Review

# Study of multidrug resistance in prevalent Gram-negative bacteria in burn patients in Iran: A systematic review and meta-analysis

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ABSTRACT

Objectives: Recently, multidrug-resistant (MDR) Gram-negative bacteria (GNB) have become a serious concern causing infections in hospitalised burn patients. This meta-analysis was conducted to detect the prevalence of infections caused by MDR-GNB in hospitalised burn patients in Iran.
Methods: An electronic search was performed using PubMed, Scopus, Web of Science, EMBASE and Iranian databases. Statistical analysis was performed using STATA13. According to the results of the heterogeneity test, a fixed- or random-effects model was used. Publication bias was detected based on Egger's test. Of 1292 articles identified in the initial search, 107 studies were included in this review.
Results: According to the results, the lowest resistance rate was observed in Acinetobacter baumannii and Pseudomonas aeruginosa to colistin, estimated at 21% [95% confidence interval (CI) 2–49%; $I^2 = 97.30\%$] and 27% (95% CI 0–82%; $I^2 = 99.27\%$), respectively. Moreover, the highest rate was to cefepime, estimated 98% (95% CI 93–100%; $I^2 = 88.28\%$) and 87% (95% CI 81–92%; $I^2 = 96.27\%$).
Conclusion: The prevalence of MDR-GNB in Iranian burn patients is very high. Thus, a comprehensive infectious control programme, a reduction in the use of antibiotic prophylaxis, and thorough information regarding antimicrobial resistance patterns is required.

## Contents

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## 1. Introduction

Despite developments in the early treatment of burn wounds, infections remain a great challenge and global health concern for burn patients. According to the physiological condition of burn patients, they are exposed to nosocomial infections more than other hospitalised patients [1]. Considering the role and importance of infections in patient treatment failure, especially for burns, infection control has become an important goal in hospital settings. Uncontrolled infection in burn victims is the main cause of increased mortality and morbidity [2].

According to several reports, Gram-negative bacteria (GNB) such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli* and *Klebsiella* spp. are the most prevalent micro-organisms causing infections in burn hospitals [3,4]. These micro-organisms are important because of their large repertoire of virulence factors and antimicrobial resistance properties [5–7]. In septic patients, the prevalence of multidrug-resistant (MDR) bacteria is a serious concern owing to limited therapeutic options and decreased treatment efficacy. On the other hand, these infections pose a high financial burden on healthcare expenditure of countries such as Iran [8]. Beside other factors such as dehydration or thermal injury that endanger the life of burn victims, infections pose a great challenge for the treatment of such injuries in the clinical setting [9]. Infectious agents are important and threaten the recovery of patients when they become resistant to the most commonly used antimicrobial agents. Owing to the ability of thermal burn injuries to induce some pseudosymptoms of infection such as systematic inflammatory response syndrome (SIRS), hyperpyrexia and immunosuppression, clinical diagnosis of infection is difficult and must be confirmed by the microbiology laboratory [10]. Although *P. aeruginosa* is one of the major infectious agents in burn hospitals in Iran, there are recent documents showing that other GNB such as *Acinetobacter* spp. are emerging in burn centres [11,12].

Considering the importance of epidemiological information related to the pattern of infections and their drug resistance in burn patients, this study was performed to determine the pooled prevalence of MDR-GNB causing burn wound infections in hospitalised patients in Iran based on published studies. This meta-analysis will provide aetiological targets for appropriate antimicrobial prescribing thus reducing antimicrobial misuse, information for the organisation of infection control programmes, and a wider economic quantification.

## 2. Methods

### 2.1. Literature search

A systematic electronic search according to Medical Subject Headings (MeSH) was performed to increase search sensitivity.

A literature search for studies conducted in Iranian hospitalised burns patients published before July 2018 was performed using Web of Science, PubMed, Scopus, EMBASE and Iranian databases such as Iran Medex and Magiran. Moreover, a manual search of relevant publications was performed for additional eligible studies. The search was limited to articles published in English and Persian languages using the keywords 'burn patients', '*Pseudomonas aeruginosa*', '*Escherichia coli*', 'drug resistance' and '*Acinetobacter baumannii*'.

### 2.2. Inclusion and exclusion criteria

Articles fulfilling the following inclusion criteria were included in the meta-analysis: (i) antimicrobial susceptibility pattern, according to Clinical and Laboratory Standards Institute (CLSI) guidelines, of the isolated organisms mentioned; (ii) study included burn patients admitted to Iranian hospital; and (iii) studies published in English or Persian language.

Articles were excluded if they did not report antimicrobial resistance or reported resistance overall. Review articles, conference papers, meta-analyses, articles in abstract form, overlapping studies and duplicate articles were also excluded.

### 2.3. Data collection and definitions

Two authors (AE and NP) independently extracted the following data from each study: name of first author; publication year; study setting; sample size; antimicrobial resistance; study points; and isolated bacteria. Supplementary Tables S1–3 in Supplementary file 1 summarises the characteristics of the included studies for the three investigated bacteria separately. In some articles, susceptibility data were changed to resistance.

### 2.4. Quality assessment of studies

Two authors (AE and FJ) independently evaluated the studies in terms of title and content using a checklist provided by the Joanna Briggs Institute to assess the study quality [13].

