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Review

Epidemiology of multidrug-resistant *Acinetobacter baumannii* strains in Iran: a systematic review and meta-analysis

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Acinetobacter baumannii is an important opportunistic pathogen that causes major public health concern especially in hospitalized patients due to the acquisition of multidrug resistance (MDR). The aim of this study was to systematically review published data about the prevalence rate of MDR-*A. baumannii* (MDR-AB) from different parts of Iran and provide an overall relative frequency (RF) using meta-analysis. All available national and international databanks were searched to find published studies up to June 2016. Quality of studies was assessed by STROB and PRISMA forms. Because of the significant heterogeneity observed, random effects model was used to combine the results. STATA SE version 11.2 was used for statistical analysis. Out of the 9646 results, 37 suitable articles were extracted according to inclusion and exlusion criteria. The pooled prevalence of MDR-AB was estimated 72% annually. Relative frequency of MDR-AB in different studies varied from 22.8 to 100%. Since the prevalence of MDR-AB is higher than many other countries, measures should be taken to keep the emergence and transmission of these strains to a minimum.

Keywords: *Acinetobacter baumannii*, Multidrug resistance, Epidemiology, Systematic review, Iran

Introduction

The genus *Acinetobacter* are ubiquitous, Gram-negative, oxidase negative, strictly aerobic, non-fermentative, pleomorphic and non-motile coccobacilli, they can easily spread from one patient to others and persist in the environment for many days.[1–3] *Acinetobacter* spp. can be found almost everywhere in nature including soil, surface water, medical equipment, food and waste.[4] They are also widely distributed in hospital environment and can be isolated readily from various surfaces and instruments such as sinks, bed rails, ventilators and even doorknobs.[5] Species of *Acinetobacter baumannii* (*A. baumannii*) accounts for more than 80% of the isolates causing human diseases.[6] *A. baumannii* is an important opportunistic pathogen which plays a significant role in nosocomial infections and cause complications in hospitalized patients, especially those in intensive care units (ICU) and burn wards.[7] This organism is frequently associated with immunosuppressed patients as well as those with serious underlying diseases or subjected to invasive procedures.[8] *A. baumannii* is considered to be responsible for 2–10% of all Gram-negative bacterial infections of patients in intensive care units in Europe and U.S.A.. *A. baumannii* infections have become a significant challenge for health care systems.[9] This bacterium is the causative agent of several types of nosocomial infections such as bacteremia, urinary tract infections, secondary meningitis, peritonitis, endocarditis, septicemia, wound infections, skin and soft tissue infections and hospital pneumonia.[10–12]

A serious concern regarding *A. baumannii* infections is the detection of an increasing rate of resistance to multiple antibiotics in this species.[13] *A. baumannii* is able to acquire different mechanisms of resistance becoming, in some cases, resistant to all commonly available antibiotics.

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For this reason, the lack of new effective antimicrobial agents is an alarming phenomenon for the treatment of *A. baumannii* infections.[13–15] Various studies show that most *A. baumannii* strains become resistant to most antibiotics and these multidrug-resistant strains are expanding rapidly among hospitalized patients.[16,17] Mobile elements include plasmids, transposons and integrons, carrying clusters of resistant genes, are the most effective genetic elements which play an important role in acquisition and dissemination of resistance factors in *A. baumannii* strains.[18,19] Extensive use of antimicrobial chemotherapy in clinical cases has contributed to emergence and dissemination of multidrug-resistant (MDR) *A. baumannii* infections. The multidrug-resistant *A. baumannii* (MDR-AB) are defined as *A. baumannii* isolates that are resistant to at least three different classes of antimicrobial agents mainly betalactams (third generation cephalosporins), aminoglycosides, fluoroquinolones and more recently carbapenems.[11,20–22] As a result of the resistant nature of *A. baumannii* and its unusual and unpredictable susceptibility patterns, limiting the spread of MDR-AB is of paramount importance for the treatment of hospitalized patients.[23–25]

There are increasing reports of MDR-AB outbreaks in various clinical settings worldwide.[11,26] Spread of MDR *A. baumannii* is not limited to hospitals of one city, but is also important in national scale.[27,28] Treatment of infections caused by this organism should be based on perfect antibiotics sensitivity tests, therefore having information regarding the prevalence and pattern of bacterial resistance to these drugs is important.[29,30] Reports of the numerous outbreaks caused by multidrug-resistant (MDR) *A. baumannii* from different regions of the world are appearing at a startling rate, posing an increased threat to hospitalized patients.[31–34] Several studies such as Pajand et al. and Farsiani et al. showed that more than 90% of *A. baumannii* strains isolated from patients become MDR. The studies of Mirnejad et al. , Khalilzadegan et al., Davoudi et al. and Michalopoulos et al. revealed that numerous clinical isolates of *A. baumannii* were resistant to the majority of consumed antibiotics.[13,35–39] Even though, many studies reported the extent of MDR-AB in different parts of Iran, the average overall rate is still unknown.[40] In present study, we aimed to systematically review published data about the prevalence rate of MDR-AB from different parts of Iran and provide an overall relative frequency (RF) using meta-analysis.

