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Original Article

Clonal relationship and the association of the ST218 strain harboring *bla*$_{OXA-72}$ gene to mortality in carbapenem-resistant *Acinetobacter baumannii* bacteremia

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Acinetobacter baumannii bacteremia;
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Clonal relationship;
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Abstract *Background/purpose:* In 2017, the World Health Organization categorized carbapenem-resistant *Acinetobacter baumannii* (CRAB) as a priority 1, critical antibiotic-resistant bacteria. This study analyzed the clinical outcomes and investigated the molecular epidemiology of CRAB bacteremia in a medical center in Northern Taiwan.
Methods: We collected 62 blood isolates from patients with CRAB bacteremia from January 2014 to December 2015 at MacKay Memorial Hospital and determined the clonal relationship using the PCR-based technique for molecular epidemiology. Medical charts were reviewed for clinical outcomes.
Results: Fifty-six isolates harbored the *bla*$_{OXA-51-like}$ and *bla*$_{OXA-23-like}$ carbapenemase genes, 4 isolates harbor the *bla*$_{OXA-51-like}$ and *bla*$_{OXA-24-like}$ carbapenemase genes and 2 isolates harbored only the *bla*$_{OXA-51-like}$ gene. After sequencing, all four isolates of *bla*$_{OXA-24-like}$ carbapenemase gene were confirmed to be isolates of *bla*$_{OXA-72}$ carbapenemase genes. In multivariate analysis in the 60 patients, the independent mortality risk factors of CRAB bacteremia included $\geq$65 years (elderly) (Odds ratio, 4.04, 95% CI, 1.10–14.83, $p = 0.035$), chronic kidney disease (4.36, 1.14–16.72, $p = 0.032$). Isolates harboring the *bla*$_{OXA-72}$ gene had the same sequence type (ST218) and PFGE pulsotype raising the possibility of intra-hospital transmission, and all infected patients died.
Conclusion: This study showed the clonal relationship of isolates harboring the carbapenemase gene in CRAB bacteremia. Patients with the ST218 strain harboring *bla*$_{OXA-72}$ gene had high

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mortality. This warrants further research to determine the mechanism of virulence and risk factors in order to reduce mortality.

Introduction

Acinetobacter baumannii has been regarded as a crucial pathogen in healthcare-associated infections.[1] Crude mortality rates varying between 30 and 76% have been reported in many studies on *A. baumannii* bacteremia.[2] In Asia, mortality rates for CRAB bacteremia were 49.06% in Korea and 60.56% in Taiwan.[3,4]

Resistance to antimicrobial agents is increasing significantly worldwide according to a global surveillance study of *A. baumannii*.[5] The main resistance mechanisms of *A. baumannii* are known to include carbapenemase, porin defects and efflux pumps systems.[6] Extremely high carbapenem resistance rates of 90% have been reported.[7] In 2017, the World Health Organization (WHO) categorized *A. baumannii* as first priority: critical; "antibiotic-resistant priority pathogen" indicating foremost importance for research and development of new antibiotics,[8] The issue of antimicrobial resistance was also emphasized in the reports by health experts at the G20 meeting in Berlin in 2017.[9] The increased antibiotic resistance and high mortality in CRAB bacteremia pose a formidable threat and is becoming increasingly challenging to treat.

The most widespread carbapenemase genes in *A. baumannii* are class D beta-lactamases genes, metallo-β-lactamase genes, and bla_{KPC} genes. It is believed that almost all imipenem-resistant *A. baumannii* contain the $bla_{OXA\text{-}51\text{-}like}$ gene, a basic and intrinsic carbapenemase gene specific to *A. baumannii*.[10]

Thus, the aims of this study were to investigate the molecular epidemiology and clinical outcomes of CRAB bacteremia in isolates harboring the carbapenemase gene in a tertiary teaching hospital in Northern Taiwan.

