Systematic review and meta-analysis of hospital acquired infections rate in a middle east country (1995-2020)

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Abstract
Background: Hospital-acquired infections (HAIs) are a global problem in hospitals and significant causes of mortality and morbidity regardless of advances in supportive care, antimicrobial therapy and prevention. The study aimed to determine a comprehensive estimate of the HAIs prevalence, influential factors, and types of these infections in Iran.

Methods: A systematic literature review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using the online databases; Medline, EMBASE, Scopus, Cochrane, SID, Magiran, and Medlib from January 1995 to September 2020 using a combination of medical subject heading terms ('Nosocomial infection [Mesh] OR ''Hospital infection [Mesh] OR Hospital Acquired Infection[Mesh]  OR Healthcare-associated infection 'AND ('Iran' [Mesh]) among observational and interventional studies. SPSS version 25 and STATA version 11 were used for data analysis.

Results: A total of 66 (cross-sectional, cohort, and case-control) observational studies were identified. More of the studies had been done before 2014(43 papers or 65%). Based on the random-effects model, the overall prevalence of HAIs in Iran was 0.111 [95% CI: 0.105 - 0.116] with a high, statistically significant heterogeneity (I²= 99.9%). The infection rate was 0.157 and 0.089 before and after the Iranian Health Transformation Plan (HTP), respectively. HAIs rates reported more in the South and West of Iran rather than other regions (0.231 and 0.164) (p= 0.001). Escherichia coli and klebsiella infections were reported in 53 and 52 papers (0.239 and 0.180, respectively). In addition, respiratory and urinary infections were reported 0.296 and 0.286 in 51 and 38 papers, respectively.

Conclusion: The prevalence of HAIs in Iran is relatively high. Preventing and decreasing hospital nosocomial infections can considerably affect reducing mortality and health-related costs. This should be taken into consideration by health policymakers for pathology and revision of some previous programs and standards as well as the development of appropriate and evidence-based control and education programs to reduce this health problem.

Keywords: Hospital infection, Nosocomial infection, Meta-analysis, Hospital, Iran

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Introduction
Hospitals are the most important and costly components of health care systems. They account for more than two-
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...thirds of health care spending. Therefore, they significantly affect the overall health care quality (1). Prevention of infections is part of efforts to improve the quality of health care services that are vital to patient safety. Hospital-acquired infections (HAIs), also known as nosocomial infections (NI), remain significant causes of mortality and morbidity regardless of advances in supportive care, antimicrobial therapy and prevention (2).

HAIs are a global problem in hospitals (3). The popular definition of hospital infection is an infection that happens within 48 hours after hospitalization, or three days after discharge, or 30 days after surgery. Therefore, symptoms of HAIs may occur at the time of patient’s hospitalization or after discharge (4). According to the World Health Organization (WHO) report, hundreds of millions of people are affected by HAIs every year throughout the world (5). Studies showed that the HAIs rates vary worldwide. In high-income countries, HAIs prevalence in hospitalized patients was 7.6%. This figure was 10.1% (varied from 5.7% to 19.1%) in low-and middle-income countries (6). Annually, roughly 2 and 4.5 million HAIs are reported in the United States (US) and the European Union, respectively (7). The infections result in 100,000 deaths and impose additional medical care costs of about $ 6.5 billion annually in the US (6, 7). According to the WHO’s report on 2001, hospital infection has the highest percentage in South-East Asia and the Eastern Mediterranean. Based on this report, one of the main reasons for HAIs is inadvertent misuse of antibiotics leading to widespread resistance. Unfortunately, hospitals in developing countries are hotbeds of infection transmission. These infections lead to increased mortality, longer periods of hospitalization cause emotional and mental stress, failure of surgeries, rejection of organ transplantation and a significant financial burden for healthcare systems and patients. Moreover, they are linked to the spread of multi-drug resistance (MDR) in pathogenic bacteria (8, 9).

The most important bacteria causing HAIs are Escherichia coli (E. coli), Klebsiella, methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa, and Enterococci (9, 10). The most common nosocomial infections are urinary tract infections, surgical wound infections, pneumonia, and septicemia (11). Risk factors of the infections for hospitalized patients are divided into two categories: unavoidable risk factors (including old age and serious underlying causes of one’s hospitalization) and risk factors that can be mitigated by appropriate treatment (including a longer period of hospitalization, use of inappropriate catheters, excessive use of broad-spectrum, prolonged use of fixed catheters, and improper hand hygiene by healthcare workers) (12).

