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# Evaluation of factors associated with fatality in hospitalized patients with *Clostridioides difficile* infection

# Hastanede yatan *Clostridioides difficile* enfeksiyonu olan hastalarda fatalite ile ilişkili faktörlerin değerlendirilmesi

**Çetin. Mortality in CDI**

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**Abstract**
**Introduction:** *Clostridioides difficile* typically arises from changes in the microbiota following antibiotic use and can be fatal, especially in hospitalized patients. This study investigates fatality and associated factors following *C.difficile* infection in hospitalized patients.
**Materials and Methods:** In this case-control study, the case group consists of deaths within 30 days, while the control group consists of survivors. Demographic and clinical data were compared between the two groups. Risk factors for 30-day fatality were analyzed using logistic regression and Kaplan-Meier survival analysis.
**Results:** A total of 67 adult patients were included in the study. All-cause mortality occurred in 14 (20.9%) patients within the 30 days of diagnosis. Procalcitonin>0.5 ng/mL at the onset of the episode [OR: 7.407 (1.487 - 39.906)], ongoing antibiotic therapy for infections other than *C.difficile* infection after the onset of a *C.difficile* infection episode [OR: 5.927 (1.053 - 33.357)], and the occurrence of *C.difficile* infection in the intensive care unit [OR: 4.800 (1.066 – 21.609)] were identified as independent risk factors for all-cause 30-day fatality. The impact of these three variables on 30-day fatality was also demonstrated using Kaplan-Meier survival analysis (log-rank test, $p<0.05$).
**Conclusion:** In conclusion, *C.difficile* infection that develops in hospitalized patients is significant due to its potential to cause mortality. The onset of *C.difficile* infection during an intensive care unit stay and elevated procalcitonin levels at the onset of the episode may be predictors of poor outcomes. The management of antibiotic use leading to *C.difficile* infection following its development may improve survival.
**Keywords:** *Clostridioides difficile*, fatality, procalcitonin

**Özet**
**Giriş:** *Clostridioides difficile* sıklıkla antibiyotik kullanımı sonrası mikrobiyotadaki değişiklikler sonucu gelişmektedir ve özellikle hastanede yatan hastalarda fatal olabilir. Çalışmamızda hastanede yatarak takip edilen hastalarda *C.difficile* enfeksiyonu sonrası gelişen ölüm oranı ve ilişkili faktörler araştırılmıştır.
**Gereç ve yöntem:** Bu vaka-kontrol çalışmasında vaka grubunu 30 gün içinde ölenler, kontrol grubunu ise hayatta kalanlar oluşturmaktaydı. İki grup arasında, demografik ve klinik veriler karşılaştırıldı. 30-günlük fatalite için risk faktörleri lojistik regresyon analizi ve Kaplan-Meier sağkalım analizi ile araştırıldı.
**Bulgular:** Toplam 67 erişkin hasta çalışmaya dahil edildi. Tanıdan sonraki 30 gün içinde 14 (%20.9) hastada tüm nedenlere bağlı ölüm meydana geldi. Atak başlangıcında prokalsitonin>0,5 ng/mL olması [OR:7,407 (1,487 – 39,906)], *C.difficile* enfeksiyonu tanısı sonrası *C.difficile* enfeksiyonu dışındaki enfeksiyonlar için devam eden antibiyotik tedavisi [OR:5,927 (1,053 – 33,357)] ve *C.difficile* enfeksiyonu atağının yoğun bakım ünitesinde gelişmesi [OR:4,800 (1,066 – 21,609)] tüm sebeplere bağlı 30-günlük fatalite için bağımsız risk faktörleri olarak saptandı. Bu üç değişkenin 30-günlük fatalite üzerine etkisi Kaplan-Meier sağkalım analizi ile de gösterildi (log-rank testi, $p<0,05$).
**Sonuç:** Sonuç olarak hastanede yatan hastalarda gelişen *C.difficile* enfeksiyonu ölüme sebep olabilmesi nedeniyle önemlidir. *C.difficile* enfeksiyonu atağının yoğun bakım ünitesinde yatarken gelişmesi ve atak başlangıcındaki prokalsitonin yüksekliği, kötü sonuçlar için öngördürücü olabilir. *C.difficile* enfeksiyonu atağına sebep olan antibiyotik kullanımının, *C.difficile* enfeksiyonu gelişimi sonrası uygun yönetimi sağkalıma fayda sağlayabilir.
**Anahtar kelimeler:** *Clostridioides difficile*, fatalite, prokalsitonin

