

Inpatient Outcomes of *Clostridioides difficile* Infection in Patients with Underlying Inflammatory Bowel Disease

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Abstract

Background:

Clostridioides difficile infection (CDI) is a common complication in patients with inflammatory bowel disease (IBD). This study aims to evaluate the association between CDI and inpatient outcomes and healthcare utilization in IBD patients.

Methods:

We utilized data from the National Inpatient Sample (NIS) database from 2016 to 2021 to identify adult IBD inpatients (>18 years) with and without a diagnosis of CDI, using ICD-10 codes A04.7, K50, and K51. Primary outcomes were in-hospital all-cause mortality, rates and odds of colectomy, ICU admission, and healthcare utilization. The analysis was conducted using SAS survey procedures.

Results:

A total of 382,498 IBD hospitalizations were identified, among which 15,822 patients had a co-existing inpatient diagnosis of CDI. Compared to IBD patients without CDI, those with CDI were more likely to be female (58.2% vs. 56.1%, $P < 0.001$), older than 65 years of age (37.0 % vs. 32.6%, $p < 0.001$) and had higher rates of comorbid conditions. Patients with IBD and CDI had higher rates of mortality (3.5% vs. 1.7%, $P < 0.001$), acute kidney injury (AKI) (23.6% vs. 16.8%, $P < 0.001$), shock (8.6% vs. 3.5%, $P < 0.001$), and ICU admission (5.0% vs. 3.0%, $P < 0.001$). However, after adjusting for confounders with multivariable analysis, CDI was associated with lower odds of ICU admission (OR 0.84, 95% CI: 0.77–0.92, $P < 0.001$) and colectomy (OR 0.49, 95% CI: 0.44–0.54, $P < 0.001$), and there was no significant difference in mortality between the two groups (OR 1.08, 95% CI: 0.97–1.20, $P = 0.16$). IBD patients with CDI had higher length of stay (8.1 ± 0.08 vs. 5.3 ± 0.01 days, $p < 0.001$) and total healthcare charges ($\$80,254.7 \pm 1392.5$ vs. $\$59,749.4 \pm 440.9$; $p < 0.001$).

Conclusion

Patients with IBD and CDI exhibit higher crude rates of mortality, AKI, shock, and ICU admission. However, after adjusting for confounders, CDI was not independently associated with increased mortality, ICU admission, or colectomy. IBD patients with CDI had higher length of stay and total healthcare charges.

Summary

In this large national study, patients with inflammatory bowel disease and *Clostridioides difficile* infection had higher rates of adverse inpatient outcomes than those without infection. After adjusting for comorbidities and other patient characteristics, there was no difference in mortality, but there were lower rates of ICU admission and colectomy.

Key message

- *Clostridioides difficile* infection (CDI) is a common complication in patients with inflammatory bowel disease (IBD) and is associated with increased morbidity and adverse patient outcomes.
- In our study, CDI was associated with higher unadjusted mortality; however, after adjustment for confounders, there was no significant difference in mortality, and the odds of ICU admission and colectomy were lower.
- These findings can help improve outcomes of patients hospitalized with CDI and IBD by considering the importance of underlying patient and disease characteristics, with increased surveillance and prompt initiation of treatment and early recognition of inpatient adverse outcomes.

Introduction

Clostridioides difficile is a fastidious, gram-positive, spore-forming organism responsible for infectious diarrhea and pseudomembranous colitis and is one of the most common and costly healthcare-associated infections^{1–3}. Risk factors associated with *Clostridioides difficile* infection (CDI) include previous exposure to antibiotics, use of proton pump inhibitors, hospitalization, advanced age, comorbidities, malnutrition, and immunosuppression⁴.

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract that encompasses both ulcerative colitis (UC) and Crohn's disease (CD)⁵. Studies have shown that IBD patients have a 4.8-fold greater risk of developing CDI than those without IBD⁶. Underlying inflammation in IBD patients leads to dysregulation of colonic flora and decreased colonization resistance, which makes IBD an independent risk factor for CDI⁷. Some studies suggest that CDI can exacerbate the underlying IBD and lead to a more severe disease course, higher rates of morbidity, prolonged hospital stays, increased healthcare costs, and greater mortality^{8,9}. Other studies, however, have shown that CDI does not worsen short-term clinical outcomes, including colon perforation, megacolon, colectomy, shock, respiratory failure, or mortality in IBD^{10,11}.

There exists a wide heterogeneity between studies showing which adverse outcomes are associated with CDI in IBD. Therefore, this study aims to determine the incidence and risk of adverse inpatient events, including mortality, ICU admission, and colectomy, in hospitalized patients with IBD with and without CDI. Additionally, the study evaluates whether CDI independently predicts these outcomes after adjusting for baseline comorbidities and acute complications.

METHODS

Study population

The National Inpatient Sample (NIS) database, managed by the Healthcare Cost and Utilization Project (HCUP) and run by the Agency for Healthcare Research and Quality¹², was utilized for this study. NIS collects information on more than 7 million hospitalizations yearly and is funded by contributions from all HCUP-affiliated states. The NIS uses publicly accessible anonymous and de-identified data, and thus, this study did not require informed permission from participants or institutional review board approval. Since NIS data is compiled annually, the data was used for analysis of disease trends over time from 2016 to 2021. NIS data was queried using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), claims codes. All the ICD codes generated are detailed in Supplementary Table S1. Individuals with age < 18 years were excluded from our study.

Study characteristics and outcomes

ICD-10 codes were used to classify patients with CDI (ICD-10 code A04.7) and to identify patients with CD (ICD-10 code K50) and UC (ICD-10 code K51)¹³. Baseline demographic characteristics, including age, gender, race, hospital type, hospital region, and hospital bed size, were obtained from available NIS variables. Clinical variables, including malnutrition, hypertension, chronic kidney disease, congestive heart failure, transplant status, severe sepsis, acute kidney injury, acute liver failure, acute heart failure, fluid imbalance, anemia, chronic pulmonary disease, and shock, were incorporated into the analysis using corresponding ICD-10 codes as detailed in Supplementary Table S1. The selection of adult hospitalizations with IBD is shown in Fig. 1.

Primary study outcomes were healthcare utilization, in-hospital all-cause mortality rates and odds of colectomy and ICU admission.

Statistical Analysis

Data was described using mean and standard error for continuous variables, and percentage and standard error for categorical variables. The chi-square test was used to compare categorical variables, and linear regression was used to compare continuous variables between groups. Multivariable logistic regression models were constructed for three binary outcomes: in-hospital mortality, ICU admission, and colectomy. Each model included CDI group, pre-specified demographic and clinical variables. Data was split chronologically into a training cohort (2016–2019) for model development and a test cohort (2020–2021) for model performance evaluation using receiver operating characteristic (ROC) curve and the area under the curve (AUC). Models were then refit using the full cohort (2016–2021) to obtain final adjusted odds ratios and 95% confidence intervals, which were interpreted as the independent association between CDI and each outcome after adjustment for demographic and clinical covariates. All analyses included sample weights, strata, and clusters to account for the complex survey design. Domain analyses were performed for adult hospitalizations with IBD, UC, and CD. All analyses were performed in SAS software using survey procedures.

RESULTS

Baseline characteristics of IBD and CDI

A total of 382,498 IBD hospitalizations were identified from 2016–2021, among which 15,822 patients had a co-existing inpatient hospital diagnosis of CDI. Demographic and clinical characteristics of IBD patients with and without CDI are described in Table 1. Compared to IBD patients without CDI, those with CDI were more likely to be female (58.2% vs. 56.1%, $p < 0.001$), more likely to be in an older age group (age > 65 years – 37.0% vs. 32.6%, $p < 0.001$) and had higher rates of comorbid conditions, including malnutrition (26.9% vs. 14.5%, $p < 0.001$), chronic kidney disease (15.7% vs. 13.8%, $p < 0.001$), congestive heart failure kidney (8.3% vs. 6.7%, $p < 0.001$) and history of organ transplant (2.3% vs. 1.6%, $p < 0.001$).

Table 1
Characteristics of Adult Hospitalizations with IBD by CDI

Factor	Overall (N = 382,498)	non-C.diff (N = 366,676)	C.diff (N = 15,822)	p-value
Age in years at admission, mean $\pm$ se	54.3 $\pm$ 0.06	54.3 $\pm$ 0.06	55.3 $\pm$ 0.18	< 0.001 ^a
Age Group, % $\pm$ se				< 0.001 ^c
. 18–40 years	28.5 $\pm$ 0.13	28.5 $\pm$ 0.13	28.7 $\pm$ 0.39	
. 41–65 years	38.8 $\pm$ 0.09	39.0 $\pm$ 0.09	34.4 $\pm$ 0.39	
. > 65 years	32.8 $\pm$ 0.13	32.6 $\pm$ 0.13	37.0 $\pm$ 0.43	
Indicator of sex, % $\pm$ se*				< 0.001 ^c
. Male	43.8 $\pm$ 0.10	43.9 $\pm$ 0.10	41.8 $\pm$ 0.41	
. Female	56.2 $\pm$ 0.10	56.1 $\pm$ 0.10	58.2 $\pm$ 0.41	
Race (uniform), % $\pm$ se*				< 0.001 ^c
. White	78.7 $\pm$ 0.17	78.8 $\pm$ 0.17	76.1 $\pm$ 0.40	
. Black	11.2 $\pm$ 0.11	11.2 $\pm$ 0.11	11.7 $\pm$ 0.29	
. Hispanic	6.2 $\pm$ 0.09	6.1 $\pm$ 0.09	7.9 $\pm$ 0.25	
. Asian or Pacific Islander	1.2 $\pm$ 0.03	1.2 $\pm$ 0.03	1.4 $\pm$ 0.10	
. Native American	0.38 $\pm$ 0.01	0.38 $\pm$ 0.01	0.41 $\pm$ 0.05	
. Other	2.3 $\pm$ 0.06	2.3 $\pm$ 0.06	2.4 $\pm$ 0.14	
Hyperlipidemia, % $\pm$ se	25.4 $\pm$ 0.12	25.4 $\pm$ 0.12	25.4 $\pm$ 0.37	0.97 ^c
Malnutrition, % $\pm$ se	15.1 $\pm$ 0.10	14.5 $\pm$ 0.10	26.9 $\pm$ 0.38	< 0.001 ^c
Diabetes, % $\pm$ se	18.3 $\pm$ 0.08	18.3 $\pm$ 0.09	18.4 $\pm$ 0.32	0.82 ^c
Hypertension, % $\pm$ se	13.6 $\pm$ 0.08	13.7 $\pm$ 0.08	11.6 $\pm$ 0.27	< 0.001 ^c
*Data not available for all subjects. Indicator of sex = 108; Race (uniform) = 10,692; Length of stay (cleaned) = 13; Disposition of patient (uniform) = 175; Died during hospitalization = 175; Primary expected payer (uniform) = 500; Total charges (cleaned) = 2,910.				
Frequencies presented are unweighted counts.				
P-values: a=linear regression; b=linear regression with log transformation; c = Rao-Scott chi-square test.				
SAS Survey Procedures used for all analyses.				

