Impact of *Clostridioides difficile* Infection on Clinical Outcomes in Hospitalized Patients With Inflammatory Bowel Disease

A Nationwide Analysis

Shivangini Duggal, MD, Sakar Khattar, MS,† Lakshmi Kattamuri, MD,* Mashal Batheja, MD,‡ Marc J. Zuckerman, MD,§ and Sherif E. Elhanafi, MD§*

Introduction: *Clostridioides difficile* infection (CDI) is a major complication in patients with inflammatory bowel disease (IBD), contributing to increased morbidity, mortality, and health care burden. This study aimed to evaluate national trends and clinical outcomes associated with CDI in hospitalized IBD patients in the United States.

Methods: We conducted a retrospective cohort study using the National Inpatient Sample (NIS) from 2012 to 2021. Adult patients hospitalized with a primary or secondary diagnosis of IBD (Crohn's disease or ulcerative colitis) were stratified into 2 groups by the status of CDI diagnosis (either primary or secondary diagnosis). Demographic characteristics, hospital outcomes, and complications were compared between CDI and non-CDI cohorts. Multivariable logistic regression was used to identify independent predictors of in-hospital mortality, septic shock, and venous thromboembolism (VTE).

Results: Among 4,193,564 hospitalized IBD patients, 534,190 (12.7%) had CDI. CDI patients were older (mean: 68.8 vs 53.3 y, $P < 0.001$), with higher in-hospital mortality (3.6% vs 2.0%, $P < 0.001$), VTE (23.7% vs 6.2%, $P < 0.001$), septic shock (5.4% vs 4.0%, $P < 0.001$), and mechanical ventilation use (4.2% vs 2.8%, $P < 0.001$). Ulcerative colitis was more frequently associated with CDI than Crohn's disease (30.3% vs 25.0%, $P < 0.001$) and independently predicted septic shock (OR: 1.09) and VTE (OR: 1.06) but was associated with lower mortality (OR: 0.81).

Conclusion: The presence of CDI in hospitalized patients with IBD led to significantly worse outcomes. Ulcerative colitis is more commonly associated with CDI and increased risk of complications. These findings highlight the need for early detection, preventive strategies, and tailored management of CDI in the IBD population.

Key Words: inflammatory bowel disease, Clostridium difficile infection, mortality

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Clostridioides difficile (*C. difficile*) is an anaerobic, spore-forming, gram-positive bacterium that can asymptomatically colonize the gastrointestinal tract.[1] However, when pathogenic, it causes a spectrum of disease ranging from mild diarrhea to life-threatening pseudomembranous colitis.[2] In healthy adults, asymptomatic carriage rates range from 0% to 15%.[3] Over the past decade, the burden of *C. difficile* infection (CDI) has increased, driven by more virulent and treatment-resistant strains.[4] CDI is associated with gut dysbiosis, marked by increased Proteobacteria and Enterobacteriaceae, and reduced Lachnospiraceae, Ruminococcaceae, and Alistipes.[5–7]

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis (UC), a chronic inflammatory condition of the gastrointestinal tract, is associated with an increased susceptibility to CDI.[8] IBD-associated gut dysbiosis varies with disease activity, showing increased Enterobacteriaceae, *R. torques*, and *R. gnavus*, and reduced Faecalibacterium, Akkermansia, and Butyricicoccus in an inflammatory state.[9] These underlying shifts in the gut microbiota may impair colonization resistance and predispose IBD patients to CDI. Hospitalized IBD patients have a reported CDI incidence of 5.5% to 7.6%, notably higher than the 1.1% to 1.9% incidence observed in the general hospitalized population and approaching the rates seen in patients with antibiotic-associated diarrhea (10.5% to 14.1%).[10,11] CDI in the context of IBD is associated with increased hospitalization rates, longer lengths of stay, higher colectomy rates, and nearly 5-fold greater in-hospital mortality. Furthermore, recurrence rates and prevalence of toxigenic *C. difficile* are significantly more common in this population.[12] Given these concerns, the aim of this study was to evaluate recent trends in hospitalizations related to CDI among patients with IBD using a large national database.

