

# Prevalence, Associated Factors, and Outcomes of Clostridioides difficile Infection Across Gastrointestinal Cancer Subtypes: A US Nationwide Analysis

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## Research Article

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## Abstract

## Purpose

This study aimed to evaluate the prevalence, factors associated with, and clinical and healthcare impact of *Clostridioides difficile* infection (CDI) among hospitalized adults with gastrointestinal (GI) cancer.

## Methods

We performed a retrospective cross-sectional analysis of the National Inpatient Sample (2018–2023). Adult hospitalizations with active GI cancer were stratified by CDI status. Survey-weighted multivariable regression identified factors associated with CDI and its associations with in-hospital mortality, mechanical ventilation, vasopressor use, renal replacement therapy (RRT), length of stay (LOS), and hospital charges.

## Results

Among 3,572,119 weighted GI cancer hospitalizations, 48,900 (1.37%; 95% CI, 1.34–1.40) involved CDI. Prevalence declined from 1.63% in 2018 to 1.22% in 2023. Inflammatory bowel disease was most strongly associated with CDI (adjusted odds ratio [aOR], 2.47; 95% CI, 2.15–2.85), followed by chronic kidney disease (aOR, 1.61; 95% CI, 1.52–1.71) and solid organ transplantation (aOR, 1.51; 95% CI, 1.15–1.98). Anal cancer had the highest CDI prevalence (2.32%). CDI was associated with higher in-hospital mortality (aOR, 1.34; 95% CI, 1.23–1.46), mechanical ventilation (aOR, 1.87; 95% CI, 1.71–2.05), vasopressor use (aOR, 1.84; 95% CI, 1.61–2.10), and RRT (aOR, 2.27; 95% CI, 2.01–2.56). CDI was associated with 65% longer LOS (LOS ratio, 1.65; 95% CI, 1.61–1.69) and 40% higher charges (charge ratio, 1.40; 95% CI, 1.35–1.45).

## Conclusion

CDI occurred in approximately 1 in 73 GI cancer hospitalizations and was associated with higher mortality, organ-support requirements, and healthcare utilization, supporting targeted prevention and early recognition strategies among hospitalized patients with GI cancer.

## Introduction

*Clostridioides difficile* infection (CDI) is a leading health care-associated infection in the United States [1, 2]. An estimated 462,100 cases occurred in the United States in 2017 [1]. Earlier national surveillance from 2011 estimated nearly 15,000 deaths directly attributable to CDI and 29,000 deaths within 30 days of diagnosis [3–5]. CDI also imposes substantial economic burden, with attributable costs exceeding \$21,000 per episode and total US hospital costs estimated at \$6.3 billion in 2015 [6]. Identifying populations at increased risk remains important despite advances in antimicrobial stewardship and infection prevention [1].

Patients with gastrointestinal (GI) cancer may be particularly vulnerable to CDI because of immunosuppression, frequent antibiotic exposure, repeated health care encounters, GI surgery, and mucosal injury from chemotherapy or abdominal radiation [3, 7–10]. In a recent nationwide analysis, GI malignancies had the highest CDI prevalence among hospitalized patients with solid tumors, at approximately 14 cases per 1,000 hospitalizations [11]. CDI in patients with cancer has also been associated with increased mortality, longer hospitalization, and greater health care utilization [11, 12].

Prior studies have generally evaluated cancer as a single group, focused on one malignancy, or lacked detailed analyses across individual GI cancer sites [11–13]. Although a recent nationwide study characterized CDI prevalence and outcomes across all cancer-related hospitalizations, it did not comprehensively evaluate factors associated with CDI or compare outcomes across the full spectrum of GI cancer subtypes [11]. We therefore aimed to estimate the prevalence of CDI, identify factors independently associated with CDI, and characterize CDI-associated inpatient outcomes across 12 GI cancer subtypes using a contemporary, nationally representative database.

## Methods

### Study Design and Data Source

We performed a retrospective cross-sectional study using the National Inpatient Sample (NIS) database from 2018 through 2023. The NIS was developed by the Healthcare Cost and Utilization Project (HCUP) and is the largest all-payer inpatient database in the United States. This database contains a 20% stratified random sample of all hospital discharges nationwide and provides information for admissions, including patient demographics, clinical diagnoses, procedures, hospital characteristics, and healthcare utilization outcomes. Discharge-level weights permit generation of nationally representative estimates. This study used deidentified data from the National Inpatient Sample and did not involve identifiable human participants. Institutional review board approval was not required. This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [14].

### Study Population and Variables

We identified hospitalizations involving adults aged 18 years or older with a principal or secondary diagnosis of GI cancer using appropriate *International Classification of Diseases, Tenth Revision (ICD-10)* codes (Supplementary Table 1). The unit of analysis was individual hospitalizations. Hospitalizations with history-of-cancer codes only without a concurrent active cancer diagnosis were excluded. CDI was identified using ICD-10 codes A04.71 and A04.72.

