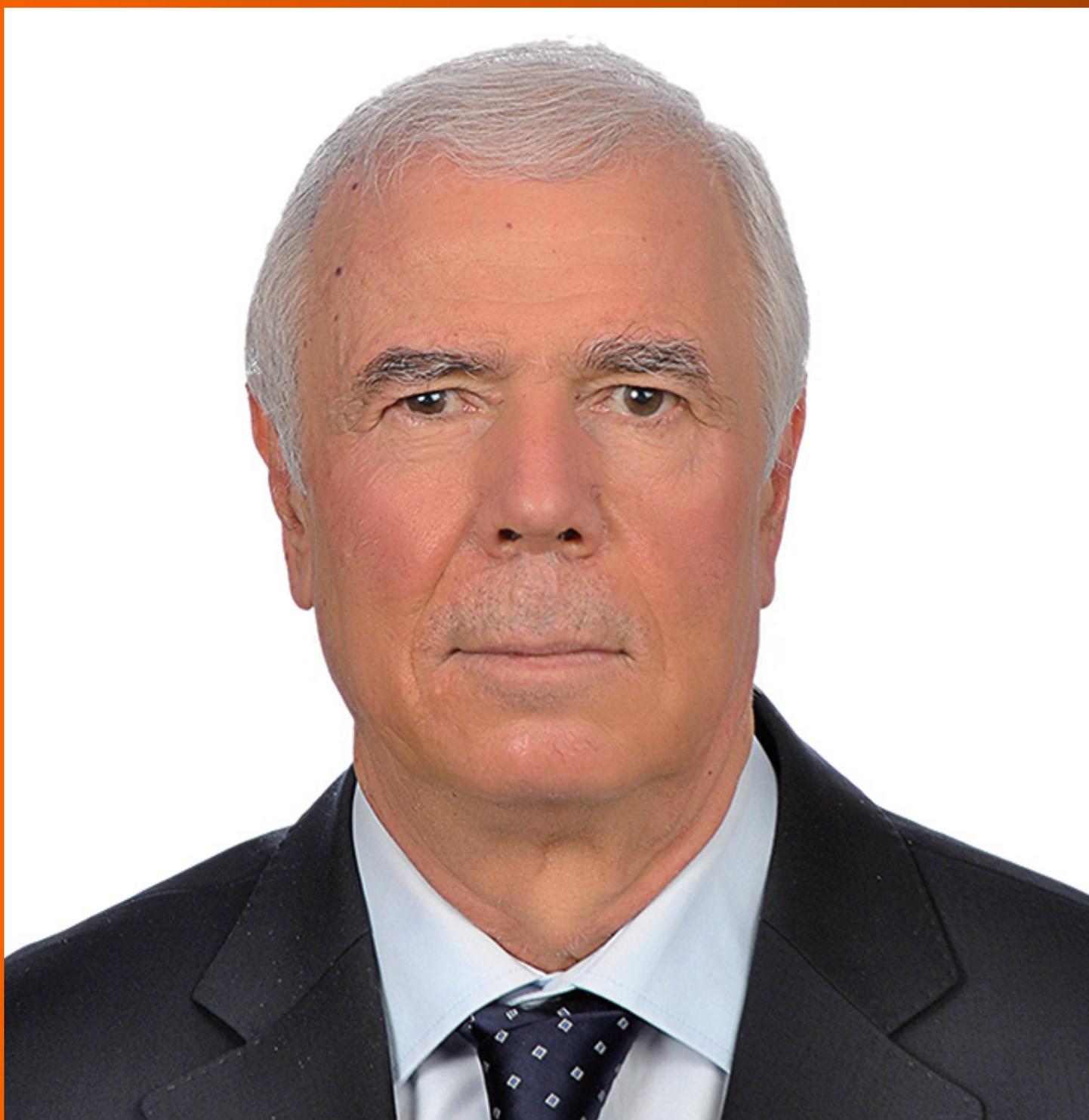


# World Journal of *Gastrointestinal Surgery*

*World J Gastrointest Surg* 2021 November 27; 13(11): 1293-1522



**REVIEW**

- 1293 Acute appendicitis—advances and controversies  
*Teng TZJ, Thong XR, Lau KY, Balasubramaniam S, Shelat VG*

**MINIREVIEWS**

- 1315 Application and progress of medical imaging in total mesopancreas excision for pancreatic head carcinoma  
*Feng P, Cheng B, Wang ZD, Liu JG, Fan W, Liu H, Qi CY, Pan JJ*
- 1327 Retrorectal tumors: A challenge for the surgeons  
*Balci B, Yildiz A, Leventoğlu S, Mentis B*
- 1338 Surgical ampullectomy: A comprehensive review  
*Scroggie DL, Mavroeidis VK*
- 1351 Is surgery the best treatment for elderly gastric cancer patients?  
*Kawaguchi Y, Akaike H, Shoda K, Furuya S, Hosomura N, Amemiya H, Kawaida H, Kono H, Ichikawa D*

**ORIGINAL ARTICLE****Case Control Study**

- 1361 Nomogram for predicting chylous ascites after right colectomy  
*Zheng HD, Liu YR, Chen ZZ, Sun YF, Xu CH, Xu JH*
- 1372 Comparison of safety, efficacy, and long-term follow-up between “one-step” and “step-up” approaches for infected pancreatic necrosis  
*Zheng Z, Lu JD, Ding YX, Guo YL, Mei WT, Qu YX, Cao F, Li F*

**Retrospective Study**

- 1390 Risk of station 12a lymph node metastasis in patients with lower-third gastric cancer  
*Dong YP, Cai FL, Wu ZZ, Wang PL, Yang Y, Guo SW, Zhao ZZ, Zhao FC, Liang H, Deng JY*
- 1405 Choice of operative method for pancreaticojejunostomy and a multivariable study of pancreatic leakage in pancreaticoduodenectomy  
*Liang H, Wu JG, Wang F, Chen BX, Zou ST, Wang C, Luo SW*
- 1414 Laparoscopic vs open surgery in ileostomy reversal in Crohn’s disease: A retrospective study  
*Wan J, Yuan XQ, Wu TQ, Yang MQ, Wu XC, Gao RY, Yin L, Chen CQ*

- 1423 Preoperative serum carbohydrate antigen 19-9 levels predict early recurrence after the resection of early-stage pancreatic ductal adenocarcinoma

*Hong S, Song KB, Hwang DW, Lee JH, Lee W, Jun E, Kwon J, Park Y, Park SY, Kim N, Shin D, Kim H, Sung M, Ryu Y, Kim SC*

- 1436 Patients with *Clostridium difficile* infection and prior appendectomy may be prone to worse outcomes

*Shaikh DH, Patel H, Munshi R, Sun H, Meher Shahi S, Baiomi A, Alemam A, Pirzada U, Nawaz I, Naher K, Hanumanthu S, Nayudu S*

#### Observational Study

- 1448 Novel roles of lipopolysaccharide and TLR4/NF- $\kappa$ B signaling pathway in inflammatory response to liver injury in Budd-Chiari syndrome

*Li J, Chen XM, Zhou CZ, Fang WW, Lv WF, Cheng DL*

- 1463 Long-term survival of patients with stage II and III gastric cancer who underwent gastrectomy with inadequate nodal assessment

*Desiderio J, Sagnotta A, Terrenato I, Garofoli E, Mosillo C, Trastulli S, Arteritano F, Tozzi F, D'Andrea V, Fong Y, Woo Y, Bracarda S, Parisi A*