Materials and methods

Collection of bacterial isolates

We collected CRAB complex blood isolates resistant to imipenem (MIC $\geq$ 8 mg/L) in MacKay Memorial Hospital in Taipei from January 2014 to December 2015. Inclusion criteria were patients over 1 year old with bacteremia due to CRAB, regardless of primary infection sites, and the blood isolates from the patients with significant bacteremia were collected consecutively during the study period. Only the first episode was included in the analysis from patients with $\geq$ two positive blood cultures. Patients those didn't belong to infect with CRAB were excluded. The study protocol (number 18MMHIS013) was reviewed and approved by the hospital's Institutional Review Board Committee. The breakpoint of minimum inhibitory concentrations (MICs) of carbapenem resistance was $\geq$8 mg/L for imipenem according to the Vitek 2 system (bioMérieux Vitek Systems Inc., Hazelwood, MO, USA).[11]

Study population and collection of clinical characteristics

A retrospective review of the medical charts was done to analyze the clinical characteristics and outcomes of patients with CRAB bacteremia. Episodes of bacteremia were considered to have been acquired in the intensive care unit (ICU) if the onset occurred during or within 48 h of ICU stay. The clinical outcome measure was all-cause mortality after the onset of CRAB bacteremia. Central line-associated infection was determined according to the definitions of the United States Centers for Disease Control and Prevention (CDC).[12] The primary infection source of bacteremia was defined according to the CDC guidelines.[13]

Genospecies identification

Genotypic identification of *A. baumannii* was performed by identifying the presence of the $bla_{OXA\text{-}51\text{-}like}$ carbapenemase gene that is specific to the *A. baumannii*.[14] Sixty-eight CRAB complex blood isolates were collected in the study period. Sixty-two isolates were identified as CRAB.

Detection of carbapenemase gene and insertion sequence (IS) element

After PCR amplification, CRAB isolates were screened by sequencing for the carbapenemase-producing genes $bla_{OXA\text{-}51\text{-}like}$, $bla_{OXA\text{-}23\text{-}like}$, $bla_{OXA\text{-}24\text{-}like}$, $bla_{OXA\text{-}58\text{-}like}$,[15] $bla_{OXA\text{-}143\text{-}like}$,[16] $bla_{OXA\text{-}235\text{-}like}$,[17] bla_{GIM}, bla_{IMP}, bla_{SIM}, bla_{SPM}, bla_{VIM},[18] bla_{KPC}, bla_{NDM},[19] and bla_{GES}.[20] The primers used in this study are listed in Table 1. The PCR products were sequenced using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) according to the instructions provided by the manufacturer. Sequence similarity searching was performed with the Basic Local Alignment Search Tool (BLAST; http://blast.ncbi.nlm.nih.gov/Blast.cgi). Detection of the IS preceding the bla_{OXA} gene was performed by PCR using the primers of the IS (Table 1),[21–24] including self-designed IS*1006*. The upstream locations of the insertion sequences were mapped by PCR using forward primers within the insertion sequences and reverse primers within the carbapenemase genes. The PCR product of insertion sequences and carbapenemase genes were sent for sequencing.

Pulsed-field gel electrophoresis (PFGE)

It is believed that almost all *A. baumannii* strains contain the $bla_{\text{OXA-51-like}}$ gene.[10] The 62 CRAB blood isolates were typed by PFGE following the digestion of intact genomic DNA with *Apa*I restriction enzyme (New England Biolabs, Beverly, MA, USA). The DNA fragments were separated in a CHEF Mapper apparatus (Bio-Rad, Hercules, CA, USA) at a potential of 6 V/cm and pulsed from 5 to 20 s for 23 h at 14 °C. Isolates were considered to belong to the same PFGE type (pulsotype) when the band-based Dice similarity coefficient reached 87%.[25]

Multilocus sequence typing (MLST)

Multilocus sequence typing (MLST) for *A. baumannii* was performed according to a reported method.[26] Seven housekeeping genes were analyzed: *gltA* (coding for citrate synthase), *gyrB* (DNA gyrase subunit B), *gdhB* (glucose dehydrogenase B), *recA* (homologous recombination factor), *cpn60* (60-kDa chaperonin), *gpi* (glucose-6-phosphate isomerase) and *rpoD* (RNA polymerase σ^{70} factor). Sequences were then compared with the *A. baumannii* MLST database (the protocol is available at http://pubmlst.org/abaumannii/).

