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Epidemiology and Outcome of Severe Sepsis and Septic Shock in Surgical Intensive Care Units in Northern Taiwan

Chun-Ta Huang, MD, Yi-Ju Tsai, PhD, Pi-Ru Tsai, RN, Chong-Jen Yu, MD, PhD,
and Wen-Je Ko, MD, PhD

Abstract: Severe sepsis remains the leading cause of mortality in the critically ill. Local epidemiological studies on sepsis are of paramount importance to increase our knowledge about sepsis features and to improve patient care and prognosis.

Adult patients (≥ 20 years) admitted to the surgical intensive care units with severe sepsis or septic shock from 2009 to 2010 were retrospectively retrieved and analyzed. The primary outcome of interest was 28-day mortality.

Of 7795 admissions, 536 (6.9%) patients had severe sepsis. The most common sites of infection were the respiratory tract (38%) and abdomen (33%). Gram-negative bacteria, particularly *Klebsiella pneumoniae* (8.6%) and *Escherichia coli* (6.0%), were the major infecting micro-organisms, responsible for approximately two-thirds of the severe sepsis episodes. The overall 28-day mortality rate was 61%, and a higher sequential organ failure assessment score and the use of mechanical ventilation were independently associated with a worse outcome.

Admissions with severe sepsis are not uncommon and are associated with substantial 28-day mortality in surgical intensive care units in northern Taiwan. Establishment and optimization of each institutional sepsis care standard to improve the outcome of sepsis are warranted.

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Abbreviations: ICUs = intensive care units, SIRS = systemic inflammatory response syndrome, SOFA = sequential organ failure assessment.

INTRODUCTION

Despite the advances in medical therapeutics, severe sepsis and septic shock remain the leading cause of morbidity and mortality in intensive care units (ICUs).^{1,2} There have been a number of studies reporting the incidence, characteristics, and outcome of severe sepsis and septic shock from different

regions and countries.^{3–6} Not surprisingly, the incidence and mortality rates widely vary throughout the world, and significant differences in the pattern of causative micro-organisms and infection sites have been observed.⁷ These facts reflect the importance of local epidemiological studies on sepsis to increase our knowledge about sepsis features in different areas and healthcare systems in order to improve patient care and prognosis.⁸

In Taiwan, a recent population-based study demonstrates that the incidence rate of severe sepsis increased from 135 per 100,000 in 1997 to 217 per 100,000 in 2006.⁹ During the same period, although the proportion of patients with multiorgan dysfunction increased from 11.7% in 1997 to 27.6% in 2006, the hospital mortality remained largely unchanged, averaging 30.8%.⁹ However, there is little, if any, information on the demographics and outcome of severe sepsis and septic shock in a specific geographical region of Taiwan. In the present work, we conducted a retrospective descriptive study to evaluate the characteristics, outcome, and prognostic factors in patients with severe sepsis and septic shock in the northern Taiwan. As epidemiology and surveillance data significantly differ between medical and surgical ICU patients,¹⁰ we further specifically focus on events in the surgical ICUs.

METHODS

Study Subjects

This retrospective descriptive study was conducted in the National Taiwan University Hospital, a tertiary referral center in the northern Taiwan. From 2009 to 2010, all patients admitted to the surgical ICUs were eligible for this study. The inclusion criteria were as follows: age ≥ 20 years, and an admission diagnosis of severe sepsis or septic shock. Severe sepsis and septic shock were defined according to the Surviving Sepsis Campaign guidelines.¹¹ In brief, severe sepsis was defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion and septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. If a patient was admitted to the ICUs more than once, only the first episode of severe sepsis or septic shock was counted. This study was approved by the Research Ethics Committee of the National Taiwan University Hospital and the need for informed consent was waived.

Data Collection

Data were collected by a single experienced data collector using standardized forms. The following information was retrieved: demographics, body mass index, comorbidities, Charlson comorbidity index,¹² no. of systemic inflammatory response syndrome (SIRS) met,¹³ sequential organ failure assessment (SOFA) score,¹⁴ smoking status (smoker or ex-smoker vs never-smoker), admission category (surgical scheduled vs surgical unscheduled vs medical), surgical procedure

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From the Department of Traumatology, National Taiwan University Hospital (C-TH); Department of Internal Medicine, National Taiwan University Hospital (C-TH, C-JY); Graduate Institute of Clinical Medicine, National Taiwan University, Taipei, Taiwan (C-TH); School of Medicine, College of Medicine, Fu-Jen Catholic University, New Taipei (Y-JT); and Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan (P-RT, W-JK).

