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The Role of APACHE-II Score in Predicting *Acinetobacter baumannii* Colonization/Infection and Its Antimicrobial Resistance Pattern in Indonesian Teaching Hospital

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Abstract **Background:** A first precautionary action against *Acinetobacter baumannii (A.baumanii)* can be conducted by identifying well-established risk factors of colonization/infection of that pathogen, such as underlying severity of illness. There are hardly any studies regarding the role of APACHE-II score in predicting risk of *A.baumannii* colonization/infection in Indonesia. **Materials and Methods:** A retrospective, case control investigation was performed with medical and microbiology records of ICU patients in an Indonesian Teaching Hospital from January 2013 to December 2014. **Results:** There were 39 patients with *A.baumannii* colonization/infection and 59 patients with non-*A.baumannii* colonization/infection enrolled in this study. Patients with *A.baumannii* colonization/infection had a significantly higher APACHE II score than non-*Acinetobacter* group, 25.7 and 23.1 (p=0.038), respectively. APACHE II score ≥ 23 had 74.4% sensitivity and 50.8 specificity to *A.baumannii* colonization/infection [odd ratio (OR) 3.00, 95% confidence interval (CI) 1.24-7.24, p=0.013], on the other hand APACHE II ≥ 27 had a 53.8% sensitivity and 78.0% specificity (OR 3.75, 95% CI 1.57-8.95, p=0.002). The highest susceptibility level of antibiotics against *A.baumannii* in this study was shown by tigecycline (82.1%) and amikacin (84.6%). **Conclusions:** APACHE-II score was strongly correlated with *A.baumannii* colonization/infection and a cut-off value of APACHE II score ≥ 23 may be used to depict increased moderate risk of *A.baumannii* colonization/infection. While the use carbapenem against *A. baumannii* infection was not recommended, tigecycline and amikacin may be considered as antibiotics of choice in treating *A.baumannii* infection in our hospital setting.

Keywords: *A.baumanii, APACHE-II score, colonization, risk factors*

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1. Introduction

Acinetobacter species, specifically its most known and studied species, *Acinetobacter baumanii (A.baumannii)*, is undoubtly recognized and on the forefront of the most feared pathogen in ICU settings worldwide [1,2,3]. The well-known capability of acquiring resistance against various types of antibiotics and the survival characteristic under wide range of environmental conditions are not only perilling infected patients, but also threaten physicians [2,3]. Underlying severity of illness has been documented as one of the risk factors for colonization with *Acinetobacter* species [3], but studies regarding the cut-off value of such scoring systems in predicting risk of *A.baumannii* colonization/infection are scarce. APACHE-II (Acute Physiology and Chronic Health Evaluation II) is one of the well-known scoring system that was found useful for classifying patients according to their disease severity [4], and still widely used among Indonesian ICU (Intensive Care Unit).

In the last decades, the emergence and rapid spread of Multidrug-resistant (MDR) *A.baumannii* have caused a serious clinical problem worldwide [1,2,3]. Ironically, the drug resistance pattern of *A.baumannii* in Indonesia, which is very critical concerning the management of infection against this pathogen, is lacking.

Therefore, the main objectives of this study were to evaluate the role of APACHE-II score in predicting *A.baumannii* colonization/infection and its antimicrobial resistance pattern in our teaching hospital setting.

2. Materials and Methods

2.1. Study Design

A retrospective, case control investigation was performed using ICU patient's records from January 2013 through December 2014 in Siloam Hospital Lippo Village, Tangerang, Indonesia. The case group was defined by patients admitted to ICU with positive culture of *A.baumannii* from any parts of body, including the excretions of secretions. Any patients in ICU with positive culture of microorganisms other than A. *baumannii* were classified as the control group.

The identification and antimicrobial susceptibilities of the isolates were done with Vitex-2 System® (bioMérieux, France). Zone diameter and MIC interpretive criteria for all antimicrobial agents based on the standards of Clinical Laboratory Standards Institute. *Escherichia coli* ATCC® 25922, *Pseudomonas aeruginosa* ATCC® 27853 were used as control strain, and *Escherichia coli* ATCC® 35218 for β-lactam/β-lactamase inhibitor combinations [5].

The multi-drug resistance (MDR) defined as *A. baumannii* who was resistant to penicillin, cephalosporin, fluoroquinolone and aminoglycoside type antibotics. Extensive-drug resistance (XDR) defined as MDR along with the carbapenem resistance. Polymyxin and tigecycline resistance along with XDR was defined as Pan Drug Resistance (PDR) [6].

