REVIEW

Prevalence of Integrons and Antibiotic Resistance Pattern in *Acinetobacter baumannii* Isolated from Clinical Samples of Iranian Patients: A Systematic Review and Meta-analysis

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ABSTRACT

BACKGROUND: *Acinetobacter baumannii is an important opportunistic nosocomial pathogen. Class 1 integrons in A. baumannii plays a significant role in antibiotic resistance. Therefore, this study aimed to investigate the prevalence of integrons and antibiotic resistance pattern in A. baumannii isolated from clinical samples of Iranian patients.*

METHODS: *The Medical Subject Headings (MeSH) and the keywords with the help of Boolean operators ("AND" or "OR") were used alone or in combination to conduct the search. The searching process was conducted in the Web of Science, PubMed, Cochrane Library, Scopus, and Google Scholar databases and, also Iranian databases. The search was restricted to relevant English and Persian cross-sectional publications reporting the prevalence of Int1 in A. baumannii isolated from clinical samples from 1 January 2000 to 31 December 2018. The data were analyzed using Comprehensive Meta-Analysis software. Regarding the heterogeneity of studies, the random effects model was used. Cochrane Q and I^2 tests was used to evaluate statistical heterogeneity between the studies.*

RESULTS: *Fifteen studies were included in the analysis. The combined prevalence of class 1 integrons in A. baumannii was 55.2% (95% CI: 44.8-65.1). The pooled prevalence of MDR A. baumannii isolates was 68.1%. The highest resistance belonged to Aztreonam, followed by Ciprofloxacin, and Ceftazidime with a resistance rate of 97.6%, 92.8%, and 91.6%, respectively. Tobramycin was reported as an effective antibiotic.*

CONCLUSIONS: *The present study reported an alarmingly high prevalence of class 1 Integrons, and MDR isolates of A. baumannii recovered from clinical samples that should be considered.*

KEYWORDS: *Prevalence, Integrons, Acinetobacter baumannii, Pathogen*

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INTRODUCTION

Acinetobacter baumannii is an important aerobic Gram-negative opportunistic nosocomial pathogen with broad dissemination in the environment (1). A range of threating nosocomial infections including septicemia, respiratory tract, urinary tract infection, and pneumonia, burn wound and soft tissue are caused by *A. baumannii* especially in the ICU and burn units (2). In the 21st century, *A. baumannii* emerged as one of the most challenging pathogens due to its high adaptation to hospital environments (3). This microorganism has been cited among the six top priority dangerous drug-resistant bacteria by Infectious Diseases Society of America (4), as its prevalence is becoming an alarming all over the world(5). The epidemiological studies concerning the MDR *A. baumannii* strains show the dissemination of different healthcare-associated MDR *A. baumannii* clones worldwide(6).

Enzyme alteration, the permeability of the outer membrane, the mutation in target genes, increased expression of efflux pumps and mobile genetic elements are the key antibiotic resistance mechanisms in *A. baumannii* microorganism (7). Among them, integrons have been known as the chief source of resistance genes in Gram-negative bacteria including *A. baumannii (8)*. Integrons are DNA elements capable of capturing genes by a site-specific recombination mechanism that often carries gene cassettes containing antibiotic resistance genes (9). Until now, six classes of integrons (according to *intl* gene) have been identified, in which classes 1, 2 and 3 showed a major role in transferring antibiotic resistance genes (10). Class 1 integrons are usually expressed in *A. baumannii* and play a significant role in antibiotic resistance and typically encode genes for aminoglycoside resistance, β-lactamases, Metallo-β-lactamases, and oxacillinases (11). Class 2 integrons are carried out inside the transposon Tn7 with gene cassettes and attributed in conferring resistance to chloramphenicol, trimethoprim, aminoglycosides, and streptomycin (12).

To our knowledge, determination of integrons prevalence in clinical isolates of *A. baumannii* provides appropriate information concerning the pattern of antibiotic resistance in each region. In the current study, due to low importance of class 2 and 3 integrons in antibacterial resistance and because of the lack of reporting these integrons in studies included in the review, this study aimed to investigate the prevalence of integrons and antibiotic resistance pattern in *A. baumannii* isolated from clinical samples of Iranian patients through systematic review and meta-analysis.