### 2.5. Statistical analysis

Stata Statistical Software: Release 13 (StataCorp LP, College Station, TX, USA) was used to obtain pooled estimates and their corresponding 95% confidence interval (CI) and for generating plots. The $I^2$ statistics and the $\chi^2$ test of heterogeneity were used to assess the statistical heterogeneity of the included studies. An $I^2$ > 50% or $P < 0.05$ were considered to demonstrate significant heterogeneity across the articles. Furthermore, a funnel plot based on Eggers's regression test was implemented to evaluate publication bias. According to the results of the heterogeneity test, either a random-effects or fixed-effects method was used to pool the estimates. In addition, subgroup analysis was performed by considering different regions.

## 3. Results

A flow chart of the data extraction process is shown in Fig. 1. The initial search strategy identified 1292 articles. Further evaluation of the titles and abstracts showed that 174 publications were eligible for full-text review. Finally, 107 studies were included in the meta-analysis.

### 3.1. Acinetobacter baumannii

In *A. baumannii*, the lowest rate of resistance was observed to colistin. Among six pooled articles, the prevalence of colistin resistance was estimated to be 21% (95% CI 2–49%). (Fig. 2). The $I^2$ statistics was 97.30%, indicating significant and high heterogeneity
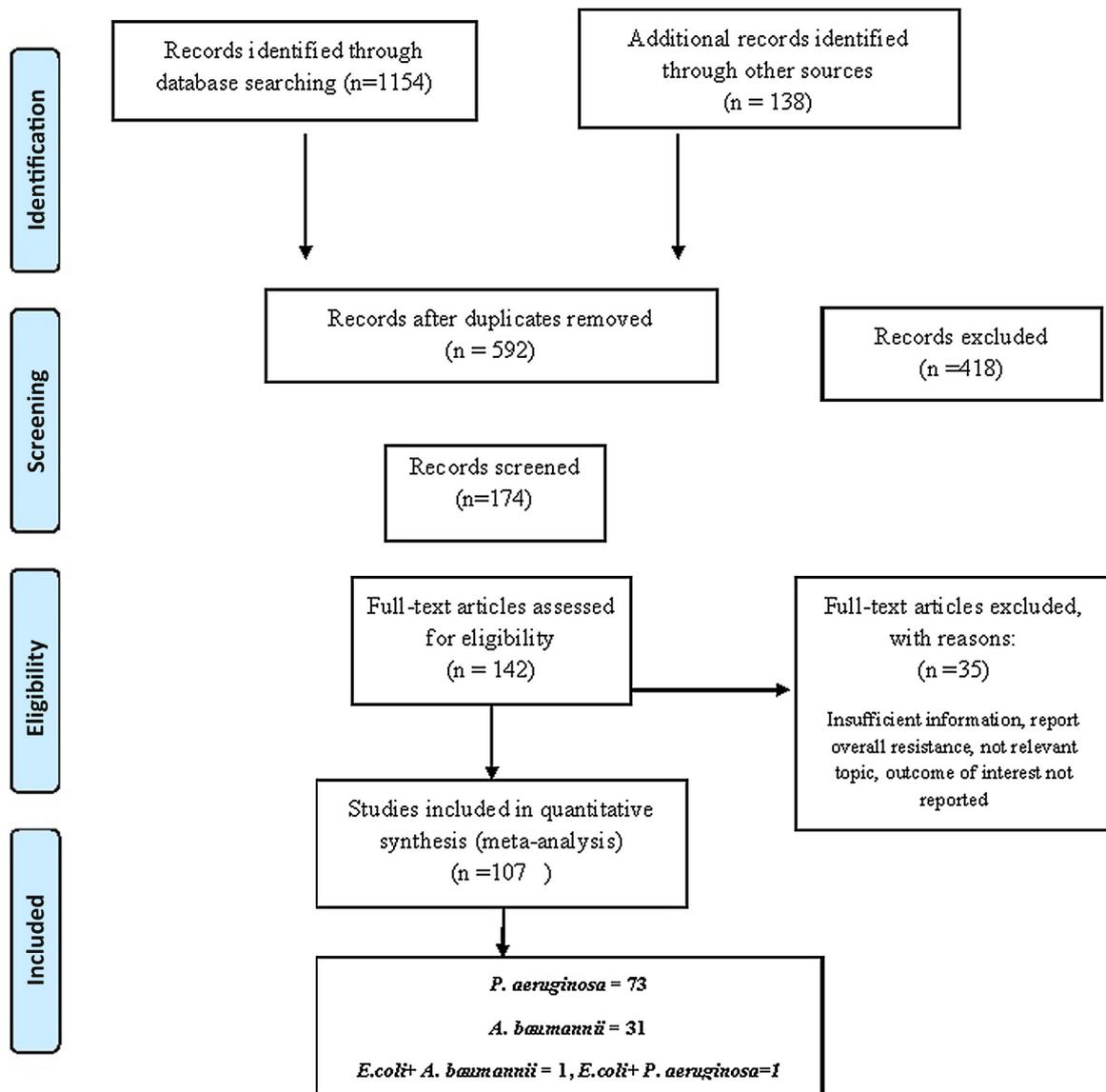
**Fig. 1.** PRISMA flow chart of the systematic literature review and article identification.

($P=0.01$). Some publication bias was detected based on Egger's regression symmetry method ($P=0.04$).