Factor	Overall (N = 382,498)	non-C.diff (N = 366,676)	C.diff (N = 15,822)	p-value
HIV AIDs, % ± se	0.30 ± 0.01	0.29 ± 0.01	0.34 ± 0.05	0.27 ^c
Cancer, % ± se	5.4 ± 0.05	5.3 ± 0.05	5.4 ± 0.19	0.96 ^c
Chronic kidney disease, % ± se	13.9 ± 0.07	13.8 ± 0.07	15.7 ± 0.30	< 0.001^c
Congestive heart failure, % ± se	6.8 ± 0.05	6.7 ± 0.05	8.3 ± 0.23	< 0.001^c
Coronary artery disease, % ± se	14.3 ± 0.08	14.3 ± 0.08	14.1 ± 0.29	0.47 ^c
Transplant, % ± se	1.6 ± 0.04	1.6 ± 0.04	2.3 ± 0.13	< 0.001^c
Nicotine dependence, % ± se	3.7 ± 0.04	3.7 ± 0.04	3.1 ± 0.14	< 0.001^c
Severe Sepsis, % ± se	1.8 ± 0.03	1.7 ± 0.02	4.0 ± 0.16	< 0.001^c
Acute Kidney Injury, % ± se	17.1 ± 0.08	16.8 ± 0.08	23.6 ± 0.34	< 0.001^c
Acute Liver Failure, % ± se	1.2 ± 0.02	1.2 ± 0.02	1.3 ± 0.09	0.057 ^c
Acute Heart Failure, % ± se	4.1 ± 0.04	4.1 ± 0.04	3.6 ± 0.15	0.002^c
Shock, % ± se	3.7 ± 0.03	3.5 ± 0.03	8.6 ± 0.23	< 0.001^c
Fluid Imbalance, % ± se	33.7 ± 0.12	32.9 ± 0.12	51.9 ± 0.42	< 0.001^c
Toxicmega, % ± se	0.07 ± 0.00	0.07 ± 0.00	0.08 ± 0.02	0.43 ^c
Intestine perforation, % ± se	0.92 ± 0.02	0.92 ± 0.02	0.95 ± 0.08	0.74 ^c
Peritonitis, % ± se	2.2 ± 0.03	2.2 ± 0.03	2.3 ± 0.12	0.41 ^c
Anemia, % ± se	1.4 ± 0.02	1.4 ± 0.02	1.6 ± 0.10	0.008^c
Pulmonary circulation disorders, % ± se	3.7 ± 0.03	3.7 ± 0.03	3.7 ± 0.15	0.79 ^c
*Data not available for all subjects. Indicator of sex = 108; Race (uniform) = 10,692; Length of stay (cleaned) = 13; Disposition of patient (uniform) = 175; Died during hospitalization = 175; Primary expected payer (uniform) = 500; Total charges (cleaned) = 2,910.				
Frequencies presented are unweighted counts.				
P-values: a=linear regression; b=linear regression with log transformation; c = Rao-Scott chi-square test.				
SAS Survey Procedures used for all analyses.				

Factor	Overall (N = 382,498)	non-C.diff (N = 366,676)	C.diff (N = 15,822)	p-value
Peripheral vascular disorders, % $\pm$ se	2.1 $\pm$ 0.04	2.1 $\pm$ 0.04	2.1 $\pm$ 0.12	0.92 ^c
Chronic pulmonary disease, % $\pm$ se	21.3 $\pm$ 0.09	21.4 $\pm$ 0.09	20.2 $\pm$ 0.33	< 0.001 ^c
ICU, % $\pm$ se	3.1 $\pm$ 0.04	3.0 $\pm$ 0.04	5.0 $\pm$ 0.18	< 0.001 ^c
Colectomy, % $\pm$ se	4.9 $\pm$ 0.07	5.0 $\pm$ 0.07	2.5 $\pm$ 0.12	< 0.001 ^c
Length of stay (cleaned), mean $\pm$ se*	5.4 $\pm$ 0.01	5.3 $\pm$ 0.01	8.1 $\pm$ 0.08	< 0.001 ^a
Region of hospital, % $\pm$ se				< 0.001 ^c
. Northeast	21.4 $\pm$ 0.35	21.4 $\pm$ 0.35	21.1 $\pm$ 0.51	
. Midwest	24.7 $\pm$ 0.36	24.7 $\pm$ 0.36	23.6 $\pm$ 0.50	
. South	36.8 $\pm$ 0.34	36.8 $\pm$ 0.34	36.5 $\pm$ 0.55	
. West	17.2 $\pm$ 0.26	17.1 $\pm$ 0.26	18.8 $\pm$ 0.44	
Bed size of hospital (STRATA), % $\pm$ se				0.084 ^c
. Small	20.4 $\pm$ 0.24	20.5 $\pm$ 0.24	19.7 $\pm$ 0.42	
. Medium	27.6 $\pm$ 0.29	27.6 $\pm$ 0.29	27.7 $\pm$ 0.48	
. Large	52.0 $\pm$ 0.37	52.0 $\pm$ 0.37	52.7 $\pm$ 0.57	
Location/teaching status of hospital (STRATA), % $\pm$ se				< 0.001 ^c
. Rural	7.2 $\pm$ 0.11	7.2 $\pm$ 0.11	5.8 $\pm$ 0.21	
. Urban nonteaching	18.9 $\pm$ 0.21	18.8 $\pm$ 0.21	19.7 $\pm$ 0.41	
. Urban teaching	74.0 $\pm$ 0.25	73.9 $\pm$ 0.25	74.5 $\pm$ 0.45	
Disposition of patient (uniform), % $\pm$ se*				< 0.001 ^c
*Data not available for all subjects. Indicator of sex = 108; Race (uniform) = 10,692; Length of stay (cleaned) = 13; Disposition of patient (uniform) = 175; Died during hospitalization = 175; Primary expected payer (uniform) = 500; Total charges (cleaned) = 2,910.				
Frequencies presented are unweighted counts.				
P-values: a=linear regression; b=linear regression with log transformation; c = Rao-Scott chi-square test.				
SAS Survey Procedures used for all analyses.				

Factor	Overall (N = 382,498)	non-C.diff (N = 366,676)	C.diff (N = 15,822)	p-value
. Routine Discharge	68.2 ± 0.11	68.5 ± 0.11	62.2 ± 0.40	
. Short-term hospital	2.0 ± 0.03	2.0 ± 0.03	2.3 ± 0.12	
. Transfer to other facilities	11.1 ± 0.07	10.8 ± 0.07	16.7 ± 0.31	
. Home Health Care (HHC)	15.0 ± 0.10	15.1 ± 0.10	14.2 ± 0.29	
. Against medical advice (AMA)	1.9 ± 0.03	1.9 ± 0.03	1.2 ± 0.09	
. Died in hospital	1.8 ± 0.02	1.7 ± 0.02	3.5 ± 0.15	
. Discharged alive, destination unknown	0.01 ± 0.00	0.01 ± 0.00	0.02 ± 0.01	
Died during hospitalization, % ± se*				< 0.001 ^c
. Alive	98.2 ± 0.02	98.3 ± 0.02	96.5 ± 0.15	
. Died	1.8 ± 0.02	1.7 ± 0.02	3.5 ± 0.15	
Primary expected payer (uniform), % ± se*				< 0.001 ^c
. Medicare	43.0 ± 0.14	42.9 ± 0.14	45.8 ± 0.43	
. Medicaid	14.8 ± 0.10	14.7 ± 0.10	15.8 ± 0.31	
. Private insurance	35.8 ± 0.16	35.9 ± 0.16	32.3 ± 0.40	
. Self-pay	3.5 ± 0.05	3.5 ± 0.05	3.4 ± 0.15	
. No charge	0.32 ± 0.02	0.32 ± 0.02	0.29 ± 0.04	
. Other	2.6 ± 0.04	2.7 ± 0.04	2.4 ± 0.13	
Total charges (cleaned), mean ± se*	60596.8 ± 446.1	59749.4 ± 440.9	80254.7 ± 1392.5	< 0.001 ^a
*Data not available for all subjects. Indicator of sex = 108; Race (uniform) = 10,692; Length of stay (cleaned) = 13; Disposition of patient (uniform) = 175; Died during hospitalization = 175; Primary expected payer (uniform) = 500; Total charges (cleaned) = 2,910.				
Frequencies presented are unweighted counts.				
P-values: a=linear regression; b=linear regression with log transformation; c = Rao-Scott chi-square test.				
SAS Survey Procedures used for all analyses.				

A total of 9,219 hospitalizations with UC had a concomitant diagnosis of CDI. Mean age was 58.8 ± 0.23 years with 44.4% being in the older age group of > 65 years. The majority of patients were females. They

had higher comorbid burden and were malnourished with higher incidence of chronic kidney disease and heart failure. Demographic and clinical characteristics of UC hospitalizations with and without CDI are compared and described in Table 2.

