

Molecular epidemiology of carbapenem-resistant *Acinetobacter baumannii* isolates in Turkiye: Systematic review

 Elmas Pinar Kahraman Kilbas,¹  Imdat Kilbas,²  Ihsan Hakki Ciftci³

¹Department of Medical Laboratory Techniques, Fenerbahce University, Health Services Vocational School, Istanbul, Turkiye

²Medical Microbiology Doctorate Program, Istanbul University, Institute of Health Sciences, Istanbul, Turkiye

³Department of Microbiology, Sakarya University Faculty of Medicine, Sakarya, Turkiye

ABSTRACT

The World Health Organization has designated carbapenem-resistant *Acinetobacter baumannii* (CRAB) as a “critical” pathogen on the global priority list of antibiotic-resistant bacteria. This study aims to discuss the molecular epidemiology of CRAB isolates in Turkiye in the last 12 years and the prevalence of gene regions associated with resistance or pathogenesis using a systematic review method. Our study consists of a literature search, determination of eligibility and exclusion criteria, qualitative analysis of studies, data extraction, and statistical analysis. All studies were analyzed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines. The incidence rates of blaOXA-23, blaOXA-23-like, blaOXA-24/40, blaOXA-24/40-like, blaOXA-51, blaOXA-51-like, blaOXA-58, and blaOXA-58-like genes in CRAB strains were 76.4%, 68.6%, 1.2%, 3.4%, 97.0%, 98.6%, 8.4%, and 17.1%, respectively. It was determined that the prevalence of the blaOXA-23 and blaOXA-58 gene regions showed a statistically significant change over the years. Due to the high prevalence of *A. baumannii* strains carrying the blaOXA-23 variant, it is necessary to follow its geographical distribution and transposon and plasmid movements. Based on available data, molecular surveillance of CRAB strains should be standardized. In addition, sterilization and disinfection processes applied within the scope of an effective struggle against CRAB strains that can remain live on surfaces for a long time should be reviewed frequently.

Keywords: *Acinetobacter baumannii*; blaOXA-23; blaOXA-24/40; blaOXA51; blaOXA58.

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Acinetobacter baumannii strains, which cause bacteremia, ventilator-associated pneumonia, meningitis, urinary tract infections, wound infections, and burn infections, are increasingly causing epidemics. Especially in critically ill patients, placing them in the first place among healthcare-associated infectious agents and causing global concern [1–3]. Multi-drug resistance (MDR), common drug resistance (WDR), and pan-drug resistance (PDR) of *A. baumannii* strains that cause hospital infections constitute the main problem that needs to be overcome [4].

MDR, WDR, and PDR observed in *A. baumannii* strains also express carbapenem resistance and occur through mechanisms including decreased permeability with changes in porin-like proteins, decreased intracellular antibiotic concentrations as a result of the activity of efflux pumps, and the production of enzymes such as β -lactamases [5].

A. baumannii, which ranks first among the most common isolated agents in healthcare-associated infections, especially in developing countries, poses serious

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Correspondence: Elmas Pinar KAHRAMAN KILBAS, MD. Fenerbahce Universitesi, Saglik Hizmetleri Meslek Yuksekokulu, Tibbi Laboratuvar Teknikleri Bolumu, Istanbul, Turkiye.

Tel: +90 216 910 19 07 e-mail: elmspnrkk@gmail.com

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difficulties in the treatment of its MDR, WDR, and PDR [6]. For this reason, the World Health Organization has designated carbapenem-resistant *A. baumannii* (CRAB) as a “critical” pathogen in the global priority list of antibiotic-resistant bacteria [1]. blaOXA-51, a species-specific chromosomal carbapenemase gene responsible for carbapenem resistance in *A. baumannii* strains, and acquired blaOXA-24, blaOXA-23, blaOXA-143, blaOXA-58, and blaOXA-235 β -lactamase genes attract attention [7, 8].

Understanding the epidemiology of healthcare-associated *A. baumannii* infections is essential to controlling the development and dissemination of MDR, WDR, and PDR strains and establishing effective strategies [9]. This study aims to discuss the molecular epidemiology of CRAB isolates in Türkiye in the last 12 years and the prevalence of gene regions associated with resistance or pathogenesis using a systematic review method.

MATERIALS AND METHOD

Literature Search and Research Strategies

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines [10]. The study examined original scientific articles published in English and Turkish in PubMed, EMBASE, Scopus, Google Scholar, Web of Science, EBSCO, and Turkish Medline databases between January 2010 and January 2022.

For all English and Turkish population-based studies reporting carbapenem resistance in Türkiye, “Karbapenem dirençli Acinetobacter izolatları,” “Karbapenem dirençli *A. baumannii* izolatları,” “Karbapenem dirençli *A. baumannii* izolatlarının moleküler karakterizasyonu,” “Karbapenem dirençli *A. baumannii* izolatlarının epidemiyolojisi,” “Türkiye’deki *A. baumannii* virülans genleri,” “Carbapenem-resistant Acinetobacter isolates,” “CRAB isolates,” “Molecular characterization of CRAB isolates,” “epidemiology of CRAB isolates,” and “*A. baumannii* virulence genes in Turkey” were searched with key terms. Three authors carried out the scanning and collection of related articles. The authors independently evaluated publications for inclusion in the study. Inconsistencies were discussed at the scientific meeting held by the team and agreed upon by consensus.

Highlight key points

- The prevalence of the blaOXA-23 and blaOXA-58 gene regions showed a statistically significant change over the years.
- In parallel with the COVID-19 pandemic, a decrease was found in the resistance reports made for CRAB strains, one of the most critical factors responsible for healthcare-associated infections.
- blaOXA-23 and blaOXA-51 genes were dominant in CRAB strains in Türkiye.
- blaOXA-24 gene expression has increased over the years; It has been determined that the presence of the blaOXA-58 gene region has increased statistically significantly over the years.
- The blaOXA-48 gene expression, which is responsible for carbapenem resistance in *Klebsiella pneumoniae* isolates, was found to be limited in *A. baumannii* isolates.

