Systematic review and meta-analysis of imipenem-resistant *Pseudomonas aeruginosa* prevalence in Iran

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Abstract

Introduction **Imipenem-resistant *Pseudomonas aeruginosa* (IRPA), due to resistance to different classes of antibiotics and its remarkable capacity to survive in harsh and adverse conditions such as those in the hospital environment, is considered a serious threat to the healthcare system. Given the great impact of IRPA on patients' outcome and in order to possibly improve antibiotic prescription, this study was conducted to determine the prevalence of clinical isolates of IRPA in different parts of Iran.**

Methods **A systematic literature search was performed in PubMed, Web of Science, Google Scholar and Scopus, as well as in two Iranian domestic search engines, i.e., Iranian Scientific Information Database and Magiran. Finally, after applying exclusion and inclusion criteria 37 articles with full-texts describing the prevalence of imipenem-resistant *P. aeruginosa* were selected for meta-analysis and systematic review.**

Results **The pooled estimation of 5227 *P. aeruginosa* isolates in this analysis showed that the percentage of imipenem-resistant *P. aeruginosa* is about 54% in the Iranian population (95%CI: 0.47-0.62, logit event rate=0.19, 95%CI: -0.12,0.49).**

Conclusion **The findings of this analysis show that in the majority of Iranian hospitals the relative frequency of IRPA is high, therefore, in order to prevent further dissemination of IRPA, more appropriate antibiotic prescription and infection control policies must be implemented by decision-makers.**

Keywords **Imipenem-resistant *Pseudomonas aeruginosa*, carbapenem resistance, *Pseudomonas aeruginosa*, multidrug resistant *Pseudomonas aeruginosa***

Introduction

Pseudomonas aeruginosa is a well-known successful opportunistic pathogen that has the remarkable capacity to cause a wide range of maladies, from superficial tissue contamination to life-treating conditions such as blood stream and central nervous system infections (CNS).[1,2] *P. aeruginosa*, due to simple nutritional requirements, has developed the ability to survive successfully in different parts of the hospital, including, but not limited to, hand washing sinks, taps, moist hospital environments, and cleaning materials.[3,4] Introduction of imipenem was a cornerstone in treating *P. aeruginosa* infections, however, as a result of indiscriminate use of antibiotics, the emergence of imipenem-resistant isolates has been facilitated.[5] Different mechanisms that confer resistance to imipenem have been described, including the reduced permeability of the outer membrane, the production of beta-lactamase enzymes, and the overexpression of efflux pumps.[6] Four classes (A, B, C, D) of beta-lactamase enzymes have been characterized. Class B, which requires the presence of Zn^{2+}, is known as metallo-beta-lactamase, and is one of the most important

Received: 12 January 2017; revised: 15 February 2017 and 26 February 2017; accepted: 21 March 2017.

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Published June 2017

ISSN 2248 – 2997
ISSN – L = 2248 – 2997

enzymes, conferring resistance against imipenem.[6,7] Treatment of *P. aeruginosa* infection is becoming more difficult with each passing day because imipenem resistance genes and other antibiotic resistance genes are usually located in the transferable genetic elements such as plasmids and integrons, allowing easy dissemination of resistance genes, simultaneously.[6-8] Several independent studies have revealed that impact of imipenem-resistant *P. aeruginosa* infections on hospital costs and healthcare settings was significantly higher than that due to imipenem-susceptible strains. For example, Lautenbach et al. reported that the emergence of imipenem-resistant *P. aeruginosa* has been associated with high hospital cost and substantial mortality.[9] In addition, Dantas et al. showed that the patients who are infected with carbapenems-resistant *P. aeruginosa* have usually worse treatment outcome, resulting in increased hospitalization and health-care associated cost.[10]

Given the great impact of imipenem-resistant *P. aeruginosa* (IRPA) on patients' outcome and in order to possibly improve antibiotic stewardship, in this study, we aimed to determine the prevalence of clinical isolates of imipenem-resistant *P. aeruginosa* in different parts of Iran, using meta-analysis based on published papers.

Methods

Search criteria

A systematic literature search was done (up to November 2016), using well-known databases including PubMed, ISI (Web of Science), Google Scholar and Scopus, as well as two Iranian domestic search engines, i.e., Iranian Scientific Information Database (www.sid.ir) and Magiran (www.magiran.com). Meanwhile, we manually reviewed citations to find relevant studies. The following search terms were used: '*Pseudomonas aeruginosa*', 'imipenem-resistant', 'multidrug resistance *Pseudomonas aeruginosa*', 'metallo-beta-lactamase producing *P. aeruginosa*' and 'Iran'. Finally, the full texts of original articles in Persian and English were selected for the study, specifically articles in which the disk diffusion method was used for the identification of imipenem resistance in *P. aeruginosa*.

