



The Prevalence of *Clostridium difficile* Colitis and Effect on All-Cause Mortality in Elderly Patients after Hip Fracture Surgery: A Korean Nationwide Cohort Study

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Background: This study aimed to investigate the prevalence of *Clostridium difficile* colitis (CDC) in elderly patients with hip fractures using a nationwide cohort database and to analyze the effect of CDC on the all-cause mortality rate after hip fracture.

Methods: This retrospective nationwide study identified subjects from the Korean National Health Insurance Service-Senior cohort. The subjects of this study were patients who were over 65 years old and underwent surgical treatment for hip fractures from January 1, 2002, to December 31, 2015. The total number of patients included in this study was 10,158. The diagnostic code used in this study was A047 of the International Classification of Diseases, 10th revision for identifying CDC. Procedure codes for *C. difficile* culture or toxin assay were BY021 and BY022. CDC patients were defined as follows: patients treated with oral vancomycin or metronidazole over 10 days and patients with procedure codes BY021 and BY022 or diagnostic code A047 after hip fracture. Incidence date (index date, time zero) of hip fracture for analyzing risk of all-cause mortality was defined as the date of discharge. A generalized estimating equation model with Poisson distribution and logarithmic link function was used for estimating adjusted risk ratios and 95% confidence intervals to assess the association between CDC and cumulative mortality risk.

Results: The prevalence of CDC during the hospitalization period in the elderly patients with hip fractures was 1.43%. Compared to the non-CDC group, the CDC group had a 2.57-fold risk of 30-day mortality after discharge, and a 1.50-fold risk of 1-year mortality after discharge ($p < 0.05$).

Conclusions: The prevalence of CDC after hip fracture surgery in elderly patients was 1.43%. CDC after hip fracture in the elderly patients significantly increased the all-cause mortality rate after discharge.

Keywords: Elderly, Hip fracture, *Clostridium difficile* colitis, Pseudomembranous colitis, National Health Insurance

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Antibiotics are commonly used in elderly patients not only for surgical treatment, but also for the treatment of peri-operative complications, such as pneumonia and urinary tract infection.^{1,2)} However, sometimes the adverse effects of antibiotics can put patients at risk. *Clostridium difficile* is a gram-positive, anaerobic bacterium and is found as part of normal flora in the intestines.³⁾ *Clostridium difficile* colitis (CDC) occurs when antibiotics disrupt the normal colonic flora and is the most common healthcare-associated infection in hospital patients.^{4,5)} Different types of toxins are expressed according to the gene type of *C. difficile* and human immune responses and patient symptoms may differ depending on the type of toxin.³⁾ These toxins locally cause intestinal epithelial disruption and systemic inflammation. As a result, it is possible to lead to electrolyte imbalance, nutritional abnormality, and systematic septic conditions. Thus, symptoms may vary from profuse diarrhea or bloody diarrhea to toxic megacolon or bowel perforation, which can lead to death.⁶⁾ CDC also increases length of hospital stay (LOS) and treatment costs.^{7,8)} The incidence of CDC in the orthopedic surgery varies depending on the surgical site and surgical method.^{1,5,9,10)}

Previously, numerous studies have reported CDC infection as a cause of increased mortality after surgery in elderly patients.^{11,12)} But, reports on the effects of CDC in elderly patients with hip fractures and relationship with high morbidity and mortality due to underlying disease are scarce.^{2,10,13)} These studies compared antibiotic regimens that may reduce the incidence of CDC. Based on the results of previous studies, the effects of CDC on mortality in elderly patients with hip fractures varied depending on the healthcare system of each institution. Therefore, in the present study, we aimed to investigate the prevalence of CDC in elderly patients with hip fractures using a nationwide cohort database to reduce selection bias and to analyze the effect of CDC on all-cause mortality after hip fracture.

METHODS

Study Subjects

This retrospective nationwide study identified subjects from the South Korean National Health Insurance Service-Senior (NHIS-Senior) cohort compiled by the NHIS. South Korea has a single-payer healthcare system for universal health coverage and the NHIS collects all personal information, such as demographics and medical treatment data for Korean people.^{14,15)} The NHIS-Senior was constructed to represent the elderly > 60 years of age in South Korea. The information in NHIS-Senior include

all outpatient and inpatient medical claims data, including treatment or procedure codes and diagnostic codes. A total of 588,147 participants who were > 60 years of age in 2002 were randomly selected from the NHIS-Senior cohort for this study using 10% simple random sampling. They had been followed up until December 31, 2015, unless disqualified for National Health Insurance due to emigration or death. This study protocol was approved by the Institutional Review Board of Eulji University Hospital (No. EMC 2018-02-011-002). Informed consent was waived because of the retrospective nature of the study.

