



Prevalence of nosocomial infections in Iran: A systematic review and meta-analysis

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Abstract

Background: Nosocomial infections represent a serious public health concern worldwide, and, especially, in developing countries where, due to financial constraints, it is difficult to control infections. This study aimed to review and assess the prevalence of nosocomial infections in Iran.

Methods: Different databases were searched between January 2000 and December 2017. To determine the pooled prevalence, the stochastic DerSimonian-Laird model was used, computing the effect size with its 95% confidence interval. To examine the heterogeneity among studies, the I² test were conducted. The reporting of observational studies in epidemiology (STROBE) checklist was used to assess the methodological quality of observational studies. To further investigate the source of heterogeneity, meta-regression analyses stratified by publication year, sample size and duration of hospitalization in the hospital were carried out.

Results: 52 studies were included. Based on the random-effects model, the overall prevalence of nosocomial infection in Iran was 4.5% [95% CI: 3.5 to 5.7] with a high, statistically significant heterogeneity (I²=99.82%). A sensitivity analysis was performed to ensure the stability results. After removing each study, results did not change. A cumulative meta-analysis of the included studies was performed based on year of publication and the results did not change. In the present study, a high rate of infections caused by *Klebsiella pneumoniae* (urinary tract, respiratory tract, and bloodstream infections) was found.

Conclusion: Preventing and reducing hospital infections can significantly impact on reducing mortality and health-related costs. Implementing ad hoc programs, such as training healthcare staff on admission to the hospital, may play an important role in reducing infections spreading.

Keywords: Nosocomial infections, Prevalence, Iran, Systematic review, Meta-analysis, Hospital

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Introduction

Nosocomial infections (NIs) represent a serious public health concern worldwide (1), and, especially, in developing countries where, due to financial constraints, it is difficult to control (2,3). Increased prevalence of NIs in some cases leads to patient's arbitrary use of drugs, causing serious health hazards as well as other problems such

as drug resistance and death in patients (4). Worldwide, about 8.7% of hospitalized patients are at risk of exposure to NIs which considered as hospital-acquired infections and can complicate certain conditions such as cancer, organ transplant, and surgery, and also increasing mortality rate. As such, NIs generate a high societal burden, taking

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↑What is "already known" in this topic:

Nosocomial infections (NIs) represent a serious public health concern worldwide. Increased prevalence of NIs in some cases leads to patient's arbitrary use of drugs, causing serious health hazards as well as significant problems such as drug resistance and death in patients.

→What this article adds:

This study aimed to inform and assess the prevalence of NIs in Iran using a meta-analytic approach. Based on the random-effects model, the overall prevalence of NIs in Iran was 4.5%. Proper training of healthcare staff in hospital, can play an important role in reducing NIs spreading in Iran.

into account the costs for treatment, the increased length of hospital stay and the related mental and emotional stress (5).

Due to the wide variation of health-care systems in different countries, numerous reports have reported varying nosocomial infection rates (6,7). The World Health Organization (WHO) carried out an epidemiological study conducted in 14 countries worldwide and found that the overall prevalence of NIs was 8.7% (ranging from 5.0% in North America and in Europe to 40.0% in Asia, Latin America, and Sub-Saharan Africa) (7). The knowledge of the epidemiology of NIs is crucial in establishing programs for controlling this acquired infection in hospitals, implementing effective and reliable plans (8).

Iran represents one of the developing countries, which faces with the issue of NIs imposing a high economic onus, in terms of high costs annually for the Ministry of Health (MoH) and private hospital managers. Several studies have been performed in different parts of the country related to the epidemiology of nosocomial infections. These studies can be valuable for healthcare workers and managers in developing an effective control program. This study aimed to review and assess the prevalence of NIs in Iran using a meta-analytic approach.

