



Investigation of Prevalence, Etiological Factors and Risk Factors of Urinary Tract Infection in Spinal Cord Injury Patients

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Abstract

Background: Urinary tract infection (UTI) is a common infection that constitutes a significant portion of all hospital infections.

Objectives: Given the importance of spinal cord trauma, this study aimed to investigate the prevalence, etiological factors, and risk factors of UTI in spinal cord injury (SCI) patients.

Methods: In this study, patients were examined daily. If a diagnosis of UTI was confirmed, based on laboratory results and the attending physician's opinion, they were included in the study. A researcher-made checklist was then completed by the researchers.

Results: The results showed that 89 (67.4%) of the patients were male, and 101 (76.5%) were married. Additionally, 44.7% of the patients were hospitalized due to traffic accidents. The results also indicated that 30.3% of patients had hematuria, 35.5% had fever, and 12.9% had scrotal pain or turbid urine. Regarding the microorganisms identified, 55.3% of patients had *Escherichia coli*, 11.4% had *Proteus*, 9.1% had *Klebsiella*, and 7.6% had *Candida* spp.

Conclusions: Given the significant prevalence of UTI in patients, necessary preventive measures should be implemented to prevent infections.

Keywords: Etiological, Urinary Tract Infection, Spinal Cord Injury

1. Background

Currently, one of the most significant problems in healthcare centers is hospital infections (1-3). Nosocomial infections are infections that either occur locally or spread throughout the hospital and are caused by pathogenic microorganisms or their toxins. Hospital infections are a major cause of disease outbreaks and patient deaths (4, 5). A hospital-acquired infection is one that a patient acquires after 48 hours of hospitalization or within 72 hours of discharge, which was not present at the time of admission and was not in a latent state (6-8). Nosocomial infections should not be present at the time of patient admission and should not be in the incubation period (4, 9).

Despite many advances in treatment methods, the risk of hospital infections has increased due to prolonged hospitalization and the increased use of invasive methods. These methods include the use of vascular catheters, ventilators, intubation, surgical

drains, long-term catheterization, immunosuppression, failure to change dressings, and improper glove use (10). Nosocomial infections prolong hospital stays, delay recovery, and reduce the patient's quality of life, leading to various complications (11).

Prolonged hospital stays increase mortality rates and, consequently, hospital costs. Additionally, they pose a risk for the spread of infections in the community, with rates varying by country. Hospital infections are associated with increased mortality, disability, prolonged hospitalization, and significant treatment costs (9). Factors such as patient age, type and severity of the disease, underlying conditions, diabetes mellitus, chronic lung disease, kidney failure, cancer, patient immunodeficiency, and overuse of antibiotics during hospitalization affect the prevalence of hospital infections (12).

A significant number of hospital infections are preventable, and medical personnel can play a crucial

role in reducing their incidence. Observing hand hygiene and basic handwashing is essential in preventing infections. Since a significant proportion of infections originate in the operating room, staff in these areas can play a critical role in preventing such infections by adhering to proper hand hygiene (4).

One type of hospital infection that can occur due to non-compliance with hand hygiene during therapeutic procedures, such as catheterization or other invasive measures in the operating room, is urinary tract infection. Urinary tract infection is a common nosocomial infection and is considered one of the most frequent hospital-acquired infections (13).

Urinary tract infection is a prevalent infection that constitutes a significant portion of all hospital infections. The infectious agents responsible for UTIs are diverse, including fungal, viral, and bacterial pathogens (14-16). Various factors contribute to the development of UTIs, including trauma (17). In cases of trauma, urinary catheterization is often required, which can increase the risk of UTIs. Trauma can affect different parts of the body, with spinal cord injury being one such type of trauma (18). Spinal cord injury is prevalent and can result in both short-term and long-term complications (19-22). These complications can lead to infections, including UTIs, which can cause additional complications for SCI patients (23-25).

2. Objectives

Given the importance of spinal cord injury (SCI), this study aimed to investigate the prevalence, etiological factors, and risk factors associated with urinary tract infections in SCI patients.

3. Methods

3.1. Study Design and Study Population

This study was conducted at a government hospital, examining patients who were admitted for spinal cord injury due to trauma.

