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Clinical characteristics of patients with *Clostridium difficile* infection and its relationship with fecal occult blood test

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Abstract

Clostridium difficile infection (CDI) is an important health problem with severe morbidity and mortality. In our study, 266 adult patients admitted to the hospital between the years 2005 and 2020, and were diagnosed with CDI were included. The relationship between CDI and fecal occult blood test (FOBT) was examined, and it was aimed to determine the clinical characteristics of CDI patients and risk factors for mortality and recurrence in these patients. FOBT was found to be positive in 42.8% of our CDI patients who underwent FOBT. Pseudomembranous enterocolitis (PME) developed in 2.2% and toxic megacolon developed in 0.8% of our patients. It was found that 10.2% of the CDI patients died within 30 days and 5.2% of the CDI patients had a recurrence. In our study, a significant relationship was found between mortality and advanced age, FOBT negativity, presence of hospitalization history. In addition, a significant relationship was found between recurrence and FOBT positivity, presence of PME. We believe that the data documented in this study are important because these data reveal both the clinical characteristics of CDI patients and its relationship with FOBT.

Keywords: clostridium difficile infection, fecal occult blood test, pseudomembranous enterocolitis, toxic megacolon

1. Introduction

Clostridium difficile (C. difficile) is a fecal-orally transmitted, gram-positive, spore- forming anaerobic bacillus that can be found in the stools of healthy individuals. *Clostridium difficile* infection (CDI) is the most common cause of nosocomial diarrhea and has recently become an important clinical problem. The overall clinical picture caused by *C. difficile* is spread across a wide range of spectrum; from asymptomatic colonization to mild diarrhea, pseudomembranous enterocolitis (PME), paralytic ileus, toxic megacolon, and mortality (Gerding et al., 1995).

Use of antiacids, recent antibiotic use (clindamycin, cephalosporin, fluoroquinolone group), advanced age, tube feeding, inflammatory bowel disease and immunosuppression are risk factors for CDI. There are tests such as fecal glutamate dehydrogenase antigen, fecal *C. difficile* toxin A-B, stool culture, nucleic acid amplification methods to detect the presence of CDI. The most commonly used method is to investigate the presence of fecal *C. difficile* toxin A-B by ELISA method. Metronidazole, vancomycin, fidaxomycin, probiotics and fecal implantation can be used in the treatment (Yolken et al., 1982; Bignardi, 1998; Bartlett and Gerding, 2008; Kılıç, 2013).

Fecal occult blood test (FOBT) is a widely used test to screen for malignancy in the gastrointestinal system (GIS) and to detect bleeding in the GIS (Feldman et al., 2016). FOBT can also be detected positive in ischemic, inflammatory and infectious bowel diseases. In this study, the relationship between CDI and FOBT was examined. It was aimed to determine the clinical characteristics of CDI patients and also to determine the risk factors for mortality and recurrence in these patients

2. Materials and methods

This is a retrospective, single-center study conducted at Ondokuz Mayıs University Hospital in Turkey. Our study included 266 adult patients who were admitted to Ondokuz Mayıs University Hospital between the years 2005 and 2020, and diagnosed with the CDI by detecting fecal *C. difficile* toxin A-B by immunochromatographic card test method (Certest Biotec). Patient information was reached using the Nucleus medical information system database. The gender (female-male) and age (>65 and ≤ 65) of the patients were recorded. By reaching the endoscopy (rectosigmoidoscopy or colonoscopy) results of the patients, the presence of PME (yellow-white plaques and membranes that are seen endoscopically) was investigated. By analyzing the clinical characteristics and laboratory findings of the patients, the presence of toxic megacolon (detection of transverse colon diameter> 6 cm by radiological methods and accompanying fever, leukocytosis,

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signs and symptoms of acute abdomen syndrome) was investigated. Hospitalization rates of patients within 14 days before the CDI detection were recorded. The recurrence and 30-day mortality rates of the patients were analyzed. The number and results of the FOBTs which performed by fluorescent immunoassay method (Boditech ichroma) between 2005 and 2020 were reached.

