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Saps II-Predicted Mortality in Ventilated Patients with Respiratory *Acinetobacter baumannii* Alone *vs.* Negative Culture

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Abstract

Background: In ventilated patients already critically ill, isolation of *Acinetobacter baumannii* from lower respiratory tract may have clinical importance and the differentiation between infection and colonization can be difficult.

Aim: We sought to overcome the confounding element of critical illness by using Simplified Acute Physiology score (SAPS II) to predict mortality risk and comparing this in critically ill ventilated patients between those with *A. baumannii* alone and those entirely negative lower respiratory tract cultures.

Methods: 138 eligible cases from an urban-based tertiary hospital intensive care unit (ICU) were retrospectively reviewed.

Results: Between 43 patients with *A. baumannii* [mean age (SD): 47 (18.5) yrs; 65% male] and 95 matched patients with negative cultures [51 (17.5); 53%], median risks of hospital mortality were not significant different but the median (IQR$_{25-75}$) length of total hospital stay [19 (11-32) *vs.* 14 (9-21) days, p=0.022] and ICU [8 (4-19) *vs.* 7 (3-9), p=0.010] were significantly longer in *A. baumannii* group. Such findings occur irrespective of whether the underlying lungs were diseased or not and whether the isolates were resistant (except for cefepime-resistance).

Conclusion: Isolation of lower respiratory tract *A. baumannii* alone in critically ill patients is no more likely to cause increased mortality risk than in those with negative culture, and prolonged ICU stay is likely responsible for the acquisition of *A. baumannii*.

Keywords: Simplified acute physiology score; SAPS II; *Acinetobacter baumannii*; Respiratory; Mortality risk; Malaysia

Introduction

Acinetobacter baumannii, a ubiquitous aerobic Gram-negative bacterium with high propensity to multi-drug resistance is a worldwide concern because of its dramatic increase over the past few decades, particularly in the setting of intensive care unit [1]. The continuing debate surrounds the question of whether it is simply colonization with little clinical relevance or requires eradication because of its potential pathogenicity [2,3].

In the obvious cases of active infection, such as overt pneumonia or multiple sites isolation especially from blood of *A. baumannii*, the decision to treat *A. baumannii* is usually straightforward. The dilemma occurs when *A. baumannii* is being isolated in the respiratory specimens of patients lacking evidence of active or ongoing lung infections, normally considered as a colonization that does not require eradication [4].

However in critically ill ventilated patients, isolation of *Acinetobacter baumannii* from lower respiratory tract may have clinical importance and the differentiation between infection and colonization is usually difficult. Furthermore, the decision to eradicate becomes all the more important because of the implications in promoting multi-drug resistance strains. This issue of colonization has added relevance in our region because of the increasing documentation of *A. baumannii* being community-acquired [5-7].

To overcome the confounding element of critical illness and the variety of primary disease conditions in studying the clinical relevance

of *A. baumannii* respiratory isolates, we sought the use of Simplified Acute Physiology Scores (SAPS II), a validated generic severity assessment chiefly based on physiological parameters that predicts mortality risk [8], as primary outcomes of our study. Our assumption is that such an approach would minimize interpretative bias of studies based on absolute mortality rates alone.

To this end, we performed a retrospective review of all our critically ill patients ventilated over a 2-year period, confining our study to cases with single cultures of *A. baumannii* from their lower respiratory microbial isolates and comparing them to a matched cohort in whom lower respiratory isolates were entirely negative for any pathogens. The comparison was carried out with *A. baumannii* as a group, its various resistant phenotypes, and separately as those with and without diseased lungs. Of secondary outcomes, we also studied the length of hospital stay (LOS), specifically looking into LOS in intensive care unit (ICU), and general wards before and after admission to ICU, in relation to

Citation: Loh LC, Yii CTJ, Tong JMG (2012) Saps II-Predicted Mortality in Ventilated Patients with Respiratory *Acinetobacter baumannii* Alone *vs.* Negative Culture. J Medical Microbiol Diagnosis 1:105. doi:10.4172/2161-0703.1000105

their associations with presence of *A. baumannii*. Data on the observed (actual) mortality was also collected for comparison with predicted mortality risk.