Materials and methods

Search strategy

International databanks (ISI Web of Science, PubMed, Scopus, Google scholar and Science Direct) were searched (up to June 2016) by using the following keywords: '*A. baumannii*', 'multidrug resistant', 'MDR', 'MDR-AB', 'Antibiotic resistant' and 'Iran'. In addition to articles published in English, four national scientific search engines including Medlib (www.medlib.ir), Magiran (www.Magiran.com), Iranian Scientific Information Database (www.sid.ir) and 'IranMedex' (www.iranmedex.ir) were searched as well for relevant articles. No limitation was used while searching databases. References lists of all related studies were also reviewed for any other related publication. The search was restricted to original Articles/abstracts published in English and Persian that reported the prevalence of MDR-AB by phenotypic method in Iran. All these steps were done by three authors (MS, EK and AZB) and any disagreements with article selection were resolved through discussion, and a fourth author (ASA) was available to resolve the disagreement.

Inclusion criteria

Among English and Persian articles/abstracts found with above strategies, those with the following features were included in the study:

(1) *A. baumannii* samples were collected from Iranian hospitals; because this review study is limited to Iran and the purpose of the present study was to measure the prevalence of strains with multidrug resistance in Iran only, (2) Personnel specimens were not included for analysis because they could be samples transferred from patients with repetitive strain and therefore not valid. All the studies included in this survey were conducted on clinical samples from patients. A phenotypic method (disc diffusion method or Kirby-Bauer) was incorporated to find MDR strains of *A. baumannii*, because this method is the standard phenotypic assay that used in majority of studies for representation of antibiotic resistance pattern and demonstration of multidrug resistance.

Exclusion criteria

Articles were excluded from the review if: (1) Samples were partially/totally selected from *A. baumannii* collections; *A. baumannii* strains that were collected and stored before. (2) Use of other phenotypic methods instead of disc diffusion for identification of resistant *A. baumannii* strains and the origin of samples was not clear; meaning that the reviewer(s) could determine which region or population (i.e. inpatients, personnel or outpatients) the specimens were gathered from. Finally, review articles, congress abstracts, studies reported in languages other than English or Persian, meta-analyses or systematic reviews and duplicate publication of the same study (or published both in English and Persian) were also excluded.

In regards to duplicate publication, studies with higher sample size and more detailed results were chosen for inclusion in this systematic review.

Study selection

We extracted full texts or abstracts, documents and reports of all evidence identified during our advanced search. To minimize the reprint bias, we tried to investigate all results in detail and remove any repeated studies.

Quality assessment

Quality of relevant articles was evaluated using the STROBE checklist (Strengthening the Reporting of

Observational Studies in Epidemiology)[41] and another checklist was used in a literature review.[42] Items related to study type, sample size, research objectives, population, inclusion/exclusion criteria for primary research, analysis method and appropriate presentation of results were determined and a score was assigned to each item. One score was assigned to each question and studies achieved at least eight quality scores were considered eligible for final meta-analysis.

Data collection

For all studies, the following data were extracted: last name of the first author, publication date, sample size, study setting, study enrollment time, number of participants with MDR-AB, the Relative Frequency (RF) of MDR-AB strains, drug resistance status (multi-drug resistant) and research location. Three authors extracted data from all of the included studies, independently. Inconsistencies between the reviewers were discussed to obtain consensus.

Statistical analysis

Total number of samples and the number of participants with *A. baumannii* resistance were used to calculate event rate which was then converted to logit event rate and its Standard Error (SE) for meta-analysis. Overall effect was derived by using DerSimonian and Liard random effects model.[43] Heterogeneity between studies was evaluated using Cochran's Q test and I-squared.[44] Sensitivity analysis was incorporated to examine the extent to which inferences might depend on a particular study. Publication