Inclusion and Exclusion Criteria

The inclusion criteria were determined as follows: studies with more than 20 samples, *A. baumannii* strains isolated from clinical samples, resistant to carbapenems, investigating more than two gene regions, published between January 1, 2010 and January 1, 2022, and being original articles.

The exclusion criteria were determined as follows: below 20 percent of the sample size, studies that did not report the total number of patients and/or samples, reporting <2 gene regions, not defining at the species level, reviews, case reports, case series, letters to the editor, and congress papers that were not accepted as original articles, studies whose full text is not available, and inconsistent data.

Data Collection and Quality Assessment

The titles and abstracts were examined during the literature review process, and the full texts of the publications that the authors found appropriate by consensus were reached. Microsoft Excel spreadsheets were prepared to collect data. These tables included the first author’s surname, year of publication, study period, study location, sample size, number of confirmed samples, and gene regions.

Statistical Analysis

The SPSS Version 25.0 Statistics for Macbook (Armonk, NY: IBM Corp.) package program was used for statistical analysis. The one-way analysis of variance (ANOVA)

test measured whether the gene regions differed statistically according to the years, geographical regions, and clinics of the patients. Studies by years it were divided into three groups: 2010–2013, 2014–2017, and 2018–2021. According to geographical regions, it was divided into seven regions (Marmara, Central Anatolia, Black Sea, Aegean, Eastern Anatolia, Southeastern Anatolia, and the Mediterranean). The clinics where the patients were hospitalized were divided into three groups: intensive care unit, service, and both intensive care unit and service. A statistically significant $p < 0.05$ was accepted. The differences between the groups that were found to be significant were made with the Tukey test, one of the post hoc analyses.

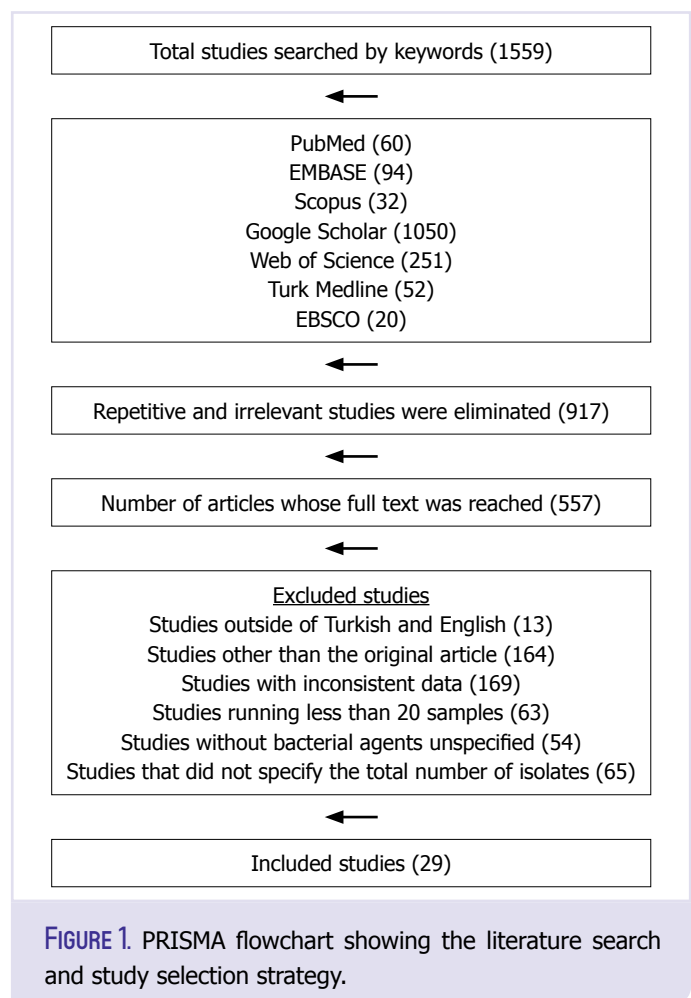
RESULTS

The total number of studies found according to the keywords determined in the databases (PubMed, EMBASE, Scopus, Google Scholar, Web of Science, EBSCO, and Turkish Medline) is 1559. The full text of 642 of them has been reached. 613 studies were excluded within the framework of the elimination criteria. A total of 29 original research articles were included in our study (Fig. 1).

Between January 1, 2010 and January 1, 2022, The incidence rates of blaOXA-23, blaOXA-23-like, blaOXA-24/40, blaOXA-24/40-like, blaOXA-51, blaOXA-51-like, blaOXA-58, and blaOXA-58-like genes in CRAB strains were 76.4%, 68.6%, 1.2%, 3.4%, 97.0%, 98.6%, 8.4%, and 17.1%, respectively (Table 1). The geographical distribution of these gene regions is shown in the map of Turkiye in Figure 2.

Table 1 shows the characteristics of the included studies [11–39].

The presence of the blaOXA-48 gene was examined in six of the 29 included studies, and blaOXA-48 positivity was not reported in any of them. The presence of the blaNDM-1 gene was investigated in eight of the studies; blaNDM-1 positivity was reported in only one study with a rate of 1.1% (Table 1). The presence of the blaPER-1 gene was examined in four studies; Positive positivity rates of 20.9% and 24.6% were reported in two studies [15, 18, 30, 31]. The presence of the blaTEM gene was investigated in 3 studies, and positivity rates of 55.7%, 53.6%, and 2.1% were reported (Table 1). The ISAbal gene was also examined in three studies, and the positivity rates of the studies were determined as 90.0%, 80.2%, and 50.0% (Table 1).



