medical recording and communication between the investigators and related ICU physicians. ICU-acquired infection was defined as infection identified ≥48 hrs after ICU admission. Criteria for invasive fungal infection and fungemia are listed in Appendix 1 (22). Antibiotic consociation application was defined as the daily administration of more than one kind of the following antibiotics: penicillins, cephalosporins, carbapenem, macrolides, glycopeptides, aminoglycosides, quinolones, sulfonamides, and other antibiotics.

Case Identification and Data Collection. Case identification and data collection were conducted by four dedicated investigators, who are residents of anesthesiology and intensive care medicine. All had received ≥1 yr of clinical training in critical care medicine and had previous research experience.

Paper medical records of each enrolled patient were reviewed. A daily evaluation based on laboratory findings and overall clinical presentation was performed at ICU admission and every 24 hrs thereafter to screen for severe sepsis. Severe sepsis was identified based only on the objective information from medical records and a good communication between investigators and related ICU physicians. Once cases meeting the criteria for severe sepsis were identified by one of the investigators, further certification was performed by a dedicated intensive care specialist in each participating center. Any queries were solved by an immediate review of the medical record.

For patients developing severe sepsis at ICU admission or during their ICU stay, the following data were collected using preprinted case report forms: age, sex, primary diagnosis, chronic comorbidities, clinical and laboratory data for admission Acute Physiology and Chronic Health Evaluation (APACHE) II (23) and SOFA score, clinical and laboratory data for maximum SOFA score, microbiological and clinical infectious information, occurrence of ICU-acquired infection, antibiotics administered, hospital length of stay (LOS), ICU LOS, clinical data for Therapeutic Intervention Scoring System-28 (TISS-28) scores (24), hospital costs, and outcome. For patients who had not developed severe sepsis at ICU admission or during the ICU stay, only age, sex, primary diagnosis, chronic comorbidities,

Table 2. Descriptive demographic characteristics of patients with severe sepsis[a] and without severe sepsis

Characteristics	Total of 3665 Patients	
	Patients Without Severe Sepsis	Patients with Severe Sepsis
n, (% of total)	3347 (91.3)	318 (8.68)
Ethnicity	Chinese Han	Chinese Han
Male sex (%)	1925 (57.5)	206 (64.8)[b]
Age in years, median (IQR)	54 (42–68)	64 (47–74)[b]
ICU LOS in days, median (IQR)	4 (2–6)	7 (3–14)[b]
28-day mortality rate, %	15.5	44.7[b]

IQR, interquartile range; ICU, intensive care unit; LOS, length of stay.

[a]Patients were diagnosed with severe sepsis based on the criteria of severe sepsis in this study; [b]$p < .01$ compared with patients without severe sepsis.

Table 3. Characteristics of patients with severe sepsis (n = 318)

Characteristics	n (%)	Hospital Mortality, %
Ethnicity	Chinese Han	
Sex		
Male	206 (64.8)	51.5
Female	112 (35.2)	43.8
Age, yrs		
≤44	69 (21.7)	34.8
45–65	91 (28.6)	46.2
≥65	158 (49.7)	56.3
With comorbidity	200 (62.9)	51.5
Cardiovascular disease	98 (30.8)	49.0
Respiratory disease	23 (7.20)	47.8
Gastrointestinal disease	64 (20.1)	59.4
Malignant neoplasm	38 (11.9)	73.7
Diabetes	41 (12.9)	46.3
Organ transplantation	16 (5.00)	56.3
Diagnosis		
Severe acute pancreatitis	64 (20.1)	51.6
Intestinal or gastric perforation[a]	62 (19.5)	48.4
Bowel obstruction	26 (8.20)	65.4
Infection of liver or gall	33 (10.4)	33.3
Trauma	59 (18.6)	32.2
Nosocomial pneumonia[b]	25 (7.90)	68.0
APACHE II score, median (IQR)	19 (14–25)	
SOFA score, median (IQR)	9 (6–13)	
No. of organs with acute dysfunction[c]		
1	48 (15.1)	10.4
2	71 (22.3)	23.9
3	74 (23.3)	41.9
≥4	125 (39.3)	81.6
Organs with acute dysfunction[d]		
Respiratory	290 (91.2)	51.4
Cardiovascular	131 (41.2)	76.3
Renal	95 (29.9)	75.8
Hematologic	123 (38.7)	58.5
Central nervous system	209 (65.7)	63.6
Hepatic	146 (45.9)	61.0

APACHE II, Acute Physiology and Chronic Health Evaluation II; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

[a]Intestinal or gastric perforation includes the iatrogenic intestinal fistula after operation; [b]nosocomial pneumonia here refers to the hospital-acquired severe pneumonia in surgical patients; [c]SOFA scores presented correspond to the maximum SOFA registered; [d]acute organ dysfunction systems here were recorded when the maximum SOFA scores were assessed.