Patients and Methods

Data collection

All eligible critically ill patients with documented single cultures of *A. baumannii* and those with entirely negative cultures of any pathogens deriving from lower respiratory tracts, ventilated in the ICU of our urban-based, 800-bed university teaching hospital, were retrospectively reviewed and relevant data collected by a single researcher (CTJY). The study included only lower respiratory tracts specimens as defined by tracheal aspirates and bronchial washings/lavages. These specimens were collected either because of clinical indications or routine microbial surveillance. They were tested based on routine microbial culture of standard bacterial organisms. Data collected consisted of patient demographic characteristics and clinical details which included primary conditions that were being treated, presence of diseased lung (defined as presence of lung pathology confirmed with radiological findings, which included consolidation, fibrosis, pleural effusions and pneumothorax), *in vitro* antimicrobial susceptibility of *A. baumannii*, SAPS II scores collected during the first 24 hrs of admission to ICU, observed hospital mortality and LOS.

Risk of hospital mortality predicted by SAPS II

Risk of hospital mortality was calculated based on SAPS II score [8]. The score consisted of 17 variables (12 physiology variables; age; type of admission, i.e. scheduled surgical, unscheduled surgical, or medical; and three underlying disease variables, i.e. immunodeficiency syndrome, metastatic cancer, and hematologic malignancy). It is a validated generic severity assessment scoring that converts into a probability of hospital mortality without having to specify a primary diagnosis.

Statistical analysis

Differences of patient characteristics between the *A. baumannii* and culture negative groups were assessed either with unpaired t tests for continuous or χ^2 tests for categorical data. Due to a non-Gaussian distribution, medians and interquartile ranges (IQR$_{25-75}$) in *A. baumannii* and culture negative groups were calculated and differences between the two groups assessed by non-parametric Mann-Whitney test for all outcome measures. All statistical analysis and graphic representation of data were carried out on the GraphPad Prism™ graphic and statistical package (Version 3, PC Windows® version). For all statistical tests, p<0.05 was considered significant and based on two-tailed analysis.

Results

One hundred and thirty-eight cases fulfilled the inclusion criteria, of which 43 cases with single cultures of *A. baumannii* alone and 95 with entirely negative cultures. Both groups were comparable in age, gender and ethnicity, and that most respiratory specimens were derived from tracheal aspirates. Importantly, the number of organ failure and comorbidity severity scorings was comparable in both groups. Although there were significant differences regarding the primary conditions being treated, the proportion of diseased lung in both groups was comparable (Table 1).

The observed mortality in the *A. baumannii* and culture-negative groups were comparable (39.5% *vs.* 40%, p=0.959) (Table 1). The

Characteristics	Entire group (n=138)	ventilated patients with respiratory isolates of		P*
		A. baumannii (n=43)	negative cultures (n=95)	
Age, mean yrs (SD)	50 (17.8)	47 (18.5)	51 (17.5)	0.285
Male	57.2	65.1	53.7	0.209
Ethnicity				
Malays	55.1	53.5	55.8	-
Chinese	18.8	16.3	20.0	-
Indians	23.9	27.9	22.1	0.880
Clinical specimens				
Tracheal aspirates	96.4	97.7	95.8	-
Bronchial washings	2.2	2.3	2.1	0.630
Multi-organ failure, n				
None	20.3	14.0	23.2	-
1 to 2	58.7	58.1	58.9	-
≥3	21.0	27.9	17.9	0.266
Comorbidity severity§				
1	50.0	51.2	49.5	-
2	45.7	44.2	46.3	-
3	4.3	4.7	4.2	0.971
Primary diseased condition				
Heart/Lung	50.7	39.5	55.8	-
Abdomen/Liver/Renal	12.3	4.7	15.8	-
Neurology/Trauma/ Orthopaedic	21.7	34.9	15.8	-
Infection/Hematology/ Metabolic/Obstetric	15.2	20.9	12.6	0.013
Presence of diseased lung€				
Yes	57.2	51.2	60.0	-
No	42.8	48.8	40.0	0.331
Hospital mortality	39.5	39.5	40.0	0.959