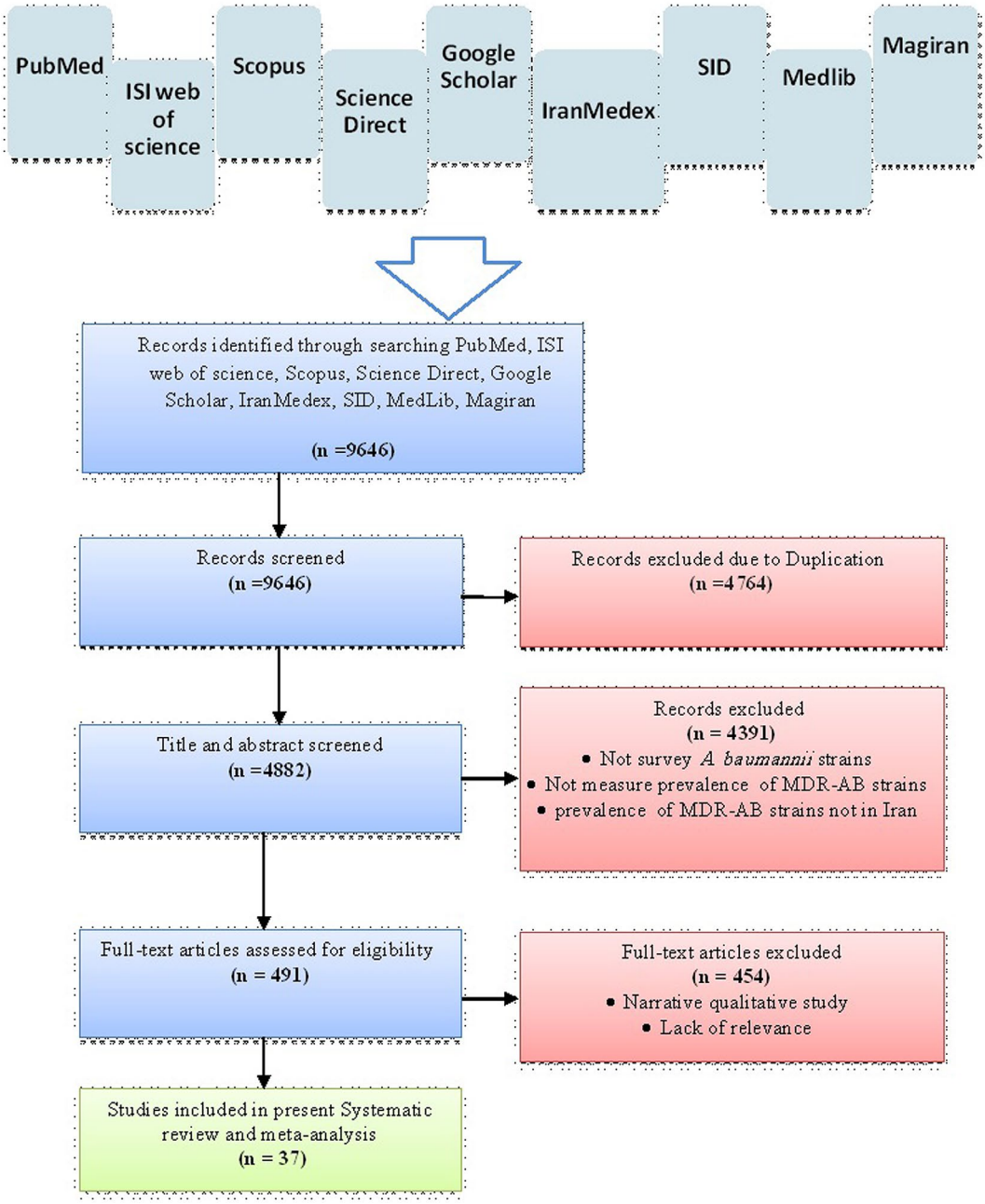

Figure 1 Flowchart for literature search and study selection

Table 1 Characteristics of studies included in the systematic review and meta-analysis after full evaluation

