Science & Technology Development Journal 2024, 26(SI):17-24

Open Access Full Text Article

Research article

Distribution of drug resistance genes and clinical characteristics of *Acinetobacter baumannii* isolated from the University Medical Center at Ho Chi Minh City

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History

- Received: 2023-10-10
- Accepted: 2024-06-05
- Published Online: 2024-06-30

DOI :

https://doi.org/10.32508/stdj.v26iSI.4198

ABSTRACT

Background: Infections resulting from *A. baumannii* in hospitals lead to numerous severe consequences as its antibiotic resistance, particularly to carbapenems, continues to rise. Given that resistance characteristics undergo constant changes due to mutations and gene transfer between species and strains, monitoring the real-time circulation of resistant strains is essential. **Methods:** A descriptive cross-sectional method with analysis and experimentation were applied in this study. All strains of *A. baumannii* were isolated at the University Medical Center at Ho Chi Minh City from May 2020 to May 2021, then underwent antimicrobial susceptibility testing. Real-time PCR was performed to identify resistance genes, including bla_{OXA-51}, bla_{OXA-23}, bla_{OXA-48}, bla_{OXA-58}, and bla_{NDM-1}. The patient's information was collected by using the designated clinical research form. **Results:** The study included 76 *A. baumannii* isolates. The resistance rates to imipenem and meropenem were 93.4%. Additionally, *A. baumannii* exhibited resistance to most of the other antibiotics investigated, with rates exceeding 80%. There was low resistance to Cefoperazone/sulbactam (6.1%) and colistin (5.3%). The distribution of resistance genes showed the prevalence of bla_{OXA-51} (100%), bla_{OXA-23} (88.2%), bla_{OXA-48} (43.4%), bla_{OXA-58} (2.6%), and bla_{NDM-1} (6.6%). The bla_{OXA-23} gene exhibited a statistically significant difference between carbapenem-susceptible *A. baumannii* (CSAB) and carbapenem-resistant *A. baumannii* (CRAB) ($p < 0.001$) and across different types of patient samples ($p = 0.004$). The distribution of the bla_{NDM-1} gene showed a statistically significant difference based on the clinical department sending the sample types ($p = 0.029$). There was a significant association between carbapenem resistance and the distribution of gene combinations ($p < 0.001$). **Conclusion:** The carbapenem resistance rate was 93.4% for imipenem and meropenem, while it was low for cefoperazone/sulbactam (6.1%) and colistin (5.3%). bla_{OXA-51} holds significant importance in the identification of *A. baumannii* bacteria, and bla_{OXA-23} (88.4%) plays a decisive role in carbapenem resistance in *A. baumannii* at this hospital.

Key words: Acinetobacter baumannii, carbapenem, antibiotic resistance

INTRODUCTION

In Vietnam, *A. baumannii* stands out as a prominent pathogen in nosocomial infections, imposing significant economic and public health burdens. Recent reviews for Southeast Asia and East Asia indicate a prevalence of carbapenem-resistant bacteria in Vietnam ranging from 43% to 92% [1]. The resistance mechanisms of *A. baumannii* to carbapenems are diverse, with particular emphasis on the β-lactamase mechanism, specifically β-lactamases of classes B and D. Notably, class D bla_{OXA} genes (bla_{OXA-51}, bla_{OXA-23}, bla_{OXA-58}, bla_{OXA-48}) and Metallo-β-lactamase enzymes are controlled by the highly concerning class B gene, bla_{NDM-1}. These genes, situated on the chromosomes and/or plasmids of bacteria, not only have the potential to be passed on to the next generation but also exhibit horizontal inheritance, spreading resistance to other bacteria. This phenomenon exacerbates the severity of Carbapenem resistance in *A. baumannii*, escalating it into an increasingly serious problem.

The prevalence of hospital infections attributed to *A. baumannii* is on the rise in many hospitals in Viet nam [2–8]. Given the ever-changing resistance characteristics resulting from mutations and gene transfers among species and strains, it is crucial to continuously monitor the circulation of resistant strains in real-time. Additionally, investigating clinical characteristics such as *A. baumannii*-caused infections, specimen type, department, and the type of medical interventions becomes imperative to understand their relationship with the distribution of the aforementioned resistance genes.