Methods

Literature search

The results and their analysis in this study were reported according to the PRISMA guidelines (Appendix 1) (9). Embase, PubMed/MEDLINE via Ovid, Web of Science, Scopus and Google Scholar as well as national Iranian databases, including SID, Magiran, and Irandoc, with medical subject headings (MeSH) terms and a proper use of keywords. The search strategy was as follows: (Nosocomial Infections OR Hospital Infections OR Healthcare Associated Infections OR Cross Infections) AND Iran. Articles written in Farsi and English were searched and a time filter (between January 2000 and December 2017) applied. Reference lists of articles as well as national and international conferences related to the topic were also searched.

Inclusion and exclusion criteria

Inclusion criteria were: 1) population-based observational studies reporting the prevalence of NIs, 2) cross-sectional, retrospective and case-control studies, and 3) pertinent studies with clear and detailed data. Case reports, case series, letters to editor, editorials, commentaries, reviews and clinical trials as well as studies not calculating the prevalence of NIs, as well as studies not calculating the prevalence of NIs were excluded.

Data extraction

From included papers, two authors independently extracted following data: first author, year of publication, sample size, number of positive cases detected, age, region, the geography of the study, study design, and prevalence rate. Disagreement between them was solved through discussion or including a third person as a judge.

Quality of studies

To check the methodological quality of included studies, the strengthening the reporting of observational studies in epidemiology (STROBE) checklist was used (10), categorizing the studies into three groups of high, medium and low quality.

Statistical analysis

To determine the pooled prevalence, the stochastic DerSimonian-Laird model was used, computing the effect size with its 95% confidence interval (CI) and pictorially representing it with a Forest plot. To examine the heterogeneity among studies, the I^2 test were conducted (11). To further investigate the source of heterogeneity, meta-regression analyses stratified by publication year, sample size and duration of hospitalization in the hospital were carried out. The sensitivity analysis was performed to ensure the stability and robustness of results. Subgroup analyses were performed based on study quality, geographic areas, sample size, year of publication, type of infection, and hospital wards. The cumulative meta-analysis was performed based on year of publication. Egger's test for publication bias was carried out (12). All analyses were performed using the commercial software Comprehensive Meta-Analysis Ver.2 (Biostat, NJ, USA). All figures with $p < 0.05$ were considered statistically significant.

Results

Selected studies

Finally, after an initial search, removing duplicates and checking the title and abstract of studies, 52 studies were selected based on inclusion and exclusion criteria (13-64). Fig. 1 shows the process of finding and selecting studies.

The total sample size consisted of 8,989,980 subjects. Table 1 shows the main characteristics of the included studies.

The overall prevalence of nosocomial infections in Iran

Based on the random-effects model, the overall prevalence of NIs in Iran was 4.5% [95% CI: 3.5 to 5.7] with a high, statistically significant heterogeneity ($I^2=99.82$). Fig. 2 shows the overall prevalence.

Sensitivity analysis

A sensitivity analysis was performed to ensure the stability results. After removing each study, results did not change. Appendix 2 shows the sensitivity analysis.

Cumulative meta-analysis

A cumulative meta-analysis of the included studies was performed based on year of publication and the results did not change. Appendix 3 shows the cumulative meta-analysis.

Sub-group analysis

Table 2 shows the results of the different sub-group analyses according to the quality of studies, geographic regions, sample size, year of publication, type of infection, and hospital wards.

