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Original Article

# Risk Factors for Recurrence of *Clostridioides difficile* in Hospitalized Patients

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ABSTRACT

*Background:* Diarrhea and pseudomembranous colitis associated with *Clostridioides difficile* – a spore-forming anaerobic Gram-positive bacillus – is a major infection in hospitalized patients with a profound impact on clinical and economic outcomes. Recurrence (rCDI) is common and predisposes to further episodes with poor outcomes.
*Method:* We aimed to identify a wide range of risk factors for recurrence to guide stewardship initiatives. After ethical approval, we commenced collecting demographic and clinical data of patients older than 18 years with clinically and microbiologically confirmed *C. difficile* infection. Data were statistically analyzed using R software.
*Results:* Of 204 patients included in the analysis, 36 (18%) suffered 90-day recurrence, rCDI was higher among females (23%) compared to males (13%), overall age median (IQR) was 66 (51–77), and for rCDI cases 81 (69–86) years. Among 26 variables analyzed to evaluate their association with rCDI, prior clindamycin exposure, concurrent use of aztreonam, patients >76 years, total hospital length of stay, and LOS before diagnosis $\leq$7 days, WBC $\leq 9.85 \times 10^3$ at discharge were more likely to experience rCDI.
*Conclusion:* As identified in this analysis, patients with risk factors for rCDI could be candidates for close monitoring, a high index of suspicion, and risk mitigation interventions to avoid rCDI and improve clinical outcomes.


## Introduction

*Clostridioides difficile* is a spore-forming anaerobic Gram-positive bacillus that is the predominant cause of diarrhea and pseudomembranous colitis in hospitalized patients. *C. difficile* infections (CDI) result in copious, watery diarrhea mediated by both enterotoxin (TcdA and TcdB) and cytotoxin production [1,2]. Many factors are associated with hospital-acquired CDI including immunocompromising conditions, older age, chronic kidney disease (CKD), and inflammatory bowel disease (IBD). Prolonged use of proton pump inhibitors (PPI) and/or broad-spectrum antibiotics are associated with disruptions in the normal intestinal microbiota enabling *C. difficile* to proliferate and cause infection [3]. CDI is characterized by $\geq$3 episodes of diarrhea in 24 hours, fever, hypovolemia, leukocytosis, and abdominal pain/distension in correlation with evidence of toxin production. Enzyme immunoassays, nucleic acid amplification tests (NAAT), colonoscopy or histopathologic findings of pseudomembranous colitis, are the diagnostic tools used to confirm CDI [4,5].

Recurrent CDI (rCDI), which can predispose patients to further subsequent recurrences, occurs in almost 20% of cases but may reach 40–60% if all episodes are included [6]. Initial infection and first recurrence are treated using oral vancomycin or fidaxomicin, with oral metronidazole now only recommended if neither of the other agents is available [4]. Recurrent infections may require a

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tapered and pulsed vancomycin regimen, fidaxomicin if not used previously, or fecal microbiota transplant [4]. Recently, the monoclonal antibody bezlotoxumab was approved to reduce the risk of rCDI [7].

Recurrent CDI hospitalizations create a substantial burden on healthcare systems due to increased costs and contribute to increases in patient morbidity, mortality, and hospital length of stay (LOS) [8–11]. Recurrent CDI rates rose in part with the spread of the hypervirulent strain ribotype 027. Furthermore, it increased healthcare costs and hospital length of stay (LOS) while contributing to negative patient outcomes greater than those seen with initial infection [8,12–19].

Previous studies have found an association between the use of immunosuppressants, systemic antibiotics, chemotherapy, or PPI, as well as (CKD), Inflammatory Bowel Disease (IBD), prior CDI history, and serum albumin with rCDI [20–22]. Antibiotics used for CDI treatment have also shown to have different recurrence rates. Metronidazole achieves lower clinical cure and higher recurrence rates compared to vancomycin [20], while using fidaxomicin demonstrated higher global cure rates than oral vancomycin due to lower recurrence rates [23].

This study's objective was to identify a wide range of risk factors contributing to CDI recurrence among hospitalized patients that could be targeted for clinical and antimicrobial stewardship intervention.

## Methods

### *Ethical approval*

The research protocol conformed to all Declaration of Helsinki standards and was approved by Institutional Review Boards at both Cooper University Hospital and the University of the Sciences. Informed consent was waived due to the retrospective nature of data collection. Study data were collected and managed in the RedCAP® electronic database hosted at the University of the Sciences.

