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IN VITRO EVALUATION OF *ACINETOBACTER BAUMANNII* RESISTANCE TO TIGECYCLINE IN IRAN: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction. *Acinetobacter baumannii (A. baumannii)* is a widespread and exclusively hospital-acquired microorganism whose new mutation is resistant to most available antibiotics, with the exception of tigecycline. Clinicians are concerned about recent evidence of resistance to this antibiotic in Iran.

Objective. This study evaluates the resistance of *Acinetobacter baumannii* (*A. baumannii*) to tigecycline in Iran, considering its clinical significance in treating multi-drug-resistant infections.

Methods. The MEDLINE, PubMed, Web of Science (WOS), and Scopus databases were searched for studies published over all this time to January 2024. The advanced search using Medical Subject Headings (MeSH) terms for "*Acinetobacter baumannii*" and "Tigecycline" was performed. The title, abstract, and full text of the articles were screened based on eligibility criteria. The cross-sectional studies reporting Tigecycline resistance in sequential isolates of *A. baumannii* in patients admitted to the hospitals in Iran were included.

Results. A total of 16 studies were included for meta-analysis. The overall prevalence of *A. baumannii* strains resistant to tigecycline in Iran equals 18.1%. Among the reviewed studies, distinct variances of resistance were detected. Although investigations were conducted in limited regions, the studies reported a wide range of resistance in Tehran (0%) and in Tabriz (100%) as minimum and maximum, respectively.

Conclusion. Despite the high level of resistance in some cities of Iran, tigecycline is still one of the most effective antibiotics for the treatment of *A. baumannii* infection. Improved control over the use of antibiotics may contribute to hampering the spread of resistance to these agents.

Keywords: *Acinetobacter baumannii*; tigecycline; drug resistance; *in vitro*; meta-analysis; multiple drug resistance

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ОЦЕНКА УСТОЙЧИВОСТИ *ACINETOBACTER BAUMANNII IN VITRO* К ТИГЕЦИКЛИНУ В ИРАНЕ: СИСТЕМАТИЧЕСКИЙ ОБЗОР И МЕТААНАЛИЗ

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Введение. *Acinetobacter baumannii (A. baumannii)* — это распространенный и исключительно госпитальный микроорганизм, новая мутация которого устойчива к большинству доступных антибиотиков, за исключением тигециклина. Клиницисты выражают озабоченность в связи с недавними данными о резистентности к этому антибиотику, зафиксированными в Иране.

Цель. Оценить устойчивость *Acinetobacter baumannii* (*A. baumannii*) к тигециклину в Иране, учитывая его клиническое значение в лечении инфекций с множественной лекарственной устойчивостью.

Материалы и методы. В базах данных MEDLINE, PubMed, Web of Science (WOS), Scopus проведен поиск исследований, опубликованных за все время до января 2024 г. Выполнен расширенный поиск с использованием медицинских тематических рубрик (MeSH) по таким терминам, как «*Acinetobacter baumannii*», «тигециклин». В соответствии с критериями приемлемости были отобраны название, аннотация и полный текст статей. Также были включены перекрестные исследования, в которых сообщалось об устойчивости к тигециклину у последовательных изолятов *A. baumannii* среди госпитализированных пациентов иранских клиник.

Результаты. В метаанализ было включено в общей сложности 16 исследований. Общая распространенность штаммов *A. baumannii*, устойчивых к тигециклину, составила 18,1%. Выявлены отчетливые различия в устойчивости. Несмотря на то, что исследования проводились в ограниченном количестве регионов, сообщалось о широком диапазоне резистентности: от минимальной в исследовании в Тегеране (0%) до максимальной в исследовании в Тебризе (100%).

Заключение. В результате проведенного исследования установлено, что, несмотря на высокий уровень резистентности в некоторых городах Ирана, тигециклин по-прежнему остается одним из наиболее эффективных антибиотиков для лечения инфекции *A. baumannii*. Существует вероятность, что, улучшив контроль за применением антибиотиков, можно замедлить или остановить распространение устойчивости к ним.