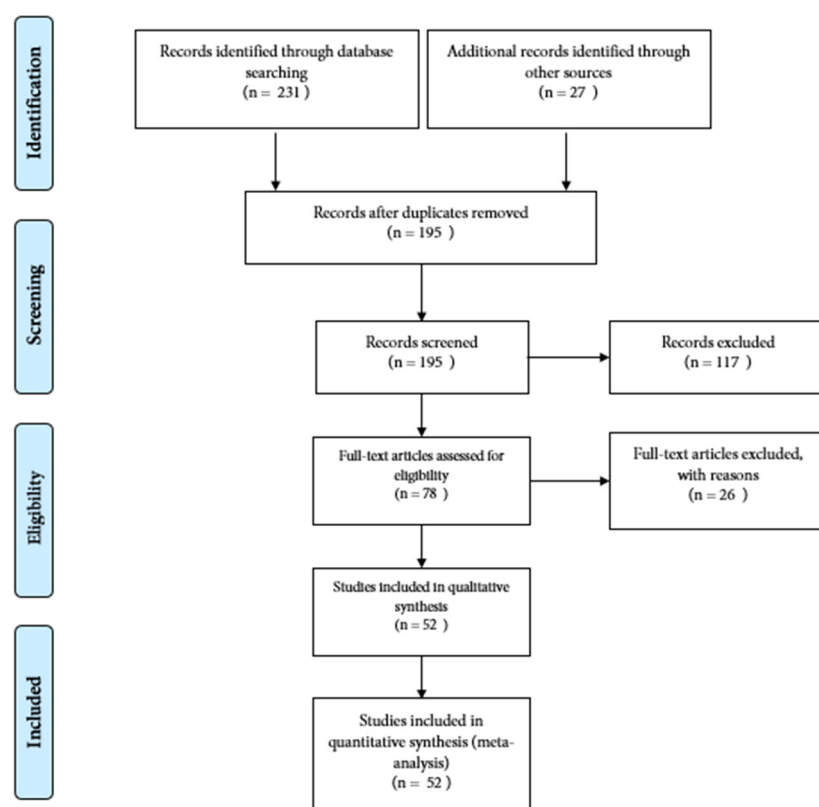


Fig. 1. Flowchart of the present systematic review and meta-analysis

Meta-regression

Table 3 shows the results of the meta-regression analysis.

Publication bias

Egger's test was carried out to assess publication bias (Fig. 3). An evidence of publication bias was found ($p=0.00$)

Table 1. The main characteristics studies included

| First Author | Year | Sample | Average Length of Stay | Common infection | Place | Common Bacteria | Hospital unit | Quality study |
|--------------------|------|---------|------------------------|-------------------------|----------|-----------------------|--------------------|---------------|
| Hajibagheri | 2003 | 160 | 16 | Pneumonia | Sanandaj | Klebsiella pneumoniae | NA | High |
| Askarian | 2003 | 170 | 19 | wound infection | Shiraz | NA | NA | High |
| Askarian | 2003 | 1483 | 7 | Surgical Site Infection | Shiraz | NA | Surgery department | low |
| Sadeghzadeh | 2005 | 150 | NA | Urinary tract infection | Zanjan | Escherichia coli | ICU | High |
| Soltani Arabshahi | 2005 | 810 | 17 | Surgical Site Infection | Tehran | NA | Surgery department | Medium |
| Rahbar | 2005 | 6492 | NA | Bloodstream infections | Orumieh | Staphylococcus | Neonatal ward | Medium |
| Sadeghifard | 2006 | 5572 | NA | Urinary tract infection | Elam | Escherichia coli | Surgery department | Medium |
| Ekrami | 2007 | 182 | NA | wound infection | Ahvaz | Pseudomonas | NA | Medium |
| Ghazvini | 2008 | 971 | 12 | Bloodstream infections | Mashhad | Staphylococcus | NICU | Medium |
| Lahsaiezadeh | 2008 | 2667 | NA | Surgical Site Infection | Shiraz | NA | Surgery department | High |
| Ghorban Alizadegan | 2008 | 3974 | 2 | Respiratory Infection | Tehran | Staphylococcus | ICU | Medium |
| Hassanzadeh | 2009 | 89 | 16 | Urinary tract infection | Shiraz | Pseudomonas | ICU | High |
| Asl | 2009 | 102 | 17 | Pneumonia | Tehran | Staphylococcus | PICU | Medium |
| Mohammadimehr | 2009 | 165 | 20 | Pneumonia | Tehran | Klebsiella pneumoniae | NA | Medium |
| Amini | 2009 | 691 | 27 | Respiratory Infection | Tehran | Acinetobacter | ICU | Medium |
| Sohrabi | 2009 | 23816 | NA | Urinary tract infection | Shahrod | Escherichia coli | ICU | Medium |
| Darvishpour | 2010 | 270 | NA | NA | NA | Enterobacter | ICU | High |
| Aletayyeb | 2010 | 1604 | 16 | Pneumonia | Ahvaz | Klebsiella pneumoniae | Neonatal ward | Medium |
| Nadi | 2011 | 353 | 4 | Pneumonia | Hamadan | Klebsiella pneumoniae | ICU | Medium |
| Tabatabaei | 2011 | 428 | 23 | Urinary tract infection | Tehran | Escherichia coli | PICU | High |
| Amini | 2011 | 691 | NA | Pneumonia | Tehran | Acinetobacter | ICU | Medium |
| Ghorbani | 2011 | 772 | NA | Urinary tract infection | Ahvaz | Pseudomonas | ICU | Medium |
| Askarian | 2011 | 4013 | NA | Urinary tract infection | Shiraz | NA | NA | Medium |
| Larypoor | 2011 | 21054 | NA | Urinary tract infection | Qom | Escherichia coli | ICU | low |
| Masoumi Asl | 2011 | 6616520 | NA | Urinary tract infection | NA | Pseudomonas | NA | Medium |
| Mobaien | 2012 | 353 | NA | Urinary tract infection | Hamadan | Staphylococcus | ICU | High |
| Soltani | 2012 | 464 | NA | Bloodstream infections | Tehran | Staphylococcus | ICU | Medium |
| Alaghehbandan | 2012 | 677 | 21 | NA | Tehran | Pseudomonas | NA | High |
| Pourakbari | 2012 | 1497 | 8 | Respiratory Infection | Tehran | Staphylococcus | Children's section | low |
| Barak | 2012 | 3254 | 27 | Sepsis | Ardabil | Klebsiella pneumoniae | NICU | Medium |
| Riahin | 2012 | 3400 | NA | Surgical Site Infection | Qom | Staphylococcus | Surgery department | Medium |