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From the *Department of Internal Medicine; †Division of Gastroenterology and Hepatology, Mayo Clinic, Phoenix, AZ; ‡Department of Augmented Reality/Virtual Reality, Google LLC, Mountain View, CA, USA; and §Division of Gastroenterology, Texas Tech University Health Sciences Center, El Paso, TX, USA.
S.D., S.K., and L.K.: conceptualization, investigation and review of relevant data and articles, and written original draft. S.K.: data analysis. M.B., M.J.Z., and S.E.E.: review and editing. S.E.E.: article guarantor. All authors agree with the findings.
The authors declare that they have nothing to disclose.
Address correspondence to: Shivangini Duggal, MD, Department of Internal Medicine, Texas Tech University Health Sciences Center, 4801, Alberta Avenue, El Paso 79905, TX (e-mail: sduggal@ttuhsc.edu).
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METHODS

Study Cohort and Outcomes

Patients aged 18 years or older hospitalized from 2012 to 2021 with a primary or secondary diagnosis of IBD were included in the study. Within this IBD cohort, admissions were stratified by the status of CDI diagnosis, either as a primary or secondary diagnosis, during the same hospitalization, yielding 2 groups including patients with IBD and CDI and patients with IBD without CDI. Patients with the diagnosis of IBD, including UC and Crohn's disease, along with CDI, were then analyzed further (see supplementary file, Supplemental Digital Content 1, http://links.lww.com/JCG/B320).

The study cohort was identified from the National Inpatient Sample (NIS) database, part of the Healthcare Cost and Utilization Project (HCUP). The NIS, the largest publicly available all-payer inpatient database in the United States, contains a 20% stratified sample of over 7 million annual discharges from 46 states. It includes data on demographics, hospital characteristics, comorbidities, procedures, and outcomes. As a de-identified public data set, the study was exempt from IRB approval and not considered human subjects research. Patients were identified using ICD-9/10-CM and PCS codes, with both systems used to capture data across the 2015 coding transition. A manual review ensured consistency, and all codes are detailed in the supplementary file (Supplemental Digital Content 1, http://links.lww.com/JCG/B320).

Patients were stratified into 2 groups based on whether they had CDI during the hospital stay or not. Demographic data, including age, gender, race, and insurance status, and clinical outcomes were compared between the two groups. Endoscopic procedures included EGD, colonoscopy, flexible sigmoidoscopy, and small bowel enteroscopy. Primary outcomes included in-hospital mortality, use of mechanical ventilation, and incidence of septic shock. Secondary outcomes of interest included frequency of blood transfusion, length of stay (LOS), and total hospital charges.

Statistical Analysis

Analyses were conducted in R v4.0.0 using gtsummary and survey. All estimates and models were design-based, incorporating NIS discharge weights (DISCWT), strata (NIS_STRATUM), and hospital clusters (HOSP_NIS) with robust SEs. Continuous and categorical variables were summarized with survey-weighted means/SEs and proportions, and compared using survey-adjusted *t* tests and χ^2 tests ($\alpha = 0.05$). Associations were estimated with survey-weighted logistic regression and reported as odds ratios with 95% CIs. Endoscopy was defined as any in-hospital endoscopy (procedure timing unavailable in NIS) and, therefore, modeled as a non–time-dependent exposure; results are interpreted cautiously. Missing data were low and handled through complete-case analysis; model assumptions and fit were checked.

RESULTS

A cohort of 4,193,564 hospitalized patients with IBD were identified, of whom 534,190 (12.7%) had a diagnosis of CDI. The mean age of admitted patients was 61.03 ± 17.12 years, with females comprising the majority (55.86%). Patients in the CDI group were significantly older, with a mean age of 68.8 years compared with 53.3 years in those non-CDI group ($P < 0.001$). CDI group had a lower proportion of females (46.4%) compared with the non-CDI group (57.3%, $P < 0.001$). White patients comprised the majority of the hospitalized IBD cohort (74%), followed by black (10.9%) and Hispanic (6.6%) patients. Racial distribution differed significantly between groups ($P < 0.001$), with white patients comprising 84.7% of the CDI group versus 76.3% of the non-CDI group. Insurance status also varied; a greater proportion in CDI group were covered by Medicare (71.3%) compared with the non-CDI group (40.5%, $P < 0.001$). Overall, missing data were low and were mainly in race 4.88% and total charges 1.45%. This was handled by complete-case analysis.

