

Original Article

## Frequency of OXA-Type carbapenemases among carbapenem-resistant *Acinetobacter baumannii* in clinical isolates from adult intensive care unit in India

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### ABSTRACT

**Objectives:** *Acinetobacter baumannii* is a highly virulent bacteria in modern health care, with a high ability to acquire antimicrobial resistance. Carbapenemases production appears to be the most common mechanism involved in drug resistance to carbapenem. As the prevalence of carbapenem-resistant *A. baumannii* was high in intensive care unit (ICU) patients, this study was designed to find the frequency of oxacillinases (OXA) genes including OXA-23, OXA-24, OXA-51, and OXA-58.

**Materials and Methods:** A clinical specimen was collected from patients admitted to the adult ICU. DNA was isolated from carbapenem-resistant *A. baumannii* and amplified using conventional polymerase chain reaction technique and gel electrophoresis for visualization of results.

**Statistical Analysis:** Data were entered into Microsoft Excel and was analyzed using SPSS version 23 (IBM SPSS statistics, Somers New York, United States).

**Results:** The frequency of the OXA-23 gene was high with 87.5%, followed by OXA-51 gene with 73.2%. All 56 isolates were negative for the OXA-24 and OXA-58 genes. We also found that both OXA-23 and OXA-51 genes coexisted in 40 (71.4%) isolates. No significant difference was found between drug-resistant genes (OXA-23 and OXA-51) and clinical outcomes. The relationship between the presence of OXA gene was compared between survivors and nonsurvivors, which was found out to be nonsignificant. The presence of OXA genes showed no significant increase in the length of hospital stay. The significant association between acute physiology and chronic health evaluation IV scores and clinical outcome was calculated, and it was evident in the comparison of the discharged and died groups.

**Conclusion:** Early detection of these drug-resistant genes by molecular methods is essential in decreasing the spread of carbapenem-resistant *A. baumannii*.

**Keywords:** *Acinetobacter*, antimicrobial resistance, carbapenemases, OXA enzymes

### INTRODUCTION

*Acinetobacter baumannii* is the significant pathogen causing infection widely in hospitals. In most *Acinetobacter* species infections, such as ventilator-associated pneumonia, meningitis, bacteremia, peritonitis, urinary tract infections, and wound infections, *Acinetobacter baumannii* accounts for about 90%.<sup>[1,2]</sup> Multidrug-resistant *A. baumannii* infection mostly occurs in critically ill patients admitted to an intensive care unit (ICU), and it is associated with a high mortality rate, ranging from 26 to 68%.<sup>[3]</sup>

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The accumulation of different resistance mechanisms has gradually lessened the use of number of antimicrobial agents available to treat *A. baumannii* infections in clinical practice. The known resistance mechanisms include enzymatic degradation of drugs by  $\beta$ -lactamases and aminoglycoside-modifying enzymes, permeability defects, multidrug efflux pumps, and modification of target sites.<sup>[4,5]</sup>

Production of carbapenemases either by acquired or naturally occurring oxacillinases (OXA) genes appears to be the most familiar mechanism seen with carbapenem-resistant *Acinetobacter baumannii*. The carbapenemase enzymes are mediated by the Ambler Class D  $\beta$ -lactamases and Ambler Class B metallo- $\beta$ -lactamases (MBL), which is of greater concern. Since 2000, the gradual development of carbapenem resistance is seen predominantly due to the emergence of the Ambler Class D OXA.<sup>[6]</sup> The five subtypes of OXA genes are OXA-23-like (OXA-23, OXA-27, OXA-49, and OXA-239); OXA-24-like (OXA-24, OXA-25, OXA-26, OXA-40, and OXA-72); OXA-51-like (which is intrinsic to *A. baumannii*), OXA-58, and OXA-143-like (OXA-143 and OXA-231). The OXA-51-like group establishes a chromosomal enzyme family naturally present in *A. baumannii*.<sup>[7]</sup> Carbapenem resistance in *A. baumannii* is mediated more frequently by OXAs and less frequently by MBL.<sup>[8]</sup>

### Objective

To determine the frequency of OXA-type carbapenemases among carbapenem-resistant *A. baumannii* in clinical isolates from adult ICU and to evaluate the relationship between OXA gene resistance and clinical outcome.

## MATERIALS AND METHODS

### Study Design

This is a cross-sectional study.

