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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 İlişkili Faktörlerin Değerlendirilmesi

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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. In this study, we investigated fatality and the associated factors following *C. difficile* infection (CDI) in hospitalized patients.
Materials and Methods: This case-control study included death cases within 30 days, with a corresponding control group comprising survivors. Demographic and clinical data were compared between the two groups. The risk factors for 30 day fatality were analyzed through logistic regression and Kaplan-Meier (KM) survival analysis.
Results: A total of 67 adult patients were enrolled. All-cause mortality occurred in 14 (20.9%) patients within 30 days of diagnosis. Procalcitonin level >0.5 ng/ml at the onset of the episode [odds ratio (OR): 7.407, confidence interval (CI) 1.487-39.906], ongoing antibiotic therapy for infections other than CDI after the onset of a CDI episode (OR: 5.927, CI 1.053-33.357), and the occurrence of CDI in the intensive care unit (ICU) (OR: 4.800, CI 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 demonstrated through KM survival analysis (log-rank test, p<0.05).
Conclusion: The occurrence of CDI in hospitalized patients warrants special attention owing to its potential to cause mortality. The onset of CDI during an ICU stay and elevated procalcitonin levels at the onset of the related episode may predict poor outcomes. The management of antibiotic use cases leading to CDI following its development may improve survival chances.
Keywords: *Clostridioides difficile*, fatality, procalcitonin

Öz

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. Otuz günlük fatalite için risk faktörleri lojistik regresyon analizi ve Kaplan-Meier (KM) 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 [olasılık oranı (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 KM 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

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Introduction

Clostridioides difficile is a Gram-positive anaerobic bacterium causing 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 a normal colonic microbiota, thereby providing an environment for *C. difficile* proliferation and toxin production[1]. The 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].

Studies on diarrhea causes across regions have implicated *C. difficile* among the most common agents[6-9]. *C. difficile* is also a significant cause of hospital-acquired diarrhea. Extensive antibiotic use, gastrointestinal procedures, and medications that suppress gastric acid increase the frequency of this disease among 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 presence of comorbid conditions, as well as laboratory parameters including high white blood cell count, elevated creatinine level, low albumin level, and ribotype 027 infection, have been associated with CDI-related mortality[13-16].

In this study, we aimed to determine the fatality rates and associated risk factors for 30-day fatality in hospitalized CDI patients so as to contribute to the design of approaches toward reducing CDI-related mortality.

Materials and Methods

Study Design and Population

This study was conducted at Giresun Training and Research Hospital, a tertiary care hospital (approval number: 19.02.2025/06, date: 20.02.2025), between September 2021 and December 2024. The hospital has a total of 450 beds [85 intensive care unit (ICU) beds], providing care to a wide range of patients, including those with various comorbidities such as cancer. Adult patients who developed acute diarrhea (characterized by three or more loose stools within 24 h) during hospitalization and with positive *C. difficile* detection in stool samples through gastrointestinal polymerase chain reaction (PCR) were included. Patients aged <18 years, 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 the hospital's electronic records. Age, gender, hospitalization unit (ward or ICU), Charlson Comorbidity Index, use history of proton pump inhibitor, statin, and corticosteroid, hospitalization in the last 3 months, gastrointestinal procedures (such as esophagogastroscopy or colonoscopy) in the last 2 months, prior antibiotic use in the past 2 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. The patients were categorized into two groups based on the occurrence of 30 day fatality, and their demographic and clinical data were compared to identify the independent risk factors for 30 day fatality in a case-control study. The case group included patients who died within 30 days following CDI diagnosis, whereas the control group included patients who survived beyond this period.

Definitions

Severe CDI was characterized by a white blood cell count of >15,000 cells/µl, serum creatinine level >1.5 mg/dl, or serum albumin level <3 g/dl at the onset of a CDI episode. Immunosuppression was defined as undergoing chemotherapy for malignancy, the use of an immunosuppressive biological agent for systemic autoimmune disease, or receiving corticosteroids 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 those induced by CDI (such as pneumonia, urinary tract infection, bacteremia, and surgical site infection) 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.) with multiplex real-time PCR. Patients who 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 the mean, standard deviation, percentage, and median (minimum-maximum). The Kolmogorov-Smirnov test was performed to assess the normality of numerical variables. Independent sample t-test was applied for variables showing a normal distribution, and the Mann-Whitney U-test was performed for variables without normal distribution to

compare the numerical variables. The chi-square or Fisher's exact test was performed 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 (KM) survival analysis was performed to evaluate the impact of these risk factors on survival, and the differences were compared using the log-rank test. The sample size was not calculated, and all patients diagnosed with CDI who met the inclusion criteria were enrolled. p<0.05 was considered to indicate statistical significance.