Patient and admission characteristics included age, sex, race and ethnicity, primary payer, median household income quartile for the patient's ZIP code, admission type, and weekend admission. Race and ethnicity were obtained as reported by participating hospitals. Hospital characteristics included bed size, rural or urban location, teaching status, and US Census region. Comorbidities of interest included inflammatory bowel disease (IBD), chronic kidney disease (CKD), solid organ transplant history, HIV/AIDS, cirrhosis, chronic obstructive pulmonary disease (COPD), diabetes mellitus, and obesity. Each comorbidity was identified using ICD-10 codes (Supplementary Table 1).

GI cancers were classified into 12 subtypes encompassing the anatomic spectrum of the alimentary tract and its accessory digestive organs, consistent with site-specific classifications used by the Global Cancer Observatory (GLOBOCAN) 2022 [15] and the World Health Organization (WHO) Classification of Digestive System Tumors (5th edition) [16]. These subtypes included esophageal, gastric, small intestine, colorectal, anal, pancreatic, gallbladder, biliary tract, cholangiocarcinoma, liver cancer, peritoneal/retroperitoneal, and colorectal carcinoid cancers. Cancer subtype indicators were analyzed separately in the regression models.

## Study Outcomes

The primary study objectives were to estimate hospitalization-level CDI prevalence and identify factors independently associated with CDI. Secondary outcomes included in-hospital mortality, invasive mechanical ventilation, vasopressor use, renal replacement therapy (RRT), hospital length of stay (LOS), and total hospital charges. Exploratory analyses examined the associations between CDI and these outcomes within individual GI cancer subtypes.

## Statistical Analysis

All analyses accounted for the NIS complex survey design, using discharge-level weights, hospital-level strata, and primary sampling units to generate nationally representative estimates. Continuous variables were reported as means with standard deviations and compared using survey-weighted linear regression. Categorical variables were summarized as proportions and compared using Rao-Scott chi-square tests. Differences in clinical outcomes between those with and without CDI were reported as odds ratios (OR) and adjusted odds ratios (aOR). Confidence intervals (CI) were reported at the 95% level.

Factors independently associated with CDI and binary clinical outcomes were evaluated using survey-weighted multivariable logistic regression. Results are reported as odds ratios (ORs) and adjusted odds ratios (aORs). Multivariable models adjusted for age category, sex, race and ethnicity, primary payer, median household income quartile, hospital bed size, hospital location and teaching status, admission type, geographic region, inflammatory bowel disease, solid organ transplant history, HIV/AIDS, cirrhosis, chronic kidney disease, chronic obstructive pulmonary disease, obesity, and diabetes mellitus. Individual GI cancer subtypes were included as separate binary indicators. The Elixhauser Comorbidity Index was used to describe overall comorbidity burden but was not included in the multivariable models because individual comorbidities of clinical interest were entered separately.

Because hospital length of stay and total hospital charges were right-skewed, length of stay was modeled using negative binomial regression, and total hospital charges were modeled using a generalized linear model with a gamma distribution and log link. Exponentiated coefficients are reported as length-of-stay ratios and charge ratios, respectively. These estimates represent the multiplicative difference in expected length of stay or hospital charges associated with CDI compared with hospitalizations without CDI.

Exploratory subtype-specific models were fit separately within 11 evaluable GI cancer subtypes; colorectal carcinoid was excluded because of insufficient CDI events. A Bonferroni-corrected threshold of  $P < .0045$  (.05/11 cancer subtypes) was applied. Subtype-specific models adjusted for age category, sex, race and ethnicity, primary payer, geographic region, chronic kidney disease, cirrhosis, inflammatory bowel disease, chronic obstructive pulmonary disease, obesity, admission type, and diabetes mellitus. A reduced covariate set was used to preserve model stability given smaller event counts. Subtype-specific findings, particularly those with borderline or nominal significance that did not meet the Bonferroni-corrected threshold, were interpreted cautiously and considered hypothesis-generating. For the primary analyses,  $P < .05$  was considered statistically significant; for subtype-specific comparisons, the Bonferroni-corrected threshold was applied. Analyses were performed using Stata version 19.0 (StataCorp).

## Results

### Baseline Characteristics and Hospital-Level Characteristics

This study included 3,572,119 weighted adult hospitalizations with an active GI cancer diagnosis from 2018 through 2023. Of these, 48,900 hospitalizations (1.37%) included a concurrent principal or secondary diagnosis of CDI. Compared with hospitalizations without CDI, those with CDI involved older patients (mean [SD] age, 68.2 [12.2] vs 66.7 [12.7] years), more women (48.0% vs 43.0%), more Medicare beneficiaries (65.1% vs 58.3%), and more nonelective (89.5% vs 74.9%) and weekend (22.3% vs 18.0%) admissions (all  $P < .001$ ). Hospitalizations with CDI more frequently involved White individuals (72.5% vs 67.5%) and less frequently involved Black individuals (11.7% vs 13.5%) and Hispanic individuals (8.9% vs 11.1%) compared with hospitalizations without CDI ( $P < .001$  for the overall comparison) (Table 1).