- 1484 Defecation disorders are crucial sequelae that impairs the quality of life of patients after conventional gastrectomy

*Nakada K, Ikeda M, Takahashi M, Kinami S, Yoshida M, Uenosono Y, Terashima M, Oshio A, Kodera Y*

#### SYSTEMATIC REVIEWS

- 1497 Is omentectomy necessary in the treatment of benign or malignant abdominal pathologies? A systematic review

*Atay A, Dilek ON*

#### SCIENTOMETRICS

- 1509 Global trends in research related to sleeve gastrectomy: A bibliometric and visualized study

*Barqawi A, Abushamma FA, Akkawi M, Al-Jabi SW, Shahwan MJ, Jairoun AA, Zyoud SH*

**ABOUT COVER**

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Ali Coskun, MD, Associate Professor, Doctor, Department of General Surgery, Izmir Bozyaka Training and Research Hospital, Izmir 35380, Turkey. dralicoskun3564@hotmail.com

**AIMS AND SCOPE**

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS, World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGS* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

**INDEXING/ABSTRACTING**

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJGS* as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Rui-Rui Wu, Production Department Director: Xiang Li, Editorial Office Director: Ya-Juan Ma.

**NAME OF JOURNAL**

*World Journal of Gastrointestinal Surgery*

**ISSN**

ISSN 1948-9366 (online)

**LAUNCH DATE**

November 30, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Shu-You Peng, Varut Lohsirawat, Jin Gu

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-9366/editorialboard.htm>

**PUBLICATION DATE**

November 27, 2021

**COPYRIGHT**

© 2021 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Retrospective Study

Patients with *Clostridium difficile* infection and prior appendectomy may be prone to worse outcomes

Danial Haris Shaikh, Harish Patel, Rezwan Munshi, Haozhe Sun, Shehriyar Mehershahi, Ahmed Baiomi, Ahmed Alemam, Usman Pirzada, Iqra Nawaz, Kamrun Naher, Siddarth Hanumanthu, Suresh Nayudu

**ORCID number:** Danial Haris Shaikh 0000-0002-5798-9046; Harish Patel 0000-0003-3638-9495; Rezwan Munshi 0000-0002-4472-775X; Haozhe Sun 0000-0002-3625-2870; Shehriyar Mehershahi 0000-0003-1261-2584; Ahmed Baiomi 0000-0003-2203-4028; Ahmed Alemam 0000-0002-2715-2624; Usman Pirzada 0000-0002-5908-8014; Iqra Nawaz 0000-0002-1576-8579; Kamrun Naher 0000-0002-5480-048X; Siddarth Hanumanthu 0000-0000-0000-000X; Suresh Nayudu 0000-0002-7829-4024.

**Author contributions:** Shaikh DH and Patel H contributed planned, designed, conducted and analyzed the result of the study as well as drafted the manuscript; Munshi R, Sun H, Mehershahi S, Baiomi A, Alemam A and Pirzada U contributed acquired the data for the study and were involved in the critical revision of the manuscript; Nawaz I and Naher K contributed acquired the data for the study and were involved in the critical revision of the manuscript; Hanumanthu S acquired the data for the study and was involved in the critical revision of the manuscript; Nayudu S contributed supervised the design and conduct of the study as well as provided interpretation of the study results; Nayudu S was also involved in drafting, critical revision; all

**Danial Haris Shaikh, Harish Patel, Haozhe Sun, Shehriyar Mehershahi, Ahmed Baiomi, Ahmed Alemam, Siddarth Hanumanthu, Suresh Nayudu**, Division of Gastroenterology, Department of Medicine, BronxCare Health System, Bronx, NY 10457, United States

**Rezwan Munshi**, Department of Medicine, Nassau University Medical Center, New York, NY 11554, United States

**Usman Pirzada, Iqra Nawaz, Kamrun Naher**, Department of Medicine, BronxCare Health System, Bronx, NY 10457, United States

**Corresponding author:** Danial Haris Shaikh, MD, Doctor, Division of Gastroenterology, Department of Medicine, BronxCare Health System, 1650 Grand Concourse, Bronx, NY 10457, United States. [dshaikh@bronxcare.org](mailto:dshaikh@bronxcare.org)

## Abstract

### BACKGROUND

*Clostridium difficile* infection (CDI) occurs due to a dysbiosis in the colon. The appendix is considered a 'safe house' for gut microbiota and may help repopulate gut flora of patients with CDI.

### AIM

To study the impact of prior appendectomy on the severity and outcomes of CDI.

### METHODS

We retrospectively reviewed data of 1580 patients with CDI, admitted to our hospital between 2008 to 2018. Patients were grouped based on the presence or absence of the appendix. The primary aim was to (1) assess all-cause mortality and (2) the severity of CDI. Severity was defined as per the Infectious Diseases Society of America criteria. Logistic regression, and propensity score analysis using inverse probability of treatment weights (IPTW) was performed.

### RESULTS

Of the 1580 patients, 12.5% had a history of appendectomy. There was no statistical difference in mortality between patients with a prior appendectomy or without (13.7% vs 14%,  $P = 0.877$ ). However, a history of appendectomy affected the severity of CDI [odds ratio (OR) = 1.32, 95% confidence interval: 1.01-1.75]. On IPTW, this association remained significant (OR = 1.59,  $P < 0.05$ ). On multivariable

authors are involved in the final review and approval of the manuscript for submission.

#### Institutional review board

**statement:** The study protocol was approved by the Institution Review Board at BronxCare Health System and was performed as per the Declaration of Helsinki (IRB No. 12131804).

#### Informed consent statement:

Patients were not required to give informed consent to the study because the analysis used anonymous data, that was obtained after each patient had agreed to the hospital evaluation and treatment *via* written consent.

**Conflict-of-interest statement:** All authors report no conflicts of interest.

**Data sharing statement:** No additional data are available.

**Country/Territory of origin:** United States

**Specialty type:** Gastroenterology and hepatology

#### Provenance and peer review:

Unsolicited article; Externally peer reviewed.

#### Peer-review report's scientific quality classification

Grade A (Excellent): 0  
Grade B (Very good): B  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

analysis of secondary outcomes, prior appendectomy was also associated with toxic megacolon (OR = 5.37,  $P < 0.05$ ) and colectomy (OR = 2.77,  $P < 0.05$ ).

#### CONCLUSION

Prior appendectomy may affect the severity of CDI, development of toxic megacolon and the eventual need for colectomy. Since treatment of CDI is governed by its severity, stronger antibiotic regimens or earlier use of fecal microbiota transplant may be a viable option for patients with prior appendectomy.

**Key Words:** Appendectomy; *Clostridium difficile*; Toxic megacolon; Colectomy; Gut microbiome

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** *Clostridium difficile* (*C. difficile*) infection occurs due to a dysbiosis of the gut. The appendix is known to host immune tissue and favorable gut microbiota, which may indirectly influence the disease course and outcomes in *C. difficile* infection. We found that prior appendectomy may affect the severity of *C. difficile* infection, and it may also increase the risk of developing toxic megacolon or requiring colectomy in these patients. Thus, earlier implementation of advanced therapeutic options may be necessary in patients without an appendix who develop *C. difficile* infection.