The highest resistance among *A. baumannii* was observed to cefepime. Among 13 pooled articles, the overall prevalence for cefepime was estimated to be 98% (95% CI 93–100%). High and significant heterogeneity ($I^2 = 88.28\%$, $P < 0.001$) was observed in the included articles (Fig. 3), and Eggers's regression method showed no publication bias ($P=0.36$). Other antimicrobial resistance rates are summarised in Table 1, and the related forest plots are shown in Supplementary file 2.
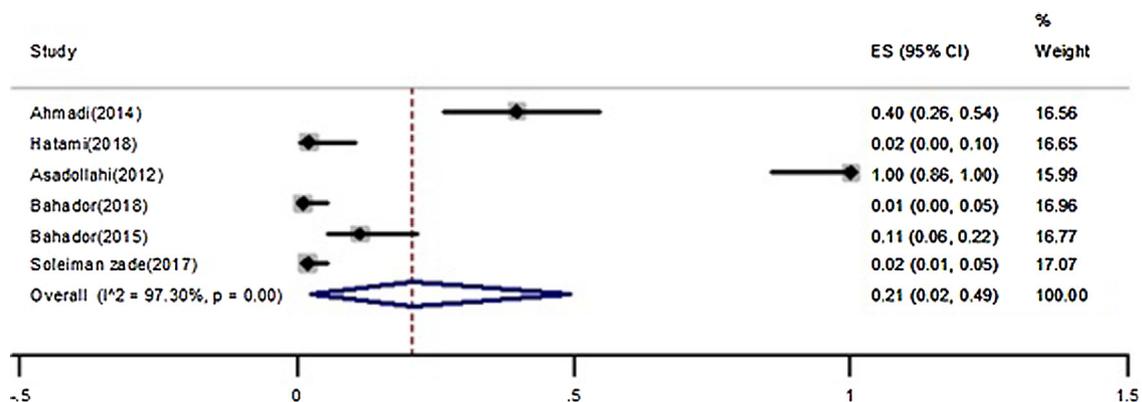


**Fig. 2.** Forest plot for prevalence of colistin resistance in *Acinetobacter baumannii* isolates.
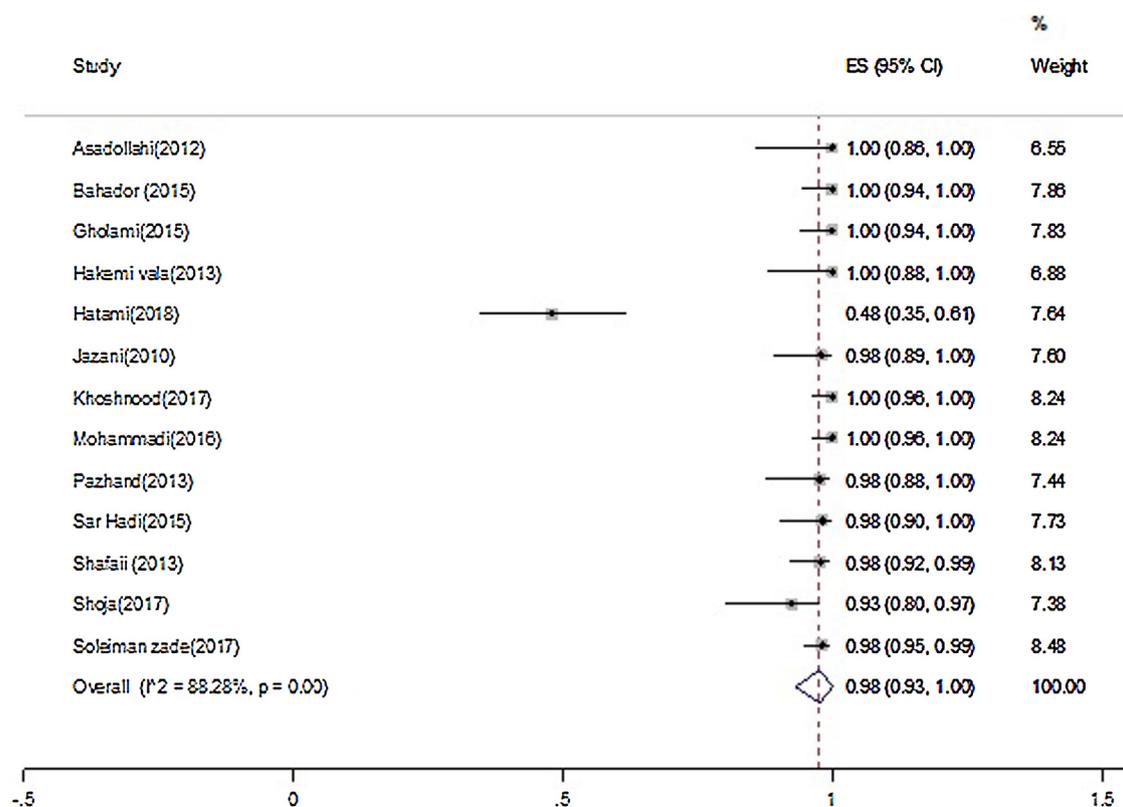
**Fig. 3.** Forest plot for prevalence of cefepime resistance in *Acinetobacter baumannii* isolates.

### 3.1.1. Sensitivity analysis

Owing to the large effect size, a sensitivity analysis was performed omitting the articles by Ahmadi et al. and Asadollahi et al. for colistin resistance [14,15]. Heterogeneity was reduced to 68.40% ($P = 0.01$) and the pooled estimate decreased to 3% (95% CI 0–7%). Excluding the article by Hatami because of the small effect size in cefepime resistance caused a significant and impressive decrease in heterogeneity ($I^2 = 19.50$) [16].

### 3.2. Pseudomonas aeruginosa

According to 29 pooled articles, the highest resistance rate was seen to cefepime and the overall estimation was 87% (95% CI 81–92%). The $I^2$ statistics (96.27%) indicated high and significant heterogeneity ($P < 0.001$) (Fig. 4). A symmetry test did not show any evidence of publication bias ($P = 0.88$).