Correspondence: Wen-Je Ko, Department of Surgery, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan (e-mail: kowj480806@gmail.com).

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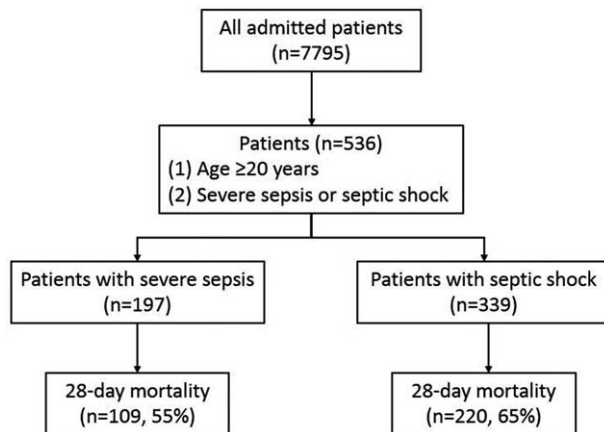


FIGURE 1. Study flow diagram.

(neurosurgery vs thoracic surgery vs cardiovascular surgery vs general surgery), sites of infection, causative micro-organisms, and sepsis-associated complications (septic shock, dialysis-requiring acute kidney injury and need for invasive mechanical ventilation). The SOFA score was determined at the time of ICU admission. Surgical admissions were defined as surgery ≤ 2 weeks preceding ICU admission. Unscheduled surgery was defined as an operation performed ≤ 24 h of onset of symptoms or injury. Considered comorbidities included the presence of diabetes mellitus, chronic obstructive pulmonary disease, malignancy, liver cirrhosis, congestive heart failure, coronary artery disease, chronic kidney disease, and cerebrovascular disease. Sepsis-associated complications were counted if they occurred ≤ 7 days of ICU admission. The main outcome measure of interest was 28-day mortality.

Statistical Analysis

Data were analyzed using the SPSS 15.0 software program (SPSS Inc., Chicago, IL). Data were reported as the mean \pm standard deviation or no. (%), as appropriate. Categorical variables were compared by the chi square or Fisher's exact test when necessary. The Student *t* test was applied to analyze continuous variables. Multivariate logistic regression analysis was used to determine independent predictors for 28-day mortality. Those variables with a *P* value of < 0.05 in the univariate analysis were entered into the multivariate model. A 2-tailed *P* value of < 0.05 was considered statistically significant.

RESULTS

Characteristics of The Study Population

Among 7795 patients admitted to the surgical ICUs during the study period, 536 (6.9%) had severe sepsis and constituted the study population (Figure 1). Clinical characteristics of our patient population stratified by 28-day mortality are shown in Table 1. The average age of patients with severe sepsis was 64.3 years and about two-thirds of them were men. The mean SOFA score and Charlson comorbidity index were 7.8 and 7.5, respectively. The majority of patients had surgery, either scheduled or unscheduled, prior to ICU admission, and general surgery was the most commonly performed surgical procedure. Respiratory failure needing mechanical ventilation, septic shock, and acute kidney injury requiring dialysis were observed in 73%, 63%, and 32% of the severe sepsis patients. Compared

with 28-day survivors, nonsurvivors had a higher SOFA score and were more likely to develop septic shock and be placed on mechanical ventilation.

Etiology and Site of Infection

The respiratory tract (38%) and abdomen (33%) were the most frequent sites of infection (Table 2). In the 28-day nonsurvivors, intra-abdominal infection seemed more common than in survivors. Micro-organisms were identified in only half of the study population and 62 (12%) patients had polymicrobial infection (Table 3). Out of 269 patients with documented microbiological results, Gram-negative bacteria, Gram-positive bacteria, and fungi were isolated in 65%, 25%, and 10% of the severe sepsis patients. The most prevalent species were *Klebsiella pneumoniae* (8.6%), *Escherichia coli* (6.0%), *Acinetobacter baumannii* (5.6%), *Pseudomonas aeruginosa* (5.4%), and *Enterococcus* species (4.5%). The distribution of infecting microorganisms was not significantly different between survivors and nonsurvivors.

Outcome and Its Predictors

The overall 28-day mortality rate was 61%. The multivariate analysis of patient variables and 28-day mortality are shown in Table 4. Patient characteristics associated with increased mortality were a higher SOFA score and the need for mechanical ventilation. On the contrary, ICU admission after surgery, particularly neurosurgery, was associated with a reduced risk of mortality.