3.2. Inclusion and Exclusion Criteria

Patients over 18 years of age who were admitted to the hospital during the first six months of 2020 were examined. Patients with a urinary tract infection at the time of admission were excluded from the study. Only patients who developed a UTI during their hospitalization or within 48 hours after discharge were included.

3.3. Data Gathering

The data collection tool included a checklist with questions about age, sex, signs and symptoms of the disease, presence of other diseases, length of hospital stay (in days), etiology of UTI (traumatic and non-traumatic causes), marital status, history of urinary tract infections in the past three years, causes of trauma (e.g., traffic accidents, fights, falls, sports accidents), type of injury (e.g., cervical, thoracic, lumbosacral), urinary incontinence (yes or no), bladder irrigation (yes or no), associated symptoms (e.g., fever, hematuria), and the type of microorganism (e.g., *E. coli*) if the patient used invasive methods such as urinary or venous catheters. The patient's profile was meticulously recorded, and the types of antibiotics used were also carefully documented.

3.4. Method of Research

Patients were examined daily. If a UTI diagnosis was confirmed based on laboratory results and the attending physician's opinion, the patient was included in the study, and the researcher-completed checklist was filled out by the researchers. Ethical considerations included obtaining an ethics approval code from the university, maintaining confidentiality in research and reporting, and adhering to all ethical guidelines established by the university.

3.5. Data Analysis

Data were analyzed using SPSS version 16 software.

4. Results

The results showed that 67.4% of the patients were male, 76.5% were married, 33.3% had a history of UTI, 44.7% had etiology related to traffic accidents, and 56.1% had urinary incontinence. The mean (SD) age of the patients was 44.77 (7.64) years, and the mean (SD) duration of illness was 14.87 (7.25) years (Table 1).

The results showed that 30.3% of patients had hematuria symptoms, 35.5% had fever symptoms, and 12.9% had scrotal pain or turbid urine (Table 2). Regarding microbial infections, 55.3% of patients had *E. coli*, 11.4% had *Proteus*, 9.1% had *Klebsiella*, and 7.6% had *Candida* spp (Table 3).

5. Discussion

This study aimed to determine the prevalence, etiological factors, and risk factors of UTIs in spinal cord

Table 1. Distribution of Demographic Characteristics of Patients with Spinal Cord Injury^a

Variables	Values
Gender	
Man	89 (67.4)
Female	43 (32.6)
Marital status	
Married	101 (76.5)
Single	31 (23.5)
History of UTI in the last three years	
Yes	44 (33.3)
No	88 (66.7)
Etiology	
Quarrel	36 (27.3)
Traffic accidents	59 (44.7)
Falling from a height	34 (25.8)
Sports events	3 (2.3)
Neurological level	
Lumbosacral	48 (36.8)
Thoracic	61 (46.2)
Cervical	23 (17.4)
Urinary incontinence	
Yes	58 (43.9)
No	74 (56.1)
Bladder irrigation	
Yes	79 (59.8)
No	53 (40.2)
Age	44.77 ± 7.64
Duration of illness	14.87 ± 7.25

^a Values are expressed as No. (%) or Mean ± SD.

Table 2. Accompanying Symptoms in Urinary Tract Infection Infections in Patients with Spinal Cord Injury

Variables	No. (%)
Hematuria	40 (30.3)
Suprapubic pain	4 (3)
Scrotal pain	17 (12.9)
Turbid urine	17 (12.9)
Fever	47 (35.6)
Scrotal pain	7 (5.3)

injury patients. Patients with SCI are particularly susceptible to surgical and hospital-acquired infections due to frequent interactions with healthcare staff and the use of invasive diagnostic and treatment methods. Among these infections and complications, pneumonia, urinary infections, and pressure ulcers are notable (26–28).