### *Study population*

This was a single-center, retrospective study of patients admitted to Cooper University Hospital, New Jersey, USA. They were included if they were diagnosed with CDI during 3 years (2011-2014), were ≥18 years of age, and received oral vancomycin as primary CDI treatment. During the study period, the first CDI episode was considered the primary infection, with subsequent infections considered as rCDI. Patients were only included one time for purposes of data analysis. Recurrence was defined as readmission with CDI symptoms and a positive laboratory test for *C. difficile* within 90-days of the previously resolved episode.

### *Collected data*

Information extracted from the electronic medical records included; patient demographics (age, gender, and ethnicity), clinical data (admission ward at diagnosis, LOS before diagnosis, temperature, frequency of diarrhea, presence of abdominal pain, hypotension/shock, and ileus), laboratory data (serum creatinine, albumin level, and white blood cell count), concurrent use of medications (antibiotics, steroids, and PPIs), comorbidities (other infections and disease states), treatment outcomes (length of infection-related hospital stay, resolution of symptoms, normalization of laboratory values, development of disease complications, intensive care unit (ICU) admission, and surgical intervention).

### C. difficile *testing*

*C. difficile* testing is performed using *C. difficile* screen test, toxin PCR test, and North American pulsed-field gel electrophoresis type 1 (NAP1). Diagnosis of CDI required the presence of ≥3 watery stools in 24 hours and a positive *C. difficile* laboratory test consisting of an enzyme immunoassay (EIA) to detect glutamate dehydrogenase (GDH) plus a positive toxin assay. If the screening test results were indeterminate, they were followed by a polymerase chain reaction (PCR) to detect TcdB.

### *Statistical analyses*

For the initial univariate analysis, nonparametric continuous data were analyzed using the Wilcoxon rank-sum test, while categorical variables were compared using a Chi-squared test or Fisher's exact test. A classification and regression tree (CART) analysis were used to identify patients at high risk for rCDI. Continuous variables were transformed into dichotomous categories for the logistic regression model. Statistical significance was defined as a P-value <0.05.

For the sake of comprehensive analysis, from the binary logistic regression, all risk factors with $P \leq 0.2$ were subsequently analyzed in a multivariate logistic regression model. Although stepwise multivariate regression analysis is a commonly used statistical tool, there is a rising number of critiques. Statisticians have noted several drawbacks to the approach, including incorrect results, an inherent bias in the process itself, the necessity for significant computing power to develop complex regression models through iteration and finally the possibility of masking clinically significant variables [24]. All statistical analyses were performed using R software version 3.6.2 (R Foundation for statistical computing platform).

## Results

A total of 204 patients were included in the study analysis, of which 36 (18%) suffered 90-day recurrence. There has been a fair distribution of females and males at 49.5% and 50.5% among the entire cohort, respectively. The rate of rCDI was higher among females (23%) compared to (13%) in males (P = 0.06). The median age of the overall study cohort (IQR) was 66 (51–77), 81 (69–86) for rCDI cases, while it was 64 (49–75) years for non-rCDI (P < 0.001).

The median LOS for the entire study cohort was 9 days [5–19]; for rCDI cases, it was 7 days [5–9], while it was 10 days [5–16] for non-rCDI (P = 0.16). Eighty-four patients (41%) required critical care admission, 13 (15%) with rCDI and 71 (85%) without (P = 0.5). Additional baseline characteristics are shown in Table 1.

Twenty-six variables were analyzed to evaluate their association with rCDI in this cohort of patients to aid in developing an antimicrobial stewardship tool (Table 1). In a univariate model; rCDI was more likely to occur in subjects who had used clindamycin prior to the index episode [P = 0.01, OR: 3.4, CI: (1.2, 8.9)], concurrent use of aztreonam during the index episode [P = 0.03, OR: 7.5, CI: (1.2, 46.9)], patients >76 years [P < 0.00, OR: 5.8, CI: (2.7, 12.6)], female [P = 0.06, OR: 2.0, CI: (0.96, 4.29)], with hospital LOS and LOS before diagnosis ≤7 days (P < 0.04) and (P < 0.02) respectively, and laboratory finding at discharge was WBC $\geq 9.85 \times 10^3$ [P < 0.01, OR: 3.1, CI: (1.3, 7.2)] (Table 1). Using CART analysis (Fig. 1) showed an initial stratification point for high risk of rCDI was age >76 years [P < 0.00, OR: 5.8, CI: (2.71, 12.6)]. Further exploration of the CART analysis identified that patients >79.5 years with a WBC at the end of treatment ≤9.85, and serum creatinine SCr at the end of treatment/SCr at baseline ≤1.43 were at an 85.7% risk of recurrence. This high-risk group had a risk ratio RR = 9.2.