Table 1. Cntd

| | | | | | | | | |
|----------------|------|---------|----|-------------------------|------------|-----------------------|--------------------|--------|
| Askarian | 2012 | 3450 | NA | Bloodstream infections | Shiraz | NA | Surgery department | Medium |
| Assar | 2012 | 9407 | NA | Urinary tract infection | Ahvaz | Enterobacter | ICU | Medium |
| Zahraei | 2012 | 1879356 | NA | Urinary tract infection | NA | NA | ICU | low |
| Askarian | 2013 | 4013 | NA | Urinary tract infection | Shiraz | NA | NA | low |
| Abdoli Oskouie | 2013 | 7744 | 4 | Urinary tract infection | Tabriz | Staphylococcus | NICU | Medium |
| Akbari | 2013 | 25776 | 22 | Respiratory Infection | Orumieh | Escherichia coli | ICU | High |
| Masoumi Asl | 2013 | 47380 | NA | Urinary tract infection | NA | Escherichia coli | Burn unit | low |
| Hamedi | 2014 | 811 | NA | Urinary tract infection | Mashhad | Pseudomonas | PICU | low |
| Hoseini | 2014 | 3129 | 10 | Pneumonia | Tabriz | Staphylococcus | NICU | High |
| Behzadnia | 2014 | 34556 | NA | wound infection | Mazandaran | Pseudomonas | NA | Medium |
| Davoudi | 2014 | 57122 | 8 | wound infection | Mazandaran | Pseudomonas | Burn unit | low |
| Shakib | 2015 | 750 | 2 | NA | Sanandaj | Klebsiella pneumoniae | ICU | low |
| Basiri | 2015 | 1000 | 13 | Bloodstream infections | Hamadan | Escherichia coli | NICU | Medium |
| Shojaei | 2015 | 12221 | NA | Surgical Site Infection | Qom | Pseudomonas | ICU | low |
| Lavakhamseh | 2015 | 32400 | NA | Urinary tract infection | Sanandaj | Escherichia coli | Woman's ward | Medium |
| Salmanzadeh | 2015 | 15779 | NA | Surgical Site Infection | Ahvaz | Staphylococcus | ICU | low |
| Bijari | 2015 | 36222 | NA | Pneumonia | NA | Klebsiella pneumoniae | ICU | low |
| Tabatabaei | 2015 | 16140 | NA | Respiratory Infection | Zahedan | Acinetobacter | ICU | High |
| Lavakhamseh | 2015 | 32400 | NA | Urinary tract infection | Sanandaj | E. coli | Woman's ward | Medium |
| Darvishpoor | 2016 | 1300 | 2 | Surgical Site Infection | Torbat | NA | NA | low |
| Kazemian | 2016 | 62601 | NA | Urinary tract infection | Ardabil | Escherichia coli | ICU | High |
| Falahi | 2017 | 35979 | NA | Pneumonia | Mashhad | Acinetobacter | ICU | High |