Table 1

Baseline Demographic, Hospital-level, and Clinical Characteristics of Adult Gastrointestinal Cancer Hospitalizations by Clostridioides difficile Infection Status.

| Characteristic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Hospitalizations, No. (%) |                  |         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------|---------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | No CDI (n = 3,523,219)    | CDI (n = 48,900) | P value |
| Demographics                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                           |                  |         |
| Age, mean (SD), yrs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 66.7 (12.7)               | 68.2 (12.2)      | < .001  |
| Female sex                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 1,516,310 (43.0)          | 23,480 (48.0)    | < .001  |
| Race/Ethnicity <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                           |                  | < .001  |
| White                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1,906,404 (67.5)          | 29,150 (72.5)    |         |
| Black                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 382,345 (13.5)            | 4,715 (11.7)     |         |
| Hispanic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 312,270 (11.1)            | 3,575 (8.9)      |         |
| Asian/Pacific Islander                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 123,455 (4.4)             | 1,425 (3.5)      |         |
| Native American                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 16,510 (0.6)              | 200 (0.5)        |         |
| Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 83,495 (3.0)              | 1,140 (2.8)      |         |
| Primary Payer <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                           |                  | < .001  |
| Medicare                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1,987,364 (58.3)          | 31,010 (65.1)    |         |
| Medicaid                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 397,365 (11.7)            | 4,895 (10.3)     |         |
| Private                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 944,970 (27.7)            | 10,990 (23.1)    |         |
| Self-pay/Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 82,180 (2.4)              | 730 (1.5)        |         |
| Median Household Income Quartile <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                           |                  | < .001  |
| Quartile 1, lowest                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 951,785 (27.5)            | 12,010 (25.0)    |         |
| Quartile 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 888,220 (25.6)            | 12,265 (25.5)    |         |
| Quartile 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 849,755 (24.5)            | 12,350 (25.7)    |         |
| Quartile 4, highest                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 777,110 (22.4)            | 11,445 (23.8)    |         |
| Admission Characteristics                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                           |                  |         |
| Non-elective admission                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 2,637,100 (74.9)          | 43,785 (89.5)    | < .001  |
| Weekend admission                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 634,965 (18.0)            | 10,920 (22.3)    | < .001  |
| Comorbidities                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                           |                  |         |
| Elixhauser Comorbidity Index, mean (SD)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 5.00 (2.21)               | 5.74 (2.11)      | < .001  |
| Inflammatory bowel disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 40,500 (1.2)              | 1,365 (2.8)      | < .001  |
| Chronic kidney disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 387,000 (11.0)            | 8,100 (16.6)     | < .001  |
| Solid organ transplant                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 14,400 (0.4)              | 360 (0.7)        | < .001  |
| HIV/AIDS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 27,100 (0.8)              | 505 (1.0)        | .004    |
| Cirrhosis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 328,000 (9.3)             | 4,155 (8.5)      | .007    |
| COPD                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 378,000 (10.7)            | 5,680 (11.6)     | .007    |
| Diabetes mellitus                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1,082,000 (30.7)          | 15,100 (30.9)    | .715    |
| Obesity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 434,000 (12.3)            | 4,885 (10.0)     | < .001  |
| Hospital Characteristics                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                           |                  |         |
| Large bed size                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 1,947,361 (55.3)          | 27,150 (55.5)    | .566    |
| Abbreviations: CDI: Clostridioides difficile infection; SD: Standard deviation; yrs: years; COPD: Chronic Obstructive Pulmonary Disease; GI: Gastrointestinal.                                                                                                                                                                                                                                                                                                                                                                            |                           |                  |         |
| <sup>a</sup> Percentages are calculated among nonmissing observations (valid percentages) and therefore may not sum to the column total. The number of hospitalizations with missing data for these variables was as follows: race/ethnicity: 698,740 (No CDI) and 8,695 (CDI); primary payer: 111,340 (No CDI) and 1,275 (CDI); median household income quartile: 56,349 (No CDI) and 830 (CDI); and hospital region: 635,254 (No CDI) and 7,860 (CDI). All other variables are reported as a proportion of the full column denominator. |                           |                  |         |