ICU LOS, and outcome were recorded. If a patient had more than one episode that met the criteria, only the data from the first episode were included in the study. The chronic comorbidity system in this study was constructed by selecting *International Classification of Diseases, Ninth Revision, Clinical Modification* codes suggestive of chronic disease within separate organ systems. According to this system, chronic comorbidities of enrolled patients were classified as cardiovascular, respiratory, renal, neurologic, gastrointestinal, hematologic/lymphatic, metabolic/endocrine disease, malignant neoplasm, and immune suppression conditions (Appendix 2). Admission APACHE II/SOFA referred to the score assessed in the first 24 hrs after ICU admission, whereas maximum SOFA referred to the highest score during the ICU stay. Costs here were exactly the patients' expenditures on medical care in the hospital, and any indirect costs were not calculated. The information of costs was abstracted from the financial network system of each center. Workload on severe sepsis presented in this study was assessed by TISS-28 (24). One TISS point equals 10.6 mins of each 8-hr nurse shift. All recorded data were screened in details by medical personnel for any missing information, logical errors, or insufficient details.

Data were entered into an Access-based database (Microsoft, Redmond, WA). At each center, data from a random sample of 5% of cases were abstracted twice by a dedicated ICU specialist. These data were reentered into the database, and a consistency of 99.8% per variable and 97.8% per patient was observed. In cases of inconsistency, data were verified and corrected via connection with the participating centers by E-mail or telephone. In the 183 randomly chosen patients, only one case with severe sepsis had been classified as a nonsevere sepsis patient by our investigators, indicating an misclassification rate of <1.0% in this study.

Statistical Analyses. Data are shown as median and interquartile range (IQR; 25th to 75th percentiles) or percentages, except for cost, which is presented as mean ± SD. The occurrence rate was calculated as patients with severe sepsis divided by adult ICU admissions other than postoperative patients with durations of <24 hrs in surgical ICUs. The prevalence or mortality between the different groups was compared using chi-square test. Mean costs between groups were compared by Student's *t*-test. Differences in median LOS and scores were tested using the Mann-Whitney test. These were two-sided tests, and statistical significance was accepted at $p < .05$.

A multivariate nonconditional logistic regression analysis was conducted in patients with severe sepsis, with hospital mortality as the dependent factor. Variables considered for the multivariate modeling included age, sex, chronic comorbidity, characteristics of infection (type and source), and admission Acute Physiology Score (derived from admission APACHE II score) (23) at ICU admission and, separately, admission SOFA score for respiratory, cardiovascular, liver, renal, coagulation, and central nervous systems. Forward elimination, which employed a combination of the procedures used in the forward entry and backward removal methods, was adopted in the analysis. The effect on the hospital mortality of severe sepsis was considered statistically significant if the regression coefficient associated with the hospital mortality had a $p < .05$. For all analyses, SPSS 13.0 for Windows (SPSS, Chicago, IL) was used.

RESULTS

Occurrence Rates and Demographics. From December 1, 2004, to November 30, 2005, a total of 6,653 critically ill patients were admitted to the surgical ICUs in the ten centers, among which 3,665 were included in our study (Fig. 1). Among the 3,665 patients, 318 patients (8.68%) developed severe sepsis, including 206 men (64.8%). The median age of patients with severe sepsis was 64 (47–74) yrs, which was greater than the age for patients without severe sepsis (54 [42–68] yrs, $p < .01$). There was a different rate of severe sepsis between men and women (9.78% vs. 7.19%; $p < .01$). All the critically ill surgical patients in this study were Chinese Han people. Descriptive demographic characteristics are shown in Table 2.

Major Diagnoses and Chronic Comorbidities. In patients with severe sepsis, severe acute pancreatitis was the most frequent primary cause of ICU admission, followed by gastrointestinal perforation or intestinal fistula after abdominal operation and trauma. Chronic comorbidities were present in 200 cases (62.9%). The most frequent chronic comorbidities were cardiovascular diseases (30.8%). In addition, a total of 97 transplant patients were included in this study, 16 of whom developed severe sepsis. None of the enrolled patients had HIV/AIDS. Details are provided in Table 3.