DISCUSSION

The objective of this descriptive study was to provide representative data on the incidence and mortality of severe sepsis in the surgical ICUs in northern Taiwan, and the main findings were summarized as follows. First, the incidence of severe sepsis was 69 per 1000 surgical ICU admissions in this study period. Second, respiratory tract infection and intra-abdominal infection were the most common sites of infection. Third, Gram-negative bacteria accounted for the majority episodes of severe sepsis, with predominant micro-organisms being *K. pneumoniae* and *E. coli*. Lastly, the patients with severe sepsis had a 28-day mortality rate of 61%, and a higher SOFA score and the need for mechanical ventilation were independent risk factors of death.

Previous studies have shown that the incidence rates of severe sepsis in ICUs ranged from 4.3% to 27%.^{15–17} Although the incidence of severe sepsis in our surgical ICUs was comparable to the reported data, it was undoubtedly that severe sepsis incidence varied significantly from place to place and from time to time.⁷ Moreover, patient characteristics are different among medical, surgical, or mixed ICUs. Thus, it is important for each ICU to access its own sepsis epidemiology and establish a management policy for patients with severe sepsis. Of note, the relatively lower incidence rate in this study may be explained by the strict inclusion criteria and characteristics of the total patient population. We only enrolled patients diagnosed with severe sepsis or septic shock on ICU admission and did not exclude those who stayed in the ICU for < 24 h for routine postoperative observation as the whole study population.

Our data showed that the respiratory tract, abdomen, and wound and soft tissue accounted for $> 80\%$ of patients with severe sepsis, and the respiratory tract was the principal source of infection, in accordance with the reports from several epidemiological studies of severe sepsis.^{5,15,18} Although respiratory tract

TABLE 1. Characteristics of Intensive Care Unit Patients With Severe Sepsis

Characteristics	Total (n = 536)	Survivors (n = 207)	Nonsurvivors (n = 329)	P Value
Age, years	64.3 ± 15.4	63.0 ± 16.2	65.1 ± 14.9	0.135
Male sex	350 (65)	137 (66)	213 (65)	0.733
Body mass index	23.0 ± 4.7	23.1 ± 4.9	23.0 ± 4.5	0.700
Smoker or ex-smoker	97 (18)	34 (16)	63 (19)	0.425
SOFA score	7.8 ± 3.4	7.2 ± 3.2	8.3 ± 3.5	<0.001
Admission category				
Surgical scheduled	151 (28)	71 (34)	80 (24)	0.036*
Surgical unscheduled	187 (35)	69 (33)	118 (36)	
Medical	198 (37)	67 (32)	131 (40)	
Charlson comorbidity index	7.5 ± 3.9	7.4 ± 3.8	7.6 ± 4.0	0.648
Comorbidity				
Diabetes mellitus	143 (27)	59 (29)	84 (26)	0.449
Liver cirrhosis	32 (6.0)	12 (5.8)	20 (6.1)	0.893
Coronary artery disease	73 (14)	22 (11)	51 (16)	0.109
Congestive heart failure	114 (21)	55 (27)	85 (26)	0.671
COPD	20 (3.7)	6 (2.9)	14 (4.3)	0.420
Chronic kidney disease	94 (18)	31 (15)	63 (19)	0.216
Cerebrovascular disease	39 (7.3)	12 (5.8)	27 (8.2)	0.296
Malignancy	89 (17)	34 (16)	55 (17)	0.929
No. of SIRS criteria met				
2	98 (18)	19 (14)	69 (21)	0.127*
3	260 (49)	106 (51)	154 (47)	
4	178 (33)	72 (35)	106 (32)	
Surgical procedure				
No surgery	198 (37)	67 (32)	131 (40)	0.002*
Neurosurgery	24 (4.5)	18 (9.0)	6 (1.8)	
Thoracic surgery	32 (6.0)	12 (5.8)	20 (6.1)	
Cardiovascular surgery	72 (13)	24 (12)	48 (15)	
General surgery	210 (39)	86 (42)	124 (38)	
Complications				
Septic shock	339 (63)	119 (58)	220 (67)	0.028
Dialysis-requiring AKI	169 (32)	69 (33)	100 (30)	0.476
Mechanical ventilation	393 (73)	142 (69)	251 (76)	0.049

Data are presented as mean ± standard deviation or number (%), as appropriate. AKI = acute kidney injury, COPD = chronic obstructive pulmonary disease, SIRS = systemic inflammatory response syndrome, SOFA = Sequential Organ Failure Assessment.