Table 2
Characteristics of Adult Hospitalizations with UC by CDI

Factor	Overall (N = 147,410)	non-C.diff (N = 138,191)	C.diff (N = 9,219)	p-value
Age in years at admission, mean $\pm$ se	56.9 $\pm$ 0.08	56.8 $\pm$ 0.08	58.8 $\pm$ 0.23	< 0.001^a
Age Group, % $\pm$ se				< 0.001^c
. 18–40 years	25.1 $\pm$ 0.16	25.3 $\pm$ 0.16	23.0 $\pm$ 0.47	
. 41–65 years	35.6 $\pm$ 0.14	35.8 $\pm$ 0.14	32.6 $\pm$ 0.51	
. > 65 years	39.3 $\pm$ 0.18	38.9 $\pm$ 0.19	44.4 $\pm$ 0.56	
Indicator of sex, % $\pm$ se*				< 0.001^c
. Male	46.1 $\pm$ 0.15	46.3 $\pm$ 0.15	43.3 $\pm$ 0.53	
. Female	53.9 $\pm$ 0.15	53.7 $\pm$ 0.15	56.7 $\pm$ 0.53	
Race (uniform), % $\pm$ se*				< 0.001^c
. White	77.7 $\pm$ 0.20	77.9 $\pm$ 0.20	75.7 $\pm$ 0.50	
. Black	9.5 $\pm$ 0.12	9.5 $\pm$ 0.12	10.2 $\pm$ 0.34	
. Hispanic	8.0 $\pm$ 0.13	7.9 $\pm$ 0.13	9.3 $\pm$ 0.34	
. Asian or Pacific Islander	1.7 $\pm$ 0.05	1.7 $\pm$ 0.05	1.8 $\pm$ 0.15	
. Native American	0.42 $\pm$ 0.02	0.42 $\pm$ 0.02	0.41 $\pm$ 0.07	
. Other	2.6 $\pm$ 0.08	2.6 $\pm$ 0.09	2.6 $\pm$ 0.19	
Hyperlipidemia, % $\pm$ se	30.4 $\pm$ 0.16	30.4 $\pm$ 0.16	29.8 $\pm$ 0.50	0.26 ^c
Malnutrition, % $\pm$ se	15.1 $\pm$ 0.12	14.3 $\pm$ 0.12	27.6 $\pm$ 0.48	< 0.001^c
Diabetes, % $\pm$ se	20.4 $\pm$ 0.12	20.4 $\pm$ 0.13	20.5 $\pm$ 0.43	0.84 ^c
Hypertension, % $\pm$ se	13.9 $\pm$ 0.11	14.0 $\pm$ 0.11	11.8 $\pm$ 0.35	< 0.001^c
*Data not available for all subjects. Indicator of sex = 48; Race (uniform) = 4,100; Length of stay (cleaned) = 5; Disposition of patient (uniform) = 69; Died during hospitalization = 69; Primary expected payer (uniform) = 210; Total charges (cleaned) = 1,207.				
Frequencies presented are unweighted counts.				
P-values: a=linear regression; b=linear regression with log transformation; c = Rao-Scott chi-square test.				
SAS Survey Procedures used for all analyses.				

Factor	Overall (N = 147,410)	non-C.diff (N = 138,191)	C.diff (N = 9,219)	p-value
HIV AIDs, % ± se	0.38 ± 0.02	0.38 ± 0.02	0.41 ± 0.07	0.66 ^c
Cancer, % ± se	6.7 ± 0.08	6.7 ± 0.09	6.2 ± 0.26	0.066 ^c
Chronic kidney disease, % ± se	13.7 ± 0.10	13.4 ± 0.11	17.2 ± 0.40	< 0.001^c
Congestive heart failure, % ± se	7.4 ± 0.08	7.2 ± 0.08	9.4 ± 0.31	< 0.001^c
Coronary artery disease, % ± se	16.1 ± 0.12	16.0 ± 0.12	16.4 ± 0.40	0.40 ^c
Transplant, % ± se	2.1 ± 0.06	2.1 ± 0.06	2.3 ± 0.17	0.15 ^c
Nicotine dependence, % ± se	2.7 ± 0.05	2.7 ± 0.05	2.5 ± 0.16	0.29 ^c
Severe Sepsis, % ± se	2.1 ± 0.04	1.9 ± 0.04	4.7 ± 0.23	< 0.001^c
Acute Kidney Injury, % ± se	17.9 ± 0.11	17.3 ± 0.11	26.3 ± 0.46	< 0.001^c
Acute Liver Failure, % ± se	1.4 ± 0.04	1.4 ± 0.04	1.6 ± 0.13	0.16 ^c
Acute Heart Failure, % ± se	4.7 ± 0.06	4.7 ± 0.06	4.2 ± 0.21	0.018^c
Shock, % ± se	4.5 ± 0.06	4.1 ± 0.06	10.4 ± 0.32	< 0.001^c
Fluid Imbalance, % ± se	35.7 ± 0.16	34.3 ± 0.16	55.9 ± 0.53	< 0.001^c
Toxicmega, % ± se	0.12 ± 0.01	0.12 ± 0.01	0.12 ± 0.04	0.94 ^c
Intestine perforation, % ± se	0.71 ± 0.02	0.71 ± 0.02	0.75 ± 0.09	0.66 ^c
Peritonitis, % ± se	1.6 ± 0.04	1.6 ± 0.04	2.0 ± 0.14	0.004^c
Anemia, % ± se	1.3 ± 0.03	1.2 ± 0.03	1.5 ± 0.13	0.013^c
Pulmonary circulation disorders, % ± se	4.2 ± 0.06	4.2 ± 0.06	4.2 ± 0.21	0.86 ^c
*Data not available for all subjects. Indicator of sex = 48; Race (uniform) = 4,100; Length of stay (cleaned) = 5; Disposition of patient (uniform) = 69; Died during hospitalization = 69; Primary expected payer (uniform) = 210; Total charges (cleaned) = 1,207.				
Frequencies presented are unweighted counts.				
P-values: a=linear regression; b=linear regression with log transformation; c = Rao-Scott chi-square test.				
SAS Survey Procedures used for all analyses.				

Factor	Overall (N = 147,410)	non-C.diff (N = 138,191)	C.diff (N = 9,219)	p-value
Peripheral vascular disorders, % $\pm$ se	2.6 $\pm$ 0.06	2.6 $\pm$ 0.06	2.8 $\pm$ 0.17	0.33 ^c
Chronic pulmonary disease, % $\pm$ se	20.3 $\pm$ 0.12	20.4 $\pm$ 0.13	19.8 $\pm$ 0.42	0.15 ^c
ICU, % $\pm$ se	3.5 $\pm$ 0.06	3.3 $\pm$ 0.06	5.6 $\pm$ 0.25	< 0.001^c
Colectomy, % $\pm$ se	4.0 $\pm$ 0.08	4.1 $\pm$ 0.09	2.1 $\pm$ 0.15	< 0.001^c
Length of stay (cleaned), mean $\pm$ se*	5.7 $\pm$ 0.02	5.5 $\pm$ 0.02	8.6 $\pm$ 0.11	< 0.001^a
Region of hospital, % $\pm$ se				0.004^c
. Northeast	22.6 $\pm$ 0.38	22.6 $\pm$ 0.38	21.6 $\pm$ 0.58	
. Midwest	23.2 $\pm$ 0.36	23.3 $\pm$ 0.37	22.2 $\pm$ 0.55	
. South	34.6 $\pm$ 0.34	34.5 $\pm$ 0.34	35.6 $\pm$ 0.62	
. West	19.7 $\pm$ 0.29	19.6 $\pm$ 0.29	20.6 $\pm$ 0.54	
Bed size of hospital (STRATA), % $\pm$ se				0.17 ^c
. Small	20.4 $\pm$ 0.25	20.4 $\pm$ 0.25	20.7 $\pm$ 0.51	
. Medium	27.5 $\pm$ 0.31	27.5 $\pm$ 0.31	28.2 $\pm$ 0.57	
. Large	52.1 $\pm$ 0.39	52.1 $\pm$ 0.39	51.1 $\pm$ 0.66	
Location/teaching status of hospital (STRATA), % $\pm$ se				< 0.001^c
. Rural	6.5 $\pm$ 0.11	6.6 $\pm$ 0.11	5.9 $\pm$ 0.26	
. Urban nonteaching	18.9 $\pm$ 0.22	18.8 $\pm$ 0.22	20.3 $\pm$ 0.49	
. Urban teaching	74.6 $\pm$ 0.26	74.6 $\pm$ 0.26	73.9 $\pm$ 0.54	
Disposition of patient (uniform), % $\pm$ se*				< 0.001^c
*Data not available for all subjects. Indicator of sex = 48; Race (uniform) = 4,100; Length of stay (cleaned) = 5; Disposition of patient (uniform) = 69; Died during hospitalization = 69; Primary expected payer (uniform) = 210; Total charges (cleaned) = 1,207.				
Frequencies presented are unweighted counts.				
P-values: a=linear regression; b=linear regression with log transformation; c = Rao-Scott chi-square test.				
SAS Survey Procedures used for all analyses.				

Factor	Overall (N = 147,410)	non-C.diff (N = 138,191)	C.diff (N = 9,219)	p-value
. Routine Discharge	66.0 ± 0.15	66.5 ± 0.16	58.4 ± 0.53	
. Short-term hospital	2.1 ± 0.04	2.1 ± 0.04	2.5 ± 0.16	
. Transfer to other facilities	12.9 ± 0.10	12.5 ± 0.10	19.5 ± 0.43	
. Home Health Care (HHC)	15.6 ± 0.13	15.7 ± 0.13	14.4 ± 0.37	
. Against medical advice (AMA)	1.2 ± 0.03	1.2 ± 0.03	0.77 ± 0.10	
. Died in hospital	2.2 ± 0.04	2.1 ± 0.04	4.5 ± 0.22	
. Discharged alive, destination unknown	0.01 ± 0.00	0.01 ± 0.00	0.02 ± 0.02	
Died during hospitalization, % ± se*				< 0.001 ^c
. Alive	97.8 ± 0.04	97.9 ± 0.04	95.5 ± 0.22	
. Died	2.2 ± 0.04	2.1 ± 0.04	4.5 ± 0.22	
Primary expected payer (uniform), % ± se*				< 0.001 ^c
. Medicare	44.8 ± 0.18	44.5 ± 0.19	49.3 ± 0.55	
. Medicaid	12.4 ± 0.12	12.4 ± 0.12	12.9 ± 0.37	
. Private insurance	36.6 ± 0.20	36.9 ± 0.21	32.1 ± 0.51	
. Self-pay	3.2 ± 0.06	3.3 ± 0.06	3.0 ± 0.19	
. No charge	0.30 ± 0.02	0.31 ± 0.02	0.24 ± 0.05	
. Other	2.7 ± 0.05	2.7 ± 0.06	2.5 ± 0.17	
Total charges (cleaned), mean ± se*	66581.6 ± 558.9	65208.9 ± 547.2	87164.0 ± 1971.5	< 0.001 ^a
*Data not available for all subjects. Indicator of sex = 48; Race (uniform) = 4,100; Length of stay (cleaned) = 5; Disposition of patient (uniform) = 69; Died during hospitalization = 69; Primary expected payer (uniform) = 210; Total charges (cleaned) = 1,207.				
Frequencies presented are unweighted counts.				
P-values: a=linear regression; b=linear regression with log transformation; c = Rao-Scott chi-square test.				
SAS Survey Procedures used for all analyses.				