Patterns of Infections. Microorganisms were isolated from 228 patients (71.7%), and mixed infections were ob-

Table 4. Distribution of various microorganisms and sites of infection in severe sepsis patients and the outcome according to the microorganisms and sites of infection in severe sepsis patients

	Cases, n (%)	Hospital Mortality, %
Documented infection	228 (71.7)	50.9
ICU-acquired infection[a]	135 (42.5)	57.0
Type of organisms		
Gram-positive bacteria	146 (45.9)	55.5
Enterococcus faecalis	43 (13.5)	55.8
Staphylococcus aureus	40 (12.6)	62.5
Staphylococcus haemolyticus	32 (10.1)	46.9
Staphylococcus epidermidis	32 (10.1)	43.8
Gram-negative bacteria	171 (53.8)	51.5
Acinetobacter baumannii	82 (25.8)	57.3
Escherichia coli	44 (13.8)	47.7
Pseudomonas aeruginosa	44 (13.8)	59.1
Klebsiella pneumoniae	27 (8.5)	33.3
Fungi[b]	90 (28.3)	67.8
Candida albicans	54 (17.0)	68.5
Candida tropicalis	27 (8.50)	74.1
Aspergillus	7 (2.20)	85.7
Mixed infection[c]	139 (43.7)	58.3
Site of infection[d]		
Abdomen	230 (72.3)	50.4
Respiratory tract	168 (52.8)	55.4
Positive blood cultures	90 (28.3)	61.1
Device related	39 (12.3)	61.5
Wound surface	54 (17.0)	31.5
Urinary tract	23 (7.20)	52.2
Multisite[e]	188 (59.1)	54.8

ICU, intensive care unit.

[a]ICU-acquired infection was defined as the infection identified ≥48 hrs after ICU admission; [b]fungal infection here refers to the invasive fungal infection and fungemia; [c]mixed infection refers to infections that were considered to have more than one type of organism per patient; [d]site of infection includes the sites of documented and suspected infection; [e]multisite infection refers to infections present in more than one site per patient. In all patients the microorganism was considered once per patient even if present in more than one site.

served in 139 patients (43.7%). Gram-negative bacteria were the most frequent pathogens and were identified in 171 patients (53.8%). Invasive fungal infections were identified in 90 cases (28.3%), including 20 patients (6.3%) with fungemia. The most common isolated microbes were *Acinetobacter baumannii* and *Candida albicans*, whereas the most fatal species were *Aspergillus* and *Candida tropicalis*. Hospital mortality was comparable between severe sepsis with and without microbiological confirmations (50.9% vs. 43.3%, $p = .225$).

The majority of infections were found in the abdomen (72.3%), and more than half of the cases (59.1%) had infections in multiple sites. Cases with positive blood cultures had the highest mortality. The details of infections are shown in Table 4.

Severity, Organ Dysfunction, and Mortality. Of the total 318 patients with severe sepsis, 142 (44.7%) died within 28 days of ICU admission, and another 4.0% died thereafter in the hospital. There was no significant difference in hospital mortality between men and women (51.5% vs. 43.8%, respectively; $p = .198$). Outcomes according to microorganisms and sites of infection are shown in Table 4.

The median admission APACHE II and SOFA scores for patients with severe sepsis were 19 (14–25) and 8 (6–12), respectively, whereas median maximum SOFA score was 9 (6–13). Relationships between admission APACHE II/maximum SOFA scores and hospital mortality are shown in Figure 2.

According to the study criteria, 48 patients (15.1%) were identified with only one dysfunctioning organ, 71 (22.3%) were identified with two, and 199 (62.6%) were identified with three or more during their ICU stay according to their maximum SOFA scores (Table 3). The lung was the most frequent organ failure observed in patients with severe sepsis (occurred in 91.2% patients). However, cardiovascular and renal dysfunction contributed to higher mortality rates (Table 3).

Predictors of Mortality. Variables retained in the final model of the multivariate logistic regression, and hence associated with increased mortality in severe sepsis patients, included age, comorbidity of malignant neoplasm, Gram-positive bacteria infection, invasive fungal infection, admission Acute Physiology Score, and admission SOFA scores of respiratory system and cardiovascular system dysfunction (Table 5).