METHODS

Information source and search strategy: The Medical Subject Headings (MeSH) and tht keywords of "Integrons", "Int1", "prevalence", "antibiotic resistance", "*A. baumannii*", "Integron prevalence", and "Iran, with the help of Boolean operators ("AND" or "OR") were used alone or in combinations to conduct a broad search. The searching process was done in the Web of Science, PubMed, Cochrane Library, Scopus and Google Scholar databases. The search was restricted to the papers published in either English or Persian from 1 January 2000 to 31 December 2018. The studies reporting the prevalence, or distribution of Int1 in *A. baumannii* isolated from clinical samples of Iranian patients were included in the present review. Correspondingly, the Persian equivalents of the keywords were used in a comparable strategy to recover Persian articles in national databases such as Magiran (www.Magiran.com), Irandoc (www.irandoc.ac.ir), Iranmedex (www.iranmedex.com), and Scientific Information Database (www.sid.ir).

Inclusion and exclusion criteria: All relevant English and Persian cross-sectional and cohort publications reporting the prevalence of Int1 in *A. baumannii* isolated from clinical samples of Iranian patients and cited by databases were retrieved and included in the current review. All review forms including (narrative, meta-analysis or systematic), prospective studies, congress, case reports, meeting, abstracts, studies in languages other than English or Persian, editorials, and letters to the editors were excluded. Furthermore, studies without full text and duplicate publications were considered as excluded criteria, too. Two independent reviewers completed all these search processes to decrease the risk of error and bias.

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Screening: All recognized articles in both languages from the mentioned databases were entered into our created file to eliminate duplicates. After that, the documents were screened by two reviewers (HV and FJJ) independently in a few levels. These levels screen included title screening, abstract screening and lastly full-text screening. At each level, the investigators individually assessed the studies, and then shared their agreements in the common file. Disagreements were resolved by discussion before including the studies for the next screening level. Dissimilarities between the assessors were argued and resolved through agreement. Where no agreement was reached, a third reviewer was involved in decision-making. Finally, records were assessed for met eligibility and final selection.

Quality assessment: For quality assessment of studies methodology was used of the criteria mentioned in Critical Appraisal Skills Programmed checklists (www.casp-UK). As for each study independently, a series of main questions were designed. If the relevant information was clearly reported, a question was scored as 'yes'. If no, or in case of any doubt, the question was marked as 'no' or 'can't tell'. Overall, studies were classified as 'strong', 'moderate', or 'weak', according to the number of questions scored as 'yes'(13). At last, weak studies were removed from the current review.

Assessing the risk of bias: For quality assessment and prevention of the risk of bias, several items including design, method, context, findings, and analyses of the study, also, interpretations of the findings were evaluated. The studies with a key flaw in the considered items were excluded. Also, it should be noted that any conflicts on the quality evaluation or the risk of bias in recording, reporting, collection, contributors, extraction of data, confusing factors, and statistical analyses were resolved by debates between the two assessors or by referring to a third reviewer (14).

Data extraction: The data were extracted from each study by a data extraction form designed for the reviewers. The extracted data included (a) the first author's name, (b) publication year, (c) study setting, (d) sample size, (e) MDR prevalence, (f) and Int1 prevalence.

Data analysis: The data were analyzed using Comprehensive Meta-Analysis software (Version 3.3.070). The prevalence was presented by a 95% Confidence Interval (CI). Regarding the heterogeneity of studies, the random-effects model was used for meta-analysis. The Cochrane Q and I^2 tests were used to evaluate the statistical heterogeneity between the studies. To estimate possible publication bias, quantitative Egger weighted regression test and funnel plot were used. Also, *P*-value <0.05 was considered as the statistical significance threshold. Additionally, the asymmetrical distribution of the studies was evaluated by Egger's linear regression test.

RESULTS

Study inclusion: The study selection route is abstracted in Figure 1. In brief, 586 relevant records were firstly identified in the initial search in scientific databases. Two hundred-eleven duplicates were removed. Regarding assessing the abstracts of the 375 studies, 286 literatures were excluded. Then, full texts of 89 studies were assessed for eligibility. About 74 articles were excluded due to lack of sufficient data and not reporting Int1 prevalence. Finally, 15 studies were included in the present systematic review and meta-analysis.