In the CD cohort, 6,693 hospitalizations were diagnosed with CDI, with a mean age of 50.6 ± 0.26 years, and most were in middle age group (41–65 years – 36.9%). They were malnourished and had coronary

artery disease but were less likely to have chronic kidney disease or chronic heart failure. Demographic and clinical characteristics of CD patients with and without CDI are compared and described in Table 3.

Table 3
Characteristics of Adult Hospitalizations with CD by CDI

Factor	Overall (N = 236,825)	non-C.diff (N = 230,132)	C.diff (N = 6,693)	p-value
Age in years at admission, mean $\pm$ se	52.7 $\pm$ 0.07	52.7 $\pm$ 0.06	50.6 $\pm$ 0.26	< 0.001^a
Age Group, % $\pm$ se				< 0.001^c
. 18–40 years	30.6 $\pm$ 0.14	30.4 $\pm$ 0.14	36.5 $\pm$ 0.63	
. 41–65 years	40.8 $\pm$ 0.12	40.9 $\pm$ 0.12	36.9 $\pm$ 0.61	
. > 65 years	28.6 $\pm$ 0.14	28.7 $\pm$ 0.14	26.6 $\pm$ 0.58	
Indicator of sex, % $\pm$ se*				< 0.001^c
. Male	42.4 $\pm$ 0.12	42.5 $\pm$ 0.12	39.7 $\pm$ 0.62	
. Female	57.6 $\pm$ 0.12	57.5 $\pm$ 0.12	60.3 $\pm$ 0.62	
Race (uniform), % $\pm$ se*				< 0.001^c
. White	79.2 $\pm$ 0.17	79.3 $\pm$ 0.17	76.5 $\pm$ 0.59	
. Black	12.3 $\pm$ 0.13	12.2 $\pm$ 0.13	14.0 $\pm$ 0.48	
. Hispanic	5.1 $\pm$ 0.09	5.1 $\pm$ 0.09	6.0 $\pm$ 0.32	
. Asian or Pacific Islander	0.91 $\pm$ 0.03	0.91 $\pm$ 0.03	0.95 $\pm$ 0.12	
. Native American	0.36 $\pm$ 0.02	0.36 $\pm$ 0.02	0.40 $\pm$ 0.08	
. Other	2.1 $\pm$ 0.06	2.1 $\pm$ 0.06	2.1 $\pm$ 0.19	
Hyperlipidemia, % $\pm$ se	22.3 $\pm$ 0.12	22.4 $\pm$ 0.12	19.2 $\pm$ 0.51	< 0.001^c
Malnutrition, % $\pm$ se	15.1 $\pm$ 0.12	14.7 $\pm$ 0.12	26.0 $\pm$ 0.56	< 0.001^c
Diabetes, % $\pm$ se	17.1 $\pm$ 0.10	17.1 $\pm$ 0.10	15.6 $\pm$ 0.46	0.002^c
Hypertension, % $\pm$ se	13.4 $\pm$ 0.09	13.4 $\pm$ 0.09	11.1 $\pm$ 0.40	< 0.001^c
*Data not available for all subjects. Indicator of sex = 61; Race (uniform) = 6,643; Length of stay (cleaned) = 8; Disposition of patient (uniform) = 106; Died during hospitalization = 106; Primary expected payer (uniform) = 292; Total charges (cleaned) = 1,713.				
Frequencies presented are unweighted counts.				
P-values: a=linear regression; b=linear regression with log transformation; c = Rao-Scott chi-square test.				
SAS Survey Procedures used for all analyses.				

Factor	Overall (N = 236,825)	non-C.diff (N = 230,132)	C.diff (N = 6,693)	p-value
HIV AIDs, % ± se	0.24 ± 0.01	0.24 ± 0.01	0.24 ± 0.06	0.97 ^c
Cancer, % ± se	4.5 ± 0.05	4.5 ± 0.05	4.2 ± 0.26	0.17 ^c
Chronic kidney disease, % ± se	14.0 ± 0.09	14.0 ± 0.09	13.5 ± 0.44	0.29 ^c
Congestive heart failure, % ± se	6.4 ± 0.06	6.4 ± 0.06	6.7 ± 0.32	0.28 ^c
Coronary artery disease, % ± se	13.1 ± 0.09	13.2 ± 0.09	10.8 ± 0.40	< 0.001 ^c
Transplant, % ± se	1.3 ± 0.03	1.3 ± 0.03	2.2 ± 0.19	< 0.001 ^c
Nicotine dependence, % ± se	4.3 ± 0.05	4.3 ± 0.06	4.0 ± 0.25	0.19 ^c
Severe Sepsis, % ± se	1.6 ± 0.03	1.6 ± 0.03	3.0 ± 0.21	< 0.001 ^c
Acute Kidney Injury, % ± se	16.6 ± 0.09	16.5 ± 0.09	20.0 ± 0.50	< 0.001 ^c
Acute Liver Failure, % ± se	1.03 ± 0.02	1.03 ± 0.02	0.97 ± 0.12	0.66 ^c
Acute Heart Failure, % ± se	3.7 ± 0.04	3.8 ± 0.04	2.9 ± 0.20	< 0.001 ^c
Shock, % ± se	3.3 ± 0.04	3.2 ± 0.04	6.2 ± 0.30	< 0.001 ^c
Fluid Imbalance, % ± se	32.4 ± 0.13	32.0 ± 0.13	46.3 ± 0.64	< 0.001 ^c
Toxicmega, % ± se	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.03	0.80 ^c
Intestine perforation, % ± se	1.06 ± 0.02	1.05 ± 0.02	1.2 ± 0.13	0.17 ^c
Peritonitis, % ± se	2.6 ± 0.04	2.6 ± 0.04	2.8 ± 0.21	0.34 ^c
Anemia, % ± se	1.4 ± 0.03	1.4 ± 0.03	1.7 ± 0.16	0.070 ^c
Pulmonary circulation disorders, % ± se	3.3 ± 0.04	3.4 ± 0.04	3.1 ± 0.21	0.27 ^c
*Data not available for all subjects. Indicator of sex = 61; Race (uniform) = 6,643; Length of stay (cleaned) = 8; Disposition of patient (uniform) = 106; Died during hospitalization = 106; Primary expected payer (uniform) = 292; Total charges (cleaned) = 1,713.				
Frequencies presented are unweighted counts.				
P-values: a=linear regression; b=linear regression with log transformation; c = Rao-Scott chi-square test.				
SAS Survey Procedures used for all analyses.				

Factor	Overall (N = 236,825)	non-C.diff (N = 230,132)	C.diff (N = 6,693)	p-value
Peripheral vascular disorders, % $\pm$ se	1.8 $\pm$ 0.04	1.8 $\pm$ 0.04	1.2 $\pm$ 0.14	< 0.001^c
Chronic pulmonary disease, % $\pm$ se	22.0 $\pm$ 0.11	22.0 $\pm$ 0.11	20.6 $\pm$ 0.51	0.007^c
ICU, % $\pm$ se	2.8 $\pm$ 0.04	2.8 $\pm$ 0.04	4.0 $\pm$ 0.24	< 0.001^c
Colectomy, % $\pm$ se	5.5 $\pm$ 0.08	5.6 $\pm$ 0.08	3.2 $\pm$ 0.21	< 0.001^c
Length of stay (cleaned), mean $\pm$ se*	5.2 $\pm$ 0.02	5.2 $\pm$ 0.02	7.6 $\pm$ 0.12	< 0.001^a
Region of hospital, % $\pm$ se				0.39 ^c
. Northeast	20.7 $\pm$ 0.35	20.7 $\pm$ 0.35	20.4 $\pm$ 0.65	
. Midwest	25.6 $\pm$ 0.38	25.6 $\pm$ 0.38	25.6 $\pm$ 0.70	
. South	38.1 $\pm$ 0.35	38.1 $\pm$ 0.35	37.6 $\pm$ 0.75	
. West	15.6 $\pm$ 0.25	15.6 $\pm$ 0.25	16.4 $\pm$ 0.55	
Bed size of hospital (STRATA), % $\pm$ se				< 0.001^c
. Small	20.4 $\pm$ 0.25	20.5 $\pm$ 0.25	18.2 $\pm$ 0.55	
. Medium	27.6 $\pm$ 0.29	27.6 $\pm$ 0.29	27.0 $\pm$ 0.66	
. Large	52.0 $\pm$ 0.38	51.9 $\pm$ 0.38	54.9 $\pm$ 0.77	
Location/teaching status of hospital (STRATA), % $\pm$ se				< 0.001^c
. Rural	7.6 $\pm$ 0.12	7.6 $\pm$ 0.12	5.8 $\pm$ 0.30	
. Urban nonteaching	18.8 $\pm$ 0.21	18.8 $\pm$ 0.21	18.9 $\pm$ 0.56	
. Urban teaching	73.6 $\pm$ 0.26	73.6 $\pm$ 0.26	75.3 $\pm$ 0.62	
Disposition of patient (uniform), % $\pm$ se*				< 0.001^c
*Data not available for all subjects. Indicator of sex = 61; Race (uniform) = 6,643; Length of stay (cleaned) = 8; Disposition of patient (uniform) = 106; Died during hospitalization = 106; Primary expected payer (uniform) = 292; Total charges (cleaned) = 1,713.				
Frequencies presented are unweighted counts.				
P-values: a=linear regression; b=linear regression with log transformation; c = Rao-Scott chi-square test.				
SAS Survey Procedures used for all analyses.				