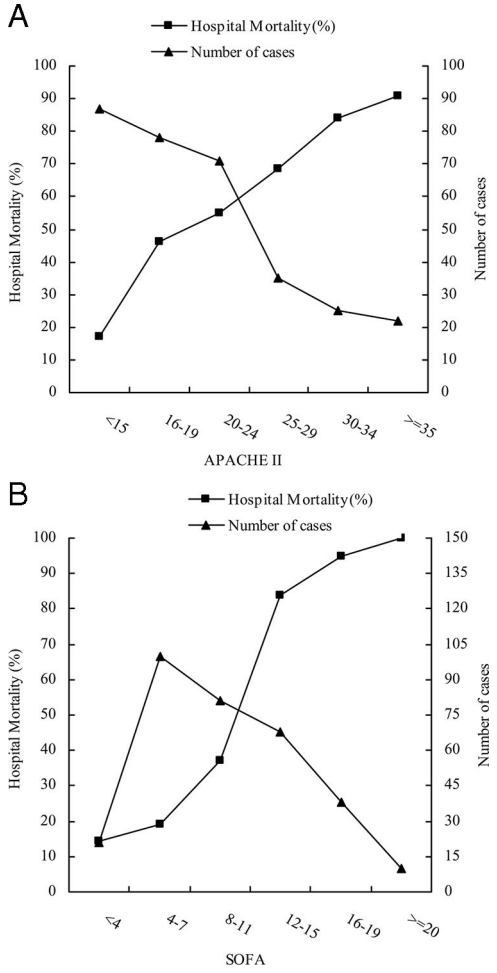

Figure 2. *A*, number and hospital mortality rate of patients with severe sepsis by divided ranges of Acute Physiology and Chronic Health Evaluation (*APACHE*) II score. *B*, number and hospital mortality rate of patients with severe sepsis by divided ranges of maximum Sequential Organ Failure Assessment (*SOFA*) score. APACHE II scores were assessed within 24 hrs after admission to intensive care units, and SOFA scores correspond to the maximum SOFA score registered. The *points* on the *lines* represent the different mortality rates and numbers of cases.

Antibiotic Consociation. In this study, antibiotic consociation applications were observed in 214 patients (67.3%) with a duration of >3 days, including 121 patients (38.1%) with a duration of >7 days. Broad-spectrum antibiotics were widely used in patients with severe sepsis. The most commonly administered antibiotics were imipenem–cilastatin (Tienam, Merck, Sharp, and Dohme Laboratories, France) in 91 patients (28.6%), piperacillin–tazobactam (Tazocin, Wyeth Pharmaceuticals, Madison, NJ) in 76 (23.9%) patients, sulbactam–cefoperazone (Sulperazon, Pfizer, Groton, CT) in 101 patients (31.8%), and Vancocin (vancomycin hydrochloride intravenously) in 62 patients (19.5%). Antifungal agents were used in 75 patients (23.6%).

Hospital Resource Use and Costs. Hospital and ICU LOS were 22 (12–39) days and 7 (3–14) days, respectively. Survivors stayed longer in the hospital than nonsurvivors (31 vs. 16 days, $p < .001$), whereas significant differences in ICU LOS between the two groups were not observed (6 vs. 8 days, $p = .32$). Hospital LOS and ICU LOS were comparable between men and women (hospital LOS: 23 [12–37] vs. 21 [12–36] days, $p = .52$; ICU LOS: 7 [3–14.7] vs. 6 [3–13.5] days, $p = .50$).

A very heavy workload of severe sepsis was presented in this study, which was assessed by TISS-28 (24). The median highest TISS score of patients with severe sepsis during their ICU stay was 43 (38–49), equaling 455.8 (402.8–508.8) mins or approximately 7.58 (6.71–8.48) hrs each 8-hr nurse shift. More working time was spent in caring for nonsurvivors than for survivors (8.48 [7.07–9.19] vs. 7.24 [6.36–7.95] hrs, $p < .001$).

The mean hospital cost per case was \$11,390 ± \$11,455, and mean cost per case per hospital day was \$502 ± \$401. The mean daily cost for nonsurvivors was much higher than that for the survivors (\$812 ± \$431 vs. \$301 ± \$155, $p < .001$). However, the overall hospital costs between nonsurvivors and survivors were comparable (\$11,102 ± \$11,907 vs. \$9,862 ± \$10,772, $p = .264$).