In the included studies, blaOXA-2, blaOXA-64, blaOXA-66, blaOXA-91, ompA, csgA, csuE, MHTs, fimH, blaCTX-M2, blaCTX-M1, and blaSHV gene regions were examined in one study, and the positivity rates were 10.4%, 100%, 100%, 100%, 21.8%, 71.8%, 32.1%, 100%, 7.1%, 12.1%, 8.1%, and 7.7%, respectively (Table 1).

CRAB isolates were most frequently isolated from the following samples, respectively: blood (70.97%), BAL (38.71%), endotracheal aspirate (45.16%), urine (45.16%), wound (41.94%), sputum (25.81%), catheter (25.81%), other samples (12.90%), CSF (9.68%), abscess (9.68%), and respiratory tract samples (6.45%). 22.58% of the studies did not specify the sample type.

The one-way ANOVA test analyzed whether the gene regions differed statistically according to the years, geographical regions, and clinics of the patients. It was determined that the prevalence rates of the blaOXA-51 and blaOXA-24/40 gene regions did not show a statistically significant difference according to years ($p > 0.05$).

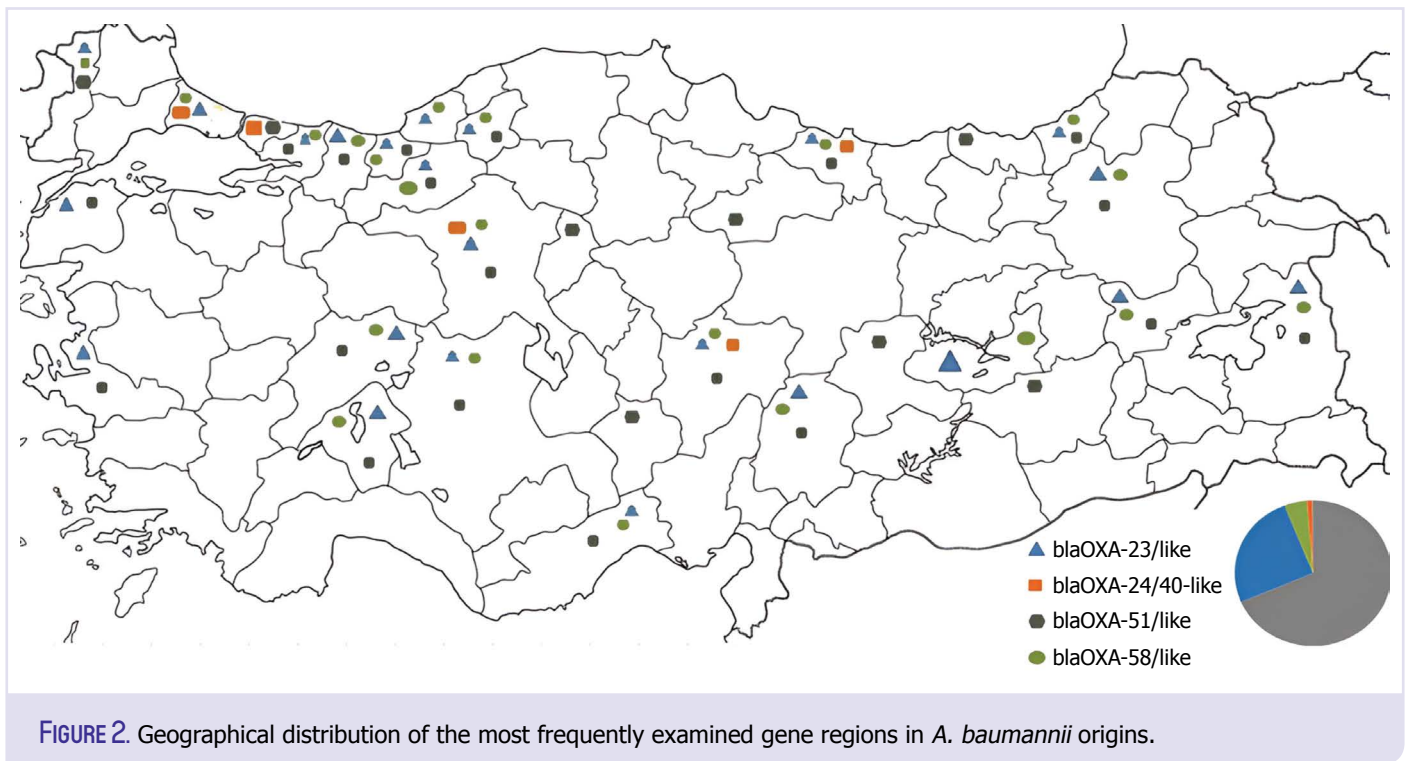


FIGURE 2. Geographical distribution of the most frequently examined gene regions in *A. baumannii* origins.

It was determined that the prevalence rates of the blaOXA-23 and blaOXA-58 gene regions showed statistically significant differences according to years ($p < 0.05$; $p = 0.005$, and $p = 0.022$, respectively). As a result of post-hoc analysis, it was found that these prevalence rates increased in parallel with time.

When the prevalence of blaOXA-23, blaOXA-24/40, blaOXA-51, and blaOXA-58 gene regions were analyzed in terms of geographical regions, a statistically significant difference was found ($p = 0.517$, $p = 0.854$, $p = 0.272$, $p = 0.750$, $p = 0.734$, respectively). Similarly, a statistically significant difference was found between the clinic where the patients were hospitalized and the prevalence of blaOXA-23, blaOXA-24/40, blaOXA-51, and blaOXA-58 gene regions ($p = 0.215$, $p = 0.779$, $p = 0.667$, $p = 0.543$, $p = 0.655$, respectively) (Fig. 2).

