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Original Article

Correlation between class I integron and imipenem resistance of acinetobacter baumannii: a systematic review and meta-analysis

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Abstract: The resistance of acinetobacter baumannii to imipenem will significantly increase the clinical mortality of patients. The purpose of this study was to evaluate the value of class I integron in the diagnosis of imipenem resistance of acinetobacter baumannii. We searched Pubmed, Embase, and Web of Science from the establishment of the database to December 2019 for articles of the correlation between class I integron and imipenem resistance of acinetobacter baumannii. The two authors extract and analyze the data independently. A total of 10 papers met the inclusion criteria, including 1269 strains of acinetobacter baumannii isolated from clinical specimens. Among them, 840 strains (66.2%) were class I integron positive and 653 strains (51.5%) were imipenem resistant. Meta-analysis showed that the detection rate of class I integron in imipenem resistant strains of acinetobacter baumannii was significantly higher than sensitive strains [odds ratio (OR) was 3.04, 95% confidence interval (CI) was 2.22-4.18]; The combined sensitivity, specificity, positive likelihood ratio and negative likelihood ratio of class I integron in the diagnosis of imipenem resistance of acinetobacter baumannii were 0.73 (95% CI was 0.70-0.77), 0.39 (95% CI was 0.35-0.43), 1.41 (95% CI was 1.25-1.59), 0.52 (95% CI was 0.37-0.74), respectively, and the area under the summary receiver operating characteristic (SROC) curve was 0.6184. In conclusion, this meta-analysis results suggest that class I integron was related to imipenem resistance of acinetobacter baumannii and it had certain diagnostic values for imipenem resistance of acinetobacter baumannii.

Keywords: Class I integron, acinetobacter baumannii, imipenem resistance, meta-analysis

Introduction

Acinetobacter baumannii (Ab) is a gram-negative, oxidase-negative aerobic bacteria, which can quickly acquire and spread drug resistance, and can cause infections in the lower respiratory tract, blood, urinary tract, and wounds [1-3]. Acinetobacter baumannii is one of the most important pathogens of nosocomial infection [4]. It has been showed that the global prevalence of hospital-acquired pneumonia and ventilator-associated pneumonia caused by drug-resistant acinetobacter baumannii is about 79.9%. The total mortality rate is about 42.6% [5]. Carbapenem, represented by imipenem, is generally considered to be a drug for the treatment of acinetobacter baumannii infection because of its effective activity and good safety against acinetobacter baumannii [6]. But due to the unreasonable use of antibiotics in the clinic and lax management policy, the situation of drug resistance of acinetobacter baumannii is becoming more and more serious [7].

The resistance mechanism of acinetobacter baumannii to antibiotics mainly includes the production of β-lactamases, the action of efflux pump, the change of adventitia permeability, the production of aminoglycoside modifying enzymes and the change of antibiotic targets, etc [8, 9]. Integrons, located on chromosomes, are common gene acquisition systems in bacterial genomes and they play an important role in the acquisition, expression, and transmission of antibiotic resistance genes [10, 11]. At present, class I, II, and III integrons are widely reported, and class I integrons are more common. In recent years, some studies have found that the class I integrons can spread or transfer drug resistance genes between bacteria, which plays a key role in the generation of drug

resistance of acinetobacter baumannii [12, 13]. However, some studies have found that although class I integrons are widely spread in clinical isolates of acinetobacter, they do not play a major role in the spread of carbapenem resistance [14]. To explore the relationship between class I integron and imipenem-resistant acinetobacter baumannii (IMPRAb), we performed this meta-analysis. This study was guided by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement of systematic review and meta-analysis of transparent reports [15].

Materials and methods

Search strategy

The literature was searched in PubMed, EMBASE, and Web OF SCIENCE. The electronic search strategy was conducted using the following format of search terms: ((Acinetobacter baumannii) OR (A baumannii) OR (acinetobacter)) AND ((integron) OR (class I integron) OR (intI1)) AND (imipenem). The search period is from the establishment of the database to December 2019. We also searched for relevant literature to avoid omissions.