**Citation:** Shaikh DH, Patel H, Munshi R, Sun H, Meher Shahi S, Baiomi A, Alemam A, Pirzada U, Nawaz I, Naher K, Hanumanthu S, Nayudu S. Patients with *Clostridium difficile* infection and prior appendectomy may be prone to worse outcomes. *World J Gastrointest Surg* 2021; 13(11): 1436-1447

**URL:** <https://www.wjgnet.com/1948-9366/full/v13/i11/1436.htm>

**DOI:** <https://dx.doi.org/10.4240/wjgs.v13.i11.1436>

#### INTRODUCTION

*Clostridium difficile* (*C. difficile*) is a gram positive, spore forming bacterium that spreads *via* the fecal-oral route, and causes an opportunistic infection when a disruption in the normal intestinal flora occurs. *C. difficile* infection (CDI) is typically acquired in the healthcare setting, such as during hospitalizations, however community spread is also established. Recent prevalence studies demonstrate a decline in health care-associated CDI (by 24% from 2011 through 2017) as a result of better prevention practices and antibiotic stewardship programs, whereas the national burden of community-associated CDI has remained unchanged[1,2]. The clinical spectrum of CDI ranges from a mild diarrheal illness to a fulminant colitis, leading to shock and possible death. It is diagnosed *via* stool studies (presence of *C. difficile* toxins or toxigenic strain of *C. difficile* in stool), or the presence of typical colonoscopy findings of pseudomembranous colitis.

Treatment of CDI is governed by its severity on presentation, and in order to define the severity, several scoring systems are available. The components of the majority of these scales include patient comorbidities, clinical manifestations, laboratory tests, and imaging studies[3]. The most widely used of these scores was published in the 2010 Society for Healthcare Epidemiology of America and Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines (Table 1). It categorizes CDI into mild, severe, and severe, complicated[4]. The term "fulminant" is sometimes used to describe severe, complicated CDI[5]. This classification was derived from expert opinion and includes factors that predict unfavorable outcomes in CDI, such as serum creatinine > 1.5 mg/dL, leukocyte count >  $15 \times 10^9/L$ , ileus, toxic megacolon and shock.

In recent times, reports have emerged that recognize a history of appendectomy as an influence on the severity of CDI[6-8]. The vermiform appendix has long been considered a vestigial organ, however recent studies have elicited an abundance of favorable gut microbiota within the appendix, with the highest concentration in the

**Received:** July 18, 2021**Peer-review started:** July 18, 2021**First decision:** August 15, 2021**Revised:** August 29, 2021**Accepted:** September 15, 2021**Article in press:** September 15, 2021**Published online:** November 27, 2021**P-Reviewer:** Yu L**S-Editor:** Gao CC**L-Editor:** A**P-Editor:** Wu RR**Table 1 Classification of *Clostridium difficile* infection severity based on the Infectious Diseases Society of America criteria**

Severity	IDSA criteria
Mild	WBC < 15 × 10 <sup>9</sup> /L and serum creatinine < 1.5 times premorbid level
Severe	WBC ≥ 15 × 10 <sup>9</sup> /L, or serum creatinine ≥ 1.5 times premorbid level
Fulminant (severe, complicated)	Hypotension, shock, ileus, or megacolon

IDSA: Infectious Diseases Society of America; WBC: White blood cell.

innermost region, safely sheltered from colonic fecal stream[9,10]. The appendix is also said to harbor gut associated lymphoid tissue comprising of plasma B cells that produce high levels of secretory immunoglobulin A[11]. These antibodies may play a protective role in CDI, as reported by several small studies[12,13]. Larger epidemiological studies have also reinforced the appendix's role as an immunomodulatory organ. A history of appendectomy is believed to prevent the development of ulcerative colitis (UC)[14,15], and reduce the risk of colectomy in these patients[16].

We postulate that the appendix may be able to repopulate the large intestine with commensal organisms, or provide passive immunity should the colon fall prey to *C. difficile*. Accordingly, its absence may be detrimental to recovery from CDI. Previous reports have corroborated a similar claim. Im *et al*[8], demonstrated the protective role of the appendix in CDI recurrences in 254 patients. Clanton *et al*[17] reported a higher rate of appendectomy in patients with fulminant CDI that resulted in a colectomy.

Based on the appendix's 'safe house' theory, we set out to determine if there exists an association between prior appendectomy and outcomes (severity, recurrence, mortality) of CDI.

## MATERIALS AND METHODS

### Study design

This was a single-center, retrospective cohort study, spanning a period of 10 years from April 2008 to November 2018. The study protocol was approved by the Institution Review Board at BronxCare Health System and was performed as per the Declaration of Helsinki (IRB # 12131804). Data for hospitalized patients with positive *C. difficile* stool test was retrieved using the electronic medical record (EMR). A positive stool test was defined as (1) positive results of stool *C. difficile* toxin (Toxin A or Toxin B) and glutamate dehydrogenase (GDH) antigen, or (2) positive *C. difficile* nucleic acid amplification test in cases of discrepancy between *C. difficile* toxin and GDH antigen. Medical records for patients with CDI were reviewed, and all asymptomatic carriers were excluded.

Baseline socio-demographic characteristics included age, gender, body mass index (BMI) and ethnicity. Data was extracted from admission records except for ethnicity, which was self-reported. EMR was used to obtain patients' comorbidities. The blood chemistry and cell counts were obtained from the first set of the laboratory parameters acquired after the diagnosis of CDI. Past surgical history was scanned for information on prior appendectomy. Available abdominal imaging [ultrasound or computed tomography (CT) scan] prior to the onset of CDI was also reviewed to assess for the presence or absence of the appendix. When information was not available on history or imaging, the patient was considered to have an intact appendix. Records were also reviewed to assess prior use (within the preceding three months of CDI onset) of antibiotics, proton pump inhibitors (PPI), steroids and chemotherapy.

### Study outcomes

The primary outcomes for the current study were: (1) All-cause mortality; and (2) Severity of CDI. The charts of all patients, including their hospital course, were reviewed to document these findings including the recurrence rate, development of toxic megacolon, and the subsequent need for colectomy attributable to CDI. Mortality was defined as death within the same hospital admission as the CDI. Ileus was obtained from reported abdominal imaging (X-ray or CT scan) during the same hospital admission as the CDI. Additionally, data regarding the incidence of toxic

megacolon was obtained from abdominal imaging (X-ray or CT scan) or the surgical operative note in cases where patients underwent colectomy during the same hospital admission as the CDI diagnosis. The severity of CDI was defined as per the IDSA guidelines (Table 1).

Recurrence was defined as a new episode of symptom onset, and positive assay result following a successfully treated prior episode of CDI in the previous 2-8 wk. Length of stay (LOS) was calculated from the EMR from the day of admission to discharge or death.

### Statistical analysis

Patients were divided into two groups based on the history of appendectomy. The demographic information, comorbid medical conditions, and laboratory parameters were collected and stratified across both groups. Frequencies and percentages were reported for categorical variables. The mean and standard deviation were used to summarize continuous normal variables, while the median and interquartile range were used for continuous non-normal variables such as the LOS.

Univariate analysis was performed using Chi-square test independence for categorical variables. Continuous variables were compared using unpaired t-test and one-way ANOVA for two and more than two groups, respectively. For non-normal variables, Mann-Whitney and Kruskal-Wallis tests were used alternatively.

Multivariate analysis was performed using two methods in order to control and reduce the selection bias and other potential confounders in retrospective studies: (1) Multivariate logistic regression; and (2) Inverse probability of treatment weights (IPTW). Logistic regression was used to assess the association of prior appendectomy with primary and secondary outcomes after correcting for age, gender, BMI, comorbidities, and the prior use of antibiotics, steroids, and PPI. The binominal logistic regression was used for mortality and recurrence. Ordinal logistic regression and Poisson regression were used for CDI severity and LOS, respectively.

