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ORIGINAL ARTICLE

# Predictors of mortality in surgical patients with *Acinetobacter baumannii* bacteremia

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**KEYWORDS**
*Acinetobacter baumannii*;
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SOFA score;
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*Background:* *Acinetobacter baumannii* has emerged as an important pathogen of nosocomial infection. The aim of this study was to evaluate the predictors of poor outcome in surgical patients with *A baumannii* bacteremia.
*Methods:* We retrospectively recruited a total of 50 patients who developed *A baumannii* bacteremia within 2 weeks after surgery during a 113-month period. The primary outcome for this study was all-cause 14-day mortality. Clinical and laboratory data, antimicrobial susceptibility, treatment, and Sequential Organ Failure Assessment (SOFA) score were evaluated as possible predictors of outcome.
*Results:* The 14-day mortality was 20% and there was no association between type of surgery and mortality. The SOFA score was the only independent predictor of 14-day mortality after adjustment for other variables. The calibration was acceptable (Hosmer-Lemeshow $\chi^2 = 3.65$, $p = 0.72$) and the discrimination was good (area under the receiver operating characteristic curve: $0.80 \pm 0.07$, 95% confidence interval, 0.67–0.94). We found that a SOFA score $\geq 7$ was a significant predictor of 14-day mortality in surgical patients with *A baumannii* bacteremia.
*Conclusions:* The SOFA score assessed at the onset of bacteremia is a reliable tool for predicting 14-day mortality in surgical patients with *A baumannii* bacteremia.


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## Introduction

*Acinetobacter baumannii* is an aerobic, nonfermentative, gram-negative coccobacillus that is widespread in the natural environment.[1,2] It has emerged as an important pathogen of nosocomial infection and has caused epidemic outbreaks in recent years.[3,4,5] Its rapid acquisition of a wide variety of antibiotic resistance genes has caused serious therapeutic problems worldwide.[6] *A baumannii* is associated with a variety of serious infections in the hospital setting, especially in patients staying in intensive care units,[7] in immunosuppressed hosts,[8,9] and in burn patients.[7] The mortality rate associated with *A baumannii* bacteremia ranges from 17% to 63%.[9,10,11,12] Factors independently associated with poor prognosis of patients with *A baumannii* bacteremia include pneumonia as the source of bacteremia, presence of septic shock, disseminated intravascular coagulation, mechanical ventilator use, acute renal failure, inappropriate antibiotic therapy, and recent surgery.[9,12,13,14]

Surgical patients are at high risk of developing a hospital-acquired infection[15] including *A baumannii* bacteremia. The aim of this study was to evaluate the predictors of poor outcome in surgical patients with *A baumannii* bacteremia.

## Methods

### Hospital setting and study population

Subjects in this retrospective study comprised surgical patients with 2-week postoperative blood cultures positive for *A baumannii* at the Taipei Veterans General Hospital, a 2,900-bed tertiary medical center in northern Taiwan, during the period June 1998 to November 2007. Patients with polymicrobial infections in addition to *A baumannii* were excluded. Patient characteristics, underlying diseases, types of surgeries (based on the *International Classification of Diseases, Ninth Revision, Clinical Modification*), invasive procedures, clinical and laboratory data, antimicrobial susceptibility, treatment, and outcomes were obtained from medical records. The Sequential Organ Failure Assessment (SOFA) score was calculated based on data that had been gathered and recorded at the onset of *A baumannii* bacteremia. Patients with missing values for the calculation of SOFA scores were excluded. The primary study outcome was all-cause 14-day mortality.