The findings indicate that the prevalence of UTI was higher among patients with a urinary catheter

compared to other patients, highlighting the high prevalence of catheter-associated urinary tract infections (CAUTI) in SCI patients. In Vinoth *et al.*'s study, the prevalence of CAUTI was 20%, with 70% of catheters placed in patients for 6 to 9 days and 30% for more than 10 days (29). Barbadoro *et al.* found that 40 (6.2%) of 641 patients had CAUTI, and the duration of hospitalization was longer for patients with CAUTI compared to those without (30). Additionally, Oumer *et al.* reported a 16.8%

Table 3. Frequency (%) of Types of Microorganisms Present in Urinary Tract Infection Infections of Patients with Spinal Cord Injury^a

Variables	Yes	No
<i>E. coli</i>	73	55.3
<i>Acinetobacter</i> spp.	9	6.8
<i>S. aureus</i>	7	5.3
<i>Proteus</i> spp.	15	11.4
<i>Klebsiella</i> spp.	12	9.1
<i>Candida</i> spp.	10	7.6
<i>Enterobacter</i> spp.	4	3
<i>Pseudomonas</i>	2	1.5
Total	132	100

^a Values are expressed as No. (%).

incidence rate of CAUTI symptoms in 231 patients, with increased incidence associated with factors such as diabetes, catheter insertion lasting more than 7 days, and insertion in the surgical department (31). Saint et al. found that implementing a specific program and interventions reduced the UTI rate from 2.4 to 2.05 per 1,000 patients (32).

Given the increased risk of UTIs and related complications associated with CAUTI, it is crucial to implement preventive measures to reduce the occurrence of UTIs and their complications (33, 34).

According to the findings, the prevalence of *E. coli* was 55.3%, and *Proteus* spp. was 11.4%. In the study by Togan et al., among patients with symptomatic urinary system infections (SUSI), the rates were as follows: *E. coli* was 10 (41.7%), *Enterococcus* spp. was 2 (8.3%), *Klebsiella* spp. was 5 (20.8%), *Acinetobacter* spp. was 3 (12.6%), and *Candida* spp. was 2 (8.3%) (35). Goodes et al. reported that among patients with SCI, the prevalence was as follows: *Escherichia coli* in 8 patients, *Klebsiella* spp. in 13 patients, *Enterobacter* spp. in 5 patients, *Enterococcus* spp. in 12 patients, *Pseudomonas aeruginosa* in 4 patients, and *Citrobacter koseri* in 1 patient (36). Bhatt et al. found that the prevalence of *S. aureus* and *E. coli* was both 12.2%, *P. mirabilis* was 9.8%, and *S. marcescens* was also 9.8% (37). Evans et al. reported the prevalence of *S. aureus* as 36.6%, *Enterococcus faecium* as 15.3%, *E. coli* as 14.9%, and *Pseudomonas aeruginosa* as 12.3% (38).

5.1. Conclusions

Given the significant prevalence of UTIs among patients, it is essential to implement preventive measures to mitigate infection risks.

Footnotes

Authors' Contribution: Study concept and design: S. S., KH. K., and R. R.; acquisition of the data: S. S. and R. R.; analysis and interpretation of the data: S. S., KH. K., and R. R.; drafting of the manuscript: S. S. and R. R.; critical revision of the manuscript for important intellectual content: S. S., KH. K., and R. R.; statistical analysis: S. S., KH. K., and R. R.; administrative, technical, and material support: S. S., KH. K., and R. R.; study supervision: S. S. and R. R.

Conflict of Interests Statement: The authors declare no conflict of interest.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: current study was conducted after approval by the Ethics Committee (IR.MEDILAM.REC.1402.022).

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References

1. Marcus JE, Shah A, Peek GJ, MacLaren G. Nosocomial infections in adults receiving extracorporeal membrane oxygenation: A review for infectious diseases clinicians. *Clin Infect Dis.* 2024;79(2):412-9. [PubMed ID: 38442737]. <https://doi.org/10.1093/cid/ciae120>.
2. Ghadiri F, Ebadi Z, Asadollahzadeh E, Sahaian MA, Azimi A, Navardi S, et al. Iranian specialists' approach to surgery in patients with multiple sclerosis. *Curr J Neurol.* 2023;22(2):96-102. eng. [PubMed ID: 38011379]. [PubMed Central ID: PMC10460921]. <https://doi.org/10.18502/cjn.v22i2.i3336>.
3. Mirmosayeb O, Barzegar M, Nehzat N, Najdaghi S, Ansari B, Shaygannejad V. Association of helicobacter pylori with multiple sclerosis: Protective or risk factor? *Curr J Neurol.* 2020;19(2):59-66. [PubMed ID: 38011437]. [PubMed Central ID: PMC7874896]. <https://doi.org/10.18502/cjn.v19i2.4942>.
4. Raoofi S, Pashazadeh Kan F, Rafiei S, Hosseinpalaangi Z, Noorani Mejareh Z, Khani S, et al. Global prevalence of nosocomial infection:

a systematic review and meta-analysis. *PLoS One.* 2023;18(1). e0274248. [PubMed ID: 36706112]. [PubMed Central ID: PMC9882897]. <https://doi.org/10.1371/journal.pone.0274248>.

5. Farahbakhsh A, Dezfoolian H, Khazaee S. Predictive classification of nosocomial infection type and treatment outcome using neural network algorithm. *Biomed Signal Processing Control.* 2024;95:106331. <https://doi.org/10.1016/j.bspc.2024.106331>.
6. Ducel G, Fabry J, Nicolle L. *Prevention of hospital acquired infections: A practical guide.* 2th ed. Geneva, Switzerland: World Health Organization; 2002.
7. Mosadeghrad AM, Afshari M, Isfahani P. [Prevalence of nosocomial infection in iranian hospitals: A systematic review and meta-analysis]. *Iran J Epidemiol.* 2021;16(4):352-62. Persian.
8. Rahimkhani M, Rajabi Z, Alavi FSS, Akbari S, Aliasghar M. [Investigation of efflux pump genes in staphylococcus aureus isolated from clinical samples]. *J Med Pharmaceutical Chem Res.* 2024;6(6):638-52. Persian.
9. Yazdani Cherati J, Shojaee J, Chaharkameh A, Rezai MS, Khosravi F, Rezai F, et al. [Incidence of nosocomial infection in selected cities according NISS software in Mazandaran province]. *J Mazandaran Univ Med Sci.* 2015;25(122):64-72. Persian.
10. Tian H, Chen L, Wu X, Li F, Ma Y, Cai Y, et al. Infectious complications in severe acute pancreatitis: Pathogens, drug resistance, and status of nosocomial infection in a university-affiliated teaching hospital. *Dig Dis Sci.* 2020;65(7):2079-88. [PubMed ID: 31691173]. <https://doi.org/10.1007/s10620-019-05924-9>.
11. Marchetti A, Rossiter R. Economic burden of healthcare-associated infection in us acute care hospitals: Societal perspective. *J Med Econ.* 2013;16(12):1399-404. [PubMed ID: 24024988]. <https://doi.org/10.3111/j13696998.2013.842922>.
12. Custovic A, Smajlović J, Husaric E, Jahic R, Dzafic F, Ibrahimagić O. Frequency and etiology of nosocomial infections in a pediatric intensive care unit. *Int Med.* 2021;3(2):59-64. <https://doi.org/10.5455/im.49683>.
13. Saedi S, Chakerzehi A, Soltani N, Honarmand M, Yazdanpanah M, Ghazvini K, et al. [Nosocomial urinary tract infections: Etiology, risk factors and antimicrobial pattern in Ghaem University Hospital in Mashhad]. *J Paramed Sci Rehabilitation.* 2013;2(1):22-5. Persian. <https://doi.org/10.22038/jpsr.2013.504>.
14. Medina-Polo J, Naber KG, Johansen TEB. Healthcare-associated urinary tract infections in urology. *GMS Infect Dis.* 2021;9. [PubMed ID: 34540531]. <https://doi.org/10.3205/ido00074>.
15. Nouri F, Karami P, Zarei O, Kosari F, Alikhani MY, Zandkarimi E, et al. Prevalence of common nosocomial infections and evaluation of antibiotic resistance patterns in patients with secondary infections in hamadan, iran. *Infect Drug Resist.* 2020;13:2365-74. [PubMed ID: 32765011]. [PubMed Central ID: PMC7369413]. <https://doi.org/10.2147/IDR.S259252>.
16. Kazeminezhad B, Taghinejad H, Borji M, Seymohammadi R. Evaluation of the prevalence of urinary tract infection in children with febrile seizure. *J Compr Ped.* 2018;9(3). <https://doi.org/10.5812/compreped.62557>.
17. Pham TB, Srinivas S, Martin JR, Brandel MG, Wali AR, Rennert RC, et al. Risk factors for urinary tract infection or pneumonia after admission for traumatic subdural hematoma at a level i trauma center: Large single-institution series. *World Neurosurg.* 2020;134:e754-60. [PubMed ID: 3172113]. <https://doi.org/10.1016/j.wneu.2019.10.192>.
18. Hatefi M, KomLakh K. Investigation of the effect of Duloxetine on pain status of patients with spinal cord injuries: A systematic review of drug therapy. *Eurasian Chemical Communications.* 2022;4(3):256-62. <https://doi.org/10.22034/ecc.2022.324516.1298>.
19. Hatefi M, Vaisi-Raygani A, Borji M, Tarjoman A. Investigating the relationship between religious beliefs with care burden, stress, anxiety, and depression in caregivers of patients with spinal cord injuries. *J Relig Health.* 2020;59(4):1754-65. [PubMed ID: 31187306]. <https://doi.org/10.1007/s10943-019-00853-3>.