For IPTW, propensity scores were created by matching groups based on gender, age, prior PPI use, prior steroid use, and use of chemotherapy. Weights were calculated as the inverse of the propensity scores for patients with appendectomy. The control group weights were calculated by subtracting the propensity scores from unity and inverting the resulting score. Boosted logistic regression (using 20000 trees) was used to calculate propensity score. Average treatment effect (ATE) was used as an estimate during calculations. The balance was measured and assessed using the standardized effect size or standardized mean difference (SMD).

SPSS version 25 and R version 3.6.3 was used to perform the analysis.

## RESULTS

CDI was diagnosed in 1580 hospitalized patients during the study period. The mean age of the patients was  $57.1 \pm 15.7$  years at diagnosis. Females represented 51.2% of all patients. Data regarding race was missing for 40% of the patients. Of the remaining, African Americans constituted the majority (39%). Less than half of the patients presented with a mild CDI presentation (45%,  $n = 710$ ), 36% ( $n = 566$ ) were categorized into the severe CDI presentation and 19% ( $n = 304$ ) presented with fulminant (severe, complicated) CDI. The all-cause mortality in the study population was 14% ( $n = 220$ ). The recurrence rate was 14.4% ( $n = 228$ ), with a mean and a median of 1.48 and 1.0 recurrences, respectively. The average LOS was  $17.8 \pm 31.89$  d.

There was evidence of prior appendectomy in 12.5% ( $n = 198$ ) of the patients. The appendectomy status in most of these patients (61%,  $n = 122$ ) was documented on the CT scan of the abdomen. Comparing baseline characteristics between both groups (Table 2) revealed some differences. The percentage of females who had a prior appendectomy was significantly higher than the percentage who did not (59% vs 50%,  $P = 0.022$ ). Information regarding BMI was available in less than half of the study population ( $n = 691$ ), and there was no significant difference observed between the two groups. The age of the patients in both groups was also comparable, with no statistical significance. The prior use of antibiotics and PPI was more prevalent in individuals with prior appendectomy than individuals with no history of appendectomy, however only prior PPI use was statistically significant ( $P = 0.001$ ). Prevalence of major comorbid conditions such as hypertension, diabetes, asthma/chronic obstructive pulmonary disease, coronary artery disease, and chronic kidney disease was comparable between the two groups. The prevalence of UC in patients with CDI was slightly higher amongst patients with a history of

**Table 2** Baseline information of patients with *Clostridium difficile* infection compared between patients with appendectomy and no history of appendectomy

Variable	All patients (%)	No prior appendectomy (%)	Prior appendectomy (%)	P value	n
	1580	1382 (87.5)	198 (12.5)		
Age	57.1 ± 15.7	57.1 ± 15.6	56.8 ± 17.0	0.812	1580
Gender				<b>0.022</b>	1580
Female	809 (51.2)	692 (50.1)	117 (59.1)		
Male	771 (48.8)	690 (49.9)	81 (40.9)		
Ethnicity				0.439	1580
African American	611 (38.67)	540 (39.1)	71 (35.9)		
Hispanic	262 (16.6)	228 (16.5)	34 (17.2)		
Caucasian	58 (3.73)	52 (3.8)	6 (3.03)		
Others	10 (0.63)	7 (0.51)	3 (1.52)		
Not available	639 (40.4)	555 (40.2)	84 (42.4)		
Comorbidities					1580
Hypertension	1210 (76.58)	1022 (73.95)	153 (77.27)	0.815	
Diabetes mellitus	741 (46.89)	618 (44.71)	102 (51.51)	0.384	
Obstructive lung disease	752 (47.56)	633 (45.80)	95 (47.97)	0.933	
Coronary artery disease	480 (30.37)	407 (29.45)	57 (28.78)	0.802	
Chronic kidney disease	477 (30.18)	406 (29.37)	56 (28.28)	0.819	
Inflammatory bowel diseases					1580
Ulcerative colitis	117 (7.40)	103 (7.45)	9 (4.54)	0.203	
Crohn's disease	42 (2.66)	37 (2.67)	4 (2.02)	0.803	
Risk Factor of CDI					
Prior use of antibiotics	768 (52.2)	656 (51.3)	112 (58.3)	0.086	1470
Prior use of PPI	429 (29.0)	353 (27.4)	76 (39.4)	<b>0.001</b>	1480
Prior use of steroids	128 (8.73)	110 (8.63)	18 (9.1)	0.838	1467
Prior chemotherapy	50 (3.35)	45 (3.46)	5 (2.59)	0.678	1492
Known malignancy	175 (11.4)	147 (11.0)	28 (14.1)	0.232	1539
Liver cirrhosis	117 (8.42)	98 (8.19)	19 (9.84)	0.531	1389
HIV infection	406 (34.5)	362 (35.2)	44 (29.3)	0.186	1389
<i>C. difficile</i> related complication					
Ileus on imaging	52 (3.90)	41 (3.59)	11 (5.67)	0.237	1335
Admission to ICU	615 (40.6)	526 (39.8)	89 (46.1)	0.113	1514
Intubation	298 (19.9)	258 (19.8)	40 (20.7)	0.846	1494
Clinical variable					
Body mass index (kg/m <sup>2</sup> )	27.69 ± 7.7	27.78 ± 7.79	26.70 ± 6.75	0.1890	690
Mean arterial pressure (mmHg)	92.4 ± 18.2	92.6 ± 18.3	90.5 ± 17.5	0.115	1467
Pulse beats per minute	91.7 ± 20.8	91.6 ± 21.0	92.3 ± 20.0	0.700	1464
Laboratory parameters					
Hemoglobin g/dL	11.2 ± 2.93	11.2 ± 2.98	11.2 ± 2.58	0.819	1533
White blood cell (cells/mm <sup>3</sup> )	11.6 ± 8.04	11.4 ± 8.06	13.1 ± 7.71	<b>0.005</b>	1533
Albumin (mg/dL)	3.37 ± 0.82	3.38 ± 0.81	3.31 ± 0.87	0.309	1502

Blood urea nitrogen (mg/dL)	26.9 ± 26.0	26.9 ± 25.8	26.7 ± 27.3	0.925	1531
Serum creatinine (mg/dL)	1.85 ± 2.26	1.85 ± 2.24	1.88 ± 2.43	0.830	1531
Lactic acid (mg/dL)	2.13 ± 2.27	2.16 ± 2.33	1.92 ± 1.82	0.127	1372

*C. difficile*: *Clostridium difficile*; CDI: *Clostridium difficile* infection; PPI: Proton pump inhibitors; HIV: Human immunodeficiency virus; ICU: Intensive care unit.

appendectomy (7.45%), compared to those with an intact appendix (4.54%), though this was not clinically significant ( $P = 0.203$ ). We found no difference in the prevalence of Crohn's disease in our study population between patients with and without an appendix (2.02% vs 2.67%,  $P = 0.803$ ). There were no differences in the laboratory parameters except for leukocytosis. Individuals with prior appendectomy demonstrated higher leukocyte counts ( $13.1 \times 10^4$  cells/dL) as compared to those without prior appendectomy ( $11.4 \times 10^4$  cells/dL) ( $P = 0.005$ ). Both groups revealed no significant difference in the requirement of critical care monitoring for CDI, the need for endotracheal intubation, or ileus on imaging studies.

