Risk factors for postoperative Clostridium difficile infection after radical cystectomy for bladder cancer: a NSQIP database analysis

Megan Prunty, MD,[1,2] Laura Bukavina, MD,[1,2] Amr Mahran, MD,[2] Kirtishri Mishra, MD,[1,2] Mostafa Abdelrazek, MD,[3] Sarah Markt, ScD,[4] Lee Ponsky, MD,[2] Adam C. Calaway, MD[2]

[1]Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

[2]University Hospitals Cleveland Medical Center, Urology Institute, Cleveland, Ohio, USA

[3]South Valley University School of Medicine, Egypt

[4]Case Western Reserve University School of Medicine, Department of Population and Quantitative Health Sciences, Cleveland, Ohio, USA

PRUNTY M, BUKAVINA L, MAHRAN A, MISHRA K, ABDELRAZEK M, MARKT S, PONSKY L, CALAWAY AC. Risk factors for postoperative Clostridium difficile infection after radical cystectomy for bladder cancer: a NSQIP database analysis. *Can J Urol* 2022;29(3):11170-11174.

Introduction: *Patients undergoing cystectomy for bladder cancer are at an increased risk for Clostridium difficile infection (CDI) due to prolonged antibiotics and underlying comorbidities. We aim to evaluate CDI risk factors in cystectomy patients.*

Materials and methods: *Utilizing National Surgical Quality Improvement Program (NSQIP), patients undergoing cystectomy with diagnosis of bladder cancer between 2015-2017 were included. Baseline demographics including age, sex, comorbidities, and preoperative labs were collected. Univariate and multivariable logistic regression were used to evaluate risk factors for and complications of CDI during the index hospitalization.*

Results: *There were a total of 6,432 patients included in the analysis, with 6,242 (96%) and 190 (4%) in the non-CDI vs. CDI groups, respectively. Patients with a diagnosis of postoperative CDI were more likely to be female [4.09% vs. 2.71%, p = 0.001] and have lower preoperative albumin [3.78 g/dL (0.52) vs. 3.92 g/dL (0.48), p = 0.003]. Patients with a history of female sex (OR 1.46, p = 0.03), neobladder (OR 1.57, p = 0.01), and low preoperative albumin (OR 1.45, p = 0.04) were at the highest risk for development of CDI postoperatively. Patients with a diagnosis of CDI were more likely to experience readmission within 30 days (31.1% vs. 19.2%, p < 0.001).*

Conclusion: *Utilizing the NSQIP database, we identified predictors for development of CDI in cystectomy patients. Female sex, continent diversion, and low preoperative albumin all significantly increased the rate of CDI. While our findings are retrospective, they are compelling enough to warrant further prospective investigation.*

Key Words: bladder cancer, cystectomy, Clostridium difficile infection, surgery, gender

Introduction

Clostridium difficile infection (CDI) is the most common nosocomial infection and represents 10%-20% of antibiotic associated diarrhea.[1] In the United States, there are an estimated 500,000 cases of CDI per year with a mortality of 15,000 to 30,000 annually.[2]

Patients with bladder cancer undergoing radical cystectomy are colonized with CDI at a much higher rate than all comers. Among all patients being admitted to the hospital, an estimated 8% are C. difficile carriers, whereas, at the time of cystectomy, 18.4% of patients carry CDI.[3,4] CDI colonization incurs a 6 times higher risk of subsequent infection, which leads to rates of CDI in cystectomy patients as high

Accepted for publication March 2022

Address correspondence to Dr. Megan Prunty, 11100 Euclid Avenue, Suite 4554, Cleveland, OH 44106 USA

as 1.4%-14%.[3,4] Specific risk factors that predispose the cystectomy cohort to CDI include preoperative antibiotics and chronic PPI use.[5,6]

In the post-cystectomy period, CDI can devastate patient recovery. Development of CDI after cystectomy is associated with a significant increase in morbidity, and up to 12.5% will experience a serious adverse event, including ICU admission and additional surgical intervention.[4,7,8] Furthermore, patients diagnosed with perioperative CDI experience a 2.5-fold to 5-fold increase in mortality during their hospitalization.[4,8,9] Up to 10% of all post-cystectomy readmission are attributable to CDI.[6]

We aim to identify predictors for development of CDI in patients undergoing radical cystectomy for bladder cancer utilizing the NSQIP database and to investigate the associations of postoperative CDI with patient morbidity. We hypothesize that host dependent characteristics and comorbidities significantly influence the rate of CDI postoperatively.