## Introduction

*Clostridioides difficile* (*C.difficile*) is a Gram-positive anaerobic bacteria that causes antibiotic-associated diarrhea. *C.difficile* infection (CDI) is characterized by colitis that frequently develops due to disruptions in the gut flora following antibiotic use. Antibiotics impair the barrier function of the normal colonic microbiota, providing an environment for *C.difficile* proliferation and toxin production (1). Other reported risk factors for CDI include advanced age, history of hospitalization, cancer chemotherapy, gastrointestinal surgery, inflammatory bowel diseases, and gastric acid suppression (2-5).

In studies including data on diarrhea causes in different regions, *C.difficile* was reported among the most common agents (6-9). *C.difficile* is a significant cause of hospital-acquired diarrhea. Extensive antibiotic use, gastrointestinal procedures, medications that suppress gastric acid increase the frequency of the disease in hospitalized patients. The development of CDI in hospitalized patients can lead to prolonged hospital stay, increased cost, morbidity, and most importantly, mortality. Previous studies have reported 30-day all-cause mortality rates following CDI ranging from 8% to 20% (10-12). Clinical variables such as advanced age, immunosuppression, and comorbid conditions, as well as laboratory parameters including high white blood cell count, elevated creatinine, low albumin, and infection with ribotype 027, have been associated with CDI-related mortality (13-16). This study aimed to determine fatality rates and risk factors for 30-day fatality in hospitalized CDI patients, thereby contributing to the development of approaches to reduce CDI-related mortality.

## Materials and Methods

### Study Design and Population

This study was conducted at xxx Training and Research Hospital between September 2021 and December 2024. The institution is a tertiary care hospital located in xxx, xxx. The hospital has a total of 450 beds (85 intensive care unit beds), providing care to a wide range of patients, including those with various comorbidities such as cancer. Adult patients who developed acute diarrhea (three or more loose stools within 24 hours) during hospitalization and had *C.difficile* detected in stool samples using gastrointestinal polymerase chain reaction (PCR) testing were included. Patients younger than 18 years of age, those who were unable to provide stool samples for *C.difficile* testing, and those with incomplete medical records or who were transferred to other hospitals during the study period were excluded from the analysis. Patient data were retrospectively collected from electronic hospital records. Age, gender, hospitalization unit (ward or intensive care unit), Charlson comorbidity index, history of proton pump

inhibitor use, statin use, corticosteroid use, hospitalization in the last three months, gastrointestinal procedures (esophagogastroscopy or colonoscopy) in the last two months, prior antibiotic use in the last two months (if any, the specific class), severity of CDI, ongoing antibiotic therapy for infections other than CDI after the onset of a CDI episode, antibiotic treatment for CDI, laboratory values at CDI onset (white blood cell count, creatinine, procalcitonin), and 30-day all-cause mortality were recorded. Patients were categorized into two groups based on the occurrence of 30-day fatality, and their demographic and clinical data were compared to identify independent risk factors for 30-day fatality in a case-control study. The case group included patients who died within 30 days following the diagnosis of CDI, while the control group included those who survived beyond this period.

**Definitions**

Severe CDI was defined by a white blood cell count exceeding 15,000 cells/μL, serum creatinine above 1.5 mg/dL, or serum albumin below 3 g/dL at the onset of a CDI episode. Immunosuppression was defined as undergoing chemotherapy for malignancy, using immunosuppressive biological agent for systemic autoimmune disease, or receiving corticosteroid at a dose equivalent to ≥20 mg/day of prednisone for at least 14 days. In a patient who developed diarrhea due to *C.difficile* during hospitalization, the continued antibiotic therapy initiated for an infection other than CDI cause (pneumonia, urinary tract infection, bacteremia, surgical site infection, etc.) in the pre-diarrhea period after diarrhea was defined as ongoing antibiotic therapy for infections other than CDI.

**Microbiology**

Stool samples from hospitalized patients with acute diarrhea were analyzed using the QIAstat-Dx Analyzer 1.0 (Qiagen N.V., Hilden, Germany) and QIAstat-Dx Gastrointestinal Panel 2 (Qiagen N.V., Hilden, Germany) with multiplex real-time PCR. Patients whose samples tested positive for *C.difficile* toxin A and B genes via this method were classified as having CDI.