Elderly Hip Fracture Cohort

Eligibility criteria for elderly patients with hip fractures were as follows: (1) first admission to an acute care hospital with diagnostic codes for femoral neck fractures (International Classification of Diseases, 10th revision [ICD-10]: S720) or intertrochanteric fracture (ICD-10: S721);^{16,17)} (2) having at least 3-year hip fracture-free period;^{18,19)} (3) recipients of typical surgical treatments including internal fixation (open reduction [femur], closed pinning [femur], hemiarthroplasty [hip], and total arthroplasty [hip]); and (4) age 65–99 years at the time of index admission to assure inclusion of only osteoporotic hip fractures.¹⁷⁾

Exclusion criteria were as follow: (1) hip fractures that had occurred less than 1 year before the end of the observation period (December 31, 2015) to ensure a minimal 1-year follow-up period, (2) hip fractures diagnosed before December 31, 2004, to guarantee at least 3-year hip fracture-free period, (3) cancer history,²⁰⁾ and (4) use of antibiotics (clindamycin, cephalosporin, and penicillin) during preoperative 1 month,⁴⁾ (5) use of nonoperative treatment. The last date of follow-up was defined as December 31, 2015, or the date of death, whichever came first. From January 1, 2002, to December 31, 2015, a total of 19,915 patients were hospitalized for hip fractures. Of those, 9,757 patients who did not meet the inclusion criteria were excluded (Fig. 1). Finally, the total number of patients included in this study was 10,158.

Clostridium difficile Colitis

The diagnostic code used in this study was A047 of ICD-10 for identifying CDC during the admission period for hip fractures. Procedure codes for *C. difficile* culture or toxin assay were BY021 and BY022. CDC patients were defined as follows: patients treated with oral vancomycin or metronidazole over 10 days and patients with the ICD-10 procedure codes or diagnostic code after hip fracture.^{4,21)}

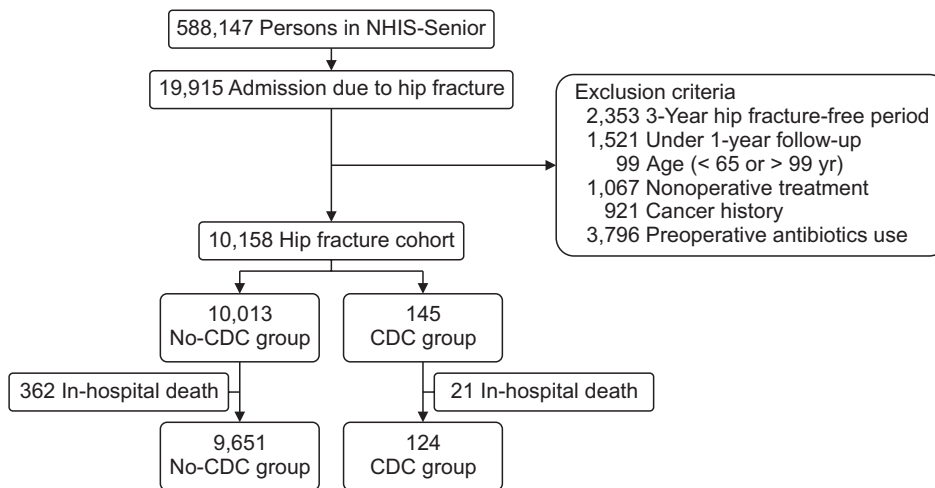


Fig. 1. Flowchart of this study. NHIS: National Health Insurance Service, CDC: *Clostridium difficile* colitis.

All-Cause Mortality

Incidence date (index date, time zero) of hip fracture for analyzing risk of all-cause mortality was defined as the date of discharge for preventing immortal time bias. The de-identified numbers of all subjects in NHIS-Senior were linked to information of mortality from the Korean National Statistical Office.¹⁵⁾ Survival time for calculating mortality rates was defined as period from the index date to date of death or December 31, 2015, whichever came first.