First author	Year	Published year	Location	No. *Acinetobacter baumannii*	No. MDR	% MDR	Ref.	Infection type
Moniri et al.	2008	2010	Kashan	60	40	66.7	[60]	Blood, urine, csf, trachea, sputum, pleural fluid
Japoni-Nejad et al.	2011	2013	Arak	63	56	89%		CSF, surgical wound swabs, urine, blood, respiratory secretions
Kamalbeik et al.	2012	2013	Tehran	40	40	100	[63]	Tracheal aspiration, urine, blood, wound
Mostofi et al.	2010	2011	Tehran	50	27	54	[64]	Blood, respiratory sections, urine, skin sores, trachea
Peymani et al.	2008–2009	2011	Tabriz	100	31	31	[65]	Tracheal aspiration, urine, blood, sptutum, catheter, bronchial washing, wound, csf, absecces drainge, ascites, pleural effusion
Bazargani et al.	2010	2011	Shiraz	69	69	100	[66]	Blood
Shahcheraghi et al.	2009–2010	2011	Tehran	203	83	40.8	[67]	Blood, wound, urine, sputum, and respiratory tract
Sohrabi et al.	2008–2009	2012	Tabriz	100	100	100	[68]	Blood, tracheal aspirates, wound, sputum, abscess drainage, wound, bronchial washing, and urine
Pajand et al.	2010–2011	2013	Tehran	76	70	92.1	[37]	Tracheal aspirates, urine, wound, blood and sputum
Mirnejad et al.	2009–2010	2013	Tehran	50	41	82	[39]	Blood cultures, trachea, wound swab
Bahador et al.	2012	2013	Gonbad,Tehran, Shiraz	94	80	84.6	[69]	Respiratory tract, postoperative wound, urine, blood, and cerebrospinal fluid (CSF)
Farahani et al.	2010	2013	Kashan	60	34	56.7	[70]	Blood,sputum, urine,cerebrospinal fluids, and pleural fluid
Goudarzi et al.	2010–2011	2013	Tehran	221	99	44.8	[71]	Clinical,patients' surroundings, medical equipment and hands of staff
Nikasa et al.	2012	2013	Tehran	65	62	95	[72]	Urine, blood and burn wound
Karmostaji et al.	2010–2011	2013	Tehran	123	43	34.95	[73]	Aspirated sputum, trachea, burn, wound and urinary tract infections.
Mirnejad et al.	2011 - 2012	2013	Tehran	400	280	70	[74]	Urine, blood, skin lesions, chips and samples isolated from the respiratory tract and areas of burn
Owlia et al.	2010–2011	2013	Tehran	126	53	42	[75]	The exudates of wounds
Farajnia et al.	2008–2009	2013	Tabriz	100	80	80	[76]	Tracheal secretion, bronchial lavage, blood, wound, sputum, abscess drainage, peritoneal fluid, and urine
Mohajeri et al.	2010–2011	2013	Kermanshah	104	34	32.7	[77]	Sputum, blood and urine clinical specimens
Feizabadi et al.	2005–2006	2008	Tehran	128	58	45	[77]	Wounds, the trachea, blood, cerebrospinal fluids, urine, other tissues
Taherikalani et al.	NA	2008	Tehran	42	24	57.1	[78]	Wound, trachea, blood, CSF, catheter, other samples
Bahador et al.	2006–2011	2014	Tehran	250	100	20.5	[79]	Wound, respiratory tract, urine, blood, CSF
Fazeli et al.	2013–2014	2014	Isfahan	121	121	100	[81]	Trachea, urine, blood, wound, cerebrospinal, fluid, pleural fluid, and others
Behzadnia et al.	2012	2013	Sari-Mazandaran	16	16	100	[80]	Wound infection, respiratory infection, UTI, and blood Infection
Vakili et al.	2011–2012	2014	Isfahan	70	68	97.1	[81]	Respiratory specimens, urine samples, blood specimens, tracheal aspirates specimens, cerebrospinal fluid (CSF) specimens, and injuries specimens
Vakili et al.	2011–2012	2014	Isfahan	60	57	95	[82]	Respiratory specimens, urine specimens, blood specimens, tracheal aspirates specimens, and cerebrospinal fluids specimens
Farsiani et al.	2012	2015	Mashhad	36	35	97	[38]	Tracheal aspirate, blood, wounds, CSF, urine, and oedema discharge
Jahani-Sherafat et al.	2011–2012	2015	Tehran	67	67	100	[83]	Urinary tract infection, bloodstream infection, surgical site infection, pneumonia
Bahador et al.	2011	2015	Tehran	85	59	69	[84]	Respiratory tract, urine, blood, wound, and cerebralspinal fluid
Armin et al.	2014–2015	2015	Tehran	198	113	57	[85]	Urine, stool and sputum samples, nasopharyngeal swabs and blood cultures
Bahador et al.	2012	2015	Tehran	62	62	100	[86]	Burn wound infections
Anvarinejad et al.	2011	2015	Shiraz	117	115	98.9	[87]	Sputum and throat secretions, wound, blood cultures, urine, trachea, body fluids, Nasocomial infections
Soroush et al.	2002–2007	2016	Tehran	145	59	40.6	[88]	Nosocomial infections- respiratory tract, sterile fluids and catheter tube, CSF, blood, and wound
Alaei et al.	2010–2011	2016	Shiraz	85	45	53	[89]	Including urine, sputum, blood, postoperative wound, cerebrospinal fluid, nasal secretion, and eye secretion
Shaykh Baygloo et al.	2013–2014	2015	Isfahan	10	10	100	[90]	Burns of ICU Patients
Davoudi et al.	2012–2014	2015	Sari-Mazandaran	7	7	100	[41]	Wounds of surgical sites, sputum, tracheal secretions, wound debridement of infected tissue, drainage of mediastinum infected tissues, urine and blood, surgical site infection (SSI), respiratory tract infection, endocarditis, urinary tract infection (UTI), blood Infection and mediastinitis
Khalilzadegan et al.	2013	2016	Tehran	131	30	22.8	[40]	Medical devices of intensive care units

bias was evaluated by looking over begg's funnel plots[45] and asymmetry tests (Egger's regression asymmetry test and Begg's adjusted rank correlation test).[43] All Statistical analyses were conducted using STATA SE version 11.2 (StataCorp, College Station, TX, USA). *P*-values less than 0.05 were considered statistically significant.