2.2. Data Collection

The data of both groups were collected from medical and microbiological records that include the patient demographic details, diagnosis and disease classification, the length of ICU stay, antimicrobial susceptibility patterns, and its outcome. APACHE-II score was calculated based on existing clinical data at 24-hour after cultures were obtained.

2.3. Statistical Analysis

Independent T-test analysis was used to look for mean difference of APACHE-II score and length of ICU stay, between the positive *A.baumannii* and non-*A.baumanii* colonization groups. Correlation of outcome between the two groups was analysed using Pearson chi-square. The APACHE-II cut off point and diagnostic value was calculated with the Receiver Operator Characteristic (ROC) curve analysis. Statistical analyses were performed using SPSS Statistics 17th version (SPSS Inc, 17).

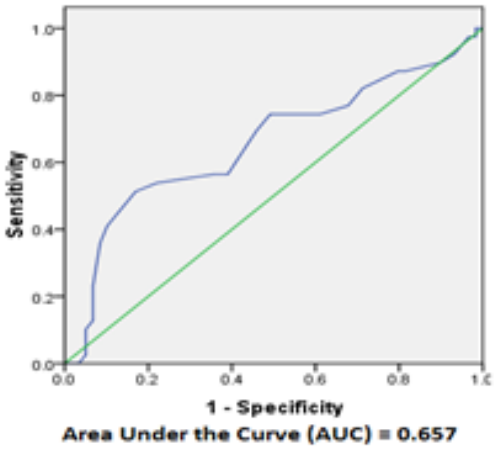

Figure 1. ROC curve for predicting *A.baumanii* colonization/infection

3. Results

3.1. Patient Characteristics

From January 2013 through December 2014, there were 53 patients with *A.baumannii* colonization/infection. Of 53 patients, 14 had either missing or incomplete information. The characteristics of study population (n= 98) were shown in Table 1. The non-*A.baumannii* group isolate was consisted of *Candida spp*. (27/59), *Pseudomonas spp*. (11/59), *Klebsiella spp*. (10/59), *Staphylococcus spp*. (6/59), *Escherichia coli* (3/59), *Aeromonas hydrophila* (1/59) and *Kodamaea Ohmeri* (1/59).

Table 1. Characteristics of the study population with *A.baumanii* and non-*A.baumanii* colonization/infection (January 2013-December 2014)[1]

Parameters	*A.baumannii* group (n=39)	Non-*A.baumannii* group (n=59)
Mean age (year)	54.6 ± 18.6	56.4 ± 14.9
Gender (%)		
Male	32 (82.1)	49 (83.1)
Female	7 (17.9)	19 (16.9)
Mean APACHE II score on ICU admission	25.7 ± 6.2	23.1 ± 6.1
Mean duration of ICU hospitalization	17.2 ± 15.4	8.6 ± 7.6
Site of clinical samples (%)		
Sputum	32 (82.0)	54 (91.5)
Bronchial fluid	2 (5.1)	2 (3.4)
Wound	1 (2.6)	2 (3.4)
Blood	2 (5.1)	1 (1.7)
Urine	1 (2.6)	0 (0)
Cerebrospinal fluid	1 (2.6)	0 (0)
Underlying Illness (%)		
Central nervous system disorder	20 (20.4)	35 (35.7)
Gastrointestinal disease	3 (3.1)	6 (6.1)
Lung disease	3 (3.1)	7 (7.1)
Renal disease	0 (0)	6 (6.1)
Sepsis	5 (5.1)	2 (2.0)
Liver disease	0 (0)	1 (1.0)
Rheumatological disease	1 (1.0)	0 (0)
Cardiovascular disease	2 (2.0)	1 (1.0)
Endocrinal disease	1 (1.0)	0 (0)
Multiple trauma	4 (4.1)	1 (1.0)

[1]Data presented as n (%) or mean ± standard deviation.

The majority site of *A.baumanii* and non-*A.baumannii* isolation were from the respiratory tract (sputum and bronchial fluid), accounting for 34/39 (87.1%) and 56/59 (94.9%) of all patients analysed (Table 1). *A.baumanii* or non-*A.baumanii* colonization in the wound, blood, cerebrospinal fluid, and urine were less common for both samples (Table 1).

