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The Extra Length of Stay, Costs, and Mortality Associated With Healthcare-Associated Infections: A Case-Control Study

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ABSTRACT

Background and Aim: This study aims to compare the mortality rate, length of stay (LOS), and hospitalization cost in patients with and without healthcare-associated infections (HCAIs).

Methods: This prospective cohort study is conducted on 396 matched patients admitted to a tertiary teaching hospital with 800 beds in the southwest of Iran from July 2021 to January 2022. The cases were patients admitted during the study period who had, at minimum, one type of HCAI. For a comparison group, we considered all patients without HCAIs who hospitalized in the same ward and at the same time with the same age and gender in a ratio of one case to three controls. Descriptive analyses were done based on direct medical costs, LOS, and mortality rate in patients. The magnitude of the relationship between potential risk factors and HCAI was quantified using logistic regression.

Results: The most common HCAI and microorganisms were urinary tract infection (UTI) and *Escherichia coli*, respectively. The mean LOS for infected patients was 20.3 (±16) days, compared to 8.7 (±8.6) days for noninfected patients (p value ≤ 0.05). Lengths of stay (odds ratio [OR] = 1.09; 95% CI = 1.06–1.19; p value = 0.000), ICU lengths of stay (OR = 1.08; 95% CI = 1.02–1.15; p value = 0.003), presence of central Catheter (OR = 0.127; 95% CI = 0.51–0.319; p value = 0.000), and urinary catheter (OR = 0.225; 95% CI = 0.122–0.415; p value = 0.000), mechanical ventilation (OR = 0.136; 95% CI = 0.57–0.325; p value = 0.000), receipt of immunosuppressors (OR = 1.99; 95% CI = 11.12–3.56; p value = 0.01), were Significantly associated with HCAI. Patients with infections had a more costly hospital stay than noninfected patients (mean diff: $2037.46 ([SD]: 482.25$) (p value = 0.000). The highest cost component was the cost of medication expenditure (mean: $1612.66 ([SD]: $2542.27).

Conclusions: UTI was the most common HCAI in our study. An infection acquired during a hospital stay may be associated with higher hospitalization costs, prolonged hospitalization, and an increase in the rate of mortality. Longer lengths of stay, presence of central and urinary Catheters, receipt of immunosuppressors, use of mechanical ventilator were common risk factors for HCAI. This study reveals that the median reimbursement cost per hospitalization of patients with HCAIs was higher than patients without HCAIs. This highlights the necessity for implementation of HCAI prevention and control measures.

1 | Introduction

Healthcare-associated infection (HCAI) is an infection acquired during hospitalization in a patient that was not present or incubating before admission. According to the World Health Organization (WHO) report, "healthcare-associated infections (HCAIs) represent the most common adverse event among hospitalized patients" [1]. The incidence of HCAIs ranged from 3.6% to 12% in high-income countries and 10.1%–15.5% in low- and middle-income countries [1]. The prevalence of HCAIs in Iran was 4.5% % in 2017 [2]. However, according to the WHO report, due to the limited and low-quality data especially in low- and middle-income countries, the burden of nosocomial infections is underestimated [1]. The Centers for Disease Control and Prevention (CDC) estimates that HCAIs occur in one out of every 25 acute care hospitalizations [3].

However, the rates and types of HCAIs differ across various hospitals and wards. Studies have confirmed that the risk of acquiring HCAIs is significantly higher in intensive care units (ICUs) [4, 5] with approximately 30% of patients affected by at least one episode of HCAIs with substantial associated morbidity and mortality [4].