**Table 1**
Baseline characteristics for the study group and risk factors for recurrence of *Clostridioides difficile*.

| Variable | | Overall (n = 204)[b] | | Recurrence (n = 36)[b] | | No recurrence (n = 168)[b] | | P value[c] | Odd ratio[c] | CI[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| Age (median – IQR) | | 66 | (51.25-77) | 81.5 | (69.5-86.75) | 64 | (49-75) | <0.001 | | |
| Age (>76 years) | | 62 | 30% | 23 | 37% | 39 | 63% | 0.00 | 5.852 | (2.7133, 12.621) |
| Gender (male) | | 103 | 50% | 13 | 13% | 90 | 87% | 0.06 | 0.490 | (0.2326, 1.0315) |
| Ethnicity | African American | 50 | 25% | 8 | 16% | 42 | 84% | 0.73 | 0.857 | (0.3628, 2.0252) |
| | Asian | 3 | 1% | 0 | 0% | 3 | 100% | 0.97 | 0.000 | (0.0000, 7.8126) |
| | Caucasian | 123 | 60% | 25 | 20% | 98 | 80% | 0.22 | 1.623 | (0.7497, 3.5153) |
| | Hispanic | 25 | 12% | 3 | 12% | 22 | 88% | 0.43 | 1.658 | (0.4683, 5.8672) |
| Admission to critical care area at diagnosis | | 84 | 41% | 13 | 15% | 71 | 85% | 0.50 | 0.772 | (0.3663, 1.6279) |
| Hospital LOS (median – IQR) | | 9 | (5 -19.75) | 7 | (5-9.75) | 10 | (5-16) | 0.161 | | |
| Hospital length of stay (>7 days) | | 111 | 54% | 14 | 13% | 97 | 87% | 0.04 | 0.466 | (0.2230, 0.9730) |
| LOS before diagnosis (median – IQR) | | 1 | (0-5) | 1 | (0-2) | 1 | (0-7.750) | 0.021 | | |
| LOS before diagnosis (>7 days) | | 44 | 22% | 2 | 5% | 42 | 95% | 0.02 | 0.177 | (0.0407, 0.7660) |
| *C. difficile* screen test (positive) | | 143 | 70% | 27 | 19% | 116 | 81% | 0.48 | 1.345 | (0.5910, 3.0603) |
| Toxin PCR test (positive) | | 61 | 30% | 9 | 15% | 52 | 85% | 0.48 | 0.744 | (0.3268, 1.6921) |
| Tmax at diagnosis (>37 °C) | | 134 | 66% | 22 | 16% | 112 | 84% | 0.53 | 0.786 | (0.3738, 1.6516) |
| Tmax at discharge (>37 °C | | 67 | 33% | 5 | 7% | 62 | 93% | 0.01 | 0.276 | (0.1019, 0.7460) |
| Fever/hypothermia at diagnosis | | 53 | 26% | 10 | 19% | 43 | 81% | 0.79 | 1.118 | (0.4987, 2.5069) |
| Fever/hypothermia at discharge | | 4 | 2% | 0 | 0% | 4 | 100% | 0.96 | 0.000 | (0.0000, 4.348) |
| WBC count at diagnosis (≥9.85) | | 175 | 86% | 31 | 18% | 144 | 82% | 0.88 | 1.084 | (0.3848, 3.0536) |
| WBC count at discharge (≥9.85) | | 87 | 43% | 8 | 9% | 79 | 91% | 0.01 | 0.322 | (0.1387, 0.7471) |
| Serum creatinine at diagnosis (>1.43) | | 77 | 38% | 15 | 19% | 62 | 81% | 0.59 | 1.221 | (0.5868, 2.5416) |
| Serum creatinine at discharge (>1.43) | | 31 | 15% | 6 | 19% | 25 | 81% | 0.79 | 1.144 | (0.4319, 3.0301) |
| Hypotension or shock at diagnosis | | 34 | 17% | 2 | 6% | 32 | 94% | 0.07 | 0.250 | (0.0571, 1.0951) |
| Disease severity at diagnosis (severe) | | 179 | 88% | 34 | 19% | 145 | 81% | 0.19 | 2.697 | (0.6063, 11.9935) |
| Concurrent use of antibiotics | | 98 | 48% | 20 | 20% | 78 | 80% | 0.32 | 1.442 | (0.6993, 2.9748) |
| Concurrent antibiotics | ß-Lactam/ß-lactamase | 27 | 13% | 2 | 7% | 25 | 93% | 0.15 | 0.337 | (0.0760, 1.4900) |