Ключевые слова: *Acinetobacter baumannii*; тигециклин; антибиотикорезистентность; *in vitro*; метаанализ; множественная антибиотикорезистентность

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INTRODUCTION

Acinetobacter baumannii (*A. baumannii*) is a ubiquitous, aerobic, gram-negative coccobacillus. This bacterium is widely spread in water, soil, and hospital environments, capable of surviving there for a long time [1, 2]. In addition, *A. baumannii* is a common pathogen identified in the blood, skin, urine, pleural fluid, and sputum [3]. Due to its capacity to transfer between non-living and living objects, this pathogen is increasingly responsible for hospital-acquired infections [4]. Moreover, the emergence, proliferation, and spread of a new drug-resistant *A. baumannii*, which is capable of transferring some genetic elements and is resistant to different antibiotics, has worsened the situation [5]. Various studies have reported the resistance of *A. baumannii* to different classes of antimicrobial agents, such as aminoglycosides, β-lactams, and quinolones, as well as carbapenems. Given the scarcity of alternatives available for treating drug-resistant infections caused by *A. baumannii*, tigecycline is currently attracting research attention [2, 6].

In comparison with other tetracyclines, tigecycline is a bacteriostatic agent with a higher binding affinity to the bacterial 30S ribosomal subunit. Tigecycline, an antibiotic based on minocycline, has a wide spectrum of action and is capable of overcoming the main mechanisms of bacterial resistance to tetracyclines, such as efflux and ribosome protection. This is achieved by adding a glycylamide fragment to the minocycline molecule [7]. The mechanism of resistance to tetracyclines is generally mediated by the following systems: the attainment of genetic sections transferring the genes particularly resistant to tetracyclines, mutations inside the attaching region of the ribosome, and/or mutations in chromosomes leading to intensified expression of fundamental resistance mechanisms. Various processes of bacterial resistance were described in [8].

Tigecycline is a semisynthetic agent known as the primary exclusive antibiotic of the glycylamide class. Tigecycline overcomes key tetracycline resistance mechanisms — namely, efflux pump activity and ribosomal protection — through the addition of a glycyclamide group to its minocycline-based structure. This structural modification contributes to its broad-spectrum antibacterial activity [7]. Tigecycline is an available drug for treating multidrug-resistant *A. baumannii* [9], showing activity against multiple drug resistant (MDR) pathogens such as *Enterobacteriaceae*, *Staphylococcus aureus*, and *Acinetobacter* species [10]. In 2005, the US Food and Drug Administration (US FDA) approved this drug for treating community-acquired pneumonia, skin infections (except for diabetes foot infection), and complicated intra-abdominal infections [11].

Tigecycline exhibits a noticeable activity against extensive drug resistance (XDR) and MDR gram-negative bacteria, particularly *A. baumannii*. The resistance of the latter to tigecycline has been reported relatively recently [12–14]. Some mechanisms, such as the chromosomal or supplemental encoding process of genes, are responsible for tigecycline resistance [7]. Since tigecycline is one of the few remaining drugs for the treatment of *A. baumannii* infection with MDR, it is necessary to determine its potential resistance in a timely manner. In comparison with developed countries, where effective preventive health measures are used, developing countries, such as Iran, require the development and implementation of measures to control the process of drug prescription, disseminate information about antibiotic resistance among patients, and regulate the proper use of medicines [15]. Thus, the study of *A. baumannii* resistance to tigecycline in Iranian patients is an important and urgent task.

The purpose of this study was to evaluate the resistance of *Acinetobacter baumannii (A. baumannii)* to tigecycline in Iran, taking into account its clinical significance in the treatment of multidrug-resistant infections.

MATERIALS AND METHODS

This research was designed in accordance with Cochrane's standard methodology and presented based on the PRISMA checklist (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Search strategy

The literature search was conducted across the Google Scholar, PubMed, Web of Science, and Scopus databases, covering all available data up to January 2024. The search algorithm based on keywords, their synonyms, and related Medical Subject Headings (MeSH terms) was as follows: ((*Acinetobacter baumannii* [title/abstract]) OR (Acinetobacter [Title/Abstract])) OR (*A. baumannii* [Title/Abstract]) AND (Tygacil [Title/Abstract])) OR ((Tigecycline [title/abstract]). In addition, a backward and forward citation search was conducted to raise the comprehensiveness of the conducted literature search.

Inclusion and exclusion criteria

The records achieved from searching the databases were combined in the EndNote X9 library (Thomson Reuters, Toronto, ON, Canada); duplicates were deleted.

The resulting sample included *in vitro* cross-sectional studies investigating the resistance of *A. baumannii* to tigecycline in sequential *A. baumannii* isolates from the patients admitted to Iranian hospitals by using different methods, such as broth microdilution, disk diffusion, and *E*-test [16]. Moreover, only patients with MDR resistance were eligible for this study. Multidrug resistance is defined as not being susceptible to at least one antibiotic in three antimicrobial classes acknowledged as treatment options for the disease associated with *A. baumannii* [17]. Biological and biomedical research studies on animal models, as well as case reports, case series, case-controls, and studies evaluating variables irrelevant to resistance rate, were excluded.