Inclusion criteria

The inclusion criteria were: (I) retrospective and cross-sectional studies; (II) *P. aeruginosa* strains isolated from patients referred to Iranian hospitals; (III) clinical specimens were collected from patients, results from the environment and personnel were not included; (IV) only the disk diffusion method according to CLSI guidelines was incorporated for the detection of imipenem-resistant *P. aeruginosa*, because the disk diffusion method is a standard procedure, available throughout Iran, and is being used widely; if different methods were applied, the results of disk diffusion were incorporated.

Exclusion criteria

We excluded articles if: (I) samples were partially or totally taken from different provinces, and we were not able to attribute the results to distinct provinces; (II) samples were partially or totally collected from imipenem-resistant isolates; (III) the origin of the sample was unclear in terms of clinical or environmental samples, we also excluded studies in which repetitive *P. aeruginosa* isolates had been used; (IV) finally, studies with unclear materials and methods were excluded, specifically regarding the concentration of imipenem in the applied disks, the producer company of the disk, and methods other than disk diffusion.

Data collection

All data were extracted and cross checked by reviewers (Vaez, Salehi-Abargouei) according to the above mentioned inclusion and exclusion criteria. Subsequently, the following data were obtained; the first author's name, publication time, sample size, study enrollment time, province where the research was conducted, and relative frequency. Disagreements between reviewers were resolved through discussion.

Statistical analysis

The total number of participants and the number of samples with imipenem-resistant *P. aeruginosa* were used to calculate event rate and

Table 1. Summary of studies involved in the systematic review and meta-analysis

First author	Publication year	Time of study	Province	Total samples	IRPA prevalence	Reference
Galvani	2015	2013-2014	Urmia	50	36 (72%)	13
Pourakbari	2016	2012	Tehran	45	12 (28%)	14
Talebi-taher	2016		Tehran	91	80 (88%)	15
Sheikh	2014	2011-2012	Ahvaz	223	131 (58.7%)	16
Radan	2016	2013-2014	Isfahan	150	144 (96%)	17
Goli	2016	2014	Tabriz	100	49 (49%)	18
Mirbagheri	2015	2011-2012	Mashhad	131	63 (48.5%)	19
Abiri	2015	2012	Kermanshah	225	76 (33.7%)	20
Bahar	2010	2007-2008	Tehran	186	115 (61.8%)	21
Shahcheraghi	2010	2005-2007	Tehran	610	76 (12.4%)	22
Khosravi	2008	2005-2006	Ahvaz	100	41 (41%)	23
Sepehriseresht	2012	2008-2009	Tehran	483	272 (56%)	24
Rahimi	2012	2010-2011	Arak	100	35 (35%)	25
Nikokar	2013	2010-2011	Gillan	86	20 (23.3%)	26
Alikhani	2014	2009	Hamedan	106	8 (7.5%)	27
Fazeli	2012	2008-2009	Isfahan	98	53 (54%)	28
Golshani	2012	2012	Isfahan	50	29 (58%)	29
Vaez	2015	2013	Isfahan	54	30 (55.6%)	30
Yousefi	2010	2007-2008	Urmia	160	61 (38.1%)	31
Mirsalehian	2010	2007	Tehran	170	112 (65.9%)	32
Saderi	2010	2008	Tehran	100	69 (69%)	33
Hakemivala	2014	2012	Tehran	47	37 (78.73%)	34
Goudarzi	2013	2011	Tehran	133	126 (94.7%)	35
Ranjbar	2011	2007	Tehran	70	68 (97.5%)	36
Kalantar	2014	2011-2012	Tehran	214	100 (46.7%)	37
Abdolahzadeh	2011	2010	Tehran	100	21 (21%)	38
Doosti	2013	2011-2012	Zanjan	70	45 (63.8%)	39
Moosavian	2015	2011-2012	Ahvaz	236	122 (51.4%)	40
Ghanbarzadeh	2015	2013	Tehran	144	114 (79.2%)	41
Goudarzi	2015	2011	Tehran	112	85 (70.3%)	42
Saderi	2015	2013	Tehran	88	30 (34.1%)	43
Sedighi	2015	2012-2013	Isfahan	106	62 (58.5%)	44
Bokaeian	2015	2012-2013	Zahedan	116	20 (17.2%)	45
Arabestani	2015	2012-2013	Hamedan	31	3 (9.6%)	46
Jabalameli	2011	2008-2009	Tehran	112	74 (66%)	47
Hemati	2014	2012-2013	Zanjan	120	35 (29.2%)	48
Zoghi	2015	2012-2013	Kermanshah	200	80 (40%)	49