| Characteristic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Hospitalizations, No. (%) |                  |         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------|---------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | No CDI (n = 3,523,219)    | CDI (n = 48,900) | P value |
| Urban teaching                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 2,802,230 (79.5)          | 37,920 (77.6)    | < .001  |
| Hospital Region <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                           |                  | < .001  |
| Northeast                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 575,965 (19.9)            | 8,570 (20.9)     |         |
| Midwest                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 620,170 (21.5)            | 10,690 (26.1)    |         |
| South                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1,106,805 (38.3)          | 13,550 (33.0)    |         |
| West                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 585,025 (20.3)            | 8,230 (20.1)     |         |
| GI Cancer Type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                           |                  |         |
| Colorectal cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1,493,000 (42.4)          | 21,770 (44.5)    | < .001  |
| Pancreatic cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 684,000 (19.4)            | 10,170 (20.8)    | < .001  |
| Liver cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 381,000 (10.8)            | 4,415 (9.0)      | < .001  |
| Gastric cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 283,000 (8.0)             | 3,230 (6.6)      | < .001  |
| Esophageal cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 251,000 (7.1)             | 2,860 (5.9)      | < .001  |
| Cholangiocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 157,000 (4.5)             | 2,475 (5.1)      | .005    |
| Anal cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 63,400 (1.8)              | 1,505 (3.1)      | < .001  |
| Peritoneal/retroperitoneal cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 84,200 (2.4)              | 1,065 (2.2)      | .181    |
| Biliary tract cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 76,800 (2.2)              | 1,050 (2.2)      | .822    |
| Small intestine cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 73,600 (2.1)              | 855 (1.8)        | .016    |
| Gallbladder cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 46,800 (1.3)              | 540 (1.1)        | .059    |
| Colorectal carcinoid                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 6,875 (0.2)               | 120 (0.2)        | .281    |
| Abbreviations: CDI: Clostridioides difficile infection; SD: Standard deviation; yrs: years; COPD: Chronic Obstructive Pulmonary Disease; GI: Gastrointestinal.                                                                                                                                                                                                                                                                                                                                                                            |                           |                  |         |
| <sup>a</sup> Percentages are calculated among nonmissing observations (valid percentages) and therefore may not sum to the column total. The number of hospitalizations with missing data for these variables was as follows: race/ethnicity: 698,740 (No CDI) and 8,695 (CDI); primary payer: 111,340 (No CDI) and 1,275 (CDI); median household income quartile: 56,349 (No CDI) and 830 (CDI); and hospital region: 635,254 (No CDI) and 7,860 (CDI). All other variables are reported as a proportion of the full column denominator. |                           |                  |         |

Hospitalizations with CDI carried a greater comorbidity burden (mean [SD] Elixhauser Comorbidity Index, 5.74 [2.11] vs 5.00 [2.21];  $P < .001$ ), with higher prevalence of IBD, CKD, and solid organ transplant (all  $P < .001$ ) and HIV/AIDS ( $P = .004$ ), and lower prevalence of cirrhosis ( $P = .007$ ) and obesity ( $P < .001$ ); diabetes mellitus did not differ (Table 1). The most frequent GI cancer subtypes were colorectal (42.4%), pancreatic (19.4%), and liver cancer (10.8%). Colorectal carcinoid was the least frequent subtype (0.2%) (Table 1).

## CDI Prevalence Patterns

The overall hospitalization-level prevalence of CDI was 1.37% (95% CI, 1.34%–1.40%), corresponding to approximately 13.7 CDI hospitalizations per 1,000 GI cancer hospitalizations, and declined from 1.63% (95% CI, 1.55%–1.71%) in 2018 to 1.22% (95% CI, 1.15%–1.30%) in 2023, a 25% relative reduction over the study period (Supplementary Table 2). Prevalence was highest in the Midwest at 1.69% (95% CI, 1.62%–1.77%) and lowest in the South at 1.21% (95% CI, 1.16%–1.26%). Among GI cancer subtypes, prevalence was highest in anal cancer (2.32%; 95% CI, 2.06%–2.60%) and lowest in esophageal (1.12%; 95% CI, 1.03%–1.22%) and gastric cancer (1.13%; 95% CI, 1.04%–1.22%) (Supplementary Table 3).

## Factors Associated with CDI

In unadjusted analyses, older age, female sex, IBD, CKD, solid organ transplant history, HIV/AIDS, and chronic obstructive pulmonary disease (COPD) were significantly associated with higher odds of CDI. Black race, Hispanic ethnicity, non-Medicare insurance, cirrhosis, and obesity were associated with lower odds of CDI (Supplementary Table 4).

In multivariable analysis, IBD was most strongly associated with CDI (aOR, 2.47; 95% CI, 2.15–2.85), followed by CKD (aOR, 1.61; 95% CI, 1.52–1.71), solid organ transplant history (aOR, 1.51; 95% CI, 1.15–1.98), HIV/AIDS (aOR, 1.37; 95% CI, 1.08–1.74), and female sex (aOR, 1.24; 95% CI, 1.18–1.30). Compared with patients aged 18–44 years, those aged 65–79 years had higher odds of CDI (aOR, 1.17; 95% CI, 1.02–1.34), whereas associations for ages 45–64 and ≥ 80 years were not significant. Obesity (aOR, 0.73; 95% CI, 0.67–0.79) and elective admission (aOR, 0.35; 95% CI, 0.33–0.37) were associated with lower odds

of CDI. Among GI cancer subtypes, anal cancer had the strongest positive association with CDI (aOR, 1.50; 95% CI, 1.22–1.83), while small intestine and liver cancer had nominal inverse associations (Table 2).