Statistical analysis

The statistical analysis was conducted using the Comprehensive Meta-Analysis software package, version 3.0 (Biostat Inc., Englewood, NJ, USA). 95% confidence intervals (CIs) and point estimates for the resistance rate to tigecycline were calculated.

The degree of existing heterogeneity between different meta-studies was assessed using the I^2 value and the *p*-criterion. The I^2 value is a quantitative indicator of heterogeneity that shows a degree of inconsistency in research results. I^2 describes the percentage of total variation between studies, which is due to heterogeneity rather than randomness. The I^2 indicator is calculated based on the basic results obtained as a result of a typical meta-analysis, as

$$I^2 = 100\% \times (Q - df) / Q, \quad (1)$$

where Q is the Cochran heterogeneity statistic and df is the degree of freedom.

Negative I^2 values were equated to zero such that I^2 were ranging from 0 to 100%. A 0% value indicates the absence of heterogeneity, with higher values indicating an increase in heterogeneity. I^2 statistics and Cochran's *Q*-test were used to assess the heterogeneity between studies. Due to the high level of heterogeneity between studies ($I^2 > 50\%$ or $p < 0.1$), a random effect model was used. To assess the reliability of the publication, we used the Egger criterion. Accordingly, the value of $p < 0.05$ was considered a statistically significant indicator for the reliability of the publication.

RESULTS

Study selection

The conducted systematic search across scientific databases produced 365 relevant articles that evaluate the prevalence of tigecycline-resistant *A. baumannii* in Iran. The first screening identified 190 articles by title and abstract, while the second screening based on full text found 53 articles. Following application of the inclusion and exclusion criteria, 16 articles were deemed satisfactory, thus being included in the current systematic review and meta-analysis (Figure 1).

Characteristics of the included studies

All selected articles reported cross-sectional studies conducted from 2014 to 2022 and spanning different geographical domains—capital (n = 10), north (n = 2), south (n = 3), and southwest (n = 1) — with various types of samples, including burn wound, urine, sputum, blood, and other body fluids (Table 1).

The quantity of MDR isolates ranged from 26 to 200. Nine, four, three, and one studies used disk diffusion, broth microdilution, E-test methods, and a combination of disk diffusion and broth microdilution methods for antimicrobial susceptibility testing on *A. baumannii*, respectively (Table 2).

Prevalence and Genetic Mechanisms of Tigecycline Resistance in *A. baumannii*

The studies under analysis reported differing data on the resistance prevalence of *A. baumannii*. Thus, although Saadati et al. [13] found all of the isolates to be MDR (100 out of 100) and reported the highest resistance rate (100%) against tigecycline in the northwest of Iran, Salehi et al. [33] identified 1.6% of MDR clinical isolates (2 out of 125) resistant to tigecycline in the North of Iran. Bahador et al. [31] conducted a five-year-long study in the north of Iran and found a notable rise in resistance to tigecycline, with all isolates demonstrating susceptibility in 2006. However, by 2011, 8% of isolates had exhibited resistance. In contrast to southern regions, a study by Kooti et al. conducted in 2015 [30] detected resistance to tigecycline in 2% (4 out of 200) of MDR isolates. However, in 2016, Alaei et al. [27] reported an estimated resistance rate of 8.8% (4 out of 45) within the same region. In investigations conducted within the capital of Iran from 2016 to 2018, a wide scattering of results spanning from 1.6 to 84% was observed. Jasemi et al. [29] carried out multi-center research to evaluate the prevalence and trajectory of drug-resistant *A. baumannii* phenotypes from 2011 to 2013 in Tehran. Eventually, the researchers observed a remarkable decrease in the resistance of this pathogen to tigecycline.

The resistance mechanism to this antibiotic refers to the genotypic profiles of multidrug-resistant *Acinetobacter baumannii* (MDR-AB) isolates and involves genes in the resistance process.

In the study by Kooti et al. [30], 0.5, 7, and 40% of isolates possessed $bla_{\text{OXA-58-like}}$, $bla_{\text{OXA-24-like}}$, and $bla_{\text{OXA-23-like}}$ (class D beta-lactamase family) genes, respectively, using multiplex-polymerase chain reaction (PCR). In another study, by Bahador et al. [31], IS*Aba1* and IS*Aba4* (transposase family) were identified upstream of $bla_{\text{OXA-23-like}}$ genes in 45.1% and 12.9% of isolates, respectively. Moreover, Sarhaddi et al. [25] estimated the occurrence rates of bla_{TEM} (class A beta-lactamase family), $bla_{\text{OXA-23-like}}$, $bla_{\text{OXA-24-like}}$, bla_{VIM}, and bla_{IMP} (subclass