Table 1 (*Continued*)

| Variable | | | Overall (n = 204)[b] | | Recurrence (n = 36)[b] | | No recurrence (n = 168)[b] | | P value[c] | Odd ratio[c] | CI[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1st/2nd cephalosporins | 8 | 4% | 2 | 25% | 6 | 75% | 0.58 | 1.588 | (0.3073, 8.2078) | |
| | 3rd/greater cephalosporin | 35 | 17% | 8 | 23% | 27 | 77% | 0.38 | 1.492 | (0.6145, 3.6227) | |
| | Carbapenem | 3 | 1% | 0 | 0% | 3 | 100% | 0.97 | 0.000 | (0.0000, 7.8126) | |
| | Aztreonam | 5 | 2% | 3 | 60% | 2 | 40% | 0.03 | 7.546 | (1.2132, 46.9269) | |
| | Aminoglycosides | 4 | 2% | 1 | 25% | 3 | 75% | 0.70 | 1.571 | (0.1588, 15.5546) | |
| | Fluoroquinolones | 38 | 19% | 7 | 18% | 31 | 82% | 0.89 | 1.067 | (0.4282, 2.6576) | |
| Prior exposure to any antibiotics[a] | | | 155 | 76% | 29 | 19% | 126 | 81% | 0.48 | 1.381 | (0.5636, 3.3838) |
| | | ß-Lactam/ß-lactamase | 40 | 20% | 6 | 15% | 34 | 85% | 0.63 | 0.788 | (0.3037, 2.0461) |
| | Prior exposure | | | | | | | | | | |
| | 1st/2nd cephalosporins | 35 | 17% | 4 | 11% | 31 | 89% | 0.30 | 0.552 | (0.1820, 1.6764) | |
| | 3rd/greater cephalosporin | 75 | 37% | 14 | 19% | 61 | 81% | 0.77 | 1.116 | (0.5325, 2.3400) | |
| | Carbapenem | 7 | 3% | 2 | 29% | 5 | 71% | 0.45 | 1.918 | (0.3571, 10.2989) | |
| | Aztreonam | 8 | 4% | 2 | 25% | 6 | 75% | 0.58 | 1.588 | (0.3073, 8.2078) | |
| | Fluoroquinolone | 99 | 49% | 19 | 19% | 80 | 81% | 0.57 | 1.229 | (0.5978, 2.5282) | |
| | TMP/SMX | 8 | 4% | 1 | 13% | 7 | 88% | 0.70 | 0.657 | (0.0783, 5.5128) | |
| | Macrolide | 18 | 9% | 3 | 17% | 15 | 83% | 0.91 | 0.927 | (0.2539, 3.3869) | |
| | Doxycycline | 3 | 1% | 1 | 33% | 2 | 67% | 0.49 | 2.371 | (0.2092, 26.8824) | |
| | Clindamycin | 21 | 10% | 8 | 38% | 13 | 62% | 0.01 | 3.407 | (1.2935, 8.9714) | |
| Any comorbid condition | | | 156 | 76% | 28 | 18% | 128 | 82% | 0.84 | 1.094 | (0.4618, 2.5905) |
| | | Active malignancy | 44 | 22% | 8 | 18% | 36 | 82% | 0.92 | 1.048 | (0.4398, 2.4952) |
| | Comorbid conditions | | | | | | | | | | |
| | Gastrointestinal surgery | 39 | 19% | 4 | 10% | 35 | 90% | 0.19 | 0.475 | (0.1575, 1.4328) | |
| | IBD | 24 | 12% | 1 | 4% | 23 | 96% | 0.10 | 0.180 | (0.0235, 1.3790) | |
| | Diabetes mellites | 57 | 28% | 12 | 21% | 45 | 79% | 0.43 | 1.367 | (0.6312, 2.9591) | |