Cite this article : Diep D T H, Phung C T. **Distribution of drug resistance genes and clinical characteristics of *Acinetobacter baumannii* isolated from the University Medical Center at Ho Chi Minh City**. *Sci. Tech. Dev. J.* 2024; 26(SI):17-24.

MATERIALS AND METHODS

Materials

All strains of *A. baumannii* were isolated at HCMC University Medical Center from May 2020 to May 2021.

Inclusion criteria: Microbiological culture-positive with *A. baumannii* from one of the following clinical specimens: blood, sputum/ bronchial fluid, pus/wound fluid, urine.

Exclusion Criteria: Samples have duplicate information previously taken; samples do not have access to medical records of treated patients whose samples have results of A. *baumanni* isolates from 05/2020-05 2021 at HCMC University Medical Center.

Research procedure: *A. baumannii* strains were isolated, identified, and subjected to antibiotic susceptibility testing on the Vitek 2 system according to the hospital's standardized procedure. DNA extraction was then performed by using QIAamp DNA Microbiome Kit of QIAGEN, the quality and quantity checking by using Nanodrop spectrophotometer, followed by Real time PCR (real time PCR machine eppendorf) to detect and classify the carbapenem resistance genes: bla_{OXA-51}, bla_{OXA-23}, bla_{OXA-48}, bla_{OXA-58}, bla_{NDM-1}. The real-time PCR reactions to identify these carbapenem resistance genes have been optimized with specific primer pairs, and the PCR reactions are quality-controlled by including internal positive and negative controls.

Statistical methods

Statistical analyses were conducted using Stata software(version 14.1). Pearson's Chi-square or Fisher's exact test with a level of confidence of 95% was used for categorical variables. Variables are: carbapenem resistance, carbapenem resistance genes, specimen type, type of *A. baumannii* infections, discharge outcomes, clinical departments sending specimens.

Ethical consideration

This study was reviewed and approved by the Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh City (decision number 10/HĐĐĐ-ĐHYD on January 13, 2022).

RESULTS

A study was conducted on 76 strains of A. baumannii isolated at the University Medical Center at Ho Chi Minh City from May 2020 to May 2021. The average age of the patients with A. baumannii infection was 71.8 ± 18.7 years, with the youngest being 20 years old and the oldest being 98 years old. Among the subjects, 44 (57.9%) were male and 32 (42.1%) were female.

Meropenem is the strongest antibiotic after vancomycin. Meropenem (Merrem, Meronem) is an antibacterial specialist of the carbapenem family with a wide scope of use. It has proven to be the definitive course of treatment before the causative organism has been identified. Meanwhile imipenem là kháng sinh carbapenem có phổ kháng khuẩn rộng hơn và hiệu lực cao hơn các kháng sinh beta-lactam khác. Both imipenem and meropenem belong to a group of antibiotics called carbapenems. Carbapenems are potent members of the β-lactam family that inhibit bacterial cell-wall biosynthesis inhibitors. They are highly effective against Gram-negative and Gram-positive drug-resistant infections. As such, carbapenems are typically reserved as an antibiotic of last resort. Therefore, we are interested in the proportion of A. baumannii strains resistant to these two antibiotics compared to the strains still sensitive to them among the total strains included in this study.

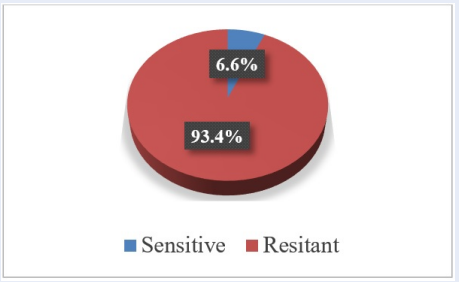

Figure 1: The proportion of imipenem- and meropenem-resistant *A. baumannii* strains compared to the sensitive strains among the total samples included in the study.

The rate of *A. baumannii* resistance to imipenem and meropenem was quite high, both of which were 93.4%. Statistical results regarding the strains indicated that when there is resistance to imipenem, there is also resistance to meropenem, and vice versa.

Afterwards, we surveyed the frequency of occurrence of the genes of interest, and the results are depicted in Figure 2.

We want to determine if there is a correlation between the presence of the genes we are investigating and the antibiotic resistance of *A. baumannii*. Therefore, statistical calculations have been conducted, and the results are presented in Table 1.