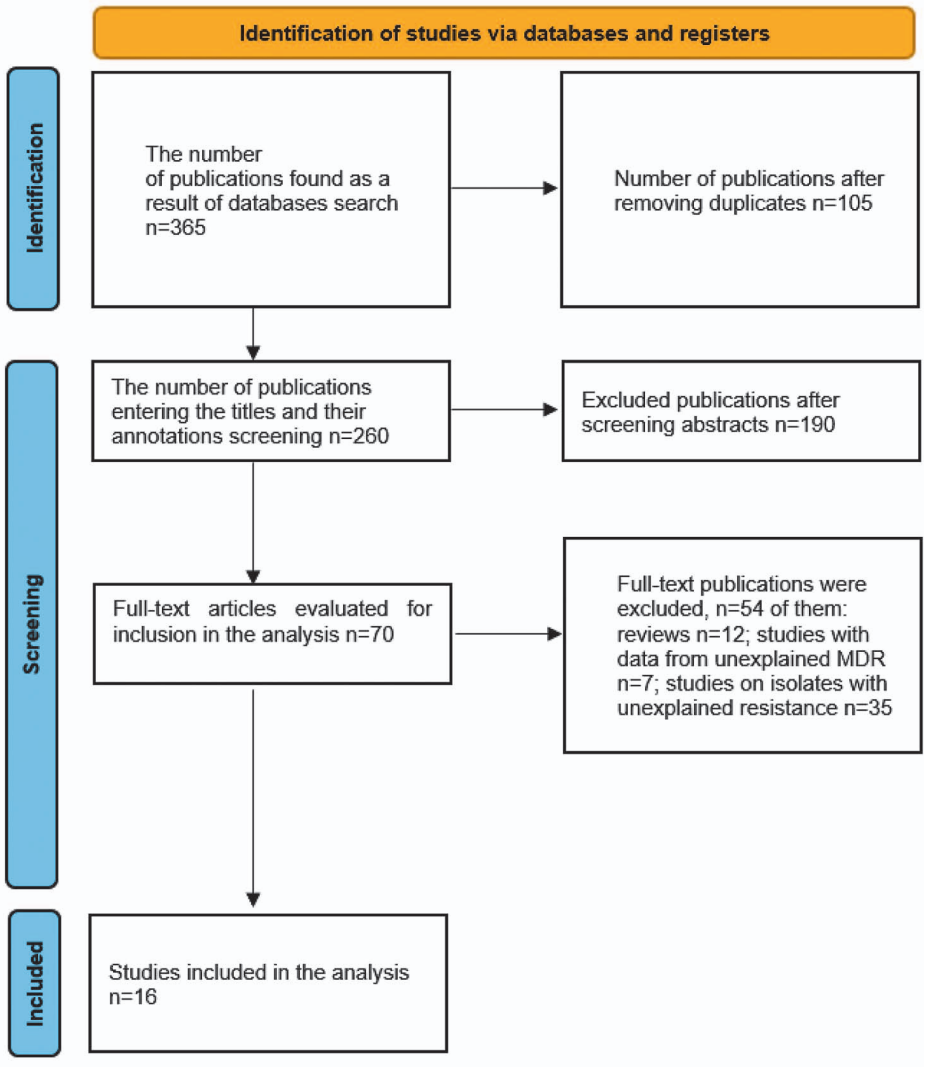

Figure prepared by the authors

Fig. 1. Flowchart diagram of the literature search procedure

B1 metallo-beta-lactamase family) at the level of 64.8, 66.7, 68.5, 70.4, and 70.4%, respectively. The presence of these genes might demonstrate a correlation with the acquisition of antimicrobial resistance.

The forest plot presented in Fig. 2 based on the meta-analysis results, demonstrates an 18.1% antimicrobial resistance to tigecycline among MDR *A. baumannii* species. Concerning the heterogeneity test, the obtained results showed *Q*-value = 305.712, *df* (*Q*) = 16, *p*-value = 0.000, and I^2 = 94.766 for the selected studies. The included studies demonstrated a publication bias, based on significant results of Egger's test (*p*-value < 0.05) and the asymmetrical funnel plot (Fig. 3).

Subgroup analysis

The overall resistance rate in ICU and non-ICU was 0.072 and 0.222, respectively (Fig. 4). The ICU subgroup had a lower heterogeneity (I^2 = 14.18%), while non-ICU patients showed a high heterogenicity (I^2 = 95.28%).