Inclusion and exclusion criteria

Acinetobacter baumannii is eligible to be included in the meta-analysis if the subject of this study is acinetobacter baumannii identified in clinic, and the genetic markers of class I integron are detected by polymerase chain reaction (PCR) and the sensitivity of acinetobacter baumannii to imipenem is detected by in vitro drug sensitivity test.

Animal experiments, literature review, only detection of class I integration factors in acinetobacter baumannii drug-resistant strains, no class I integron distribution in acinetobacter baumannii drug-resistant and sensitive strains, repeated publication, poor quality, and unclear data description will be excluded.

Data extraction and quality assessment

Two researchers independently retrieved the literature as required: read the title, abstract and full text, select the relevant literature according to the inclusion criteria and exclusion criteria, and extract the following data, including the author's name, publication time, research area, study time, sample source, sample type, strain identification system, drug sensitivity determination system, class I integron distribution and other indicators. When differences arise between the two researchers, we resolve them through discussion and negotiation.

After determining the final included literature, we used the diagnostic research quality evaluation tool QUADAS-2 (quality assessment of diagnostic accuracy studies) to evaluate the quality of the literature. Research of poor quality will be excluded.

Data analysis and statistical methods

Meta-analysis was performed with RevMan 5.3 software to evaluate the relationship between class I integron and imipenem resistance of acinetobacter baumannii. The homogeneity test was carried out based on the chi-square test, so as to determine the inconsistency index (I^2) statistics. If I^2 is greater than or equal to 50%, it is considered that there is heterogeneity between studies. Sensitivity analysis and subgroup analysis were carried out to find the source of heterogeneity. If the source of heterogeneity cannot be found, the random effect model is used for analysis. If I^2 is less than 50%, it is considered that there is no heterogeneity, and the fixed effect model analysis is used. A funnel plot was used to evaluate the publication bias of the article.

Diagnostic meta-analysis was performed by metadisc1.4 software. The heterogeneity caused by the threshold effect was evaluated by the Spearman coefficient, and the difference was statistically significant as $p<0.05$. If there is heterogeneity between the studies, the random effect model is used to analyze the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and 95% confidence interval to fit the comprehensive subject working characteristic curve and calculate the area under the curve. If there is no heterogeneity, the fixed effect model is used for analysis.

Results

Flow diagram of included studies

By searching the three designated databases, a total of 462 related articles were found. Ac-