Only the *blaOXA-23* gene was significantly different between the CRAB and CSAB groups.

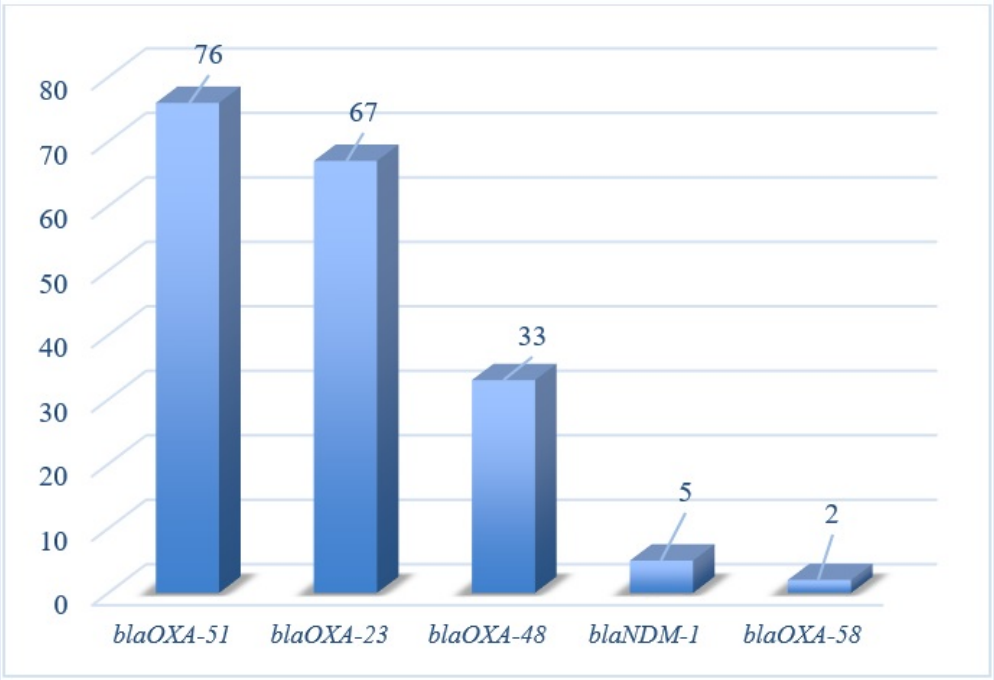

Figure 2: The frequency of occurrence of the target genes among the isolated strains of *A. baumannii*.

Table 1: Relationship between genes and carbapenem resistance

Genes	CRAB (n=71)	CSAB (n=5)	p (*Fisher's exact*)
blaOXA-23	65	5	**< 0,001**
blaOXA-48	32	1	0,381
blaNDM-1	5	0	1,000
blaOXA-58	2	0	1,000

CRAB: carbapenem-resistant *A. baumanii*, CSAB: carbapenem-sensitive *A. baumannii*

Table 2: Gene distribution according to clinical departments sending specimens

Departments	ICU	Departments of Internal Medicine	Departments of Surgery	p
Genes				
blaOXA-23	38	21	8	0,084**
blaOXA-48	22	8	3	0,243*
blaNDM-1	0	4	1	0,029**
blaOXA-58	0	2	0	0,221**

**Pearson's chi-square test, **Fisher's exact test*

Table 3: Gene distribution according to specimen type

Specimens Genes	Sputum, bronchial fluid	Pus, wound fluid	Others	p
blaOXA-23	47	11	9	**0,004****
blaOXA-48	21	6	6	0,976*
blaNDM-1	1	2	2	0,069**
blaOXA-58	1	0	1	0,587**

**Pearson's chi-square test, **Fisher's exact test*

Only the *blaNDM-1* gene distribution significantly differed according to the clinical department that sent the specimen (p=0.029).

The distribution of *blaOXA-23* was significantly different for different types of patient samples (p=0.004).

There was no statistically significant association between gene distribution and the type of *A. baumannii* infection.

There was no statistically significant association between gene distribution and discharge outcome.

The two-gene combination accounted for the largest proportion (51.3%), followed by the three-gene combination. There are few *blaNDM-1* and *blaOXA-58* genes, and they do not appear alone but rather in combination with other genes.

There was a statistically significant difference between carbapenem resistance and the distribution of gene combinations (p < 0.001).