Prior appendectomy was associated with the severity of presentation, toxic megacolon attributable to *C. difficile* colitis, and colectomy (Table 3). The association with the latter two parameters was statistically significant at the 0.1 level, whereas, association of prior appendectomy with the severity of presentation was significant at  $P < 0.05$  level. Patients with prior appendectomy were more likely to present with a higher grade of severity [odds ratio (OR) = 1.32,  $P < 0.05$ ]. The rates of severe and fulminant CDI were higher in patients with prior appendectomy (39% and 23%, respectively) than patients with no prior appendectomy (35% and 19%, respectively). Mild presentation was more common in patients with no prior appendectomy. There was no significant difference in the recurrence rates of CDI.

After the use of IPTW, the association between prior appendectomy and the IDSA severity did not change (OR = 1.59,  $P < 0.05$ ), which indicates that a history of appendectomy in CDI is associated with 59% higher odds of presenting with a higher IDSA severity. The association between appendectomy and toxic megacolon did not change either. Prior appendectomy did not show a statistically significant association with recurrence, LOS, the need for colectomy, or mortality after the use of IPTW.

The severity of *C. difficile* (Table 4) was associated with mortality. Mortality was highest in patients with a fulminant presentation (46%,  $n = 146$  of 314), as compared to the severe or mild manifestation of CDI ( $P < 0.001$ ). The severity of CDI was as per the IDSA criteria, and patients with toxic megacolon and colectomy were considered in the fulminant *C. difficile* colitis category. The median LOS increased with increasing IDSA severity. Patients with mild CDI had a median LOS of 8 d, while patients with severe and fulminant CDI had median LOS of 10 and 19 d, respectively ( $P < 0.001$ ). The mean BMI was similar between mild and severe presentations of CDI, whereas, patients with fulminant CDI were noted to have a slight increase in mean BMI, though not statistically significant (Table 5).

Multivariate logistic regression analysis (Table 6) showed that older age was associated with higher mortality in CDI patients (OR = 1.02,  $P < 0.001$ ). Age did not show a statistically significant association with recurrence, toxic megacolon, or the need for colectomy. None of the included factors showed a statistically significant association with recurrence of CDI. Interestingly, prior appendectomy status was associated with higher odds of toxic megacolon (OR = 5.37,  $P < 0.05$ ) and higher odds of requiring a colectomy (OR = 2.77,  $P < 0.05$ ).

## DISCUSSION

Appendectomy remains the standard of care for the treatment of acute uncomplicated appendicitis. More than 300000 appendectomies are performed annually in the United States, making it one of the most commonly performed procedures by general surgeons. Our study demonstrated a 12.5% prevalence of prior appendectomy in our patient population, which is similar to the general population (12%-23%), based on epidemiological studies. More females had prior appendectomy compared to males (59% vs 50%,  $P = 0.019$ ), a claim which is also consistent with population studies that demonstrate a higher lifetime risk of appendectomy in females compared to males[18].

**Table 3 Comparison of the *Clostridium difficile* infection outcomes based on the prior appendectomy status and the inverse probability of treatment weights analysis**

Outcome	Total	No prior appendectomy	Prior appendectomy	OR (95%CI)	P value
<i>n</i>	1580	1382	198		
<i>n</i> IP-weighted		1572	1354		
<b>Mortality</b>					
<i>n</i> (%)	220 (13.9)	193 (14.2)	27 (13.7)	0.97 (0.61-1.47)	0.877
<i>n</i> IP-weighted (%)		218 (14)	207 (15.5)	1.12 (0.65-1.92)	0.685
<b>Recurrence</b>					
<i>n</i> (%)	228 (14.4)	199 (14.4)	29 (14.6)	1.02 (0.66-1.54)	0.915
<i>n</i> IP-weighted (%)		228 (14.5)	204 (15.1)	1.05 (0.66-1.67)	0.847
<b>Toxic megacolon</b>					
<i>n</i> (%)	7 (0.4)	4 (0.34)	3 (1.57)	4.75 (0.87-22.9)	<b>0.069</b>
<i>n</i> IP-weighted (%)		5 (0.3)	19 (1.5)	4.32 (0.91-20.57)	<b>0.066</b>
<b>Colectomy</b>					
<i>n</i> (%)	22 (1.4)	16 (1.19)	6 (3.06)	2.65 (0.93-6.59)	<b>0.067</b>
<i>n</i> IP-weighted (%)		18 (1.2)	24 (1.8)	1.53 (0.55-4.27)	0.413
<b>Severity (IDSA)</b>					
<b>Before IPTW</b>				1.32 (1.01-1.75)	<b>0.043</b>
Mild, <i>n</i> (%)	710 (44.9)	634 (45.9)	76 (38.4)		
Severe, <i>n</i> (%)	566 (35.8)	489 (35.4)	77 (38.9)		
Fulminant, <i>n</i> (%)	304 (19.2)	259 (18.7)	45 (22.7)		
<b>After IPTW</b>				1.59 (1.15-2.18)	<b>0.005</b>
Mild, <i>n</i> (%)		724 (46.1)	472 (34.8)		
Severe, <i>n</i> (%)		557 (35.4)	526 (38.8)		
Fulminant, <i>n</i> (%)		291 (18.5)	356 (26.3)		
<b>LOS among survivors</b>					
Median (IQR)		9 (5.00; 18.0)	10 (6.50; 20.0)	1.1 (0.94-1.28)	0.233
Median (IQR)-IPTW		10 (5.00; 20.0)	12 (7.00; 23.00)	0.9 (0.74-1.1)	0.318

Data were summarized using counts and percentages before inverse probability of treatment weights (IPTW) and weighed counts and percentages after IPTW. Statistical analysis was performed using logistic regression for categorical variables and Poisson regression for length of stay (LOS). Analysis for LOS included only patients who were discharged. Ordinal logistic regression was used to assess the association between history of appendectomy and Infectious Diseases Society of America severity. CI: Confidence interval; OR: Odds ratio; IQR: Interquartile range; IPTW: Inverse probability of treatment weights; LOS: Length of stay; IDSA: Infectious Diseases Society of America.

CDI is the leading cause of hospital-acquired diarrhea in the United States and accounts for significant morbidity and mortality, burdening the healthcare system an additional 1 to 3 billion dollars in costs annually[7]. The all-cause mortality, attributable to CDI in our study population was 14%, whereas epidemiological studies estimate a mortality rate directly related to CDI at 5%, and a mortality associated with CDI complications between 15%-25% [19].

Our results show that patients with a prior appendectomy had a more severe course of CDI (Figure 1), and outcomes of toxic megacolon and colectomy were also higher (Figure 2). Even though patients with appendectomy did have more severe and fulminant course of CDI, our research did not demonstrate a higher rate of mortality in these patients. Of the two markers of severity, namely serum creatinine and white cell count, there was no significant difference seen in the serum creatinine level between the two groups. Thus the higher severity was mostly attributable to a higher leukocyte count in CDI patients with a prior appendectomy. Furthermore, a history of

**Table 4 Association between *Clostridium difficile* infection outcomes and severity of the presentation**

Outcomes	Severity (IDSA)			P value
	Mild (n = 710)	Severe (n = 566)	Fulminant (n = 304)	
Mortality (%)	29 (4.1)	44 (7.7)	147 (48.3)	< 0.001
Recurrence (%)	98 (13.8)	81 (14.3)	49 (16.1)	0.063
Toxic megacolon (%)	0	0	7 (2.3)	< 0.001
Colectomy (%)	0	0	22 (7.2%)	< 0.001
Length of stay (median)	8 (4.00; 14.00)	10.0 (6.00; 18.0)	19 (10.0; 30.0)	< 0.001

Counts and percentages were used to summarize categorical variables. The median (interquartile range) was used to summarize length of stay (LOS). Statistical analysis was performed using the Chi-square test of independence. LOS was compared using the Kruskal-Wallis test. Analysis for LOS included only patients who were discharged. IDSA: Infectious Diseases Society of America.