Materials and methods

Study population

The National Surgical Quality Improvement Program (NSQIP) database includes over 150 data elements, which were collected from 600 hospitals from 2015-2018. Patients with diagnosis of open or laparoscopic cystectomy as identified by Current Procedural Terminology (CPT) codes (51570, 51596, 51595, 50820, 51597, 51999, 51590, 51575, and 51580) were utilized to determine the associated cohort. In order to restrict the cystectomy cohort to patients with the diagnosis of bladder malignancy. Additional International Classification of Diseases (ICD)-9 codes (188.x, 233.7, and V10.51) and ICD-10 codes (C67.x and Z85.D) identified patients with a postoperative diagnosis of bladder malignancy. Patients with incomplete demographic or clinical data were excluded (n= 744). Our final study population included 6,432 individuals. The cohort was further broken down by CDI status during their cystectomy index hospitalization. ICD-9 (008.45) and ICD-10 (A04.72) codes identified patients with diagnosis of postoperative CDI (n = 190). Our outcome of interest included identification of risk factors for CDI development during hospitalization. Secondary analysis evaluated CDI-associated complications including: any complication, rate of readmission, 30 day mortality, and length of stay.

Statistical analysis

Descriptive statistics were reported as means with standard deviations. Fisher's exact test and Student t-test were used to compare categorical and continuous variables, respectively. We conducted stepwise mixed (backward and forward) multivariable logistic regression to determine the candidate variables in each model, to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between each potential risk factor and CDI infection. Similarly, we used logistic regression models to investigate the association between CDI and complications in the immediate recovery period. Univariate and multivariable logistic regression analyses were used to evaluate whether female sex was significantly associated with outcomes of interest. The outcomes of interest included preoperative characteristics such as type of urinary diversion, sex, ASA class, functional health status, and preoperative hematocrit and albumin. Functional health status was defined by NSQIP as independent, partially dependent, and totally dependent. All statistical analyses were performed using R 3.5. All p values of < 0.05 were considered to be statistically significant.

Studies from the NSQIP database are considered exempt from approval by the institutional review board.

Results

There were a total 6,432 patients included in the analysis, with 6,242 (96%) and 190 (4%) in the non-CDI and CDI groups, respectively. Differences in patient characteristics were seen in preoperative albumin level [3.78 (0.6) vs. 3.9 (0.5) $p < 0.001$], hematocrit [36.3 (5.4) vs. 37.7 (5.7), $p = 0.001$], and female sex [(23.7) vs. (16.9), $p = 0.02$], Table 1.

Preoperative predictors of CDI included female sex (OR 1.52, $p = 0.02$), poor/dependent functional health status (OR 2.73, $p = 0.01$) and hematocrit (OR 0.96, $p = 0.001$) on univariate analysis, Table 2. Upon multivariate analysis, preoperative predictors of CDI development postoperatively included female sex (OR 1.46, $p = 0.03$), neobladder (OR 1.57, $p = 0.01$), poor/dependent functional health status (OR 2.36, $p = 0.03$), and preoperative hematocrit (OR 0.96, $p = 0.004$), Table 2.

After cystectomy, mean time to CDI development was 8.7 days (SD ± 5.7 days), Table 1. Postoperatively, patients with CDI were more likely to develop any complication (OR 1.66, $p = 0.002$), including infectious (OR 2.65, $p < 0.001$), respiratory (OR 2.68, $p < 0.001$), and cardiac complications (OR 2.71, $p < 0.001$), Table 3 as compared to the non-CDI group on multivariable analysis.