### Settings

After getting approval from Institutional Ethics Committee (AIIMS/IEC/2019-20/847), the clinical specimen of the patients admitted in adult ICU was collected and sent to the department of microbiology for culture and sensitivity from June 2019 to March 2021.

### Participants

Patients with carbapenem-resistant *A. baumannii* infection in adult ICU and who gave written informed consent were included in the study.

### Variables

The isolates were obtained from various clinical specimens such as blood samples, urine samples, bronchoalveolar lavage (BAL), and wound samples.

### Data Sources/Measurements

A total of 56 patients in adult ICU who gave written informed consent were included in the study, and their demographic details were recorded in case record form. A brief clinical history was recorded including the patient's chief complaints, comorbidities such as diabetes mellitus, hypertension, coronary heart disease, thyroid disorder, and history of any surgery. General physical examination of the patients was done, which included anemia, cyanosis, and jaundice. acute physiology and chronic health evaluation (APACHE) IV score was calculated for all the patients who are enrolled in the study. Bacterial identification was performed by routine conventional Gram staining, microbial culture, and biochemical tests using the standard recommended techniques. Antimicrobial susceptibility testing was done using E (Epsilometer) strip test to determine the minimum inhibitory concentration (MIC) of meropenem and imipenem. MIC values of  $\leq 8$   $\mu\text{g/mL}$  were taken as resistant for both meropenem and imipenem according to Clinical and Laboratory Standards Institute 2019 guidelines.<sup>[9]</sup>

The isolates of patients with carbapenem-resistant *A. baumannii* infection were stored at  $-80^\circ\text{C}$  from sample collection till molecular analysis. Genomic DNA was extracted from bacterial isolate by using QIAamp DNA Mini Kit extraction kits (Qiagen). DNA concentrations were determined by the nanodrop technique at 260 nm. Amplification of target genes OXA-23, OXA-24, OXA-51, and OXA-58 was done by conventional polymerase chain reaction. Primers were selected according to a previous study exploring the OXA genes for carbapenemases.<sup>[10]</sup> Primer pair was used to amplify OXA genes are OXA-23 (501 bp: 5'-GAT CGG ATT GGA GAA CCA GA and 5'-ATT TCT GAC CGC ATT TCC AT), OXA-24 (246 bp: 5'-GGT TAG TTG GCC CCC TTA AA and 5'-AGT TGA GCG AAA AGG GGA TT), OXA-51 (353 bp: 5'-TAA TGC TTT GAT CGG CCT TG and 5'-TGG ATT GCA CTT CAT CTT GG), and OXA-58 (599 bp: 5'-AAG TAT TGG GGC TTG TGC TG and 5'-CCC CTC TGC GCT CTA CAT AC).

The amplification conditions were initial denaturation at  $94^\circ\text{C}$  for 5 minutes 35 cycles of  $94^\circ\text{C}$  for 25 seconds,  $52^\circ\text{C}$  for 40 seconds and  $72^\circ\text{C}$  for 50 seconds, and a final elongation at  $72^\circ\text{C}$  for 6 minutes. Amplified desired DNA fragments were verified by agarose gel electrophoresis.<sup>[11]</sup> Electrophoresis was carried out using Bio-Rad Mini-Sub Electrophoresis System.

Ultraviolet transilluminator gel documentation system was used for the visualization of bands.

APACHE IV score was calculated using the online calculator, which predicts the estimated mortality rate and estimated length of ICU stay in the hospital. The variables collected within the first 24 hours after admission of study participants in an ICU were determined. APACHE IV score was calculated based on the worst values for each variable.<sup>[12,13]</sup>

### Study Size

Sample size was calculated based on the previously conducted study by Vijayakumar et al (2016).<sup>[14]</sup> The OXA-23 proportion in the study was 98%. Considering this as expected frequency, in this study with 95% confidence interval and 5% absolute error, the sample size was 53 isolates. Additional subjects were enrolled considering the probable drop outs resulting from errors in the sample processing.

### Statistical Analysis

Data were entered into Microsoft Excel and was analyzed using SPSS version 23 (IBM SPSS statistics, Somers New York, United States). Data were reported as mean T standard deviation (SD) for continuous variables and percentage for categorical variables. Descriptive statistics were used to summarize demographic characteristics and APACHE IV score. Association between the OXA gene resistance with clinical outcome and OXA gene resistance with survivors was assessed using chi-square test. Comparison of quantitative variables (ICU stay, ward stay, and total stay) between the two independent groups (OXA gene resistance and length of stay in the hospital) was analyzed using Student “t” test. APACHE IV score was compared between three independent groups (discharge, died, and leave against medical advice [LAMA]) by using one-way analysis of variance test. A *p*-value of <0.05 was considered statistically significant.