DISCUSSION

As a result of the indiscriminate use of a wide spectrum of antimicrobial agents, the antibiotic resistance of *A. baumannii* strains is increasing day by day, leading to the emergence of MDR, WDR, and PDR strains due to the high ability of these isolates to acquire multiple resistance genes. In particular, CRAB has been recognized as an important pathogen causing healthcare-associated infections worldwide [2]. Enzymes are class A, B, and D

β -lactamases, which can hydrolyze carbapenems and are responsible for CRAB strains' resistance [40]. It has also been emphasized that the acquisition of class D β -lactamases is an enzyme associated with resistance to carbapenems in *A. baumannii* strains [1].

blaOXA-type carbapenemases are not integrated into integrons as gene cassettes like other class D oxacillinases but are instead encoded by chromosomal genes. These blaOXA-type carbapenemases are widely distributed, particularly in *A. baumannii* [41]. They are often poorly expressed and poorly hydrolyzed carbapenems and do not by themselves cause clinically significant resistance [42]. As a result of our study, the most common blaOXA type carbapenemase gene regions in CRAB isolates are blaOXA-51, blaOXA-51-like, blaOXA-23, blaOXA-23-like, blaOXA-58-like, blaOXA-58, blaOXA-24/40-like, and blaOXA-24/40, respectively.

blaOXA-51-like encoded genes occur naturally in *A. baumannii* strains [43, 44]. However, a study conducted in Poland reported that the main cause of carbapenem resistance in *A. baumannii* is the result of increased expression of the chromosomal blaOXA-51-like β -lactamase [44]. With the data analyzed in our study, the blaOXA-51 gene positivity rate was 97.0%, and the blaOXA-51-like gene positivity rate was 98.6%. In the studies included in the systematic

TABLE 1. Characteristics of the included studies

Ref.	[11]	[12]	[13]	[14]	[15]	[16]	[17]	[18]	[19]	[20]	[21]	[22]	[23]	[24]	[25]	[26]	[27]	[28]	[29]	[30]	[31]	[32]	[33]	[34]	[35]	[36]	[37]	[38]	[39]	AV		
Year	2010	2013	2013	2014	2014	2014	2014	2014	2015	2015	2015	2015	2016	2016	2016	2016	2016	2016	2017	2019	2019	2019	2020	2020	2020	2020	2020	2021	2021			
Country	ZG	MC	AK	KY	AK	IS	RZ	MC	BL	IS	ED	MR	MC	OR	KL	KS	AK	AY	KR	MC	DZ	IS	IS	AK	AK	RZ	MC	AK	MC			
Clinics	ICU	IS	ICU+IS	ICU	IS	ICU+IS	ICU	ICU+IS	ICU	ICU+IS	ICU	ICU+IS	ICU	ICU	ICU	ICU	IS	IS	ICU+IS	ICU	ICU	IS	ICU	ICU	ICU	ICU	ICU	ICU	ICU			
N	145	834	100	105	201	101	109	763	62	72	52	79	519	50	100	205	44	41	69	172	96	20	100	112	61	70	156	44	177			
blaOXA23	0			91.5						70.8	100	89.9		100	93.0		31.8	43.9	94.2	96.5	100	50	91	100	82.0		63.6		76.4			
blaOXA23L	53.7	31.0	46.7	78.2	94.5	100							17.6												95.7		100	68.6				
blaOXA24/40				1.99						0	0	0	6.0	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	1.2			
blaOXA24/40L	0	0	0	0.9	0	0							30.2												0		3.4					
blaOXA48										0	0	0	0	0	0	0	0	0	0	0							0.00					
blaOXA48 L				0																							0.00					
blaOXA51				100						100	100	100	100	100	93		56.1			100	100	100	100	100	100	100	100	100	97.0			
blaOXA51 L	100	100	100	100	100	100							91.7												95.7		100	98.6				
blaOXA58	78.6			7.0						2.8	0	0	0	0	0	4.6	12.2	0	2.9	0	0	0	0	0	18.0		8.4					
blaOXA58 L	17.3	23	53.3	0	0	0							14.6												0		28.3	17.1				
blaOXA2																			10.4								10.4					
blaOXA64																									100		100					
blaOXA66																									100		100					
blaOXA91																									100		100					
NDM-1				0						0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.1	0.1				
PER-1				20.9			24.3														0	0			3.2		9.7					
ISAba1				80.2																					90.0		50.0	73.4				
TEM								55.7										53.6		2							37.1					
ompA																									21.8		21.8					
csgA																									71.8		71.8					
csuE																									32.1		32.1					
MHTs																									100		100					
fimH																											7.1		7.1			
blaCTX-M2													12.1														12.1					
blaCTX-M1													8.1														8.1					
blaSHV													7.7														7.7					

Ref; Reference; AV; Average; ZG; Zonguldak; MC; Multicenter; AK; Ankara; KY; Konya; IS; Istanbul; RZ; Rize; BL; Bolu; ED; Edirne; MR; Mersin; OR; Ordu; KL; Kocaeli; KS; Kayseri; AY; Aydin; KR; Karabuk; DZ; Duzce; ICU; Intensive care unit; IS; Inpatient service; N; Total number of isolates.

review, the relationship between increase and resistance in neither blaOXA-51 nor blaOXA-51-like gene expression could not be discussed because there was no data in this context.

To date, more than 25 variants have been identified. The average positivity rates (76.4%, 68.6%) of blaOXA-23 and blaOXA-23-like gene regions, which can be transferred by transposons (such as Tn2006, Tn2007, Tn2008, and Tn2009), have been reported worldwide. Consistent with the literature data, it was found to be higher with ISAba1 in our study [45, 46]. The active struggle with CRAB, which has blaOXA-23 variants and causes significant resistance problems in our country as it does worldwide, depends on the development of strategies in health-care areas. For this reason, first of all, it is necessary to follow the geographical distribution and transposon and plasmid movements of *A. baumannii* strains carrying the blaOXA-23 variant within the scope of clearly revealing the problem.