Table 2  
Factors Independently Associated with Clostridioides difficile Infection Among Adult Hospitalizations with Gastrointestinal Cancers

| Variable                                                                                                                                                      | Adjusted Odds Ratio | 95% CI    | P Value |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|-----------|---------|
| Demographics                                                                                                                                                  |                     |           |         |
| Age 18–44                                                                                                                                                     | Reference           | -         | -       |
| Age 45–64                                                                                                                                                     | 1.13                | 1.00–1.27 | .055    |
| Age 65–79                                                                                                                                                     | 1.17                | 1.02–1.34 | .024    |
| Age ≥ 80                                                                                                                                                      | 1.02                | 0.88–1.18 | .790    |
| Female sex                                                                                                                                                    | 1.24                | 1.18–1.30 | < .001  |
| Race/Ethnicity                                                                                                                                                |                     |           |         |
| White                                                                                                                                                         | Reference           | -         | -       |
| Black                                                                                                                                                         | 0.84                | 0.78–0.91 | < .001  |
| Hispanic                                                                                                                                                      | 0.84                | 0.77–0.92 | < .001  |
| Asian/Pacific Islander                                                                                                                                        | 0.79                | 0.69–0.89 | < .001  |
| Native American                                                                                                                                               | 0.76                | 0.54–1.08 | .127    |
| Other                                                                                                                                                         | 0.93                | 0.80–1.07 | .290    |
| Primary Payer                                                                                                                                                 |                     |           |         |
| Medicare                                                                                                                                                      | Reference           | -         | -       |
| Medicaid                                                                                                                                                      | 0.88                | 0.80–0.97 | .013    |
| Private                                                                                                                                                       | 0.81                | 0.75–0.87 | < .001  |
| Self-pay/Other                                                                                                                                                | 0.66                | 0.54–0.81 | < .001  |
| Income Quartile                                                                                                                                               |                     |           |         |
| Quartile 1                                                                                                                                                    | Reference           | -         | -       |
| Quartile 2                                                                                                                                                    | 1.07                | 1.00–1.14 | .062    |
| Quartile 3                                                                                                                                                    | 1.09                | 1.02–1.17 | .010    |
| Quartile 4, highest                                                                                                                                           | 1.13                | 1.05–1.21 | .002    |
| Hospital Characteristics                                                                                                                                      |                     |           |         |
| Bed size: Medium (vs Small)                                                                                                                                   | 0.99                | 0.92–1.06 | .750    |
| Bed size: Large (vs Small)                                                                                                                                    | 1.00                | 0.93–1.06 | .931    |
| Urban non-teaching (vs Rural)                                                                                                                                 | 0.97                | 0.87–1.09 | .628    |
| Urban teaching (vs Rural)                                                                                                                                     | 0.89                | 0.80–0.98 | .015    |
| Elective admission                                                                                                                                            | 0.35                | 0.33–0.37 | < .001  |
| Region                                                                                                                                                        |                     |           |         |
| Northeast                                                                                                                                                     | Reference           | -         | -       |
| Midwest                                                                                                                                                       | 1.17                | 1.08–1.26 | < .001  |
| South                                                                                                                                                         | 0.85                | 0.79–0.91 | < .001  |
| West                                                                                                                                                          | 0.98                | 0.91–1.06 | .667    |
| Comorbidities                                                                                                                                                 |                     |           |         |
| Inflammatory bowel disease                                                                                                                                    | 2.47                | 2.15–2.85 | < .001  |
| Chronic kidney disease                                                                                                                                        | 1.61                | 1.52–1.71 | < .001  |
| Solid organ transplant                                                                                                                                        | 1.51                | 1.15–1.98 | .003    |
| HIV/AIDS                                                                                                                                                      | 1.37                | 1.08–1.74 | .010    |
| Cirrhosis                                                                                                                                                     | 1.04                | 0.93–1.16 | .475    |
| Abbreviations: CDI: Clostridioides difficile infection; SD: Standard deviation; yrs: years; COPD: Chronic Obstructive Pulmonary Disease; GI: Gastrointestinal |                     |           |         |