DISCUSSION

The present study documented an 8.68% occurrence rate of severe sepsis in surgical ICUs in China, with a hospital mortality rate of 48.7%. There was a higher occurrence rate of severe sepsis in men than in women. Abdomen and lung were the most common sites of infection, and Gram-negative bacteria were predominant among all isolated microbes. In patients with severe sepsis, the lung was the organ affected most often, and cardiovascular and renal dysfunction contributed to higher mortality rate. Comorbidity of malignant neoplasm, admission Acute Physiology Score, invasive fungal infection, Gram-positive bacterial infection, age, and SOFA scores for cardiovascular system and respiratory system were risk factors for hospital mortality in patients with severe sepsis. To our knowledge, this study is the first nationwide multicenter investigation of epidemiology and outcome of severe sepsis in critically ill patients in China.

Concordant to previous studies, severe sepsis was a common syndrome in the ICU and associated with a high mortality rate in China (Table 6). Severe sepsis accounted for 8.68% of admissions to the ICUs in this study, which is similar to the 6–14% range reported by most previous epidemiologic studies (3, 5–8, 15). However, it is significantly different from that reported by Padkin et al. (12) in the United Kingdom (27.1%) and the SOAP study in European countries (30%) (4). The relatively lower occurrence rate in this study may be explained by the strict approach to capture patients with severe sepsis, the characteristics of patient population, the diverse allocation of resources, and the heterogeneous access to health services. In the present study, strict criteria were used to diagnose severe sepsis, which suggests a clear causal relationship between sepsis and acute organ dysfunction, whereas some of the previous studies did not specifically determine this issue (3, 4, 7, 9, 11–13, 15–16). Also, patients admitted for routine surveillance after scheduled surgery with ICU LOS of >24 hrs in the enrolled patients contributed to the underevaluation of prevalence. Meanwhile, fewer patients with immunocompromised admissions, such as AIDS (0 cases in 3,665 patients) and organ transplantation (97 cases in 3,665 patients), which predisposes to severe sepsis, were included. In addition, although ICU resource was shown to be relatively adequate in this study, for more access to intensive care for less sick patients (for example, routine postoperative patients), the incidence of severe sepsis may be potentially underestimated due to the specific routines of the healthy insurance system in China.

Table 5. Multivariate, forward stepwise logistic regression analysis in severe sepsis patients (n = 318), with hospital mortality as the dependent factor

Variables	OR	95% CI for OR	*p* Value
Age[a]	1.52	1.06–2.17	.023
Comorbidity of malignant neoplasm	4.60	1.83–11.55	.001
Gram-positive bacteria infection	1.82	1.01–3.28	.048
Fungal infection	2.21	1.16–4.21	.016
APS[b]	1.84	1.45–2.34	<.001
Respiratory system-related SOFA score[c]	1.36	1.01–1.83	.047
Circulation system-related SOFA score[c]	1.59	1.27–1.99	<.001

OR, odds ratio; CI, confidence interval; APS, Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

[a]Age was divided into the following ranges: <44 yrs, 44–65 yrs, ≥65 yrs; [b]at admission, APS was divided into the following ranges: <5, 5–9, 10–14, 15–19, 20–24, ≥25; [c]at admission, SOFA was divided into the following ranges: <4, 4–7, 8–11, 12–15, 16–19, ≥20.

Table 6. Comparison of epidemiologic studies of severe sepsis

	Setting			Demography of Study Cohort			Demography of Severe Sepsis Patients			
Reference	Time Frame	Region	ICU Characteristic	Median Age, yrs	Male Sex, %	Ethnicity	Median Age, yrs	Male Sex, %	ICU Prevalence, %	Hospital Mortality, %
Present study	Dec 2004 to Nov 2005	China	Surgical	55	58.1	Chinese Han	64	64.8	8.68	48.7
Brun-Buisson et al. (5)	Jan 1993 to Feb 1993	France	General	NA	NA	NA	61.4 (mean)	63.0	9.0	59
Sands et al. (6)	Jan 1993 to Apr 1994	U.S.	General	NA	NA	NA	59[a]	56.0	10.1	34.0[b] (28-day)
Angus et al. (3)[c]	1995	U.S.	General	NA	NA	NA	59	53	11.2	34.1
Wichmann et al. (7)	Feb 1991 to Jun 1998	Germany	Surgical	NA	64.2	NA	61 (mean)	71.3	9.4	65.5
Finfer et al. (8)	May 1999 to Jul 1999	Australia/ New Zealand	General	55.9 (mean)	59.6	NA	60.7 (mean)	56.9	11.8	37.5
Adrie et al. (9)	Nov 2001 to Dec 2001	France	General/surgical/ medical	65.0	63.0	NA	70	70.1	42.0	50.0
Silva et al. (10)	May 2001 to Jan 2002	Brazil	General	65.2	58.7	NA	66.4[a]	59.0[a]	17.4	47.3

ICU, intensive care unit; NA, not applicable.