### Identification and antimicrobial susceptibility testing

The *A baumannii* isolates had been phenotypically identified by ID 32 GN (Biomerieux, St. Louis, MO, USA) and verified to the genomic species level as *A baumannii* (genomic species 2) by a multiplex polymerase chain reaction method.[16] The antimicrobial agents tested were as follows: amikacin, sulbactam, ceftazidime, ciprofloxacin, cefepime, colistin, gentamicin, imipenem, trimethoprim/sulfamethoxazole, and piperacillin/tazobactam. The minimal inhibitory concentrations of sulbactam, colistin, and imipenem was determined by the agar dilution method and interpreted according to the Clinical Laboratory Standards Institute guidelines;[17] the rest of other antibiotics were performed by the disc diffusion method. A reference strain of *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 was used as the control. Multidrug-resistant *A baumannii* (MDRAB) was defined if the isolate was resistant to three or more classes of antimicrobial agents (including amikin, sulbactam, ceftazidime, ciprofloxacin, cefepime, colistin, gentamicin, imipenem, trimethoprim/sulfamethoxazole, and piperacillin/tazobactam). Extensively drug-resistant *A baumannii* was defined if the isolate was resistant to all commercially available antimicrobial agents except for colistin and tigecycline.

### Definitions

The definition of a surgical patient is someone who had operative procedures performed in the operation rooms. *A baumannii* bacteremia was diagnosed in patients with clinical evidence of infection (such as fever, chills, rigor, leukocytosis, elevated C-reactive protein, or sepsis) and one or more blood isolates of *A baumannii* at the same time.[12] The date of the first positive blood culture was considered the onset of *A baumannii* bacteremia, and the survival time was calculated from the onset of bacteremia. The origin of bacteremia was determined when a specific focus of infection was identified during the bacteremia episode. Pneumonia was defined if there was isolation of *A baumannii* from pulmonary secretion with concurrent infiltrates on chest radiography and clinical signs and symptoms of infection. Central venous catheter infection was defined if there was isolation of *A baumannii* from tip cultures with concurrent clinical signs and symptoms. Urinary tract infection was defined if there was isolation of *A baumannii* from urine cultures with urinalysis demonstrating pyuria. Wound infection was defined based on the clinical judgment of the treating physicians along with an isolation of *A baumannii* from the wound. Intra-abdominal infection was defined if there was isolation of *A baumannii* from specimen obtained from the intra-abdominal cavity.[18]

End-stage renal disease was defined as a creatinine clearance rate $<5$ mL/min that required hemodialysis. Immunosuppressive status was defined in patients with one or more of the following: solid organ or stem cell transplantation, human immunodeficiency virus infection, or treatment with cytotoxic chemotherapy within the previous 6 weeks or more than two doses of steroid or other immunosuppressive agents within 2 weeks before the first episode of *A baumannii* bacteremia.[12] Shock was defined according to the American College of Chest Physicians-Society of Critical Care Medicine consensus conference as evidence of organ hypoperfusion, and either a systolic blood pressure of $<90$ or $>30$ mmHg less than baseline values, or the need for vasopressor/inotropes to maintain blood pressure despite adequate fluid resuscitation.[19] Appropriate antimicrobial therapy was defined as treatment with at least one antibiotic that had *in vitro* activity against the pathogen and administered within 2 days on the date of the blood culture obtained, with correct dosage, and with the use of at least 48 hours; otherwise, it was defined as "inappropriate".

### Statistical analysis

Patients were stratified into two groups according to survival status on Day 14 after the first positive blood culture had been

obtained. Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as a percentage of the total number of patients analyzed. $\chi^2$ test with Yates' correction or Fisher's exact test was used for categorical variables, and Student *t* test or Mann-Whitney rank sum test was used to compare continuous variables as appropriate. The survival curve was plotted by means of the Kaplan-Meier method. Variables with a *p* value $<0.1$ in the univariate analysis were included in a multiple logistic regression model.

The area under the receiver operating characteristic curve was used to test the discrimination ability of the SOFA score.[20,21] We used Hosmer-Lemeshow $\chi^2$ goodness of fit (C statistic) to assess the calibration by comparing the observed mortality rate with the predicted mortality rate.[22] A small $\chi^2$ value suggested good calibration.

All tests were 2-tailed. A *p* value less than 0.05 was considered to represent statistical significance. All statistical analyses were performed with the statistical package SPSS for Windows (Version 17, SPSS Inc., Chicago, IL, USA).