The pooled estimate on colistin resistance showed the lowest rate of 27% (95% CI 0–82%) among the studied antibiotics (Fig. 5). According to the heterogeneity results, a random-effects model was implemented ($I^2 = 99.27$%) and no evidence of publication bias was found ($P = 0.52$). Table 2 shows the pooled antimicrobial resistance data for *P. aeruginosa*. Related forest plots are shown in Supplementary file 2.

### 3.2.1. Sensitivity analysis

Owing to the large effect size, the article by Goudarzi et al. was excluded, decreasing the pooled estimate and heterogeneity in colistin resistance to 2% (95% CI 0–6%; $I^2 = 80.82$%) [17].

### 3.3. Escherichia coli

Three studies considered *E. coli* resistance to amikacin and gentamicin. There were not enough reports regarding other

**Table 1**
Summary of the prevalence of multidrug resistance in *Acinetobacter baumannii*.

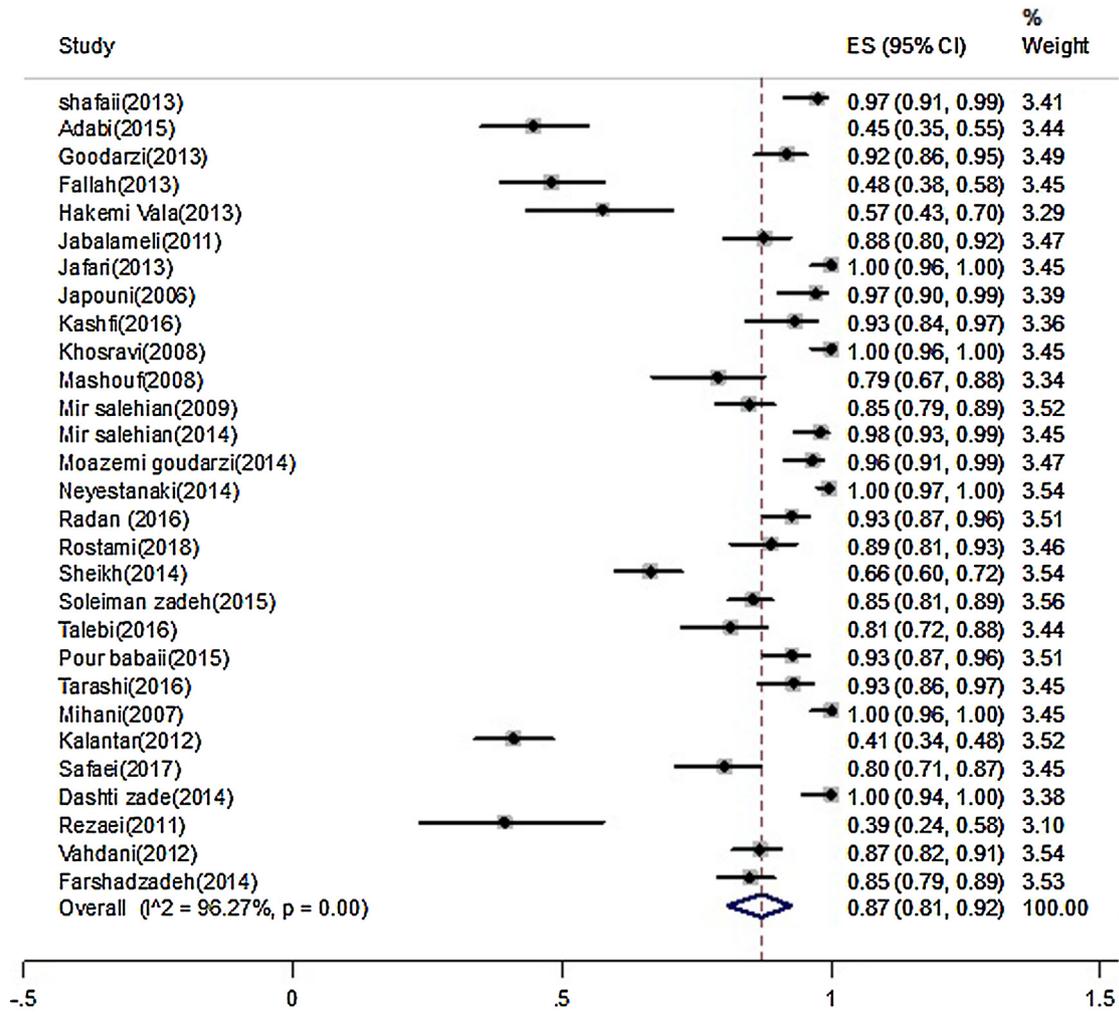| Antimicrobial agent | No. of studies | Prevalence of resistance (%) (95% CI) | $I^2$ (%) | Heterogeneity test | | Egger's test | |
|---|---|---|---|---|---|---|---|
| | | | | Z | P-value | t | P-value |
| Ampicillin/sulbactam | 3 | 31 (15–49) | 79.02 | 5.41 | <0.001 | −1.11 | 0.46 |
| Piperacillin | 18 | 92 (85–97) | 92.82 | 21.58 | <0.001 | −2.36 | 0.03 |
| Cefepime | 13 | 98 (93–100) | 88.28 | 25.82 | <0.001 | −0.65 | 0.53 |
| Ceftazidime | 18 | 94 (88–98) | 90.23 | 25.52 | <0.001 | −1.25 | 0.22 |
| Imipenem | 27 | 79 (68–88) | 96.07 | 16.89 | <0.001 | −1.66 | 0.11 |
| Meropenem | 10 | 91 (78–99) | 94.65 | 13.35 | <0.001 | −1.46 | 0.18 |
| Gentamicin | 20 | 84 (74–91) | 93.34 | 18.69 | <0.001 | −0.01 | 0.99 |
| Tobramycin | 17 | 71 (55–84) | 96.51 | 11.41 | <0.001 | 0.45 | 0.66 |
| Amikacin | 19 | 86 (78–93) | 91.04 | 21.04 | <0.001 | −1.08 | 0.29 |
| Colistin | 6 | 21 (2–49) | 97.30 | 2.71 | 0.01 | 2.85 | 0.04 |
| Ciprofloxacin | 22 | 97 (94–99) | 80.40 | 37.73 | <0.001 | −0.93 | 0.36 |