[a]Age and gender was for patients only with sepsis; [b]mortality for all patients (ICU and non-ICU) with severe sepsis in this study; [c]demography of severe sepsis patients here were derived from the data of ICU admissions in this article.

The analysis of microbiological characteristics of severe sepsis in this study showed that Gram-negative bacteria were the most common pathogens in severe sepsis, which was quite different from the report that Gram-positive bacteria were predominant in previous studies (3, 5–17, 25). Furthermore, fungi, which have been considered to be caused by extensive use of extended-spectrum antibiotics, were frequently isolated in cases of severe sepsis in this study, with 28.3% of the severe sepsis patients having invasive fungal infection. However, microbiological patterns in this study were consistent with some of the previous studies. Tanriover et al. (26) reported that Gram-negative bacteria were the predominant microbes, isolated in 65.9% of sepsis patients in a tertiary care hospital in Turkey. Liu et al. (27) reported that invasive fungal infection was found in 11.6% of ICU admissions in a Chinese university hospital between January 1997 and September 2000 in a retrospective investigation. The SOAP study reported that fungal infection was identified in 17% of ICU admissions with sepsis in multiple European countries (4). The reasons for the changes in the microbiological patterns of severe sepsis in this study are unknown. However, it is probably a result of complex interactions involving patients' underlying conditions, the characteristics of the patient population, the extensive use of extended-spectrum antibiotics, less attention to sanitary precautions, the invasive interventions, and the quality of care provided. The results of this study may directly influence empirical antimicrobial therapy and draw attention to sanitary precautions, such as handwashing in the ICU. In addition, a high isolation rate of *A. baumannii* was found in this study. It is considered to correlate with the high rate of ICU-acquired infection in patients with severe sepsis, as *A. baumannii* has been reported to be the most common source of nosocomial infections in Chinese ICUs (28, 29).

Factors related to an increased mortality in severe sepsis in the present study were consistent with the previous reports (3–5, 7–9, 11–12, 15–17, 30). Higher admission SOFA score of either cardiovascular or respiratory system correlated with increased hospital mortality rate in patients with severe sepsis (Fig. 3). The respiratory dysfunction score may be more noteworthy in the initial stage of severe sepsis because deterioration of lung function occurs earlier and more frequently, whereas the cardiovascular dysfunction score may be more pivotal in predicting the fatal outcome of sepsis. Furthermore, increased mortality caused by invasive fungal infection may suggest that physicians should be more cautious in treating severe sepsis with extended-spectrum antibiotics, as overuse of antibiotics may add risk.

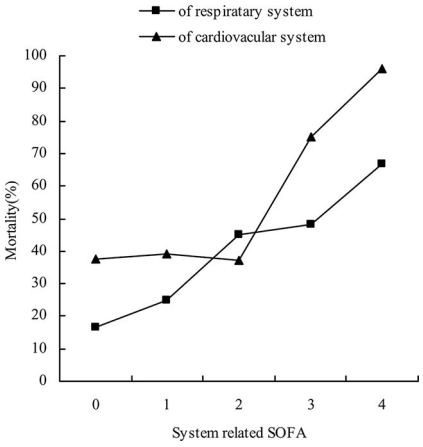

Figure 3. Hospital mortality rate of patients with severe sepsis by cardiovascular system– and respiratory system–related Sequential Organ Failure Assessment (*SOFA*) score at admission to intensive care units. The *points* on the *lines* represent the different mortality rates.

Long ICU LOS and high TISS scores in this study reflected the fact that severe sepsis consumes large ICU resources in China and mean hospital cost for each patient with severe sepsis was ¥ 83,120, which equals to $10,390. Although it seems to be only half of that reported in the United States (3), according to the theory of purchasing power parity (PPP), it is a heavy burden for patients and the public health in China.

The potential limitation of this study relates to the use of a relatively small sample to define the characteristics of severe sepsis in the most populous country of the world. Unfortunately, no national hospital database of sepsis, such as in the United States and European countries, can be accessed on the Internet in China (3, 7–9, 11–13, 15–17). This led to a huge investment of time and money in this study and restrained our team from extending this study to more medical centers and a larger geographical scale. However, the ten participating medical centers in this study are representative of the overall population, for they are located in six provinces that cover almost one third of the nation's population and are large university hospitals, either regionally or nationally (Appendix 3). Moreover, variation in availability of ICU resources and variation in practice patterns in end-of-life care may affect the treatment rate of sepsis. In China, almost all patients with from severe sepsis would be treated in the hospital. However, limited by personnel and financial resources, severe sepsis outside the ICU was not investigated in this study, which disenabled the estimation of the treated rate of severe sepsis (31).