IRPA – imipenem-resistant *Pseudomonas aeruginosa*

its confidence interval.[11] The DerSimonial and Laird random effects model was used to derive the summary estimate.[11] The I-squared and Cochran's Q test were used to assess heterogeneity between studies.[11] We used subgroup analysis to explore the prevalence rates according to sampling year and the province in which the study was conducted. Furthermore, meta-regression was performed to check if there is a linear association between publication year and heterogeneity between study results. To explore the extent to which the overall calculations might depend on a specific study, sensitivity analysis was done. Publication bias was evaluated by inspecting Begg's funnel plots and asymmetry tests including Egger's regression

asymmetry test and Begg's adjusted rank correlation test.[11,12] Statistical analyses were performed using the STATA software package version 11.2 (STATA Corp, College Station, TX, USA). Results were considered statistically significant if the p value was below 0.05.

Results

It has been widely accepted that *P. aeruginosa* is one of the most important pathogens in both hospital-acquired and community-acquired infections, due to the presence of multiple virulence factors and also its ability to survive in difficult environmental conditions.[1-4]

In this study, a total of 3500 articles were found by the aforementioned search strategies (Figure 1). After title and abstract screening and evaluation, 1500 articles were excluded. Finally, after applying the exclusion criteria 37 articles[13-49] with full-texts describing the prevalence of imipenem-resistant *P. aeruginosa* were selected for systematic review and meta-analysis (Table 1). Most of the studies were performed in Tehran (16), and Isfahan (5), followed by Ahvaz (3), Hamedan (2), Kermanshah (2), Zanjan (2), Urmia (2), Arak (1), Gillan (1), Mashhad (1), Tabriz (1), and Zahedan (1). The highest and lowest prevalence rates of IRPA were seen in Tehran (97.5%) and Hamedan (7.5%) provinces.

The pooled estimation of 5227 *P. aeruginosa* isolates in our analysis showed that the prevalence rate of imipenem-resistant *P. aeruginosa* is about 54 percent in the Iranian patient population. Between study heterogeneity was high (Cochrane Q test, $p<0.001$, $I^2=95.5$) (Figure 2). We also checked the prevalence rate of imipenem-resistant *P. aeruginosa* based on the sampling year of the included studies. As illustrated in Figure 3, the prevalence rate has increased from about 41% in 2006 to 88% in 2015. Although there was an increasing trend between the sampling year and the prevalence rate, we found no association between sampling year and the heterogeneity between study results using meta-regression (B=0.016, p=0.38) (Figure 4). We also conducted a subgroup analysis based on the region where the study was conducted. The results are presented in Figure 5. The analysis revealed that the highest prevalence is in Isfahan province with 65% (95%CI: 42-88) and the lowest prevalence was seen in Hamedan province (prevalence rate=8%, 95%CI: 3-13).

Sensitivity analysis showed that none of the included studies can significantly change the overall prevalence. Although there was a slight asymmetry in Begg´s funnel plot, asymmetry tests did not show any evidence of publication bias (Egger´s test p=0.115, Begg´s test p=0.229).

Discussion

Active surveillance of trends in antibiotic resistance, due to high use and misuse of antibiotics, is necessary for the appropriate selection of antibiotics.[10,50,51] In the past few decades, an alarming increase in the prevalence of multidrug resistant *P. aeruginosa* isolated from clinical samples has been shown worldwide, including Iran.[13-49,51] During the past decade, multiple investigations have been conducted by Iranian researchers to determine the antibiotic resistance profile of *P. aeruginosa* using phenotypic and genotypic methods, in different regions, showing the importance of *P. aeruginosa* in the clinic.[13-49] Based on these studies, we conducted the present systematic review and meta-analysis to estimate the cumulative prevalence of IRPA using data collected from studies performed in different hospitals in Iran. A total of 37 publications were found. According to our meta-analysis, the prevalence of IRPA was 54% and was higher than fifty percent in many Iranian cities (Table 1). In a provincial perspective, Isfahan showed the highest prevalence of IRPA, with 65%, followed by Tehran with 61%, according to our meta-analysis. Our findings also revealed that the lowest percentage of resistance was reported from the Hamedan province (8%). The study by Suwantarat et al. reported carbapenem-resistant *P. aeruginosa* rates for southeast Asia countries and showed a lower percentage of resistance in those countries compared to Iran, including Philippines 31.1%, Singapore 23.3%, and Thailand 28.7%.[52] In addition, the findings of Hong et al. demonstrated that the percentage of imipenem-resistant *P. aeruginosa* in Japan and