Statistical Analysis

Baseline characteristics were identified on the day of acute care hospitalization. Survival curves and cumulative survival probabilities were estimated and diagrammed by the Kaplan-Meier method using the product-limit formula. A generalized estimating equation model with Poisson distribution and logarithmic link function was used for estimating adjusted risk ratios (aRRs) and 95% confidence intervals (CIs) to assess the association between CDC and cumulative mortality risk at 30 days, 60 days, 90 days, 180 days, and 1 year.

Included covariates were age group, sex, residential area, household income level, Charlson Comorbidity Score (CCS), type of fracture, type of surgery, type of anesthesia, LOS, number of hospital beds, and calendar year of the hip fracture incidence. Each subject's number of comorbidities was assessed by diagnostic codes during 3 years before the index date using the ICD-10 coding algorithm for the CCS suggested by Quan et al.²²⁾ The presence of CCS disease-constituting categories was defined as at least two outpatient visits or one admission upon the primary or first secondary diagnosis. Statistical analyses were conducted using SAS Enterprise Guide ver. 7.1 (SAS Institute, Cary,

NC, USA). The p -values < 0.05 were considered statistically significant.

RESULTS

Included patients were divided into two groups: 145 (1.43%) in the CDC group and 10,013 (98.57%) in the non-CDC group (Table 1). There were 383 deaths in the hospital. In-hospital mortality rate was 3.62% (362 patients) in the non-CDC group and 14.48% (21 patients) in the CDC group. Enrolled subjects for analysis of all-cause mortality were 9,775 patients (CDC group: 124 patients, non-CDC group: 9,651 patients) (Table 1). There were statistically significant differences in age group, number of hospital beds, and calendar year between the two groups (all $p < 0.05$). The mean LOS was 35.02 ± 35.89 days in the non-CDC group and 67.91 ± 63.80 days in the CDC group ($p < 0.001$).

The 30-day, 60-day, 90-day, 180-day, and 1-year cumulative mortality rates after discharge were 2.27%, 3.92%, 5.29%, 8.38%, and 13.50%, respectively, in the non-CDC group, and 6.45%, 11.29%, 13.71%, 18.55%, and 21.77%, respectively, in the CDC group (Fig. 2). Compared to the non-CDC group, the CDC group was 2.57 times (aRR, 2.57; 95% CI, 1.51–4.37; $p = 0.001$) and 2.17 times (aRR, 2.17; 95% CI, 1.51–3.11; $p = 0.001$) more likely to experience all-cause mortality within 30 days and within 90-days, respectively. Then, the risk continued to decrease in the CDC group to 1.50 times (aRR, 1.50; 95% CI, 1.16–1.93; $p = 0.002$) the risk of 1-year all-cause mortality after discharge of the non-CDC group (Table 2).

Table 1. Baseline Characteristics of Study Participants at Time Zero

| Variable | No-CDC group | CDC group | p-value |
|----------------------------|---------------|---------------|---------|
| Number | 9,651 (98.73) | 124 (1.27) | - |
| Age group (yr) | | | 0.008 |
| 65–69 | 557 (5.77) | 4 (3.23) | |
| 70–79 | 4,039 (41.85) | 36 (29.03) | |
| 80–89 | 4,248 (44.02) | 70 (56.45) | |
| ≥ 90 | 807 (8.36) | 14 (11.29) | |
| Sex | | | 0.375 |
| Male | 2,192 (22.71) | 24 (19.35) | |
| Female | 7,459 (77.29) | 100 (80.65) | |
| Income | | | 0.342 |
| Low | 1,350 (13.99) | 24 (19.35) | |
| Middle–low | 1,793 (18.58) | 24 (19.35) | |
| Middle–high | 2,263 (23.45) | 25 (20.16) | |
| High | 4,245 (43.99) | 51 (41.13) | |
| Residential area | | | 0.116 |
| Metropolitan | 3,943 (40.86) | 42 (33.87) | |
| Non-metropolitan | 5,708 (59.14) | 82 (66.13) | |
| Charlson Comorbidity Score | | | 0.158 |
| 0 | 2,592 (26.86) | 23 (18.55) | |
| 1–2 | 4,471 (46.33) | 63 (50.81) | |
| 3–5 | 2,236 (23.17) | 31 (25.00) | |
| ≥ 6 | 352 (3.65) | 7 (5.65) | |
| Fracture type | | | 0.785 |
| Neck fracture | 5,100 (52.84) | 64 (51.61) | |
| Intertrochanter fracture | 4,551 (47.16) | 60 (48.39) | |
| Surgery type | | | 0.110 |
| Hemiarthroplasty | 4,853 (50.28) | 74 (59.68) | |
| Internal fixation | 4,556 (47.01) | 48 (38.71) | |
| Total hip arthroplasty | 242 (2.51) | 2 (1.61) | |
| Length of stay (day) | 35.02 ± 35.89 | 67.91 ± 63.80 | < 0.001 |
| Anesthesia | | | 0.106 |
| General | 2,224 (23.04) | 37 (29.84) | |
| Spinal | 6,904 (71.54) | 78 (62.90) | |
| Unknown | 523 (5.42) | 9 (7.26) | |

