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# Microbiological and clinical characteristics of *Acinetobacter baumannii* bacteremia: Implications of sequence type for prognosis

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SUMMARY

*Objectives:* *Acinetobacter baumannii* (*Ab*) is an important cause of healthcare-associated infections. Multilocus sequence typing (MLST) provides a highly discriminative typing method. We aimed to determine the clinical impact of *Ab* sequence types (ST) in patients with bloodstream infection (BSI).
*Methods:* Patients with *Ab*-BSI were followed prospectively from 2009 to 2014. We randomly selected one-third of non-duplicate bacteremic isolates for MLST and correlated the *Ab* ST with the clinical course. The primary outcome was all-cause in-hospital mortality.
*Results:* We enrolled 148 patients. Seventy-seven (52.0%) of the isolates were ST2. Patients with ST2-BSI were less likely to be treated with appropriate empirical antimicrobial agents (31.1% vs. 60.6%; $P < 0.001$). They had greater mortality (66.2% vs. 40.8%; $P = 0.003$) than patients with non-ST2-BSI. In the multivariable analysis, ST2 independently predicted greater severity of infection (Pitt bacteremia score) (adjusted odds ratio (aOR), 3.38; 95% confidence interval (CI), 1.75–6.54; $P < 0.001$). Mediated by a higher Pitt bacteremia score (Sobel test $P < 0.001$), ST2 is an independent prognostic factor that predict mortality (aOR, 2.34; 95% CI, 1.07–5.11; $P = 0.03$).
*Conclusions:* ST2 was associated with high rates of inappropriate antimicrobial therapy, severe infection and mortality. Further studies are needed to confirm our findings and explore the potential of role of the virulence.



## Introduction

*Acinetobacter baumannii* is a non-fermentative gram-negative aerobic coccobacillus. It is an important cause of healthcare-associated infections, particularly among immunocompromised patients[1,2] and those in intensive care units.[3,4] *A. baumannii* infections are complicated by prolonged hospital stays, high mortality rates[5,6] and increasing resistance to antimicrobial agents.[7] The mortality rate of *A. baumannii* bloodstream infection (BSI) continues to be high even when treated with appropriate antimicrobial therapy.[8] The factors that contribute to the epidemiology and virulence of *A. baumannii* require further study.

Multilocus sequence typing (MLST) is a highly discriminative method of typing microorganisms.[9] Typing by sequencing the housekeeping genes is used to delineate the clonal relationships of bacterial isolates in epidemiological studies and investigations of outbreaks.[10–12] MLST can be used to study the population biology of bacterial species. For example, sequence type (ST) 8 of methicillin-resistant *Staphylococcus aureus* (MRSA), which contains SCC*mec* IVa, is associated with community-acquired MRSA[13] and the Panton–Valentine leukocidin gene.[14] ST17 vancomycin-resistant enterococci (VRE) possess pathogenicity islands and are resistant to ampicillin. This clonal group has successfully adapted to the hospital environment and is associated with hospital outbreaks.[15] A newly emerging ST414 of VRE has been shown to effect the outcome of VRE BSI.[16]

Similar clonal relationships have been shown for blood isolates of *A. baumannii* isolates.[17,18] *A. baumannii* ST2 has been reported to be a major cause of outbreaks and is associated with antimicrobial resistance.[10,19–21] ST2 exhibits several important virulence factors. These include high biofilm formation and adhesion to A549 pneumocytes[22,23]. ST2 is accounting for 98% of the dominant pulsotypes of *A. baumannii* in Taiwan.[12] However, the association of the various STs of *A. baumannii* with severity of disease and mortality still needs to be defined. The primary aim of the current study was to

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determine whether there are differences in the clinical characteristics of patients with *A. baumannii* BSI according to their STs.

## Patients and methods

### *Hospital settings, isolates, and patients*

This study was conducted at the National Taiwan University Hospital (NTUH), a 2200-bed medical center located in Taipei City. We prospectively enrolled patients with *A. baumannii* BSI during the period from January 2009 through December 2014. Only the first episode was included if the patient had multiple episodes of *A. baumannii* BSI. The study was approved by the Research Ethics Committee of the NTUH (NTUH 201008047R). The committee waived the need for informed consent.