Figures are in percentages unless otherwise stated.
* p between *A. baumannii* and negative culture groups
¶ SAPS II scores ⁹: Simplified Acute Physiology Scores collected within the first 24 hrs of admission to intensive care unit
§ Comorbidity severity scoring [14]: 1= no important chronic disease; 2= moderate/ severe disease of heart, lungs, gastrointestinal tract; 3= any cancer (except skin), end-stage renal/liver disease.
€ Defined as presence of lung pathology confirmed with radiological findings, which included consolidation, fibrosis, pleural effusions and pneumothorax.

Table 1: Clinical characteristics of ventilated patients with *Acinetobacter baumannii* respiratory isolates alone and those with entirely negative respiratory isolates.

median percentage (IQR$_{25-75}$) risk of hospital mortality between the two groups was not significantly different [43% (18-67) *vs.* 38% (22-57), p=0.632]. When compared with the different phenotypes of resistant *A. baumannii* with culture negative group, cefepime-resistant isolates [59% (28-70)] carried a significantly higher median risk of hospital mortality [p=0.037] (Figure 1A). When comparing total length of hospital stay with culture negative group, the *A. baumannii* group had a significantly longer median (IQR$_{25-75}$) length of stay in days [19 (11-32) *vs.* 14 (9-21), p=0.022]. Except for *A. baumannii* isolates resistant to 3rd generation cephalosporins, this significant difference was also observed with all other *A. baumannii* phenotypes [p=0.006 to 0.014] (Figure 1B).

There was also a higher degree of significant difference in median length of stay in ICU between culture negative group and *A. baumannii* group in totality, [7 (3-9) *vs.* 8 (4-19) days, p=0.010] and with other groups of resistant *A. baumannii* [p<0.001 to 0.003], with the exception of those resistant to 3rd generation cephalosporins (Figure 2A). There

were however no differences in length of stay in the general wards prior to ICU admission and following discharge from ICU between culture negative group with *A. baumannii* group and its various resistant isolate groups (Figure 2B and C). These findings suggest that the significant association with total hospital LOS is primarily contributed by its stay in ICU.

When separated into diseased (57.2%) and non-diseased (42.8%) lung groups, their risks of hospital mortality were not significantly different between *A. baumannii* and culture negative patients [p=0.738 and 0.476 respectively] (Figure 3A). Interestingly, the total hospital LOS between these patients was also not significantly different from each other when patients with diseased and non-diseased lungs were looked at separately [p=0.08 and 0.216 respectively], and only in non-diseased category was patients with *A. baumannii* had significantly longer stay in ICU compared to those with culture negative [median (IQR$_{25-75}$): 8 (5-18) *vs.* 5 (3-9) days; p=0.014] (Figure 3B). When comparing patients with *A. baumannii* and diseased lung with those without *A. baumannii*
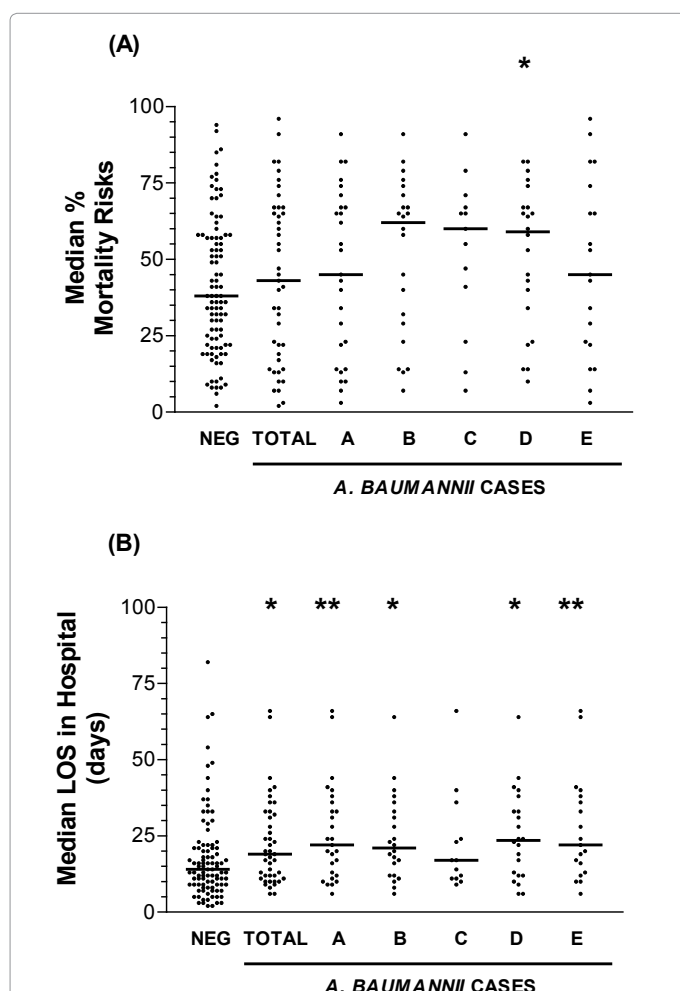