DISCUSSION

***Carbapenem resistance:** Since carbapenem-resistant *A. baumannii* was identified in 1991, there has been a worldwide surge in the prevalence of *A. baumannii* strains exhibiting resistance to these antibacterial antibiotics. This phenomenon poses a public health threat in Europe, as well as in South and Southeast Asia, particularly within intensive care units (ICUs)[2]. *A. baumannii* was 93.4% resistant to both carbapenems tested in this study (imipenem and meropenem). In other words, the carbapenem susceptibility rate of *A. baumannii* is less than 10%. According to the following comparison table from recent years, the resistance rate is quite high, above 90%; there are also studies where this rate is up to 100%[3]. This rate is similar to that reported in some recent studies and is also consistent with predictions that the rate of resistance to antibiotics in this group will increase in previous years.

*** Distribution of resistance genes in the study**

Survey of 5 resistance genes in 76 strains of *A. baumannii* using real-time PCR. Our results are similar to those of many other domestic and foreign studies, and *blaOXA* genes, especially *blaOXA-23* , are the most common carbapenemase-encoding genes in *A. baumannii* worldwide.

BlaOXA-51 : The results of this study are consistent with those of all the abovementioned domestic studies. One hundred percent of *A. baumannii* strains carry the *blaOXA*-51 gene. This gene is the natural intrinsic gene of *A. baumannii*, and research has also used this gene in combination to identify *A. baumannii*[12]. The *blaOXA-51* gene is located on the chromosome, which usually does not lead to carbapenem resistance due to poor hydrolysis; however, in the presence of the upstream *ISAba1* insertion sequence, the *blaOXA-51* gene can provide a promoter that allows overproduction and overexpression of this gene[14].

BlaOXA-23 : Among the carbapenem-resistant strains, the *blaOXA-23* gene carrier accounted for 93.0% (66/71), similar to the findings of the Luu Thi Vu Nga study (2016)[12], Reza Beigverdi (2019)[15], and Hoang Quoc Cuong et al. (2019)[7]. Looking for an association between *blaOXA-23* and carbapenem resistance, the difference was statistically significant (p=0,001), which may demonstrate that the findings of this study are consistent and reinforce the finding that *blaOXA-23* is the main gene affecting carbapenem resistance in *A. baumannii*[16]. Reviewing the distribution of the *blaOXA-23* gene by specimen type revealed statistically significant differences (p=0.004) other characteristics, such as the clinical department sending samples, infectious pathology or discharge status, did not show statistically significant differences.

BlaOXA-48 : This gene was first identified in a strain of *Klebsiella pneumoniae* from Turkey[17]. In our study, 43.4% of the strains of *A. baumannii* carried this gene however, this percentage is quite low compared to that reported in Tarafdar F's study in Iran (92%)[4]. In contrast, many early studies have not detected this gene in *A. baumannii*. *BlaOXA*-48 is located on the plasmid, and previous studies have not detected *this*

Table 4: Gene distribution according to the type of *A. baumannii* infection

Genes	*blaOXA-23* n=67		*blaOXA-48* n=33		*blaNDM-1* n=5		*blaOXA-58* n=2	
A. baumannii infection								
Lower respiratory tract infection	48	0,713**	22	0,460*	4	1,000**	1	0,498**
Bloodstream infection	27	0,142*	13	0,519*	1	0,646**	0	0,528**
Dermal infection, cellulitis	17	0,345**	9	0,519*	1	0,674**	0	1,000**
Others	17	1,000**	10	0,350*	2	0,594**	1	0,440**

**Pearson's chi-square test, **Fisher's exact test*

Table 5: Gene distribution according to discharge outcome

Outcome Genes	Good	Bad	p
blaOXA-23 (n=67)	25	42	0,306**
blaOXA-48 (n=33)	12	21	0,627*
blaNDM-1 (n=5)	3	2	0,378**
blaOXA-58 (n=2)	1	1	1,000**

**Pearson's chi-square test, **Fisher's exact test*

Table 6: Gene combinations

Characteristics	Number	%
Only one gene	**3**	**4,0**
Only blaOXA-51	3	4,0
2-gene combination	**39**	**51,3**
BlaOXA-51+blaOXA-23	37	48,7
BlaOXA-51+blaOXA-48	1	1,3
BlaOXA-51+blaNDM-1	1	1,3
3-gene combination	**34**	**44,7**
BlaOXA-51+blaOXA-23+blaOXA-48	30	39,5
BlaOXA-51+blaOXA-48+blaNDM-1	2	2,6
BlaOXA-51+blaOXA-58+blaNDM-1	2	2,6