### *Microbiological studies*

The blood cultures were processed by the clinical microbiology laboratory. *A. baumannii* was preliminarily identified by biochemical methods. All the isolates were identified to the genospecies.[24] Patients with BSI caused by *A. nosocomialis* or *A. pittii* were excluded.[25] Sequence typing was performed on one third of randomly selected, non-duplicate isolates of *A. baumannii* collected each year.

### *Antimicrobial susceptibility testing*

MICs were determined using the agar dilution method for ampicillin–sulbactam, levofloxacin, and imipenem, and using the broth microdilution for colistin according to the Clinical and Laboratory Standards Institute (CLSI),[26] and were interpreted according to the CLSI criteria.[26] MICs of tigecycline were determined using agar dilution methods (BBL, BD Diagnostic Systems, Sparks, MD). The FDA approved breakpoints referring to *Enterobacteriaceae* were used for *Acinetobacter* spp. Isolates with an MIC $\leq 2$ mg/L were considered as susceptible.[27]

### MLST

Primer pairs were designed according to the method of Diancourt et al.[10] for polymerase chain reaction amplification and sequencing of internal portions of seven housekeeping genes (*cpn60, fusA, gltA, pyrG, recA, rplB*, and *rpoB*). Details about this MLST scheme can be found at www.pasteur.fr/mlst.[10] Sequence chromatograms were edited and stored using BioNumerics software v6.0. Allele sequences and allelic profiles were compared with those available on the Institut Pasteur's MLST web site at www.pasteur.fr/mlst.

### *Clinical data collection and definitions*

We prospectively recorded the patients' demographic data, underlying diseases, and sites of infection. The sites of primary infection were identified according to definitions of the US Centers for Disease Control and Prevention.[28] When no infectious focus of BSI could be identified, the BSI was classified as primary bacteremia. The Charlson comorbidity index was used to adjust for underlying conditions.[29] Patients with congestive heart failure were defined as those patients regularly had followed-up for chronic congestive heart failure at the out-patient department, and the *A. baumannii* BSI corresponding admission were not due to acute heart failure. BSI severity was assessed using the Pitt bacteremia score at the onset of BSI.[30] All-cause in-hospital mortality was recorded. Only patients whose isolates identified as genospecies of *A. baumannii* were enrolled for clinical analysis.

Onset of BSI was defined as the day when the blood culture was drawn and reported as positive for *A. baumannii*. Appropriate empirical antimicrobial therapy was defined as administration of intravenous antibiotics, to which the isolate was susceptible *in vitro*, within 2 days of the onset of BSI. Tigecycline monotherapy was considered appropriate only if the MIC was $< 1$ mg/L.[31] Healthcare-associated BSI (HA-BSI) was defined as the onset of BSI after a patient had been hospitalized for $> 48$ h.[32] Polymicrobial BSI was defined as other bacteria were co-isolated with *A. baumannii* in the same blood culture. Use of immunosuppressive agents was defined as the receipt of antineoplastic drugs, cyclophosphamide, or other immunosuppressive agents within 6 weeks or receipt of corticosteroids at a dosage $\geq 20$ mg of prednisolone daily for $\geq 2$ weeks or 30 mg of prednisolone daily for $\geq 1$ week before the onset of BSI.[25] The primary outcome was all-cause in-hospital mortality following the onset of *A. baumannii* BSI.

### *Statistical analysis*

Median and interquartile range (IQR) were calculated for continuous variables and percentages for categorical variables. The Mann–Whitney U test was used to compare continuous variables, and $\chi^2$ or 2-tailed Fisher's exact test was used to compare categorical variables. Ordered logistic regression was used to identify factors associated with BSI severity (indicated by the Pitt bacteremia score). Logistic regression and Kaplan–Meier survival analysis were used for outcome analysis. Variables with a $P$ value $\leq .2$ in the univariable regression were added in a stepwise manner and selected for the final model in multivariable analysis. Intermediate variables were tested using the Sobel test.[33,34] Because of over adjustment bias, intermediate variables were not included in the outcome analysis in the final model.[35] Analysis was performed using Stata software (version 14, StataCorp, College Station, TX). Two-sided $P$ values $\leq 0.05$ were considered significant and $\leq 0.10$ were considered borderline significant.