Results

During the study period, 67 adult patients who developed acute diarrhea during hospitalization and tested positive for *C. difficile* in gastrointestinal PCR testing were enrolled in the study. The mean age of the study population was 75.5±15.8 (range: 22-100) years. Of the total, 37 (55.2%) were male. The most frequently observed comorbidities included hypertension, coronary artery disease, and chronic kidney disease. A total of 62 (92.5%) patients had used antibiotics within the last 2 months before the occurrence of 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 ICU was 26.9%, whereas that of severe CDI was 62.7%. The medications used for CDI treatment were metronidazole (61.2%), oral vancomycin (28.4%), and their combination (10.4%). leukocyte count and the levels of creatinine and procalcitonin were higher in the fatality group; however, statistical significance was detected only for procalcitonin. A comparison of patients' demographic, clinical, and laboratory values is shown in Table 1.

Among all patients, 14 (20.9%) died within 30 days after the CDI episode. In the 30-day fatality group, ICU-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 cases of ICU-onset CDI, severe CDI, continued antibiotic treatment for infections other than CDI after the onset of a CDI episode, and procalcitonin level >0.5 ng/ml, the following were identified as independent risk factors for 30 day fatality: procalcitonin level >0.5 ng/ml [odds ratio (OR): 7.407, confidence interval (CI) 1.487-39.906], continued antibiotic treatment for infections other than CDI after the onset of a CDI episode (OR: 5.927, CI 1.053-33.357), ICU-onset CDI (OR: 4.800, CI 1.066-21.609) (Table 2). KM survival analysis revealed that ICU-onset CDI, continued antibiotic treatment for infections other than CDI after the onset of a CDI episode, and procalcitonin level ≥0.5 ng/ml had a significant impact on the survival time (log-rank test, p<0.05). The KM survival analysis curves for these three risk factors are depicted in Figure 1.

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

	Died within 30 days (n=14)	Survived (n=53)	p-value
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

Table 1. Continued

	Died within 30 days (n=14)	Survived (n=53)	p-value
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, min.-max.: Minimum-maximum, 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-value	OR (95% CI)	p-value
CDI episode in the 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

Discussion

CDI is a significant nosocomial infection occurring in hospitalized patients that can lead to mortality. In this study, the 30 day fatality rates and the 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 ICU 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 having fatal outcomes. In logistic regression analysis, ICU-acquired CDI, continuation of antibiotic therapy for infections other than CDI, and elevated procalcitonin level were recognized as independent risk factors for 30 day fatality. The impact of these variables on 30 day survival was also evaluated through KM survival analysis. The examination of survival curves revealed a significant survival disadvantage among patients with these risk factors.

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

Past studies have also reported the association of CDI with increased all-cause mortality and the higher mortality rate in hospital-acquired CDI[19,20]. These findings highlight CDI as a critical cause of mortality and a significant healthcare concern, especially among hospitalized patients. Previous studies have