Table 1. Continued

| Variable | No-CDC group | CDC group | p-value |
|----------------------|---------------|------------|---------|
| No. of hospital beds | | | 0.004 |
| < 200 | 2,001 (20.73) | 35 (28.23) | |
| 200–499 | 1,694 (17.55) | 19 (15.32) | |
| 500–799 | 3,484 (36.10) | 54 (43.55) | |
| ≥ 800 | 2,472 (25.61) | 16 (12.90) | |
| Calendar year | | | 0.003 |
| 2006–2007 | 1,569 (16.26) | 6 (4.84) | |
| 2008–2009 | 1,689 (17.50) | 19 (15.32) | |
| 2010–2011 | 2,064 (21.39) | 27 (21.77) | |
| 2012–2013 | 2,178 (22.57) | 32 (25.81) | |
| 2014–2015 | 2,151 (22.29) | 40 (32.26) | |

Values are presented as number (%).
CDC: *Clostridium difficile* colitis.

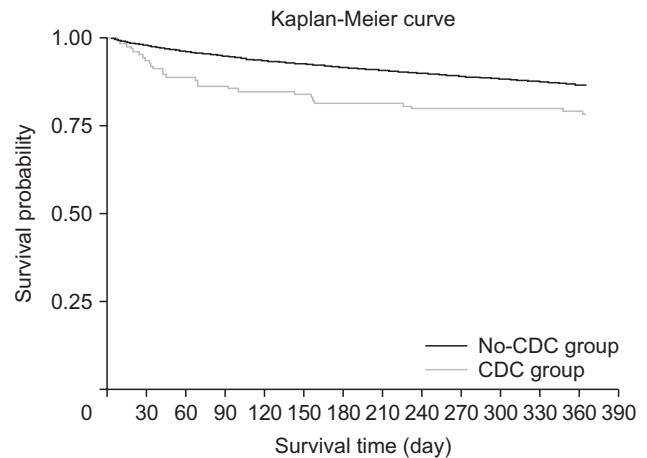


Fig. 2. Kaplan-Meier curve of hip fracture patients according to *Clostridium difficile* colitis (CDC). The p-value of the log-rank test was < 0.001.

DISCUSSION

The main findings of this study are as follows: The prevalence of CDC during hospitalization in the elderly patients with hip fractures was 1.43% (145 of 10,158 patients). Compared to the non-CDC group, the CDC group was 2.57 times and 1.50 times more likely to experience 30-day mortality and 1-year mortality after discharge, respectively. Although use of broad spectrum antibiotics, such as fluoroquinolones or cephalosporins, is the main causal factor of CDC, various preoperative and postoperative factors are associated with development of CDC.^{23,24)} Bovon-

Table 2. Effect of CDC on All-Cause Mortality of Different Time Frame after Discharge

| Variable | No. of deaths | No. of subjects | Mortality rate (%) | aRR | 95% CI | p-value |
|------------------|---------------|-----------------|--------------------|---------------|-----------|---------|
| 30-Day mortality | | | | | | |
| No-CDC group | 219 | 9,651 | 2.27 | 1 (Reference) | | |
| CDC group | 8 | 124 | 6.45 | 2.57 | 1.51–4.37 | 0.001 |
| 90-Day mortality | | | | | | |
| No-CDC group | 511 | 9,651 | 5.29 | 1 (Reference) | | |
| CDC group | 17 | 124 | 13.71 | 2.17 | 1.51–3.11 | < 0.001 |
| 1-Year mortality | | | | | | |
| No-CDC group | 1,303 | 9,651 | 13.50 | 1 (Reference) | | |
| CDC group | 27 | 124 | 21.77 | 1.50 | 1.16–1.93 | 0.002 |