HCAI can bring a severe burden to patients and healthcare systems. In addition to increasing morbidity and mortality, it can prolong hospitalization stays and raise hospitalization costs [6, 7]. Stewart et al. [8] found that the excess length of stay (LOS) attributable to HCAI was 7.8 days. They estimated a reduction of 10% in HCAI incidence could make 5800 bed-days available to treat 1706 elective patients. Stewardson et al., estimated that the average extra LOS attributable to various types of HCAIs was 12.22 days for acute care admissions at 10 European hospitals [9]. For different infection sites, the extra LOS was reported to exceed 27 days [10]. Another study found that the mean LOS attributable to Central Line–Associated Blood Stream Infections (CLABSIs) was 19 days [11]. The extra LOS was 3.48 days for blood stream infection (BSI), 3.59 days for urinary tract infections (UTIs), 7.23 days for surgical site infections (SSIs), and 11.52 days for ventilator-associated pneumonia (VAP) in the medical-surgical ICUs [6].

HCAIs contribute to increase patient mortality rate. According to the US Center for Disease Control and Prevention (CDC), 1.7 million hospitalized patients acquire HCAIs per year while being treated for other health-related problems; one out of these seventeen infected patients dies as a result of HCAIs [12]. In Spain, the mortality rate among patients with SSIs after surgery was about 2.4 times higher than among those who did not develop an SSI [13]. Similarly, in France, the mortality rate was significantly higher in infected patients relative to controls (8.3% vs. 2.0%, respectively) [14]. Although comprehensive data are limited, available evidence indicates that the burden of HCAIs may be even more substantial in low- and middle-income countries. For example, Yepez et al. reported mortality rates in ICUs of 30.9% for CLABSIs, 14.5% for VAP, and 17.6% for catheter-associated urinary tract infections (CAUTIs) [15]. Likewise, Kumar et al. found that over one-third (39.8%) of patients who acquired nosocomial infections died, compared to a mortality rate of 5.0% in patients without such infections [16].

HCAIs also have a substantial impact on financial burden on healthcare systems. Baier et al. reported that the additional hospital costs directly associated with CLABSIs amount to €8810 per case in Germany [17]. In China, a study estimated that the excess costs attributable to HCAIs reaches $6127.65 annually [18]. Similarly, Arefian et al. found that HCAIs result in considerable additional costs, ranging from $7453 to $15,155 per patient [19]. In Iran, Soleymani et al. demonstrated that the hospitalization costs for patients with HCAIs (mean: $3264 ± 6078) were higher compared to controls ($2451 ± 3098) [20].

Few studies focused on a comprehensive assessment of the HCAI burden. Many studies concentrate solely on one type of infection like BSIs [21–23], often omitting other highly prevalent HCAIs, such as UTIs [24]. Our literature search revealed a knowledge gap on the burden, the mortality rate, LOS, and cost attributable to the HCAI in low- and middle-income countries in a comprehensive assessment. Therefore, this study was conducted as a nested case-control study to estimate the mortality rate, LOS, and hospitalization cost for patients with and without HCAIs in a large academic hospital.

2 | Methods

2.1 | Study Design

The study is a prospective nested case-control investigation conducted on patients admitted to a tertiary teaching hospital with 800 beds in the southwest of Iran from July 2021 to January 2022.

2.2 | Case- and Control Patients

A total of 396 patients were enrolled in the study. Of these, 100 cases (with HCAIs) and 296 controls (without HCAIs) were recruited into the study (ratio 1:3). Sampling was done a non-probability method; from the beginning of the study, all patients who met the inclusion criteria were selected as the sample, and this process continued throughout the study period.

In our study, the cases were patients admitted during the study period who had at least one type of HCAI and a length of hospitalization greater than 2 days. One hundred infected cases were recorded across different wards during the study period. For the comparison group, we selected all patients hospitalized in the same ward and at the same time, matching them by age (±5 years) and gender, with a ratio of one case to three controls. Thus, a total of 296 patients were enrolled as the control group. Our inclusion criteria were hospitalization at the facility, any sex, and age 18 years or older.

2.3 | Ethical Consideration

Written informed consent was obtained from each participant. In addition, ethics approval was obtained from the Ethical Review Committee of Ahvaz Jundishapur University of Medical Sciences. This study was conducted under the principles of the Helsinki declaration (Ethics code: IR.AJUMS.REC.1400.193).

2.4 | Data Collection

Demographic and clinical information related to patients in both groups included age, gender, diagnosis, types of antibiotics used, types and number of invasive medical procedures performed, LOS, and discharge status.