Figure 1: Comparison of (A) median percentage SAPS II-predicted mortality risk and (B) median length of stay (LOS) in hospital in ventilated patients with single cultures of *Acinetobacter baumannii* alone and those with entirely negative respiratory cultures. NEG= negative cultures (n=95); TOTAL= all *A. baumannii* cases (n=43); A= cases resistant to β-lactam/β-lactamase antibiotics (n=27); B= resistant to aminoglycosides (n=22); C= resistant to 3rd generation cephalosporins (n=13); D= resistant to cefepime (n=22); E= resistant to carbopenams (n=19). Bar = median; * = p<0.05; ** = p<0.01.
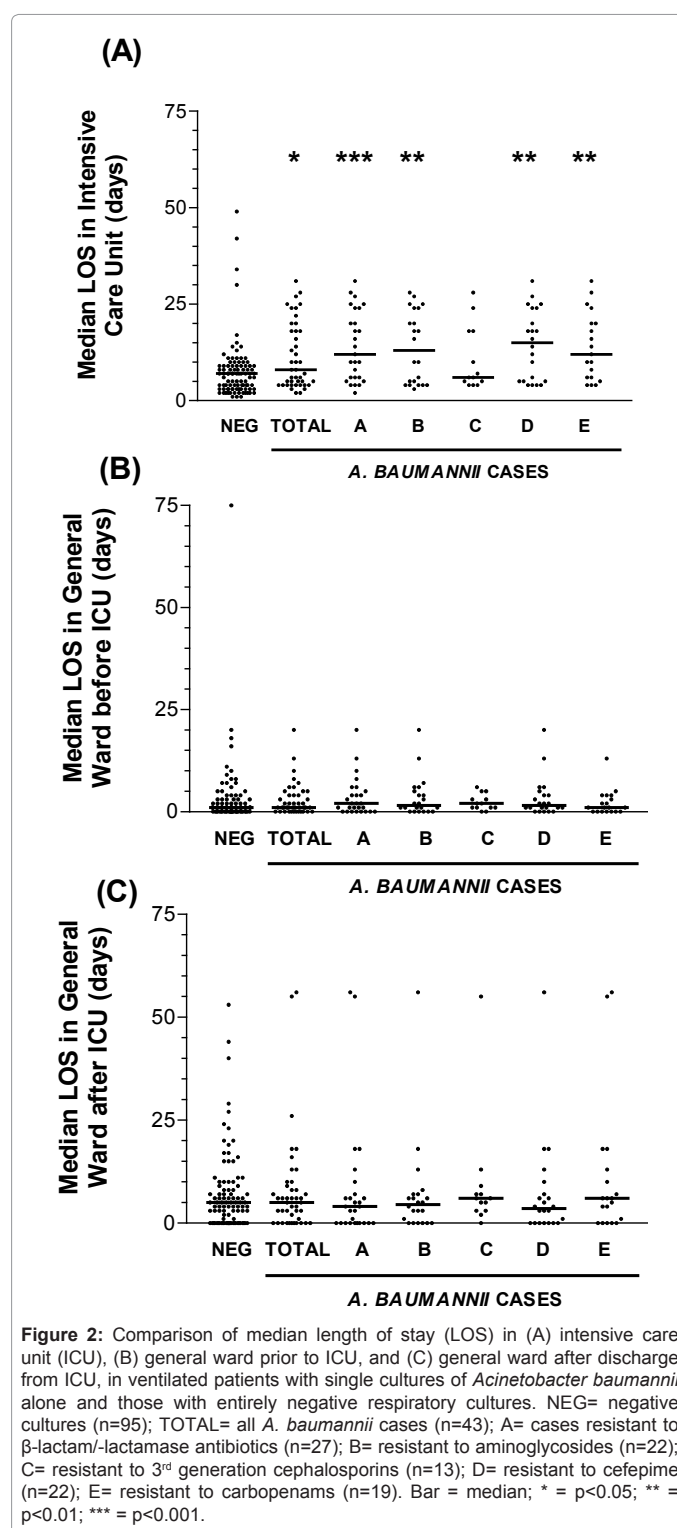