Antimicrobial susceptibility testing

MICs for imipenem and colistin were determined for the genospecies via the agar dilution method in a research laboratory.[27] The sensitivities and MICs of tested antibiotics were interpreted according to guidelines from the Clinical and Laboratory Standards Institute.[11]

Statistical analysis

Categorical variables were analyzed using the chi-squared test or Fisher's exact test as appropriate, especially for nonparametric statistics. Student's two-sample t-test was used for the analysis of continuous parametric data while the Mann—Whitney U test was used for the analysis of nonparametric data as appropriate. Univariate analysis was performed for each risk factor to determine odds ratio (OR) and 95% confidence interval. In univariate analysis, all biologically variables with a p value < 0.20 were considered to be included in multivariate analysis by the logistic regression model.

All biological variables with a two-tailed p value < 0.05 were considered significant. All data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Detection of carbapenemase genes and insertion sequence (IS) elements

Among the 62 CRAB blood isolates, 56 (90.32%) harbored the $bla_{\text{OXA-51-like}}$ and $bla_{\text{OXA-23-like}}$ carbapenemase genes, 4 (6.45%) harbored both the $bla_{\text{OXA-51-like}}$ and $bla_{\text{OXA-24-like}}$ carbapenemase genes and 2 (3.23%) harbored only the $bla_{\text{OXA-51-like}}$ gene. After further identification by sequencing, the 4 isolates carrying the $bla_{\text{OXA-24-like}}$ carbapenemase gene were all confirmed to be isolates carrying the $bla_{\text{OXA-72}}$ carbapenemase gene.

IS*Aba1* was associated with both the $bla_{\text{OXA-23-like}}$ gene and the $bla_{\text{OXA-51-like}}$ gene. IS*Aba1* was found upstream of all $bla_{\text{OXA-23-like}}$, but not found in $bla_{\text{OXA-72}}$ genes (Fig. 1). The other IS elements (IS*Aba2*, IS*Aba3*, IS*Aba4*, IS*18*, IS*1006*, and IS*1008*) were not detected and the 4 $bla_{\text{OXA-72}}$ isolates were not associated with any IS elements tested in this study.

Table 1 Primers used in this study.

Primer	Sequence (5′ to 3′)
Oxa-51-like-F	TAATGCTTTGATCGGCCTTG
Oxa-51-like-R	TGGATTGCACTTCATCTTGG
Oxa-23-like-F	GATCGGATTGGAGAACCAGA
Oxa-23-like-R	ATTTCTGACCGCATTTCCAT
Oxa-24-like-F	GGTTAGTTGGCCCCCTTAAA
Oxa-24-like-R	AGTTGAGCGAAAAGGGGATT
Oxa-58-like-F	AAGTATTGGGGCTTGTGCTG
Oxa-58-like-R	CCCCTCTGCGCTCTACATAC
Oxa-143-like-F	TGGCACTTTCAGCAGTTCCT
Oxa-143-like-R	TAATCTTGAGGGGGCCAACC
Oxa-235-like-F	TTGTTGCCTTTACTTAGTTGC
Oxa-235-like-R	CAAAATTTTAAGACGGATCG
Gim-F	TCGACACACCTTGGTCTGAA
Gim-R	AACTTCCAACTTTGCCATGC
Imp-F	GGAATAGAGTGGCTTAAYTCTC
Imp-R	CCAAACYACTASGTTATCT
Sim-F	TACAAGGGATTCGGCATCG
Sim-R	TAATGGCCTGTTCCCATGTG
Spm-F	AAAATCTGGGTACGCAAACG
Spm-R	ACATTATCCGCTGGAACAGG
Vim-F	GATGGTGTTTGGTCGCATA
Vim-R	CGAATGCGCAGCACCAG
KPC-F	CGTCTAGTTCTGCTGTCTTG
KPC-R	CTTGTCATCCTTGTTAGGCG
NDM-F	GGTTTGGCGATCTGGTTTTC
NDM-R	CGGAATGGCTCATCACGATC
GES-C	GTTTTGCAATGTGCTCAACG
GES-D	TGCCATAGCAATAGGCGTAG
IS*Aba1*A	GTGCTTTGCGCTCATCATGC
IS*Aba1*B	CATGTAAACCAATGCTCACC
IS*Aba2*A	AATCCGAGATAGAGCGGTTC
IS*Aba2*B	TGACACATAACCTAGTGCAC
IS*Aba3*A	CAATCAAATGTCCAACCTGC
IS*Aba3*B	CGTTTACCCCAAACATAAGC
IS*Aba4*A	ATTTGAACCCATCTATTGGC
IS*Aba4*B	ACTCTCATATTTTTTCTTGG
IS*18*A	CACCCAACTTTCTCAAGATG
IS*18*B	ACCAGCCATAACTTCACTCG
IS*1006*(MK)	CCACCAGACCTTGAGCACAG
IS*1008*F	TCTAGATCGGCACTTTCAAGGTGAAAT