Table 1 (*Continued*)

| Variable | | Overall (n = 204)[b] | | Recurrence (n = 36)[b] | | No recurrence (n = 168)[b] | | P value[c] | Odd ratio[c] | CI[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| Chronic liver disease | 14 | 7% | 3 | 21% | 11 | 79% | 0.70 | 1.298 | (0.3429, 4.9091) | |
| Chronic renal failure | 76 | 37% | 14 | 18% | 62 | 82% | 0.82 | 1.088 | (0.5192, 2.2797) | |
| ICU admission during treatment | | 48 | 24% | 4 | 8% | 44 | 92% | 0.06 | 0.352 | (0.1179, 1.0528) |
| ICU LOS (>7 days) | | 18 | 9% | 1 | 6% | 17 | 94% | 0.19 | 0.254 | (0.0327, 1.9713) |
| Other risk factors | Proton pump inhibitors | 67 | 33% | 11 | 16% | 56 | 84% | 0.75 | 0.880 | (0.4041, 1.9165) |
| Mechanical ventilation | 27 | 13% | 2 | 7% | 25 | 93% | 0.15 | 0.337 | (0.0760, 1.4900) | |
| Vasopressor use | 17 | 8% | 4 | 24% | 13 | 76% | 0.51 | 1.490 | (0.4564, 4.8673) | |
| Surgical intervention | 4 | 2% | 0 | 0% | 4 | 100% | 0.96 | 0.000 | (0.0000, 4.348) | |
| Initial treatment regimens | Vancomycin started initially or after ≤1 dose of metronidazole | 96 | 47% | 15 | 16% | 81 | 84% | 0.48 | 0.767 | (0.3703, 1.5895) |
| Vancomycin started ≥48 hours after initial treatment with metronidazole | 17 | 8% | 4 | 24% | 13 | 76% | 0.51 | 1.490 | (0.4564, 4.8673) | |
| Vancomycin 125 mg po q6h | 65 | 32% | 12 | 18% | 53 | 82% | 0.84 | 1.085 | (0.5046, 2.3327) | |
| Vancomycin 250 mg po q6h | 19 | 9% | 4 | 21% | 15 | 79% | 0.68 | 1.275 | (0.3970, 4.0953) | |
| Vancomycin 500 mg po q6h | 7 | 3% | 1 | 14% | 6 | 86% | 0.81 | 0.771 | (0.0900, 6.6113) | |
| Treatment duration (>7 days) | | 147 | 72% | 24 | 16% | 123 | 84% | 0.43 | 0.732 | (0.3379, 1.5843) |
| Number of risk factors median (IQR) | | 8 | (6-10) | 8 | (6-9) | 8 | (6-11) | 0.68 | | |

(IQR): interquartile range, (LOS): length of stay, (PCR): polymerase chain reaction, (WBC): while blood cells, (TMP/SMX): trimethoprim/sulfamethoxazole, (IBD): irritable bowel disease, (ICU): intensive care unit.

[a] The receipt of antibiotic treatment course within 90 days prior to CDI diagnosis.

[b] Numbers are percentage unless otherwise specified.

[c] Binary logistic regression.