Seven variants of blaOXA-24/40 (blaOXA-24, blaOXA-25, blaOXA-26, blaOXA-72, blaOXA-139, blaOXA-160, and blaOXA-207) have been reported; although it has been reported to be related to class D beta-lactamases that hydrolyze carbapenems, such as blaOXA-143 and blaOXA-182, their contribution to carbapenem resistance is limited due to structural limitations in the enzyme's access to the active site on the antibiotic [47, 48]. It is endemic in the Iberian Peninsula [49, 50], with sporadic cases in Italy and France, and outbreaks have been reported in the United States [51–53]. In a meta-analysis study conducted in Iran, our border neighbor, the mean of blaOXA-24 prevalence was expressed as 21.9% [40]. In light of the data obtained from studies that met the inclusion criteria, the mean of blaOXA-24/40 in our country was 1.2%, and the mean of blaOXA-24/40-like was calculated as 3.4%. The rates obtained in our study are quite low. However, blaOXA-24/40 should be followed in detail in terms of possible variants that may occur as a result of epidemics and possible mutations due to geographical proximity to widespread areas.

blaOXA-48 is common in *Klebsiella pneumoniae* and plays several critical roles in biofilm formation and resistance to carbapenems. More studies have shown the presence of blaOXA-48 in *A. baumannii* strains [54, 55]. A study conducted in Iran showed that blaOXA-48 positivity was found at a very high rate of 92% in *A. baumannii* strains [56]. No blaOXA-48 positivity was reported

in any of the studies included in the systematic review. However, blaOXA-48 positive *A. baumannii* strains will likely come to our country, both from countries we have received immigration from, such as Libya and Syria, and from neighboring countries, such as Iran. Therefore, there is a need to continue to focus on blaOXA-48 studies in *A. baumannii* strains.

The blaOXA-58 gene, identified in a CRAB isolate that caused a hospital outbreak, is plasmid localized and has been found in clinical examples in Spain (20.3%), Iran (6.2%), Palestine (3.0%), the United States (2.0%), and Egypt (1.4%), as demonstrated in clinical samples [40, 57–61]. In our study, the mean positivity rates of blaOXA-58 and blaOXA-58-like genes were 8.4% and 17.1%, respectively. Considering that the presence of blaOXA-58 revealed by the study has increased statistically significantly over the years, It should be investigated how intensive care use during the COVID-19 epidemic affects the prevalence of blaOXA-58 and blaOXA-58-like genes.

The mobile resistance gene blaNDM encodes the NDM enzyme that hydrolyzes carbapenems and spreads among Gram-negative bacteria via plasmid [62]. In a study by Lukovic et al., [63] blaNDM-1 gene positivity was reported at 3.2% in *A. baumannii* strains. In studies conducted in our country, an average of 0.1% blaNDM positivity was found. This observation suggests that some constraints for the gene region, such as host adaptation, plasmid transport, or transposon jumps, limit the prevalence of the blaNDM gene among *A. baumannii* strains.

It has been stated that blaTEM is associated with sulbactam resistance, which is among the treatment alternatives for infections caused by *A. baumannii* [64]. Asgin et al. [29] reported the blaTEM positivity rate as 55.7% in a study conducted in our country with ampicillin-sulbactam-resistant *A. baumannii* strains. The average rate of blaTEM gene positivity was also high in the studies examined in the systematic review (average 37.1%). The ability to develop new resistance mechanisms and blaTEM variants propagated through mobile genetic elements should be considered when planning the treatment of infections caused by *A. baumannii*.

The blaPER-1 gene, known as *Pseudomonas* spp. extended resistance, is a beta-lactamase found in *P. aeruginosa* and *Acinetobacter* strains and was first shown in a Turkish patient in France [65, 66]. It has been reported that the blaPER-1 gene positivity rate is up to 74.2% in our country [18]. In our study, the blaPER-1 gene positivity rate was calculated at 9.7%. We believe that this

may be due to the selection in relation to the increase in the prevalence of MDR, WDR, and PDR strains of *A. baumannii*. In addition, factors such as geographic location, climate, hospital type, clinic type, clinical sample type, and resistance status may also be influential.

The problems encountered and the limitations of our study:

- The prevalence of carbapenem resistance and carbapenemase genes in Türkiye could not be fully demonstrated since all cities were not reported.
- The fact that different molecular methods determined the findings discussed in the study was ignored.
- Most of the studies reviewed did not have clonal reporting.
- The clinical and demographic characteristics of the patients could not be presented in detail since the publications meeting the inclusion criteria were not standardized.

Conclusions

In parallel with the COVID-19 pandemic, a decrease was found in the resistance reports made for CRAB strains, one of the most critical factors responsible for health-care-associated infections. Our study showed that the blaOXA-23 and blaOXA-51 genes were dominant in CRAB strains in Türkiye. blaOXA-24 gene expression has increased over the years. It has been determined that the presence of the blaOXA-58 gene region has increased statistically significantly over the years.

Due to the high prevalence of *A. baumannii* strains carrying the blaOXA-23 variant, it is necessary to follow its geographical distribution and transposon and plasmid movements.

It should be investigated how the increased use of intensive care during the COVID-19 epidemic affects the prevalence of all resistance-related gene regions.

It has been observed that blaOXA-48 gene expression, which is responsible for carbapenem resistance in *K. pneumoniae* isolates, is limited in *A. baumannii* isolates, and continuation of blaOXA-48-related studies is needed.

To frequently review the sterilization and disinfection procedures applied within the scope of an effective fight against CRAB strains that can remain stable on surfaces for a long time in the health care process. There is a need for detailed molecular follow-up of CRAB strains, which are nosocomial infection agents.

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Authorship Contributions: Concept – EPKK, IK, IHC; Design – IK, IHC; Supervision – EPKK, IK, IHC; Fundings – IK, IHC; Materials – IK, IHC; Data collection and/or processing – EPKK, IK, IHC; Analysis and/or interpretation – IHC; Literature review – EPKK, IHC; Writing – EPKK, IK, IHC; Critical review – EPKK, IK, IHC.