Korea is lower than our findings, with 28.5% and 22% of isolates being resistant, respectively.[53] However, findings similar to the results of this study were reported from Pakistan, in a study done by Ameen et al., which showed that out of 230 investigated strains of *P. aeruginosa*, 49.5% were imipenem-resistant.[54]

Internationally, most of the European countries such as Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Luxemburg, Malta, and the Netherlands reported prevalences of resistant isolates below 20%, However, in some countries such as Romania and Greece reported figures are approximately similar to our findings, with more than 45% being resistant.[55]

The emergence and dissemination of IRPA is of importance because these isolates show resistance to multiple antibiotics simultaneously, hence, physicians in the majority of Iranian hospitals, as shown by the results of this study, may face difficulties in the treatment of IRPA infections. The use of synergistic antibiotics might be a suitable choice to fight this problem.

There are some limitations that should be considered while interpreting the results. First, some of the studies might have been missed, due to limited access to some data including those presented in theses or in-press articles. Second, our findings cannot completely represent the prevalence rate for Iran, because for most parts of the country relevant data were not available. Third, differences between phenotypic methods and genotypic methods should be taken into account, because different methods may result in different reports on the prevalence of IRPA.

Conclusions

In summary, the findings of this analysis underscore the point that the relative frequency of IRPA is high in the majority of Iranian hospitals. Therefore, in order to prevent further dissemination of IRPA, more appropriate antibiotic stewardship and infection control measures must be considered by decision-makers. Additionally, this study emphasized the need to establish reference laboratories with standard guidelines for antimicrobial resistance surveillance in different provinces of Iran to allow constant monitoring of changes in antibiotic resistance profiles.

Authors' contributions statement: HV and FK were involved in study design and data collection. ASA performed the statistical analysis. HV and ASA wrote and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of interest: All authors – none to declare.

Funding: None.

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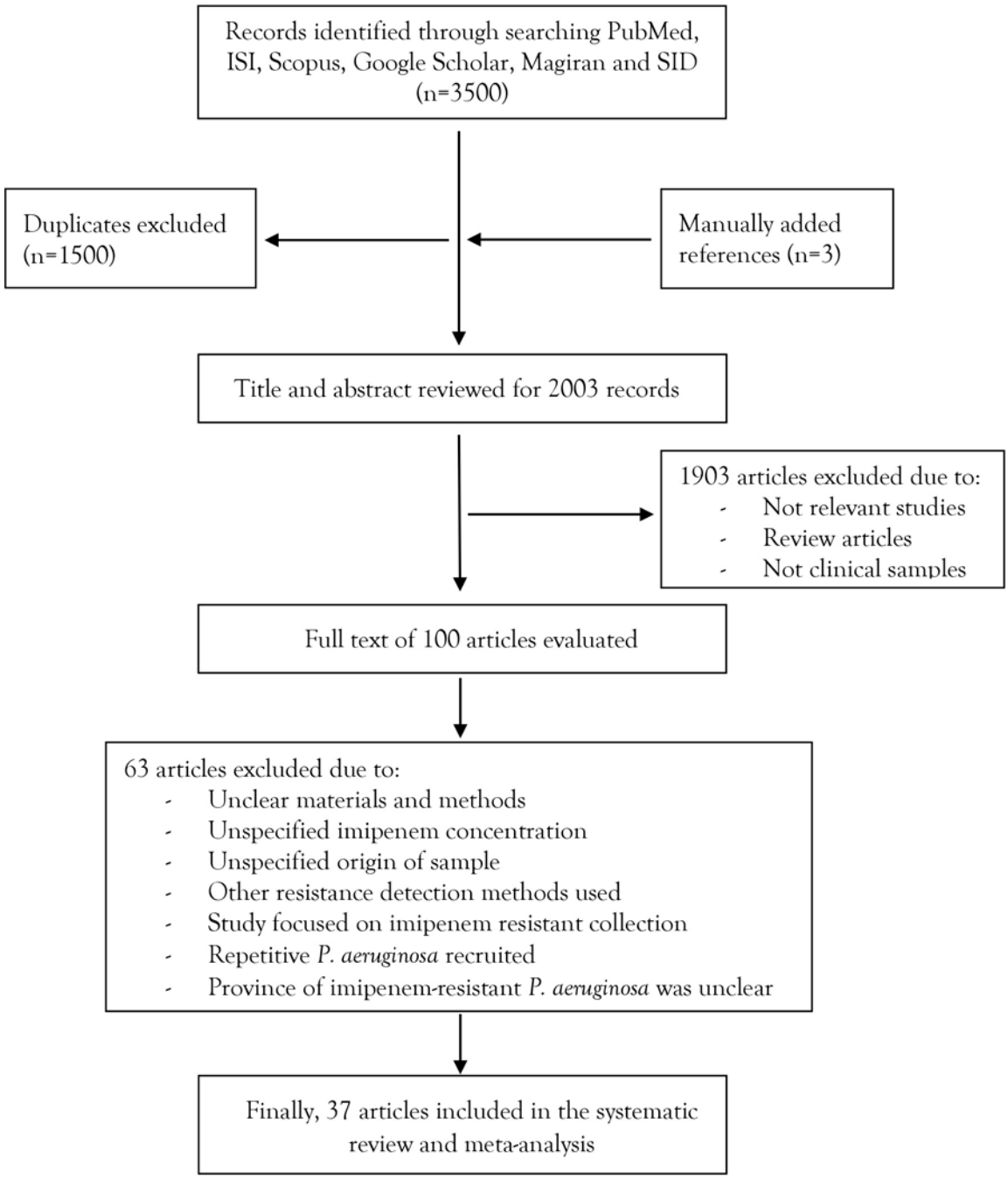
Please cite this article as:
Vaez H, Salehi-Abargouei A, Khademi F. Systematic review and meta-analysis of imipenem-resistant *Pseudomonas aeruginosa* prevalence in Iran. GERMS 2017;7(2):86-97. doi: 10.18683/germs.2017.1113