F, forward; R, reverse.

PFGE

Fig. 1 also shows the PFGE of blood isolates of CRAB containing IS*Aba1*-$bla_{\text{OXA-23-like}}$, IS*Aba1*-$bla_{\text{OXA-51-like}}$ and carbapenemase genes. The 62 blood isolates were classified into 18 PFGE pulsotypes, and the most common one was

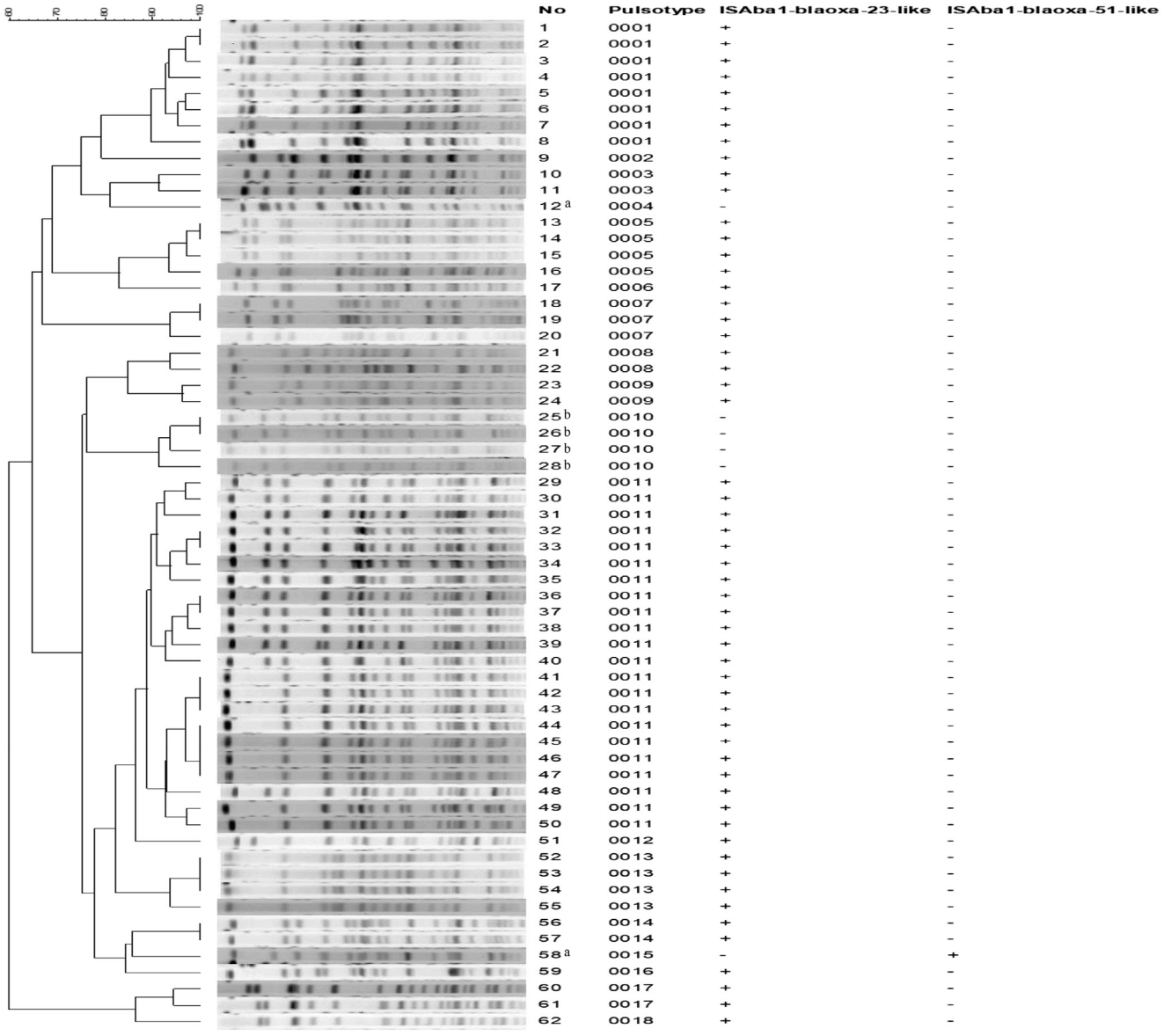
Type 0011 (35.48%, 22/62), followed by Type 0001 (12.90%, 8/62). The PFGE patterns of four isolates of CRAB harboring the bla_{OXA-72} gene were identified as belonging to the same pulsotype (Type 0010).