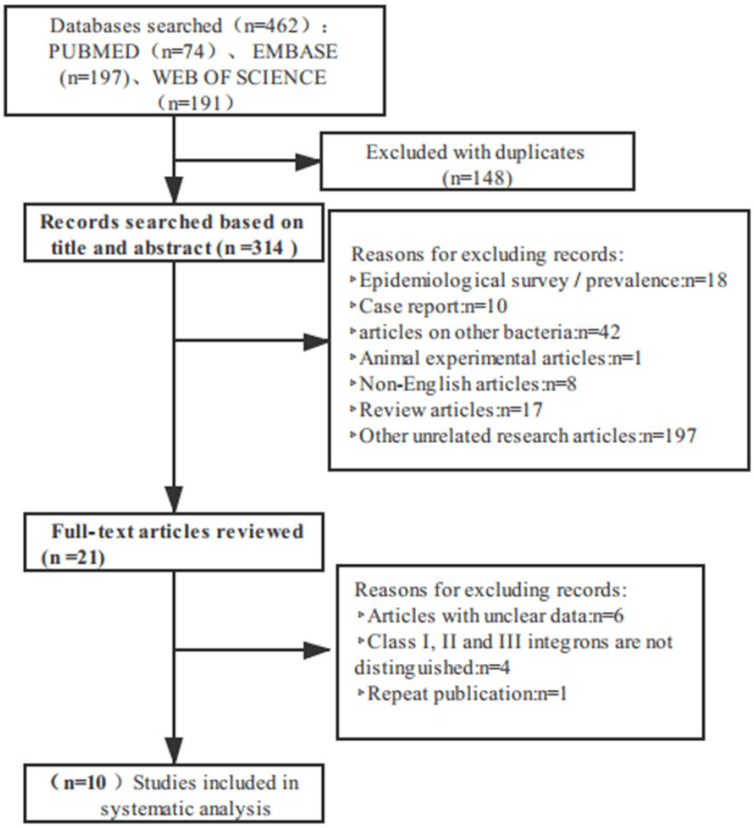

Figure 1. Flow diagram of literature search and study selection process. **Figure 1** is a flow diagram of article screening. First of all, according to the format of search terms, a total of 462 articles were searched from the three databases (PUBMED, EMBASE, and Web OF SCIENCE). Second, we use EndNote software to delete 148 repetitive articles, leaving 314. Third, we read the title and abstract of the article. According to the inclusion and exclusion criteria, 293 articles were excluded, leaving 21. Finally, we read the full text, excluding 11 articles that do not meet the requirements, leaving 10.

cording to the inclusion criteria and exclusion criteria, 10 articles [16-25] were finally included. The flow diagram of the literature screening is shown in **Figure 1**.

Characteristics of included studies

The basic features included in the literature are shown in **Table 1**. These studies were published between 2008 and 2017. The sample size ranged from 35-425. These studies are mainly carried out in China and Iran. A total of 1269 strains of acinetobacter baumannii isolated from clinical departments were included in the 10 studies, of which 840 strains were positive for class I integron and 653 strains were resistant to imipenem. The positive rate of class I integron and imipenem resistance rate were 66.2% and 51.5%, respectively.

Quality of the included studies

The QUADAS-2 scale suitable for the diagnostic experiment was used to evaluate the quality of the included study. The results of the quality evaluation are shown in **Figure 2**. The selection risk bias of the subjects of 8 articles, the risk of bias of diagnostic tests to be evaluated in 9 articles, the bias risk of the gold standard of 9 articles, and the bias risk of flow and progress of 8 articles, are all small. The literature included in the analysis is of high quality.

Meta-analysis

Because the index (I^2) to evaluate the heterogeneity between studies is 49% (<50%), it is considered that there is no substantial heterogeneity among the studies, so the fixed effect model is used for analysis. The results showed that the detection rate of class I integron in imipenem resistant strains of acinetobacter baumannii was higher than that of sensitive strains, and the odds ratio (OR) was 3.04, 95% confidence interval (CI) was (2.22-4.18). The results suggested that there was a certain correlation between class I integron and imipenem resistance of acinetobacter baumannii. The forest plot analyzed by meta-analysis is shown in **Figure 3**.

Diagnostic meta-analysis

To evaluate the diagnostic value of class I integron to imipenem resistance of acinetobacter baumannii, we used MetaDiSc1.4 software for diagnostic meta-analysis. First of all, we carried on the threshold effect analysis to the included literature, the summary receiver operating characteristic (SROC) curve did not show the typical “shoulder-arm shape” distribution, and the Spearman correlation coefficient was 0.533 (P=0.139>0.05), which sug-

Table 1. Basic information and data included in the literature

Author and Year Published	Study area	Time of study	source of the sample	Types of samples	Strain identification system	Criteria for determining drug sensitivity	Number of bacteria (n)	IMPRAB (n)		IMPSAB (n)	
								Intl (+)	intl (-)	Intl (+)	intl (-)
Sirichot, S. 2009	Thailand	2006	Multi-department	tracheal aspirates	-	CLSI 2007	52	20	14	5	13
Huang, L.Y. 2008	Taiwan	1996-2004	Multiple hospitals	-	bioMerieux	CLSI	283	17	1	185	80
Lin, Ming-Feng 2013	Taiwan	2009	Multiple hospitals	-	bioMerieux	CLSI	65	32	4	15	14
Chen, Jing 2015	China	2009-2012	Multiple hospitals	-	bioMerieux	CLSI	425	256	85	40	44
Chang-Tai, Z. 2011	China	2006-2008	Multiple hospitals	Sputum/wound/throat/swab/blood	bioMerieux	CLSI 2005	96	7	1	59	29
Deylam Salehi, M. 2017	Iran	2015	ICU	Bronchoalveolar lavage fluid	-	CLSI	35	9	26	0	0
Koczura, R. 2014	Poland	2000-2010	Multi-department	Urine/blood/wound/trachea and bronchi	bioMerieux	CLSI	63	18	8	22	15
Mirnejad, Reza 2013	Iran	2009-2010	Multiple hospitals	Blood/trachea/wound/urine, etc.	-	CLSI	50	19	24	2	5
Peymani, Amir 2012	Iran	2007-2009	Multi-department	-	-	CLSI	100	54	5	22	19
Taherikalani, Morovat 2011	Iran	2007-2009	Multiple hospitals	Wound/trachea, etc	bioMerieux	CLSI	100	31	22	27	20