3.2. Association of APACHE II and *A. Baumannii* Colonization/Infection

Patients with *A.baumannii* colonization/infection have a significantly higher mean of APACHE-II score than non-*A.baumanni* group, 25.72 ± 6.20 and 23.07 ± 6.05 (p=0.038), respectively. The study found that APACHE-II score of ≥ 23 defined predicting *A.baumanii* colonization/infection with sensitivity of 74.4%, specificity 50.8%, accuracy level 75.0%, and likelihood ratio (LR) 1.5 as shown in Table 2.

3.3. Antibiotic Susceptibility Patterns of *A.baumannii*

The antibiotic susceptibility level of *A.baumannii* to 20 antibiotic regimens was shown in Table 3. Only 1 out of 39 samples considered MDR *A.baumannii*. The highest susceptibility level was shown by tigecycline (82.1%) and amikacin (84.6%). Carbapenem-Resistant *A.baumannii* was found in 29/39 (74.4%) samples. Trimetoprim/ sulfamethoxazole was 56,4% susceptible to *A.baumannii*.

Table 2. Diagnostic value of various cut-off point of the APACHE-II in predicting risk of *A.baumannii* colononization/infection

APACHE II	Sensitivity (%)	Specificity (%)	LR +	Accuracy (%)
≥ 21	76.9	32.2	1.134	67.9
≥ 22	74.4	39.0	1.220	71.9
≥ 23*	74.4	50.8	1.512	75.0
≥ 24	69.2	54.2	1.511	72.7
≥ 25	56.4	61.0	1.446	67.9
≥ 26	56.4	64.4	1.584	69.1
≥ 27	53.8	78.0	2.445	71.4

*Best cut off point.

Table 3. Antibiotics susceptibility patterns of *A.baumanii*

Antibiotics	Resistant n (%)	Sensitive n (%)
Amikacin	6 (15.4%)	33 (84.6%)
Gentamicin	28 (71.8%)	11 (28.2%)
Ampicillin/sulbactam	31 (79.5%)	8 (20.5%)
Piperacillin/tazobactam	27 (69.2%)	12 (30.8%)
Ceftazidime	32 (82.1%)	7 (17.9%)
Ceftriaxone	37 (94.8%)	2 (5.2%)
Cefepime	27 (69.2%)	12 (30.8%)
Ciprofloxacin	28 (71.8%)	11 (28.2%)
Levofloxacin	30 (76.9%)	9 (23.1%)
Meropenem	29 (74.4%)	10 (25.6%)
Tigecycline	7 (17.9%)	32 (82.1%)
Trimetoprim/sulfamethoxazole	17 (43.6%)	22 (56.4%)

4. Discussion

APACHE II score and its studies regarding its role in predicting *A.baumannii* colonization/infection were scarce. Several studies concerning APACHE II score and increased risk of mortality rate in *A.baumannii* colonization/infection, and APACHE II score and increased risk of *A.baumannii* bacteremia were well documented [7,8,9,10]. Higher mean of APACHE II score or modified APACHE II in patients with *A.baumannii* colonization/infection were also documented previously and in accordance with the result of this present study [11], but its cut-off value in depicting risk of *A.baumannii* acquisition was never been studied.

There were two cut-off value worthy to be considered, those were, higher or equal to 23 and ≥ 27. Both scores had their own strengths and weaknesses. APACHE II score higher or equal to 23 had lower specificity (53.8% vs. 78.0%), lower odds ratio (OR) and positive likelihood ratio (3.00 vs 3.75 and 1.51 vs. 2.45), but had higher sensitivity (74.4% vs. 53.8%), and more negative likelihood ratio (0.50 vs 0.59) than APACHE II score higher or equal to 27, respectively. The sensitivity and specificity of this APACHE II score may not matter much, but the result of odd ratio, LR+, and LR- may depict risk of *A.baumannii* colonization/infection. APACHE II score ≥ 23 can be used as a threshold of increased moderate risk of colonization/infection by *A.baumannii* (OR 3.00; LR+ 1.5), while score below the cut-off value may be considered low risk. [12]. APACHE II score ≥ 27 were more specific and implied a greater risk of colonization/infection by *A.baumannii* (OR 3.7; LR+ 2.45). We suggest using cut off value greater or equal to 23 as a cut-of value of an increased moderate risk of *A.baumannii* colonization/infection in ICU settings. Together with previously documented risk factors [3,10], such as, prolonged length of hospital stay, use of mechanical ventilation, colonization pressure, prior antibiotic therapy, recent surgery, and invasive procedures, a score of APACHE II ≥ 23 increase risk greatly to *A.baumannii* colonization/infection. A cut off value of ≥ 23 may not be used as an indication of empirical antibiotic therapy against *A.baumanii*, as study conducted in Taiwan concluded that only patients with high APACHE II score had therapeutic benefit (OR for patients with scores > 25 and ≤ 35, 0.16 [95% CI, 0.07–0.37]; OR for those with scores > 35, 0.06; 95% CI, 0.01–0.25) [13].