## Results

A total of 148 patients with *A. baumannii* BSI were enrolled during the 6-year study period (2009–2014). About half of the isolates were ST2, 77/148 (52.0%). ST2 were much more likely to be highly resistant to multiple antibiotics than non-ST2 isolates, Table 1. More than 90% of the ST2 were highly resistant to levofloxacin, imipenem, and ampicillin–sulbactam compared to about 30% of non-ST2 isolates ($P < 0.001$). ST2 were also more frequently resistant to tigecycline 36% vs. 5.9%, than non-ST2 isolates ($P < 0.001$). Only one non-ST2 isolates and two ST2 isolates were resistant to colistin.

The demographic and clinical characteristics of the patient population according to sequence type are presented in Table 2. Patients with ST2 BSI were significantly more likely to have a healthcare-associated infection, ($P = 0.003$), ventilator associated pneumonia ($P < 0.001$), a higher Pitt score ($P < 0.001$), inappropriate empirical antimicrobial therapy and all cause, 14 and 28-day mortality ($P < 0.001$). Among the 121 HA-BSI, thirty-nine out of 70 (55.7%) of ST2 and 11 out of 51 (21.6%) of non-ST2 group had infection focus of pneumonia ($P \leq 0.001$). Patients with non-ST2 BSI were more likely to have received immunosuppressive agents ($P = 0.002$), a solid or metastatic malignancy ($P < 0.001$, 0.007) primary bacteremia ($P = 0.003$) and appropriate empirical antimicrobial therapy ($P < 0.001$). Univariable logistic regression showed that appropriate empirical antimicrobial therapy was not significantly associated with mortality (odds ratio (OR), 0.70; 95% confidence interval (CI), 0.37–1.35; $P = 0.29$) (Table 3). After stratification, mortality rates did not differ significantly between patients who received appropriate and those who received inappropriate empir-

**Table 1**
Comparison of minimum inhibitory concentrations and resistance rates of *Acinetobacter baumannii* multilocus sequence type 2 (ST2) and nonsequence type 2 (non-ST2).

| | ST2 ($n=77$) | | Non-ST2 ($n=71$) | | ST2 ($n=77$) | Non-ST2 ($n=71$) | $P$[a] |
|---|---|---|---|---|---|---|---|
| | $MIC_{50}$, $MIC_{90}$ (mg/L) | Range (mg/L) | $MIC_{50}$, $MIC_{90}$ (mg/L) | Range (mg/L) | Resistance, $n$ (%) | Resistance, $n$ (%) | |
| Levofloxacin | 16, 64 | 0.125 to 128 | 0.125, 32 | 0.06 to 64 | 73 (97.3) | 21 (31.3) | <0.001 |
| Imipenem | 32, 128 | 0.125 to > 128 | 0.5, 32 | 0.125 to > 128 | 67 (90.5) | 16 (25.4) | <0.001 |
| Sulbactam | 32, 64 | 2 to > 128 | 2, 32 | 0.5 to 64 | 71 (94.7) | 22 (32.4) | <0.001 |
| Tigecycline | 2, 8 | 0.25 to 16 | 0.25, 2 | 0.125 to 8 | 27 (36) | 4 (5.9) | <0.001 |
| Colistin | 1, 2 | 1 to 4 | 1, 2 | 1 to 4 | 2 (2.6) | 1 (1.4) | 0.99 |

Abbreviations: $MIC_{50}$, 50% minimum inhibitory concentration; $MIC_{90}$, 90% minimum inhibitory concentration.
[a] The susceptibility to various antimicrobial agents was compared between *A. baumannii* sequence types using Fisher's exact test.