In conclusion, the present study shows severe sepsis is a common, frequently fatal, and expensive condition in ICUs in China. Gram-negative bacteria are the most frequent isolated pathogens in critically ill surgical patients, and invasive fungal infections are identified to be common in these patients. Comorbidity of malignant neoplasm, invasive fungal infection, Gram-positive bacteria infection, Acute Physiology Score at ICU admission, age, and dysfunction of respiratory and cardiovascular systems are the major risk factors contributing to fatal outcome. To establish a national data-handling process for sepsis would be helpful to fulfill longitudinal, large-scale national or international studies in sepsis, to allocate health resource, to improve the outcome of sepsis, to optimize healthcare quality, and to evaluate the effectiveness and efficiency of ICU utilization and care strategies.

ACKNOWLEDGMENTS

We thank ShuiJing Wu, Department of Anesthesiology and Intensive Care Unit, First Affiliated Hospital, School of Medicine, Zhejiang University, and HaiHong Wang, Department of Anesthesiology and Intensive Care Unit, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, for data investigation; Xin Yu and Tao Zhu, Department of Anesthesiology and Intensive Care Unit, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, for data review and management; Hong Xu, Institution of Medical Statistics and Epidemiology, School of Medicine, Zhejiang University, for statistical analysis; Yi Shen, Institution of Medical Statistics and Epidemiology, School of Medicine, Zhejiang University, for statistical review and comments; and Lan Zhang, Department of Anesthesiology and Intensive Care Unit, Sir Run Run Shaw Hospital, School of

Medicine, Zhejiang University, and Qixing Chen, Institution of Organ Transplantation, First Affiliated Hospital, School of Medicine, Zhejiang University, for assistance with manuscript preparation.

REFERENCES

1. Bone RC, Balk RA, Cerra FB, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis: The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101:1644–1655
2. Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31:1250–1256
3. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
4. Vincent JL, Sakr Y, Sprung CL, et al: Sepsis in European intensive care units: Results of the SOAP study. *Crit Care Med* 2006; 34: 344–353
5. Brun-Buisson C, Doyon F, Carlet J, et al: Incidence, risk factors, and outcome of severe sepsis and septic shock in adults: A multicenter prospective study in intensive care units. *JAMA* 1995; 274:968–974
6. Sands KE, Bates DW, Lanken PN, et al: Epidemiology of sepsis syndrome in 8 academic medical centers. *JAMA* 1997; 278: 234–240
7. Wichmann MW, Inthorn D, Andress HJ, et al: Incidence and mortality of severe sepsis in surgical intensive care patients: The influence of patient gender on disease process and outcome. *Intensive Care Med* 2000; 26: 167–172
8. Finfer S, Bellomo R, Lipman J, et al: Adult-population incidence of severe sepsis in Australia and New Zealand intensive care units. *Intensive Care Med* 2004; 30:589–596
9. Adrie C, Alberti C, Chaix-Couturier C, et al: Epidemiology and economic evaluation of severe sepsis in France: Age, severity, infection site, and place of acquisition (community, hospital, or intensive care unit) as determinants of workload and cost. *J Crit Care* 2005; 20:46–58
10. Silva E, Pedro MA, Sogaya ACB, et al: Brazilian Sepsis Epidemiological Study (BASES study). *Crit Care* 2004; 8:R251–R260
11. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554
12. Padkin A, Goldfrad C, Brady AR, et al: Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. *Crit Care Med* 2003; 31:2332–2338
13. Alberti C, Brun-Buisson C, Burchardi H, et al: Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med* 2002; 28:108–121
14. Guidet B, Aegerter P, Dreyfuss D, et al: Incidence and impact of organ dysfunctions associated with sepsis. *Chest* 2005; 127: 942–951
15. Angus DC, Wax RS: Epidemiology of sepsis: An update. *Crit Care Med* 2001; 29(7 Suppl): S109–S116
16. Danai P, Martin GS: Epidemiology of sepsis: Recent advances. *Curr Infect Dis Rep* 2005; 7:329–334
17. Michael R, Karin T, Kirsty B: Epidemiology, prevalence, and sites of infections in intensive care units. *Semin Respir Crit Care Med* 2003; 24:3–22
18. Wang C, Zhang SW, Wang BE, et al: Epidemiologic investigation on multiple organ dysfunction syndrome occurred in Beijing in recent years. *Chin J Trauma* 2004; 20: 730–733
19. Dai JH, Qiu HB, Yang Y, et al: Severe sepsis in ICU during 1991 to 2001: A clinical epidemiologic analysis. *Chin J Multiple Organ Dis Elderly* 2003; 2:114–118
20. Vincent JL, Moreno R, Thijs LG, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996; 22: 707–710
21. Ferreira FL, Bota DP, Vincent JL, et al: Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001; 286:1754–1758
22. Ascioglu S, Rex JH, Pauw B, et al: Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: An international consensus. *Clin Infect Dis* 2002; 34:7–14
23. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13: 818–829
24. Miranda DR, Rijk A, Schaufeli W: Simplified Therapeutic Intervention Scoring System: The TISS-28 items: Results from a multicenter study. *Crit Care Med* 1996; 24:64–73
25. Sundararajan V, Korman T, Visvanathan K, et al: The microbiology and outcome of sepsis in Victoria, Australia. *Epidemiol Infect* 2006; 134:307–314
26. Tanriover MD, Guven GS, Sen D, et al: Epidemiology and outcome of sepsis in a tertiary-care hospital in a developing country. *Epidemiol Infect* 2006; 134:315–322
27. Liu L, Qiu HB, Zhou SX, et al: Epidemiology of invasive fungal infection in intensive care units. *Chin Crit Care Med* 2001; 13:302–303
28. Ye JY, Feng XF, Lin XF, et al: Changes of Gram-negative bacilli and drug resistances of nosocomial infections in intensive care units. *Chin J Microbiol* 2006; 18:236–237
29. Wang GR, Huang YS: Prevailing strains and their drug-resistances of nosocomial infections in intensive care units. *World J Infect* 2005; 5:316–318
30. Moss M: Epidemiology of sepsis: Race, sex, and chronic alcohol abuse. *Clin Infect Dis* 2005; 41(Suppl 7):S490–S497
31. Linde-Zwirble WT, Angus DC: Severe sepsis epidemiology: Sampling, selection, and society. *Crit Care* 2004; 8:222–226