The research team developed a data collection tool to record variables for both cases and controls. Relevant information was extracted from patient records and the hospital information system (HIS).

- Researchers contacted patients or their families using the phone numbers provided in the patient records to capture actual data on 30-day mortality. If there was no response, they made up to three additional calls over 3 days to the indicated relative of hospitalized patients. Non-responses were recorded as missing data.
- Microorganism identification was conducted based on laboratory tests.
- Additionally, several risk factors were considered based on previous studies, including ICU admission, immunosuppressive therapies, surgical procedures, exposure to invasive medical procedures, and mechanical ventilation.
- The hospitalization cost in the study was based on the total cost of treatment from admission to discharge, as detailed in the patient's bill. The cost for each patient was obtained from the HIS. Cost elements were examined in detail, and comparisons were made by calculating total treatment costs for each patient. Hospitalization costs were categorized into seven groups: drug costs, expendable supplies, paraclinical services (e.g., laboratory tests and imaging), surgery charges, nursing care charges, physiotherapy, and other costs. All costs were calculated in US dollars in 2021.

2.5 | Statistical Analysis

Data were entered into Microsoft Excel, cleaned, and then transferred to SPSS version 24. Values were expressed as means, standard deviations, and percentages. Our variables were age, gender, discharge status, types of invasive medical procedures, types of HCAI and microorganisms, LOS, ICU LOS, mortality rate, and hospitalization costs. Normality was tested using the Kolmogorov-Smirnov test. Subsequently, patient characteristics in both groups were compared using nonparametric tests (Mann–Whitney *U* test for continuous variables and chi-square test for categorical variables). The relationship between risk factors and HCAIs was quantified using logistic regression. A *p*-value of less than 0.05 was considered statistically significant.

3 | Results

3.1 | Characteristics of Cases and Controls

In this study, the case group consisted of 100 patients, while the control group comprised 296 patients, resulting in a total of 396 patients analyzed. The mean ages of patients in the case and control groups were 54.4 and 53.7 years, respectively. Additionally, 52% of the patients were female (see Table 1).

The percentages of each type of HCAI, listed in descending order of incidence, were as follows: UTIs (51%), primary BSIs (20%), SSIs (19%), and lower respiratory tract infections (10%). The four most common types of infections were associated with the most prevalent pathogens. *Escherichia coli*, Klebsiella species, and *Pneumonia* were the most common pathogens, accounting for 33% and 30% of all HCAIs, respectively (see Table 2).

3.2 | Risk Factors for HCAI

Regarding risk factors, 17% of patients in the case group had immunodeficiency, 85% had a urinary catheter, 16% had a blood catheter, 17% had mechanical ventilation, and 24% had tracheal intubation. Logistic regression analysis revealed that lengths of stay (odds ratio [OR] = 1.09; 95% CI = 1.06–1.19; $p = 0.000$), ICU lengths of stay (OR = 1.08; 95% CI = 1.02–1.15; $p = 0.003$), presence of central catheters (OR = 0.127; 95% CI = 0.51–0.319; $p = 0.000$), urinary catheters (OR = 0.225; 95% CI = 0.122–0.415; $p = 0.000$), mechanical ventilation (OR = 0.136; 95% CI = 0.57–0.325; $p = 0.000$), and receipt of immunosuppressive therapy (OR = 1.99; 95% CI = 1.12–3.56; $p = 0.010$) were significantly associated with HCAI (see Table 3).

TABLE 1 | Characteristics of cases and controls.

Variable	With HCAI ($n = 100$)	Without HCAI ($n = 296$)	*p*-value*
Age (years), mean (SD)	54.40 (14.99)	53.79 (14.27)	0.9
LOS (days) mean (SD)	20.3 (16)	8.7 (8.6)	0.000
ICU LOS (days) mean (SD)	21.25 (24.24)	5.33 (4.43)	0.007
Discharge type			0.000
Discharge	83 (83)	282 (95.3)	
Dead	17 (17)	14 (4.7)	
Gender			0.8
Male	48 (48)	141 (48)	
Female	52 (52)	155 (52)	

TABLE 2 | Costs, LOS, and mortality rates for each type of the HCAI.

