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REVIEW MICROBIOLOGY

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

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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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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 Turkiye in the last 12 years and the prevalence of gene regions associated with resistance or pathogenesis using a systematic review method.

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 Turkiye.
- 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.

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 Turkiye, "Karbapenem dirençli Acinetobacter izolatlari," "Karbapenem dirençli *A. baumannii* izolatlari," "Karbapenem dirençli *A. baumannii* izolatlarinin moleküler karakterizasyonu," "Karbapenem dirençli *A. baumannii* izolatlarının epidemiyolojisi," "Turkiye'deki *A. baumannii* virülans genleri," "Carbapenem-resistant Acinetobacter isolates," "CRAB isolates," "Molecular characterization of CRAB isolates," "epidemiology of CRAB isolates," and "*A. baumannii* virulance 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.

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 ISAba1 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).

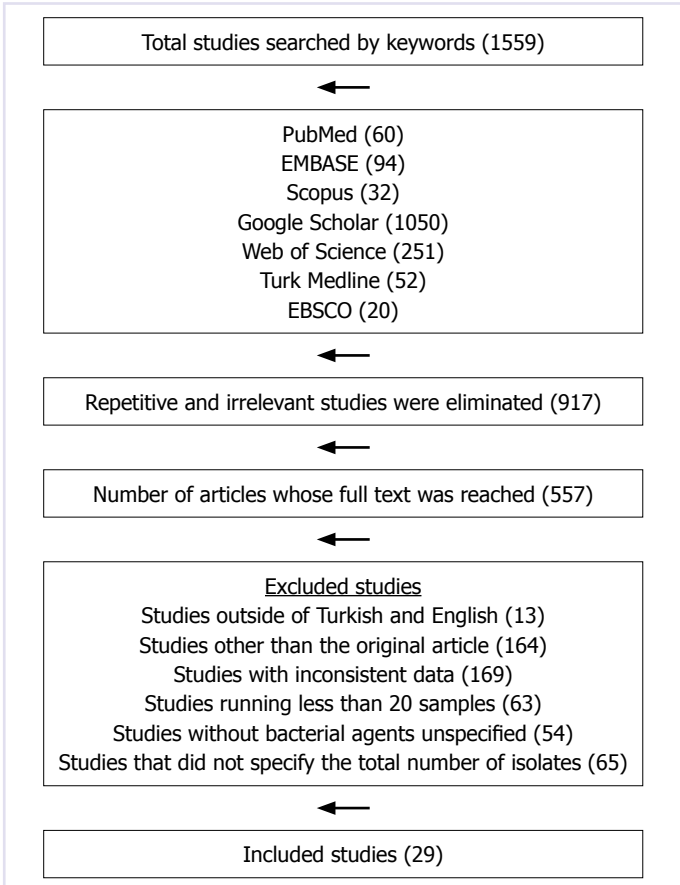

FIGURE 1. PRISMA flowchart showing the literature search and study selection strategy.

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 ($p>0.05$).

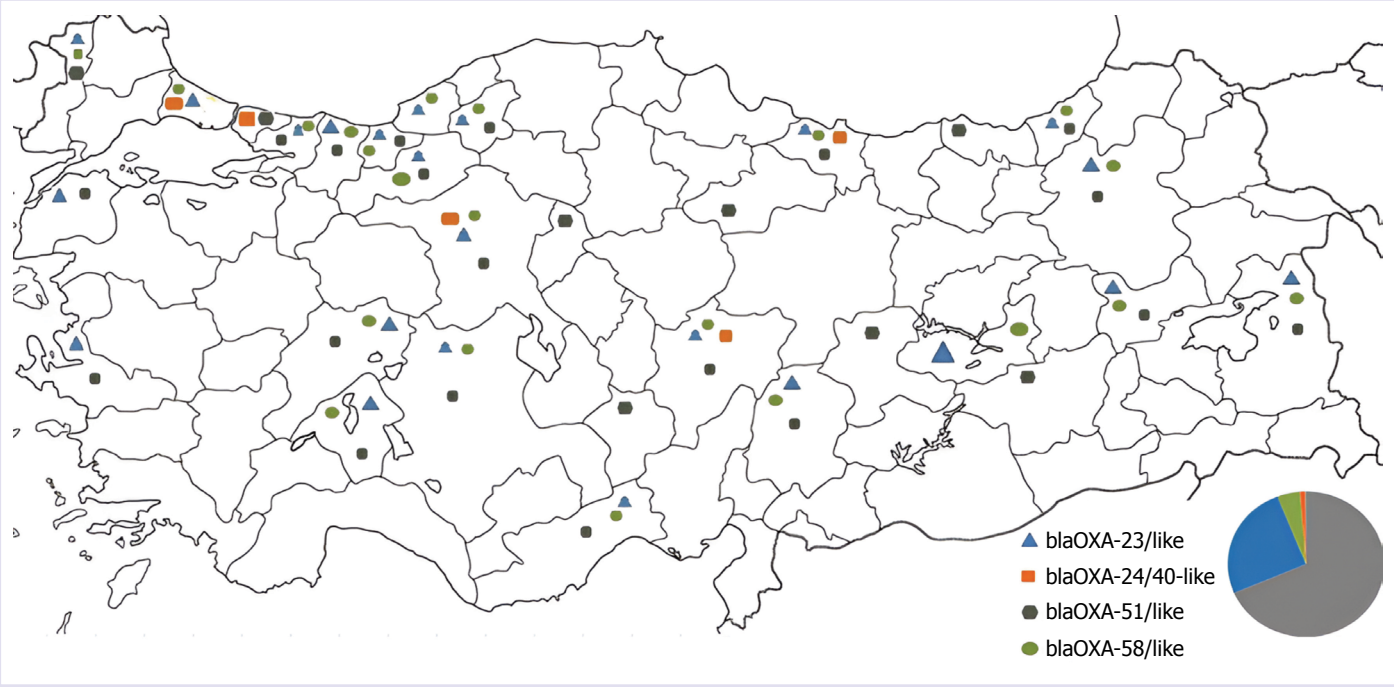

FIGURE 2. Geographical distribution of the most frequently examined gene regions in *A. baumannii* origins.

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	2019	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	ICU+IS	ICU+IS	ICU	–	ICU+IS	ICU+IS	–	ICU+IS	–	ICU	ICU	ICU	IS	IS	ICU+IS	ICU	ICU	IS	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		6.0	0			0	0		0	5	0	0	0					1.2
blaOXA24/40L	0	0	0	0		0.9	0		0							30.2										0				3.4
blaOXA48												0		0			0			0										0.00
blaOXA48 L							0																							0.00
blaOXA51					100			100		100	100	100	100	100	93			56.1		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		4.6	12.2	0	2.9	0		0	0	18.0					8.4
blaOXA58 L		17.3	23	53.3			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	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 Turkiye 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 Turkiye. 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.

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