The overall resistance rate in Shiraz and Tehran was 0.079 and 0.161, respectively (Fig. 5). I^2 for these analyses was 91.31% for Shiraz and 95.14% for Tehran.

DISCUSSION

A. baumannii is a key agent of hospital-acquired infections due to its resistance to various classes of antibiotics [34, 35]. For this reason, the use of effective antibiotics, and the ongoing monitoring of antimicrobial resistance may contribute to *A. baumannii* eradication. Tigecycline, a potent semi-synthetic derivative of tetracycline, is recognized as the primary option among novel pharmaceuticals for infections caused by MDR strains of *Acinetobacter spp.* and carbapenem-resistant *A. baumannii* [7, 36]. The varied resistance rates could be explained by prescribing patterns and differences in regional epidemiology. Since 2005, the resistance rate to tigecycline has risen significantly as a result of long-term administration of this drug as a monotherapy and FDA approval.

In 2006, tigecycline was approved by the European Medicines Agency (EMA); in 2011, it was introduced in China. Since 2007, global reports have been published on tigecycline resistance. The *Acinetobacter* resistant strains had been reported before 2011 [37]. Overprescription of antibiotics has been associated with a higher rate of resistance [38]. There is probably an indirect correlation

Table 1. Characteristics of the included studies

	Study	Published year	Year of study	Type of study	City of study	Study population
1	Sepahvand et al. [18]	2022	no data	Cross-Sectional	Shiraz	hospital patients
2	Saadati et al. [13]	2021	August 2017 to February 2018	Cross-Sectional	Tabriz	hospital patients
3	Alavi-Moghaddam et al. [19]	2020	January 2016 to November 2018	Cross-Sectional	Tehran	hospital patients
4	Salehi et al. 2019 [20]	2019	August 2016 and February 2017	Cross-Sectional	Tehran	hospital patients
5	Tafreshi et al. [21]	2019	between 2016 and 2018	Cross-Sectional	Tehran	hospital patients
6	Yazdansetad et al. [22]	2019	during 2013	Cross-Sectional	Tehran	hospital burned patients
7	Salehi et al. 2018 [23]	2018	no data	Cross-Sectional	Tehran	patients, staff, and environment of an educational hospital
8	Zafari et al. [24]	2017	September 2015 to June 2016	Cross-Sectional	Tehran	hospital patients
9	Sarhaddi et al. [25]	2017	January and December 2014	Cross-Sectional	Mashhad	hospital patients
10	Ansari et al. [26]	2017	September 2015 to April 2016	Cross-Sectional	Shahrekord	hospital patients
11	Alaei et al. [27]	2016	February 2010 and March 2011	Cross-Sectional	Shiraz	ICU patients
12	Pourhajibagher et al. [28]	2016	no data	Cross-Sectional	Tehran	hospital patients
13	Jasemi et al. [29]	2016	August 2011 to December 2013	Cross-Sectional	Tehran	hospital patients
14	Kooti et al. [30]	2015	December 2012 to May 2013	Cross-Sectional	Shiraz	hospital patients
15	Bahador et al. 2015 [31]	2015	2012	Cross-Sectional	Tehran	Burned patients
16	Bahador et al. 2014 [32]	2014	2011	Cross-Sectional	Tehran	ICU patients
17	Bahador et al. 2014 [32]	2014	2006	Cross-Sectional	Tehran	ICU patients

Table prepared by the authors using data from the included studies [13, 18–32]

Table 2. List of selected samples and research methods

	Study	Sample source	MDR isolates	TGC /MDR	Diagnostic test
1	Sepahvand et al [18]	blood, wound, respiratory and urine samples	100	22	disc diffusion
2	Saadati et al [13]	tracheal secretion, blood, wound, catheter, bronchial washing, CSF, urine, sputum, and ascites fluid	100	100	disk diffusion
3	Alavi-Moghaddam et al [19]	blood, trachea, urine, cerebrospinal fluid, catheter and pleural fluid	109	35	disc diffusion
4	Salehi et al 2019 [20]	various specimens mostly sputum	180	152	disk diffusion
5	Tafreshi et al [21]	burn wound infection	84	28	broth microdilution
6	Yazdansetad et al [22]	burn wound	63	22	broth microdilution
7	Salehi et al 2018 [23]	wet swab from clothes and hands of staff, medical equipment, and patients' environment	125	2	disk diffusion
8	Zafari et al [24]	blood, wound, urine, sputum, and respiratory tract	100	2	disc diffusion
9	Sarhaddi et al [25]	burnt wound	54	2	*E*-test
10	Ansari et al [26]	clinical samples	30	18	disk diffusion
11	Alaei et al [27]	urine, sputum, blood, postoperative wound, cerebrospinal fluid, nasal secretion, eye secretion	45	4	broth microdilution
12	Pourhajibagher et al [28]	burn wound	33	2	disk diffusion and broth microdilution
13	Jasemi et al [29]	clinical specimens	26	8	disk diffusion
14	Kooti et al [30]	urine, wound, blood, sputum, ETT, body fluid, nose, throat and eye	200	4	disk diffusion
15	Bahador et al 2015 [31]	clinical samples	62	11	broth microdilution
16	Bahador et al 2014 [32]	wound, respiratory tract, urine, blood, and CSF	50	4	*E*-Test
17	Bahador et al 2014 [32]	wound, respiratory tract, urine, blood, and CSF	50	0	*E*-Test