Prevention of hospital infections is a key way to improve the quality of healthcare. Detailed information on the extent of these infections is essential for evaluating current infection prevention activities and planning for further intervention in the hospitals nationally. An overall review of the documents shows that the reported incidence of all types of HAIs in Iran is very different; so a systematic review of all the documents and their combinations can provide a complete picture of the dimensions of this problem in Iranian society, as well as increase the use of the best and the highest quality documents available. In fact, the purpose of this study was to determine a comprehensive estimate of the prevalence of HAIs, affective factors, and types of these infections in Iran. Our study updates a systematic review that was published in 2018 (13).

Methods

A systematic and meta-analysis study was done in 2020. Relevant studies were found in PUBMED, EMBASE, SCOPUS and WEB OF SCIENCES as international databases and Magiran, SID and Medlib as Persian databases from 1995 to September 2020. The following search terms were used: ‘Nosocomial infection [Mesh] OR ‘Hospital infection [Mesh] OR Hospital acquired infection [Mesh] OR health care associated infection ‘AND (‘Iran’ [Mesh]). Also, the references of identifies papers were studied and if their title were in line with the topic, they were investigated by the authors.

The searches were done from July to September 2020. The observational studies (cohorts, case-control, and cross-sectional) both in English and Persian Language were investigated.

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

Abstract of all papers were imported into Endnote software version 16 then the duplicates were removed. After that, the authors read the full text, and if they had the inclusion criteria, they were kept for more investigation.

Also, the review and editorial articles were excluded. The checklist was prepared by examining the content of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(14). The PRISMA Statement comprises a 27-item checklist and a four-phase flow diagram. The checklist includes items considered essential for the transparent reporting of a systematic review. In this Explanation and Elaboration document, the meaning and rationale for each checklist item were explained. For each item, an example of good reporting was included and, anywhere possible, references to pertinent empirical studies and methodological literature.

In the next stage, we checked the results of the papers. If they had reported the rate of nosocomial infection, they were kept as the final suitable papers for analysis.

Data extraction

A data sheet was created in the Excel software and imported the data of suitable variables. The extracted data were as follows: title, year of the study, HAIs rate, gender of patients, type of infection and bacteria, setting, type of hospital, and sample size.

The search generated a total of 1320 records, of which 602 papers were duplicated, and 718 titles and abstracts...
were reviewed. The most fundamental reasons for omission were: studies conducted outside Iran, publication type, and studies not reporting HAIs’ rate. A total of 66 articles were included in the meta-analysis and data were extracted. Supplementary information can be accessed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flow diagram (Fig. 1). Also, for assessing the risk of bias, we used ROBVIS as a web app designed for visualizing risk-of-bias.

Data analysis
Data imported into the STATA software version 11 for analysis. To identify the pooled prevalence, the stochastic DerSimonian-Laird model was applied, computing the effect size with its 95% confidence interval (CI) and pictorially representing it through a Forest plot. Combined estimates were obtained for the HAIs’ overall and in detail by means of random effect models. RR Pooled data were used for the data analysis and mean instruction was used in STATA software. To further examine the source of heterogeneity, meta-regression analyses stratified by publication year and sample size in the hospital. Subgroup analyses were conducted based on study quality, geographic areas, sample size, year of publication, type of infection and hospital. Additionally, the possible sources of heterogeneity were examined using I² statistics and Cochran’s Q test (15). Also, Begg’s Rank correlation test and Egger’s regression method were used to measure the propagation bias.

Results

Quality assessment of studies
The quality assessment of the studies was appraised by the PRISMA checklist. As shown in Figure 1, 66 studies entered to meta-analysis phase. The studies are shown in Table 1.

As shown in Table 2, the odds ratio of hospital infections was reported 0.111 in the studies hospitals in Iran. Although Ecoli was investigated in 53 papers, it found 0.239 in the hospitals. Respiratory infections were reported 0.296 in the studies. In addition, more of the nosocomial infection was described in the South and West of Iran (0.231 and 0.164, respectively). As a result, male patients had acquired infection more than female (about 0.239 vs. 0.216).