**Statistical Analysis**

Statistical analysis was performed using IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics included mean, standard deviation, percentage, and median (minimum-maximum). The Kolmogorov-Smirnov test was used to assess the normality of numerical variables. Independent samples t-test was used for variables with normal distribution, and the Mann-Whitney U test was used for variables without normal distribution to compare numerical variables. The chi-square or Fisher's exact test was used to compare categorical variables. Variables with $p<0.05$ in univariable analysis were included in a multivariable logistic regression model (backward:LR) to determine independent risk factors for 30-day fatality. Kaplan-Meier survival analysis was used to evaluate the impact of these risk factors on survival, and differences were compared using the log-rank test. The sample size was not calculated, all patients diagnosed with CDI who met the inclusion criteria were included. A p-value<0.05 was considered statistically significant.

**Ethics**

The study was approved by the Scientific Research Ethics Committee of xxx Training and Research Hospital with the date and decision number 19.02.2025/06.

**Results**

During the study period, 67 adult patients who developed acute diarrhea during hospitalization and were found to have *C.difficile* in gastrointestinal PCR testing were included in the study. The mean age of the study population was 75.5±15.8 years (range: 22–100). Thirty-seven (55.2%) were male. The most frequently observed comorbidities were hypertension, coronary artery disease, and chronic kidney disease. A total of 62 patients (92.5%) had used antibiotics within the last two months before the CDI episode, with cephalosporins and beta-lactam/beta-lactamase inhibitors being the most frequently used antibiotic groups. The rate of CDI episodes occurring in the intensive care unit was 26.9%, and the rate of severe CDI was 62.7%. The medications used for CDI treatment were metronidazole (61.2%), oral vancomycin (28.4%), and a combination of these two drugs (10.4%). Leukocyte count, creatinine, and procalcitonin levels were higher in the fatality group; however, statistical significance was found only for procalcitonin. A comparison of patients' demographic, clinical, and laboratory values was shown in Table 1.

Among all patients, 14 (20.9%) died within 30 days after the CDI episode. In the 30-day fatality group, intensive care unit-onset CDI, severe CDI, ongoing antibiotic therapy for infections other than CDI after the onset of a CDI episode, and elevated procalcitonin levels were more common (p-values were 0.004, 0.009, 0.002, and 0.004, respectively).

In the logistic regression model that included intensive care unit-onset CDI, severe CDI, continued antibiotic treatment for infections other than CDI after the onset of a CDI episode, and procalcitonin>0.5 ng/mL, the following were identified as independent risk factors for 30-day fatality: procalcitonin>0.5 ng/mL [OR: 7.407 (1.487–39.906)], continued antibiotic treatment for infections other than CDI after the onset of a CDI episode [OR: 5.927 (1.053–33.357)], intensive care unit-onset CDI [OR: 4.800 (1.066–21.609)] (Table 2). Kaplan-Meier survival analysis results showed that intensive care unit-onset CDI, continued antibiotic treatment for infections other than CDI after the onset of a CDI episode, and procalcitonin≥0.5 ng/mL had a significant impact on survival time (log-rank test, $p<0.05$). The Kaplan-Meier survival analysis curves for these three risk factors are shown in Figure 1.

**Discussion**

CDI is a significant nosocomial infection in hospitalized patients and can lead to mortality. In this study, 30-day fatality rates and fatality-associated risk factors were analyzed in 67 hospitalized patients diagnosed with CDI. The 30-day fatality rate was 20.9%, which is similar to the rates reported in studies involving hospitalized CDI cases (12,17,18). In our study, the onset of CDI during an intensive care unit stay, severe CDI episode, ongoing antibiotic therapy for infections other than CDI after the onset of a CDI episode, and elevated procalcitonin level were more frequently observed in patients with fatal outcomes. In logistic regression analysis, intensive care unit-acquired CDI, continuation of antibiotic therapy for infections other than CDI, and elevated procalcitonin level were recognized as an independent risk factors for 30-day fatality. The impact of these variables on 30-day survival was also evaluated using Kaplan-Meier survival analysis. Examination of survival curves showed a significant survival disadvantage in patients with these risk factors.

Although current guidelines recommend oral vancomycin or fidaxomicin as first-line therapies for CDI, the majority of patients in our cohort received metronidazole, due to the limited availability of these drugs and suboptimal adherence to guidelines. Oral vancomycin was available but used only 38.8% of cases, whereas fidaxomicin was not accessible at our center during the study period. These findings reflect real-world challenges in resource-limited settings and may have influenced treatment decisions.