Results

A total of 9646 articles were retrieved by database search. Summary of the literature search and study selection was showed in Figure 1. In a secondary screening process, 4391 of the publications were excluded based on title and abstract evaluation, and 491 articles were retained for detailed full-text evaluation. After full-text evaluation, 37 articles (abstract with full-text articles) describing the prevalence of multi-drug resistant *A. baumannii* in Iran were selected for analysis and are presented in Table 1. In the studies included in the analysis, samples included various infectious specimens from both male and female patients of different ages. Most of the studies were conducted in central regions of Iran. Figure 2 shows the distribution of MDR-*A. baumannii* in different parts of Iran. Meta-analysis revealed that the prevalence rate of multi-drug resistance in *A. baumannii* samples is about 72% in Iranian population (95% CI: 0.63–0.80; Figure 3). Between study heterogeneity was high (Cochrane *Q* test, $p < 0.001$, $I^2 = 98.2$). We also tried to assess the prevalence of drug resistance according the locations where samples were collected. Subgroup analysis showed that the prevalence of drug resistance was higher in Isfahan, Mashhad, Mazandaran and Arak (Figure 4) while the prevalence was lowest in Kermanshah. Sensitivity analysis showed that none of included studies can significantly change the overall prevalence (Figure 5). There was a significant asymmetry in the begg′s funnel plot and asymmetry tests showed a statistically significant publication bias (Egger′s test, *p* value < 0.001, Begg′s test, *p* value < 0.001; Figure 6).

Discussion

In the last few years, *A. baumannii* has posed a critical challenge to health care systems and was responsible for increased mortality and morbidity among patients in Iran. Control of *A. baumannii* infections is increasingly difficult due to *its* resistance to different antimicrobial agents, including imipenem, which remains as the drug of choice. Frequency of carbapenem-resistant isolates has also been reported to be on the rise worldwide.[46] The widespread emergence of MDR, Extensive Drug Resistance (XDR)

Figure 2 **Distribution of MDR – *A. baumannii* in different regions of Iran**

and Pandrug Resistance (PDR) *A. baumannii* infections have become a serious problem that have made it difficult to choose an effective antimicrobial regimen for the treatment of *A. baumannii* infections. Screening the antibiotic resistance patterns of this organism over time may provide valuable data with respect to its treatment strategy. This study reviewed systematically the published data up to Jun 2016 and considered the prevalence rate of MDR-AB from different parts of Iran in CLSI-approved studies and provides an overall RF for Iran using meta-analysis.

The prevalence of MDR *A. baumannii* in Iran increased from 50% in 2001–2007 to 74% in 2010–2015, with a mean prevalence of 71%. Conceivable reasons for such increase are: trade among nations, for example, Iran, Turkey and Iraq, which reports the highest number of MDR cases; Uncontrolled accessibility and/or overuse of antimicrobial agents, such as imipenem; Improved surveillance and reporting of MDR cases because of increased awareness of infection control experts and clinical microbiologists concerning imipenem resistance; Use of sensitive techniques for MDR identification in diagnostic labs; A rise in the number of immuno-suppressed chronically ill patients with prolonged hospitalization; Implementation of insurance reform approaches and a sharp rise in the number of hospital beds prompting a more extensive access for Iranian patient population; as well as expanded access to services such as procedures including bronchoscopy, which might prompt an increased rate of inadvertent complication including *A. baumannii* infections in health care centres.[8,25,47] The incidence rate of MDR strains derived in this survey was similar to previously published meta-analysis reporting 74%; and 55% imipenem resistance rate.[48] Our reported rate is slightly higher than that form a prior study reporting 67% in Iraq.[49] However, our reported rate is lower than those reported from neighbouring countries, such as United Arab Emirates (83%),[50]