Table 7: Relationship between gene combination distribution and carbapenem resistance

	CSAB (n=5)	CRAB (n=71)	p (*Fisher's exact*)
Only one gene	3 (100%)	0 (0,0%)	< 0,001
2-gene combination	2 (5,1%)	37 (94,9%)	
3-gene combination	0 (0,0%)	34 (100%)	

Table 8: Comparison of carbapenem resistance of *A. baumannii* in several domestic and foreign studies

Study	Shahid Motahari Hospital, Tehran, Iran (2018-2019) [4]	HCMC UMC, (2015) [5]	Kien Giang General Hospital (2016-2017) [6]	Thong Nhat General Hospital, Dong Nai (2017-2018) [7]	Tay Nguyen Region General Hospital năm 2018-2019 [8]	This study
Carbapenem						
n =	50	22	53	97	59	76
Imipenem	94,0	-	88,7	84,5	95	93,4
Meropenem	94,0	63,2	88,7	86,6	93	93,4

Table 9: Comparison of gene distribution rates

Study	Location	n	bla OXA-51	bla OXA-23	bla OXA-48	bla OXA-58	bla NDM-1
Nguyen AT et al (2012-2014) [9]	3 hospitals in southest Vietnam	160	100	80,0	-	6,3	-
Le NTAP, Nguyen TB (2015-2016) [10]	HCMC UMC	162	100	93,8	-	6,3	-
Le TNX et al (2016) [11]	Hue central hospital Hue Hospital of University of Medicine and Pharmacy	90	100	85,3	-	27,9	11,8
Luu NTV (2016) [12]	9 hospitals in 3 regions of Vietnam	144	100	79,9	-	5,6	6,3
Hoang QC et al (2018) [7]	Thong Nhat General Hospital, Dong Nai	97	100	78,4	-	10,3	6,2
Our (2020)	**HCMC UMC**	**76**	**100**	**88,2**	**43,4**	**6,6**	**2,6**
Hou Cheng (2010-2014) [13]	Zhumadian central hospital, China	339	48,8	46,31	-	5,31	-

gene in A. baumannii, as there is likely no transverse inheritance through this plasmid, and the rapid spread of this β-lactamase may have occurred in recent years. In Vietnam, no studies of the *blaOXA-48* gene have been conducted in strains of *A. baumannii*. Although the activity of carbapenemase is lower than that of other class D β-lactamases, *blaOXA-48* is reported to undergo faster hydrolysis of imipenem than meropenem [16]. In this study, the distribution of the *blaOXA-48* gene did not significantly differ between the CRAB and CSAB groups, perhaps due to the co-emergence of multiple variants in the study or due to interactions with other carbapenemases without seeing the above differences. Because studies of this gene in *A. baumannii* are limited, we do not have data to compare and investigate conformity with other studies.

BlaOXA-58 : The detection rate of this gene was the lowest among the survey genes (2.6%). In the CRAB group, this rate was 7.7%, and this gene only appeared in the CRAB group. This rate is also consistent with that of *blaOXA-58* , which is usually the lowest gene identified in many studies, but our results were significantly lower than those of several other studies, such as those of Hoang Quoc Cuong (10.3%) [7], Luu Thi Vu Nga (5,6%) [12], Udomluk Leungtongkam (6.5%) [18], and Hou Cheng (5.3%) [13]; in particular, in the study of Le Nu Xuan Thanh, this rate reached 27.9% [11]. According to a study in China, until 2008, *blaOXA-58* was the most common gene (more than *blaOXA-23*) in this country until the replacement of *blaOXA-23* in 2009, and the resistance level of *blaOXA-58* was also lower than that of *blaOXA-23.* [19] More recently, in Vietnam, research has indicated that when *blaOXA-58* has increased expression of imipenem resistance in

the presence of ISAba3 insertion sequences, this combination may make blaOXA-58 worrisome[20].