In the total cohort, we observed more patients with Crohn's disease admitted to the hospital (74.35%) compared with UC. However, among the CDI group, UC was more common as compared with the non-CDI group (30.3% vs 25.0%, $P < 0.001$). Patients in CDI group experienced higher in-hospital mortality (3.61% vs 2.03%, $P < 0.001$), and a higher frequency of complications including venous thromboembolism (VTE; 23.7% vs 6.2%, $P < 0.001$), septic shock (5.4% vs 4.0%, $P < 0.001$), and need for mechanical ventilation (4.2% vs 2.8%, $P < 0.001$). Blood transfusions were also more common in the CDI group (9.0% vs 7.0%, $P < 0.001$). In addition, CDI patients had a longer hospital stay (mean: 5.93 vs 5.87 d, $P < 0.001$) and higher total hospital charges (median: \$34,911 vs \$29,660, $P < 0.001$; Table 1).

Stratified Analysis Based on Inflammatory Bowel Disease Type

Among hospitalized patients with CDI, 372,210 (69.7%) had Crohn's disease and 161,980 (30.3%) had ulcerative colitis (UC). The mean age at admission was slightly higher among UC patients (69.9 ± 14.1 y) compared with those who had Crohn's disease (68.4 ± 14.4 y), $P < 0.001$. In-hospital mortality was also marginally lower in UC patients (3.12%) compared with Crohn's disease (3.83%), $P < 0.001$. A greater proportion of Crohn's patients were females (48.5%) than UC patients (41.6%), $P < 0.001$. Racial distribution was similar between groups, though UC patients had a slightly higher proportion of White individuals (85.7% vs 84.2%), $P < 0.001$. The majority in both groups were covered by Medicare, with similar rates (71.2% vs 71.4%), though private insurance was more common in UC (20.2% vs 18.5%), $P < 0.001$.

Smoking was slightly more prevalent in UC patients (35.1%) compared with those who had Crohn's disease (34.2%), $P = 0.009$. Rates of alcohol use were comparable between the two groups. Anxiety and depression were both significantly more common in patients with Crohn's disease ($P < 0.001$). Patients with Crohn's also had higher rates of mechanical ventilation (4.4% vs 3.7%), while UC patients had higher rates of endoscopy (8.8% vs 7.3%) and blood transfusion (9.9% vs 8.6%), all $P < 0.001$. UC patients had shorter hospital stays on average (mean: 5.68 vs 6.04 d, $P < 0.001$), but incurred higher hospital charges (median: \$39,303 vs \$33,046, $P < 0.001$; Table 2).

In survey-weighted temporal analyses (2012-2021), in-hospital mortality among patients hospitalized with IBD and CDI remained ~3% before 2015, declined markedly in 2016 (~1.3%), and then increased steadily through 2021 (~2.2%; Fig. 1A). Septic shock followed a comparable pattern, with higher rates in 2014-2015 (~4.6%–4.7%), a trough in 2016 (~3.4%), and a rise thereafter, peaking in