CI, confidence interval.

**Fig. 4.** Forest plot for prevalence of cefepime resistance in *Pseudomonas aeruginosa* isolates.
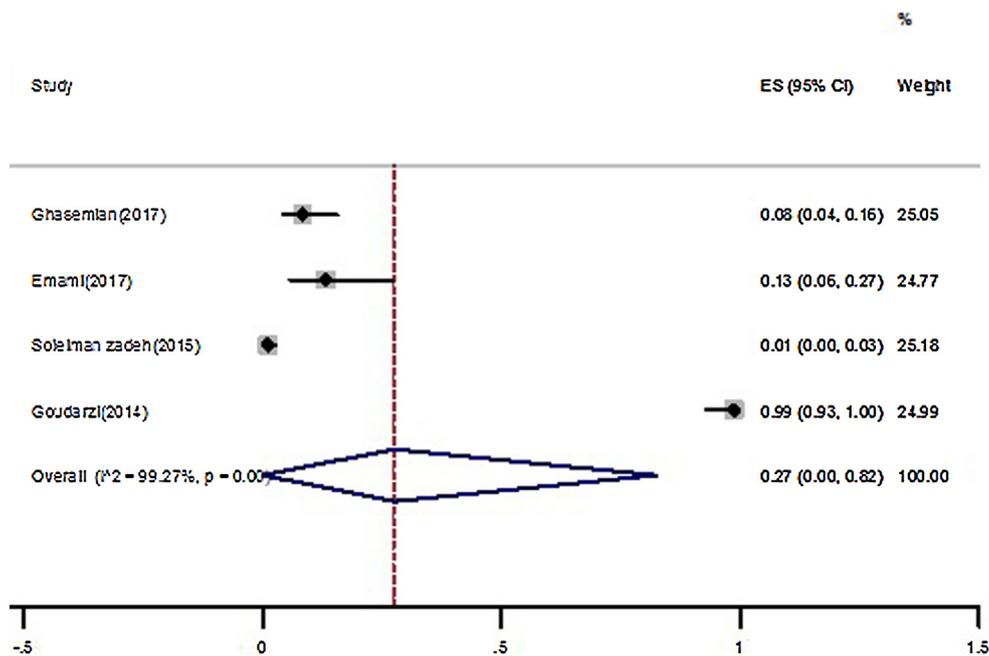


**Fig. 5.** Forest plot for prevalence of colistin resistance in *Pseudomonas aeruginosa* isolates.

**Table 2**
Summary of prevalence rate for multidrug resistance in *Pseudomonas aeruginosa*.

| Antimicrobial agent | No. of studies | Prevalence of resistance (95% CI) | $I^2$ (%) | Heterogeneity test | | Egger's test | |
|---|---|---|---|---|---|---|---|
| | | | | Z | P-value | t | P-value |
| Piperacillin | 30 | 74 (65–82) | 97.12 | 19.37 | <0.001 | −0.14 | 0.88 |
| Cefepime | 29 | 87 (81–92) | 96.27 | 26.16 | <0.001 | −0.15 | 0.88 |
| Imipenem | 64 | 64 (56–72) | 97.80 | 21.54 | <0.001 | 0.18 | 0.86 |
| Meropenem | 40 | 60 (49–71) | 98.27 | 14.11 | <0.001 | 0.66 | 0.51 |
| Gentamicin | 48 | 75 (61–88) | 99.69 | 12.41 | <0.001 | −0.03 | 0.97 |
| Tobramycin | 26 | 84 (61–98) | 99.63 | 4.48 | <0.001 | 7.36 | <0.001 |
| Amikacin | 57 | 75 (63–85) | 99.54 | 15.44 | <0.001 | 0.62 | 0.53 |
| Colistin | 4 | 27 (0–82) | 99.27 | 1.69 | <0.001 | 0.69 | 0.52 |
| Ciprofloxacin | 64 | 77 (67–86) | 99.46 | 17.77 | <0.001 | 1.36 | 0.17 |

CI, confidence interval.

antibiotics. The overall estimate for *E. coli* resistance to amikacin and gentamicin was 44% (95% CI 28–61%) and 66% (95% CI 49–81%), respectively (Figs. 6 and 7).

### 3.4. Subgroup analysis

In the stratified analysis, the antimicrobial resistance of the bacterial isolates was shown according to difference provinces of Iran. The results are shown in Supplementary Tables S4 and S5 in supplementary file 2. Figs. 8 and 9 show the distribution of highest and lowest resistance in different regions of Iran. According to these maps, different resistant rates are seen in Iran, indicating the lack of a comprehensive infection control programme that should be considered in health policy.