CDC: *Clostridium difficile* colitis, aRR: adjusted risk ratio, CI: confidence interval.

ratwet et al.²⁴⁾ analyzed the risk factors of CDC in geriatric hip fractures from National Surgical Quality Improvement Program database. They found that identifiable preoperative factors were admission from a chronic care facility and anemia and postoperative factors were any infections, such as pneumonia or sepsis. In a study using a large national database, Malik et al.²³⁾ reported that preoperative factors for CDC were smoking, hypertension, hyponatremia, and prior systemic inflammatory response syndrome and postoperative factors were deep surgical site infection and unplanned reoperation. Also, several studies previously reported that smoking was the risk factor for development of CDC.^{23–25)} Because CDC is a typical nosocomial infection, long-term hospitalization is also a risk factor.²³⁾ Napolitano and Edmiston²⁶⁾ mentioned that increased age, nasogastric tube, and kidney disease were also included in risk factors for CDC.

Delanois et al.⁵⁾ reported risk factors and costs for CDC in 40,876 patients with prosthetic joint infection undergoing revision arthroplasty in National Inpatient Sample database. They suggested that despite the overall incidence of 1.7%, CDC is an uncommon event following revision THA and can have potentially devastating consequences. Jenkins et al.⁹⁾ reported the incidence of CDC was 17 per 1,000 cases of primary total joint arthroplasty. Bovonratwet et al.²⁷⁾ investigated the incidence of CDC in 23,981 patients after spine surgery through an analysis of a national database. The incidence of CDC was about 0.11%. It seems that the incidence of CDC varies depending on the type of orthopedic surgery and the target patients. Sharma et al.¹⁰⁾ reported the incidence of CDC was 7.1% in 239 patients with intertrochanteric fractures after inter-

nal fixation. Starks et al.¹³⁾ also reported the results of their 4-year case-control study about the incidence of CDC after change of antibiotics in hip fracture patients from 2003 to 2005. The incidence of CDC was 4.2% in the initial group (912 patients) and 1.6% in the new regimen group (899 patients). These studies have a weakness in that the number of included patients with hip fractures was small. Bovonratwet et al.²⁴⁾ reported that the incidence of CDC was 1.05% in 6,928 patients with elderly hip fractures through an analysis of National Surgical Quality Improvement Program dataset. In our study, the prevalence of CDC during hospitalization in elderly patients with hip fractures was 1.43%. The incidence of CDC appeared to be comparable among studies using large national databases.

Bovonratwet et al.²⁴⁾ reported that 30-day mortality rate in patients with CDC was 15% of the total 6,928 elderly patients with hip fractures in a large national database, which was 3.41 times higher than that of the patients without CDC. In a matched cohort study by Gulihar et al.,²⁾ the cumulative 6-month mortality rate was 71% in 170 CDC patients after hip fracture and 27% in 3,247 non-CDC patients with hip fracture. Starks et al.¹³⁾ reported that 30-day mortality rate after hip fracture surgery was 31.8% in a CDC group and 9% in a non-CDC group, showing statistically significant difference. In our study, mortality rates were 6.45%, 11.29%, 13.71%, and 21.77% within 30 days, 60 days, 90 days, and 1 year after discharge, respectively. It is difficult to directly compare mortality rates between studies because patient profile, surgery type, antibiotic regimens, and healthcare systems vary.¹⁰⁾ However, CDC seems to be a factor influencing not only short-term mortality but also long-term mortality after hip fracture sur-

gery.

Our study has several limitations. First, this study did not consider severity of CDC because CDC was defined by diagnostic and procedure codes, and there is a possibility that the number of CDC patients was underestimated. Second, the national medical claims data did not collect information about preoperative medical optimization or perioperative antibiotics use. Therefore, the protocols of each hospital were not considered in this study. Third, we could not analyze risk factors of CDC due to the inherent limitations of national claims data with insufficient clinical information. In conclusion, the prevalence of CDC after hip fracture surgery in elderly patients was 1.43%. CDC after hip fracture in elderly patients significantly increased the all-cause mortality rate after discharge.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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