The association of CDI with increased all-cause mortality and the higher mortality rate in hospital-acquired CDI have been previously reported (19,20). This finding highlights CDI as a critical cause of mortality and a significant healthcare concern, especially among hospitalized patients. Previous studies have identified risk factors for 30-day mortality in these patients, including advanced age, malignancy, Charlson comorbidity index, elevated serum creatinine, intensive care unit admission, high leukocyte count, and low albumin levels (18,21,22). The mean age of our patient population was generally high, with only eight patients under 60 years old. Consequently, although the median age was higher in the fatality group, statistical significance was not observed in our already older cohort. Laboratory findings such as leukocyte count and creatinine were also higher in the fatality group but did not show statistical significance. No differences were observed between the two groups in terms of comorbid conditions or Charlson comorbidity index. Because the overall sample size was limited, our study is susceptible to a type II error; therefore, the lack of statistical significance for variables that have been associated with mortality in larger cohorts should be interpreted with caution, as it may reflect insufficient power rather than a true absence of association.

In our study, intensive care unit-acquired CDI was identified as an independent risk factor that increased 30-day fatality by 4.8 times. This result may be explained by intensive care unit patients typically having more comorbidities, undergoing invasive procedures, and receiving broad-spectrum antibiotics more frequently. Similar findings in the literature indicate that intensive care unit-acquired CDI cases have higher mortality rates (23,24). Additionally, factors such as immunosuppression, gastrointestinal stress, and a higher incidence of sepsis in critically ill patients may contribute to worse prognoses in intensive care unit-acquired CDI cases. Furthermore, nutritional deficiencies common among intensive care unit patients may also be additional factors increasing mortality. Another identified risk factor for fatality was the ongoing antibiotic therapy for infections other than CDI after the onset of a CDI episode, which increased fatality risk by approximately 5.9 times. It has been previously demonstrated that antibiotics disrupt

the gut microbiota, promoting *C.difficile* proliferation, increasing toxin production, and weakening the intestinal barrier function (1). Continuing the use of antibiotics that triggered CDI after its onset may create a vicious cycle, leading to a more severe and persistent disease and worse clinical outcomes. The use of broad-spectrum antibiotics, in particular, is a significant factor contributing to CDI recurrence and mortality. Therefore, when considering the continuation of causative antibiotics in CDI-diagnosed patients, the necessity of such treatment should be carefully evaluated, and narrow-spectrum agents should be preferred whenever possible.

Procalcitonin can indicate systemic inflammation and the severity of bacterial infections. Previous studies have shown that elevated procalcitonin level can serve as a biomarker for disease severity and complications in various bacterial and even viral infections (25-30). The prognostic value of procalcitonin was investigated by Rao et al., who found that procalcitonin levels in CDI patients were associated with infection severity and were significantly elevated in severe cases (31). Similarly, Dazley et al. reported that procalcitonin could indicate CDI severity, with levels above 0.5 ng/mL showing high sensitivity, specificity, and positive predictive value for severe disease (32). In more recently published studies investigating the relationship between procalcitonin and mortality, it has also been reported that procalcitonin may be useful in predicting mortality in the course of CDI (33,34). In our study, procalcitonin level above 0.5 ng/mL was recognized as the strongest risk factor for 30-day fatality, increasing the risk by 7.4 times. Furthermore, Kaplan-Meier survival analysis revealed a significantly reduced survival time in patients with procalcitonin>0.5 ng/mL ($p=0.005$). These findings suggest that procalcitonin is not only an inflammatory marker in CDI patients but may also serve as a prognostic parameter in clinical management. Additionally, patients with high procalcitonin levels may require more aggressive treatment and closer monitoring.

**Study Limitations**

Our study has some limitations, including its retrospective design, single-center nature, and limited sample size. As a single-center study, its generalizability may be restricted. Another limitation of this study is that the comparison between the two groups was not performed in a matched or one-to-one manner with respect to risk factors, comorbidities, and other baseline characteristics. In addition, the study did not adjust for certain potential confounding factors, such as the time interval between hospital admission and initiation of antibiotic therapy, due to inconsistent availability of this data in the medical records.