| Variable                                                                                                                                                      | Adjusted Odds Ratio | 95% CI    | P Value |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|-----------|---------|
| COPD                                                                                                                                                          | 1.04                | 0.96–1.12 | .334    |
| Obesity                                                                                                                                                       | 0.73                | 0.67–0.79 | < .001  |
| Diabetes mellitus                                                                                                                                             | 0.97                | 0.92–1.02 | .275    |
| GI Cancer Subtype                                                                                                                                             |                     |           |         |
| Anal cancer                                                                                                                                                   | 1.50                | 1.22–1.83 | < .001  |
| Colorectal carcinoid                                                                                                                                          | 1.31                | 0.82–2.10 | .264    |
| Pancreatic cancer                                                                                                                                             | 1.08                | 0.92–1.26 | .368    |
| Cholangiocarcinoma                                                                                                                                            | 1.05                | 0.88–1.25 | .569    |
| Colorectal cancer                                                                                                                                             | 1.05                | 0.89–1.23 | .583    |
| Biliary tract cancer                                                                                                                                          | 1.03                | 0.84–1.26 | .801    |
| Gastric cancer                                                                                                                                                | 0.86                | 0.73–1.03 | .100    |
| Esophageal cancer                                                                                                                                             | 0.83                | 0.69–1.00 | .050    |
| Peritoneal/retroperitoneal cancer                                                                                                                             | 0.86                | 0.69–1.06 | .158    |
| Liver cancer                                                                                                                                                  | 0.83                | 0.70–1.00 | .049    |
| Gallbladder cancer                                                                                                                                            | 0.81                | 0.63–1.05 | .109    |
| Small intestine cancer                                                                                                                                        | 0.80                | 0.65–1.00 | .046    |
| Abbreviations: CDI: Clostridioides difficile infection; SD: Standard deviation; yrs: years; COPD: Chronic Obstructive Pulmonary Disease; GI: Gastrointestinal |                     |           |         |

## Clinical Outcomes

Hospitalizations with CDI had worse clinical outcomes than those without CDI. In-hospital mortality occurred in 8.3% of hospitalizations with CDI compared with 6.3% of hospitalizations without CDI. After multivariable adjustment, CDI remained associated with higher odds of in-hospital mortality (aOR, 1.34; 95% CI, 1.23–1.46;  $P < .001$ ). Invasive mechanical ventilation was required in 6.7% of hospitalizations with CDI compared with 3.7% of those without CDI. CDI was independently associated with higher odds of invasive mechanical ventilation after adjustment (aOR, 1.87; 95% CI, 1.71–2.05;  $P < .001$ ). Vasopressors were used in 3.5% of hospitalizations with CDI compared with 1.9% of those without CDI. CDI was associated with higher adjusted odds of vasopressor use (aOR, 1.84; 95% CI, 1.61–2.10;  $P < .001$ ). Renal replacement therapy (RRT) was used in 4.7% of hospitalizations with CDI compared with 1.8% of those without CDI. Among the binary clinical outcomes examined, the largest effect estimate was observed for RRT. CDI was associated with more than twice the adjusted odds of RRT (aOR, 2.27; 95% CI, 2.01–2.56;  $P < .001$ ) (Table 3).

Table 3  
Unadjusted and Adjusted Clinical Outcomes and Resource Utilization by CDI Status.

| Outcome                                                                                                                                                                                                  | No CDI, n (%)        | CDI, n (%)            | Unadjusted OR (95% CI) | Adjusted Effect Estimate (95% CI) | P Value |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-----------------------|------------------------|-----------------------------------|---------|
| Clinical Outcomes (aOR)                                                                                                                                                                                  |                      |                       |                        |                                   |         |
| In-hospital mortality                                                                                                                                                                                    | 222,265 (6.3%)       | 4,050 (8.3%)          | 1.34 (1.25–1.44)       | 1.34 (1.23–1.46)                  | < .001  |
| Mechanical ventilation                                                                                                                                                                                   | 131,065 (3.7%)       | 3,265 (6.7%)          | 1.85 (1.71–2.00)       | 1.87 (1.71–2.05)                  | < .001  |
| Vasopressor use                                                                                                                                                                                          | 67,335 (1.9%)        | 1,735 (3.5%)          | 1.88 (1.68–2.11)       | 1.84 (1.61–2.10)                  | < .001  |
| RRT                                                                                                                                                                                                      | 62,615 (1.8%)        | 2,315 (4.7%)          | 2.74 (2.49–3.01)       | 2.27 (2.01–2.56)                  | < .001  |
| Resource Utilization (LOS ratio/CR)                                                                                                                                                                      |                      |                       |                        |                                   |         |
| Length of stay, days, mean (SD)                                                                                                                                                                          | 6.5 (7.3)            | 10.9 (11.9)           | —                      | LOS ratio 1.65 (1.61–1.69)        | < .001  |
| Total charges, \$, mean (SD)                                                                                                                                                                             | \$89,019 (\$127,563) | \$124,114 (\$205,185) | —                      | CR 1.40 (1.35–1.45)               | < .001  |
| Abbreviations: CDI: Clostridioides difficile infection; aOR: Adjusted Odds Ratio; CI: Confidence Interval; RRT: Renal Replacement Therapy; CR: Charge Ratio; LOS: Length of stay; SD: Standard deviation |                      |                       |                        |                                   |         |

## Healthcare Utilization Outcomes

Mean hospital length of stay (LOS) was 10.9 days among hospitalizations with CDI compared with 6.5 days among those without CDI ( $P < .001$ ). In adjusted negative binomial regression, CDI was associated with a 65% longer expected hospital stay (LOS ratio, 1.65; 95% CI, 1.61–1.69;  $P < .001$ ). Mean total hospital

charges were also higher among hospitalizations with CDI than among those without CDI (\$124,114 vs \$89,019;  $P < .001$ ). In the adjusted generalized linear model, CDI was associated with 40% higher expected hospital charges (charge ratio [CR], 1.40; 95% CI, 1.35–1.45;  $P < .001$ ) (Table 3).