TABLE 1. Characteristics of the Overall Cohort

Variable	Patients with CDI (N = 534,190)	Patients without CDI (N = 3,659,374)	*P*
Age in years at admission			< 0.001
Mean (SD)	68.82 (14.34)	53.25 (19.91)	—
Median (IQR)	71.00 (61.00, 79.00)	55.00 (37.00, 69.00)	—
Missing data	0	110	—
Mortality; n (%)	19,295.00 (3.61)	74,244.98 (2.03)	< 0.001
Missing data	60	870	—
Gender; n (%)			
Females	247,964 (46.42)	2,094,769 (57.26)	< 0.001
Males	286,226 (53.58)	1,564,605 (42.74)	—
Missing data	15	420	—
Race; n (%)			< 0.001
White	434,089.95 (84.66)	2,665,739.54 (76.30)	—
Black	40,515.00 (7.90)	415,785.03 (11.90)	—
Hispanic	21,329.99 (4.16)	255,239.93 (7.31)	—
Asian or Pacific Islander	5759.99 (1.12)	54,670.00 (1.56)	—
Native American	1720.00 (0.34)	15,419.99 (0.44)	—
Other	9345.00 (1.82)	87,089.96 (2.49)	—
Missing data	5340	94,725	—
Insurance status; n (%)			< 0.001
Medicare	380,234.94 (71.25)	1,478,699.65 (40.47)	—
Medicaid	34,014.99 (6.37)	528,244.92 (14.46)	—
Private insurance	101,440.00 (19.01)	1,372,209.82 (37.56)	—
Self-pay	7550.00 (1.41)	152,734.98 (4.18)	—
No charge	655.00 (0.12)	15,880.00 (0.43)	—
Other	9750.00 (1.83)	105,935.01 (2.90)	—
Missing data	165	3440	—
IBD type; n (%)			< 0.001
Crohn's disease	372,209.98 (69.68)	2,746,069.58 (75.04)	—
Ulcerative colitis	161,979.95 (30.32)	913,304.80 (24.96)	—
Smoking	184,065.00 (34.46)	901,909.87 (24.65)	< 0.001
Alcohol use	10,549.99 (1.97)	117,854.99 (3.22)	< 0.001
Anxiety	74,660.02 (13.98)	577,439.89 (15.78)	< 0.001
Depression	76,710.00 (14.36)	529,704.89 (14.48)	0.333
VTE	126,529.98 (23.69)	227,969.94 (6.23)	< 0.001
Septic shock	28,935.00 (5.42)	145,374.98 (3.97)	< 0.001
Mechanical ventilation	22,375.00 (4.19)	102,839.98 (2.81)	< 0.001
Endoscopy	41,339.99 (7.74)	301,144.95 (8.23)	< 0.001
Blood transfusion	48,184.99 (9.02)	256,539.96 (7.01)	< 0.001
Length of stay			< 0.001
Mean (SD)	5.93 (6.96)	5.87 (8.09)	—
Median (IQR)	4.00 (2.00, 7.00)	4.00 (2.00, 7.00)	—
Missing data	0	150	—
Total charges			< 0.001
Mean (SD)	61,587.19 (95,240.09)	55,021.04 (103,832.19)	—
Median (IQR)	34,910.99 (18,623.00, 68,682.00)	29,660.00 (16,145.00, 57,829.00)	—
Missing data	1640	28,150	—

TABLE 2. Subgroup Analysis by IBD Type

Variable	Crohn's disease (N = 372,210)	Ulcerative colitis (N = 161,980)	*P*
Age in years at admission			< 0.001
Mean (SD)	68.35 (14.43)	69.89 (14.07)	—
Median (IQR)	70.00 (60.00, 79.00)	72.00 (62.00, 80.00)	—
Mortality; n (%)	14,240.00 (3.83)	5055.00 (3.12)	< 0.001
Missing data	40	5	—
Gender; n (%)			< 0.001
Females	180,650.00 (48.54)	67,314.96 (41.57)	—
Males	191,560.00 (51.46)	94,666 (58.43)	—
Missing data	10	5	
Race; n (%)			< 0.001
White	300,424.99 (84.22)	133,664.96 (85.67)	—
Black	30,505.01 (8.55)	10,010.00 (6.42)	—
Hispanic	14,559.99 (4.08)	6770.00 (4.34)	—
Asian or Pacific Islander	3765.00 (1.06)	1995.00 (1.28)	—
Native American	1305.00 (0.37)	415.00 (0.27)	—
Other	6175.00 (1.73)	3170.00 (2.03)	—
Missing data	3825	1515	—
Insurance status; n (%)			< 0.001
Medicare	264,744.97 (71.20)	115,489.96 (71.37)	—
Medicaid	25,604.99 (6.89)	8410.00 (5.20)	—
Private insurance	68,755.01 (18.49)	32,684.99 (20.20)	—
Self-pay	5670.00 (1.52)	1880.00 (1.16)	—
No charge	470.00 (0.13)	185.00 (0.11)	—
Other	6570.00 (1.77)	3180.00 (1.97)	—
Missing data	150	15	—
Smoking	127,285.01 (34.20)	56,779.99 (35.05)	0.009
Alcohol use	7309.99 (1.96)	3240.00 (2.00)	0.703
Anxiety	53,200.02 (14.29)	21,460.00 (13.25)	< 0.001
Depression	54,660.01 (14.69)	22,049.99 (13.61)	< 0.001
VTE	88,939.99 (23.90)	37,589.99 (23.21)	0.019
Septic shock	20,050.00 (5.39)	8885.00 (5.49)	0.514
Mechanical ventilation	16,460.00 (4.42)	5915.00 (3.65)	< 0.001
Endoscopy	27,049.99 (7.27)	14,289.99 (8.82)	< 0.001
Blood transfusion	32,140.00 (8.63)	16,044.98 (9.91)	< 0.001
Length of stay			< 0.001
Mean (SD)	6.04 (7.17)	5.68 (6.45)	—
Median (IQR)	4.00 (2.00, 7.00)	4.00 (2.00, 7.00)	—
Total charges			< 0.001
Mean (SD)	59,499.60 (93,178.89)	66,381.66 (99,648.98)	—
Median (IQR)	33,045.99 (17,665.98, 66,119.00)	39,303.00 (21,268.00, 74,430.99)	—
Missing data	1140	500	—