Factor	Overall (N = 236,825)	non-C.diff (N = 230,132)	C.diff (N = 6,693)	p-value
. Routine Discharge	69.7 ± 0.12	69.7 ± 0.12	67.5 ± 0.60	
. Short-term hospital	2.0 ± 0.03	2.0 ± 0.03	2.0 ± 0.18	
. Transfer to other facilities	9.9 ± 0.07	9.8 ± 0.07	12.7 ± 0.42	
. Home Health Care (HHC)	14.7 ± 0.11	14.7 ± 0.11	13.9 ± 0.43	
. Against medical advice (AMA)	2.3 ± 0.03	2.3 ± 0.04	1.7 ± 0.16	
. Died in hospital	1.5 ± 0.02	1.4 ± 0.03	2.1 ± 0.18	
. Discharged alive, destination unknown	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	
Died during hospitalization, % ± se*				< 0.001 ^c
. Alive	98.5 ± 0.02	98.6 ± 0.03	97.9 ± 0.18	
. Died	1.5 ± 0.02	1.4 ± 0.03	2.1 ± 0.18	
Primary expected payer (uniform), % ± se*				< 0.001 ^c
. Medicare	41.9 ± 0.15	41.9 ± 0.15	40.9 ± 0.63	
. Medicaid	16.3 ± 0.11	16.2 ± 0.11	19.8 ± 0.52	
. Private insurance	35.3 ± 0.17	35.3 ± 0.17	32.6 ± 0.60	
. Self-pay	3.6 ± 0.06	3.6 ± 0.06	4.1 ± 0.25	
. No charge	0.34 ± 0.02	0.33 ± 0.02	0.36 ± 0.08	
. Other	2.6 ± 0.05	2.6 ± 0.05	2.3 ± 0.19	
Total charges (cleaned), mean ± se*	56930.0 ± 429.3	56526.0 ± 426.7	70842.0 ± 1605.9	< 0.001 ^a
*Data not available for all subjects. Indicator of sex = 61; Race (uniform) = 6,643; Length of stay (cleaned) = 8; Disposition of patient (uniform) = 106; Died during hospitalization = 106; Primary expected payer (uniform) = 292; Total charges (cleaned) = 1,713.				
Frequencies presented are unweighted counts.				
P-values: a=linear regression; b=linear regression with log transformation; c = Rao-Scott chi-square test.				
SAS Survey Procedures used for all analyses.				

Healthcare utilization

Compared to IBD hospitalizations without CDI, those with CDI had higher length of stay (LOS) (8.1 ± 0.08 days vs. 5.3 ± 0.01 days, $p < 0.001$) and total healthcare charges ($\$80,254.7 \pm 1392.5$ vs. $\$59,749.4 \pm 440.9$; $p < 0.001$). Similar findings were present for the CD and UC subgroups.

In-hospital complications

Primary endpoints:

Compared to IBD hospitalizations without CDI, those with CDI had higher crude rates of mortality (3.5% vs. 1.7%, $p < 0.001$) and ICU stay (5.0% vs. 3.0%, $p < 0.001$), but lower crude rates of undergoing colectomy (2.5% vs. 5.0%, $p < 0.001$).

Secondary endpoints:

Compared to IBD hospitalizations without CDI, those with CDI had higher crude rates of fluid imbalance (51.9% vs. 32.9%, $p < 0.001$), acute kidney injury (23.6% vs. 16.8%, $p < 0.001$), shock (8.6% vs. 3.5%, $p < 0.001$) and severe sepsis (4.0% vs. 1.7%, $p < 0.001$), but lower crude rates of acute heart failure (3.6% vs. 4.1%, $p = 0.002$). No differences were found in rates of acute peritonitis, intestinal perforation and toxic megacolon.

Multivariable Analysis for Outcomes

Given the higher rates of comorbid conditions and complex disease outcomes in IBD hospitalizations with CDI we performed multivariable logistic regression to reassess the primary endpoints. After adjusting for age, sex, race, comorbidities, and acute in-hospital complications, CDI was not independently associated with increased odds of in-hospital mortality compared to IBD hospitalizations without CDI (OR: 1.08, 95% CI: [0.97–1.20], $p = 0.16$). CDI was associated with lower odds of ICU admission (OR: 0.84, 95% CI: [0.77–0.92], $p < 0.001$) and lower odds of colectomy (OR: 0.48, 95% CI: [0.44–0.54], $p < 0.001$) compared to IBD hospitalizations without CDI; Tables 4–6. The models showed good discrimination for mortality (AUC: 0.89, 95% CI: 0.89–0.90; Fig. 2) and ICU admission (AUC: 0.86, 95% CI: 0.85–0.87; Fig. 3), and modest discrimination for colectomy (AUC: 0.68, 95% CI: 0.67–0.68; Fig. 4) in the test cohort.

Table 4

Multivariable Logistic Regression Analysis of Mortality in the Full Cohort (Adult Hospitalizations with IBD)

Variable	Odds Ratio	95% Confidence Interval		P-value
Group: CDiff	1.08	0.97	1.20	0.16
Age: 41–65 years	2.50	2.22	2.82	< .001
Age: > 65 years	5.64	5.01	6.35	< .001
Gender: Male	1.11	1.05	1.17	< .001
Race: White	0.93	0.87	1.00	0.049
Malnutrition	1.67	1.56	1.78	< .001
Hypertension	0.81	0.74	0.88	< .001
Chronic kidney disease	0.97	0.90	1.04	0.38
Congestive heart failure	1.44	1.32	1.56	< .001
Transplant	1.24	1.04	1.48	0.015
Severe Sepsis	2.81	2.48	3.18	< .001
Acute Kidney Injury	1.98	1.85	2.12	< .001
Acute Liver Failure	4.68	4.19	5.21	< .001
Acute Heart Failure	1.56	1.42	1.72	< .001
Fluid Imbalance	1.75	1.64	1.87	< .001
Anemia	1.07	0.88	1.29	0.50
Chronic pulmonary disease	1.21	1.14	1.29	< .001
Shock	13.83	12.92	14.80	< .001
NOTE: Group (reference = non-CDiff); Age (reference = 18–40 years); Gender (reference = Female); Race (reference = non-White); Binary variables (reference = No)				

Table 5

Multivariable Logistic Regression Analysis of ICU Admission in the Full Cohort (Adult Hospitalizations with IBD)

Cohort	Outcome	AUC (95% CI)
IBD test cohort	Mortality	0.89 (0.89–0.90)

Variable	Odds Ratio	95% Confidence Interval		P-value
Group: CDiff	0.84	0.77	0.92	< .001
Age: 41–65 years	1.44	1.34	1.55	< .001
Age: > 65 years	1.37	1.27	1.49	< .001
Gender: Male	1.20	1.14	1.25	< .001
Race: White	0.94	0.89	1.00	0.038
Malnutrition	1.43	1.35	1.50	< .001
Hypertension	1.33	1.25	1.41	< .001
Chronic kidney disease	0.76	0.72	0.81	< .001
Congestive heart failure	1.37	1.27	1.48	< .001
Transplant	1.23	1.06	1.41	0.005
Severe Sepsis	2.53	2.25	2.83	< .001
Acute Kidney Injury	1.72	1.63	1.82	< .001
Acute Liver Failure	3.62	3.26	4.03	< .001
Acute Heart Failure	2.10	1.94	2.28	< .001
Fluid Imbalance	2.27	2.14	2.42	< .001
Anemia	0.90	0.77	1.06	0.22
Chronic pulmonary disease	1.44	1.36	1.51	< .001
Shock	24.37	23.02	25.79	< .001
NOTE: Group (reference = non-CDiff); Age (reference = 18–40 years); Gender (reference = Female); Race (reference = non-White); Binary variables (reference = No)				

Table 6
Multivariable Logistic Regression Analysis of Colectomy
in the Full Cohort (Adult Hospitalizations with IBD)

Cohort	Outcome	AUC (95% CI)
IBD test cohort	ICU Admission	0.86 (0.85–0.87)

Variable	Odds Ratio	95% Confidence Interval		P-value
Group: CDiff	0.49	0.44	0.54	< .001
Age: 41–65 years	0.88	0.85	0.91	< .001
Age: > 65 years	0.60	0.57	0.62	< .001
Gender: Male	1.23	1.19	1.26	< .001
Race: White	1.29	1.24	1.35	< .001
Malnutrition	1.77	1.70	1.85	< .001
Hypertension	1.10	1.05	1.15	< .001
Chronic kidney disease	0.48	0.45	0.52	< .001
Congestive heart failure	0.50	0.45	0.55	< .001
Transplant	0.39	0.32	0.48	< .001
Severe Sepsis	0.74	0.63	0.87	< .001
Acute Kidney Injury	0.72	0.69	0.76	< .001
Acute Liver Failure	0.42	0.34	0.52	< .001
Acute Heart Failure	0.34	0.29	0.39	< .001
Fluid Imbalance	0.69	0.66	0.73	< .001
Anemia	0.55	0.45	0.66	< .001
Chronic pulmonary disease	0.65	0.62	0.68	< .001
Shock	2.73	2.53	2.94	< .001
NOTE: Group (reference = non-CDiff); Age (reference = 18–40 years); Gender (reference = Female); Race (reference = non-White); Binary variables (reference = No)				

In subgroup analyses of UC and CD, CDI was similarly not independently associated with mortality in either subtype. The lower odds of ICU admission with CDI were significant only in UC (OR: 0.80, 95% CI: [0.71–0.90], $p < 0.001$) but not in CD (OR: 0.94, 95% CI: [0.80–1.09], $p = 0.39$). Both UC and CD subgroups had lower odds of colectomy in the CDI group than in those without CDI.

Discussion

We used a large nationally representative inpatient database to examine the impact of CDI on hospitalized patients with IBD, focusing on healthcare utilization, in-hospital mortality, ICU admission, and colectomy. Among 382,498 hospitalizations for IBD, including 15,822 cases with a concurrent CDI diagnosis, CDI was consistently associated with higher costs and longer hospital stays. After adjusting

for age and comorbidity and complication burdens among CDI patients, CDI was not independently associated with increased mortality and was linked to lower odds of ICU admission and colectomy. These results contribute to the growing body of evidence indicating that the apparent severity of CDI in IBD is attributable to the underlying vulnerability of the patient population rather than a direct, independent effect of the infection itself.

Healthcare Utilization

Hospitalizations with both CDI and IBD were associated with significantly increased healthcare utilization. The median length of stay was 3 days longer compared to IBD patients without CDI, consistent with findings from multiple studies¹⁴ found variability in length of stay across studies, though most reported increased duration. This is corroborated by retrospective studies by Rezapour et al.¹⁵ and Issa et al.¹⁶, as well as a meta-analysis of 21 studies which reported longer hospitalizations in the CDI cohort⁹.