REFERENCES

1. Zarrilli R, Pournaras S, Giannouli M, Tsakris A. Global evolution of multidrug-resistant *Acinetobacter baumannii* clonal lineages. *Int J Antimicrob Agents* 2013;41:11–9.
2. Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: emergence of a successful pathogen. *Clin Microbiol Rev* 2008;21:538–582.
3. Maragakis LL, Perl TM. *Acinetobacter baumannii*: epidemiology, antimicrobial resistance, and treatment options. *Clin Infect Dis* 2008;46:1254–63.
4. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;18:268–81.
5. Abozahra R, Abdelhamid SM, Elsheredy AG, Abdulwahab KE, Baraka K. Genotyping and molecular characterization of carbapenem-resistant *Acinetobacter baumannii* strains isolated from intensive care unit patients. *Microbiol Biotechnol Lett* 2021;49:239–42.
6. Tuon FF, Rocha JL, Merlini AB. Combined therapy for multi-drug-resistant *Acinetobacter baumannii* infection is there evidence outside the laboratory? *J Med Microbiol* 2015;64:951–9.
7. Perez F, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. Global challenge of multidrug-resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2007;51:347–8.
8. Çiftçi İH, Aşık G. Antibiotic resistance mechanisms of *Acinetobacter baumannii*. [Article in Turkish]. *ANKEM Derg* 2011;25:196–207.
9. Lob SH, Hoban DJ, Sahm DF, Badal RE. Regional differences and trends in antimicrobial susceptibility of *Acinetobacter baumannii*. *Int J Antimicrob Agents* 2016;47:317–23.
10. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
11. Kulah C, Mooij MJ, Comert F, Aktas E, Celebi G, Ozlu N, et al. Characterisation of carbapenem-resistant *Acinetobacter baumannii* outbreak strains producing OXA-58 in Turkey. *Int J Antimicrob Agents* 2010;36:114–8.
12. Ciftci İH, Aşık G, Karakeçe E, Oksüz L, Yağcı S, Sesli Çetin E, et al. Distribution of blaOXA genes in *Acinetobacter baumannii* strains: a multicenter study. [Article in Turkish]. *Mikrobiyol Bul* 2013;47:592–602.
13. Ergin A, Hascelik G, Eser OK. Molecular characterization of oxacillinases and genotyping of invasive *Acinetobacter baumannii* isolates using repetitive extragenic palindromic sequence-based polymerase chain reaction in Ankara between 2004 and 2010. *Scand J Infect Dis* 2013;45:26–31.