2020 (~4.9%) with a slight decrease in 2021 (~4.0%; Fig. 1B). Because the national transition from ICD-9-CM to ICD-10-CM on October 1, 2015, can transiently reduce/alter code capture, we interpret the 2015-2016 discontinuity as at least partly methodological rather than purely epidemiologic.

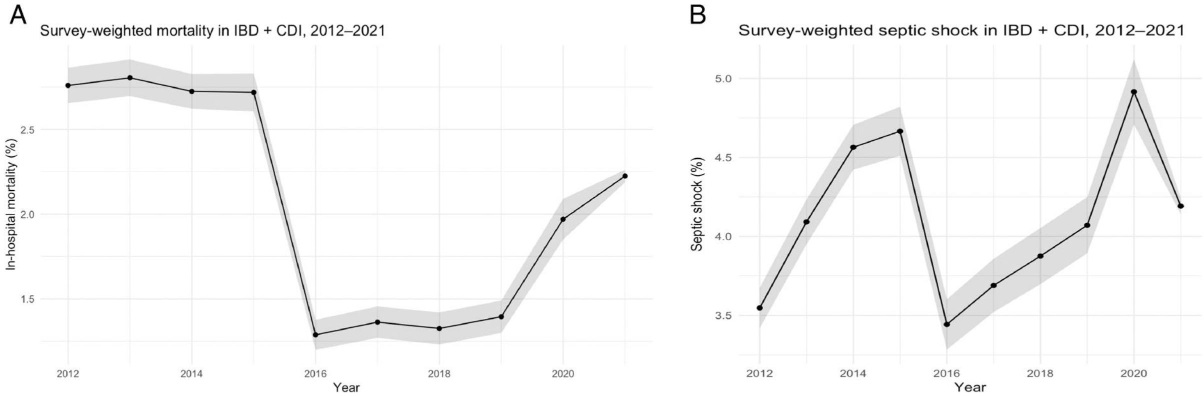

FIGURE 1. A, Survey-weighted in-hospital mortality in IBD + CDI, 2012-2021. Black line/points show annual survey-weighted estimates; light-gray shaded ribbon indicates the 95% CI (from Taylor-linearized SEs). Estimates derived from NIS with discharge weights, strata, and clusters applied. Note: the 2015-2016 step reflects the national ICD-9→ICD-10 transition and may affect code capture. B, Survey-weighted septic shock in IBD + CDI, 2012-2021. Black line/points show annual survey-weighted estimates; light-gray shaded ribbon indicates the 95% CI (from Taylor-linearized SEs). Estimates derived from NIS with discharge weights, strata, and clusters applied. Note: the 2015-2016 step reflects the national ICD-9→ICD-10 transition and may affect code capture.

TABLE 3. Logistic Regression Analysis for Mortality

Predictor	OR (95% CI)	P
Age in years at admission	1.05 (1.05, 1.06)	< 0.001
Females	0.99 (0.92, 1.08)	0.9
Race	1.04 (1.00, 1.09)	0.040
Insurance	1.13 (1.08, 1.18)	< 0.001
Total charges	1.00 (1.00, 1.00)	0.015
Region of hospital	0.98 (0.94, 1.02)	0.2
Bed size of hospital	1.07 (1.01, 1.13)	0.019
Location/teaching status of hospital	0.93 (0.87, 0.98)	0.012
IBD type		
Crohn's disease	—	—
Ulcerative colitis	0.81 (0.75, 0.89)	< 0.001
Smoking		
No	—	—
Yes	0.74 (0.67, 0.80)	< 0.001
Alcohol use		
No	—	—
Yes	1.15 (0.86, 1.53)	0.3
Anxiety		
No	—	—
Yes	0.72 (0.62, 0.84)	< 0.001
Depression		
No	—	—
Yes	0.87 (0.77, 1.00)	0.043
VTE		
No	—	—
Yes	0.87 (0.78, 0.96)	0.007
Septic shock		
No	—	—
Yes	6.39 (5.75, 7.10)	< 0.001
Mechanical ventilation		
No	—	—
Yes	16.6 (14.7, 18.6)	< 0.001
Endoscopy		
No	—	—
Yes	0.70 (0.59, 0.83)	< 0.001
Blood transfusion		
No	—	—
Yes	1.33 (1.17, 1.51)	< 0.001

OR indicates odds ratio.