### 4. Discussion

This study was established to evaluate antimicrobial resistance in prevalent GNB in burn hospital settings in Iran. According to the current meta-analysis, the pooled prevalence of colistin resistance in *A. baumannii* and *P. aeruginosa* was 21% and 27%, respectively. These data indicate the lowest rate of colistin resistance among isolates in comparison with other common antibiotics. Although the colistin resistance rate in Iran is low, in comparison with nearby countries it is at the high-risk level. This rate can be alarming for eliminating the last appropriate drug choice in MDR-GNB infections in our country.

Similar to the current findings, other retrospective studies conducted in bordering countries (Turkey and Iraq) and in South Africa detected colistin as the most active drug against *A. baumannii*, with a low resistance rate of this organism against this antibiotic [18–20]. According to the results in Pakistan regarding antimicrobial resistance among GNB isolated from burn patients, the colistin resistance rate was low, estimated at 1.28% [21]. In contrast to the current study, a study in Egypt evaluating the aetiological agents of burn wound infections indicated low resistance in GNB to imipenem and ciprofloxacin [22]. Similar articles in industrial countries showed similar results compared with our analysis. In developed countries such as the USA and the UK, colistin is an effective choice drug and no resistance against it is observed [23,24].

Pooled evidence of drug resistance for *A. baumannii* and *P. aeruginosa* to cefepime reported 98% and 87% resistance, respectively, which was the highest resistance rate compared with other antibiotics. These findings are similar to several other studies in Pakistan, Iraq, India and Egypt [22,25–27]. An evaluation of other studies showed that the risk of cefepime resistance in South Asia and Africa is greater than other regions.

According to the current analysis, unfortunately it appears that the antimicrobial resistance of nosocomial infection isolates to commonly used antibiotics in Iranian burn units is higher than in other countries. Several factors may contribute to this situation: (i) overuse and uninterrupted prescribing of one group of antibiotics for a long time, as use of antibiotics empirically for a long time
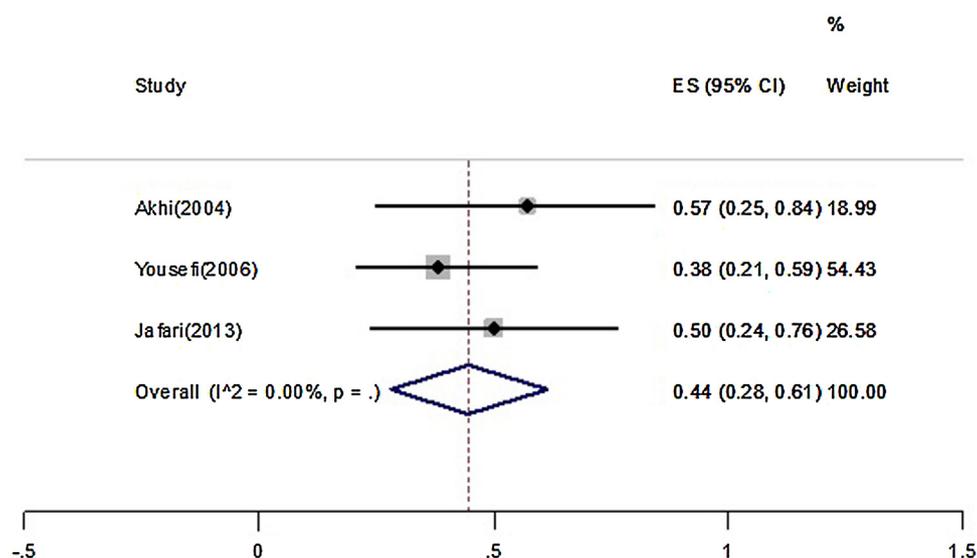