IMPRAB, Imipenem resistant Acinetobacter baumannii; IMPSAB, Imipenem sensitive Acinetobacter baumannii; ICU, Intensive care unit; CLSI, Clinical and Laboratory Standards Institute; Intl, integron; Resistance included R and I by CLSI.

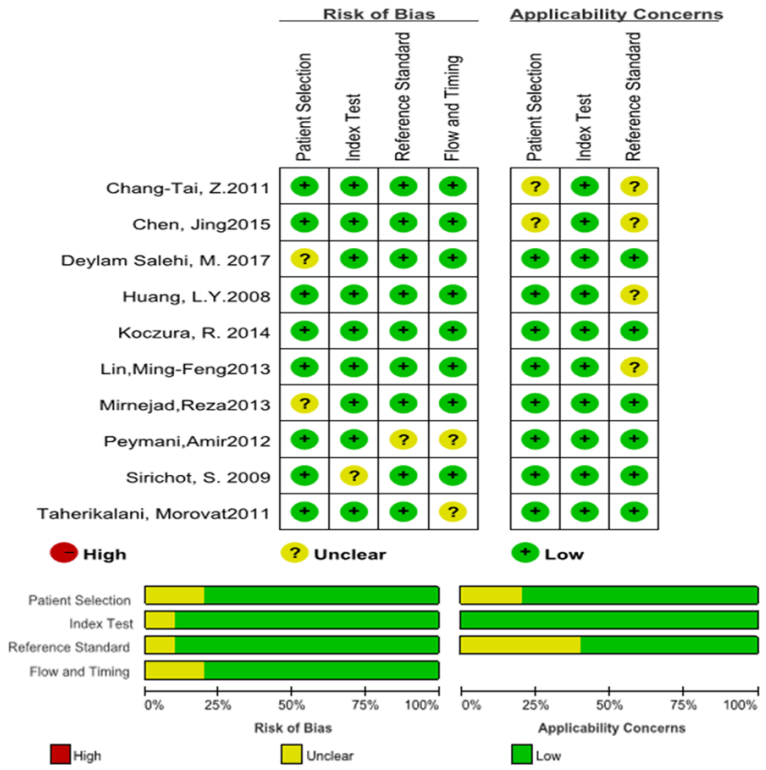

Figure 2. Quality evaluation chart of 10 included studies. Green represents low risk. Yellow represents unclear risk. Red represents high risk. **Figure 2** shows the quality evaluation of 10 articles by using the QUADAS-2 scale of the RevMan 5.3 software. The QUADAS-2 tool mainly consists of four parts: Patient selection, Index Text, Reference standard, Flow and Timing. All components are assessed in the Risk of Bias, and the first three parts are also assessed in Applicability Concerns. Green means low risk, yellow means you don't know the risk, and red means high risk.