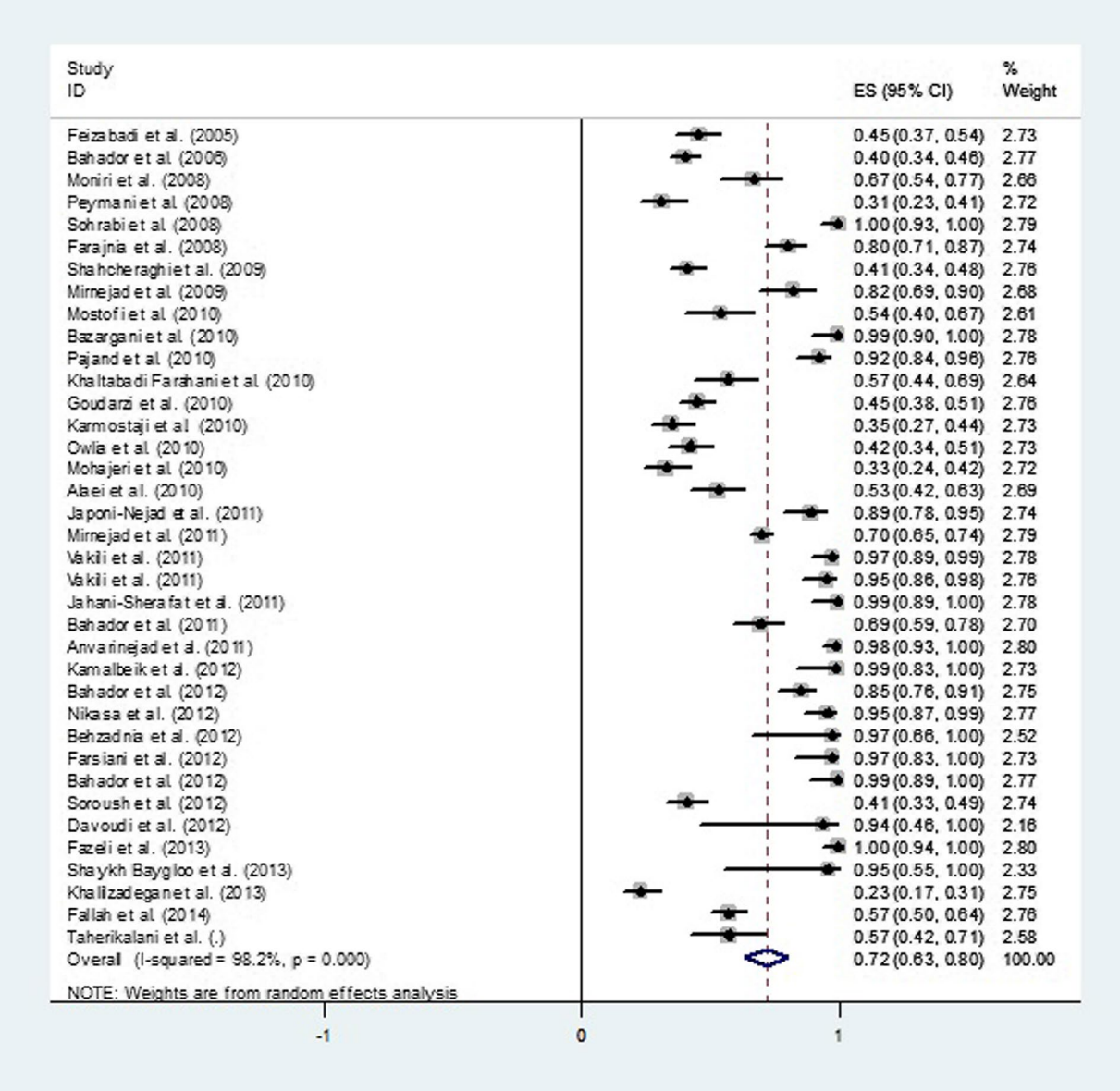

Figure 3 Forest plot of meta-analysis on log prevalence of MDR-AB with 95% CI (Illustration of weighted relative frequency using random effects model for assessing overall prevalence of positive MDR-AB samples)

Kuwait (85%)[51] and Pakistan (100%).[52] Treatment of MDR strains is typically troublesome and causes difficulties for medical personnels.[17] Presently, the antibiotic choice for the treatment of MDR *A. baumannii* infections is likewise restricted and is limited to the use of lipopeptides.[53] One antimicrobial agent of this class is polymyxin B, which in spite of past concerns with respect to its toxicity, has been executed in treatment more frequently.[54] Another lipopeptide antibiotic is colistin, which seems to be effective in the treatment of urinary tract, wound and bloodstream infections.[55] However, its nephrotoxicity is a detriment to its utilization.[53] Although use of this antibiotic class has limitations due to toxicity, they are frequently utilized for the treatment of life-threatening infections.