**Conclusion**

In this study, intensive care unit-acquired CDI, continuation of antibiotic therapy that triggered CDI after a CDI episode, and high procalcitonin level were identified as independent risk factors for fatality. The strengths of our study include the use of multivariable regression analysis to identify factors associated with 30-day fatality and the reassessment of these variables using Kaplan-Meier survival analysis. These findings highlight the importance of managing antibiotic therapy following CDI onset. Additionally, initial and follow-up measurement of procalcitonin level may be useful in assessing disease progression. Close monitoring and aggressive treatment strategies for intensive care unit-acquired CDI episodes may contribute to improved survival. Larger, multicenter studies will provide valuable contributions to the understanding of this subject.

**Conflict of Interest:** The author stated that there are no conflicts of interest.
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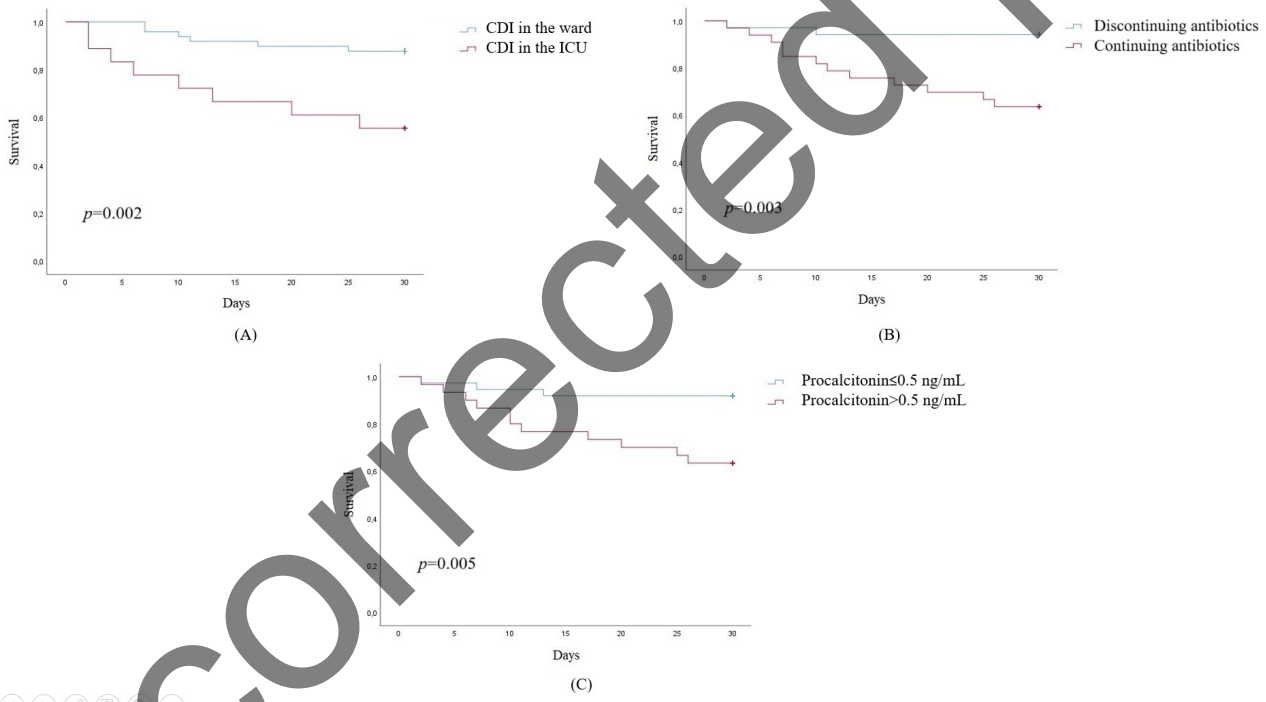


Figure 1. Kaplan-Meier survival curves demonstrating the effect of (A) *Clostridioides difficile* infection onset in the intensive care unit, (B) continued antibiotic use for infections other than *Clostridioides difficile*, and (C) elevated procalcitonin levels on 30-day fatality