**Table 2**
Demographics and clinical characteristics of patients with *Acinetobacter baumannii* bloodstream infection.

| Variable[a] | Sequence type 2 ($n=77$) | Nonsequence type 2 ($n=71$) | $P$ |
|---|---|---|---|
| Demographics | | | |
| Age (years) | 61.1 (44.9–76.2) | 64.3 (52.8–71.5) | 0.78 |
| Sex, male/female | 46 (59.7) | 34 (47.9) | 0.15 |
| Healthcare-associated bloodstream infection | 70 (90.9) | 51 (71.8) | 0.003 |
| Polymicrobial bloodstream infection | 20 (26) | 19 (26.8) | 0.91 |
| Underlying conditions | | | |
| Charlson score | 3 (2–5) | 3 (2–6) | 0.28 |
| Diabetes mellitus with end-organ damage | 4 (5.2) | 1 (1.4) | 0.37 |
| Liver cirrhosis | 12 (15.6) | 16 (22.5) | 0.28 |
| Cerebrovascular disease | 10 (13.0) | 3 (4.2) | 0.06 |
| Coronary artery disease | 2 (2.6) | 0 (0) | 0.50 |
| Congestive heart failure | 10 (13.0) | 2 (2.8) | 0.02 |
| Renal-replacement therapy | 15 (19.5) | 8 (11.3) | 0.17 |
| Chronic obstructive pulmonary disease | 5 (6.5) | 5 (7.0) | 0.99 |
| Autoimmune disease | 3 (3.9) | 2 (2.8) | 0.99 |
| Usage of immunosuppressive agent | 17 (22.1) | 33 (46.5) | 0.002 |
| Leukemia | 8 (10.4) | 2 (2.8) | 0.10 |
| Lymphoma | 4 (5.2) | 1 (1.4) | 0.37 |
| Solid malignancy | 10 (13.0) | 28 (39.4) | <0.001 |
| Metastatic malignancy | 6 (7.8) | 17 (23.9) | 0.007 |
| Infection source[b] | | | |
| Pneumonia | 43 (55.8) | 16 (22.5) | <0.001 |
| Ventilator-associated pneumonia | 37 (48.1) | 10 (14.1) | <0.001 |
| Catheter-related bloodstream infection[c] | 16 (20.8) | 9 (12.7) | 0.19 |
| Intra-abdominal infection | 2 (2.6) | 3 (4.2) | 0.67 |
| Surgical site infection | 4 (5.2) | 7 (9.9) | 0.28 |
| Urinary tract infection | 7 (9.1) | 1 (1/4) | 0.07 |
| Primary bacteremia | 27 (35.1) | 42 (59.2) | 0.003 |
| Clinical characteristic | | | |
| Pitt bacteremia score | 7 (4–8) | 2 (1–5) | <0.001 |
| White blood cell count ($\times 10^3/\mu L$) | 10.8 (2.4–17.2) | 7.3 (3.3–11.6) | 0.21 |
| Leukopenia ($< 4000/\mu L$) | 23 (29.9) | 21 (29.6) | 0.97 |
| Hemoglobin (g/dL) | 9.3 (8.3–10.4) | 10 (8.7–11.7) | 0.03 |
| Anemia ($< 10$ g/dL) | 52 (67.5) | 35 (49.3) | 0.02 |
| Platelet count ($\times 10^3/\mu L$) | 82 (36–161) | 128 (75–205) | 0.01 |
| Thrombocytopenia ($< 50{,}000/\mu L$) | 25 (32.5) | 12 (16.9) | 0.03 |
| Aspartate aminotransferase (U/L) | 49 (24–95) | 38 (27–96) | 0.78 |
| Total bilirubin (mg/dL) | 1.7 (0.9–4.4) | 1.1 (0.7–4.4) | 0.19 |
| Appropriate empirical antimicrobial therapy | 24 (31.1) | 43 (60.6) | <0.001 |
| Outcomes | | | |
| All cause in-hospital mortality | 51 (66.2) | 29 (40.8) | 0.002 |
| 28-day mortality | 46 (59.7) | 22 (31.0) | <0.001 |
| 14-day mortality | 40 (51.9) | 18 (25.4) | <0.001 |

[a] Data are median values (interquartile range) for continuous variables, and number of cases (percentage) for categorical variables. Mann–Whitney U test was used to compare continuous variables, and $\chi^2$ or 2-tailed Fisher's exact test was used to compare categorical variables.
[b] One patient might have more than one infection focus.
[c] All received catheter removal.

ical antimicrobial therapy (62.5% vs. 67.9%; $P=0.80$). There were no significant differences in mortality between the ST2 group and within the non-ST2 group in relation to appropriate therapy (41.9% vs. 39.3%; $P=0.99$). The non-ST2 group had a lower mortality compared with the ST2 group (39.3% vs. 67.9%; $P=0.02$) despite inappropriate empirical antimicrobial therapy. There was a modest, but non-significant lower mortality associated with appropriate empirical antimicrobial therapy in the non-ST2 compared with the ST2 group (41.9% vs. 62.5%, $P=0.13$).

*Mortality analysis*

All-cause in-hospital mortality was significantly greater for the ST2 than the non-ST2 group by univariable logistic analysis (OR 2.84; $P=0.002$) and the Kaplan–Meier survival analysis (hazard ratio (HR) 1.78; 95% CI, 1.12–2.82; log-rank $P=0.01$) (Fig. 1).