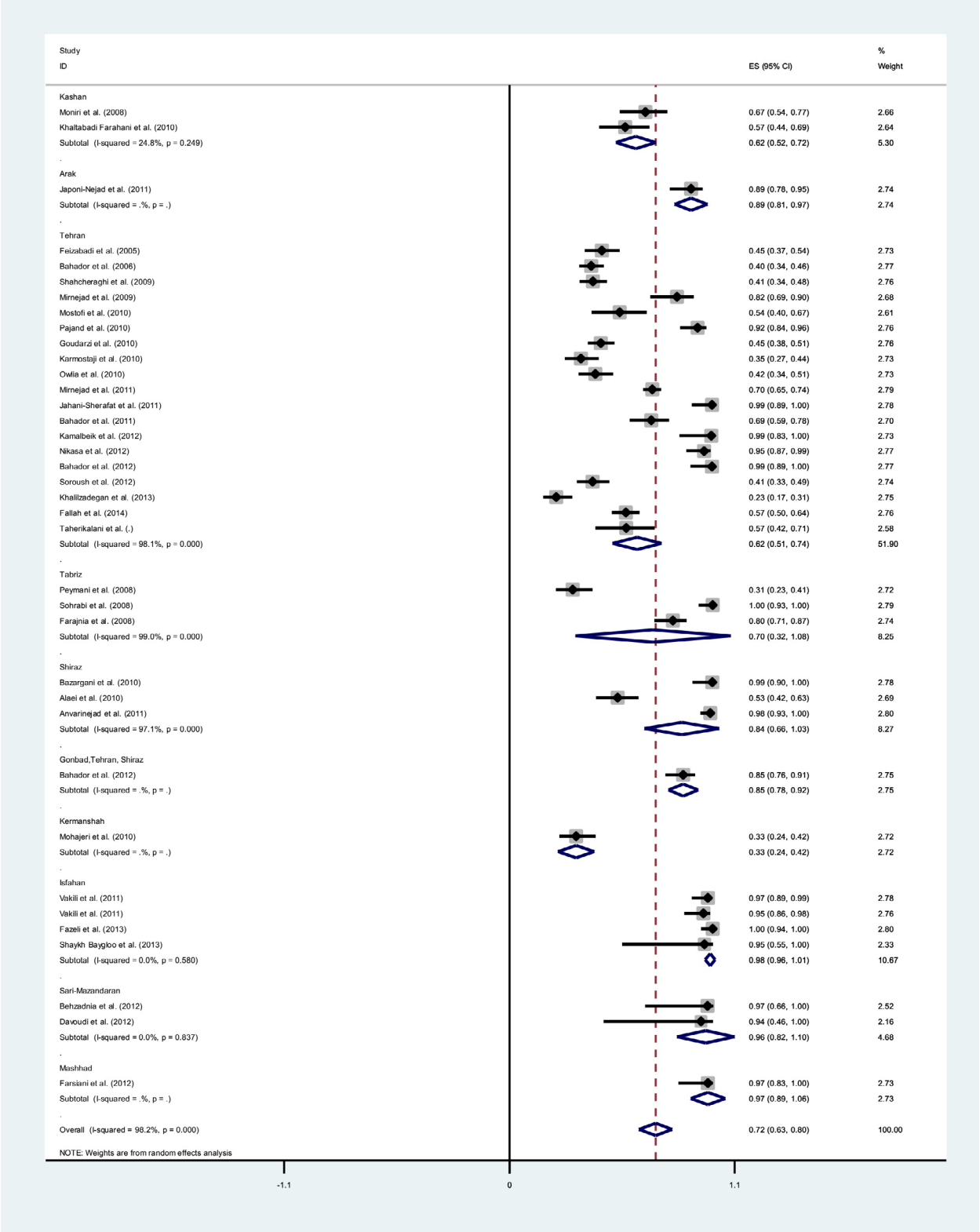

Figure 4 Forest plot of meta-analysis on log prevalence of MDR-AB with 95% CI (based on location)

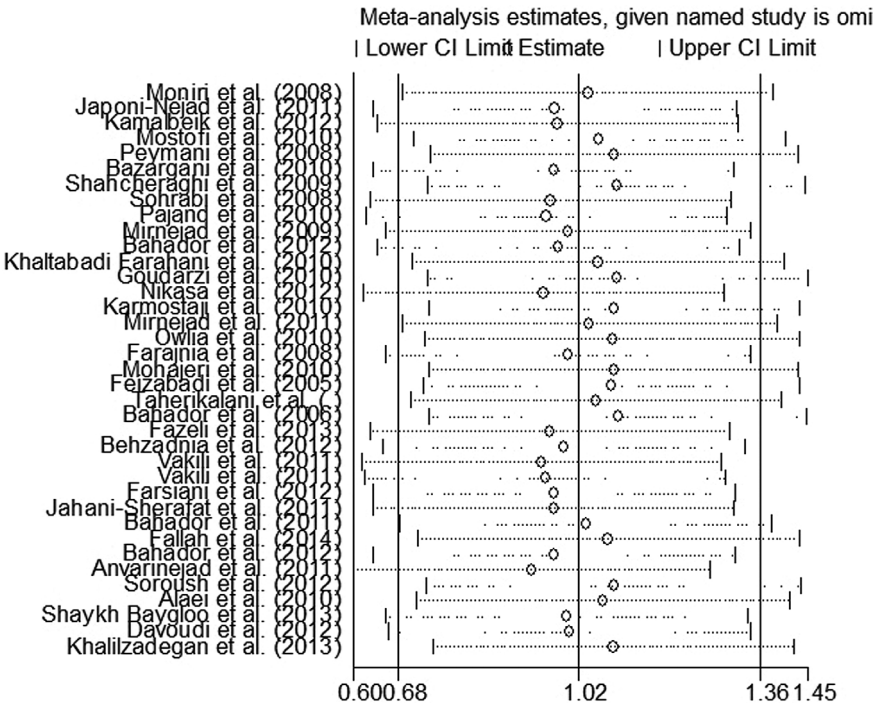

Figure 5 Influence or sensitivity plot of studies included in the systematic review and meta-analysis