**Table 5 Association between body mass index and severity of *Clostridium difficile* infection presentation**

Severity (IDSA)	Body mass index (kg/m <sup>2</sup> )	P = 0.412
Mild	27.66 ± 7.39	
Severe	27.34 ± 7.63	
Fulminant	28.4 ± 8.59	

IDSA: Infectious Diseases Society of America.

appendectomy was positively associated with the development of toxic megacolon and the need for colectomy at the  $P < 0.1$  level on bivariate analysis. We postulate that significance was not met at the  $P < 0.05$  level due to a small overall number of patients with toxic megacolon ( $n = 7$ ) and those that underwent colectomy ( $n = 22$ ), in our study population. However, the trajectory of data suggests a possible association that could have yielded significance at the  $P < 0.05$  level, if the study power was increased. Our conjecture was confirmed on multivariate regression analysis, where prior appendectomy in CDI patients was identified as an independent predictor of both toxic megacolon ( $P = 0.031$ ) and colectomy ( $P = 0.044$ ).

Prior antibiotic use, defined as use of antibiotics within 3 months prior to the onset of CDI, was more likely in patients with appendectomy than those without, however this was not statistically significant. Similarly, PPI use was also more likely in patients with a history of appendectomy, and this was met with statistical significance. Antibiotic use has a known association with the development of CDI[20], and several meta-analysis have also reported PPI use as a risk factor for CDI, even in the absence of antibiotics[21,22]. However, to date, both antibiotics and PPI have not been shown to affect the severity of CDI at presentation.

Our study did not demonstrate an increased risk of CDI recurrence in patients with prior appendectomy compared to those without, contrary to previous reports[8]. Although PPI use has also been associated with an increased risk of recurrent CDI[23], this was not observed in our study cohort.

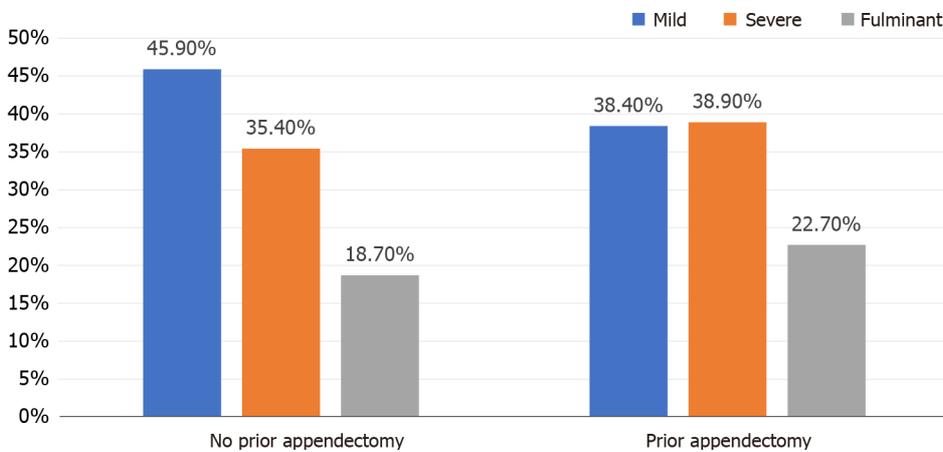
Other risk factors for acquiring CDI, such as a history of steroid use, chemotherapy, cirrhosis and HIV infection were evenly distributed between the appendectomy and non-appendectomy group.

In 2015, an estimated 1.3% of US adults (3 million) reported being diagnosed with inflammatory bowel diseases (IBD), namely Crohn's disease or UC[24]. The appendix may also serve a role in IBD. Several large epidemiological cohort studies have demonstrated the preventive effect of appendectomy on the development of UC, a finding that has been confirmed in murine colitis models[14], though this has not been replicated in CDI populations. A recent systematic review showed a significant inverse association between an appendectomy and the development of UC with an overall OR of 0.39 (95% confidence interval: 0.29-0.52)[15]. While it is known that CDI can complicate underlying IBD, given the immunosuppressive nature of the disease[25], a higher prevalence of UC was seen in our patients with CDI and appendectomy keeping in line with prior studies.

**Table 6** Multivariate analysis for primary and secondary outcomes

Variable	Mortality		Recurrence		Toxic megacolon		Need for colectomy	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Age	1.02 (1.01-1.03)	< 0.001	1.00 (0.99-1.01)	0.626			0.99 (0.96-1.02)	0.547
Female gender	Ref		Ref		Ref		Ref	
Male gender	1.32 (0.97-1.81)	0.079	0.91 (0.67-1.22)	0.518	0.86 (0.17-4.00)	0.846	1.36 (0.55-3.46)	0.501
Prior appendectomy = no	Ref		Ref		Ref		Ref	
Prior appendectomy = yes	1.03 (0.64-1.59)	0.905	0.92 (0.58-1.42)	0.727	5.37 (1.03-25.09)	<b>0.031</b>	2.77 (0.95-7.17)	<b>0.044</b>
Prior antibiotics (no)	Ref		Ref		Ref		Ref	
Prior antibiotics (yes)	1.04 (0.76-1.43)	0.788	1.07 (0.79-1.44)	0.668	0.13 (0.01-0.81)	0.065	1.58 (0.62-4.31)	0.348
Prior steroids (no)	Ref		Ref		Ref		Ref	
Prior steroids (yes)	0.72 (0.37-1.30)	0.309	1.08 (0.63-1.77)	0.774	1.99 (0.10-12.38)	0.533	0.41 (0.02-2.07)	0.391
Prior PPI (no)	Ref		Ref		Ref		Ref	
Prior PPI (yes)	0.89 (0.62-1.27)	0.530	1.05 (0.74-1.46)	0.790	1.08 (0.15-5.38)	0.933	1.83 (0.71-4.60)	0.196
Prior chemotherapy (no)	Ref		Ref		Ref		Ref	
Prior chemotherapy (yes)	0.92 (0.34-2.07)	0.851	0.76 (0.26-1.79)	0.570	-		4.26 (0.65-16.24)	0.063

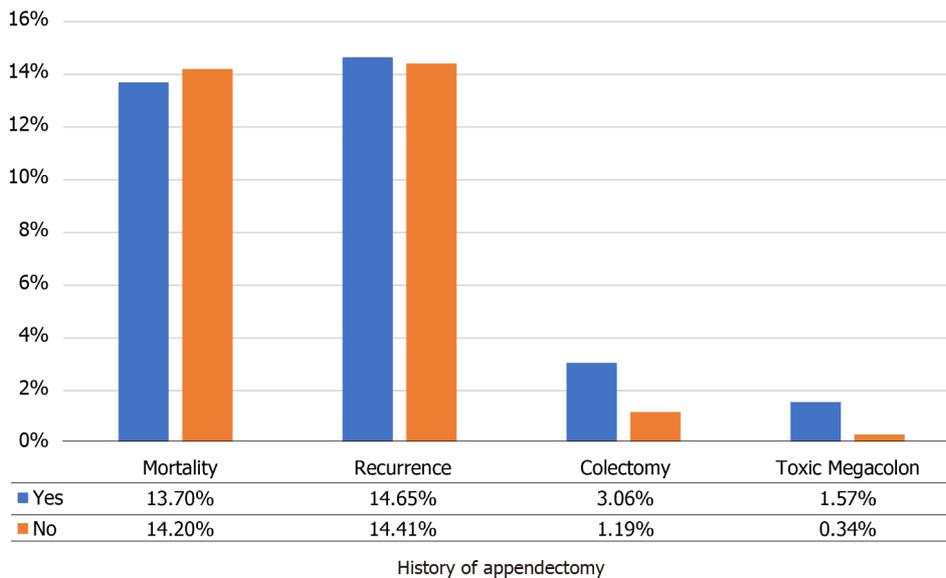
Multivariate analysis for mortality and recurrence was performed using binomial logistic regression. Chemotherapy was not included in the analysis of toxic megacolon due to convergence issues. OR: Odds ratio; CI: Confidence interval; PPI: Proton pump inhibitors.