**Fig. 6.** Forest plot of prevalence of amikacin resistance in *Escherichia coli* isolates.
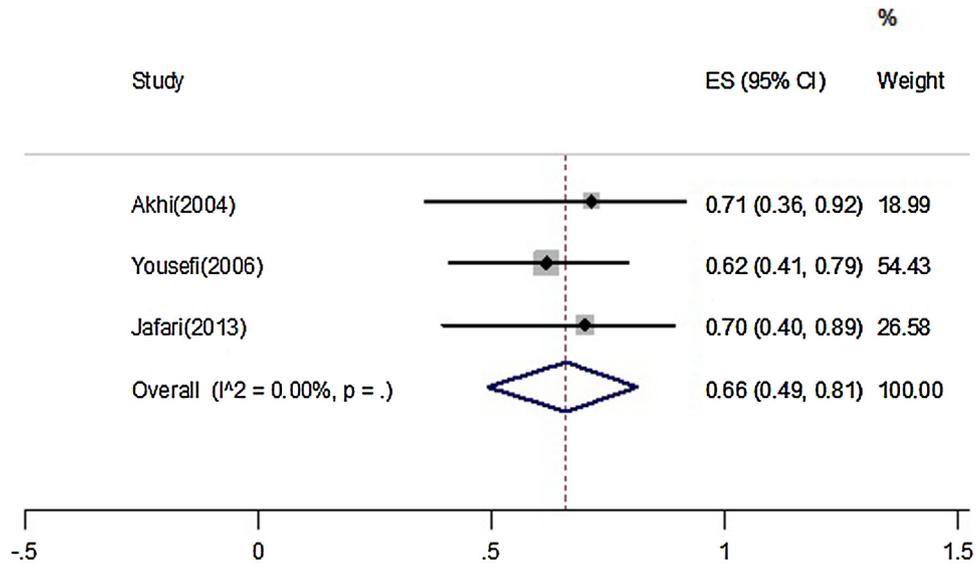
**Fig. 7.** Forest plot for prevalence of gentamicin resistance in *Escherichia coli* isolates.
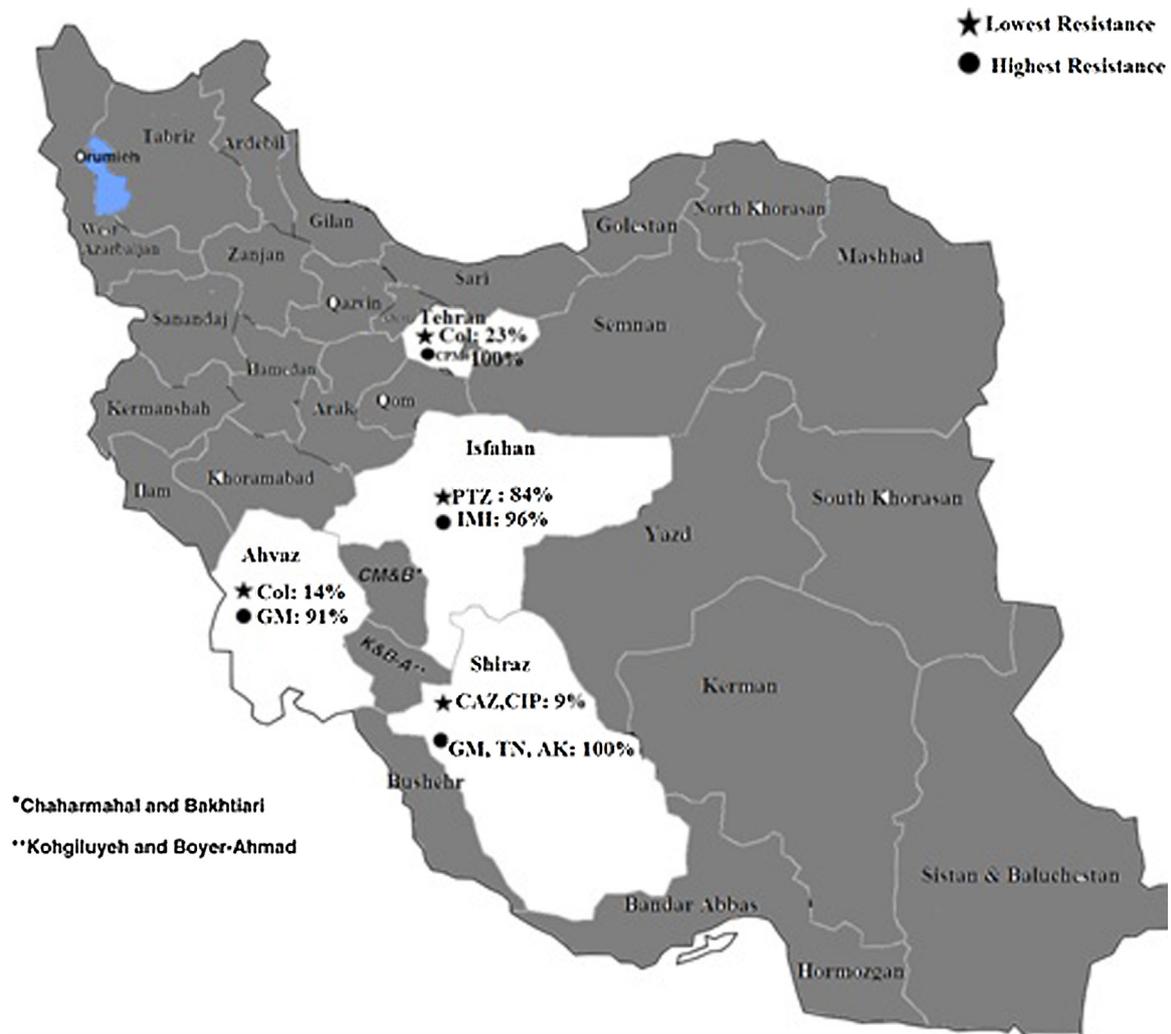