There were 64 patients had followed-up blood culture within 14 days of onset of *A. baumannii* BSI. Thirteen out of the 64 patients yielded *A. baumannii* in the followed-up blood cultures. The

**Table 3**
Univariable logistic regression analysis of the factors associated with mortality.

| Variables | Univariable | |
|---|---|---|
| | Crude odds ratio (95% CI) | *P* |
| Demographics | | |
| Age (years) | 1.02 (1.00–1.04) | 0.07 |
| Sex, male | 1.35 (0.71–2.59) | 0.36 |
| Healthcare-associated bloodstream infection | 2.84 (1.18–6.83) | 0.02 |
| Polymicrobial bloodstream infection | 1.75 (0.82–3.73) | 0.15 |
| Underlying conditions | | |
| Charlson score | 0.99 (0.87–1.12) | 0.82 |
| Diabetes mellitus with end-organ damage | 1.29 (0.21–7.93) | 0.79 |
| Liver cirrhosis | 0.98 (0.43–2.22) | 0.96 |
| Cerebrovascular disease | 2.03 (0.60–6.91) | 0.26 |
| Coronary artery disease | 0.85 (0.05–13.82) | 0.91 |
| Congestive heart failure | 2.75 (0.71–10.59) | 0.14 |
| Renal-replacement therapy | 1.73 (0.68–4.37) | 0.25 |
| Chronic obstructive pulmonary disease | 0.84 (0.23–3.03) | 0.79 |
| Autoimmune disease | 3.53 (0.38–32.33) | 0.27 |
| Usage of immunosuppressive agent | 1.44 (0.72–2.87) | 0.30 |
| Leukemia | 8.49 (1.05–68.86) | 0.05 |
| Lymphoma | 3.53 (0.38–32.33) | 0.27 |
| Solid malignancy | 0.39 (0.18–0.83) | 0.02 |
| Metastatic malignancy | 1.13 (0.46–2.76) | 0.80 |
| Infection source | | |
| Pneumonia | 2.02 (1.03–3.98) | 0.04 |
| Ventilator-associated pneumonia | 3.13 (1.48–6.62) | 0.003 |
| Catheter-related bloodstream infection | 1.34 (0.56–3.21) | 0.51 |
| Primary bacteremia | 0.62 (0.33–1.20) | 0.16 |
| Clinical characteristic | | |
| Pitt bacteremia score | 1.57 (1.37–1.81) | <0.001 |
| White blood cell count ($\times 10^3/\mu$L) | 0.99 (0.96–1.03) | 0.69 |
| Leukopenia ($<4000/\mu$L) | 2.31 (1.10–4.86) | 0.03 |
| Hemoglobin (g/dL) | 0.81 (0.68–0.97) | 0.02 |
| Anemia ($<10$ g/dL) | 1.25 (0.65–2.41) | 0.51 |
| Platelet count ($\times 10{,}000/\mu$L) | 0.90 (0.86–0.94) | <0.001 |
| Thrombocytopenia ($<50{,}000/\mu$L) | 6.54 (2.53–16.92) | <0.001 |
| Aspartate aminotransferase (U/L) | 1.00 (0.99–1.00) | 0.50 |
| Total bilirubin (mg/dL) | 1.07 (0.99–1.14) | 0.09 |
| Appropriate empirical antimicrobial therapy | 0.70 (0.37–1.35) | 0.29 |
| Sequence type 2 | 2.84 (1.46–5.54) | 0.002 |