## Results

During the study period, there were approximately 373,100 patients received operative procedures in the operation rooms in our hospital. A total of 179 patients suffered from symptomatic bacteremia because of *Acinetobacter calcoaceticus-baumannii complex* within 2 weeks after having undergone surgery. Among them, 71 episodes of bacteremia because of *A baumannii* genomic species 2 were identified. After excluding the duplicated episodes and those with missing data, we finally recruited 50 patients in our study. There were 17 (34%) patients underwent thoracoabdominal surgeries [intra-abdominal surgery ($n = 15$), heart surgery ($n = 1$), lung surgery ($n = 1$)] and 33 (66%) patients underwent nonthoracoabdominal surgeries [tracheostomy ($n = 15$), permanent catheter implantation ($n = 6$), orthopedic surgery ($n = 4$), wound debridement ($n = 3$), brain surgery ($n = 2$), genitourinary tract surgery ($n = 2$), thyroidectomy ($n = 1$)]. There was no significant difference in mortality between patients who received thoracoabdominal surgeries and those who received nonthoracoabdominal surgeries (mortality rate 29.4% *vs.* 15.2%, $p = 0.277$). The mean age of our study patients was 73.0 ± 17.1 (mean ± standard deviation) years and 39 (78%) patients were male. There was no statistical difference on age or gender among survivors and nonsurvivors (data not shown). The overall mortality rate was 20% at 14 days and 36% at 30 days, and the in-hospital mortality was 48%.

Patient characteristics, underlying conditions, and disease-related characteristics are listed in Table 1. The number of underlying comorbid conditions or the number of invasive procedures before bacteremia onset was not significantly associated with the prognosis (data not shown).

The origin of bacteremia was undetermined in 15 (30%) patients. The most common primary origin was pneumonia (50%) followed by central venous catheter infection (32%), and urinary tract infection (12%). Only three (6%) patients had *A baumannii* bacteremia because of postoperative wound infection and all of them survived. Multiple origins of bacteremia ($\geq 2$) were identified in 14 (28%) patients. Among them, three patients had three sources of bacteremia (one patient had pneumonia, central venous catheter infection, and urinary tract infection, one patient had pneumonia, central venous catheter infection, and intra-abdominal infection, and the other one had pneumonia, central venous catheter infection, and wound infection); all of them survived in 14 days. The other 11 patients had two sources of bacteremia (7 patients had pneumonia combined with central venous catheter infections, 4 patients had pneumonia combined with other site of infections such as urine, wound, and intra-abdominal infections). There was no significant difference in 14-day mortality between patients with single-origin and patients with multiple-origin bacteremia.

Results of *in vitro* antimicrobial susceptibility tests are shown in Table 2. Colistin was the most active agent (100% susceptible), followed by imipenem (72%), sulbactam (44%), and cefepime (38%). Of the 14 imipenem nonsusceptible isolates, 2 were susceptible to sulbactam, 2 were susceptible to cefepime, 2 were susceptible to piperacillin/tazobactm, 1 was susceptible to trimethoprim/sulfamethoxazole, and the other 7 isolates were extensively drug-resistant *A baumannii*. There was no significant difference in mortality between patients with bacteremia caused by carbapenem-resistant *A baumannii* (CRAB) or MDRAB and patients with bacteremia because of carbapenem-susceptible or non-MDR isolates (mortality rate of CRAB *vs.* non-CRAB: 22.2% *vs.* 19.5%, $p = 0.845$; mortality rate of MDRAB *vs.* non-MDRAB: 20% *vs.* 20%, $p = 1.000$). Empiric antimicrobial therapy was administered in 43 (86%) patients at bacteremia onset, but was appropriate in only 10 (23.3%) of them. The rates of appropriate antimicrobial therapy within 2 days are lower in the CRAB and MDRAB groups, but without significant difference (CRAB *vs.* non-CRAB: 11.1% *vs.* 43.9%, $p = 0.066$; MDRAB *vs.* non-MDRAB: 35% *vs.* 50%, $p = 0.382$).

Significant predictors of 14-day mortality in the univariate analysis included inappropriate antimicrobial therapy administered within 2 days of bacteremia onset [odds ratio (OR), 9; 95% confidence interval (CI), 1.15−86.01] and SOFA score (OR, 1.25; 95% CI, 1.00−1.44). Multivariate analysis revealed that SOFA score was the only independent predictor of 14-day mortality (OR, 1.20; 95% CI, 1.00−1.44).