Table 1. Comparison of demographic data and clinical characteristics of patients with fatality and survivors

| | Died within 30 days (n=14) | Survived (n=53) | P |
|---|---|---|---|
| Age, median (min-max) | 86 (22 – 100) | 78 (29 – 96) | 0.177 |
| Female gender, n (%) | 9 (64.3) | 21 (39.6) | 0.099 |
| CDI episode in ICU, n (%) | 8 (57.1) | 10 (18.9) | **0.004** |
| CCI, median (min-max) | 5.5 (0 – 9) | 5 (0 – 10) | 0.666 |
| Hypertension, n (%) | 11 (78.6) | 35 (66.0) | 0.369 |
| Diabetes mellitus, n (%) | 6 (42.9) | 12 (22.6) | 0.129 |
| Coronary artery disease, n (%) | 5 (35.7) | 24 (45.3) | 0.520 |
| Congestive heart failure, n (%) | 0 (0.0) | 7 (13.2) | 0.151 |
| Chronic pulmonary disease, n (%) | 2 (14.3) | 12 (22.6) | 0.494 |
| Malignancy, n (%) | 1 (7.1) | 13 (24.5) | 0.155 |
| Immunosupression, n (%) | 2 (14.3) | 13 (24.5) | 0.414 |
| Chronic kidney disease, n (%) | 5 (35.7) | 16 (30.2) | 0.692 |
| Hemodialysis, n (%) | 1 (7.1) | 3 (5.7) | 0.835 |

| | | | |
|---|---|---|---|
| Cerebrovascular disease, n (%) | 6 (42.9) | 11 (20.8) | 0.091 |
| Dementia, n (%) | 3 (21.4) | 5 (9.4) | 0.218 |
| PPI use, n (%) | 9 (64.3) | 27 (50.9) | 0.373 |
| Hospitalization in the last 3 months, n (%) | 11 (78.6) | 38 (71.7) | 0.606 |
| GI procedure in the last 2 months, n (%) | 1 (7.1) | 13 (24.5) | 0.155 |
| Statin use, n (%) | 3 (21.4) | 14 (26.4) | 0.703 |
| Corticosteroid use, n (%) | 2 (14.3) | 4 (7.5) | 0.432 |
| Antibiotic use in the last 2 months, n (%) | 13 (92.9) | 49 (92.5) | 0.959 |
| Cephalosporin use, n (%) | 10 (71.4) | 28 (52.8) | 0.212 |
| Beta-lactam/beta-lactamase inhibitor use, n (%) | 4 (28.6) | 20 (37.7) | 0.525 |
| Fluoroquinolone use, n (%) | 0 (0.0) | 6 (11.3) | 0.187 |
| Carbapenem use, n (%) | 1 (7.1) | 12 (22.6) | 0.192 |
| Severe infection, n (%) | 13 (92.9) | 29 (54.7) | **0.009** |
| Continued antibiotic use for infections other than CDI after CDI diagnosis, n (%) | 12 (85.7) | 21 (39.6) | **0.002** |
| Metronidazole treatment, n (%) | 9 (64.3) | 32 (60.4) | 0.790 |
| Oral vancomycin treatment, n (%) | 3 (21.4) | 16 (30.2) | 0.518 |
| Metronidazole and oral vancomycin combined treatment, n (%) | 2 (14.3) | 5 (9.4) | 0.598 |
| WBC, median (min-max) | 13.44 (2.77 – 23.28) | 8.59 (0.44 – 27.56) | 0.060 |
| Creatinine, median (min-max) | 1.84 (0.19 – 4.25) | 0.98 (0.34 – 7.72) | 0.367 |
| Procalcitonin, median (min-max) | 1.58 (0.17 – 49.80) | 0.35 (0.08 – 17.66) | **0.002** |
| Procalcitonin>0.5 ng/mL, n (%) | 11(78.6) | 19 (35.8) | **0.004** |

CCI: Charlson comorbidity index, CDI: *Clostridioides difficile* infection, GI: Gastrointestinal, ICU: Intensive care unit, PPI: Proton pump inhibitor, SD: Standard deviation, WBC: White blood cell

Table 2. Univariable and multivariable logistic regression analyses of risk factors associated with 30-day fatality

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| | OR (95% CI) | p | OR (95% CI) | p |
| CDI episode in ICU | 5.733 (1.622 – 20.263) | 0.007 | 4.800 (1.066 – 21.609) | 0.041 |
| Severe infection | 10.759 (1.311 – 88.265) | 0.027 | - | - |
| Continued antibiotic use for infections other than CDI after CDI diagnosis | 9.143 (1.855 – 44.056) | 0.007 | 5.927 (1.053 – 33.357) | 0.044 |
| Procalcitonin>0.5 ng/mL | 6.561 (1.627 – 26.464) | 0.008 | 7.407 (1.487 – 39.906) | 0.015 |

CDI: *Clostridioides difficile* infection, CI: Confidence interval, ICU: Intensive care unit, OR: Odds ratio