Discussion

This study was a comprehensive study on the prevalence of NIs in Iran using a systematic review and meta-analytic approach. The prevalence of NIs in Iran was found as 4.5% (95% CI: 3.5-5.7). Hospital infection rates

range between 3.5% and 12% in developed countries and between 5.7% and 19.1% in developing countries (7), calling for the urgent need of better allocating resources and implementing a program for controlling infections (65). Differences in NIs rates among countries may not

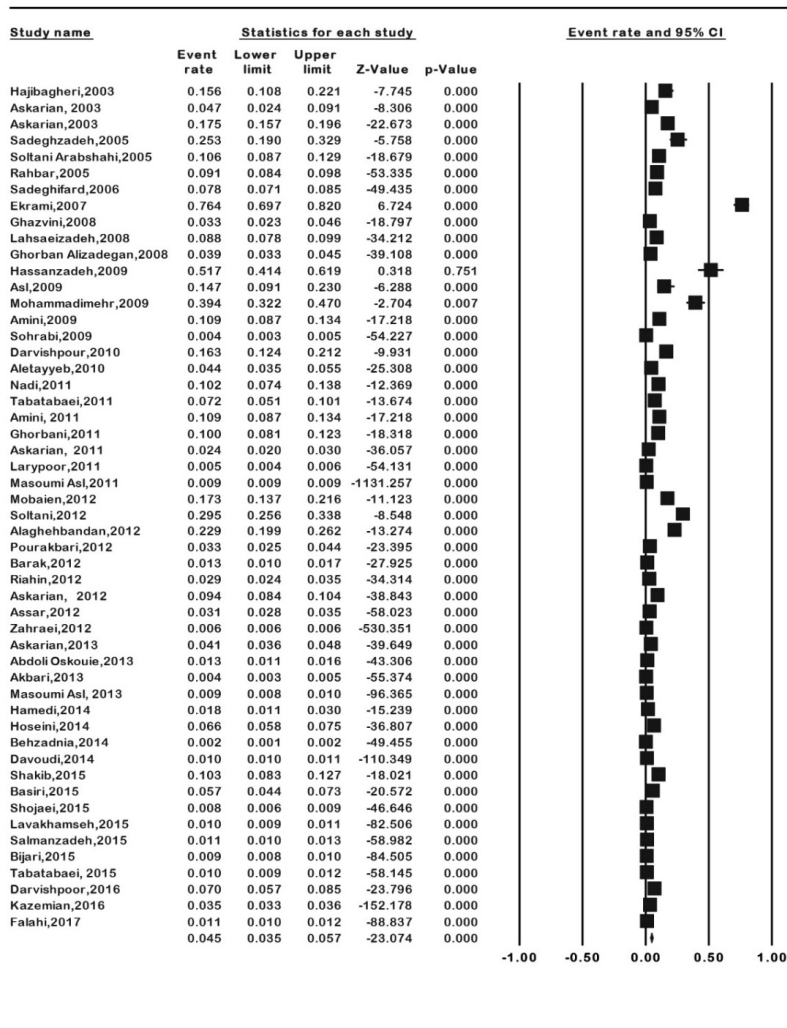


Fig. 2. The forest plot of the overall prevalence of nosocomial infections in Iran