The calibration was acceptable (Hosmer-Lemeshow $\chi^2 = 3.65$, $p = 0.72$) and discrimination was excellent (area under the receiver operating characteristic curve: 0.80 ± 0.07, 95% CI, 0.67−0.94, $p = 0.003$) for SOFA score in predicting 14-day mortality (Fig. 1). The cut-off point with the best sensitivity and specificity was a SOFA score $>7$ (sensitivity: 70, specificity 71). Kaplan-Meier survival curve showed that a SOFA score $>7$ was significantly predictive of 14-day mortality in surgical patients with *A baumannii* bacteremia ($p = 0.024$) (Fig. 2).

## Discussion

Infections caused by *A baumannii* are of great concern worldwide. Although many studies on *A baumannii* bacteremia have been reported, most have involved populations with both monomicrobial and polymicrobial infections.[23] Therefore, we selected surgical patients with monomicrobial bacteremia. To the best of our knowledge, this is the first retrospective study to provide detailed epidemiological characteristics and outcomes of

**Table 1** Demographic and disease-related characteristics in surgical patients with *Acinetobacter baumannii* bacteremia according to 14-day survival status

| Patient characteristics | Alive ($n = 40$)[a] | Dead ($n = 10$)[a] | Total ($n = 50$)[a] | $p$ |
|---|---|---|---|---|
| Underlying condition | | | | |
| Alcoholism | 4 (10) | 3 (30) | 7 (14) | 0.133 |
| Chronic renal insufficiency | 6 (15) | 2 (20) | 8 (16) | 0.653 |
| Chronic obstructive pulmonary disease | 5 (12.5) | 0 (0) | 5 (10) | 0.569 |
| Coronary artery disease | 10 (25) | 3 (30) | 13 (26) | 0.707 |
| Hypertension | 7 (17.5) | 3 (30) | 10 (20) | 0.397 |
| Immunosuppressive status | 23 (57.5) | 4 (40.0) | 27 (54.0) | 0.480 |
| Old cerebral vascular accident | 3 (7.5) | 3 (30) | 6 (12) | 0.086 |
| Smoking | 8 (20) | 4 (40) | 12 (24) | 0.225 |
| Solid tumor | 15 (37.5) | 2 (20) | 17 (34) | 0.461 |
| Type 2 diabetes mellitus | 9 (22.5) | 2 (20) | 11 (22) | 1.000 |
| Invasive procedures before bacteremia onset | | | | |
| Abdominal drain | 9 (22.5) | 3 (30) | 12 (24) | 0.686 |
| Central venous catheter | 32 (80) | 9 (90) | 41 (82) | 0.665 |
| Hemodialysis | 4 (10) | 1 (10) | 5 (10) | 1.000 |
| Infusion of total parenteral nutrition | 5 (12.5) | 3 (30) | 8 (16) | 0.331 |
| Mechanical ventilation | 25 (62.5) | 9 (90) | 34 (68) | 0.138 |
| Origins of bacteremia | | | | |
| Pneumonia | 21 (52.5) | 4 (40) | 25 (50) | 0.725 |
| Central venous catheter infection | 15 (37.5) | 1 (10) | 16 (32) | 0.198 |
| Unknown | 10 (25) | 5 (50) | 15 (30) | 0.247 |
| Urinary tract infection | 5 (12.5) | 1 (10) | 6 (12) | 1.000 |
| Postsurgical wound infection | 3 (7.5) | 0 (0) | 3 (6) | 0.882 |
| Intra-abdominal infection | 2 (5) | 1 (10) | 3 (6) | 1.000 |
| Origins $> 2$ | 12 (30) | 2 (20) | 14 (24) | 1.000 |
| ICU stay at bacteremia onset | 22 (55) | 6 (60) | 28 (56) | 1.000 |
| Inappropriate empiric antimicrobial therapy at bacteremia onset | 29 (72.5) | 10 (100) | 39 (78) | 0.092 |
| Inappropriate antimicrobial therapy within 2 d | 20 (50) | 9 (90) | 29 (58) | 0.031 |
| MDRAB | 32 (80) | 8 (80) | 40 (80) | 1.000 |
| CRAB | 7 (17.5) | 2 (20) | 9 (18) | 1.000 |
| Shock within 1 wk | 13 (32.5) | 5 (50) | 18 (36) | 0.463 |
| SOFA score | $4.9 \pm 4.3$ | $9.3 \pm 4.0$ | $5.8 \pm 4.5$ | 0.005 |