Table prepared by the authors using data from the included studies [13, 18–32]

Note: TGC — Tigecycline; CSF — cerebrospinal fluid, ETT — endotracheal tube.

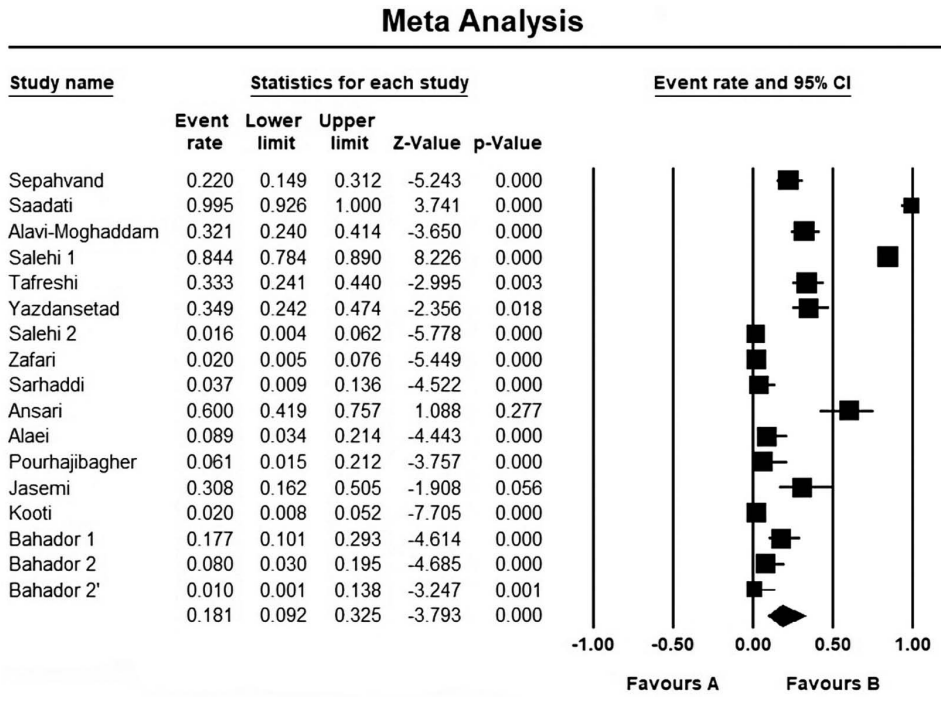

Figure prepared by the authors

Fig. 2. The results of the meta-analysis evaluating the resistance of different isolates of *A. baumannii* to tigecycline in Iran