## RESULTS

### Participants

In the present study, 56 patients with carbapenem-resistant *A. baumannii* infection were recruited from the adult ICU, AIIMS, Jodhpur.

### Descriptive Data

Demographic characteristics, clinical examination, duration of ICU and hospital stay, and type of clinical specimens including BAL, blood, urine, and wound sample were recorded for all the patients as per the case record form submitted. The frequency of demographic and clinical characteristics is presented in Table 1.

**Table 1:** Demographic and clinical characteristics related to patients with infections to carbapenem-resistant *Acinetobacter baumannii* in adult ICU

Variables	Number (%)
Gender	
Male	38 (67.9)
Female	18 (32.1)
Age (y) (mean T SD)	
Clinical specimen	46.36 T 17.404
Bronchoalveolar lavage	42 (75)
Blood	13 (23.2)
Urine	0
Wound sample	1 (1.8)
Reason for hospitalization	
Clinical complication	15 (26.8)
Neurological complication	15 (26.8)
Respiratory complication	10 (17.8)
Surgical complication	9 (16.1)
Trauma	6 (10.7)
Malignancy	1 (1.8)
Comorbidities	
Diabetes	12 (21.4)
Hypertension	10 (17.9)
Chronic kidney disease	6 (10.7)
Tuberculosis	5 (8.9)
Thyroid disorder	2 (3.6)
Bronchial asthma	2 (3.6)
History of surgery	2 (3.6)

Abbreviations: ICU, intensive care unit; SD, standard deviation.

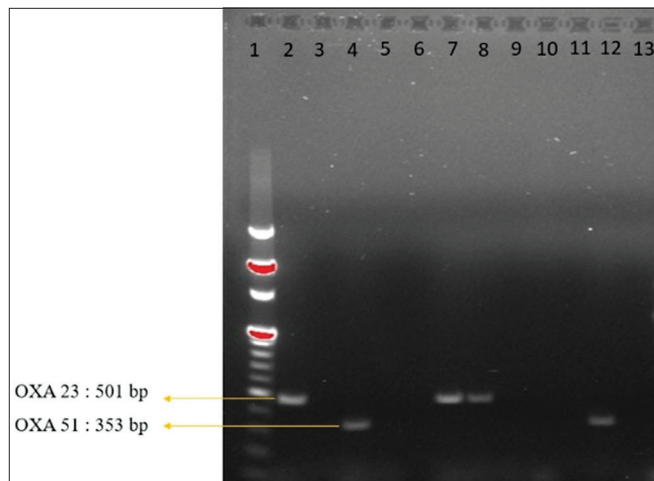
Note: *n* = 56.

### Main Results

With respect to the presence of drug-resistant gene among the collected isolates, OXA-23 gene was detected in 49 (87.5%) and OXA-51 gene was detected in 41 (73.2%) isolates. All 56 isolates were negative for OXA-24 and OXA-58 genes. Both OXA-23 and OXA-51 genes were coexisted in 40 (71.4%) isolates. Either OXA-23 or OXA-51 gene was present in 10 isolates, in which 9 isolates had OXA-23 gene and only 1 isolate had OXA-51 gene. Detection of genes encoding OXA-23 and OXA-51 is shown in Figure 1.

The relation between OXA gene resistance (OXA-23 and OXA-51) and clinical outcomes (discharge, died, and LAMA) was also studied. In the association between clinical outcomes and OXA-23 gene, the *p*-value was found nonsignificant (*p*-value = 0.573). For the relationship between OXA-51 and clinical outcomes, the *p*-value was found nonsignificant (*p*-value = 0.913). The presence of both the genes (OXA-23 and OXA-51) was also not associated significantly with any of the outcomes (*p*-value = 0.905).

The relationship between presence of OXA gene was compared between survivors and nonsurvivors. Considering



**Figure 1:** Detection of genes encoding OXA-23 and OXA-51. Lane 1 shows 100 bp DNA ladder, Lane 2 shows OXA-23 (positive control), Lane 4 shows OXA-51 (positive control), Lanes 7 and 8 show OXA-23, and Lane 11 shows OXA-51.