Logistic Regression Analysis

In a multivariable logistic regression analysis evaluating predictors of in-hospital mortality among IBD patients with CDI, several significant associations were observed. Increasing age was significantly associated with higher mortality (OR: 1.05; 95% CI: 1.05-1.06; $P < 0.001$). Receiving blood transfusion was associated with higher odds of death (OR: 1.33; 95% CI: 1.17-1.51; $P < 0.001$). Septic shock was associated with a markedly elevated risk of death (OR: 6.39; 95% CI: 5.75-7.10; $P < 0.001$). Mechanical ventilation was the strongest independent predictor of mortality, associated with more than a 16-fold increased risk (OR: 16.6; 95% CI: 14.7-18.6; $P < 0.001$). Hospital characteristics such as bed size and teaching status showed variable associations, with teaching hospitals associated with slightly lower odds of mortality (OR: 0.93; 95% CI: 0.87-0.98; $P < 0.001$). Regarding IBD type, ulcerative colitis was associated with significantly lower odds of in-hospital death compared with Crohn's disease (OR: 0.81; 95% CI: 0.75-0.89; $P < 0.001$; Table 3).

In the multivariable logistic regression analysis assessing predictors of septic shock among IBD patients with CDI, several significant associations were observed. Increasing age was associated with a modest increase in odds of septic shock (OR: 1.01; 95% CI: 1.00-1.01; $P < 0.001$). Blood transfusion was associated with a significantly higher risk of septic shock (OR: 1.75; 95% CI: 1.61-1.91; $P < 0.001$), and mechanical ventilation was the strongest independent predictor, associated with a 19-fold increased risk (OR: 19.3; 95% CI: 18.0-20.8; $P < 0.001$). Patients with ulcerative colitis had slightly higher odds of septic shock compared with those with Crohn's disease (OR: 1.09; 95% CI: 1.02-1.16; $P = 0.008$; Table 4).

In the multivariable logistic regression model evaluating predictors of VTE among IBD patients with CDI, several significant associations were observed. Female sex was linked to increased risk (OR: 1.45; 95% CI: 1.40-1.49; $P < 0.001$). Compared with Crohn's disease, ulcerative colitis was associated with a modestly increased risk of VTE (OR: 1.06; 95% CI: 1.02-1.09; $P = 0.001$). depression was linked to increased odds (OR: 1.13; 95% CI: 1.08-1.18; $P <$

TABLE 4. Logistic Regression Analysis for Septic Shock

Predictor	OR (95% CI)	P
Age in years at admission	1.01 (1.00, 1.01)	< 0.001
Females	1.05 (0.99, 1.11)	0.11
IBD type		
Crohn's disease	—	—
Ulcerative colitis	1.09 (1.02, 1.16)	0.008
Smoking		
No	—	—
Yes	0.65 (0.61, 0.70)	< 0.001
Alcohol use		
No	—	—
Yes	1.00 (0.82, 1.21)	> 0.9
Anxiety		
No	—	—
Yes	0.74 (0.67, 0.82)	< 0.001
Depression		
No	—	—
Yes	0.89 (0.81, 0.98)	0.016
Blood transfusion		
No	—	—
Yes	1.75 (1.61, 1.91)	< 0.001
Mechanical ventilation		
No	—	—
Yes	19.3 (18.0, 20.8)	< 0.001
VTE		
No	—	—
Yes	0.95 (0.88, 1.02)	0.13
Endoscopy		
No	—	—
Yes	0.78 (0.69, 0.87)	< 0.001

OR indicates odds ratio.