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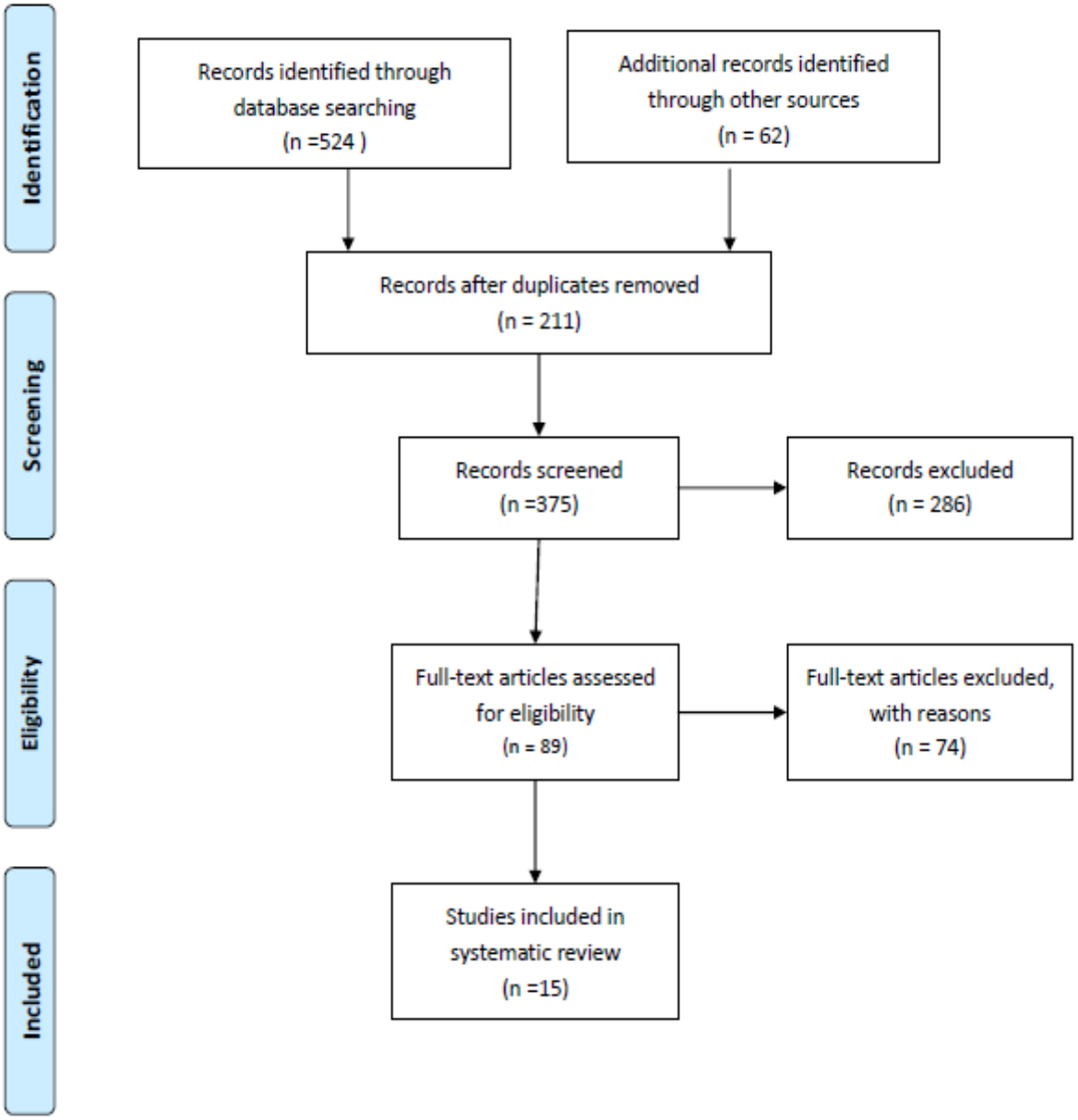

Figure1: *Flow chart diagram of studies included in the present review*

Characteristics of the included studies: As presented in Table 1, the selected articles covered various areas of Iran (i.e. Center, Northwest, West, and South). The prevalence of Int1 in *A. baumannii* isolated from clinical samples of Iranian patients varied from 12% to 98.4% (Figure 2). The highest prevalence of Int1 was reported in a study conducted by Japoni-Nejad et al.(15) with a frequency of 98.4%. The frequency of MDR *A. baumannii* isolates varied from 29% to 100%. As shown in Figure 3, the publication bias was checked using Funnel plot. Regarding possible asymmetrical data distribution in included studies, the findings of the Egger's linear regression test did not show any publication bias (*P=0.6*).

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Table 1: Characteristics of included studies in clinical specimens.