Appendix – Figures



SID – Iranian Scientific Information Database

Figure 1. Schematic flow diagram for literature review and study selection

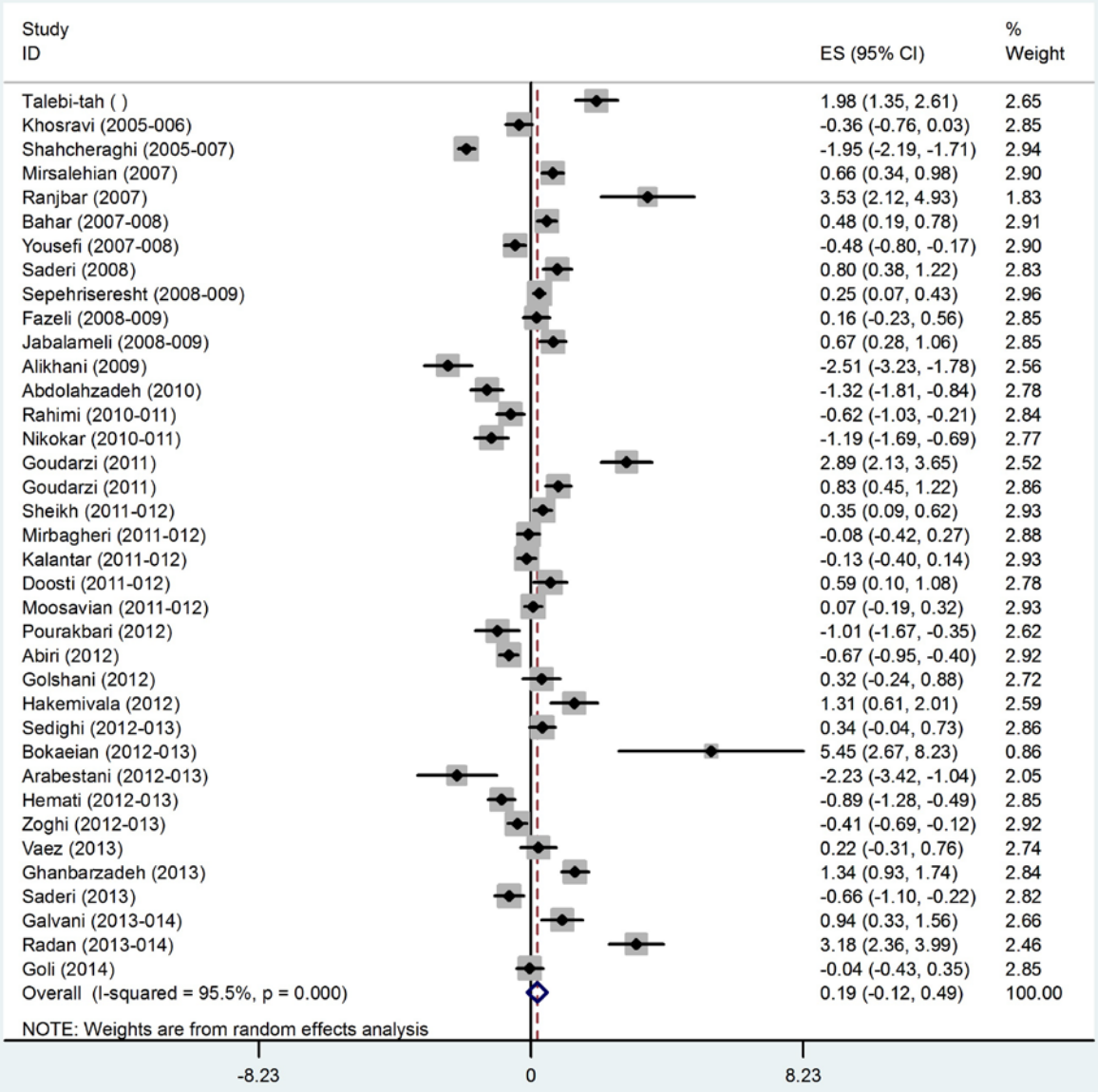


Figure 2. Forest plot depicting the overall logit event rate for the prevalence of imipenem-resistant *P. aeruginosa* in Iran. The conversion of the summary logit event rate to the prevalence rate revealed that about 54% of samples of *P. aeruginosa* were imipenem-resistant in the Iranian patient population (95%CI: 0.47-0.62).