Patients with diagnosis of CDI were more likely to experience a prolonged hospitalization, with average

TABLE 1. **Patient demographics and clinical characteristics**

	Overall (n = 6432)	No C. diff (n = 6242)	C. diff (n = 190)	p value
Age (years)	70 (63, 76)	70 (63, 76)	71 (62, 76)	0.54
Race				0.02
White	4759 (74.0)	4605 (73.8)	154 (81.1)	
Black or African American	272 (4.2)	262 (4.2)	10 (5.3)	
Other/unknown	1401 (21.8)	1375 (22.0)	26 (13.7)	
Gender: female	1100 (17.1)	1055 (16.9)	45 (23.7)	0.02
Body mass index	28 (25, 32)	28 (25, 32)	27 (25, 32)	0.82
Current smoker	1532 (23.8)	1491 (23.9)	41 (21.6)	0.49
Diabetes mellitus				0.11
No diabetes	5149 (80.1)	4987 (79.9)	162 (85.3)	
Insulin dependent	422 (6.6)	410 (6.6)	12 (6.3)	
Non-insulin dependent	861 (13.4)	845 (13.5)	16 (8.4)	
Congestive heart failure	45 (0.7)	41 (0.7)	4 (2.1)	0.04
Dyspnea	502 (7.8)	484 (7.8)	18 (9.5)	0.41
Functional health status	93 (1.4)	86 (1.4)	7 (3.7)	0.02
Hx. severe COPD	479 (7.4)	463 (7.4)	16 (8.4)	0.57
Hypertensive on meds	3894 (60.5)	3780 (60.6)	114 (60.0)	0.88
Chronic steroid use	194 (3.0)	189 (3.0)	5 (2.6)	1
Weight loss	139 (2.2)	135 (2.2)	4 (2.1)	1
ASA class ≥ 3	4983 (77.5)	4824 (77.3)	159 (83.7)	0.04
Bleeding disorders	212 (3.3)	203 (3.3)	9 (4.7)	0.30
Preop transfusion	74 (1.2)	72 (1.2)	2 (1.1)	1
Preoperative acute renal failure	17 (0.3)	17 (0.3)	0 (0.0)	1
On dialysis	23 (0.4)	22 (0.4)	1 (0.5)	0.50
Preoperative albumin	4.0 (3.7, 4.3)	4.0 (3.7, 4.3)	3.9 (3.5, 4.2)	0.003
Preoperative hematocrit	38.0 (33.7, 41.9)	38.0 (33.8, 42.0)	36.7 (32.5, 40.5)	0.001

Continuous variables are reported as median (IQR) and categorical variables are reported as total (%)

of 4 days longer stay [12.1 (8.6) vs. 8.2(5.8), $p < 0.001$]. Similarly, patients in CDI group had higher rates of DVT [12 (6.3) vs. 143 (2.3), $p = 0.002$], acute renal failure [9 (4.7) vs. 72 (1.2), $p = 0.001$], septic shock [16 (8.4) vs. 151 (2.3), $p < 0.001$] and mortality [13 (6.8) vs. 148 (2.4), $p < 0.001$]. Furthermore, the CDI group experienced an increased risk of procedure related readmission within 30 days (OR 1.90, $p < 0.001$).

Discussion

This study is the first large cohort descriptive study assessing risk factors for development of CDI based on evaluation of preoperative factors that were associated with CDI after radical cystectomy. Of the data points reviewed, female sex, dependent health status, continent diversion, and hypoalbuminemia were all associated with increased rate of CDI.

The association between female sex and increased risk for CDI has not previously been reported in the bladder cancer or cystectomy literature. This finding is not unique to cystectomy patients, and has been reported in females undergoing cardiac, bariatric and vascular procedures, although no plausible biological explanation for this alarming discrepancy has been elucidated.[10-12]

Antibiotic use is one of the most established risk factors for CDI.[2] Women with bladder cancer are more

TABLE 2. **Preoperative predictors for Clostridium difficile infection after cystectomy**

		Univariable regression			Multivariable regression		
Variable	**Level**	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Procedure	Cystectomy with conduit/sigmoid bladder	-			-		
	Cystectomy with neobladder	1.41	1.00-1.99	0.05	1.57	1.10-2.23	0.01
Gender	Male	-			-		
	Female	1.52	1.09-2.15	0.02	1.46	1.03-2.06	0.03
Diabetes mellitus	No	-			-		
	Insulin dependent	0.90	0.50-1.63	0.73	0.82	0.45-1.49	0.51
	Non-insulin dependent	0.58	0.35-0.98	0.04	0.57	0.34-0.95	0.03
Congestive heart failure	No	-			-		
	Yes	3.25	1.15-9.17	0.03	2.78	0.97-7.97	0.06
ASA class ≥ 3	No	-			-		
	Yes	1.50	1.02-2.23	0.04	1.53	1.03-2.28	0.04
Functional health status: dependent	No	-			-		
	Yes	2.73	1.25-6.00	0.01	2.36	1.07-5.24	0.03
Preoperative hematocrit	--	0.96	0.94-0.98	0.001	0.96	0.94-0.99	0.004