14. Keyik S, Arslan U, Türk Dağı H, Seyhan T, Fındık D. Investigation of OXA type beta-lactamases and PFGE patterns in *Acinetobacter baumannii* strains resistant to carbapenems. [Article in Turkish]. Mikrobiyol Bul 2014;48:556–65.
15. Keskin H, Tekeli A, Dolapçı İ, Öcal D. Molecular characterization of beta-lactamase-associated resistance in *Acinetobacter baumannii* strains isolated from clinical samples. [Article in Turkish]. Mikrobiyol Bul 2014;48:365–76.
16. Cicek AC, Saral A, Iraz M, Ceylan A, Duzgun AO, Peleg AY, et al. OXA- and GES-type β -lactamases predominate in extensively drug-resistant *Acinetobacter baumannii* isolates from a Turkish University Hospital. Clin Microbiol Infect 2014;20:410–5.
17. Ertürk A, Çiçek AÇ, Gümüş A, Cüre E, Şen A, Kurt A, et al. Molecular characterisation and control of *Acinetobacter baumannii* isolates resistant to multi-drugs emerging in inter-intensive care units. Ann Clin Microbiol Antimicrob 2014;13:36.
18. Aşık G, Özdemir M, Güzel Kurtoğlu M, Yağcı S, Öksüz L, Gül M, et al. Detection of the frequency of PER-1 type extended-spectrum β -lactamase-producing *Acinetobacter baumannii* clinical isolates in Turkey: a multicenter study. Turk J Med Sci 2014;44:1041–6.
19. Sarı B, Baran I, Alaçam S, Mumcuoğlu İ, Kurşun Ş, Aksu N. Investigation of oxacillinase genes in nosocomial multidrug-resistant *Acinetobacter baumannii* isolates by multiplex PCR and evaluation of their clonal relationship with Rep-PCR. [Article in Turkish]. Mikrobiyol Bul 2015;49:249–58.
20. Cakirlar FK, Ciftci IH, Gonullu N. OXA-type carbapenemases and susceptibility of colistin and tigecycline among carbapenem-resistant *Acinetobacter baumannii* isolates from patients with bacteremia in Turkey. Clin Lab 2015;61:741–7.
21. Aksoy MD, Çavuşlu Ş, Tuğrul HM. Investigation of metallo beta lactamases and oxacilinas in carbapenem resistant *Acinetobacter baumannii* strains isolated from inpatients. Balkan Med J 2015;32:79–83.
22. Direkel Ş, Çopur Çiçek A, Karagöz A, Aydoğan Ejder N, Oktay E, Delialioğlu N, et al. Antimicrobial susceptibility and molecular characterization of multidrug-resistant *Acinetobacter baumannii* isolated in an university hospital. [Article in Turkish]. Mikrobiyol Bul 2016;50:522–34.
23. Beriş FŞ, Budak EE, Gülek D, Uzun A, Çizmecci Z, Mengeloğlu FZ, et al. Investigation of the frequency and distribution of beta-lactamase genes in the clinical isolates of *Acinetobacter baumannii* collected from different regions of Turkey: a multicenter study. [Article in Turkish]. Mikrobiyol Bul 2016;50:511–21.
24. Çetinkol Y, Telli M, Altunçekiç Yıldırım A, Çalgın MK. Evaluation of the efficacy of colistin/sulbactam combination on carbapenem-resistant *Acinetobacter baumannii* strains. [Article in Turkish]. Mikrobiyol Bul 2016;50:460–5.
25. Gür Vural D, Durupınar B. Investigation of the presence of class D Beta-lactamases in clinical isolates of carbapenem-resistant *Acinetobacter baumannii*. [Article in Turkish]. Türk Mikrobiyol Cem Derg 2016;46:181–7.
26. Ahmed SS, Alp E, Ulu-Kilic A, Dinc G, Aktas Z, Ada B, et al. Spread of carbapenem-resistant international clones of *Acinetobacter baumannii* in Turkey and Azerbaijan: a collaborative study. Eur J Clin Microbiol Infect Dis 2016;35:1463–8.
27. Altun Ş, Koçak Tufan Z, Altun B, Önde U, Kınıklı S, Demiröz AP. Growing OXA-23 type strains among carbapenem-resistant *Acinetobacter baumannii* and tigecycline as an alternate combination therapy. Turk J Med Sci 2016;46:1894–9.
28. Telli M, Eyigör M, Korkmazgil B, Aydın N, Atalay MA. Molecular epidemiology of carbapenem resistance in clinical isolates of *Acinetobacter* spp. [Article in Turkish]. Türk Mikrobiyol Cem Derg 2017;47:190–6.
29. Asgin N, Otlu B, Cakmakliogullari EK, Celik B. High prevalence of TEM, VIM, and OXA-2 beta-lactamases and clonal diversity among *Acinetobacter baumannii* isolates in Turkey. J Infect Dev Ctries 2019;13:794–801.
30. Boral B, Unaldi Ö, Ergin A, Durmaz R, Eser ÖK; Acinetobacter Study Group. A prospective multicenter study on the evaluation of antimicrobial resistance and molecular epidemiology of multidrug-resistant *Acinetobacter baumannii* infections in intensive care units with clinical and environmental features. Ann Clin Microbiol Antimicrob 2019;18:19.
31. Say Coskun US, Caliskan E, Copur Cicek A, Turumtay H, Sandalli C. β -lactamase genes in carbapenem resistance *Acinetobacter baumannii* isolates from a Turkish university hospital. J Infect Dev Ctries 2019;13:50–5.
32. Demirci M, Yiğın A, Demir C. Distribution of OXA-type carbapenemase genes in carbapenem-resistant *Acinetobacter baumannii* strains: an investigation by real-time PCR method. [Article in Turkish]. Klimik Derg 2019;32:123–6.
33. Kula Atik T, Özyurt M, Atik B, Bektöre B, Selek BM, Çetinkaya RA, et al. Identification of OXA-gene in *Acinetobacter baumannii* isolates obtained from clinical specimens and the clonality between these isolates. Nobel Med 2019;15:44–51.
34. Gözalan A, Ünalı Ö, Kırcı F, Çöplü N, Müderris T, Açıkgöz ZC, et al. Molecular characterization of carbapenem-resistant *Acinetobacter baumannii* isolates causing bloodstream infections in intensive care unit. [Article in Turkish]. Turk Hij Den Biyol Derg 2020;77:15–24.
35. Guclu AU, Gozen AG. Genetic diversity of OXA-like genes in multidrug-resistant *Acinetobacter baumannii* strains from ICUs. Clin Lab 2020;66(10).
36. Ozyurt S, Kostakoglu U, Yildiz IE, Erturk A, Sonmez E, Sahin U, et al. Investigation of the clonal associations in *Acinetobacter baumannii* strains isolated from the respiratory samples of patients in a tertiary research hospital. Niger J Clin Pract 2020;23:1155–62.
37. Altınok Ö, Boral B, Ergin A, Eser ÖK. Existence of biofilm and biofilm-associated virulence genes in multi-drug resistant invasive *Acinetobacter baumannii* Isolates. [Article in Turkish]. Mikrobiyol Bul 2020;54:40–9.
38. Özkul C, Hazırolan G. Oxacillinase gene distribution, antibiotic resistance, and their correlation with biofilm formation in *Acinetobacter baumannii* bloodstream isolates. Microb Drug Resist 2021;27:637–46.
39. Gozalan A, Unaldi O, Guldemir D, Aydogan S, Kuzucu C, Cakirlar FK, et al. Molecular characterization of carbapenem-resistant *Acinetobacter baumannii* blood culture isolates from three hospitals in Turkey. Jpn J Infect Dis 2021;74:200–8.
40. Beigverdi R, Sattari-Maraji A, Emaneini M, Jabalameli F. Status of carbapenem-resistant *Acinetobacter baumannii* harboring carbapenemase: first systematic review and meta-analysis from Iran. Infect Genet Evol 2019;73:433–43.
41. Walther-Rasmussen J, Høiby N. OXA-type carbapenemases. J Antimicrob Chemother 2006;57:373–83.
42. Héritier C, Poirel L, Aubert D, Nordmann P. Genetic and functional analysis of the chromosome-encoded carbapenem-hydrolyzing oxacillinase OXA-40 of *Acinetobacter baumannii*. Antimicrob Agents Chemother 2003;47:268–73.