TABLE 5. Logistic Regression Analysis for VTE

Predictor	OR (95% CI)	P
Age in years at admission	0.96 (0.96, 0.96)	< 0.001
Females	1.45 (1.40, 1.49)	< 0.001
IBD type		
Crohn's disease	—	—
Ulcerative colitis	1.06 (1.02, 1.09)	0.001
Smoking		
No	——	
Yes	0.89 (0.87, 0.92)	< 0.001
Alcohol use		
No	——	
Yes	0.80 (0.72, 0.89)	< 0.001
Anxiety		
No	—	—
Yes	1.02 (0.98, 1.07)	0.4
Depression		
No	—	—
Yes	1.13 (1.08, 1.18)	< 0.001
Septic shock		
No	—	—
Yes	0.95 (0.88, 1.02)	0.2
Mechanical ventilation		
No	—	—
Yes	0.68 (0.62, 0.74)	< 0.001
Endoscopy		
No	—	—
Yes	1.02 (0.97, 1.08)	0.5
Blood transfusion		
No	—	—
Yes	1.11 (1.06, 1.17)	< 0.001

OR indicates odds ratio.

0.001). Blood transfusion was significantly associated with increased risk of VTE (OR: 1.11; 95% CI: 1.06-1.17; $P < 0.001$). Increasing age was associated with a slightly reduced odds of VTE (OR: 0.96; 95% CI: 0.96-0.96; $P < 0.001$). Mechanical ventilation was associated with decreased odds of VTE (OR: 0.68; 95% CI: 0.62-0.74; $P < 0.001$; Table 5).

Endoscopy and certain patient characteristics, including anxiety, depression, smoking, and alcohol use, showed inverse associations with mortality and septic shock; however, the significance of these associations is unclear.

DISCUSSION

In this nationally representative cohort of hospitalized IBD patients, superimposed CDI was associated with greater health care burden, morbidity, and mortality. CDI was identified in ~12.7% of IBD-related hospitalizations. Affected patients experienced worse outcomes, including higher in-hospital mortality, increased rates of septic shock, VTE, need for mechanical ventilation, longer hospital stays, and greater hospital charges. Importantly, UC was more frequently associated with CDI than Crohn's disease and was independently linked to higher odds of septic shock and VTE, though paradoxically with lower mortality risk. Our findings also highlight key demographic and clinical factors associated with adverse outcomes, including older age, blood transfusion, and mechanical ventilation, which were consistently associated with increased risk of mortality.

Patients with IBD who develop CDI experience significantly worse clinical outcomes compared with the general population. These include higher rates of hospitalization, longer lengths of stay, increased health care costs, and a greater need for surgical interventions such as colectomy. This may be because IBD itself increases susceptibility to CDI. Once infected, IBD patients are more prone to recurrent CDI (rCDI), treatment failure, hospitalization, and adverse events such as colectomy and death.[13] Studies have demonstrated that the risk of CDI is up to eight times higher in individuals with IBD than in those without,[14] and the recurrence rate is 4.5 times higher in this population.[15] The burden of CDI in IBD is further amplified by high health care costs, longer hospital stays, and more frequent surgical interventions, as was also demonstrated in our study.

The increased susceptibility to CDI in patients with IBD occurs due to a complex interplay of immunologic, microbial, and mucosal factors. IBD is characterized by chronic intestinal inflammation and microbial dysbiosis, which together reduce microbial diversity and impair colonization resistance, key defenses against CDI.[16] The frequent use of antibiotics, immunosuppressants, and corticosteroids in this population further disrupts the gut microbiome, creating an environment conducive to *C. difficile* spore germination and vegetative growth.[17] These spores, transmitted through the fecal–oral route, are acid-resistant and can reach the colon where they proliferate in the presence of dysbiosis and increased primary bile acids. Once germinated, the vegetative forms produce Toxin A and Toxin B, which disrupt the tight junction in the intestinal epithelium by damaging the actin cytoskeleton, leading to fluid loss, cell death, and diarrhea.[18,19] Moreover, underlying immune dysfunction in IBD, including impaired T-cell regulation and antigen-presenting cell activity, further diminishes the host's ability to respond to microbial threats, making severe IBD a recognized risk for rCDI.[4,8]

Several factors like advanced age (>65 y), impaired immune status, and CDI infection with hypervirulent strains (BI/NAP1/027 infection) increase the risk of developing CDI.[20–22] Among IBD subtypes, ulcerative colitis has been more strongly linked with CDI than Crohn's disease, possibly due to the extent and severity of colonic involvement. Extensive colitis has been identified as a significant predictor of CDI.[23,24] The use of immunosuppressive therapies, particularly corticosteroids and tumor necrosis factor-alpha (TNF-α) inhibitors such as infliximab, has been shown to significantly elevate the risk of CDI and rCDI.[25] Broad-spectrum antibiotic use is another major contributor, with evidence suggesting that alterations in bile acid composition, increased primary and decreased secondary bile acids, may promote *C. difficile* overgrowth.[26] In addition, NSAID use has emerged as an independent risk factor, with a study showing nearly 4-fold increased risk of CDI in IBD patients using NSAIDs within 2 months before hospitalization.[27] Finally, continued immunosuppressive therapy during acute CDI episodes may double or even triple the risk of infection. This highlights the need for careful therapeutic planning in this vulnerable population.[28,29]