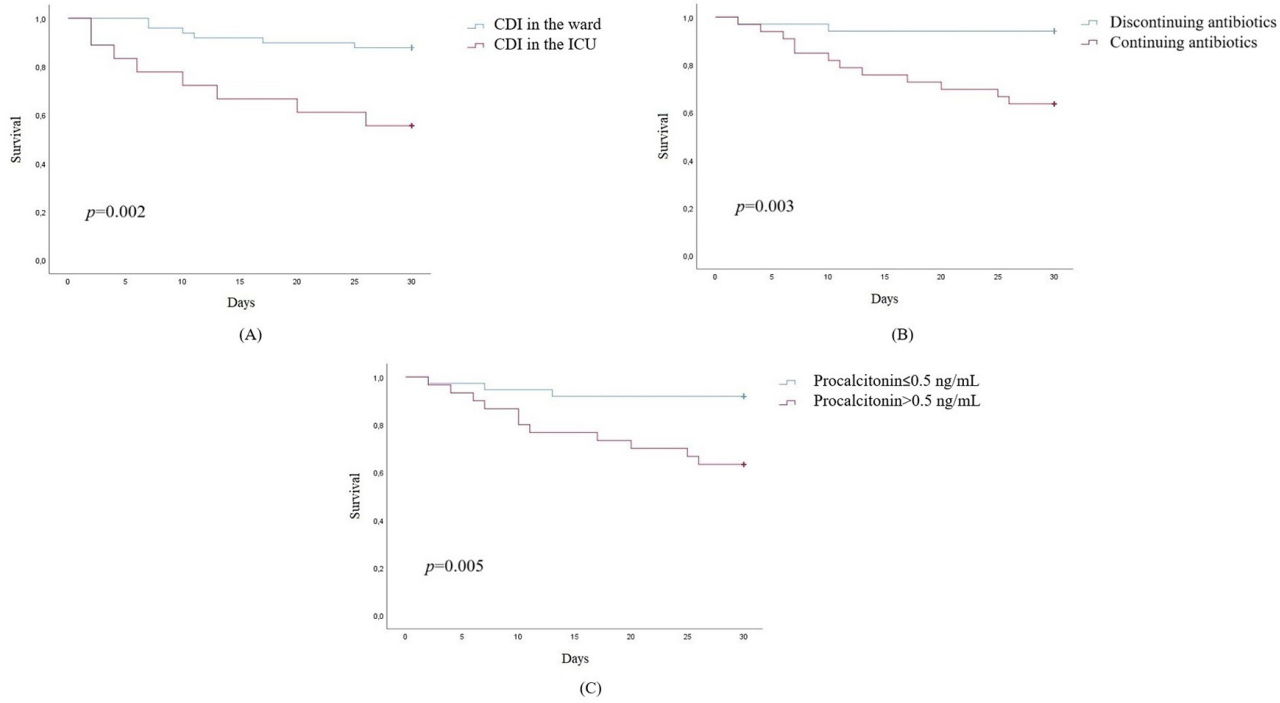

Figure 1. Kaplan-Meier survival curves demonstrating the effect of (A) *Clostridioides difficile* infection onset in the intensive care unit, (B) continued antibiotic use for infections other than *C. difficile*, and (C) elevated procalcitonin levels on 30 day fatality

identified risk factors for 30 day mortality in these patients, including advanced age, malignancy, Charlson Comorbidity Index, elevated serum creatinine levels, ICU admission, high leukocyte count, and low albumin levels[18,21,22]. The mean age of our patient population was relatively high, with only 8 patients aged <60 years. Consequently, although the median age was higher in the fatality group, no statistical significance was observed in our already older cohort. Laboratory findings such as the leukocyte count and creatinine level were also higher in the fatality group, albeit without any statistical significance. No differences were observed between the two groups in terms of comorbid conditions or the Charlson Comorbidity Index. In our study, ICU-acquired CDI was identified as an independent risk factor that increased 30 day fatality by 4.8 times, which may be explained by the fact that ICU patients typically have more comorbidities, undergo invasive procedures, and receive broad-spectrum antibiotics more frequently. Similar findings in the literature have indicated that ICU-acquired CDI cases have higher mortality rates[23,24]. In addition, factors such as immunosuppression, gastrointestinal stress, and a higher incidence of sepsis in critically ill patients may contribute to worse prognoses in ICU-acquired CDI cases. Furthermore, nutritional deficiencies are common among ICU patients may be additional factors that increase the mortality rate. Another identified risk factor for fatality was an ongoing antibiotic therapy for infections other than CDI after the onset of a CDI episode, which increased the fatality risk by approximately 5.9 times. Previously, it was 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 trigger CDI after its onset may create a vicious cycle, resulting in a more severe and persistent disease and worse clinical outcomes. The application of broad-spectrum antibiotics, particularly, 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, with a preference for narrow-spectrum agents.

Procalcitonin can indicate systemic inflammation and the severity of bacterial infections. In the past, it has been shown that elevated procalcitonin levels can serve as a biomarker for disease severity and complications in different bacterial and viral infections[25-30]. The prognostic value of procalcitonin investigated by Rao et al.[31] revealed that the procalcitonin levels in CDI patients were associated with infection severity and were significantly elevated in severe cases. Similarly, Dazley et al.[32] reported that procalcitonin could indicate CDI severity, with levels >0.5 ng/ml indicating high sensitivity, specificity, and positive predictive value for severe disease. In more recently published studies investigating the relationship between procalcitonin level and mortality, procalcitonin was found useful in predicting mortality during CDI[33,34]. In our

study, a procalcitonin level >0.5 ng/ml emerged as the strongest risk factor for 30 day fatality, increasing the overall risk by 7.4 times. Furthermore, KM survival analysis revealed a significantly reduced survival time among patients with procalcitonin level >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. In addition, 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. Moreover, the comparison between the two groups could not be performed in a matched or one-to-one manner concerning 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 the initiation of antibiotic therapy, due to the inconsistent availability of related data in the medical records. Furthermore, as the overall sample size was limited, our study could have been susceptible to a type II error; therefore, the lack of statistical significance for variables associated with mortality in larger cohorts should be interpreted with caution, as it may reflect insufficient power rather than a true absence of association.

Conclusion

Thus, ICU-acquired CDI, continuation of antibiotic therapy that triggers CDI after a CDI episode, and high procalcitonin levels act 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 KM survival analysis. These findings highlight the importance of managing antibiotic therapy following CDI onset. In addition, the initial and follow-up measurement of procalcitonin levels may help in assessing the disease progression. Close monitoring and aggressive treatment strategies for ICU-acquired CDI episodes may thus contribute to improved survival. Larger, multicenter studies are expected to provide valuable contributions to the deeper understanding of this subject.

Ethics

Ethics Committee Approval: This study was conducted at Giresun Training and Research Hospital, a tertiary care hospital (approval number: 19.02.2025/06, date: 20.02.2025), between September 2021 and December 2024.

Informed Consent: Retrospective study.

Footnotes

Financial Disclosure: The authors declared that this study received no financial support.

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