LAMA to be best case scenario, it was included in survivors. The presence of OXA-23 gene was found to be nonsignificant between 23 (46.9%) survivors and 26 (53.06%) nonsurvivors with  $p$ -value of 0.443. For the relationship between OXA-51 between 19 (46.34%) survivors and 22 (53.65%) nonsurvivors, the  $p$ -value was 0.767. The presence of both the genes (OXA-23 and OXA-51) was also not associated significantly between 19 (47.5%) survivors and 21 (52.5%) nonsurvivors with  $p$ -value of 0.767.

The severity of patient infection was evaluated by using the APACHE IV score, which was retrieved from medical charts within 24 hours of ICU admission. The mean and SD of APACHE IV score was 58.66 T 23.48. Association of APACHE IV score with clinical outcomes including discharge, died, and LAMA was calculated. The mean T SD for discharge, died, and LAMA were 45.71 T 14.54, 66.45 T 26.011, and 66.25 T 7.500, respectively, with a  $p$ -value of 0.004, which was significant (Table 2). After post hoc analysis, significant value was seen between discharge and died groups (Table 3).

## DISCUSSION

*Acinetobacter baumannii* is one of highly virulent bacteria in modern health care, with a high ability to acquire antimicrobial resistance. In clinical practice, the number of antibiotic classes available to treat *A. baumannii* infection is decreasing due to the accumulation of resistance mechanisms.<sup>[8]</sup> Clinically, carbapenems are most commonly used to treat critically ill patients with gram-negative infection resistant to conventional antibiotics.<sup>[7]</sup> Carbapenemases production appears to be the most common mechanism involved in drug resistance to carbapenem in *A. baumannii* and is most commonly mediated by OXA type  $\beta$  lactamases and MBL.<sup>[15]</sup>

**Table 2:** Association between APACHE IV score and clinical outcome

Outcome	APACHE IV score (mean T SD)	95% CI		$p$ -Value
		Lower limit	Upper limit	
Discharge	45.71 T 14.54	39.10	52.33	0.004 <sup>a</sup>
Died	66.45 T 26.011	56.91	75.99	
LAMA	66.25 T 7.500	54.32	78.18	

Abbreviations: CI, confidence interval; LAMA, leave against medical advice; SD, standard deviation.

<sup>a</sup> $p < 0.05$  is taken as significant.

**Table 3:** Post hoc analysis of the association between APACHE IV and clinical outcomes

Outcome	Mean difference	Standard error	$p$ -Value
Discharge vs. died	20.737	6.10	0.004 <sup>a</sup>
Died vs. LAMA	0.202	11.968	1.000
LAMA vs. discharge	20.536	11.776	0.261

Abbreviation: LAMA, leave against medical advice.

<sup>a</sup> $p < 0.05$  is taken as significant.

The present study was done to find the frequency of OXA genes including OXA-23, OXA-24, OXA-51, and OXA-58 in carbapenem-resistant *A. baumannii* isolates from adult ICU. Out of 56 carbapenem-resistant *A. baumannii* isolates, the OXA-23 gene was present in 49 (87.5%) isolates and the OXA-51 gene was present in 41 (73.2%) isolates. OXA-23 gene was solely present in nine isolates, and the OXA-51 gene was solely present in one isolate. The carbapenemases encoded by these genes have been described to confer reduced susceptibility to carbapenems.<sup>[16,17]</sup> The high frequency of the OXA-23 gene was observed among different studies. Kuo et al reported that the frequency of the OXA-23 gene was 58% in a hospital in Northern Taiwan.<sup>[18]</sup> Chusri et al also reported that the frequency of the OXA-23 gene was 95% in Thailand.<sup>[19]</sup>

According to Chuang et al, the frequency of the OXA-23 gene among carbapenem-resistant *A. baumannii* isolates is gradually increasing.<sup>[20]</sup>

Vijayakumar et al studied the molecular characterization of carbapenem-resistant *A. baumannii* from a tertiary care hospital in the southern part of India and exhibited the presence of the OXA-23 gene and OXA-51 gene. In contrast to our study, they found that the OXA-51 gene was highly prevalent in all isolates followed by the OXA-23 gene with 98%.<sup>[14]</sup> A study conducted by Niranjana et al in North India showed the presence of OXA-51 gene in all isolates (100%) with high frequency of OXA-23 gene (46.6%).<sup>[21]</sup> Dias et al also showed the presence of the OXA-51 gene in all isolates