20. Hatefi M, Abdi A, Tarjoman A, Borji M. Prevalence of depression and pain among patients with spinal cord injury in Iran: A systematic review and meta-analysis. *Trauma Mon.* 2019;24(4):1-8. <https://doi.org/10.5812/traumamon.87503>.
21. Komlakh K, Karbasfrushan A. The effect of Pregabalin on the pain status of patients with disc and spinal surgeries: A systematic review of drug therapy. *Eurasian Chem Communications.* 2022;4(11):1147-55. <https://doi.org/10.22034/ecc.2022.348692.1491>.
22. Youzbashizadeh Y, Saeedi M, Abbasi SZ, Bolvardi E, Sobhani M, Foroughian M, et al. [Serum troponin level relationship with prognosis of nontraumatic cerebral hemorrhage]. *J Med Pharmaceutical Chem Res.* 2023;6(4):447-55. Persian. <https://doi.org/10.48309/JMPCR.2024.430139.1057>.
23. Wang B, Zheng P, Zhang Y, Liu W, Liu L, Wang Y. A nomogram for predicting the hospital-acquired infections in children with spinal cord injuries: A retrospective, multicenter, observational study. *Spinal Cord.* 2024;62(4):183-91. [PubMed ID: 38409493]. <https://doi.org/10.1038/s41393-024-00966-x>.
24. Brady J, Loyola-Sánchez A, Crochetiere S, MacIsaac R, Kulik E, Okuma Y, et al. Urinary tract infections and urinary bladder health experiences of persons with spinal cord injury in a Canadian province: A mixed methods study showcasing infection prevention as health inequity case. *J Spinal Cord Med.* 2024:1-13. [PubMed ID: 38232152]. <https://doi.org/10.1080/10790268.2023.2287253>.
25. Yan L, Ge H, Zhang Y, Li N. Epidemiology of pathogens and antimicrobial resistance of nosocomial urinary tract infections in patients with spinal cord injuries in china: A systematic review and meta-analysis. *J Spinal Cord Med.* 2023;46(4):632-48. [PubMed ID: 36622339]. [PubMed Central ID: PMC10274538]. <https://doi.org/10.1080/10790268.2022.2129154>.
26. Karimian M, Khalighi E, Salimi E, Borji M, Tarjoman A, Mahmoudi Y. The effect of educational intervention on the knowledge and attitude of intensive care nurses in the prevention of pressure ulcers. *Int J Risk Saf Med.* 2020;31(2):89-95. [PubMed ID: 32039864]. <https://doi.org/10.3233/JRS-191038>.
27. Garcia-Arguello LY, O'Horo JC, Farrell A, Blakney R, Sohail MR, Evans CT, et al. Infections in the spinal cord-injured population: A systematic review. *Spinal Cord.* 2017;55(6):526-34. [PubMed ID: 27922625]. <https://doi.org/10.1038/sc.2016.173>.
28. Kinnear N, Barnett D, O'Callaghan M, Horsell K, Blakney R, Sohail MR, Evans CT, et al. The impact of catheter-based bladder drainage method on urinary tract infection risk in spinal cord injury and neurogenic bladder: A systematic review. *Neurourol Urodyn.* 2020;39(2):854-62. [PubMed ID: 31845396]. <https://doi.org/10.1002/nau.24253>.
29. Vinoth M, Prabagaravarthanam R, Bhaskar M. Prevalence of microorganisms causing catheter associated urinary tract infections (CAUTI) among catheterised patients admitted in a tertiary care hospital. *Int J Res Med Sci.* 2017;5(6):2367-72. <https://doi.org/10.18203/2320-6012.ijrms20172084>.
30. Barbadoro P, Labricciosa FM, Recanatini C, Gori G, Tirabassi F, Martini E, et al. Catheter-associated urinary tract infection: Role of the setting of catheter insertion. *Am J Infect Control.* 2015;43(7):707-10. [PubMed ID: 25840715]. <https://doi.org/10.1016/j.ajic.2015.02.011>.
31. Oumer Y, Regasa Dadi B, Seid M, Biresaw G, Manilal A. Catheter-associated urinary tract infection: Incidence, associated factors and drug resistance patterns of bacterial isolates in Southern Ethiopia. *Infect Drug Resist.* 2021;14:2883-94. [PubMed ID: 34335034]. [PubMed Central ID: PMC8318706]. <https://doi.org/10.2147/IDR.S311229>.
32. Saint S, Greene MT, Krein SL, Rogers MA, Ratz D, Fowler KE, et al. A program to prevent catheter-associated urinary tract infection in acute care. *N Engl J Med.* 2016;374(22):2111-9. [PubMed ID: 27248619].