Only 1 out of 39 isolates was considered as MDR-*Acinetobacter* species in this current study. These inconsistencies with previous studies, where MDR Acinetobacter isolates were found in majority or all isolates [11,14], may be resulted because of different definition of multi-drug resistant used in the studies. Previous study conducted by Emine et al., 2009 in Turkey used the definition of MDR as diminished susceptibility to 2 or more of the following 5 antibiotic classes: antipseudomonal cephalosporins, antipseudomonal fluoroquinolones, carbapenems, β-lactam–β-lactamase inhibitor combinations, and aminoglycosides which were

suggested by Paterson, 2006 [11,15]. In this current study, MDR-Acinetobacter was defined as resistant against penicillin, cephalosporin, aminoglycoside, and fluoroquinolone [5], whereas resistant against more than three classes of antibiotics was categorized as MDR-*Acinetobacter* in study by Dent et al., 2010 [14]. To date, internationally, there are no accepted definitions to describe the extent of antimicrobial resistance among *Acinetobacter species*. Thus, a great confusion of the terms was ensued and the urgency of clarifying the definition was enforced more than ever [16].

The highest susceptibility level was shown by tigecycline (82.1%) and amikacin (84.6%) from this study. Amikacin and trimethoprim-sulfamethoxazole susceptibility level of this study differed greatly from the other studies. Amikacin susceptibility is still high (84.6%) compared to 15% in Emine et al., 2009 and 3% in Ntusi et al., 2012 [9,11]. Low susceptibility of *Acinetobacter* to trimethoprim-sulfamethoxazole (18.5%) was found by Ntusi et al., 2012 in South Africa, while only 43.6% trimethoprim-sulfamethoxazole-resistant strain was isolated in this current study [9]. An inconsistent finding was found in the Indonesian studies in neonatal intensive care unit [17]. The different patterns of antimicrobial resistance may represent patterns of antibiotics usage in each hospital. While more studies of *A.baumannii* antimicrobial resistance pattern in Indonesia were needed, amikacin and tigecycline may still be considered as antibiotics of choice in treating *A.baumannii* infection in this local hospital. The isolation rate carbapenem-resistant strains were similar with other studies, ranging from 69-89% of all isolates [9,18]. The high rates of resistance against carbapenems may be an indication of inappropriate or overuse of carbapenems in the hospital. This emerging resistance should not be taken lightly and must be acted upon promptly by the international health care community [17,19].

This study had several limitations. First, the limited methodological study design in assessing risk factors for *A. baumannii* acquisition may lead to selection bias, especially because of the undocumented colonization pressure and the usage of invasive equipment, such as central venous catheter (CVC), endotracheal tube (ETT), and ventilator. Second, no classification between colonization and infection of *A.baumannii* may statistically influence the result this study. Last, the small sample size may have affected the power of the study.

5. Conclusions

APACHE-II score was strongly correlated with *A.baumannii* colonization/infection and a cut-off value of APACHE II score $\geq$ 23 may be used to depict increased moderate risk of acquiring *A.baumannii* colonization/ infection. No accepted definitions to describe the extent of antimicrobial resistance among *Acinetobacter species* may resulted in discrepancies of the prevalence of MDR-*Acinetobacter*, therefore the need to clarify the definition was enforced. While the use carbapenems against *A. baumannii* infection was not recommended, tigecycline and amikacin may be considered as antibiotics choice in treating *A.baumannii* infection in this local hospital.

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Author's Contributions

All authors equally contributed in this work.

Statement of Competing Interest

The authors have no competing interest.

Ethic

This article is original and contains unpublished material. All authors have read and approved the final manuscript and no ethical issued involved.

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