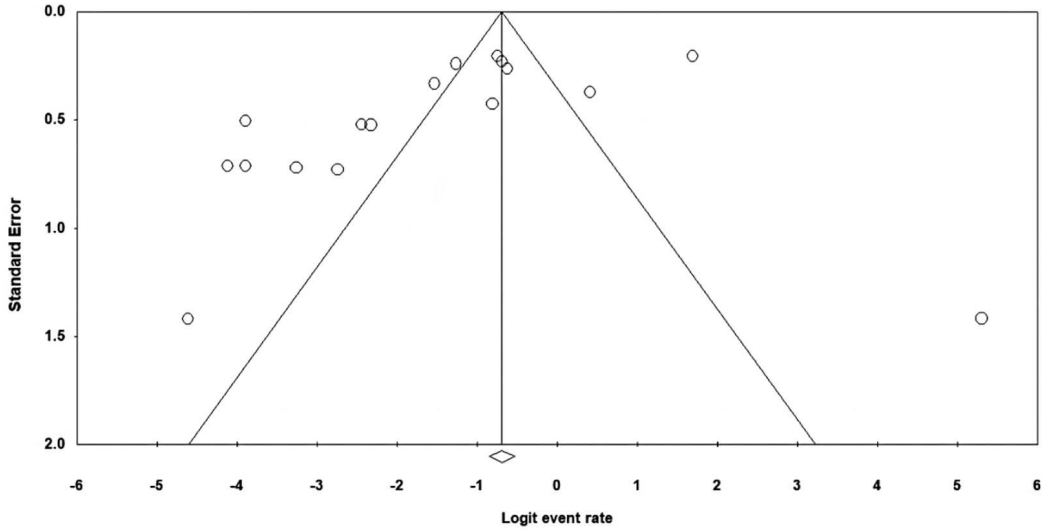

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Fig. 3. Funnel plot

between the previous use of other antibiotics and tigecycline resistance because of transportation by the similar efflux pump [39]. In addition, treatment by a wide-spectrum antibiotic instead of a narrow-spectrum drug, e.g., due to the inaccurate diagnosis of infection, inappropriate differentiation between virus or bacterium and the resulting improper prescription, as well as self-medication, leads to a growth in drug resistance [40].

The resistance mechanism to tigecycline is mediated by efflux pumps such as *AdeABC*. The overexpression in *AdeABC* caused by amino acid and nucleotide changes in the *AdeRS* two-component system and modified expression of *AdeA* and *AdeB* by the BaeSR system is another possible mechanism. In addition, mutations in genes encoding 1-acyl-sn-glycerol-3-phosphate acyltransferase and S-adenosyl-L-methionine (SAM)-dependent methyltransferase result in lower susceptibility [7].

Despite our findings, other review studies indicated conflicting results. In the review of Ni et al. [17], administration of tigecycline was discouraged based on assessment of cohorts and RCT studies. This review demonstrated a higher in-hospital mortality rate, a lower rate of bacterial eradication, and insufficiency of combination therapy in treatment groups compared to the control. Sodeifian et al. applied an approach similar to that used in our work to analyze observational studies. As a result, tigecycline was not recommended for treatment regimens. The researchers found that the overall efficacy of tigecycline in patients was comparable with other antimicrobial agents. Furthermore, a higher death rate and a lower bacterial