likely than men to present with dysuria and are more likely to receive empiric antibiotics for lower urinary tract symptoms within 1 year of diagnosis of bladder cancer.[13] In fact, 15.8% of women receive three or more courses of antibiotics for UTI prior to bladder cancer diagnosis, whereas only 3.8% of men experience the same treatment.[13] Empiric use of antibiotics for dysuria in women with bladder cancer could account for the

TABLE 3. **Association between Clostridium difficile infection and postoperative complications**

Outcomes	**C. difficile**	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Any complication[1]	No: 3071 (49.2)	-			-		
	Yes: 124 (65.3)	1.94	1.43-2.63	< 0.001	1.66	1.21-2.27	0.002
Any infectious complications[2]	No: 1327 (21.3%)	-			-		
	Yes: 80 (42.15%)	2.69	2.01-3.62	< 0.001	2.65	1.96-3.57	< 0.001
Any respiratory complications[3]	No: 340 (5.4)	-			-		
	Yes: 26 (13.7)	2.75	1.79-4.22	< 0.001	2.68	1.73-4.15	< 0.001
Any cardiac complications[4]	No: 307 (4.9)	-			-		
	Yes: 25 (13.2)	2.93	1.89-4.53	< 0.001	2.71	1.74-4.24	< 0.001
Procedure-related readmissions[5]	No: 1201 (19.2)	-			-		
	Yes: 59 (31.1)	1.89	1.38-2.59	< 0.001	1.90	1.38-2.61	< 0.001

[1]multivariable model adjusted for age, procedures, gender, BMI, diabetes, dyspnea, CHF, COPD, weight loss, ASA ≥ 3, functional status, bleeding disorder, and preoperative hematocrit value.
[2]multivariable model adjusted for procedures, BMI, diabetes, COPD, functional status, and bleeding disorder.
[3]multivariable model adjusted for age, gender, smoking, CHF, COPD, functional status.
[4]multivariable model adjusted for age, procedures, BMI, diabetes, hypertension on meds, COPD, ASA ≥ 3, bleeding disorder, and preoperative hematocrit value.
[5]multivariable model adjusted for procedures, BMI, diabetes, hypertension on meds, COPD.

differential rate of CDI between men and women. Potentially, a higher cumulative lifetime antibiotic exposure in women could predispose them to CDI development.[14]

Because studies in other disciplines have highlighted the association between hypoalbuminemia and CDI, it is particularly important that our findings confirm the correlation between hypoalbuminemia and CDI.[1] A wide range of theories exist to explain this association. Hypoalbuminemia acts as a marker of poor nutritional status, chronic disease and, thus, immune suppression.[1,15] There is also evidence in animal models that albumin binding may impair C. difficile toxin internalization to the host cell and act directly as a self-defense mechanism against CDI.[16] Similarly to hypoalbuminemia, low preoperative hematocrit has been interpreted as a marker of malnutrition and anemia, both of which have been independently associated with CDI in surgical patients.[17]

The role of poor functional status is increasingly recognized as an important and independent risk factor for poor outcomes in older adults with infection, especially with CDI. Similar to the results shown in our study, poor functional status predisposes to the development of CDI.[18]

In this NSQIP study, patients undergoing neobladder urinary diversion were more likely to have CDI postoperatively. Potentially, the higher rate of wound and deep surgical site infections in patients undergoing neobladder and subsequent treatment with antibiotics may increase risk of CDI.[19] This finding contradicts previous single institution studies show no correlation between the type of urinary diversion and CDI.[20]

Our study design has several limitations. In using a retrospective database, results may be confounded by variables not reported in NSQIP (for example, antibiotic use and proton pump inhibitor use). Data is collected across many institutions so heterogeneity in reporting may exist. In summary, this study offers additional insights on the complex interplay between sex, comorbid disease, functional status, and surgical intervention and the risk for development of CDI in patients undergoing cystectomy.