The cost differential was also substantially higher in patients with both conditions, running approximately \$20,000 higher than those without CDI. Rezapour et al.¹⁵ similarly found substantially higher charges, with the widest gap in the CD subgroup. A systematic review of real-world CDI costs found that patients with primary CDI incur roughly \$24,000 more than non-CDI controls, suggesting the financial impact we observed is not unique to IBD but rather amplified by it¹⁷. These increased costs and prolonged stays likely reflect the higher comorbidity burden in CDI patients, who also experience greater rates of complications, including acute kidney injury, electrolyte and fluid abnormalities, and shock requiring more intensive management.

Mortality

On unadjusted analysis, CDI was associated with higher in-hospital mortality, more than double the rate seen in non-CDI hospitalizations (3.5% vs. 1.7%). However, after adjusting for age, sex, comorbidities, and acute in-hospital complications in a multivariable logistic regression model, CDI was no longer independently associated with mortality (OR: 1.08, 95% CI: [0.97–1.20], $p = 0.16$). This gap between crude and adjusted findings is likely related to the fact that CDI patients were older, had more comorbid conditions, and experienced higher rates of serious complications during their hospitalization. Each of these factors independently worsened mortality, and, after adjustment, CDI did not confer an additional mortality risk. These findings align with hospital-based studies utilizing laboratory-confirmed CDI cases that similarly showed no significant mortality difference between IBD patients with and without CDI after appropriate adjustment^{2,6,18}. In contrast, several studies have reported increased mortality in CDI and IBD patients, though these differences may be attributable to study design, patient populations, and inadequate confounder adjustment. Meta-analyses on this question have produced widely varying estimates, and a recent global systematic review noted substantial heterogeneity across studies, with higher-quality adjusted analyses generally showing weaker or non-significant associations^{9,15,19–21,21–23}.

The lack of mortality difference in our adjusted analysis likely reflects several contemporary factors in CDI management. Patients with IBD undergo increased surveillance for enteric infections, likely leading to earlier detection and treatment of CDI. Additionally, there has been a national trend of decreased CDI rates and related mortality in the United States, as documented by Spartz et al²⁴ and Guh et al²⁵. Finally, the use of assays which detect toxins has improved differentiation between active CDI and colonization, potentially reducing overtreatment of colonized patients while ensuring appropriate therapy for those with actual infection.

In subgroup analyses, CDI was not independently associated with mortality in either the UC or CD subgroups, which is reassuring given the distinct clinical profiles of those populations.

ICU Admission

Our study found decreased odds of ICU admission in patients with IBD and CDI compared to those without CDI. These results are consistent with the findings of Law et al.²⁶. This seemingly counterintuitive finding may reflect heightened clinical awareness and earlier diagnostic testing for CDI during IBD flares, leading to prompt initiation of appropriate antibiotics and aggressive supportive care secondarily lowering the risk of decompensation and need for ICU admission despite the presence of CDI²⁷. This also fits with the broader observation that ICU triage in IBD is driven far more by hemodynamic instability, multi-organ failure, and septic shock than by any specific infectious etiology^{9,28,29}.

A retrospective cohort study of critically ill IBD patients found that annual ICU admission rates in this population are actually increasing, and that in-hospital morbidity and 30-day mortality are substantial when IBD patients do reach the ICU. These were driven primarily by the degree of physiological compromise at admission rather than by any single precipitating trigger^{29,30}.

In subgroup analyses, the lower odds of ICU admission associated with CDI were significant only in UC (OR: 0.80, 95% CI: [0.71–0.90], $p < 0.001$) but not in CD (OR: 0.94, 95% CI: [0.80–1.09], $p = 0.39$). This difference makes clinical sense: UC, as a purely colonic disease, tends to present with more overt and recognizable symptoms when associated with CDI, like worsening bloody diarrhea, increased stool frequency, and systemic signs, making it easier for early identification and treatment of decompensated disease. In CD, where inflammation can be transmural and distributed across the GI tract, distinguishing a CDI-related flare from underlying disease activity is considerably harder, and the relationship may be harder to detect.

Colectomy

CDI was associated with significantly lower odds of inpatient colectomy compared to IBD hospitalizations without CDI (OR: 0.48, 95% CI: [0.44–0.54], $p < 0.001$). This is consistent with multiple meta-analyses and systematic reviews demonstrating that although CDI may increase the risk of long-term colectomy, it does not significantly affect short-term surgical rates^{26,31}. This finding may again be

related to increased awareness of CDI risk in IBD patients, earlier diagnosis, and prompt initiation of treatment. In addition, data also show that colectomy rates in IBD have declined significantly over the past two decades, attributed in part to earlier diagnosis and wider use of effective biologics³². Both UC and CD subgroups showed similarly lower odds of colectomy in the CDI group. This is in line with previous studies suggesting that improvements in the treatment of CDI and IBD have reduced the short-term effect of CDI on surgical outcomes in both ulcerative colitis and Crohn's disease¹¹.

Limitations

Potential limitations of our study include that the results are retrospective, observational, and derived from an administrative claims database, which is prone to coding errors. Due to reliance on ICD-10 codes, there is limited data on IBD severity, CDI severity, and disease recurrence. We were unable to distinguish active CDI from colonization because diagnostic codes do not differentiate between these states, potentially leading to the inclusion of patients without clinically significant infection. There is a lack of imaging, procedural, medication, and laboratory data from the NIS database. Although we used a multivariable logistic regression model to adjust for patient comorbidities across groups, there may be other unmeasured confounders which could influence outcomes. The model demonstrated poor discrimination for colectomy despite the addition of variables; this may be attributable to insufficient data granularity, as described above. Nonetheless, this nationwide database has been utilized extensively in medical research and is considered dependable when subjected to appropriate analytical methods. The use of multivariate logistic regression to identify factors associated with the outcomes and of ROC curves to assess the model's discriminative performance in the test cohort can be considered key strengths of the study.

Conclusion

In this large nationwide study of 382,498 IBD hospitalizations, including 15,822 with concomitant CDI, we found that CDI significantly increased healthcare utilization (longer length of stay and higher costs) but, after adjusting for confounders, CDI was not independently associated with increased in-hospital mortality and was actually linked to lower odds of ICU admission and colectomy. These findings suggest that improved awareness, early detection, and prompt treatment of CDI in IBD patients could be contributing to improved outcomes. Prospective studies with detailed clinical, laboratory, and treatment data are needed to validate these factors and optimize risk stratification strategies in this vulnerable population.

Declarations

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None

Author Contribution

U.B. contributed to study conception and design, interpretation of results, and manuscript drafting. Q.Y. and Y.W. contributed to data analysis, chart generation, and interpretation of results. B.B., T.Q., and J.A. provided supervision, contributed to study conception and interpretation of the findings, and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

References

1. Burke KE, Lamont JT. Clostridium difficile infection: a worldwide disease. *Gut Liver*. 2014;8(1):1–6. doi:10.5009/gnl.2014.8.1.1
2. Drozdinsky G, Atamna A, Banai H, Ben-Zvi H, Bishara J, Eliakim-Raz N. Clinical outcomes for Clostridioides difficile associated diarrhea in inflammatory bowel disease patients versus non-IBD population: A retrospective cohort study. *Medicine (Baltimore)*. 2023;102(6):e32812. doi:10.1097/MD.00000000000032812
3. 2019 Antibiotic Resistance Threats Report. Published online 2019. <https://www.cdc.gov/antimicrobial-resistance/data-research/threats/index.html>
4. Boeriu A, Roman A, Fofiu C, Dobru D. The Current Knowledge on Clostridioides difficile Infection in Patients with Inflammatory Bowel Diseases. *Pathogens*. 2022;11(7):819. doi:10.3390/pathogens11070819
5. Patel RS, Rohit Reddy S, Llukmani A, et al. Cardiovascular Manifestations in Inflammatory Bowel Disease: A Systematic Review of the Pathogenesis and Management of Pericarditis. *Cureus*. 2021;13(3):e14010. doi:10.7759/cureus.14010
6. Singh H, Nugent Z, Yu BN, Lix LM, Targownik LE, Bernstein CN. Higher Incidence of Clostridium difficile Infection Among Individuals With Inflammatory Bowel Disease. *Gastroenterology*. 2017;153(2):430–438.e2. doi:10.1053/j.gastro.2017.04.044
7. Moens A, Verstockt B, Machiels K, et al. Clostridium difficile infection in inflammatory bowel disease: epidemiology over two decades. *Eur J Gastroenterol Hepatol*. 2019;31(6):668–673. doi:10.1097/MEG.0000000000001394
8. Singh S, Graff LA, Bernstein CN. Do NSAIDs, antibiotics, infections, or stress trigger flares in IBD? *Am J Gastroenterol*. 2009;104(5):1298–1313; quiz 1314. doi:10.1038/ajg.2009.15
9. Qi HX, Wang Q, Zhou GQ. Association of Clostridium difficile infection with clinical outcomes of patients with inflammatory bowel disease: A meta-analysis. *World J Gastrointest Surg*. 2025;17(4):100555. doi:10.4240/wjgs.v17.i4.100555
10. Ben-Horin S, Margalit M, Bossuyt P, et al. Prevalence and clinical impact of endoscopic pseudomembranes in patients with inflammatory bowel disease and Clostridium difficile infection. *J Crohns Colitis*. 2010;4(2):194–198. doi:10.1016/j.crohns.2009.11.001
11. Kariv R, Navaneethan U, Venkatesh PGK, Lopez R, Shen B. Impact of Clostridium difficile infection in patients with ulcerative colitis. *J Crohns Colitis*. 2011;5(1):34–40. doi:10.1016/j.crohns.2010.09.007