(100%) and a higher frequency of the OXA-23 gene with 72.7%.<sup>[22]</sup>

All isolates in our study were negative for the OXA-24 and OXA-58 genes. These results were similar to the results published by Dias et al,<sup>[22]</sup> Petrova et al,<sup>[23]</sup> and Niranjana et al.<sup>[21]</sup> Niranjana et al found all isolates were negative for OXA-24 and OXA-58.<sup>[21]</sup> According to Petrova et al findings, 97.7% of the OXA-23 gene was present, and OXA-51, OXA-24, and OXA-58 genes were not present in clinical isolates of carbapenem-resistant *A. baumannii* from ICU patients.<sup>[23]</sup> Similar findings were seen with Stoeva et al, where OXA-23 gene was present in all isolates and negative for OXA-51, OXA-24, and OXA-58 genes.<sup>[24]</sup>

Castilho et al's study showed the high prevalence of multidrug resistance including carbapenems among *A. baumannii* strains isolated from ICU patients. It showed the presence of OXA-51 in all isolates with a high prevalence of the OXA-23 gene (55.1%) followed by the OXA-58 gene with 3.6%.<sup>[25]</sup> A study in Uruguay conducted by Bado et al showed the presence of OXA-51 gene in all isolates with a high frequency of OXA-23 gene (79.5%) and OXA-58 genes with 3.8%.<sup>[26]</sup> Wang et al failed to identify the presence of the OXA-58 gene among carbapenem-resistant *A. baumannii* exclusively in the blood sample in Taiwan. In this study, all isolates were positive for the OXA-51-like gene with a high frequency of the OXA-23-like gene (88.1%) and 4.09% of the OXA-24-like gene.<sup>[27]</sup>

In the present study, 40 (71.4%) isolates reported the coexistence of the OXA-23 and OXA-51 genes. Amudhan et al showed a high prevalence of the OXA-51 gene followed by the OXA-23 gene with 84% coexistence.<sup>[28]</sup> Furthermore, a study by Khajuria et al also showed 33.3% coexistence of the OXA-23 gene and the OXA-51 gene.<sup>[29]</sup> This indicates that the coexistence of the OXA-23 and OXA-51 genes is most common among carbapenem-resistant *A. baumannii*. In contrast to this, Higgins et al, who conducted a global study, showed most of the isolates had the OXA-23 and OXA-58 genes instead of the OXA-51. This suggested the clonal spread of a resistant organism, but it was not associated with a particular cluster.<sup>[30]</sup>

A few studies showed the presence of all four OXA genes that is OXA-23, OXA-24, OXA-51, and OXA-58 genes. Khajuria et al studied the prevalence of OXA and MBL genes in carbapenem-resistant *A. baumannii* among the Indian population in central India. It showed a high frequency of the OXA-23 gene with 52.4%, followed by the OXA-51, OXA-58, and OXA-24 genes with 44.8, 14.3, and 9.52%, respectively.<sup>[29]</sup>

A similar report was published by Amudhan et al in the South Indian population, where OXA-51 gene was present in 93.4%, followed by OXA-23, OXA-24, and OXA-58 in 89.6, 1.8, and 0.94%, respectively.<sup>28</sup> Simo Tchuinte et al's study

in Madagascar showed OXA-51-like gene was present in all isolates. OXA-23, OXA-24, and OXA-58 genes were present in 53.3, 13.3, and 6.7% of carbapenem-resistant *A. baumannii* isolates, respectively.<sup>[31]</sup>

Carbapenem resistance due to the synthesis of OXA-type carbapenemases is growing drastically. OXA enzymes are the most important reason for resistance to imipenem and meropenem in *A. baumannii* infection worldwide. All isolates in our study were resistant to imipenem and meropenem with MIC values above 32 µg/mL. Simo Tchuinte et al conducted a study in Madagascar, where all the isolates showed MIC value similar to that of our study.<sup>[31]</sup>