Conclusion

Using the NSQIP database, we identified predictors for CDI development in cystectomy patients. Female sex, continent diversion, and low preoperative albumin were all associated with CDI. While our findings are retrospective, they are compelling enough to warrant further prospective investigation. □

References

1. Southern WN, Rahmani R, Aroniadis O et al. Postoperative Clostridium difficile-associated diarrhea. *Surgery* 2010;148(1):24-30.
2. Lessa FC, Mu Y, Bamberg WM et al. Burden of Clostridium difficile infection in the United States. *N Engl J Med* 2015;372(9):825-34.
3. Zacharioudakis IM, Zervou FN, Pliakos EE et al. Colonization with toxinogenic C. difficile upon hospital admission, and risk of infection: a systematic review and meta-analysis. *Am J Gastroenterol* 2015;110(3):381-390;quiz 91.
4. Calaway AC, Jacob JM, Tong Y et al. A prospective program to reduce the clinical incidence of Clostridium difficile colitis infection after cystectomy. *J Urol* 2019;201(2):342-349.
5. Kim SP, Shah ND, Karnes RJ et al. The implications of hospital acquired adverse events on mortality, length of stay and costs for patients undergoing radical cystectomy for bladder cancer. *J Urol* 2012;187(6):2011-2017.
6. Liu NW, Shatagopam K, Monn MF et al. Risk for Clostridium difficile infection after radical cystectomy for bladder cancer: analysis of a contemporary series. *Urol Oncol* 2015;33(12):503 e17-22.
7. Li X, Wilson M, Nylander W et al. Analysis of morbidity and mortality outcomes in postoperative Clostridium difficile infection in the Veterans Health Administration. *JAMA Surg* 2016;151(4):314-322.
8. Waltz PK, Zuckerbraun BS. The high stakes of postoperative Clostridium difficile infection. *JAMA Surg* 2016;151(4):322.
9. Zerey M, Paton BL, Lincourt AE et al. The burden of Clostridium difficile in surgical patients in the United States. *Surg Infect (Larchmt)* 2007;8(6):557-566.
10. Egorova NN, Siracuse JJ, McKinsey JF, Nowygrod R. Trend, risk factors, and costs of Clostridium difficile infections in vascular surgery. *Ann Vasc Surg* 2015;29(4):792-800.
11. Dang TT, Dang JT, Moolla M et al. Clostridium difficile and laparoscopic bariatric surgery: an analysis of the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program Database. *Obes Surg* 2019;29(6):1881-1888.
12. Sanaiha Y, Sareh S, Lyons R et al. Incidence, predictors, and impact of Clostridium difficile infection on cardiac surgery outcomes. *Ann Thorac Surg* 2020;110(5):1580-1588.
13. Henning A, Wehrberger M, Madersbacher S et al. Do differences in clinical symptoms and referral patterns contribute to the gender gap in bladder cancer? *BJU Int* 2013;112(1):68-73.
14. Tomas ME, Getman D, Donskey CJ, Hecker MT. Overdiagnosis of urinary tract infection and underdiagnosis of sexually transmitted infection in adult women presenting to an emergency department. *J Clin Microbiol* 2015;53(8):2686-2692.
15. Tokunaga R, Sakamoto Y, Nakagawa S et al. CONUT: a novel independent predictive score for colorectal cancer patients undergoing potentially curative resection. *Int J Colorectal Dis* 2017;32(1):99-106.
16. Di Bella S, Ascenzi P, Siarakas S et al. Clostridium difficile toxins A and B: insights into pathogenic properties and extraintestinal effects. *Toxins (Basel)* 2016;8(5):134.
17. Ananthakrishnan AN, Guzman-Perez R, Gainer V et al. Predictors of severe outcomes associated with Clostridium difficile infection in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2012;35(7):789-795.
18. Kyne L, Merry C, O'Connell B et al. Factors associated with prolonged symptoms and severe disease due to Clostridium difficile. *Age Ageing* 1999;28(2):107-113.
19. van Hemelrijck M, Thorstenson A, Smith P et al. Risk of in-hospital complications after radical cystectomy for urinary bladder carcinoma: population-based follow-up study of 7608 patients. *BJU Int* 2013;112(8):1113-1120.
20. Cotter KJ, Fan Y, Sieger GK et al. Prevalence of Clostridium difficile infection in patients after radical cystectomy and neoadjuvant chemotherapy. *Bladder Cancer* 2017;3(4):305-310.