Study	Publication (Year)	Location	Sample Size	MDR prevalence	Int1 prevalence
Asadollahi (32)	2011	Tehran	40	40(100%)	27(67.5%)
Taherikalani et al(33)	2011	Tehran	100	-	58 (58%)
Asadollahi et al(34)	2012	Tehran	23	-	13(56.5%)
Farajnia et al(35)	2013	Tabriz	100	80(80%)	74(74 %)
Mirnejad et al(36)	2013	Tehran	50	41(82%)	15(21%)
Japoni-Nejad et al(15)	2013	Arak	63	-	62(98.4%)
Kamalbeik et al(37)	2014	Tehran	42	-	5(12%)
Azizi et al(38)	2016	Kerman	65	65(100%)	46 (70.8%)
Goudarzi (39)	2016	Tehran	120	120(100%)	89(74.2%)
Goudarzi et al(40)	2017	Tehran	105	105(100%)	70(66.7%)
Eghbalimoghadam(41)	2017	Kermanshah	100	29(29%)	42(42%)
Mirshekar et al(42)	2018	Tehran	72	-	42(58.3%)
Halaji et al(43)	2018	Isfahan	147	-	94(63.9%)
Eftekhar et al(44)	2018	Tehran	50	-	11 (22%)
Shaheli et al(45)	2018	Shiraz	83	77 (92.9%)	27 (32.5%)

Table 2: Analysis of prevalence of class 1 integron in *P. aeruginosa* recovered from Iranian burn patients

Subgroups	Number of studies	Heterogeneity test			Egger's test			Random model	
		Prevalence (95% CI) (%)	Z	P	Q	P	I^2	T	P
Overall effect(Int1)	15	55.2(44.8-65.1)	0.97	0.00	137	0.60	92	0.53	0.37
MDR	8	68.1(61.9-73.7)	5.4	0.00	121.3	0.04	94.2	6	0.04

Overall effects: Regarding the heterogeneity test, the values were attained as Q2=137, I^2=92, t=0.5 (*P=0.6*) for the selected studies. Therefore, according to the findings of heterogeneity test, the random effects model was used to combine the data on prevalence of class 1 integron in *A. baumannii* recovered from clinical samples. The combined prevalence of class 1 integrons in *A. baumannii* recovered from clinical samples was 55.2% (95% CI: 44.8-65.1) (Figure 2). The clinical samples were mostly collected from ICU and other wards. The pooled prevalence of MDR *A. baumannii* isolates was 68.1% (95% CI: 61.9-73.7). As presented in Table 3, subgroups analysis of antibiotic resistance pattern of *A. baumannii* revealed that the highest combined resistance belonged to Aztreonam, followed by Ciprofloxacin, and Ceftazidime with a resistance rate of 97.6%, 92.8%, and 91.6%**,** respectively**.** As well as, the least resistance was against Tobramycin with a resistance rate of 38.7%. The detailed information about antibiotic susceptibility is listed in Table 3.

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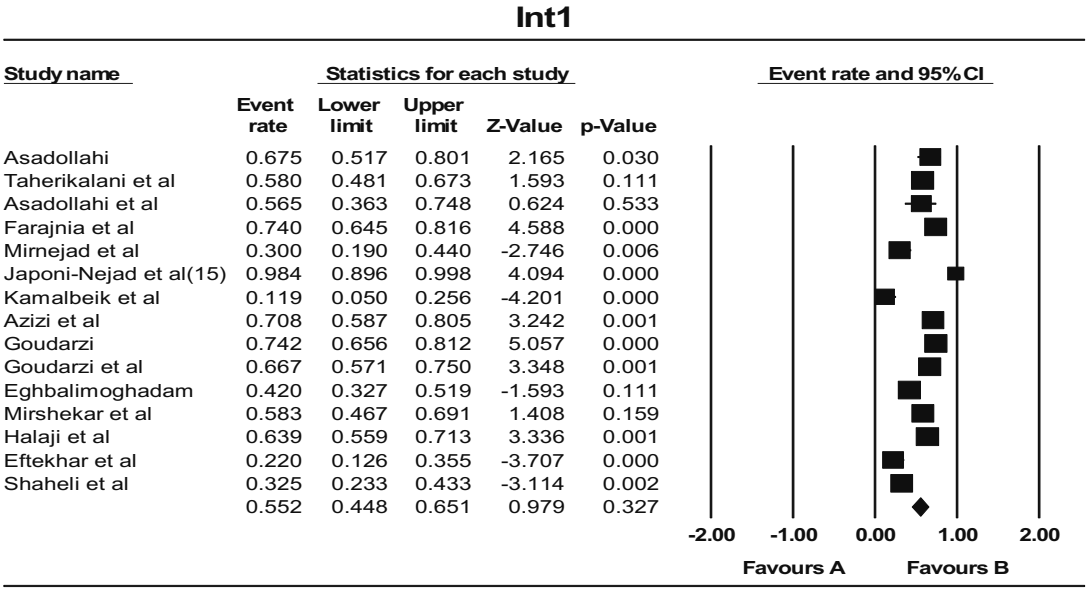