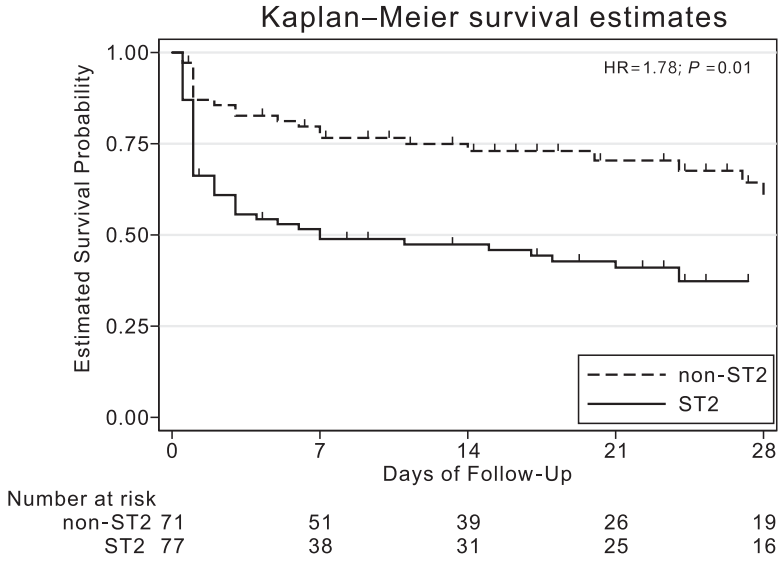


**Fig. 1.** Comparison of Kaplan–Meier survival curves between multilocus sequence type 2 (ST2) and non-sequence type 2 (non-ST2) at 28 days in patients with *Acinetobacter baumannii* bloodstream infection. Abbreviation: HR, hazard ratio.

**Table 4**
Multivariable logistic regression analysis of the factors associated with mortality.

| Variables | Model 1[a] | | Model 2[b] | |
|---|---|---|---|---|
| | Adjusted odds ratio (95% Confidence interval) | *P* | Adjusted odds ratio (95% Confidence interval) | *P* |
| Pitt bacteremia score | 1.64 (1.37–1.95) | <0.001 | Intermediate variable[c] | |
| Age | 1.04 (1.00–1.07) | 0.03 | 1.04 (1.01–1.07) | 0.003 |
| Healthcare-associated bloodstream infection | 2.94 (0.81–10.62) | 0.10 | 3.10 (1.07–9.00) | 0.04 |
| Platelet count (× 10,000/$\mu$L) | 0.88 (0.82 – 0.93) | <0.001 | 0.90 (0.86–0.94) | <0.001 |
| Sequence type 2 | 0.72 (0.25–2.09)[d] | 0.55 | 2.34 (1.07–5.11) | 0.03 |

[a] Pearson goodness-of-fit test, $P = 0.74$.
[b] Pearson goodness-of-fit test, $P = 0.52$.
[c] Pitt bacteremia score was considered as an intermediate variables and not included in the model 2.
[d] If Sequence type 2 was included in model 1.

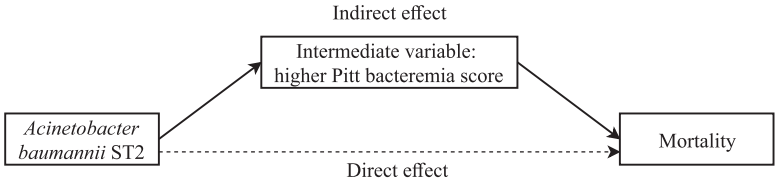


**Fig. 2.** Schematic diagram of the causal pathway between *Acinetobacter baumannii* multilocus sequence type 2 (ST2) and mortality.

mortality group had the median duration of bacteremia (IQR) of 3 days (2–6), and the survival group of 4 days (4–6) ($P = 0.26$). There were 121 patients with HA-BSI. Forty-six out of 70 (65.7%) of ST2 group had mortality, and 25 out of 51 (49.0%) of non-ST2 group had mortality ($P = 0.07$). In the univariable analysis, the significant variables associated with all-cause in-hospital mortality were severity of infection (indicated by the Pitt bacteremia score and thrombocytopenia), underlying malignancy (leukemia or solid malignancy), HA-BSI, VAP, and ST2 (Table 3). Multivariable logistic regression analysis showed that the significant independent predictors for mortality were age (adjusted OR, 1.04; 95% CI, 1.00–1.07; $P = 0.03$), a per 10,000/$\mu$L increment in platelet count (aOR, 0.88; 95% CI, 0.82–0.93; $P < 0.001$), and Pitt bacteremia score (aOR, 1.64; 95% CI, 1.37–1.95; $P < 0.001$) (Table 4, Model 1). ST2 did not independently predict high mortality.

### *ST2 and Pitt bacteremia score*

ST2 was associated with a higher Pitt bacteremia score (7 vs. 2; $P < 0.001$). We analyzed the factors associated with the higher Pitt bacteremia score. ST2 (aOR, 3.38; 95% CI, 1.75–6.54; $P < 0.001$), age (aOR, 1.02; 95% CI, 1.00–1.04; $P = 0.02$), thrombocytopenia (aOR, 2.35; 95% CI, 1.18–4.68; $P = 0.02$) and VAP (aOR, 5.90; 95% CI, 2.88–12.05; $P < 0.001$) were independently associated with a higher Pitt bacteremia score.