[a] Data are presented as $n$ (%) or mean $\pm$ SD.
CRAB = carbapenem-resistant *Acinetobacter baumannii*; ICU = intensive care unit; MDRAB = multidrug-resistant *Acinetobacter baumannii*; SD = standard deviation; SOFA = sequential organ failure assessment.

surgical patients with *A baumannii* (genomic species 2) bacteremia.

In our study, the 14-day mortality rate was 20% and the 30-day mortality rate was 36%. The origin of bacteremia, the number of co-morbidities, and the number of invasive procedures before bacteremia onset were not significantly associated with 14-day mortality. Although CRAB and inappropriate antimicrobial therapy administered within 2 days have the trend toward poor outcome, we are unable to prove that these factors are significant predictors of increased mortality. This may be because of the small patient number of the present investigation. In our study, all isolates were susceptible to colistin. Because of concerns about the serum concentration of colistin, some authors have proposed that colistin be reserved for salvage therapy rather than being routinely administered as a first-line therapy.[24] Prospective clinical trials are warranted to evaluate the usefulness of colistin as part of empirical antimicrobial therapy in patients suspected of having MDRAB bacteremia. New antimicrobial agents are also urgently needed for the treatment of carbapenem-resistant *A baumannii* infections.

We used the SOFA score to assess the severity of illness. The SOFA score is a well-validated method by which to measure the severity of organ dysfunction.[25,26] The total score consists of components of six major organ systems and a high-SOFA score for any individual organ system is associated with increased mortality. The reason we used the SOFA score instead of other scoring systems is because the SOFA score is easier to calculate. Although we found that the SOFA score is a good predictor of outcome of surgical patients with *A baumannii*, it should be noted that we used one-time scoring at bacteremia onset rather than serial scoring. Ferreira et al.[27] reported that the use of serial SOFA scores provides a more effective representation of the

**Table 2** Antimicrobial susceptibility of *Acinetobacter baumannii* isolates determined by agar dilution and disc diffusion methods

| Antimicrobial agent[a] | MIC (μg/mL) | | | No. of isolates (%) | | |
|---|---|---|---|---|---|---|
| | Range | $MIC_{50}$ | $MIC_{90}$ | Susceptible | Intermediately resistant | Resistant |
| Colistin | 0.25—2 | 1 | 2 | 50 (100) | 0 (0) | 0 (0) |
| Imipenem | 0.25—32 | 2 | 32 | 36 (72) | 4 (8) | 10 (20) |
| Sulbactam | 1 to >64 | 16 | 64 | 22 (44) | 5 (10) | 23 (46) |
| Cefepime | | | | 19 (38) | 9 (18) | 22 (44) |
| Amikacin | | | | 12 (24) | 1 (2) | 37 (74) |
| Ceftazidime | | | | 10 (20) | 0 (0) | 40 (80) |
| Gentamicin | | | | 10 (20) | 0 (0) | 40 (80) |
| Ciprofloxacin | | | | 9 (18) | 2 (0) | 29 (58) |
| Piperacillin-tazobactam | | | | 9 (18) | 10 (20) | 31 (62) |
| Trimethoprim-sulfamethoxazole | | | | 6 (12) | 0 (0) | 44 (88) |

[a] MICs of colistin, imipenem, and sulbactam were performed by agar dilution method; cefepime, amikacin, ceftazidime, gentamicin, ciprofloxacin, piperacillin-tazobactam, and trimethoprim/sulfamethoxazole were performed by disc diffusion method.
MIC = minimum inhibitory concentration; $MIC_{50}$ = minimum concentration inhibiting 50% of isolates; $MIC_{90}$ = minimum concentration inhibiting 90% of isolates.

dynamics of illness. Such calculations, however, can be very laborious. For clinicians, the use of a one-time scoring system is much easier and more practical.