The synthesis of β-lactamase enzyme, that is OXA, might be a molecular mechanism of carbapenem resistance among the *A. baumannii* isolates evaluated in our study.<sup>[22]</sup> The recent emergence and dissemination of the OXA-23 gene have been reported in India and in other countries such as Poland, Brazil, Italy, Spain, and Portugal and represent a major mechanism of resistance to imipenem and meropenem among clinical isolates of *A. baumannii*.<sup>14, [32-36]</sup> The insertion element ISAbal is the most important factor associated with the increased expression of OXA genes. Especially, upstream of the OXA-23 and OXA-51 genes by ISAbal has been shown to be associated with carbapenem resistance in *A. baumannii* isolates.<sup>[25]</sup>

BAL was the clinical specimen most commonly associated with the carbapenem-resistant *A. baumannii*. This indicates that the use of mechanical ventilation as clinical support is contributing to the spread of infections. Dias et al<sup>[22]</sup> and Nowak et al<sup>[32]</sup> also isolated carbapenem-resistant *A. baumannii* more frequently in the tracheal aspirate.

We also studied the relationship between the presence of the OXA gene resistance and clinical outcomes including discharge, died, and LAMA. No significant difference was found between OXA-23 gene and OXA-51 gene with clinical outcomes, and the *p*-value was 0.573, and 0.913, respectively. The presence of both the genes (OXA-23 and OXA-51) was also not associated significantly with any of the clinical outcomes (*p*-value = 0.905).

In our study, the APACHE IV score, the most recent version of the APACHE scoring system was used for the prediction of estimated mortality rate and estimation of the length of ICU stay in the hospital. The mean and SD of APACHE IV score was 58.66 T 23.48. The mean predicted length of ICU stay by the APACHE IV model was 6.44 T 1.76, and the estimated length of the mortality rate was 22.59 T 18.25. Association between the APACHE IV score and clinical outcome including discharge, died, and LAMA was calculated and found to be significant with the *p*-value of 0.004. In the post hoc analysis, the *p*-value was significant in the discharge versus expired group. Bado et al used the

APACHE II scoring system for the estimation of the length of ICU stay in the hospital. The mean predicted length of ICU stay by APACHE IV model was 23.1 T 6.0, and the estimated mortality rate was 14.7 T 12.1. APACHE II scoring system was developed in 1985 as a modification of the original APACHE score. This study did not compare the molecular characterization of carbapenem-resistant *A. baumannii* with the clinical outcomes of the patients admitted to the ICU.<sup>[26]</sup>

Multidrug-resistant *A. baumannii* infection mostly occurs in critically ill patients in ICU, and it is associated with high mortality, ranging from 26 to 68%.<sup>3</sup> So, we also studied and compared the OXA gene resistance with survivors and non-survivors. The presence of the OXA-23 gene was found to be nonsignificant between survivors and nonsurvivors with a *p*-value of 0.443. The OXA-51 gene was found to be nonsignificant between survivors and nonsurvivors with a *p*-value of 0.767. The presence of both the genes (OXA-23 and OXA-51) was found to be nonsignificant between survivors and nonsurvivors with a *p*-value of 0.767.

The relationship between OXA gene resistance and length of stay in the hospital including ICU stay, ward stay, and total stay was compared. The presence of OXA-23 gene showed an increase in ICU stay and total stay with a *p*-value of 0.098 and 0.797, respectively. The presence of OXA-51 gene showed an increase in ICU stay, ward stay, and total stay with a *p*-value of 0.094, 0.859, and 0.206, respectively. The presence of both OXA-23 and OXA-51 genes showed an increase in ICU stay and total stay with a *p*-value of 0.252 and 0.642, respectively. However, we did not find any significant difference between the presence and absence of the OXA-23, OXA-51, and both OXA-23 and OXA-51 genes with the length of hospital stay.

## CONCLUSIONS

Our study reports the emergence of the OXA-23 and OXA-51 genes as the predominant cause of carbapenemases production among clinical isolates of carbapenem-resistant *A. baumannii* infections in our health care settings. It also has major significance for both antibacterial therapy and prognosis of infectious disease, and infection control. Hence, early detection of these drug-resistant genes by molecular methods is essential in decreasing the spread of carbapenem-resistant *A. baumannii*.

The strengths of our study are that we compared the relationship between OXA gene resistance with a length of stay in the hospital as well as clinical outcomes including discharge, died, and LAMA. We used the most recent version of the APACHE scoring system, the APACHE IV score for analyses of an association with clinical outcomes.

## Limitation

We studied only the frequency of OXA-type carbapenemases producing genes, but coexistence with MBL producing genes was not studied.

## Conflict of Interest

None declared.

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