12. AHRQ HCUP NIS. Published online 2022. <https://hcup-us.ahrq.gov/nisoverview.jsp>
13. International Statistical Classification of Diseases and Related Health Problems (ICD). <https://www.who.int/standards/classifications/classification-of-diseases>
14. Trifan A, Stanciu C, Stoica O, Girleanu I, Cojocariu C. Impact of Clostridium difficile infection on inflammatory bowel disease outcome: a review. *World J Gastroenterol*. 2014;20(33):11736–11742. doi:10.3748/wjg.v20.i33.11736
15. Rezapour M, Galoosian A, Liu B, Bhuket T, Wong RJ. Clostridium difficile co-infection in inflammatory bowel disease is associated with significantly increased in-hospital mortality. *Eur J Gastroenterol Hepatol*. 2018;30(9):1041–1046. doi:10.1097/MEG.0000000000001185
16. Issa M, Vijayapal A, Graham MB, et al. Impact of Clostridium difficile on inflammatory bowel disease. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2007;5(3):345–351. doi:10.1016/j.cgh.2006.12.028
17. Malone DC, Armstrong EP, Gratie D, Pham SV, Amin A. A systematic review of real-world healthcare resource use and costs of Clostridioides difficile infections. *Antimicrob Steward Healthc Epidemiol ASHE*. 2023;3(1):e17. doi:10.1017/ash.2022.369
18. Joshi NM, Marks IH, Crowson R, Ball D, Rampton DS. Incidence and Outcome of Clostridium difficile Infection in Hospitalized Patients with Inflammatory Bowel Disease in the UK. *J Crohns Colitis*. 2017;11(1):70–76. doi:10.1093/ecco-jcc/jjw117
19. Amakye D, Ssentongo P, Patel S, et al. Global Patterns of Clostridioides difficile Infection in Patients with Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis of Prevalence, Epidemiology, and Risk Factors. *Crohns Colitis* 360. 2025;7(2):otaf024. doi:10.1093/crocol/otaf024
20. Tariq R, Law CCY, Khanna S, Murthy S, McCurdy JD. The Impact of Clostridium difficile Infection on Mortality in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol*. 2019;53(2):127–133. doi:10.1097/MCG.0000000000000968
21. Balram B, Battat R, Al-Khoury A, et al. Risk Factors Associated with Clostridium difficile Infection in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *J Crohns Colitis*. 2019;13(1):27–38. doi:10.1093/ecco-jcc/jjy143
22. Khanna S, Shin A, Kelly CP. Management of Clostridium difficile Infection in Inflammatory Bowel Disease: Expert Review from the Clinical Practice Updates Committee of the AGA Institute. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2017;15(2):166–174. doi:10.1016/j.cgh.2016.10.024
23. Drobnik J, Pobrotyn P, Belovičová M, Madziarska K, Trocha M, Baran M. Mortality in clostridioides difficile infection among patients hospitalized at the university clinical hospital in Wroclaw, Poland - a 3-year observational study. *BMC Infect Dis*. 2024;24(1):625. doi:10.1186/s12879-024-09495-7
24. Spartz EJ, DeDecker LC, Fansiwala KM, et al. Recent trends and risk factors associated with Clostridioides difficile infections in hospitalized patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2024;59(1):89–99. doi:10.1111/apt.17777

25. Guh AY, Mu Y, Winston LG, et al. Trends in U.S. Burden of *Clostridioides difficile* Infection and Outcomes. *N Engl J Med*. 2020;382(14):1320–1330. doi:10.1056/NEJMoa1910215
26. Law CCY, Tariq R, Khanna S, Murthy S, McCurdy JD. Systematic review with meta-analysis: the impact of *Clostridium difficile* infection on the short- and long-term risks of colectomy in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;45(8):1011–1020. doi:10.1111/apt.13972
27. Martínez-Lozano H, Saralegui-Gonzalez P, Reigadas E, et al. Risk factors for *Clostridioides difficile* infection among patients diagnosed with inflammatory intestinal and rheumatological diseases in the biologic era. *BMC Gastroenterol*. 2025;25(1):70. doi:10.1186/s12876-025-03650-3
28. Zhang Z, Zhao C, Zhou Y, et al. Random forest-driven mortality prediction in critical IBD care: a dual-database model integrating comorbidity patterns and real-time physiometrics. *Front Med*. 2025;12:1624899. doi:10.3389/fmed.2025.1624899
29. Böttcher M, Bertram F, Sabihi M, et al. Clinical Presentation and Outcome of Critically Ill Patients with Inflammatory Bowel Disease. *Visc Med*. 2024;40(2):75–81. doi:10.1159/000537885
30. Marrie RA, Garland A, Peschken CA, et al. Increased incidence of critical illness among patients with inflammatory bowel disease: a population-based study. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2014;12(12):2063–2070.e1-4. doi:10.1016/j.cgh.2014.03.033
31. Chen Y, Furuya-Kanamori L, Doi SA, Ananthakrishnan AN, Kirk M. *Clostridium difficile* Infection and Risk of Colectomy in Patients with Inflammatory Bowel Disease: A Bias-adjusted Meta-analysis. *Inflamm Bowel Dis*. 2017;23(2):200–207. doi:10.1097/MIB.0000000000000998
32. Ghaz H, Kesler A, Hoogenboom SA, et al. Decreasing Colectomy Rates in Ulcerative Colitis in the Past Decade: Improved Disease Control? *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2020;24(2):270–277. doi:10.1007/s11605-019-04474-9

Figures

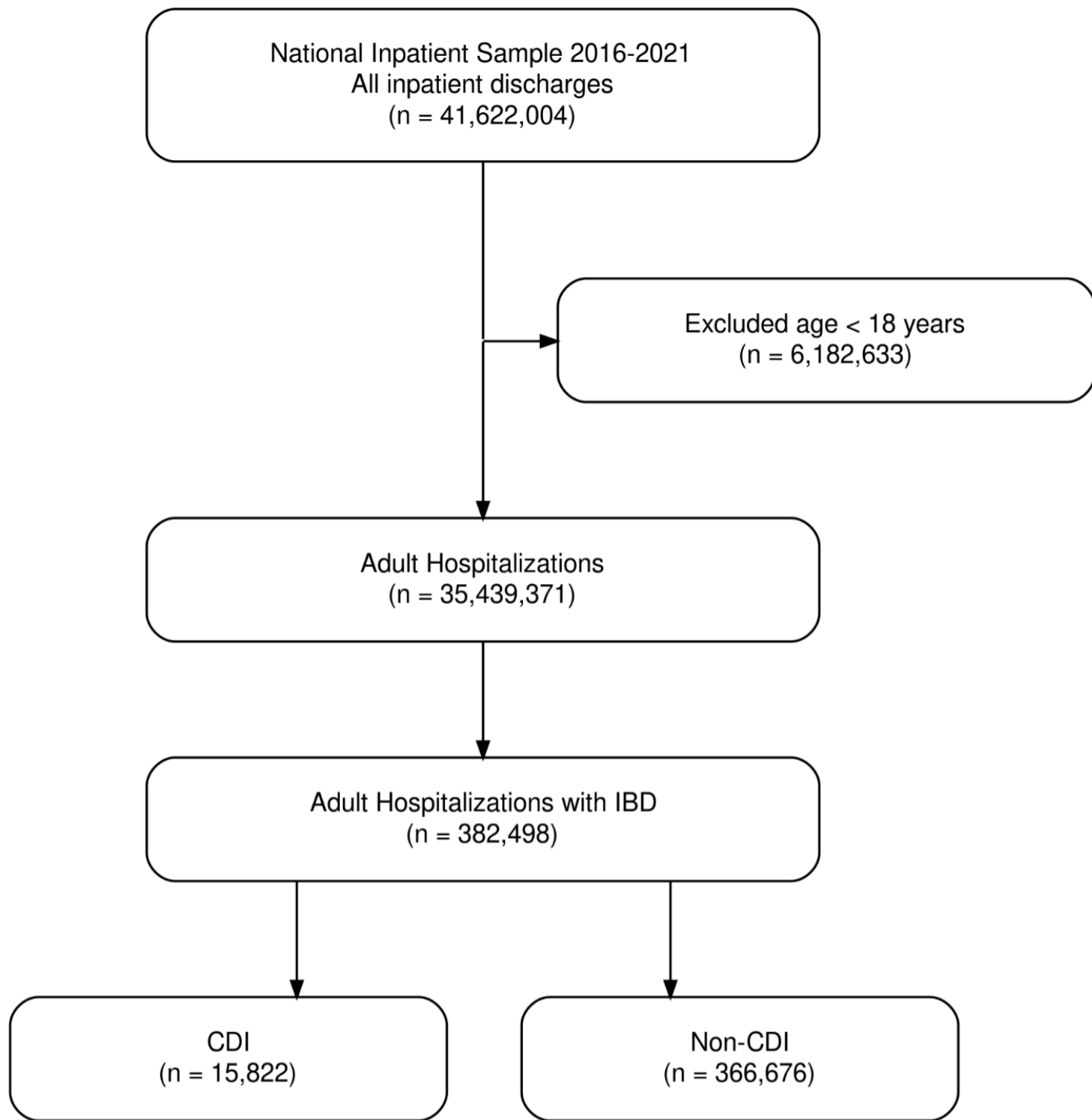


Figure 1

Selection of Adult Hospitalizations with IBD from the National Inpatient Sample (2016-2021)