***Figure** 2: Forest plot of the meta-analysis of prevalence of class 1 integron in A. baumannii isolated from clinical samples*

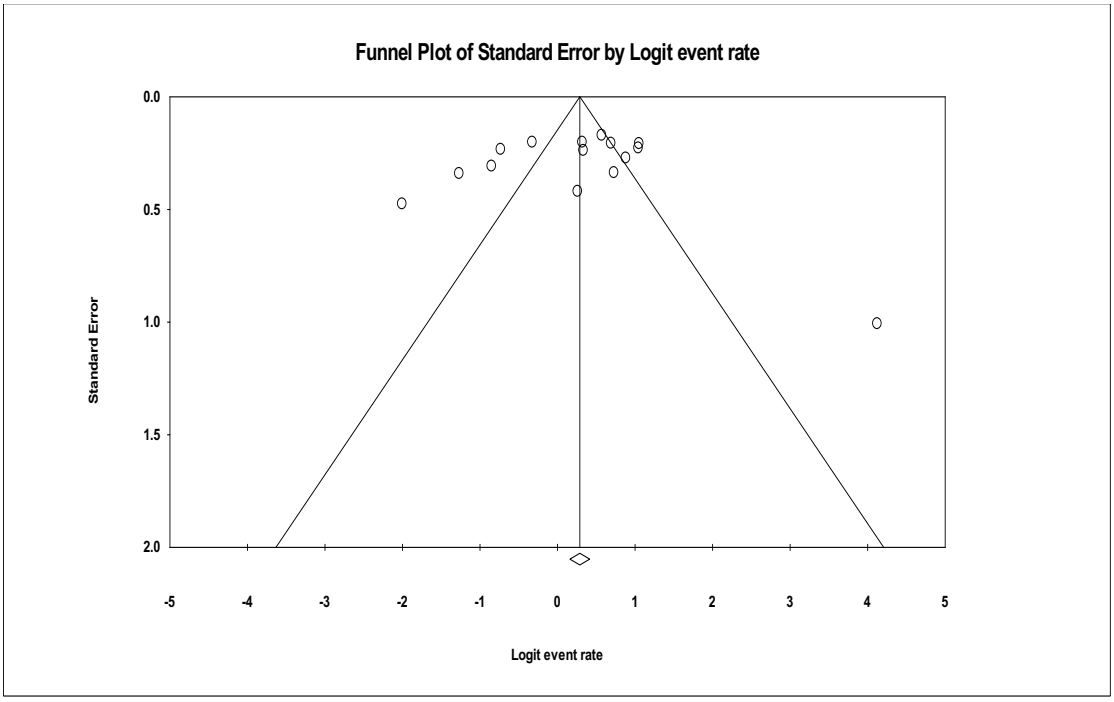

***Figure** 3: Funnel plot of meta-analysis on the prevalence of class 1 integron in A. baumannii recovered from clinical samples*

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Table 3: Subgroups analysis for antibiotic resistance in *P. aeruginosa* isolated from Iranian burn patients

Subgroups	Number of studies	**Heterogeneity test**			**Egger's test**		**Random model**		
		Prevalence (95% CI) (%)	Z	P	Q	P	I^2	T	P
Imipenem	14	75.9(63.5-85.1)	3.7	0.00	171.5	0.00	92.4	2.1	0.05
Ciprofloxacin	14	92.8(85.2-96.6)	6.2	0.00	161.8	0.00	91.9	2.8	0.01
Gentamicin	15	72.5(61.3-81.5)	3.7	0.00	191.7	0.00	92.6	1.9	0.07
Amikacin	11	74.2(58.1-85.6)	2.8	0.005	197.3	0.00	94.9	1.1	0.26
Ceftriaxone	7	90.6(73.1-97.2)	3.5	0.00	119.5	0.00	94.9	2.5	0.05
Ceftazidime	11	91.6(80.3-96.7)	4.7	0.00	187.9	0.00	94.6	5.7	0.00
Cefepime	10	56.3(51.3-61.7)	2.4	0.00	105.2	0.00	91.4	8.6	0.00
Piperacillin/ tazobactam	11	59.7(55.6-63.7)	4.5	0.00	131.5	0.00	92.3	3.9	0.00
Aztreonam	2	97.6(95.1-98.9)	9.7	0.00	0.5	0.000	0.00	0.00	0.00
Tobramycin	2	38.7(19.5-62.2)	0.94	0.34	16.4	0.00	93.9	0.00	0.00
Cefotaxime	11	65.6(60.4-70.4)	5.6	0.00	106.3	0.00	91.5	3.8	0.00