BlaNDM-1 : The percentage in our study was 6.6%, which is similar to that reported in other studies[7,12] and higher than that reported in Iran (2.7%)[15]. Some studies of this topic, such as Le Nu Xuan Thanh et al. (2016) (11.8%)[11] and Udomluk Leungtongkam et al.[18](9.2%), have reported higher rates. Although there are disparities, there are generally few such studies, and studies with higher rates often come from populations sampled from 2-4 hospitals in the region or in the country. Regarding the distribution of the *blaNDM-1* gene according to some clinical features in the study, since the frequency of occurrence of the gene was quite small in the study, it is impossible to make a meaningful difference. However, in terms of characteristics such as resistance to carbapenems, 5/5 strains were found to carry the *blaNDM-1* gene (100%) resistant to carbapenems (both imipenem and meropenem), and according to the clinical department's results, there was a difference in the number of samples sent by the clinical department (p=0.026), which was mainly concentrated in 4/5 genes in the internal medicine department (one in the respiratory department, two in the neurology department, one in the Geriatric-Palliative Care Department), and one in the Neurosurgery Department. In terms of distribution by infectious disease, specimen type and discharge outcome did not significantly differ.

*** Gene combinations**

The occurrence of single-gene strains was only 3.9% (3 out of 76) with the blaOXA-51 gene, while the remaining 73 strains all carried more than one gene, with 54.0% having 2-gene combinations and 42.1% having 3-gene combinations. In both our research and the studies referenced above, all *A. baumannii* strains consistently exhibited 100% expression of the blaOXA-51 gene. Therefore, when encountering a single-gene strain, the blaOXA-51 gene is invariable. This study aligns with those referenced studies, albeit with a slightly lower percentage[7,9,12]. The appearance rate of the blaOXA-23 gene in this study is comparable to that in many previous studies, but it has the highest rate among the examined studies. In contrast, the aforementioned studies did not include a survey of the blaOXA-48 gene, which constituted 43.4% of the genes identified in our study. This difference may contribute to a reduction in the monogenic ratio of blaOXA-51 compared to findings in other studies. Additionally, the distribution of gene combinations showed a statistically significant association with carbapenem resistance ($p < 0.001$), implying that the increase in carbapenem resistance may be attributed to an increase in the number of combinations of resistance genes.

The 2-gene combinations used were *blaOXA-51+blaOXA-23*, *blaOXA-51+blaOXA-48* and *blaOXA-51+blaNDM-1*. In particular, the percentage of patients with the *blaOXA-51+blaOXA-23* gene combination was 94.9%. The 3-gene combinations used were *blaOXA-51+blaOXA-48+blaNDM-1* and *blaOXA-51+blaOXA-23+blaOXA-48* và *blaOXA-51+blaOXA-58+blaNDM-1*. In our study, we did not have any findings containing 4 genes in the same survey strain, while the study of Hoang Quoc Cuong et al. showed that up to 2 strains had all 4 genes: *blaNDM-1* + *blaOXA-51* + *blaOXA-23* + *blaOXA-58*[7].

CONCLUSION

The occurrence rate of the blaOXA-23 gene in this study was comparable to that in many previous studies, but it had the highest rate among the examined studies. In contrast, the aforementioned studies did not include a survey of the blaOXA-48 gene, which constituted 43.4% of the genes identified in our study. This difference may contribute to a reduction in the monogenic ratio of blaOXA-51 compared to findings in other studies. Additionally, the distribution of gene combinations showed a statistically significant association with carbapenem resistance ($p < 0.001$), implying that the increase in carbapenem resistance may be attributed to an increase in the number of combinations of resistance genes.

ACKNOWLEDGMENTS

We would like to sincerely thank the University of Medicine and Pharmacy at Ho Chi Minh City (UMP) and the University Medical Center (UMC) for their help and for creating the best conditions for us in research and completing the project.

ABBREVIATIONS

non

AUTHOR CONTRIBUTIONS

Duong Thi Hong Diep: conceived the idea, designed the study, collected specimens and patient information, and edited the manuscript.

Cao Thi Phung: performed experiments, performed statistical analysis, wrote the manuscript.

FUNDING

Duong Thi Hong Diep received the funding from the University of Medicine and Pharmacy at Ho Chi Minh City for this work.

AVAILABILITY OF DATA AND MATERIALS

none

COMPETING INTERESTS

The authors declare that they have no competing interests.

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