Appendix 1. Definition of invasive fungal infection

	Invasive Fungal Infection
Deep tissue infections	Positive culture result for a sample obtained by sterile procedure from normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine and mucous membranes, or histopathologically or cytopathologically confirmed by needle aspiration or biopsy specimen.
Fungemia	Blood culture that yields fungi in patients with temporally related clinical signs and symptoms compatible with relevant organism.

Appendix 2. Comorbidities

System/Classification	Disease
Cardiovascular	Old myocardial infarction
	Cardiac dysrhythmia
	Congestive heart failure/left heart failure
	Essential hypertension
	Cardiogenic shock or cardiac arrest
	Congenital heart disease
	Rheumatic heart disease
	Peripheral vascular disease
	Cardiomyopathy
	Cardiac pacemaker or defibrillator: electrode(s), lead(s), pulse generator, subcutaneous pocket, coronary artery bypass graft, heart valve prosthesis
Respiratory	Chronic obstructive pulmonary disease
	Asthma and allergies
	Bronchiectasis
	Tuberculosis
	Chronic respiratory failure
	Pulmonary embolism and infarction
Gastrointestinal	Hepatic failure/hepatic coma
	Peptic ulcer disease
	Hepatitis (viral)
	Generalized peritonitis
	Gastrointestinal hemorrhage
	Ill-defined intestinal infections
Neurologic	Intracerebral hemorrhage
	Stroke
	Epilepsy
	Myotonic disorders
	Muscle weakness (generalized)
	Parkinson's disease
Metabolic and endocrine	Diabetes
	Hyperthyroidism or hypothyroidism
Hematologic/lymphatic	Hemophilia
	Secondary thrombocytopenia/primary thrombocytopenia
	Leukemia
	Multiple myelomatosis
	Anemia in chronic kidney disease, congenital anemia, pernicious anemia, constitutional aplastic anemia, sideroblastic anemia, vitamin B_{12} deficiency anemia, folate-deficiency anemia
	Lymphangioma, any site
Renal	Chronic renal disease
	Chronic renal failure
	Vascular disorders of kidney
	Urinary obstruction/urethral stricture (severe)
Immune suppression	Human immunodeficiency virus/acquired immunodeficiency syndrome
	Organ or tissue replaced by transplant
Malignant neoplasm	Malignant neoplasm, except of lymphatic and hematopoietic tissue

APPENDIX 3

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