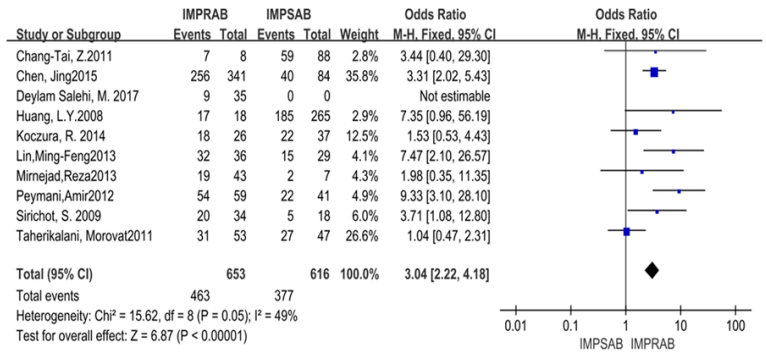

Figure 3. A meta-analysis of the positive rate of class I integron in acinetobacter baumannii imipenem resistant group and imipenem sensitive group. **Figure 3** shows the forest plot of 10 articles by using the RevMan 5.3 software. By carefully reading each selected article, extract the integron distribution of the IMPRAB (imipenem resistant acinetobacter baumannii) group and the IMPSAB (imipenem sensitive acinetobacter baumannii) group, input it into the RevMan 5.3 software, and get the figure. The following data in the events group represent the number of class I integron positive strains in the study. The data below the total group represent the total number of strains in a research group. Weight represents the weight of each included study in the combination of effects. The squares in the forest map represent the point estimates of the OR values of each study, and the size of the squares represents the weight of each study. The straight lines extending from both sides of the square represent the confidence interval of the OR value. The prism represents the combined OR value of all studies, the center of the prism represents the point estimate of the combined OR value of all studies, and the width is the confidence interval of the combined OR. Heterogeneity Chi^2 and I^2 are the results of the heterogeneity test. Test for overall effect is the result of effect test. In this meta-analysis, I^2 is 49% (<50%), it is considered that there is no substantial heterogeneity among the studies. Z is 6.87 (P<0.00001), It can be considered that the combined result is statistically significant.

gest that there was no threshold effect among these included studies. However, we found that except for the positive likelihood ratio, there was heterogeneity in the sensitivity, specificity, and negative likelihood ratio among these studies and the corresponding I^2 were 0.84, 0.732 and 0.614 respectively. Therefore, we used the random effect model for analysis. The combined results showed that the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of class I integron in the diagnosis of imipenem resistance of acinetobacter baumannii were 0.73 (95% CI was 0.70-0.77), 0.39 (95% CI was 0.35-0.43), 1.41 (95% CI was 1.25-1.59) and 0.52 (95% CI was 0.37-0.74), respectively. **Figure 4** shows the combined sensitivity and specificity of class I integron in the diagnosis of imipenem resistance of acinetobacter baumannii. The area under the sroc curve is 0.6184, indicating that the class I integron has a certain degree of accuracy in the diagnosis of imipenem resistance of aci-

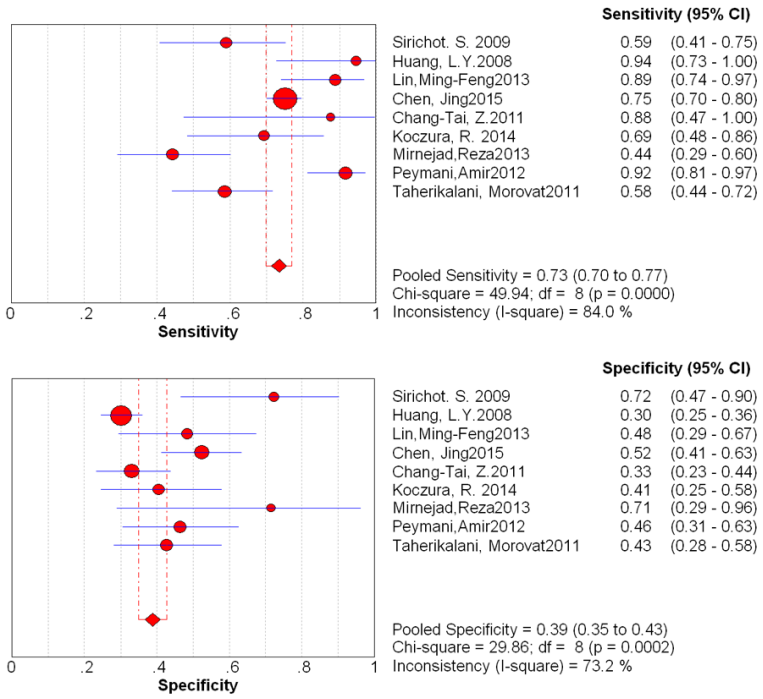

Figure 4. A meta-analysis of sensitivity and specificity of class I integrons for diagnosis of imipenem resistance in acinetobacter baumannii. By carefully reading each selected article, extract the integron distribution of the IMPRA group and the IMPSAB group, input it into the metadisc1.4 software, and get the **Figure 4**. The circle in the forest plot represents the point estimate of the sensitivity (specificity) of each study, and the size of the circle represents the weight of each study. The lines extending from both sides of the circle represent the confidence interval of sensitivity (specificity). The prism represents the sensitivity of the summary, and the lines extending from both sides of the prism represent the confidence interval of the sensitivity (specificity) of the summary. The right side of the chart shows the specific point estimates and confidence intervals of the sensitivity (specificity) of each study and summary study.