## Subgroup analyses by GI cancer subtypes

Colorectal carcinoid was excluded from subtype-specific modeling due to insufficient CDI events ( $< 50$ ), resulting in 11 evaluable subtypes. After Bonferroni correction, CDI was associated with higher in-hospital mortality only in gastric cancer (aOR, 1.76; 95% CI, 1.34–2.30). CDI was associated with invasive mechanical ventilation in esophageal, gastric, colorectal, liver, cholangiocarcinoma, peritoneal/retroperitoneal, and pancreatic cancer, with the largest estimates in peritoneal/retroperitoneal (aOR, 3.23; 95% CI, 1.91–5.47) and gastric cancer (aOR, 2.60; 95% CI, 1.96–3.43) (Supplementary Table 5).

For renal replacement therapy, associations remained significant in esophageal, gastric, colorectal, liver, cholangiocarcinoma, and pancreatic cancer (aORs 1.78–3.27; largest in esophageal cancer, aOR 3.27; 95% CI, 1.89–5.67). Vasopressor use was significant after correction in gastric (aOR 2.43; 95% CI, 1.62–3.65), colorectal (aOR 1.49; 95% CI, 1.19–1.85), peritoneal/retroperitoneal (aOR 2.92; 95% CI, 1.46–5.81), and pancreatic cancer (aOR 2.09; 95% CI, 1.61–2.70) (Supplementary Table 5).

CDI was associated with longer LOS across all 11 subtypes, with all associations remaining significant after correction (all  $P < .001$ ). The largest increases occurred in peritoneal/retroperitoneal (LOS ratio, 1.88; 95% CI, 1.58–2.22), gastric (1.82; 95% CI, 1.65–2.00), and esophageal cancer (1.78; 95% CI, 1.61–1.97). Total charges were significantly higher in most subtypes, with the largest increases in peritoneal/retroperitoneal (charge ratio, 1.93; 95% CI, 1.51–2.46), esophageal (1.78; 95% CI, 1.55–2.06), and gastric cancer (1.76; 95% CI, 1.55–1.99) (Supplementary Table 6).

## Discussion

In this nationally representative analysis of more than 3.5 million hospitalizations involving adults with GI cancer, CDI was identified in 1.37% of hospitalizations and was associated with higher in-hospital mortality, need for organ support, longer LOS, and higher hospital charges. The analysis also provides granular estimates across 12 GI cancer subtypes. Anal cancer had both the highest observed CDI prevalence and the strongest adjusted association with CDI. CDI was consistently associated with longer length of stay across all evaluable GI cancer subtypes, with all associations remaining significant after Bonferroni correction. CDI was also associated with higher hospital charges across most subtypes. Associations with mortality and organ support were less consistent and should be considered exploratory.

The observed CDI prevalence of 13.7 per 1,000 hospitalizations is consistent with prior estimates in patients with cancer. Using the NIS from 2016 through 2022, Roldan et al. [11] reported a prevalence of 14 per 1,000 GI cancer hospitalizations with a similar temporal decline, and earlier nationwide studies reported comparable rates of 8.6 to 11 per 1,000 discharges [12, 17]. The decline we observed is consistent with national trends and likely reflects the impact of antibiotic stewardship, reduced fluoroquinolone prescribing, and improved infection prevention practices [1, 18, 19]. The COVID-19 pandemic may have also contributed through enhanced infection control measures, changes in hospitalization patterns, and adaptations in healthcare delivery [20]. CDI prevalence was highest in the Midwest and lowest in the South, consistent with previously described regional variations in the United States, although earlier studies identified the Northeast as having the highest burden [21, 22], possibly reflecting variations in study populations, antimicrobial prescribing, diagnostic testing, and healthcare facility characteristics [22, 23].

IBD was the factor most strongly associated with CDI (aOR 2.47), consistent with the population-based study by Singh et al. [24], which demonstrated a 4.8-fold increased risk, and with American College of Gastroenterology (ACG) Clinical Guidelines, identifying IBD as a major CDI risk factor [25]. CKD (aOR 1.61), solid organ transplant (aOR 1.51), and HIV/AIDS (aOR 1.37) are also well-established risk factors for CDI in immunocompromised populations [7, 25, 26]. Female sex was associated with modestly higher odds of CDI, consistent with other national analyses [4, 11]. The absence of a significant association among patients aged 80 years or older may reflect the high burden of competing cancer- and hospitalization-related risk factors in this population [27]. The inverse association between obesity and CDI (aOR 0.73) was consistent with a recent meta-analysis by Charoenngam et al. [28] (pooled OR 0.88), although the association was stronger in our study. This finding should be interpreted with caution, as administrative datasets may underreport obesity and introduce coding bias [29]. Differences in gut microbiota and antimicrobial pharmacokinetics have been proposed as possible explanations, but these mechanisms remain uncertain and residual confounding cannot be excluded [28].