DISCUSSION

A. baumannii has an important role in nosocomial infection owing to its resistance to different classes of antibiotics (16). This resistance is caused by different mechanisms. Among them, Integrons plays an important role, and spreading of antibiotic resistance genes via them is problematic in treatment of infections caused by this microorganism (4,17). The findings of the current study showed the combined prevalence of 55.2% of class 1 integrons in *A. baumannii* recovered from clinical specimens. The pooled prevalence of MDR *A. baumannii* isolates was 68.1%. The prevalence of class 1 integrons are increased all over the world. In aagreement with our findings, other reports from Italy (18), and China (19) showed the prevalence 44% and 71%, respectively. However, Javier Ariza, et al. reported a lower prevalence (25%) from Spain (20).

This high prevalence of integron class 1 in *A. baumannii* isolates is attributed to several reasons such as inappropriate use of antibiotics for treatment of *A. baumannii* infections, and consequently, the high expression of gene cassettes containing integrons class 1 and, secondly, the ability of integrons to acquire new gene cassettes lead to disseminating antibiotic resistance among clinical isolates. Finally, failure in establishment of a national surveillance program as part of the Global Strategy for Containment of Antimicrobial Resistance in medical centers leads to survival of MDR *A. baumannii* isolates carrying integron and spreading of resistance integrons among other *A. baumannii* isolates (21). Class 1 integrons are prevalent as compared to the other classes of

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integrons possibly due to the location of class 1 integrons on genetic elements such as conjugative plasmids and transposons (22). As stated in the present review, the pooled prevalence of MDR *A. baumannii* isolates was 68.1%.

This subject leads to MDR *A. baumannii* isolates carrying integron and spreading of resistance integrons among other *A. baumannii* isolates. Inconsistent with the present review, another review from Iran showed that the frequency of MDR *A. baumannii* isolates increased from 50% in 2001–2007 to 74% in 2010–2015, with a mean prevalence of 71% (23). Prolonged hospital stay especially in Intensive Care Unit (ICU), receiving of ventilator, recent surgery, medical interventions, colonization pressure, and use of overdose of antibiotics such as Carbapenems, Colistin, invasive procedures, underlying diseases are the main risk factors for colonization or infection with MDR *A. baumannii* isolates (24). To our knowledge, Imipenem acts as a choice drug in the treatment of infections caused by *A .ba*umannii (5). As shown in the results section, the resistance rate against Imipenem was reported as 75.9%. The resistance against Imipenem is increased worldwide as some studies from other countries including Pakistan (100%), Turkey (98%), United Arab Emirates (76%) and Saudi Arabia (63%) reported the same pattern (25-28). In confirmation of our results, a study from Taiwan revealed that MDR-AB isolates carrying integrons were significantly more resistant to almost all antibiotics used than non-integron-carrying isolates (19). In geographical districts including China and Spain, Integron-carrying MDR-AB isolates have been reported, too (29,30). Their results showed that MDR-AB strains carrying different gene cassettes including different integron cassette types 2, 3, 4 and 6 have been found to have similar multidrug resistance patterns, indicating the correlation of integrons and multidrug resistance. Then, we can conclude that the high MDR isolates in the current review can possibly be attributed to the existence of class 1 integrons. Clinical isolates of *A. baumannii* all over the world share different resistance mechanisms with other bacterial genera (30). Therefore, the high prevalence of the Integrons in clinical isolates of *A. baumannii* from Iran can be very worrying, and *A. baumannii* isolates will not respond to existing antibiotics any more and cause transmission of resistance through the Integrons. Establishing a national surveillance program as part of the Global Strategy for Containment of Antimicrobial Resistance in medical centers is critical (31). When antibiotics become ineffective due to bacterial resistance, implement, and evaluate new specific containment interventions is crucial to collect specific information regarding MDR isolates of *A. baumannii*.

The present study reported alarming high prevalence of class 1 Integrons and MDR isolates of *A. baumannii* are recovered from clinical samples that should be considered.

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