**Figure 1** Infectious Diseases Society of America severity amongst *Clostridium difficile* infection patients with and without a history of prior appendectomy.

The study data was further validated as it rightfully portrayed the highest mortality and increased LOS in those with the most fulminant presentation of CDI. Our data also demonstrated that older age had a higher risk of mortality. Age is a well-known risk factor for CDI, especially greater than 65 years, and it also correlates with increasing severity of infection[26].

Based on our results and analysis, we postulate that a history of appendectomy may lead to worse outcomes in CDI, likely secondary to an attenuated response to the dysbiosis of the gut, leading to an increased inflammatory reaction. Since disease severity is used to guide therapy, perhaps it's prudent to screen patients with new onset CDI for factors associated with impaired immune response, such as an absent appendix. It would be worthwhile to investigate stronger antibiotic regimens or earlier institution of fecal microbiota transplantation in such patients.



**Figure 2** Outcomes of *Clostridium difficile* infection stratified according to the prior appendectomy status.

Contrary to our hypothesis, deterministic ecological models of the colon microbiome have not demonstrated a protective role of the appendix in CDI. These models studied the effect of the appendicular migration rate of commensal microbiota, and the boost to antibody production exerted by the appendix[27]. Further, a handful of small retrospective studies did not show a positive correlation between a history of appendectomy and CDI. Khanna *et al*[28], reported no difference in outcomes such as severity, treatment failure or recurrence in patients who had undergone an appendectomy before the development of CDI as compared to patients without an appendectomy. Ward *et al*[29], studied the presence and severity of CDI in relation to the presence or absence of an appendix, which did not demonstrate a statistically significant association. More recently, two further analyses demonstrated that *C. difficile* recurrence rate is not affected by a prior appendectomy[30], nor is there any statistical difference in the severity or complications of CDI in the presence or absence of the appendix[31]. It is worth noting that all of the above mentioned negative studies had a smaller patient population compared to ours, with most under 500 patients. Yet interestingly, the prevalence of patients with appendectomy in these studies was similar to ours and the general population at large.

The limitations of our study include its inherent retrospective design. Our case-control methodology does not allow for us to determine causality between appendectomy and CDI. It is also subject to selection bias, as the history of appendectomy was obtained *via* CT findings and on chart review. Our study, in keeping with the common narrative, did not show a statistical increase in mortality in patients with CDI and a history of appendectomy. Nevertheless, larger prospective studies are needed to establish significant causation and validate our findings. To date, no prospective studies have elicited the relationship between appendectomy and CDI.

## CONCLUSION

Prior appendectomy may affect the severity of CDI, development of toxic megacolon and the eventual need for colectomy. Since treatment of CDI is governed by its severity, stronger antibiotic regimens or earlier use of fecal microbiota transplant may be a viable option for patients with prior appendectomy.

## ARTICLE HIGHLIGHTS

### Research background

*Clostridium difficile* (*C. difficile*) is the leading cause of hospital-acquired diarrhea in the United States and accounts for significant morbidity, mortality and healthcare costs.

### Research motivation

The vermiform appendix hosts immune tissue and favorable gut microbiota, which may indirectly influence the disease course and outcomes in *C. difficile* infection (CDI).

### Research objectives

We aimed to study the association between prior appendectomy and outcomes (severity, recurrence, mortality) of CDI.

### Research methods

Retrospective review of 1580 patients with CDI, assessing mortality and severity based on the presence or absence of the appendix, using logistic regression and propensity score analysis.

### Research results

There was no statistical difference in mortality between *C. difficile* patients with a prior appendectomy or without (13.7% *vs* 14%,  $P = 0.877$ ). However, a history of appendectomy affected the severity of CDI [odds ratio (OR) = 1.32, 95% confidence interval: 1.01-1.75] and was also associated with the development of toxic megacolon (OR = 5.37,  $P < 0.05$ ), and colectomy (OR = 2.77,  $P < 0.05$ ).

### Research conclusions

A history of appendectomy may lead to worse outcomes in CDI, likely secondary to an attenuated response to the dysbiosis of the gut, leading to an increased inflammatory reaction.

### Research perspectives

Clinicians should be aware of the association between CDI and a history of appendectomy, and may consider screening all patients with *C. difficile* for a history of appendectomy. Further investigation into stronger antibiotic regimens or earlier institution of fecal microbiota transplantation for patients with prior appendectomy should be conducted if larger prospective studies can confirm and validate our results.

---

## REFERENCES

- 1 **Lessa FC**, Winston LG, McDonald LC; Emerging Infections Program *C. difficile* Surveillance Team. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med* 2015; **372**: 2369-2370 [PMID: 26061850 DOI: 10.1056/NEJMc1505190]
- 2 **Guh AY**, Mu Y, Winston LG, Johnston H, Olson D, Farley MM, Wilson LE, Holzbauer SM, Phipps EC, Dumyati GK, Beldavs ZG, Kainer MA, Karlsson M, Gerding DN, McDonald LC; Emerging Infections Program *Clostridioides difficile* Infection Working Group. Trends in U.S. Burden of *Clostridioides difficile* Infection and Outcomes. *N Engl J Med* 2020; **382**: 1320-1330 [PMID: 32242357 DOI: 10.1056/NEJMoa1910215]
- 3 **Hamo Z**, Azrad M, Nitzan O, Sagie A, Tkhawkho L, Binyamin D, Peretz A. Role of Single Procalcitonin Test on Admission as a Biomarker for Predicting the Severity of *Clostridium difficile* Infection. *Front Microbiol* 2017; **8**: 2532 [PMID: 29312224 DOI: 10.3389/fmicb.2017.02532]
- 4 **Cohen SH**, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol* 2010; **31**: 431-455 [PMID: 20307191 DOI: 10.1086/651706]
- 5 **Debast SB**, Bauer MP, Kuijper EJ; European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. *Clin Microbiol Infect* 2014; **20** Suppl 2: 1-26 [PMID: 24118601 DOI: 10.1111/1469-0691.12418]
- 6 **Merchant R**, Mower WR, Ourian A, Abrahamian FM, Moran GJ, Krishnadasan A, Talan DA. Association Between Appendectomy and *Clostridium difficile* Infection. *J Clin Med Res* 2012; **4**: 17-19 [PMID: 22383922 DOI: 10.4021/jocmr770w]
- 7 **Na X**, Kelly C. The vermiform appendix and recurrent *Clostridium difficile* infection: a curious connection. *Clin Gastroenterol Hepatol* 2011; **9**: 1017-1019 [PMID: 21893132 DOI: 10.1016/j.cgh.2011.08.025]
- 8 **Im GY**, Modayil RJ, Lin CT, Geier SJ, Katz DS, Feuerman M, Grendell JH. The appendix may protect against *Clostridium difficile* recurrence. *Clin Gastroenterol Hepatol* 2011; **9**: 1072-1077 [PMID: 21699818 DOI: 10.1016/j.cgh.2011.06.006]
- 9 **Killinger B**, Labrie V. The Appendix in Parkinson's Disease: From Vestigial Remnant to Vital