Figure 2: Comparison of median length of stay (LOS) in (A) intensive care unit (ICU), (B) general ward prior to ICU, and (C) general ward after discharge from ICU, in ventilated patients with single cultures of *Acinetobacter baumannii* alone and those with entirely negative respiratory cultures. NEG= negative cultures (n=95); TOTAL= all *A. baumannii* cases (n=43); A= cases resistant to β-lactam/-lactamase antibiotics (n=27); B= resistant to aminoglycosides (n=22); C= resistant to 3rd generation cephalosporins (n=13); D= resistant to cefepime (n=22); E= resistant to carbopenams (n=19). Bar = median; * = p<0.05; ** = p<0.01; *** = p<0.001.

and non-diseased lung, there were no significant differences between mortality risk (40 vs 45%; p=0.241) or length of hospital stay (7 vs 8 days; p=0.211).

To ensure that there were no factors unaccounted for that might explain the differences between culture negative groups and various *A. baumannii* resistant isolates groups and between patients with

diseased and non-diseased lungs, clinical characteristics between them were also compared and did not show any significant differences except for the primary condition being treated [data not shown]. The reason why isolates resistant to 3rd generation cephalosporins, unlike other *A. baumannii* groups, were not significantly different in length of total hospital stay and ICU stay, is unclear. It is possible that the absence of statistical significance here represents a statistical anomaly, since this group had the smallest number of cases (n= 13).

It should be pointed out that we did not capture data on the type(s) of antibiotic used on these patients or whether they were considered appropriate or shown to be susceptible to in vitro microbial data. As such, these data and their association with hospital mortality based on SAPS II were not studied. It is also important to note that our study protocol did not capture data of whether other pathogens including *A. baumannii* were cultured from sites other than respiratory tract. We recognize that all these factors represented real possibilities that could influence our clinical outcomes.

Figure 3: Comparison of (A) median percentage SAPS II-predicted mortality risk and (B) median length of stay (LOS) in intensive care unit (ICU) in ventilated patients with single cultures of *Acinetobacter baumannii* alone and those with entirely negative respiratory cultures, separated into groups with diseased (57 *vs.* 22 patients) and non-diseased lungs (38 *vs.* 21 patients). Bar = median; * = p<0.05.

Discussion

In a study confined to comparing ventilated patients with single culture of *A. baumannii* with those with entirely negative lower respiratory tract isolates, we have shown that *A. baumannii* per se, whether separately in those with or without diseased lungs, or its resistant phenotypes (except for cefepime-resistant *A. baumannii*) for were not associated with increased risk of hospital mortality based on SAPS II. There was significant increase in length of total hospital stay, chiefly contributed by ICU stay, in *A. baumannii* per se and its various resistant phenotype groups (except for 3rd generation cephalosporins-resistant *A. baumannii*) compared to the matched culture-negative group. The significance faded when separated into cohorts with diseased and non-diseased lungs, showing only patients with non-diseased lung culturing *A. baumannii* had significantly longer ICU stay compared to their counterpart.