[PubMed Central ID: [PMC9661888](https://doi.org/10.1056/NEJMoa1504906)].

33. Parker V, Giles M, Graham L, Suthers B, Watts W, O'Brien T, et al. Avoiding inappropriate urinary catheter use and catheter-associated urinary tract infection (CAUTI): A pre-post control intervention study. *BMC Health Serv Res.* 2017;17(1):314. [PubMed ID: [28464815](https://doi.org/10.1186/s12913-017-2268-2)]. [PubMed Central ID: [PMC5414128](https://doi.org/10.1186/s12913-017-2268-2)]. <https://doi.org/10.1186/s12913-017-2268-2>.

34. Advani SD, Fakih MG. The evolution of catheter-associated urinary tract infection (CAUTI): Is it time for more inclusive metrics? *Infect Control Hosp Epidemiol.* 2019;40(6):681-5. [PubMed ID: [30915925](https://doi.org/10.1017/ice.2019.43)]. <https://doi.org/10.1017/ice.2019.43>.

35. Togan T, Azap OK, Durukan E, Arslan H. The prevalence, etiologic agents and risk factors for urinary tract infection among spinal cord injury patients. *Jundishapur J Microbiol.* 2014;7(1):e8905. [PubMed ID: [25147663](https://doi.org/10.5812/jjm.8905)]. [PubMed Central ID: [PMC4138667](https://doi.org/10.5812/jjm.8905)]. <https://doi.org/10.5812/jjm.8905>.

36. Goodes LM, King GK, Rea A, Murray K, Boan P, Watts A, et al. Early urinary tract infection after spinal cord injury: A retrospective inpatient cohort study. *Spinal Cord.* 2020;58(1):25-34. [PubMed ID: [31388122](https://doi.org/10.1038/s41393-019-0337-6)]. <https://doi.org/10.1038/s41393-019-0337-6>.

37. Bhatt K, Cid E, Maiman D. Bacteremia in the spinal cord injury population. *J Am Paraplegia Soc.* 1987;10(1):11-4. [PubMed ID: [3572393](https://doi.org/10.1080/01952307.1987.11719628)]. <https://doi.org/10.1080/01952307.1987.11719628>.

38. Evans CT, Burns SP, Chin A, Weaver FM, Hershow RC. Predictors and outcomes of antibiotic adequacy for bloodstream infections in veterans with spinal cord injury. *Arch Phys Med Rehabil.* 2009;90(8):1364-70. [PubMed ID: [19651270](https://doi.org/10.1016/j.apmr.2009.02.012)]. <https://doi.org/10.1016/j.apmr.2009.02.012>.