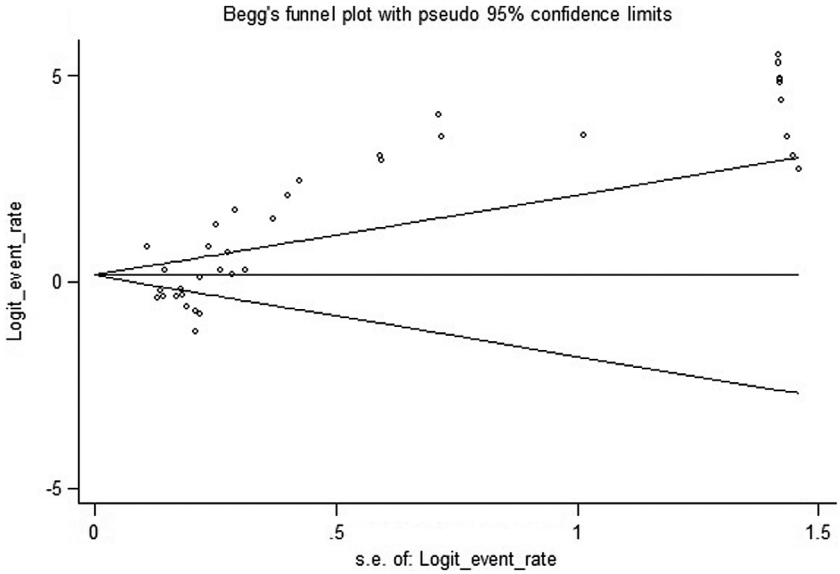

Figure 6 Funnel plot of the relative frequencies (RFs) vs. the standard errors of the Framingham risks in studies that evaluated the positive MDR-AB samples in Iranian patients (with pseudo 95% confidence intervals)

Although polymyxins display good *in vitro* antimicrobial activity against MDR *A. baumannii*, the plasma concentration achieved in patients is low and regrowth is usually observed in time-kill assays. For this reason, monotherapy with polymyxin requires alert.[56] Many researchs on the synergistic effect against MDR *A. baumannii* have been conducted with the utilization of imipenem in combination with aminoglycosides, glycylcyclines, ampicillin, rifampicin, aztreonam, sulbactam and lipopeptides.[17,23,57,58] A previous meta-analysis arrived at the conclusion that different antibiotics in combination could act synergistically against *A. baumannii*.[59] For colistin–glycopeptide and polymyxin–carbapenem combinations, effective synergistic effects were noted for > 70% isolates with relative low toxicity. Compared with monotherapy, combination therapies significantly enhanced bactericidal activity from 8.4–26.4 to 60.3–86.7%.[53]

Our meta-analysis has a few limitations, with most of them being related to those inherent in the available literature. The heterogeneity of information could be because of differences in study plan or methodologies in data collection. In a few studies, it was hard to achieve definitive conclusions because of small sample size and low confounders; this clearly lessens the power of any statistical

analysis. Only a small number of studies met our inclusion criteria, none of which were randomized controlled trials. Subsequently, the quality of information extracted from these studies could not be considered optimal.

In summary, the MDR *A. baumannii* susceptibility profiling highlights the critical need for a comprehensive Iranian national antimicrobial drug resistance survey to monitor *A. baumannii* isolates from all parts of country. It is very obvious that the prevalence of MDR-AB is currently high and on the rise in Iran, particularly for the antibiotics of choice. The complex nature of *A. baumannii* as a pathogen, the diversity of settings in which MDR-AB strains and the growing geriatric population in combination presents a serious challenge to health care facilities, public health and older adults in general. Drug susceptibility testing, establishing advanced diagnostic facilities and continuous monitoring of drug resistance are recommended for prevention and control of MDR-AB.

Contributors

MS contributed to the conception and design of the work; the acquisition, analysis and interpretation of data for the work. EK and AZ-B contributed to data collection and interpretation of data for the work. RR contributed to design of the work, data collection and final approval of the version to be published. AS-A and NA contributed in data analysis, drafting the work and revising it critically for important intellectual content. MS, AZ-B and EK contributed in the revising the draft and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AG-D contributed in revising the article and final approval of the version to be published.

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Conflict of interest

Authors declare that there are no conflict of interests in the present study.

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