Considering the independent ability to predict Pitt bacteremia score by ST2 and the temporal relationship of this association, we reasoned that the Pitt bacteremia score might act as an intermediate variable. The Sobel test showed a significant mediation effect of Pitt bacteremia score between ST2 and mortality (Fig. 2) ($P < 0.001$). Final multivariable logistic regression analysis showed that excess all-cause in-hospital mortality was predicted by ST2 (aOR, 2.34; 95% CI, 1.07–5.11; $P = 0.03$) (Table 4, Model 2).

## Discussion

*Acinetobacter baumannii* has emerged as an important cause of healthcare-associated infections in structurally and immunocompromised patients in large part due to the selective pressure of antimicrobial therapy on more invasive microorganisms. This study was designed to determine whether some strains of *Acinetobacter baumannii* are more virulent than others, and if so, why. We found in this and our previous molecular epidemiology study[12] that sequence type 2 accounted for about half of all bacteremic isolates and were highly resistant to most of the major antibiotics for nosocomial gram-negative bacterial infections. ST2 tended to occupy a special niche as a cause of ventilator-associated pneumonia. Non-ST2 isolates were more likely to be associated with malignancies and immunosuppressive agents and primary bacteremia. ST2 was associated with greater severity of disease and mortality than non-ST2 isolates. We could not find an association with appropriate or inappropriate therapy between the two groups. ST2 was significantly associated with mortality by Kaplan–Meier survival curves, but not independently associated with mortality in model 1, only marginally in model 2 ($P = 0.03$) in the multivariable logistic regression analysis.

The association of ST2 with ventilator-associated pneumonia suggests that it might it have a special ability to colonize mechanically compromised bronchi and lungs. This effect might be related to capsular polysaccharides (CPS). CPS have long been recognized as important virulence determinants.[36] CPS provide protection from host immune responses such as complement-mediated killing and phagocytic killing.[37] CPS of *A. baumannii* has been documented as a major virulence factor.[38] Most of the *cps* gene cluster KL2 containing isolates belongs to ST2.[39] ST2 exhibits virulence features of high biofilm formation and A549 pneumocytes adhesion[22,23]. VAP has been shown to be associated with high mortality among patients with *A. baumannii* BSI.[40]

It is also possible that, because of its high rate of antimicrobial resistance, it accounted for superinfection in severely ill patients who had received multiple antibiotics. Either or both of these factors might explain the independent association of ST2 with ventilator-assisted pneumonia, severity of disease, failure to respond to appropriate therapy and increased mortality.

The Pitt bacteremia score is a good indicator of the severity of BSI[41] and has been shown to have good predictive value in terms of mortality associated with *A. baumannii*.[42]. In our analysis, we found that ST2 (aOR, 3.38; 95% CI, 1.75–6.54; $P < 0.001$) was independently associated with a higher Pitt bacteremia score. There was a reasonable temporal relationship for the association between infection with ST2, greater BSI severity (indicated by the Pitt bacteremia score), and mortality. The Sobel test supported the hypothesis that there was a significant indirect effect.[33,34]

This study has several limitations. First, it was conducted in a single center. The findings need to be validated by a larger multi-

center study. Second, it was a prospective observational study. The patients could not be randomized according to sequence type, demographic characteristics, underlying diseases and therapy. Most of the patients were critically ill with irreversible pathological changes that could not be altered once they developed BSI. Third, although there was a trend for lower mortality with appropriate empirical antimicrobial therapy it did not achieve statistical significance, possibly due to the small sample size.

## Conclusions

In conclusion, *Ab* ST2 was the most common cause of *A. baumannii* BSI in a major teaching hospital in Taiwan. It was associated with high rates of resistance to commonly used antimicrobial agents, ventilator-associate infections, severity of infection and mortality. Its strong association with assisted ventilation may be related to special affinity for respiratory tissues or superinfection in severely ill patients who had received multiple antibiotics, or both. Further studies are needed to confirm our findings and explore the potential of role of special pulmonary virulence.

## Funding

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## Transparency declarations

Conflict of Interest: None to declare.

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