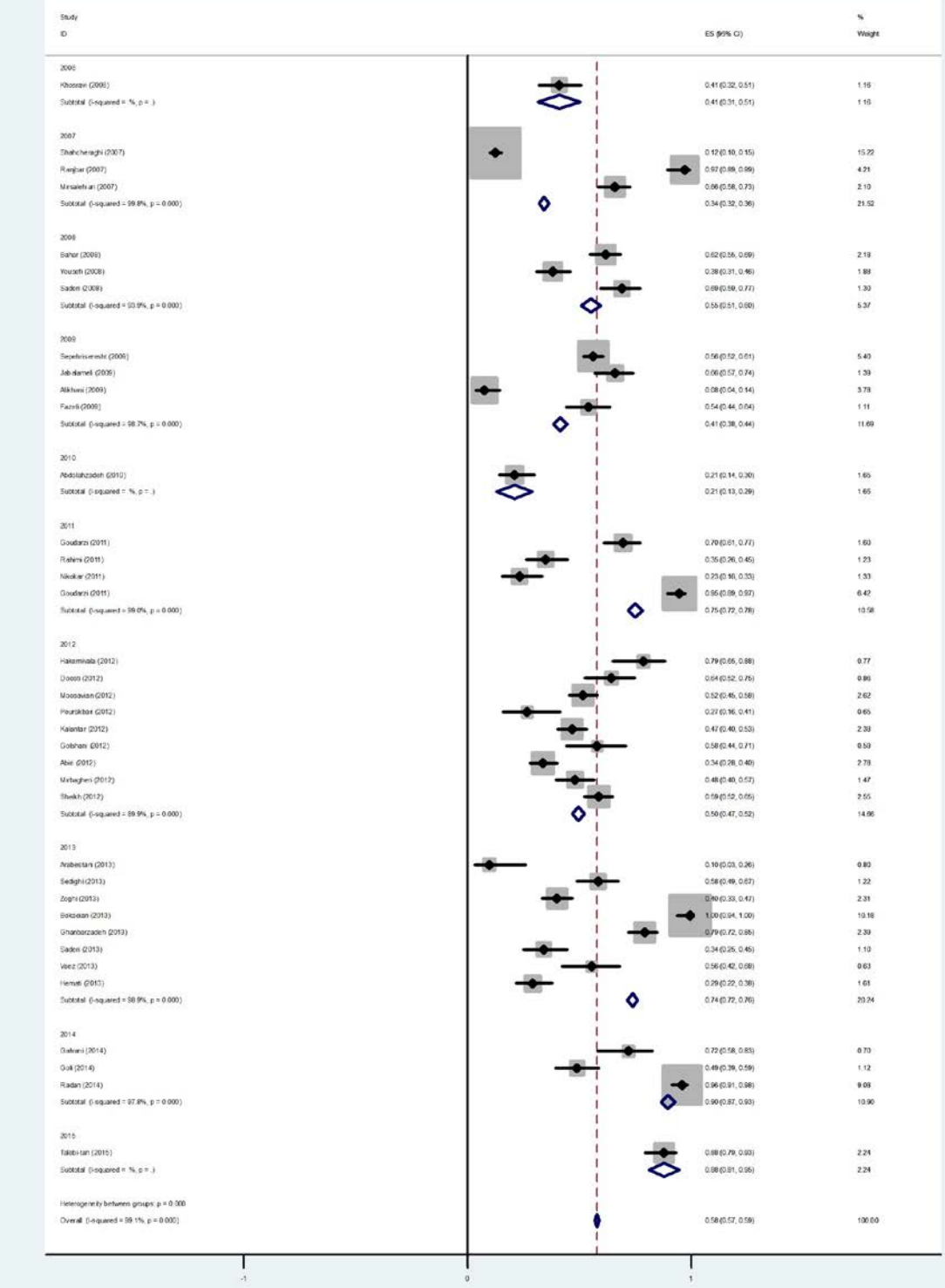


Figure 3. Prevalence of imipenem-resistant *P. aeruginosa* based on different years