Pooled estimate of HAIs in Iran is shown in Figure 2.
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Table 1. Characteristics of primary studies related to the prevalence of hospital infection in Iranian hospitals in the meta-analysis

| Author                          | Year  | Setting          | Type of hospital | Sample size | HAIs rate | HAIs in males | HAIs in females | Quality |
|---------------------------------|-------|------------------|------------------|-------------|------------|---------------|----------------|---------|
| Rastegar lari et al. (16)       | 1998  | Tehran Public    | 6329             | 0.532       | N/A        | N/A           | Low            | Medium  |
| Talebi Taher et al. (17)        | 2001  | Qazvin Public    | 546              | 0.041       | N/A        | N/A           | Low            | Medium  |
| Shojaee et al. (18)             | 2002  | Shahrekord Public| 845              | 0.049       | N/A        | N/A           | Low            | Medium  |
| Samadzadeh et al. (19)          | 2002  | Oromeca Public   | 942              | 0.049       | N/A        | N/A           | Low            | Medium  |
| Askarani et al. (20)            | 2003  | Shiraz Public    | 1066             | 0.453       | N/A        | N/A           | Medium         | Low     |
| Ekrami et al. (21)              | 2005  | Ahwaz Public     | 182              | 0.769       | N/A        | N/A           | Medium         | Medium  |
| Sadegh Zadeh et al. (22)        | 2005  | Zanjan Public    | 150              | 0.025       | N/A        | N/A           | High           | Low     |
| Mousaviani et al. (23)          | 2006  | Ahwaz Public     | 1601             | 0.044       | N/A        | N/A           | High           | Low     |
| Qurbanalizadegan et al. (24)    | 2006  | Tehran Public    | 6817             | 0.013       | N/A        | N/A           | Medium         | Medium  |
| Gorbanalizadegan et al. (25)    | 2006  | Tehran Public    | 155              | 0.039       | N/A        | N/A           | Medium         | Low     |
| Naderi Nasab et al. (26)        | 2006  | Mashhad Public   | 1341             | 0.039       | N/A        | N/A           | Low            | Medium  |
| Nik Bakhit et al. (27)          | 2007  | Tabriz Public    | 460              | 0.348       | 0.333      | 0.358         | Low            | Low     |
| Ajal Loeyan et al. (28)         | 2007  | Tehran Private   | 234              | 0.183       | N/A        | N/A           | Medium         | Medium  |
| Esmaili et al. (29)             | 2007  | Tehran Public    | 116              | 0.017       | N/A        | N/A           | Medium         | Low     |
| Mohammadi Mehr et al. (30)      | 2008  | Tehran Public    | 165              | 0.393       | N/A        | N/A           | Medium         | Medium  |
| Sharifl et al. (31)             | 2008  | Qazvin Public    | 1083             | 0.052       | N/A        | N/A           | Medium         | Low     |
| Ghazvini et al. (32)            | 2008  | Mashhad Public   | 971              | 0.033       | N/A        | N/A           | Medium         | Low     |
| Oskouee et al. (33)             | 2009  | Tabriz Public    | 103              | 0.331       | N/A        | N/A           | Medium         | Low     |
| Asgare Moghadam et al. (34)     | 2009  | Tehran Public    | 181              | 0.741       | N/A        | N/A           | Medium         | Medium  |
| Amini et al. (35)               | 2009  | Tehran Private   | 691              | 0.109       | N/A        | N/A           | Medium         | Medium  |
| Talaei et al. (36)              | 2010  | Tehran Public    | 582              | 0.08        | N/A        | N/A           | Medium         | Low     |
| Darvishpor et al. (37)          | 2010  | Rasht Public     | 270              | 0.163       | N/A        | N/A           | Low            | Low     |
| Khani et al. (38)               | 2011  | Tehran Public    | 256              | 0.341       | 0.323      | 0.359         | Medium         | Medium  |
| Afkhamzadeh et al. (39)         | 2011  | Sanandaj Public  | 149              | 0.322       | 0.237      | 0.351         | Medium         | Medium  |
| Larypoor et al. (40)            | 2011  | Qom Public       | 29631            | 0.001       | N/A        | N/A           | Low            | Low     |
| Banek et al. (41)               | 2011  | Tehran Public    | 1795             | 0.039       | N/A        | N/A           | Medium         | Medium  |
| Ghorbani Birgani et al. (42)    | 2011  | Ahwaz Public     | 772              | 0.101       | 0.129      | 0.075         | Medium         | Medium  |
| Mobin et al. (43)               | 2012  | Hamedan Public   | 353              | 0.171       | N/A        | N/A           | Low            | Medium  |
| Saedi et al. (44)               | 2012  | Mashhad Public   | 647              | 0.172       | N/A        | N/A           | Medium         | Medium  |
| Pourakbari et al. (45)          | 2012  | Tehran Public    | 1497             | 0.034       | N/A        | N/A           | Low            | Medium  |
| Ghazvini et al. (46)            | 2012  | Mashhad Public   | 971              | 0.033       | N/A        | N/A           | Low            | Low     |
| Soltani et al. (47)             | 2012  | Tehran Public    | 464              | 0.373       | N/A        | N/A           | Low            | Medium  |
| Hashemi et al. (48)             | 2013  | Hamedan Public   | 574              | 0.528       | N/A        | N/A           | Low            | Medium  |
| Heydari Sour Shojaee et al. (48)| 2013  | Chamsahalehakhtye Public | 848 | 0.087  | N/A        | N/A           | Medium         | Medium  |