Current guidelines offer limited consensus on managing immunosuppressive therapy in IBD patients with concurrent CDI. The 2019 British Society of Gastroenterology advises that corticosteroids may be continued in acute severe UC during CDI treatment.[30] In contrast, the American Gastroenterological Association recommends delaying immunosuppressive escalation until 72 to 96 hours after starting antibiotics, and patients should be monitored for worsening symptoms and complications.[8] European Crohn's and Colitis Organization 2021 guidelines emphasize individualized decision-making, highlighting that the impact of immunosuppressants on CDI progression remains unclear.[31] In clinical practice, however, patients with an active IBD flare and concurrent CDI are often treated with both antibiotics and immunosuppressive therapy simultaneously. This approach aims to balance infection control with inflammation management. Ultimately, decisions regarding timing and intensity of immunosuppression should be guided by clinical judgment, IBD severity, and response to CDI therapy.

Given these complexities, the treatment of CDI in IBD must be approached with care. Vancomycin and fidaxomicin (FDX) are currently recommended as first-line treatments for moderate and rCDI, while metronidazole is no longer recommended due to lower efficacy. For fulminant CDI, high-dose oral vancomycin with intravenous metronidazole is standard, with rectal vancomycin reserved for patients with ileus.[32] FDX, a narrow-spectrum macrocyclic antibiotic, has demonstrated superior outcomes in preventing recurrence and is now recommended as a first-line agent when available.[33] Fecal microbiota transplantation (FMT) is an emerging therapy for recurrent or refractory CDI, including in IBD patients, and has shown high success rates in restoring microbial balance and reducing recurrence risk.[34] Adjunctive therapies such as bezlotoxumab, a monoclonal antibody against toxin B, and rifaximin as a posttreatment "chaser," have also been shown to reduce recurrence in high-risk patients.[35,36]

This study has limitations inherent to administrative data. ICD-9/10-CM coding may misclassify diagnoses/procedures, and the NIS lacks clinical granularity (IBD activity, laboratories, medications/antibiotics, and timing of CDI vs admission), so we cannot distinguish active flares, nor assess outpatient CDI or postdischarge recurrence. Endoscopy was analyzed as static exposure rather than time-dependent exposure, which can introduce immortal-time and confounding-by-indication biases. The observational design further limits causal inference. Finally, the 2015 ICD-9→ICD-10 transition may affect comparisons across years.

Despite its limitations, this study has several strengths. It leverages data from the NIS, the largest publicly available all-payer inpatient database in the United States, which provides a robust, nationally representative cohort of hospitalized patients with IBD over a 10-year period. The large sample size of over 4 million patients, including more than half a million with concurrent CDI, allows for powerful statistical analysis and generalizable insights into real-world clinical outcomes. In addition, comprehensive data on demographics, comorbidities, and hospital outcomes enabled in-depth multivariable regression analyses to adjust for potential confounders. The inclusion of stratified subgroup analyses by IBD subtype (Crohn's vs UC) and the assessment of specific complications such as septic shock, VTE, and mechanical ventilation further enhance the clinical relevance of the findings.

CONCLUSION

The presence of CDI in hospitalized IBD patients was associated with significantly worse clinical outcomes, including higher mortality, septic shock, VTE, need for mechanical ventilation, and greater health care resource utilization. Ulcerative colitis was more frequently associated with CDI than Crohn's disease and was independently linked to higher odds of septic shock and VTE, though with lower overall mortality. These findings highlight the importance of early recognition, preventive strategies, and tailored management approaches for CDI in IBD patients. As the therapeutic landscape for both CDI and IBD evolves, with the introduction of biologics, small molecules, and precision diagnostics, the clinical approach to managing CDI in IBD must also be redefined. Current guidelines provide general recommendations, but there is a need for high-quality evidence specific to the IBD population.

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