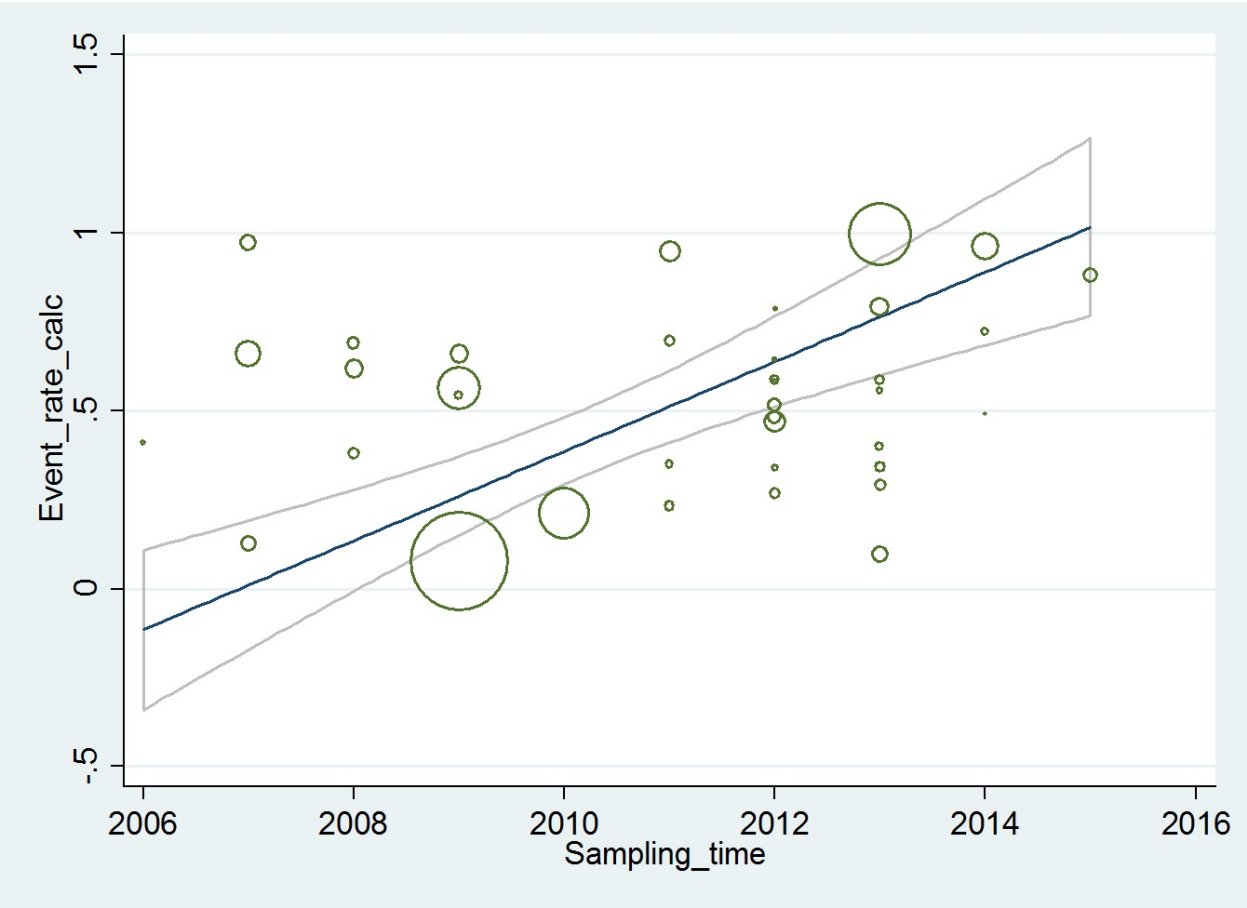


Figure 4. Association between sampling year and heterogenicity