* By chi-square testing.

infection increased over time and has been associated with the highest mortality,^{19,20} our results did not show a significant difference in 28-day mortality between sites of infection. In the present work, microbial isolates were obtained in only 50% of patients with severe sepsis and 12% of the episodes were polymicrobial. Both the figures were lower than those reported in

the literature. The isolation rates were 60% to 70% and 16% to 55% of severe sepsis were associated with multiple microorganisms in other studies.^{5,10,21–24} The case definition in this study may explain the discrepancy. Our patients had established severe sepsis or septic shock at the time of ICU admission, and this indicates that the culture specimens were mainly collected

TABLE 2. The Source of Infection in Severe Sepsis Patients

	Total (n = 536)	Survivors (n = 207)	Nonsurvivors (n = 329)	P Value
Respiratory	203 (38)	86 (42)	117 (36)	0.164
Urinary tract	41 (7.6)	12 (5.8)	29 (8.8)	0.201
Intra-abdominal	179 (33)	60 (29)	119 (36)	0.086
Wound and soft tissue	94 (18)	42 (20)	52 (16)	0.184
Bone or joint	2 (0.4)	1 (0.5)	1 (0.3)	1.000
Primary bacteremia	45 (8.4)	18 (8.7)	27 (8.2)	0.842
Infective endocarditis	8 (1.5)	4 (1.9)	4 (1.2)	0.493
Prosthesis infection	14 (2.6)	4 (1.9)	10 (3.0)	0.434
Others	17 (3.2)	4 (1.9)	13 (4.0)	0.194

TABLE 3. Distribution of Causative Micro-organisms Isolated From Severe Sepsis Patients

Micro-organisms	Total (n = 536)	Survivors (n = 207)	Nonsurvivors (n = 329)	P Value
Gram-positive bacteria				
Methicillin-susceptible <i>Staphylococcus aureus</i>	21 (3.9)	5 (2.4)	16 (4.9)	0.155
Methicillin-resistant <i>Staphylococcus aureus</i>	14 (2.6)	8 (3.9)	6 (1.8)	0.149
Enterococcus species	24 (4.5)	11 (5.3)	13 (4.0)	0.458
Coagulase negative Staphylococci	6 (1.1)	2 (1.0)	4 (1.2)	1.000
Viridans streptococci	8 (1.5)	1 (0.5)	7 (2.1)	0.160
Other Streptococcus species	7 (1.3)	6 (2.9)	1 (0.3)	0.015
Other Gram-positive bacteria	3 (0.6)	1 (0.5)	2 (0.6)	1.000
Gram-negative bacteria				
<i>Klebsiella pneumoniae</i>	46 (8.6)	19 (9.2)	27 (8.2)	0.696
<i>Acinetobacter baumannii</i>	30 (5.6)	11 (5.3)	19 (5.8)	0.821
<i>Escherichia coli</i>	32 (6.0)	9 (4.3)	23 (7.0)	0.209
<i>Pseudomonas aeruginosa</i>	29 (5.4)	11 (5.3)	18 (5.5)	0.938
<i>Enterobacter</i> species	22 (4.1)	5 (2.4)	17 (5.2)	0.118
<i>Stenotrophomonas maltophilia</i>	10 (1.9)	4 (1.9)	6 (1.8)	1.000
<i>Serratia marcescens</i>	7 (1.3)	3 (1.4)	4 (1.2)	1.000
<i>Citrobacter</i> species	4 (0.7)	2 (1.0)	2 (0.6)	0.642
<i>Burkholderia cepacia</i>	5 (0.9)	3 (1.4)	2 (0.6)	0.379
Other Gram-negative bacteria	31 (5.8)	16 (7.7)	15 (4.6)	0.126
Fungi				
<i>Candida albicans</i>	17 (3.2)	9 (4.3)	8 (2.4)	0.218
Non-albicans <i>Candida</i> species	8 (1.5)	5 (2.4)	3 (0.9)	0.271
Other fungi species	8 (1.5)	4 (1.9)	4 (1.2)	0.493
None isolated	267 (50)	99 (48)	168 (51)	0.465
Multiple pathogens	62 (12)	27 (13)	35 (11)	0.397

outside the ICU setting. In this way, a number of specimens may not be retrieved in a timely manner, more specifically, prior to antimicrobial administration. As we know, antibiotic therapy is anticipated to decrease the yield of cultures.²⁵