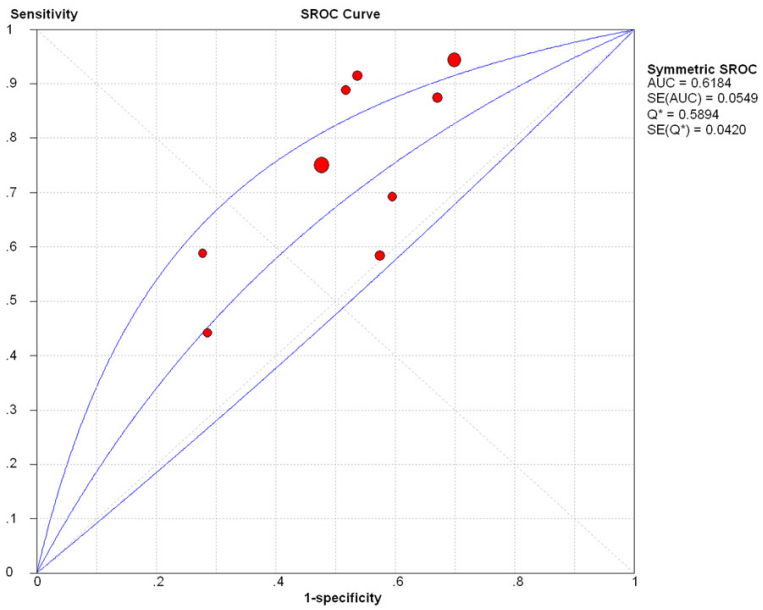

Figure 5. Summary receiver operating characteristic (sROC) curves of class I integron in the diagnosis of imipenem resistance of acinetobacter baumannii. AUC represents Area Under Curve. SE represents standard error. By carefully reading each selected article, extract the integron distribution of the IMPRA group and the IMPSAB group, input it into the metadisc1.4 software, and get the **Figure 5**. The ordinate of the graph is sensitivity. The abscissa of the graph is "1-sensitivity". SROC curve is an integrated ROC curve drawn according to the weight of the diagnostic odds ratio in a single diagnostic test. In this meta-analysis, the area under the sroc curve is 0.6184, indicating that the class I integron has a certain degree of accuracy in the diagnosis of imipenem resistance of acinetobacter baumannii.

netobacter baumannii, as shown in **Figure 5**.

Evaluation of publication bias of articles

We use the funnel plot to evaluate the publication bias of the included articles, and the funnel plot is shown in **Figure 6**. As can be seen from the picture, the funnel plot is symmetrical, except for one point in the two diagonal lines, the rest are in it, indicating that there is no obvious publication bias.

Discussion

Acinetobacter baumannii is an important pathogen of nosocomial infection and Carbapenem antibiotics are the first choice for the treatment of acinetobacter baumannii infection in recent years [26]. With the widespread use of antibiotics, the drug resistance of acinetobacter baumannii is becoming more and more serious. China antibiotic