43. Mohammadi F, Goudarzi H, Hashemi A, Yousefi N, Khoshnood S, Sabzehali F. Detection of ISAbal in *Acinetobacter baumannii* strains carrying OXA genes isolated from Iranian burns patients. *Arch Pediatr Infect Dis* 2017;5:e39307.
44. Nowak P, Paluchowska P, Budak A. Distribution of blaOXA genes among carbapenem-resistant *Acinetobacter baumannii* nosocomial strains in Poland. *New Microbiol* 2012;35:317–25.
45. Hamidian M, Nigro SJ. Emergence, molecular mechanisms and global spread of carbapenem-resistant *Acinetobacter baumannii*. *Microb Genom* 2019;5:e000306.
46. Nigro SJ, Hall RM. Structure and context of *Acinetobacter* transposons carrying the OXA23 carbapenemase gene. *J Antimicrob Chemother* 2016;71:1135–47.
47. Cayó R, Merino M, Ruiz Del Castillo B, Cano ME, Calvo J, Bou G, et al. OXA-207, a novel OXA-24 variant with reduced catalytic efficiency against carbapenems in *Acinetobacter pittii* from Spain. *Antimicrob Agents Chemother* 2014;58:4944–8.
48. Acosta J, Merino M, Viedma E, Poza M, Sanz F, Otero JR, et al. Multidrug-resistant *Acinetobacter baumannii* harboring OXA-24 carbapenemase, Spain. *Emerg Infect Dis* 2011;17:1064–7.
49. Grosso F, Quinteira S, Peixe L. Understanding the dynamics of imipenem-resistant *Acinetobacter baumannii* line ages with in Portugal. *Clin Microbiol Infect* 2011;17:1275–9.
50. Quinteira S, Grosso F, Ramos H, Peixe L. Molecular epidemiology of imipenem-resistant *Acinetobacter haemolyticus* and *Acinetobacter baumannii* isolates carrying plasmid-mediated OXA-40 from a Portuguese hospital. *Antimicrob Agents Chemother* 2007;51:3465–6.
51. D'Andrea MM, Giani T, D'Arezzo S, Capone A, Petrosillo N, Visca P, et al. Characterization of pABVA01, a plasmid encoding the OXA-24 carbapenemase from Italian isolates of *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2009;53:3528–33.
52. Lolans K, Rice TW, Munoz-Price LS, Quinn JP. Multicity outbreak of carbapenem-resistant *Acinetobacter baumannii* isolates producing the carbapenemase OXA-40. *Antimicrob Agents Chemother* 2006;50:2941–5.
53. Héritier C, Poirer L, Lambert T, Nordmann P. Contribution of acquired carbapenem-hydrolyzing oxacillinases to carbapenem resistance in *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2005;49:3198–202.
54. Aruhomukama, D, Najjuka CF, Kajumbula H, Okee M, Mboowa G, Sserwadda I, et al. blaVIM- and blaOXA-mediated carbapenem resistance among *Acinetobacter baumannii* and *Pseudomonas aeruginosa* isolates from the Mulago hospital intensive care unit in Kampala, Uganda. *BMC Infect Dis* 2019;19:853.
55. Mathlouthi N, Areig Z, Al Bayssari C, Bakour S, Ali El Salabi A, Ben Gwierif S, et al. Emergence of carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* clinical isolates collected from some Libyan hospitals. *Microb Drug Resist* 2015;21:335–41.
56. Tarafdar F, Jafari B, Azimi T. Evaluating the antimicrobial resistance patterns and molecular frequency of bla_{oxa}-48 and bla_{GES-2} genes in *Pseudomonas aeruginosa* and *Acinetobacter baumannii* strains isolated from burn wound infection in Tehran, Iran. *New Microbes New Infect* 2020;37:100686.
57. Poirer L, Nordmann P. Genetic structures at the origin of acquisition and expression of the carbapenem-hydrolyzing oxacillinase gene bla_{OXA-58} in *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2006;50:1442–8.
58. Villalon P, Valdezate S, Medina-Pascual MJ, Carrasco G, Vindel A, Saez-Nieto JA. Epidemiology of the *Acinetobacter*-derived cephalosporinase, carbapenemhydrolysing oxacillinase and metallo-beta-lactamase genes, and of common insertion sequences, in epidemic clones of *Acinetobacter baumannii* from Spain. *J Antimicrob Chemother* 2013;68:550–3.
59. Kamel NA, El-Tayeb WN, El-Ansary MR, Mansour MT, Aboshanab KM. Phenotypic screening and molecular characterization of carbapenemase-producing gram-negative bacilli recovered from febrile neutropenic pediatric cancer patients in Egypt. *PLoS One* 2018;13:e0202119.
60. Huang XZ, Cash DM, Chahine MA, Nikolich MP, Craft DW. Development and validation of a multiplex TaqMan real-time PCR for rapid detection of genes encoding four types of class D carbapenemase in *Acinetobacter baumannii*. *J Med Microbiol* 2012;61:1532–7.
61. Handal R, Qunibi L, Sahouri I, Juhari M, Dawodi R, Marzouqa H, et al. Characterization of carbapenem-resistant *Acinetobacter baumannii* strains isolated from hospitalized patients in Palestine. *Int J Microbiol* 2017;2017:8012104.
62. Acman M, Wang R, van Dorp L, Shaw LP, Wang Q, Luhmann N, et al. Role of mobile genetic elements in the global dissemination of the carbapenem resistance gene bla_{NDM}. *Nat Commun* 2022;13:1131.
63. Lukovic B, Gajic I, Dimkic I, Kekic D, Zornic S, Pozder T, et al. The first nationwide multicenter study of *Acinetobacter baumannii* recovered in Serbia: emergence of OXA-72, OXA-23 and NDM-1-producing isolates. *Antimicrob Resist Infect Control* 2020;9:101.
64. Krizova L, Poirer L, Nordmann P, Nemecek A. TEM-1 β -lactamase as a source of resistance to sulbactam in clinical strains of *Acinetobacter baumannii*. *J Antimicrob Chemother* 2013;68:2786–91.
65. Nordmann P, Ronco E, Naas T, Duport C, Michel-Briand Y, Labia R. Characterization of a novel extended-spectrum beta-lactamase from *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 1993;37:962–9.
66. Kolayli F, Gacar G, Karadenizli A, Sanic A, Vahaboglu H; Study Group. PER-1 is still widespread in Turkish hospitals among *Pseudomonas aeruginosa* and *Acinetobacter* spp. *FEMS Microbiol Lett* 2005;249:241–5.