Anal cancer had the highest CDI prevalence and strongest independent association with CDI (aOR 1.50). Potential contributors include concurrent chemoradiation [30] and the higher prevalence of HIV/AIDS in this population [31, 32]. Although HIV/AIDS was included as a covariate, administrative coding likely underestimates its true prevalence in this population, and residual confounding from incompletely captured immunosuppression may contribute to the observed association [33, 34].

CDI was associated with 34% higher adjusted odds of in-hospital mortality, broadly consistent with prior national studies of patients with cancer [11, 12, 17]. The smaller effect size in our study may reflect the higher baseline mortality among GI cancers [11]. RRT showed the strongest association among clinical outcomes (aOR 2.27), likely reflecting sepsis-related acute kidney injury [35]. These outcomes may reflect greater acute illness among CDI hospitalizations, but the NIS cannot establish whether CDI preceded or directly contributed to organ failure. CDI was associated with 65% longer stays and 40% higher charges, consistent with Roldan et al., who reported a 76% increase in LOS and 46% increase in total costs [11]. Because the timing of CDI relative to admission is not captured, these associations are likely bidirectional: CDI may prolong hospitalization, while longer stays independently increase the risk of acquiring CDI through greater cumulative exposure to spores and antibiotics [25, 36].

The clinical impact of CDI was not uniform across GI cancer subtypes on subgroup analysis. After Bonferroni correction, CDI remained associated with mortality only in gastric cancer, while associations with mechanical ventilation and RRT persisted across several subtypes. In contrast, CDI was consistently associated with longer LOS across all 11 evaluable subtypes and with higher charges in most subtypes.

This study has several strengths, including a large nationally representative sample, contemporary data spanning six years, and granular analyses across 12 GI cancer subtypes. Survey-weighted methods generated national hospitalization-level estimates, and the sample size permitted evaluation of uncommon cancer subtypes that would be difficult to study in single-center cohorts.

Several limitations should be acknowledged. First, the NIS relies on ICD-10 administrative codes, which are subject to coding variability and cannot distinguish CDI severity or whether CDI was present on admission versus hospital-acquired. Second, the cross-sectional design precludes causal inference or the determination of the temporal relationships between CDI and clinical outcomes. Third, cancer stage, treatment regimen, antibiotic exposure, proton pump inhibitor use, laboratory data, microbiologic results, and CDI treatment are unavailable, leaving potential for residual confounding. Fourth, the unit of analysis is hospitalizations rather than individual patients; therefore, readmissions may be counted as separate events. Fifth, subtype-specific analyses involved multiple comparisons; findings that did not remain significant after Bonferroni correction, including the nominal inverse associations between small intestine cancer and liver cancer and CDI, should be interpreted with caution.

In conclusion, CDI occurred in approximately 1 in 73 hospitalizations involving adults with GI cancer and was independently associated with higher in-hospital mortality, greater use of organ support, longer hospitalization, and higher charges. IBD, CKD, solid organ transplant history, and HIV/AIDS were the factors most strongly associated with CDI, and anal cancer had the highest subtype-specific prevalence and adjusted odds. Studies incorporating treatment exposure, cancer stage, microbiologic data, and longitudinal follow-up are needed to clarify mechanisms, evaluate effect modification across cancer subtypes, and inform targeted prevention strategies.

## Declarations

**Ethics approval:** This study used the National Inpatient Sample, a de-identified administrative database maintained by the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality. The database contains no protected health information and does not permit identification of individual patients, clinicians, or hospitals. In accordance with the U.S. Common Rule (45 CFR 46), secondary analysis of these de-identified data does not constitute human subjects research; therefore, institutional review board review and approval were not required.

**Consent to participate:** Not applicable.

**Consent for publication:** Not applicable. This study does not contain data from any identifiable individual.

**Conflict of interest:** The authors declare no competing interests.

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**Data availability:** The data used in this study are available from the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS), subject to HCUP data-use requirements and purchase. The authors are not permitted to redistribute the data.

**Author contributions:** Carlos Marin-Lopez contributed to the conceptualization, methodology, formal analysis and investigation, and preparation of the original draft. Amir Reza Akbari contributed to the methodology, formal analysis and investigation, preparation of the original draft, and review and editing of the manuscript. Carmen Cajina Aguirre contributed to the formal analysis and investigation and preparation of the original draft. Lucas Monteiro Delgado contributed to the formal analysis and investigation. Mrigya Sharma contributed to the preparation of the original draft. Breanna Dobberpuhl, Beyamin Alam, and Shahryar Khan contributed to the review and editing of the manuscript. Daniel C. Buckles and Wissam El Atrouni provided supervision, critically revised the manuscript for important intellectual content, and contributed to the final approval of the version to be published. All authors reviewed and approved the final manuscript.

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