MLST

In the $bla_{OXA-23-like}$ gene group, the most common sequence type was ST455 (48.21%, 27/56), followed by ST789 (14.29%, 8/56), ST473 (8.93%, 5/56), ST229, ST687, ST787 (each 5.36%, 3/56), ST208, ST436, ST549 (each 3.57%, 2/56) and ST810 (1.79%, 1/56). The allelic profiles of ST455 and ST789 were 1-87-3-2-2-83-3 and 18-87-3-2-1-83-4, respectively. In the bla_{OXA-72} gene group, all four isolates were identified as ST218. The allelic profile of ST218 was 1-3-3-2-2-102-3.

Clinical characteristics and outcomes of patients infected with CRAB bacteremia

CRAB bacteremia patients with isolates (60) harboring other carbapenemase genes in addition to the $bla_{OXA-51-like}$ gene were investigated for risk factors, clinical outcomes and molecular epidemiology, as shown in Table 2. The mortality rate of CRAB bacteremia was 55% (33/60), including 51.79% (29/56) in the $bla_{OXA-23-like}$ group and 100% (4/4) in the bla_{OXA-72} group ($p = 0.120$). Compared to those who survived, patients who died were older (mean age of 72.39 $\pm$ 13.34 years *vs.* 52.56 $\pm$ 21.03 years). Population more than 65 years old (elderly) (72.73% [24/33] *vs.* 29.63% [8/27]; $p = 0.001$), and chronic kidney disease (CKD) (72.73% [24/33] vs. 33.33% [9/27]; $p = 0.002$) was more frequent.



No	Pulsotype	ISAba1-blaoxa-23-like	ISAba1-blaoxa-51-like
1	0001	+	-
2	0001	+	-
3	0001	+	-
4	0001	+	-
5	0001	+	-
6	0001	+	-
7	0001	+	-
8	0001	+	-
9	0002	+	-
10	0003	+	-
11	0003	+	-
12[a]	0004	-	-
13	0005	+	-
14	0005	+	-
15	0005	+	-
16	0005	+	-
17	0006	+	-
18	0007	+	-
19	0007	+	-
20	0007	+	-
21	0008	+	-
22	0008	+	-
23	0009	+	-
24	0009	+	-
25[b]	0010	-	-
26[b]	0010	-	-
27[b]	0010	-	-
28[b]	0010	-	-
29	0011	+	-
30	0011	+	-
31	0011	+	-
32	0011	+	-
33	0011	+	-
34	0011	+	-
35	0011	+	-
36	0011	+	-
37	0011	+	-
38	0011	+	-
39	0011	+	-
40	0011	+	-
41	0011	+	-
42	0011	+	-
43	0011	+	-
44	0011	+	-
45	0011	+	-
46	0011	+	-
47	0011	+	-
48	0011	+	-
49	0011	+	-
50	0011	+	-
51	0012	+	-
52	0013	+	-
53	0013	+	-
54	0013	+	-
55	0013	+	-
56	0014	+	-
57	0014	+	-
58[a]	0015	-	+
59	0016	+	-
60	0017	+	-
61	0017	+	-
62	0018	+	-