Type of infection	*N* (%)	Total cost ($), mean (SD)	LOS, mean (SD)	ICU LOS, mean (SD)	Mortality, *N* (%)
UTI	51 (51)	2088.77 (2061.31)	15.6 (12.4)	23.4 (27.50)	4 (12.9)
VAP	10 (10)	3753.23 (1690)	41.7 (15.1)	38.16 (19.36)	4 (45.5)
BSI	20 (20)	2323.96 (1959.75)	21.9 (18.7)	27.4 (26.14)	4 (12.9)
SSI	19 (19)	3822.20 (2721.99)	19.7 (13.5)	23 (0.86)	5 (16.1)

TABLE 3 | Risk factors of cases and controls.

Variables	With HCAI ($n = 100$)	Without HCAI ($n = 296$)	OR (95% CI)	*p*-value
LOS (days), mean (SD)	20.3 (16)	8.7 (8.6)	1.09 (1.06–1.19)	0.000
ICU LOS (days), mean (SD)	21.25 (24.24)	5.33 (4.43)	1.08 (1.02–1.15)	0.003
ICU admission	20 (20)	40 (13)	0.625 (0.34–1.13)	0.12
Immunosuppression, *N* (%)	17 (17)	86 (29)	1.99 (1.12–3.56)	0.01
Surgery, *N* (%)	65 (65)	186 (62)	.993 (0.621–1.58)	0.97
Urinary catheter, *N* (%)	85 (85)	171 (57)	0.225 (0.122–0.415)	0.000
Ventilator, *N* (%)	17 (17)	8 (2.7)	0.136 (0.57-.325)	0.000
Tracheal intubation, *N* (%)	24 (24)	62 (20.9)	0.828 (0.48–1.41)	0.492
Blood Catheter, *N* (%)	16 (16)	7 (2)	0.127 (0.051–0.319)	0.000

3.3 | LOS

The mean LOS for infected patients was 20.3 (±16) days, compared to 8.7 (±8.6) days for noninfected patients. The mean ICU LOS for cases and controls was 21.25 (±24.24) days and 5.33 (±4.43) days, respectively. There was a significant difference in both total LOS and ICU LOS between the case and control groups ($p \leq 0.05$). Thus, we conclude that both total LOS and ICU LOS were longer for cases than for controls (see Table 1). The longest LOS was observed in patients infected with VAP, with a mean of 38.16 (±19.36) days, and BSI, with a mean of 27.4 (±26.14) days (see Table 3). Additionally, patients infected with *Pseudomonas* and *Klebsiella* had the longest LOS, with a mean of 26.7 (±12.2) days (see Table S1).

3.4 | Infection-Attributable Mortality

We recorded 31 deaths (7.8%) in our study; 27 (87%) of these patients died in the hospital, and 4 (13%) died after discharge. Of the deaths, 17 (54%) were related to the case group. A significant difference in the mortality rate between the two groups was observed (OR = 0.242; 95% CI = 0.115–0.512; $p = 0.000$). Among the infected patients who died in the hospital, the most common infection type was SSI, accounting for five deaths (see Table 2).

3.5 | Infection-Attributable Cost

Patients with infections had a more costly hospital stay compared to noninfected patients, with a mean difference of $2037.30 (SD = $347.30; $p = 0.000$). The median reimbursement cost per hospitalization for patients with HCAIs was 2.12 times higher than for patients without HCAIs ($3850.80 for cases vs. $1813.33 for controls; $p = 0.000$). Medication expenditure was the highest cost for infected patients, with a mean of $1612.66 (SD = $2,542.27), which was on average twice as high as for noninfected patients ($p = 0.000$). The second highest cost component was medical equipment, with a mean of $564.08 (SD = $809) in infected patients, which was on average 1.5 times higher than in noninfected patients ($p = 0.000$). Antibiotics represented a substantial cost, with a mean of $319.28 (SD = $513.49), which was 4.08 times higher in infected patients compared to noninfected patients. Overall, all costs were significantly higher in the case group compared to the control group ($p = 0.000$), except for the cost of surgery, where no significant difference was observed ($p = 0.547$) (see Table 4).