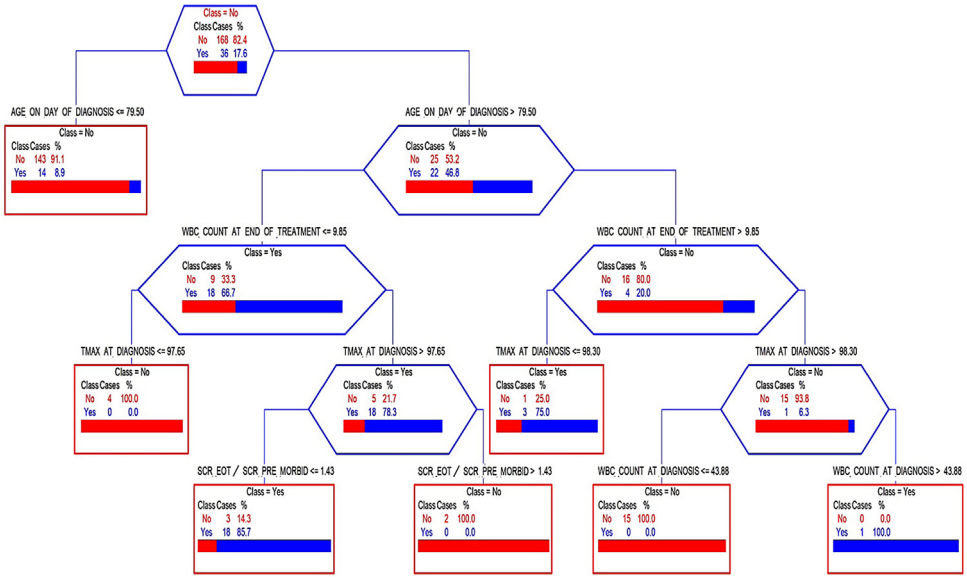


**Fig. 1.** Classification and regression tree analysis.

*Results of stepwise regression analysis*

The initial model included (Age, Gender, Hospital LOS, Hospital LOS before Diagnosis, Hypotension/Shock at Diagnosis, Disease Severity at Diagnosis, Concurrent penicillin β-lactam β-lactamase, Concurrent aztreonam, WBC Count at Discharge, Prior clindamycin use, GI. Surgery, IBD, Crohn's and ulcerative colitis, ICU Admission During Treatment, ICU LOS, Mechanical Ventilation + Tmax at discharge).

Stepwise regression recommended to include the next variables in multiple logistic regression (Age, LOS before diagnosis, Hypotension/Shock at Diagnosis, Disease Severity at Diagnosis, Concurrent aztreonam, Prior clindamycin, IBD, Crohn's and ulcerative colitis, Tmax at discharge, WBC Count at Discharge).

The final model showed that Age and prior exposure to clindamycin are statistically significant contributors to 90-day recurrence ($P < 0.0004$) and ($P < 0.023$) respectively.

## Discussion

The early identification of patients at high risk of rCDI may allow for prompt intervention and clinicians' mitigation strategies. Previously identified causes of recurrence include: severity at time of diagnosis, treatment regimen, and the involvement of a hypervirulent ribotype (e.g., ribotype 027) [25]. This study evaluated a cohort of hospitalized patients with CDI and then stratified them into groups with or without recurrent infections. Patient characteristics and clinical factors were assessed to determine which were associated with recurrence. The recurrence rate of 17.6% is similar to what has been reported in previous studies [20,26,27]. The binary logistic regression model identified many primary risk factors for 90-day recurrence: age, LOS, WBC count and $T_{max}$ at discharge, concurrent treatment with aztreonam, and prior exposure to clindamycin.

Patients >76 years were at significantly greater risk of rCDI ($P < 0.05$, OR: 5.8), which is consistent with the findings of the U.S. National Hospital Discharge Surveys for CDI over 10 years [28], and other meta-analyses [29–31]. Our model identified a non-significant statistical tendency of the female gender to acquire rCDI ($P < 0.06$, OR: 2.0), while other studies significantly correlated rCDI to females [32,33]. This is often attributed to alterations in the intestinal microbiota between genders [34].

Admission to ICU was associated with fewer odd ratios of recurrence ($P < 0.06$, OR: 0.352), this may be explained by the assumption that those patients were subjected to closer care and prompt stabilization of their clinical status. Meanwhile, the majority of them had shorter total hospital LOS and LOS before diagnosis (≤7 days) (i.e., early diagnosed) that were statistically associated with lower rates of rCDI ($P = 0.04$) and ($P = 0.02$), respectively. The contrary was concluded by Lofgren and colleagues, who found that patients who suffered CDI experienced more extended hospitalization and ICU admissions. They need greater attention to prevent poor clinical outcomes [35]; the same was supported by other studies [36,37].

Many researchers statistically correlated uncontrolled underlying diseases to rCDI [38,39]. In our work, we investigated the impact of many underlying comorbid conditions: chronic kidney (CKD) and hepatic failures (CHF), diabetes mellitus (D.M.), and malignancies; we could not correlate them to rCDI, due to the scarcity of patients with complicated or uncontrolled chronic conditions among our cohort. Malignancies, D.M., CHF, CKD tend to show statistically non-significant high odds of rCDI, which could be emphasized with bigger populations, like been reported with other studies that statistically correlated IBD colectomy to rCDI [33,40,41]. Do et al. [42], Abdelfatah et al. [43] and fellows particularly correlated renal impairment to rCDI, ($P < 0.01$) and ($P = 0.04$), respectively. A multivariate analysis of 149 immunocompromised patients showed a higher incidence of rCDI compared to a control group [44].