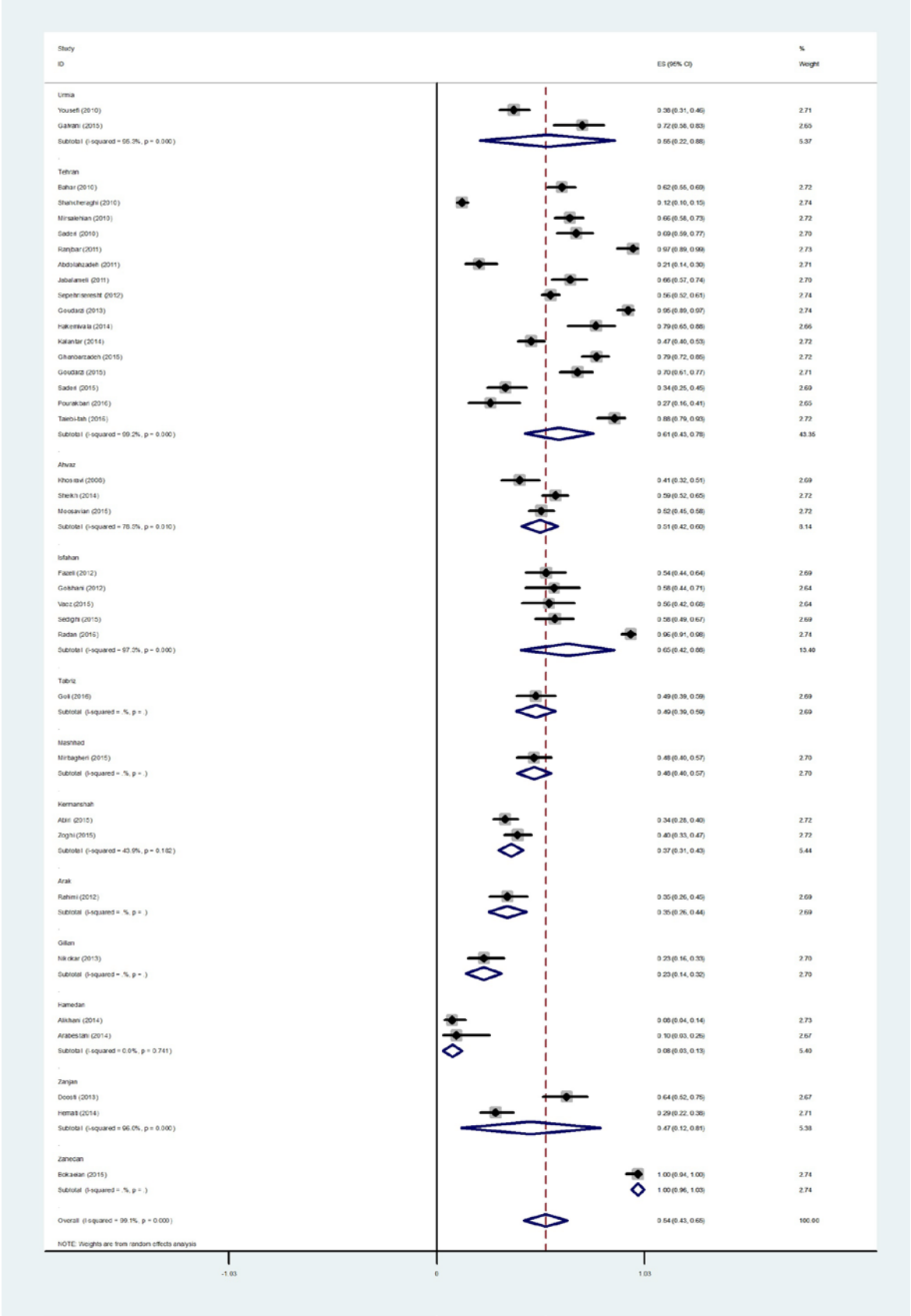


Figure 5. Prevalence of imipenem-resistant *P. aeruginosa* based on the provinces of the study