The analysis of microbial characteristics of severe sepsis in this study showed that Gram-negative bacteria were the most common pathogens in severe sepsis, and the information was quite different from prior reports that Gram-positive bacteria were predominant.^{1,5,26} However, our microbial

patterns were consistent with some studies in Asia; Tanriover et al²⁷ and Zhou et al³ also reported that Gram-negative bacteria were isolated in >60% of sepsis patients. The reason for the diverse microbiological patterns of severe sepsis is probably a result of complex interactions involving the characteristics of the patient population, institutional infection control measures, hospital policies for antimicrobial therapy, invasive interventions, and healthcare quality provided. In addition, *K. pneumoniae* was the most prevalent

TABLE 4. Multivariate Analysis of Risk Factors for 28-Day Mortality in Patients With Severe Sepsis

Variables	Odds Ratio	95% Confidence Interval	P Value
SOFA score (per point)	1.078	1.018–1.141	0.010
Admission category			
Medical	Reference		
Surgical	0.594	0.371–0.949	0.029
Surgical procedure			
No surgery	Reference		
Neurosurgery	0.266	0.097–0.733	0.010
Thoracic surgery	1.545	0.634–3.766	
Cardiovascular surgery	1.356	0.717–2.564	
General surgery	0.992	0.624–1.579	
Complications			
Septic shock	1.259	0.856–1.850	
Mechanical ventilation	1.542	1.025–2.319	0.038
Micro-organisms			
Other Streptococcus species	0.116	0.013–1.030	

SOFA = sequential organ failure assessment.

pathogen in severe sepsis in this study, a finding reflecting the local-regional microbiological epidemiology. In Taiwan, *K. pneumoniae* is the major cause of liver abscess, brain abscess, lung abscess, thoracic empyema, prostatic abscess, deep neck infection, and complicated skin and soft tissue infection.^{28–30} In short, the results of this study may direct empirical antimicrobial therapy and draw attention to the importance of individual ICU sepsis guidelines.

Respiratory failure and septic shock were observed in >60% of the study subjects and were significantly more common in nonsurvivors than in survivors. In the multivariate model, need for mechanical ventilation was an independent risk factor for sepsis mortality. Previous studies have demonstrated that the use of mechanical ventilation was associated with increased disease severity and long-term mortality.^{31,32} It is speculative that mechanical ventilation *per se* may not only precipitate pre-existing lung injury, but contribute to the development of multiorgan dysfunction syndrome.^{33,34} Therefore, our finding emphasizes the prognostic role of the application of mechanical ventilation in severe sepsis and reminds clinicians of the downsides of invasive ventilatory support.

The outcome of severe sepsis patients varies considerably across different studies. In the past 2 decades, the observed 28-day mortality rates ranged from 13% to 61%,^{35,36} with a pooled mortality of 33%.³⁷ In comparison, the mortality rate of 61% in patients with severe sepsis and septic shock in the present study was higher than that in most studies. A number of factors can explain the difference, such as the patient age, variation in the definition of severe sepsis, comorbidities, sites and types of infection, involved microorganisms, principles of antimicrobial therapy, severity of organ dysfunction, and standard of sepsis care. Several lines of evidence indicate a declining trend in severe sepsis mortality despite the absence of novel sepsis therapeutics.^{6,37} The reason behind this observation may be due to the improved care process, including early antimicrobial administration,³⁸ adherence to early goal-directed therapy,³⁹ and application of lung-protective ventilatory strategy.⁴⁰ Accordingly, so-called standard of sepsis care may contribute to the wide range of mortality rates in various studies. However, this important confounding factor is hard to access from the literature.

Our study has some limitations. First, the generalizability of the single-center experience is limited, but we intend to establish local-regional epidemiology of severe sepsis to improve our understanding and patient care. Second, we studied only patients with severe sepsis and septic shock on ICU admission, but did not include those developing severe sepsis during the ICU stay. In this way, the composition of our study population is more homogeneous and we can provide more specific information to clinicians about severe sepsis, who will accommodate these critically ill patients.

In conclusion, the present study shows that severe sepsis was not an uncommon event in surgical ICUs in northern Taiwan and was frequently associated with a fatal outcome. Respiratory tract infection and intra-abdominal infection were predominant sources of severe sepsis, and Gram-negative bacteria, particularly *K. pneumoniae*, were the major causative micro-organisms. The use of mechanical ventilation in severe sepsis patients was associated with worse prognosis. Undoubtedly, severe sepsis remains an important public health issue, and establishment and optimization of each ICU's sepsis care standard to improve the outcome of sepsis are warranted.

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