For some time now, several studies have looked into the clinical impact of *A. baumannii* associated pneumonia in ventilated patients but findings to date have been inconsistent. A case-control study 87 ventilated patients showed that *A. baumannii* acquisition caused increased mortality only in patients with proven infection, as well as excess hospital stay in all cases [9]. However, findings from another similarly designed study of 60 patients did not show that pneumonia by *A. baumannii* was significantly associated with attributable mortality rate, except in patients with imipenem-resistant strains. There was also no association with an increased length of intensive care unit stay [10]. A very recent systematic review observed that infection with or acquisition of *A. baumannii* suggests an association with increased hospital mortality, although the authors admitted that methodological heterogeneity such as appropriateness of matched cohorts and the pooling together of both respiratory and non-respiratory *A. baumannii* cases, makes any conclusion difficult [11]. The controversy seems to hinge upon how confidently infection, rather than colonization, is proven. Moreover it is likely that the appropriateness of initial anti-microbial therapy and adequacy of supportive management would have an influence on clinical outcomes. In critically ill patients where pathogens other than *A. baumannii* are also isolated and in whom use of potent, broad-spectrum antibiotics has taken place, such delineation between 'infection' and 'colonization' can be difficult.

Another important consideration concerns the pathogenicity and virulence of *A. baumannii* which is much less known that its resistance mechanisms. Its virulence is likely to be multifactorial [12]. Antunes LC and colleagues [13] studied four *A. baumannii* strains of different origin and showed that clinical strains, in contrast to non-human isolates, are virulent and that their virulence are comparable regardless of whether they are outbreak or sporadic strains. These virulence factors include exoproducts with hemolytic, phospholipase, protease and iron-chelating activities, as well as those related to biofilm formation, surface motility and stress resistance. What we are observing in clinical practice may be a selected population adapted to infect human host originating from a highly diverse pool of environmental *A. baumannii* genotypically and phenotypically. More research in ongoing with this regard.

Our approach to address the clinical relevance of respiratory *A. baumannii* is generally a pragmatic one. Our findings support the notion that isolation of lower respiratory tract *A. baumannii* alone is no more likely to cause increased risk of hospital mortality than in those with negative culture. Such findings are attested by a study methodology that utilized a generic mortality risk prediction, matched cohort with only
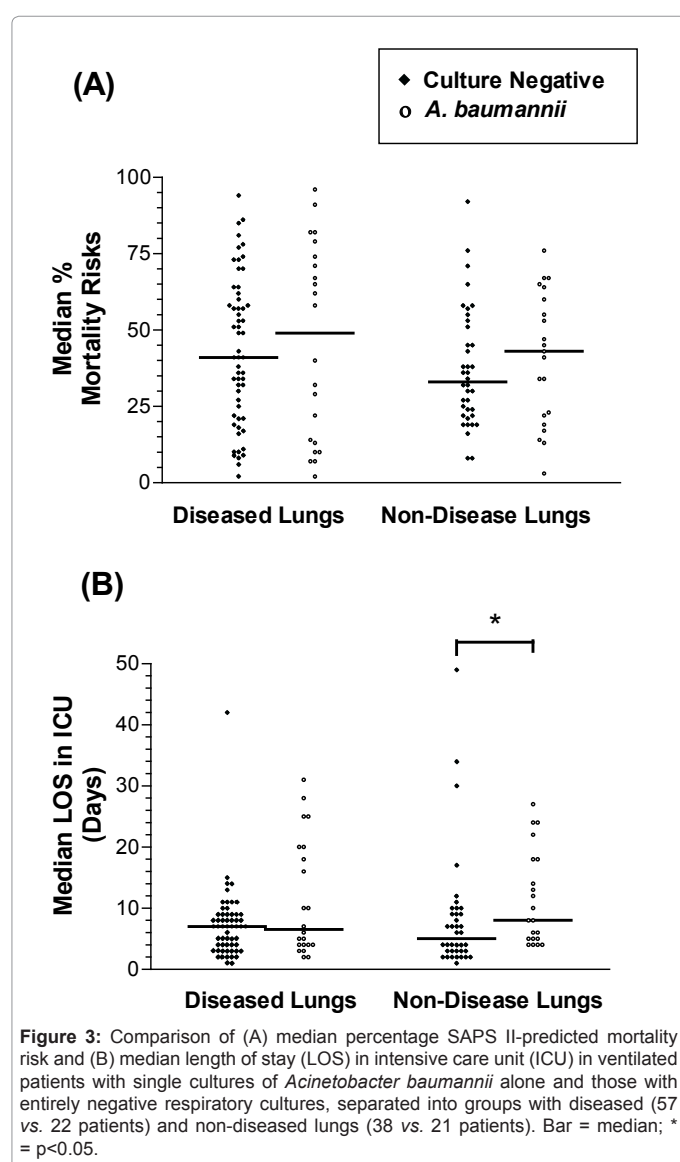
negative respiratory specimens, and separately studying patients with and without diseased lungs, in an effort to reduce bias brought about by the heterogeneity of primary conditions that were being treated and the various treatment interventions as such the type of antibiotic regimes administered during the course of hospital stay. The impact of antimicrobial therapy in such retrospective studies like ours is difficult to be factored in due to the dynamics of prescribing (choices consisting of various drug combinations, timing of initiating and ending courses, varying dosing and clinical indications etc) especially in critically ill patients. Using SAPS II predicted mortality risks as outcome measures instead of crude hospital mortality helps circumvent this problem to a large degree and provides a more reliable indication of the clinical relevance of respiratory *A. baumannii*. In our study, the observed hospital mortality between the two groups was similar.