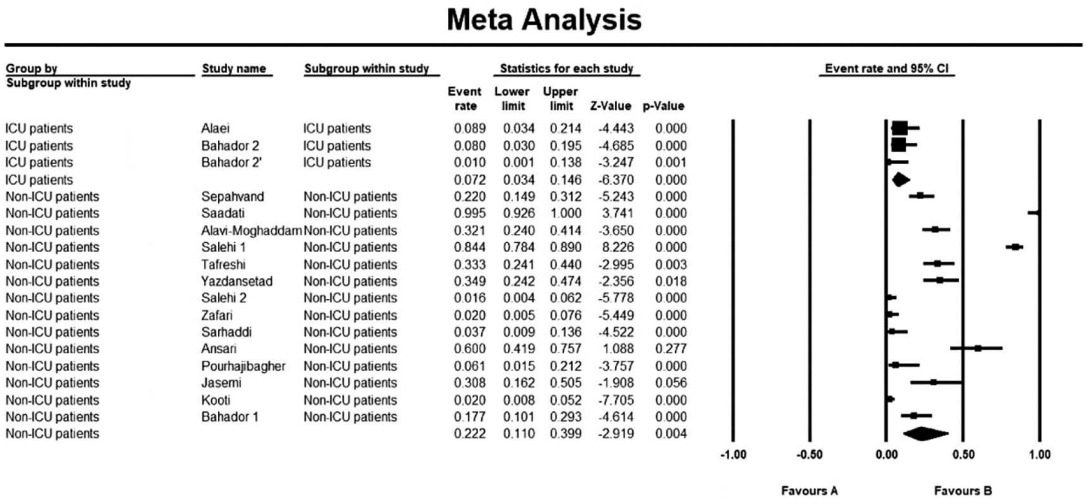

Figure prepared by the authors

Fig. 4. Subgroup analysis of patients admitted to ICU and non-ICU wards

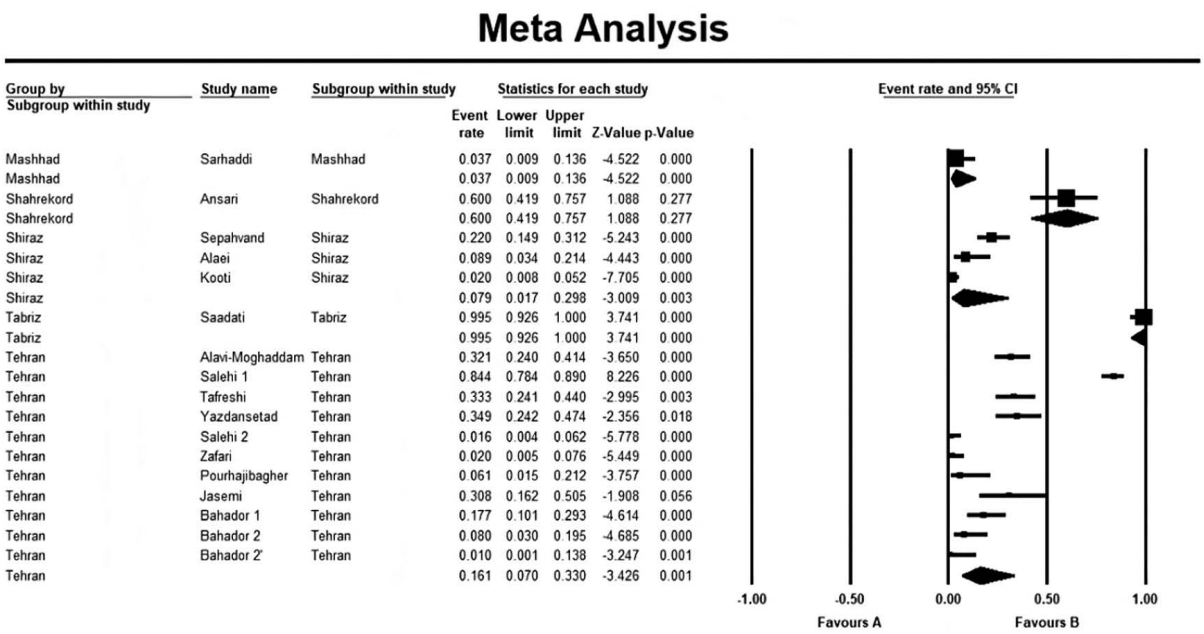

Figure prepared by the authors

Fig. 5. Subgroup analysis based on location

eradication rate compared to medication regimens based on colistin were established [41].

Care should be taken when interpreting the results due to the limited data. There are few studies on the prevalence of *A. baumannii* with MDR in Iran, with their majority covering large cities, Tehran in particular. Therefore, more data from other Iranian locations should be obtained to verify the results. In addition, the small size of samples for a subgroup analysis of statistical tests should be considered. There is a high potential of bias when evaluating research studies based on the JBI checklist. None of the studies mentioned confounding factors and the respective corrective approaches; in some studies, statistical methods were not described appropriately. The study setting and validity, as well as the reliability of outcome measurement, remain unclear, thus rendering the interpretation unreliable. Moreover, the clinical samples were obtained from intensive care unit (ICU) patients and individuals hospitalized in various wards, including the burn unit. Variations in isolate extraction methods and the challenging conditions experienced by ICU patients may have potentially impacted the outcomes of antimicrobial susceptibility testing. Additionally, the choice of antimicrobial susceptibility testing methodologies, such as disc diffusion, *E*-test, or broth microdilution, could also have contributed to discrepancies in results. This variability poses challenges in drawing unequivocal conclusions. This study contributes to the information about the susceptibility of different *A. baumannii* isolates to tigecycline, thus facilitating a grounded choice of antibiotics for MDR strains. However, further research is needed to obtain more reliable data on the level of such resistance.

CONCLUSION

In the present review and meta-analysis, we evaluated the resistance rate among patients infected by *A. baumannii* and admitted to hospitals in some cities of Iran. Our findings indicate a high resistance rate of *A. baumannii* strains against tigecycline; however, tigecycline is still considered an effective drug against MDR bacteria. The meta-analysis results show that the reviewed publications do not provide clear evidence of the overall effect of tigecycline on the resistance rate. In other words, the increase in *A. baumannii* resistance to tigecycline is not statistically significant, which is confirmed by the results of other studies conducted earlier in Iran.

Increased resistance of *A. baumannii* to most antibiotics, established in the present study, may be due to improper use or unjustifiably high consumption of broad-spectrum antimicrobial agents, the lack of access to clean water, irregularity of algorithms for sanitary and hygienic and disinfection measures, and administration of antimicrobial combinations in fixed doses, even without knowledge of proven advantages over individual medicinal compounds. There are also social factors, such as self-medication, over-the-counter antimicrobial use, inadequate prevention of infections and diseases, and limited access to high-quality, affordable medicines, vaccines, and diagnostic tools. Given the current situation with the spread of resistant isolates, it is necessary to introduce comprehensive infection control programs aimed at localizing and limiting the spread of *A. baumannii* strains in medical institutions.

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