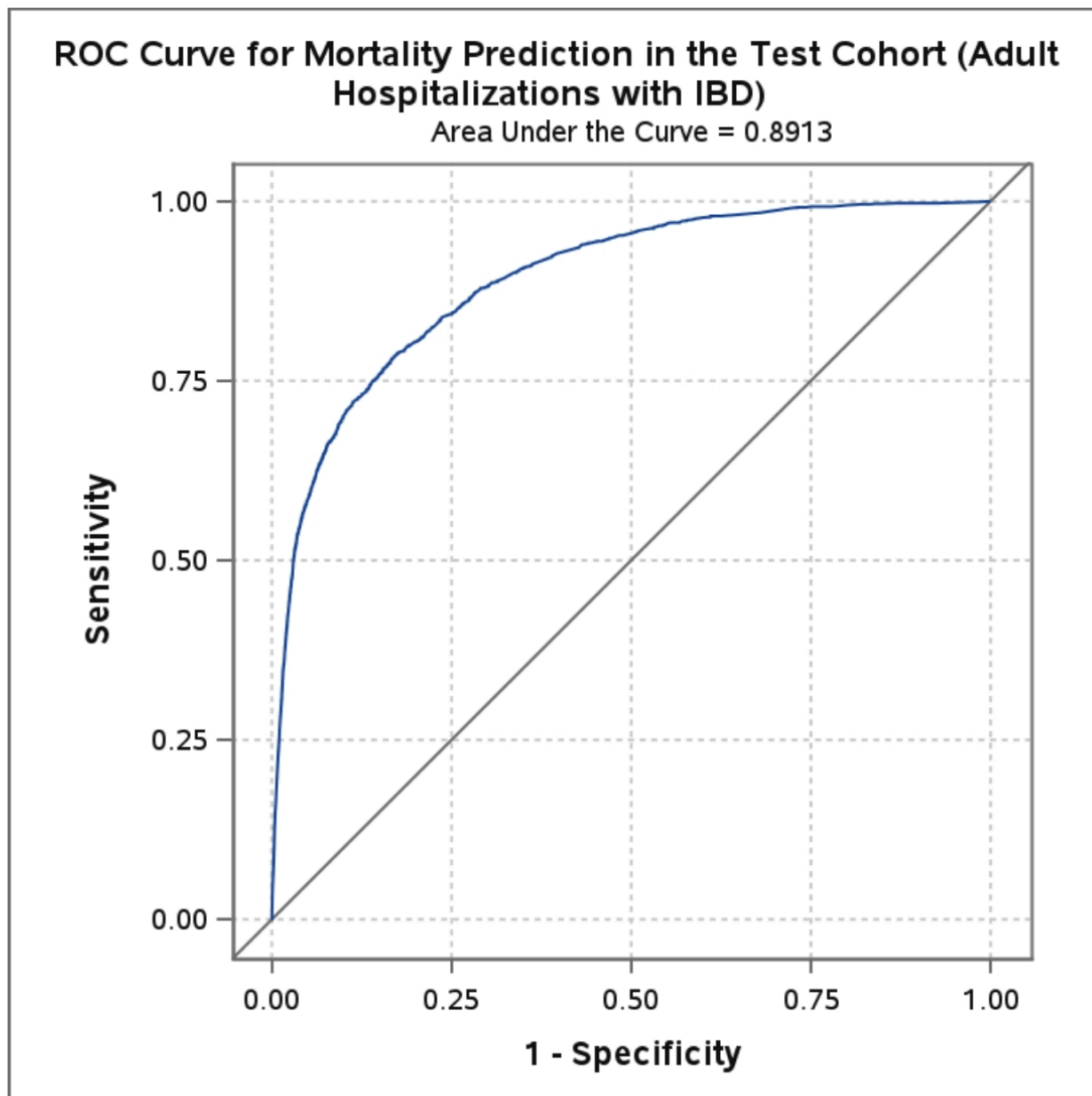


Figure 2

ROC- AUC for Mortality Prediction in the Test Cohort (Adult Hospitalizations with IBD)

**ROC Curve for ICU Admission Prediction in the Test Cohort
(Adult Hospitalizations with IBD)**

Area Under the Curve = 0.8603

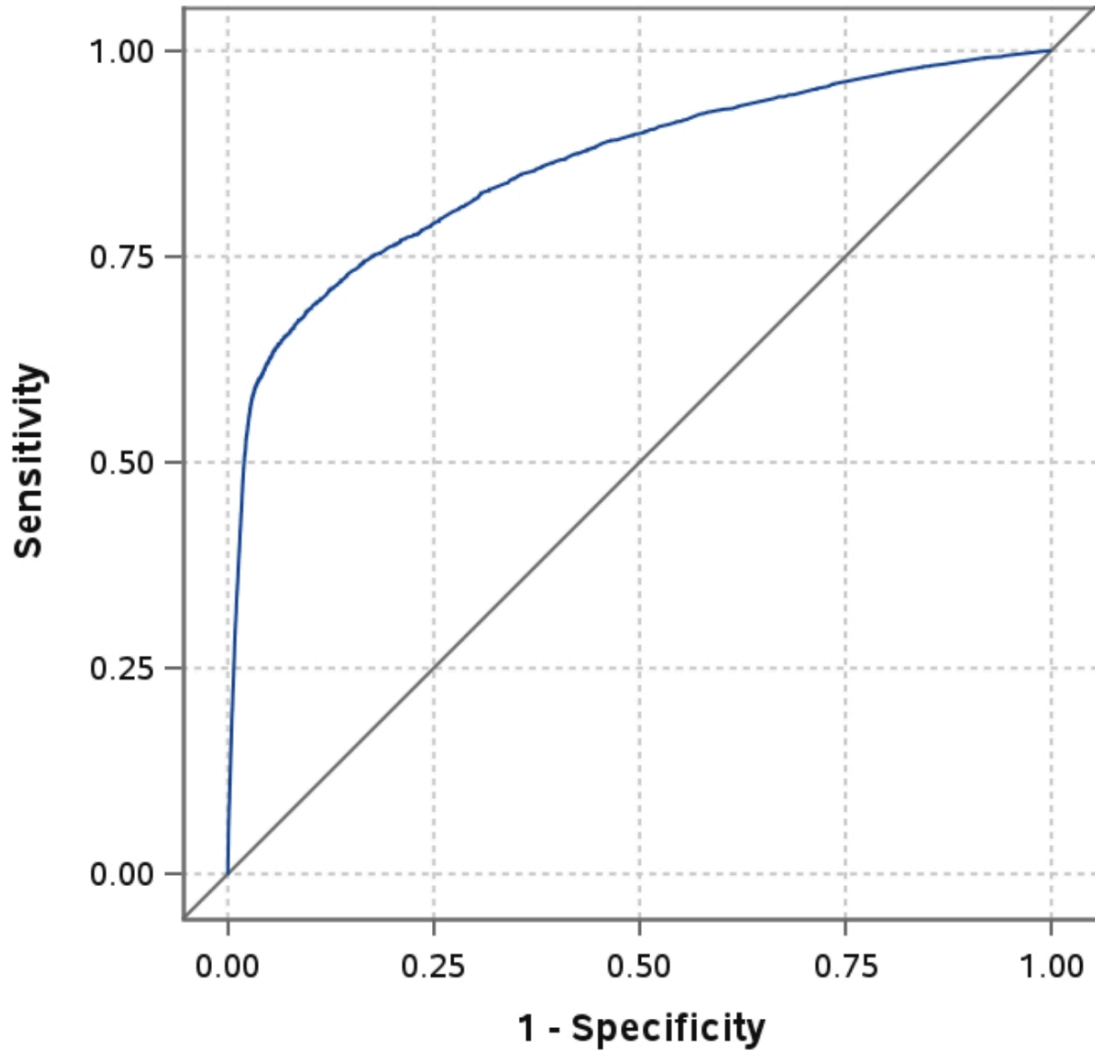


Figure 3

ROC- AUC for ICU Admission Prediction in the Test Cohort (Adult Hospitalizations with IBD)

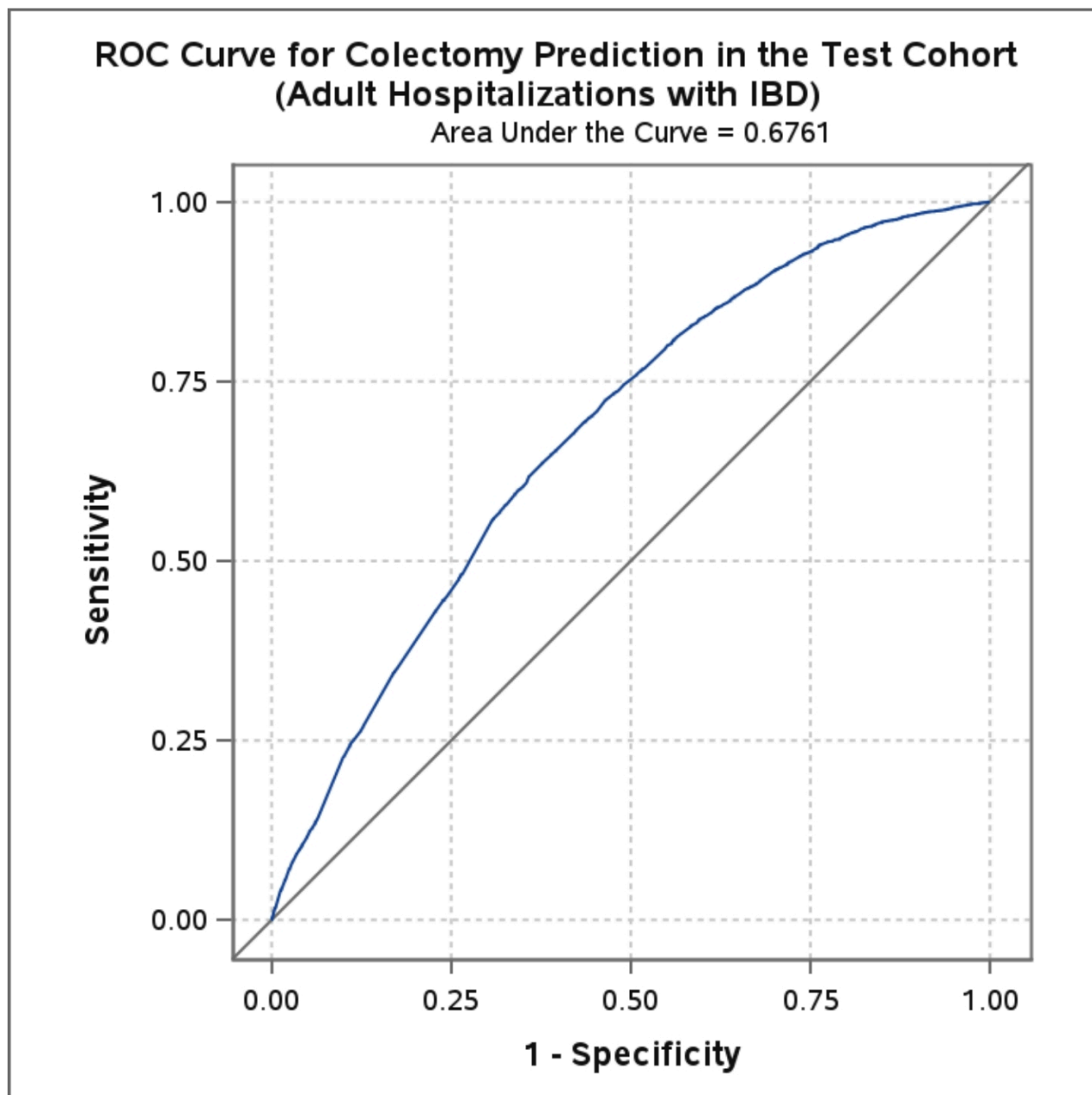


Figure 4

ROC- AUC for Colectomy Prediction in the Test Cohort (Adult Hospitalizations with IBD)