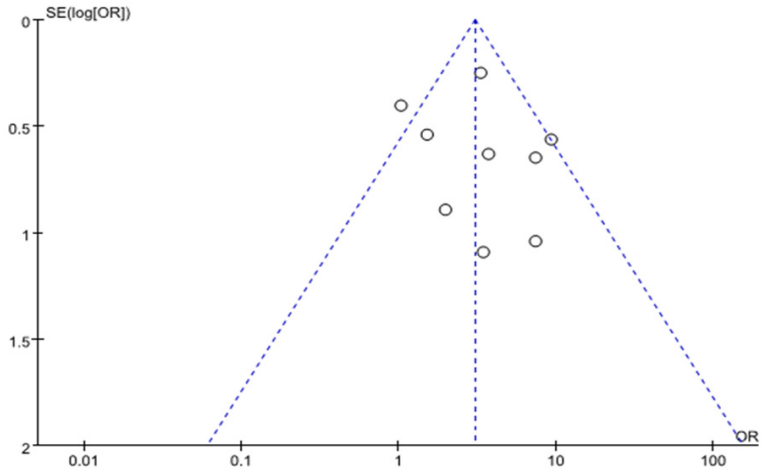

Figure 6. Funnel plot of meta-analysis of the correlation between class I integron and imipenem resistance of acinetobacter baumannii. OR represents the Odds Ratio. SE (log[OR]) represents standard error of logarithm of OR. By carefully reading each included article, extract the integron distribution of the IMPRA group and the IMPSAB group, input it into the RevMan 5.3 software, and get the **Figure 6**. The funnel plot is mainly used to evaluate the publication bias of the included articles. The funnel plot symmetrical, indicating that there is no publication bias.

Surveillance Network in 2018 showed that about 80% of acinetobacter baumannii strains were resistant to imipenem and meropenem, respectively [27] and a study in South Korea showed that the resistance rate of acinetobacter baumannii to imipenem increased to 85% [28]. The resistance of acinetobacter baumannii to carbapenem antibiotics will significantly increase the clinical mortality of patients [29, 30], so rapid diagnosis is particularly important. Clinical resistance to acinetobacter baumannii is mainly evaluated by the drug sensitivity test, which takes a long time and is not conducive to the timely evaluation of patients' condition, so it is necessary to develop some new rapid detection reagents.

There has been a lot of research on the relationship between class I integron and bacterial drug resistance in recent years. Heidarzadeh [31], S. conducted a meta-analysis of the detection rate of class I integrons of pseudomonas aeruginosa in Iranian burn patients and its relationship with antibiotic resistance. The results showed that the overall prevalence rate of class I integrons in pseudomonas aeruginosa isolates was 69% and there was a significant correlation between the existence of class I integrons and antibiotic resistance. A study by Halaji, M showed that the high prevalence and drug resistance of class I integrons were associated with uropathogenic escherichia coli [32]; besides, Najafgholizadeh Pirzaman did a similar study in klebsiella and the results showed that there was a significant correlation between the existence of integrons and the drug resistance of clinical isolates of klebsiella [33]. However, there was little similar comprehensive analysis on the relationship between class I integron and acinetobacter baumannii. In our study, we selected 10 studies from 462 articles for meta-analysis. The results showed that there was a correlation between class I integron and imipenem resistance of acinetobacter baumannii, and the odds ratio (OR) was 3.04. The combined sensitivity and specificity of class I integron in the diagnosis of imipenem resistance of acinetobacter baumannii were 0.73 and 0.39, respectively, and the area under the summary receiver operating characteristic (SROC) curve was 0.6184. It shows that class I integron has certain sensitivity, specificity, and accuracy in the diagnosis of imipenem resistance of acinetobacter baumannii. Also, it is worth mentioning that bacteria can spread drug resistance through class I integrons, resulting in the prevalence of drug-resistant bacteria, so the detection of class I integrons is also conducive to the control of nosocomial infection of acinetobacter baumannii [34].

However, our research also has some limitations. First, the bacterial strains studied are all from clinical, and the sources of patients may be heterogeneous to our research, for example, some suspicious patients are not routinely collected samples, so they are not included in the study. Second, we have included only 10 studies, the sample size is not large enough, and the scope of the study is concentrated in Asia and Europe, and the global representation is not enough, so studies should be conducted in more regions (such as America) to confirm our conclusions. Last, we only choose English articles, which will limit the scope of

our analysis, such as articles published in Chinese are not taken into account.

In conclusion, the results of this meta-analysis suggest that class I integron was related to imipenem resistance of acinetobacter baumannii and it had certain diagnostic value for imipenem resistance of acinetobacter baumannii. Considering the limitations of the current meta-analysis, larger-scale studies with different races and different regions should be further developed to reach a comprehensive conclusion.

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Disclosure of conflict of interest

None.

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