Table 3 shows the results of the meta-regression analysis. Egger’s test was done to evaluate publication bias (Fig. 3 & Table 5). Evidences of publication bias was found.
Discussion

HAIs have always been a major health problem as hospitals expand that, despite multiple attempts, no country or organization has managed to fully resolve (81). In this systematic review and meta-analysis, we have shown that the overall prevalence of HAIs in Iran was 0.111 (95% CI: 0.105 – 0.116). The previously systematic review by Ghashghaee et al. (13). revealed the HAIs rate in Iran was 4.5%. HAIs rates are also 10.1% (varied from 5.7% to 19.1%) in developing countries and 7.6% (varied from 3.5% to 12%) in developed countries (5). According to WHO reports, the HAIs rate is between 5% – 22% in the world (82). The high prevalence of HAIs in Iran highlights the need for urgent attention and implementation of a comprehensive plan to control these infections. Variations in HAI rates can, however, be due to differences in diagnostic criteria and tests for infection diagnosis, as well as differences in reporting systems and their consistency. 

According to the findings, the HAIs had decreased from 0.157 to 0.089 after HTP in Iran, which was statistically significant (p=0.001). This indicates that the measures taken in HTP have affected the quality of health services and reduced nosocomial infections. In this regard, Ghashghaee in his study, found that HAIs had decreased from 7.6% to 2.4% after HTP (13). Moreover, Braithwaite et al. in their Book in 2018 (83) reported that In Iran, a government policy initiative called HTP was implemented to decrease inequality and improve public health coverage and reached more objectives especially patient safety. 

Based on our measurement, the most common bacteria causing HAIs were Escherichia coli and Klebsiella. The findings also demonstrated that respiratory infections and urinary infections were the most common HAIs. These infections are directly related to contamination of equipment, especially urinary catheters, environment and operating room personnel, and air conditioning systems, which in many developing countries is due to lack of proper equipment. 

Our findings showed that the male is more likely to have HAIs than the female. A similar result was reported in the systematic review study conducted in EMRO (82). Clinicians should be mindful of these differences and take them under consideration when managing patients with HAIs. However, one of the probable reasons could also be the lower number of women surveyed in the total papers reviewed in the present study. 

According to the results, the prevalence of HAIs in the south and west was more than in other regions of the country. The high rate of HAIs in some parts of the country is the characteristics of studied patients, their underlying diseases and the hospitalized ward. Most of the patients in south Iran were hospitalized in intensive care

Table 2. The results of sub-groups analysis of hospital infection in Iranian hospitals from 1995-2020