Fig. 1. Pulsed-field gel electrophoresis (PFGE), IS*Aba1*-$bla_{OXA-23-like}$, IS*Aba1*-$bla_{OXA-51-like}$ and carbapenemase genes from blood isolates of carbapenem-resistant *Acinetobacter baumannii* ([a]: isolate No. with superscript "a", only harboring the $bla_{OXA-51-like}$ genes; [b]: isolate No. with superscript "b", harboring both the $bla_{OXA-51-like}$ and the bla_{OXA-72} genes; the isolate No. without superscript "a" or "b": harboring both the $bla_{OXA-51-like}$ and the $bla_{OXA-23-like}$ genes).

Table 2 Demographic information, clinical characteristics, and outcomes according to variates of mortality among 60 patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia.

Demographic and Clinical characteristics	Mortality		Survival		*p* value
	n = 33		n = 27		
	n (Median)	% (IQR)	n (Median)	% (IQR)	
Male Sex	19	57.58%	21	77.78%	0.099
≥65 years (Elderly)	24	72.73%	8	29.63%	0.001**
ICU stay	32	96.97%	24	88.89%	0.318
ICU period[a]	19.5	10—35.25	31	15—49.75	0.061
Comorbidity					
CKD	24	72.73%	9	33.33%	0.002**
Diabetes mellitus	16	48.48%	10	37.04%	0.373
COPD	1	3.03%	1	3.70%	>0.99
Malignancy	7	21.21%	2	7.41%	0.166
Invasive procedure					
Foley	27	81.82%	23	85.19%	>0.99
CVC	31	93.94%	22	81.48%	0.226
MV	29	87.88%	22	81.48%	0.718
Microbiological characteristics					
$bla_{\text{OXA-23-like}}$ gene	29	87.88%	27	100.00%	0.120
$bla_{\text{OXA-72}}$ gene	4	12.12%	0	0.00%	0.120
IS*Aba1*-$bla_{\text{OXA-23-like}}$	29	87.88%	27	100.00%	0.120

[a] Data are presented as the median with the inter-quartile range (IQR) for ICU period.
ICU, intensive care unit; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; MV, mechanical ventilation.
**: significance level <0.01; *: significance level <0.05.

In multivariate analysis, the independent mortality risk factors of CRAB bacteremia included population more than 65 years old (elderly) (Odds ratio, 4.04, 95% CI, 1.10—14.83, $p = 0.035$), and chronic kidney disease (4.36, 1.14—16.72, $p = 0.032$) (Table 3).

Clinical characteristics and outcome in patients with bacteremia from CRAB ST218

The clinical characteristics of CRAB bacteremia patients infected with ST218 strains harboring the $bla_{\text{OXA-24-like}}$ ($bla_{\text{OXA-72}}$) genes are described as below. These 4 patients (94y male, 67y male, 75y female, 56y male, respectively) were admitted to different divisions (infectious diseases, cardiovascular medicine, plastic surgery and gastroenterology). They had multiple comorbidities, including CKD, diabetes mellitus, coronary artery disease and cirrhosis. All were critically ill stayed in ICU, and had healthcare-associated infection, insertion of central venous catheter (CVC) and mechanical ventilation (MV) and none survived. The isolates with CRAB ST218 harboring the $bla_{\text{OXA-72}}$ carbapenemase gene also showed extremely highly resistance to imipenem (MICs for IPM ≥ 64 mg/L) and sensitive to colistin (MIC for CLI = 0.5 mg/L).

Discussion

This study examined clonal relationship of isolates and risk factors for mortality in CRAB bacteremia. Data from studies on patients with *A. baumannii* bacteremia report varying crude mortality rates between 30 and 76%.[2] In this study, the mortality rate of CRAB bacteremia was 53.23% (33/62) overall but 100% (4/4) in the ST218 $bla_{\text{OXA-72}}$ group. Our results of a high

Table 3 Univariate and multivariate analyses of risk factors according to mortality among 60 patients with carbapenemase-resistant *Acinetobacter baumannii* bacteremia.