Univariate analysis showed that administration of inappropriate antimicrobial agents within 2 days of *A baumannii* bacteremia onset was associated with increased mortality; however, it was not a significant predictive variable when we controlled for SOFA score. This result may be partly explained by the fact that the severity of illness has a larger impact on 14-day mortality than discordant antimicrobial therapy. We also found that SOFA score >7 is associated with a higher 14-day mortality. This finding may help clinicians to identify patients at high risk of death.

In conclusion, the present study is unique in evaluating factors predictive of mortality among surgical patients with monomicrobial bacteremia caused by *A baumannii*. The SOFA score obtained at bacteremia onset was the only independent predictor of mortality. This result highlights the importance of severity of illness in the outcome of *A baumannii* bacteremia in this patient group. However, the impacts of inappropriate antimicrobial therapy and antibiotic resistant strains are not negligible and should, therefore, be verified by further prospective and randomized studies.

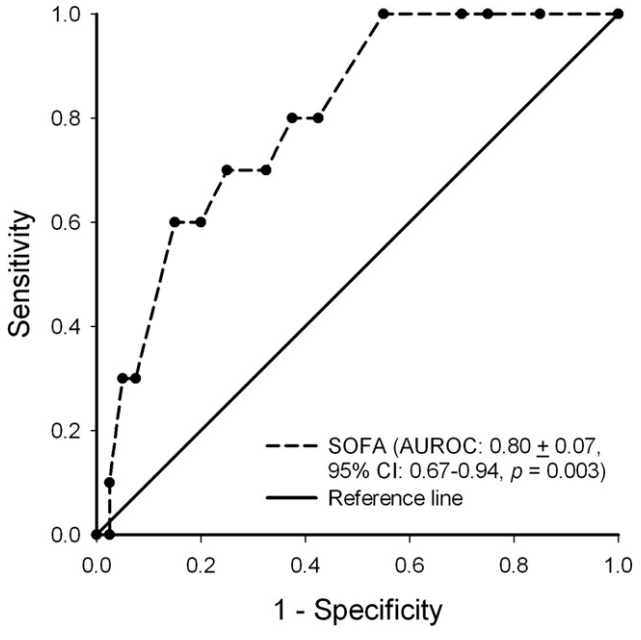


**Figure 1.** Receiver operating characteristic plot of 14-day mortality predictions using the SOFA score for 50 surgical patients with *Acinetobacter baumannii* bacteremia. CI = confidence interval; AUROC = area under the receiver operating characteristic curve; SOFA = sequential organ failure assessment.

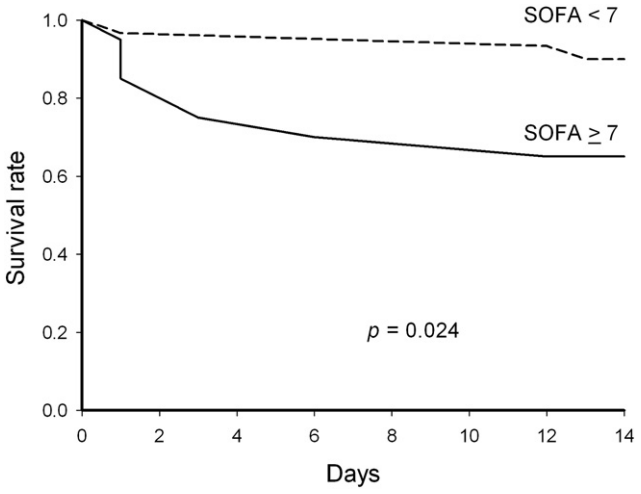


**Figure 2.** Survival curve for surgical patients with *Acinetobacter baumannii* bacteremia. Kaplan-Meier survival analysis showed a significantly reduced 14-day survival rate for patients with SOFA >7. SOFA = sequential organ failure assessment.

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