| Variable                  | No. reports | Pooled (95% CI) | I2 (%) | p     |
|---------------------------|-------------|----------------|--------|-------|
| Quality of studies        |             |                |        |       |
| High                      | 16          | 0.193 (0.143-0.242) | 99.9%  | 0.001 |
| Medium                    | 35          | 0.097 (0.089-0.106) | 99.9%  | 0.001 |
| Low                       | 15          | 0.120 (0.104-0.137) | 99.9%  | 0.001 |
| Time                      |             |                |        |       |
| <2014                     | 43          | 0.157 (0.142-0.172) | 99.9%  | 0.001 |
| >2014                     | 23          | 0.089 (0.082-0.097) | 99.9%  | 0.001 |
| Patients’ gender          |             |                |        |       |
| Male                      | 6           | 0.239 (0.160-0.318) | 99.7%  | >0.5  |
| Female                    | 6           | 0.216 (0.124-0.307) | 99.6%  | >0.5  |
| Age                       |             |                |        |       |
| ≤50                       | 44          | 0.117 (0.111-0.124) | 99.6%  | >0.5  |
| >50                       | 22          | 0.111 (0.098-0.123) | 99.9%  | 0.001 |
| Sample Size               |             |                |        |       |
| ≤ 1500                    | 42          | 0.191 (0.162-221)  | 99.8%  | 0.001 |
| > 1500                    | 24          | 0.087 (0.080-0.095) | 99.9%  | 0.001 |
| Region                    |             |                |        |       |
| Center                    | 30          | 0.124 (0.112-0.136) | 99.5%  | 0.001 |
| East                      | 7           | 0.083 (0.071-0.096) | 99.9%  | 0.001 |
| North                     | 4           | 0.081 (0.071-0.142) | 99.9%  | 0.001 |
| South                     | 7           | 0.231 (0.121-0.341) | 99.9%  | 0.001 |
| West                      | 19          | 0.164 (0.143-0.185) | 99.9%  | 0.001 |
| Type of Hospital          |             |                |        |       |
| Public                    | 63          | 0.112 (0.107-0.118) | 97.9%  | >0.5  |
| Private                   | 3           | 0.100 (0.015-0.186) | 97.9%  | >0.5  |
| Type of bacteria          |             |                |        |       |
| Staphylococcus aureus     | 49          | 0.166 (0.151-0.182) | 99.9%  | 0.001 |
| Klebsiella                | 52          | 0.180 (0.163-0.196) | 99.9%  | 0.001 |
| Escherichia coli          | 53          | 0.239 (0.212-0.266) | 99.9%  | 0.001 |
| Type of infection         |             |                |        |       |
| Respiratory               | 38          | 0.286 (0.261-0.310) | 99.9%  | >0.5  |
| Urinary                   | 51          | 0.296 (0.255-0.337) | 99.9%  | >0.5  |
| Overall                   | 66          | 0.111 (0.105-0.116) | 99.9%  |       |
units (20, 79). Moreover, Ahmadinejad declared that about 50% of the studied patients were addicts and they are prone to nosocomial infections (79).

Monitoring and controlling HAIs is difficult, costly, and time-consuming; however, it is necessary and cost-effective. Adherence to hygiene principles and methods of microbiological diagnosis can prevent and control HAIs with lower costs. Using minimally invasive devices and methods, paying close attention to non-intravenous nutrition, preventing misuse and overuse of antibiotics, monitoring the pattern of infection, improving hospital environmental health, training personnel, and effective hand hygiene strategies are methods that can significantly reduce HAIs (84, 85).

Conclusion

According to the reviewed studies, the prevalence of HAIs in Iran is relatively high. Despite the increasing development of health standards and quality development of hospitals in recent years, the prevalence findings indicate
a relatively uneven trend in this development and an increase in the prevalence of HAIs in different parts of the country. This should be taken into consideration by health policymakers for pathology and revision of some previous programs and standards as well as the development of appropriate and evidence-based control and education programs to reduce this health problem in Iran. Efforts to improve the quality of nursing care, applied staff training, continuous monitoring HAIs, provision of facilities, implementation of infection control programs, prioritization of hospital wards for more stringent health measures, emphasis on preventive cares such as hand washing and appropriate training through mass media are the most important actions suggested in this regard.

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Conflict of Interests
The authors declare that they have no competing interests.

Table 3. The overall prevalence of nosocomial infections in the south of Iran

| Study                | ES   | 95 % Conf. Interval | Weight |
|----------------------|------|---------------------|--------|
| Askarian et al.      | 0.451| 0.356-0.546         | 13.28  |
| Ahmadinejad et al.   | 0.401| 0.333-0.469         | 13.94  |
| Emami et al.         | 0.281| 0.266-0.296         | 14.69  |
| Hosini et al.        | 0.254| 0.192-0.316         | 14.07  |
| Saadat et al.        | 0.146| 0.118-0.174         | 14.59  |
| Hashemizadeh et al.  | 0.114| 0.101-0.127         | 14.70  |
| Rahmani et al.       | 0.002| 0.002-0.002         | 14.72  |
| Pooled ES            | 0.231| 0.121-0.341         | 100.00 |

Table 4. Results of the meta-regression

| Overall prevalence | Coef. | Std. Error | t     | p     |
|--------------------|-------|------------|-------|-------|
| Year of publication| -0.006| 0.004      | -1.49 | 0.141 |
| Region             | 0.008 | 0.018      | 0.43  | 0.670 |
| Type of hospital   | -0.070| 0.107      | -0.65 | 0.516 |

Fig. 3. The Egger test for publication bias

Table 5. The Egger test for publication bias

| Beta coefficient | Std. Err | t     | p     |
|------------------|----------|-------|-------|
| Slop             | .0107469 | .001112 | 9.66  | 0.001|
| bias             | 13.41402 | 3.581168 | 3.75  | 0.001|

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