Table 2. The results of sub-group analyses

| Variables | No. studies | Prevalence% (95% CI) | I2 (%) | p | No. participants |
|------------------------------------|-------------|-------------------------|--------|--------|------------------|
| Quality of studies | | | | | |
| High | 14 | 7.2% (4-12.6) | 99.54% | 0.0001 | 148589 |
| Medium | 25 | 5.2% (2.9-9) | 99.82% | 0.0001 | 6762403 |
| Low | 13 | 2% (1.1-3.6) | 99.75% | 0.0001 | 2078988 |
| Regional | | | | | |
| Center | 13 | 7.1% (3.2-15) | 99.43% | 0.0001 | 46174 |
| East | 8 | 1.4 (0.9-2.2) | 98.49% | 0.0001 | 147639 |
| North | 2 | 0.4% (0.1-2.4) | 99.42% | 0.0001 | 91678 |
| South | 12 | 8.8% (4.8-15.7) | 99.41% | 0.0001 | 43629 |
| West | 13 | 5.7% (3.6-8.8) | 99.34% | 0.0001 | 117334 |
| Several regional | 4 | 1.5% (1.1-2.1) | 99.85% | 0.0001 | 8543526 |
| Sample size | | | | | |
| ≤1500 | 24 | 13.3% (9.6-18.2) | 97.79% | 0.0001 | 14339 |
| >1500 | 28 | 17% (13-22) | 99.84% | 0.0001 | 8975641 |
| Year of publication | | | | | |
| 2000-2005 | 6 | 12.8% (8.8-18.2) | 96.00% | 0.0001 | 9265 |
| 2006-2011 | 19 | 7.6% (3.7-14.8) | 99.78% | 0.0001 | 6683934 |
| 2012-2017 | 27 | 2.4% (1.6-3.8) | 99.82% | 0.0001 | 2296781 |
| Common infections | | | | | |
| Wound | 4 | 4% (3-3.6) | 99.76% | 0.0001 | 92030 |
| Bloodstream | 5 | 9% (5.4-14.6) | 98.33% | 0.0001 | 12377 |
| NA | 3 | 15.8% (9.2-25.9) | 94.99% | 0.0001 | 1697 |
| Pneumonia | 9 | 7.1% (3-15.6) | 99.50% | 0.0001 | 78405 |
| Respiratory | 5 | 2.3% (0.8-6.6) | 99.38% | 0.0001 | 48078 |
| Sepsis | 1 | 1.3% (1-7) | - | - | 3254 |
| Surgical site | 7 | 4.4% (1.7-10.9) | 99.55% | 0.0001 | 37660 |
| Urinary tract | 18 | 3.1% (2.3-4.2) | 99.85% | 0.0001 | 8716479 |
| Common infection in hospital units | | | | | |
| Burn unit | 2 | 1% (0.8-1.1) | 82.49% | 0.0001 | 104502 |
| Children's section | 1 | 3.3% (2.5-4.4) | - | - | 1497 |
| ICU | 22 | 3.9% (2.3-6.5) | 99.83% | 0.0001 | 2146908 |
| Others | 10 | 7.1% (2.3-20.3) | 99.80% | 0.0001 | 6661756 |
| Neonatal | 2 | 6.4% (3.1-12.7) | 97.19% | 0.0001 | 8096 |
| NICU | 5 | 2.9% (1.3-6.3) | 98.36% | 0.0001 | 16098 |
| PICU | 3 | 5.9% (2-16.6) | 94.39% | 0.0001 | 1341 |
| Surgery department | 6 | 8.5% (5.8-12.4) | 98.19% | 0.0001 | 17382 |
| Woman's ward | 1 | 1(0.9-1.1) | - | - | 32400 |
| Common bacteria | | | | | |
| Klebsiella pneumonia | 7 | 6.6% (2.1-19.6) | 99.46% | 0.0001 | 42508 |
| Escherichia coli | 10 | 2.2% (1.1-4.2) | 99.67% | 0.0001 | 220177 |
| Staphylococci | 11 | 5.4% (2.9-9.8) | 99.29% | 0.0001 | 43905 |
| Pseudomonas | 9 | 4.9% (2-11.3) | 99.78% | 0.0001 | 6722950 |
| Acinetobacter | 4 | 3.5% (1-10.8) | 99.52% | 0.0001 | 53501 |
| Enterobacter | 2 | 7.3% (1.3-31.4) | 99.04% | 0.0001 | 9677 |
| Other infections | 9 | 5.3% (1.5-16.9) | 99.90% | 0.0001 | 1897262 |
| Gram bacteria | | | | | |
| Positive | 10 | 5.1% (2.5-10.2) | 99.23% | 0.0001 | 37413 |
| Negative | 32 | 4% (2.8-5.7) | 99.77% | 0.0001 | 7048813 |
| NA | 10 | 5.6% (1.7-16.7) | 99.92 | 0.0001 | 1903754 |