**Fig. 8.** Distribution of multidrug resistance in *Acinetobacter baumannii*. Col, colistin; IMI, imipenem; GM, gentamicin; *CAZ*, ceftazidime; CIP, ciprofloxacin; TN, tobramycin; AK, amikacin; PTZ, piperacillin/tazobactam; CPM, cefepime.
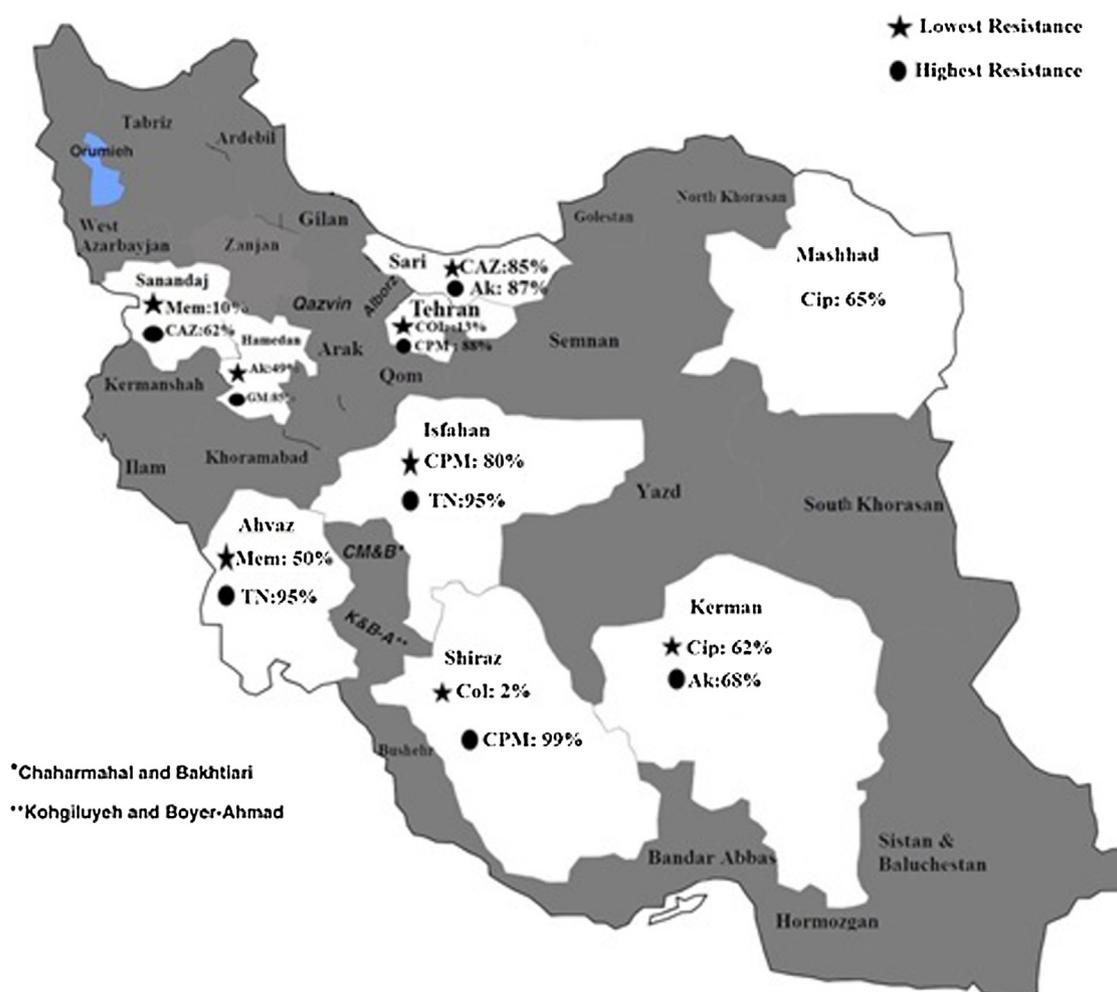
**Fig. 9.** Distribution of multidrug resistance in *Pseudomonas aeruginosa*. COL, colistin; Mem, meropenem; GM, gentamicin; CAZ, ceftazidime; Cip, ciprofloxacin; TN, tobramycin; Ak, amikacin; CPM, cefepime.

without following antimicrobial stewardship rules and changing the orders will increase the risk of resistant strains in a hospital; (ii) using prophylactic antibiotics in unnecessary situations (first 3 days of new burn cases); (iii) misuse of antibiotics in inappropriate bacterial infections; (iv) lack of financial support to establish an infection control programme; (v) insufficient information about local antibiotic resistance patterns; (vi) overuse of broad-spectrum antibiotics owing to their low price, which promotes resistance; and (vii) infrastructure of burn hospitals (lack of standard facilities in primitive settings or heavy work load). Moreover, ignoring hand-washing and lack of knowledge about the importance of hand hygiene as the simplest and low cost action in infection control, keeping infected patients in multi-bed rooms and not considering the antimicrobial stewardship programme are other factors influencing the increased risk of spread of MDR infections in burn hospitals [28,29].

Despite major advances in the treatment of burn patients, nosocomial infections, especially MDR forms, remain the most significant complication and are considered a major threat for the health of burn victims. Thus, having proper regulations and guidance will help us to improve patient surveillance.

Moreover, considering an antimicrobial stewardship programme could be useful to select an appropriate empirical antibiotic therapy regimen. In the current meta-analysis, significant and statistical heterogeneity was found among the included studies, whilst it was reduced in the subgroup analyses. This heterogeneity could be due to several reasons. The first and most important is the diversity of antimicrobial susceptibility testing methods, i.e. disk diffusion, microdilution, Etest, minimum inhibitory concentration (MIC). Bias in results may depends on different quality of test drugs produced by different pharmaceutical companies. Another reason for this bias could be attributed to lack of standard data reporting in different studies, whilst in some studies it was hard to identify the sample size clearly. This reduces the power of any statistical test. The main limitation of the current study that should be considered in interpreting the results is the lack of relevant data in some parts of country. Therefore, these findings do not accurately represent the prevalence rate in Iran. Also, owing to incomplete information, additional subgroups were missing such as age, sex and burn percentage.

In conclusion, the current meta-analysis showed high antimicrobial resistance in Iranian burn patients causing an increasing rate of mortality and morbidity, which is a serious problem. Therefore, special attention is needed for infection control programmes, which consist of hand hygiene, training, education and implementation of programmes, availability and monitoring of agreements with local antimicrobial agent guidelines, and development of antimicrobial stewardship programmes in burn centres.

## Funding

**Competing interests**

None declared.

**Ethical approval**

Not required.

**Appendix A. Supplementary data**

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jgar.2019.04.017.

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