Demographic and clinical characteristics	Univariate analysis				Multivariate analysis			
	Odds ratio	(95% CI)		*p* value	Odds ratio	(95% CI)		*p* value
Male Sex	0.39	0.12	1.21	0.103	0.41	0.09	1.78	0.231
≥65 years elderly	6.33	2.05	19.54	0.001	4.04	1.10	14.83	0.035
ICU period	0.98	0.95	1.00	0.047	0.98	0.95	1.01	0.187
CKD	5.33	1.76	16.15	0.003	4.36	1.14	16.72	0.032
CVC	3.52	0.63	19.84	0.153	2.61	0.19	35.39	0.472

CI, confidence interval; ICU, intensive care unit; CKD, chronic kidney disease; CVC, central venous catheter.

prevalence of the $bla_{OXA\text{-}23\text{-}like}$ gene (90.32%, 56/62) and the relative rarity of the $bla_{OXA\text{-}24\text{-}like}$ gene ($bla_{OXA\text{-}72}$ gene) are consistent with other studies.[7,10] Interestingly, although the $bla_{OXA\text{-}24\text{-}like}$ gene is relatively rare, it has been reported to cause a large outbreak in Spain.[28]

Over a two-year period, we found four blood isolates of CRAB harboring the $bla_{OXA\text{-}72}$ gene that had the same pulsotype (Type 0010) and the sequence type. In our previous study from 2012 to 2013, the predominant pulsotype isolates were typed by MLST. The most common strain was ST787 (54.84%), followed by ST455 (45.16%).[29] However, in this study, the most common strain of the $bla_{OXA\text{-}23\text{-}like}$ group was ST455 (48.21%), followed by ST789 (14.29%). Sequencing showed many distinct patterns in the $bla_{OXA\text{-}23\text{-}like}$ group. The ST218 strain harboring $bla_{OXA\text{-}72}$ gene could be described as a unique strain in this study, and raised the possibility of intra-hospital transmission.

The presenting upstream IS*Aba1* of the bla_{OXA} gene indicate that it may provide promoter for the bla_{OXA} genes and start the act of carbapenem resistance.[30] The isolates with IS*Aba1*-$bla_{OXA\text{-}23\text{-}like}$ was consistently found in all isolates harboring the $bla_{OXA\text{-}23\text{-}like}$ gene and consistent with the study of Turton et al.[31]

In multivariate analysis, the independent mortality risk factors of CRAB bacteremia included elderly and chronic kidney disease. The pharmacokinetics and pharmacodynamics of drugs and treatment of complications are geriatric issues which must be considered in the management of elderly patients with CKD.[32,33] The management of risk factor is important to such patient due to the increased risk of mortality in CKD and nephrotoxicity of drugs, especially in the elderly.

Antibiotics for effective treatment for CRAB are limited, and colistin is considered the final drug capable of treating infections caused by CRAB.[34] However, nephrotoxicity is a serious side effect limiting the empirical therapy of colistin in treating infections, especially in patients with CKD and renal failure.[35,36]

To the best of our knowledge, this study is the first to describe bacteremia related to the CRAB ST218 strain harboring the $bla_{OXA\text{-}72}$ carbapenemase gene and its association with high mortality. Only limited data could be obtained in this study due to the relative rarity of the CRAB ST218 carrying the $bla_{OXA\text{-}72}$ gene strain, resulting in small sample size of blood isolates.

In conclusion, CRAB bacteremia is associated with high mortality, regardless of whether isolates harbor the $bla_{OXA\text{-}72}$ genes or $bla_{OXA\text{-}23\text{-}like}$ genes. Extremely high mortality was found in four patients who contracted bacteremia from CRAB ST218 harboring the $bla_{OXA\text{-}72}$ gene.

This warrants further research to determine the mechanism of virulence and risk factors in order to reduce mortality in CRAB bacteremia.

Conflicts of interest statement and funding/support statement

The authors declare that they have no conflicting interests. This study was supported by grants MMH107-29 from MacKay Memorial Hospital.

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