Table 3. Results of the meta-regression

| Moderator | No studies | No. participants | Coefficient | Z-value | p |
|------------------------|------------|------------------|-------------|---------|------|
| Year of publication | 52 | 8,989,980 | -0.06 | -24.51 | 0.00 |
| Sample size of studies | 52 | 8,989,980 | -0.00 | -67.90 | 0.00 |
| Average length of stay | 23 | 113,249 | 0.02 | 9.23 | 0.00 |

only reflect a socio-economical feature of each country but also depend on criteria and diagnostic tests used to detect infections, as well as on the different reporting systems and their quality (66).

We found that bloodstream infections, surgical site infections, and pneumonia were the most common NIs observed (67). Hospital-acquired pneumonia is directly related to air conditioning systems. In many developing countries due to lack of proper facilities, the installed ventilation systems may increase pneumonia rate (68). Studies have shown that surgical infection rates vary between 10% and 20%, and are mainly due to *Staphylococcus* au-

reus (69). In cases of complications, wound healing is delayed, the possibility of further surgery increases, and patients have to be treated with antibiotics. This increases the length of hospital stay and the health-related expenditure (70).

In our study, most infections occurred in the surgical ward. A study carried out in America reported a 2-5% rate (71), while a meta-analysis of surgical infection rate estimated a pooled prevalence of 3.7% (72). Surgical infections are particularly challenging (73). Identifying patients who are prone to such infections could minimize the incidence of nosocomial infections and reduce their burden in

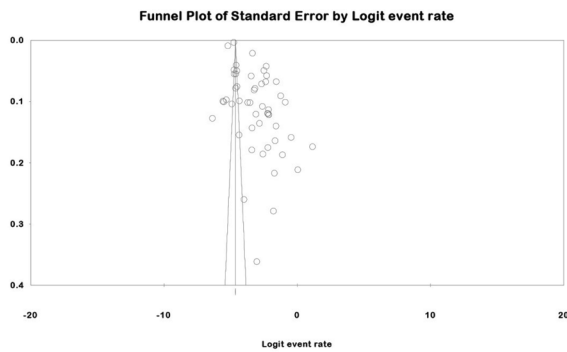


Fig. 3. The Egger test for publication bias

terms of deaths (71).

Further, our study computed a higher effect-size of infections caused by Gram-positive bacteria. A study computed a prevalence of these infections of about 5% (3). Similar results were found by other scholars (74, 75). In the ICU, a significant amount of infections are due to Gram-positive bacteria, and this trend is increasing (76).