Its significant association with particularly ICU stay, and not general wards per se, makes a strong case for high *A. baumannii* acquisition from ICU, and not so much community-acquired, an observation already well attested in many Western studies [1,2]. This is especially relevant for East Asia region in view of the frequency of community-acquired *A. baumannii* reported here [4,5,11]. Our observation that only patients without diseased lungs demonstrated significant differences in ICU length of stay between *A. baumannii* and culture negative group is interesting and argues for the equal opportunity for *A. baumannii* existence in both healthy and diseased lungs.

Overall, *A. baumannii* resistant phenotypes defined by their *in vitro* susceptibility profile are not associated with increased mortality risk or length of hospital stay compared with negative cultures alone. The exception observed in patients with cefepime-resistant isolates in relation to mortality risk may suggest a clinical relevance if *A. baumannii* becomes highly resistant. This hypothesis is not borne out with those resistant to carbopenam where no association with increased mortality risk was observed, although carbopenem-resistant strains have been shown to be associated with increased mortality in one study [10]. Furthermore, microbial resistance per se is a distinct characteristic of *A. baumannii* or possibly a reflection of being hospital acquired, and consequently, not always indicative of pathogenicity.

Our study has all the inherent limitations of a retrospective study. The huge degree of exclusion of other *A. baumannii* cases (from an original pool of 523 potential cases that cultured *A. baumannii*) is inevitable at the expanse of searching out a more homogenous study population. Failure to detect significance in differences of mortality may be subjected to Type II error here because of the possibility of a more subtle difference between purely *A. baumannii* and entirely negative cohort, requiring many more cases to refute the pathologenic role of hospital acquired *A. baumannii*. Another important limitation of our study is the absence of quantitative culture to provide support to implicate infection with the organism under study. As a routine, only qualitative culture is conducted in our hospital although quantitative results can be separately requested. We appreciate the lack of this data compromise the accuracy in interpreting the significance of positive cultures. Nevertheless, our findings provide another important perspective in the continuing controversy surrounding the clinical relevance of *A. baumannii*. Particularly, we argue that the presence of lower respiratory tract *A. baumannii* alone is no more likely to cause increased risk of hospital mortality than in those with negative culture in critically ill ventilated patients, and prolonged ICU stay is likely responsible for the acquisition of *A. baumannii* in these patients.

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