- Organ? *J Parkinsons Dis* 2019; **9**: S345-S358 [PMID: 31609697 DOI: 10.3233/JPD-191703]
- 10 **Kooij IA**, Sahami S, Meijer SL, Buskens CJ, Te Velde AA. The immunology of the vermiform appendix: a review of the literature. *Clin Exp Immunol* 2016; **186**: 1-9 [PMID: 27271818 DOI: 10.1111/cei.12821]
  - 11 **Male DK**. Immunology. Milton Keynes, MK, United States: Elsevier/Saunders, 2013
  - 12 **Johal SS**, Lambert CP, Hammond J, James PD, Borriello SP, Mahida YR. Colonic IgA producing cells and macrophages are reduced in recurrent and non-recurrent *Clostridium difficile* associated diarrhoea. *J Clin Pathol* 2004; **57**: 973-979 [PMID: 15333661 DOI: 10.1136/jcp.2003.015875]
  - 13 **Mulligan ME**, Miller SD, McFarland LV, Fung HC, Kwok RY. Elevated levels of serum immunoglobulins in asymptomatic carriers of *Clostridium difficile*. *Clin Infect Dis* 1993; **16** Suppl 4: S239-S244 [PMID: 8324125 DOI: 10.1093/clinids/16.Supplement\_4.S239]
  - 14 **Cheluvappa R**, Thomas DG, Selvendran S. The Role of Specific Chemokines in the Amelioration of Colitis by Appendicitis and Appendectomy. *Biomolecules* 2018; **8** [PMID: 30037025 DOI: 10.3390/biom8030059]
  - 15 **Koutroubakis IE**, Vlachonikolis IG. Appendectomy and the development of ulcerative colitis: results of a metaanalysis of published case-control studies. *Am J Gastroenterol* 2000; **95**: 171-176 [PMID: 10638578 DOI: 10.1111/j.1572-0241.2000.01680.x]
  - 16 **Myrelid P**, Landerholm K, Nordenvall C, Pinkney TD, Andersson RE. Appendectomy and the Risk of Colectomy in Ulcerative Colitis: A National Cohort Study. *Am J Gastroenterol* 2017; **112**: 1311-1319 [PMID: 28653667 DOI: 10.1038/ajg.2017.183]
  - 17 **Clanton J**, Subichin M, Drolshagen K, Daley T, Firstenberg MS. Fulminant *Clostridium difficile* infection: An association with prior appendectomy? *World J Gastrointest Surg* 2013; **5**: 233-238 [PMID: 23983904 DOI: 10.4240/wjgs.v5.i8.233]
  - 18 **Addiss DG**, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 1990; **132**: 910-925 [PMID: 2239906 DOI: 10.1093/oxfordjournals.aje.a115734]
  - 19 **Czepiel J**, Drózdź M, Pituch H, Kuijper EJ, Perucki W, Mielimonka A, Goldman S, Wultańska D, Garlicki A, Biesiada G. *Clostridium difficile* infection: review. *Eur J Clin Microbiol Infect Dis* 2019; **38**: 1211-1221 [PMID: 30945014 DOI: 10.1007/s10096-019-03539-6]
  - 20 **Alekhova TA**. [Isolation of a plasmid from actinomycin C-producing *Streptomyces chrysomallus* and its characteristics]. *Mol Gen Mikrobiol Virusol* 1985; 26-29 [PMID: 2432422 DOI: 10.1093/jac/dkt477]
  - 21 **Trifan A**, Stanciu C, Girleanu I, Stoica OC, Singeap AM, Maxim R, Chiriac SA, Ciobica A, Boiculese L. Proton pump inhibitors therapy and risk of *Clostridium difficile* infection: Systematic review and meta-analysis. *World J Gastroenterol* 2017; **23**: 6500-6515 [PMID: 29085200 DOI: 10.3748/wjg.v23.i35.6500]
  - 22 **Leonard J**, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol* 2007; **102**: 2047-56; quiz 2057 [PMID: 17509031 DOI: 10.1111/j.1572-0241.2007.01275.x]
  - 23 **Deshpande A**, Pasupuleti V, Thota P, Pant C, Rolston DD, Hernandez AV, Donskey CJ, Fraser TG. Risk factors for recurrent *Clostridium difficile* infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol* 2015; **36**: 452-460 [PMID: 25626326 DOI: 10.1017/ice.2014.88]
  - 24 **Dahlhamer JM**, Zammitti EP, Ward BW, Wheaton AG, Croft JB. Prevalence of Inflammatory Bowel Disease Among Adults Aged ≥18 Years - United States, 2015. *MMWR Morb Mortal Wkly Rep* 2016; **65**: 1166-1169 [PMID: 27787492 DOI: 10.15585/mmwr.mm6542a3]
  - 25 **Ananthakrishnan AN**, McGinley EL, Binion DG. Excess hospitalisation burden associated with *Clostridium difficile* in patients with inflammatory bowel disease. *Gut* 2008; **57**: 205-210 [PMID: 17905821 DOI: 10.1136/gut.2007.128231]
  - 26 **Leffler DA**, Lamont JT. *Clostridium difficile* Infection. *N Engl J Med* 2015; **373**: 287-288 [PMID: 26176396 DOI: 10.1056/NEJMc1506004]
  - 27 **Joshi T**, Elder BD, Abbott KC. No appendix necessary: Fecal transplants and antibiotics can resolve *Clostridium difficile* infection. *J Theor Biol* 2018; **442**: 139-148 [PMID: 29355542 DOI: 10.1016/j.jtbi.2018.01.013]
  - 28 **Khanna S**, Baddour LM, Dibaise JK, Pardi DS. Appendectomy is not associated with adverse outcomes in *clostridium difficile* infection: a population-based study. *Am J Gastroenterol* 2013; **108**: 626-627 [PMID: 23552320 DOI: 10.1038/ajg.2012.475]
  - 29 **Ward WH**, Putter KM, Lucha PA. *Clostridium difficile* colitis: is severity increased with previous appendectomy? *Am Surg* 2013; **79**: E258-E259 [PMID: 23896227 DOI: 10.1177/000313481307900801]
  - 30 **Franko J**, Ferrel B, Pierson P, Raman S, Frankova D, Rearigh LM, Afroze A, Guevara Hernandez MA, Terrero-Salcedo D, Kermodé D, Gorvet M. Influence of prior appendectomy and cholecystectomy on *Clostridioides difficile* infection recurrence and mortality. *Am J Surg* 2020; **220**: 203-207 [PMID: 31668774 DOI: 10.1016/j.amjsurg.2019.10.038]
  - 31 **Essrani R**, Saturno D, Mehershahi S, Essrani RK, Hossain MR, Ravi SJK, Berger A, Mehmood A. The Impact of Appendectomy in *Clostridium difficile* Infection and Length of Hospital Stay. *Cureus* 2020; **12**: e10342 [PMID: 33062466 DOI: 10.7759/cureus.10342]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