In the present study, a high rate of infections caused by *Klebsiella pneumoniae* (urinary tract, respiratory tract, and bloodstream infections) was found (77). This is particularly alarming in that the organism can become resistant to Carbapenem, which leads to increased use of Colistin, absorbing higher costs (78). Moreover, our study showed a strong correlation between length of stay in the hospital and hospital infections rate, in agreement with other studies (79-81). Based on geographical regions of Iran, the south of the country reported the highest incidence of NIs (8.8%), due to weather conditions, being warm and dry, with high air temperature and humidity. The prevalence of NIs can vary according to the specific month of the year (82).

Meta-regression analysis based on year of publication showed a significant decreasing trend over the years, which may be due to the recent implementation of health promotion programs (83). Despite some strengths (including the systematic approach, and the robustness of findings as proven by the meta-regressions and by the subgroup, cumulative, and sensitivity analyses), some limitations of this study should be properly recognized. First, the heterogeneity was significantly high. This could reflect methodological differences among studies. Moreover, insufficient information was available to stratify the prevalence by gender. Further, in some provinces of Iran, epidemiological studies related to the prevalence of NIs were missing and, therefore, urgently needed.

Conclusion

The prevalence of NIs in Iran was determined as 4.5%. Preventing and reducing hospital infections can significantly impact on reducing mortality and health-related costs. Implementing *ad hoc* programs, such as training healthcare staff in hospital, can play an important role in reducing spread of infections. The use of appropriate and advanced features for secure hospital environment is a major contribution to the decrease of NIs. Health policy-makers in Iran can help reduce hospital infections by im-

plementing appropriate policies, such as educational programs and improving the quality of surveillance system.

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Conflict of Interests

The authors declare that they have no competing interests.

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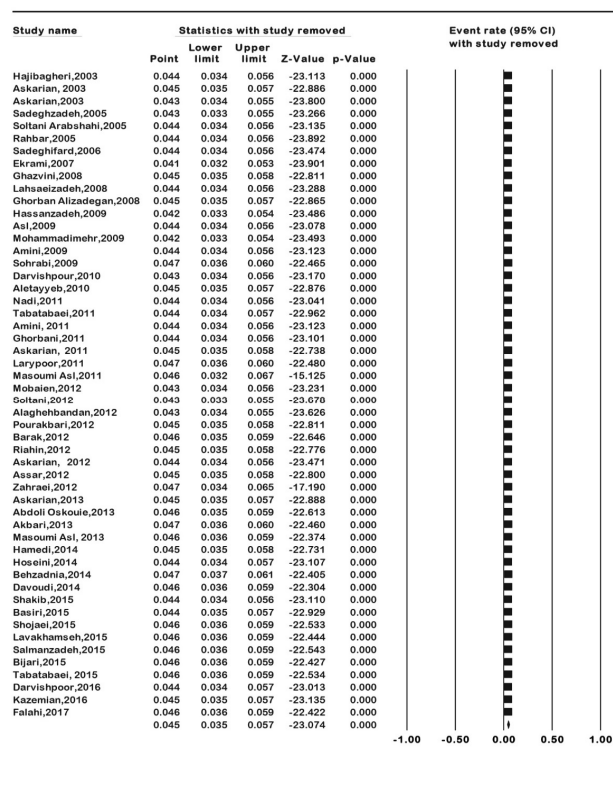
Appendix 1. PRISMA checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|----|---|--------------------|
| TITLE: Prevalence of nosocomial infections in Iran: a systematic review and meta-analysis | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | Title |
| Abstract | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | Abstract |
| Introduction | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | Background |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | Background |
| Methods | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Methods |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | Methods |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | Methods |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Methods |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | Methods |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | Methods |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Methods |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | Methods |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | Methods |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis. | Methods |

Appendix 1. PRISMA checklist

| Section/topic | # | Checklist item | Reported on page # |
|-------------------------------|----|--|--------------------|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Methods |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | Methods |
| Results | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Results |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Results |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Results |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Results |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Results |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Results |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Results |
| Discussion | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Discussion |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | Discussion |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | Conclusion |
| Funding | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | Funding |

Appendix 2. Result of sensitivity analysis



Appendix 3. Result of cumulative meta-analysis based on year of publication