4 | Discussion

We designed this prospective study to assess the impacts of HCAIs on LOS, mortality, and hospitalization costs in both infected and uninfected patients at an educational hospital in Ahvaz, Iran. Our results demonstrated that HCAIs were associated with increased in-hospital mortality, longer LOS, and higher hospitalization costs.

Based on our results, the most common HCAI was UTI, followed by BSI and SSI, which is consistent with findings from other studies [25, 26]. It has been shown that up to 80% of HCAIs are associated with indwelling medical devices [27]. Additionally, the main microorganisms identified in our study that led to HCAIs were *E. coli* and Klebsiella. Elliott's review also noted that common pathogens responsible for these infections include *E. coli*, Klebsiella, and Pseudomonas [25].

TABLE 4 | Infection-attributable medical cost ($).

Variables	With HCAI ($n = 100$)	Without HCAI ($n = 296$)	Mean diff (SE)	*p*-value
Cost of antibiotics, mean (SD)	319.28 (513.50)	78.49 (210.69)	240.79 (36.48)	0.000
Cost of nursing care, mean (SD)	112.35 (159.23)	39.60 (45.74)	72.7 (10.30)	0.000
Cost of testing and pathology, mean (SD)	364.08 (450.22)	141.35 (208.44)	222.73 (33.41)	0.000
Cost of imaging, mean (SD)	171.90 (309.34)	84.69 (104.96)	87.21 (20.78)	0.000
Cost of surgery, mean (SD)	524.26 (711.18)	464.33 (651.89)	59.92 (77.18)	0.547
Cost of physiotherapy, mean (SD)	25.84 (71.48)	1.99 (10.66)	23.85 (4.28)	0.000
Cost of drugs, mean (SD)	1612 (2542.27)	565.70 (1185.55)	1046.97 (189.22)	0.000
Cost of medical equipment, mean (SD)	564.09 (809)	374.53 (701.79)	189.56 (84.45)	0.000
Other costs, mean (SD)	156.33 (331.17)	62.67 (146.10)	93.66 (141.11)	0.000
Total cost, mean (SD)	3850.80 (4652.20)	1813.33 (2185.97)	2037.30 (347.30)	0.000

We observed an 11-day difference in LOS between patients with HCAIs and those without. Additionally, ICU stay was nearly four times longer for patients with HCAIs compared to those without. Previous studies have confirmed that HCAIs are associated with increased hospital stay. For instance, Lü et al. [28] reported that HCAIs increased the LOS by an average of 5 days. Similarly, Stewart et al. [8] showed that patients with HCAI had a significantly longer hospital stay compared to those without HCAIs, with an excess LOS attributable to HCAIs of 7.8 days. Ak et al., [29] reported the median LOS in the ICU was more than four times longer for infected patients compared to uninfected patients. Additionally, Dasgupta et al. [30] showed that the median ICU stay for patients with HCAI was nearly 11 days longer than for those without HCAIs. In other words, some studies have shown that a longer hospital stay is a risk factor for HCAIs. Extended hospitalization increases the risk of infection due to prolonged exposure to pathogenic microorganisms, which can result from extended durations of invasive procedures and pharmacotherapy [31–33].

The mortality rate was 17% in patients with HCAIs, and these patients faced nearly a fivefold increased risk of death compared to those without HCAIs. Several studies have confirmed the impact of HCAIs on the rate of mortality [34, 35]. Mortality rate of patients with HCAIs have been reported to range from 17.1% to 48% [36]. The impact of HCAI on patient mortality rates is controversial. Several factors, including patient demographics, co-morbidities, the severity of illness, and antibiotic resistance, significantly influence patient outcomes [37, 38]. Prevalence rates of infections acquired in ICUs vary from 9% to 37% [39]. Even in advanced hospitals in developed countries with better standards of care, HCAIs can affect up to 25% of ICU patients [40].