Excessive exposure to certain antibiotics remains influential in the occurrence and recurrence of CDI; in the univariate model, we found a relationship between prior exposure to clindamycin ($P < 0.01$, OR: 3.4), concurrent use of aztreonam ($P < 0.03$, OR: 7.5) and rCDI, this effect vanished using a multivariate stepwise logistic model. In a similar statistical model, Karaoui et al. found that fluoroquinolone exposure was the only predictor of recurrence (OR = 2.9) [45]. While, Castro-Cordova related severity of recurrence episode to clindamycin and B-lactams use [46], another Japanese study concluded the use of probiotics, antibiotics, PPIs, and chemotherapy as a statistically significant risk factor for recurrence [22]. Some even concluded that patients admitted to a bed previously occupied by other patients exposed to antibiotics appeared to be at risk for CDI ($P < 0.01$) [47]. The emergence of a statistical significance for prior exposure to clindamycin and the concomitant use of aztreonam as a risk factor for recurrence of *C. difficile* infections in our study is an affirmation of an interfering opportunity for the antimicro-

bial stewardship team to rationalize the use of these antibiotics in elderly patients at risk of acquiring *C. difficile* infections.

As all treatment regimens in our study were concordant with Infection Diseases Society of America IDSA guidelines [48], minimal rates of complications have emerged during treatment (5/204 patients develop ileus or toxic megacolon), and no impact on recurrence was noticed. A study conducted by Texas university hospital concluded that patients who received guideline-concordant therapy were less likely to experience complications nor recurrences ($P < 0004$) [49]. A Japanese study enrolled 3250 patients with rCDI, found that treatment with metronidazole at the index episode contributes to 90% of rCDI [22]. Our findings represent a live proof of better outcomes related to adherence to guidelines in treating CDIs.

We found no statistical relation between rCDI and PPI administration. Meanwhile, other studies significantly correlated PPIs use with relapses ($P = 0.029$), with no impact on case severity nor LOS ($P = 0.55$) [50], which can be explained by the inclusion of long-term users of PPIs in their studies.

WBC at discharge ($\leq 9.85 \times 10^3$) was an independent risk factor associated with rCDI ($P < 0.01$, OR: 3.1067), which can be explained by the high percentage of patients with underlying comorbidities within this group (73%). Altered count and the impaired response of WBC due to underlying diseases play an essential role in the immune response against *C. difficile* infection [51]. Patients who suffer low WBC are less able to fight infection, which explains the post-discharge recurrence. Thus, patients suffering low WBC count due to bone marrow problems, immune disorders, spleen problems, infections, or exposure to certain types of drugs should undergo more in-depth large-scale studies to determine this confounder's effect on exposure to *C. difficile* infections.

Our study's limitations include data collection from a single center with only one geographic location and the study's retrospective nature dictating the sample size. However, being a tertiary care teaching hospital widens the scope of patient characteristics and improves the results' generalizability.

## Conclusion

Patient demographics, treatment history, and laboratory findings available to clinicians at the time of diagnosis could be used for outcome prediction and risk stratification to select patients who may need closer monitoring or more aggressive CDI treatment. Endorsement of CDI patient's discharge should be done after conducting laboratory investigations or other investigational procedures that prove the steadiness in their health conditions. (CBC, stool culture, Ultrasound abdomen. . .).

Patients subjected to prior or concurrent treatment with aztreonam or clindamycin may require close monitoring by the antimicrobial stewardship team for the risk of rCDI

## Author Contributions

Diaa Alrahmany contributed to data analysis and writing of the manuscript. Benjamin Ereshfsky contributed to data collection, data analysis, and writing the manuscript. Wasim S. El Nekiedy contributed to data analysis and writing of the manuscript. Gehan Harb and Laura Pontiggia contributed to statistical analysis. Islam M. Ghazi contributed to the study conception, data collection, data analysis, and writing of the manuscript.

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## Institutional review board

Expedited approval was obtained for data collection.

## Informed consent statement

Informed consent was waived as the study only involves retrospective data collection with no active interventions on patients.

## Competing interests

None declared

## Ethical approval

Not required.

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