The cost per case in our study is comparable to previous studies conducted in Iran [20] but is significantly lower than in high-income settings. The differences in cost may be attributed to lower overall costs in Iran's public hospitals. Notably, human resources and hospitalization costs are substantially lower in the public sector compared to the private sector.

The results indicate that 8% of the total cost is attributed to antimicrobial expenses. The average cost of medical procedures was higher for patients with HCAIs compared to noninfected patients. Other studies have similarly reported increased treatment costs for patients with HCAI [41, 42]. Specifically, the costs of antibiotics, medications, and laboratory tests were higher for patients with HCAIs compared to those without infections. The results are consistent with other studies [43]. The most significant cost difference between cases and controls was for pharmaceuticals. VAP was the most costly type of HCAI in the infected group. Manookian et al. [41] also found that pneumonia increased hospitalization costs more than other types of HCAIs. The total medical cost in the case group was higher than the total medical cost in the control group. All costs, except for those related to surgery, showed significant differences between the case and control groups. Our cost analysis revealed a significant association between LOS and HCAIs.

Other studies have found results similar to ours regarding risk factors for HCAIs. Previous research has indicated that the presence of invasive devices [35], use urinary catheters [44], central vascular catheters [45], and mechanical ventilation [46] are significant risk factors for HCAIs. Our study confirmed that the use of ventilators, presence of central stream and urinary catheters, longer LOS, ICU LOS, receipt of receipt of immunosuppressive therapy were associated with higher odds for HCAIs. Additionally, hospital-acquired infections [47, 48], the use of mechanical ventilation [47], prolonged hospitalization [47], and increased ICU LOS [49] are associated with a higher mortality rate.

4.1 | Limitations

This study has some limitations. First, we focused on a relatively small number of risk factors for hospital-acquired infections. Second, the costs of hospitalization were assessed using the patient's bill that did not account for indirect costs. Third, it was not possible in this study to investigate illness severity as a potential predictor of death. Finally, the COVID-19 epidemic led to the expansion of certain hospital departments or their conversion into inpatient units for COVID-19 patients, which resulted in limitations in sampling and matching.

5 | Conclusion

UTI was the most common HCAI in our study. An infection acquired during a hospital stay may be associated with higher hospitalization costs, prolonged hospitalization, and an increase in the rate of mortality. Longer lengths of stay, presence of central and urinary Catheters, receipt of immunosuppressors, use of mechanical ventilator were common risk factors for HCAI. This study reveals that the median reimbursement cost per hospitalization of patients with HCAIs was higher than patients without HCAIs. This highlights the necessity for implementation of HCAI prevention and control measures.

6 | Policy Implications

The confirmation of higher healthcare costs, prolonged hospital stays, and increased mortality rates associated with nosocomial infections underscores the need for targeted policy interventions. These findings suggest that allocating resources toward infection prevention campaigns and enhanced hospital hygiene protocols could reduce the economic and human burden of hospital-acquired infections. Investments in staff training, improved sanitation practices, and infection monitoring systems would not only reduce costs and patient stay durations but also significantly improve patient outcomes, thereby reducing overall healthcare system strain.

Author Contributions

Conceptualized and designed the study and prepared the first draft of the manuscript: Zhila Najafpour. Data collection, helped to prepare the initial draft: Samaneh Moradi. Helped to revise the initial draft: Iman Keliddar and Razieh Mombeyni. Analyzed and interpreted data and helped revise the initial draft: Bahman Cheraghian. All authors read and approved the final manuscript.

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Ethics Statement

Written informed consent was obtained from each participant. In addition, ethics approval was obtained from the Ethical Review Committee of Ahvaz Jundishapur University of Medical Sciences. This study was conducted under the principles of the Helsinki Declaration (Ethics code: IR.AJUMS.REC.1400.193).

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Transparency Statement

The lead author Zhila Najafpour affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.