The research data were uploaded and evaluated using IBM SPSS 25 (IBM Statistical Package for Social Sciences). Descriptive statistics of categorical variables are presented as numbers and percentages. For a comparison of categorical variables, using cross tables, Pearson chi-square test, Yates continuity correction or Fisher's exact test were applied. Sub-group ratio test and Bonferonni correction were used for significant results. Statistical significance levels were accepted as $p < 0.05$, $p < 0.01$ and $p < 0.001$.

3. Results

Between the years 2005 and 2020, 16642 FOBTs were performed in adult patients, and 2330 (14%) FOBT positivity were detected. While 113 of 266 patients (42.5%) with CDI who participated in the study were female, 153 of them (57.5%) were male.

While 213 of the patients (80.1%) were equal to or less than 65 years old, 53 of them (19.9%) were older than 65. 91 of the female patients (80.5%) were under or equal to 65 and 122 of the men patients (79.7%) were under or equal to 65. No statistically significant difference was found between age groups according to gender ($p = 0.873$). Descriptive statistics regarding the patients' FOBT results, lower GIS endoscopy findings, presence of PME, presence of toxic megacolon, 30-day mortality, hospitalization within 14 days before CDI detection and presence of recurrence are given in Table 1. According to this; FOBT was not examined in 86 CDI patients (32.3%). FOBT was found to be positive in 77 of CDI patients (42.8%) who were examined. Lower GIS endoscopy was performed in 63 patients (23.7%) and PME was detected in six of these patients (9.5%).

Table 1. Clinical and endoscopic features in patients with *C. difficile* infection

Variables		n (%)
FOBT	Positive	77 (42.8)
	Negative	103 (57.2)
Lower GIS Endoscopy	Performed	63 (23.7)
	Not Done	203 (76.3)
PME	Yes	6 (9.5)
	No	57 (90.5)
Toxic Megacolon	Yes	2 (0.8)
	No	264 (99.2)
Mortality	Yes	27 (10.2)
	No	239 (89.8)
Hospitalization History	Yes	97 (78.8)
	No	26 (21.2)
Recurrence	Yes	14 (5.3)
	No	252 (94.7)

FOBT fecal occult blood test, PME pseudomembranous enterocolitis, GIS gastrointestinal system. Variables are expressed as numbers

Toxic megacolon developed in two patients (0.8%). There were 27 patients (10.2%) who died within 30 days. The hospitalizations of 143 patients (53.8%) were unknown. It was observed that 97 of the patients (78.8%) whose condition was known had a hospitalization history within 14 days before CDI detection.

Table 2. Variables associated with mortality in patients with *C. difficile* infection

		Mortality	No Mortality	p
Gender	Female	10 (8.8)	103 (91.2)	0.690
	Male	17 (11.1)	136 (88.9)	
Age	<=65	17 (8.0)	196 (92.0)	0.036*
	>65	10 (18.9)	43 (81.1)	
FOBT	Positive	7 (9.1)	70 (90.9)	0.045*
	Negative	16 (15.5)	87 (84.5)	
Hospitalization	Yes	24 (24.7)	73 (75.3)	<0.001*
	No	1 (3.8)	25 (96.2)	

FOBT, fecal occult blood test; variables are expressed as numbers (% columns) *p <0.05 or p <0.001

The relationship of the variables with the mortality is given in Table 2. A significant relationship was found between the 30-day mortality and the age, FOBT results, hospitalizations of the patients.

The 30-day mortality rate in the patients was 10.2%. While 8% of patients aged 65 and under were mortal, this rate was 18.9% for patients over 65 years old ($p = 0.036$). While 9.1% of patients with positive FOBT result were mortal, this rate was 15.5% in FOBT negative patients ($p = 0.045$). While 24.7% of patients who had a history of hospitalization within 14 days before CDI detection ended with mortality, this rate was 3.8% in patients without a history of hospitalization ($p < 0.001$). In other words, mortality was found to be significantly higher in patients with advanced age, FOBT negativity and a history of hospitalization. The relation of variables with recurrence is given in Table 3. Accordingly, the recurrence rate was found to be 5.2%. A statistically significant relationship was found between recurrence and FOBT positivity, presence of PME. Recurrence developed in 11.7% of the patients with positive FOBT result, while this rate was 2.9% in FOBT negative patients ($p = 0.011$). While 33.3% of the patients with PME have recurrence, this rate was 15.8% in patients without PME ($p < 0.001$).

4. Discussion

C. difficile infection is a serious health problem with an increasing prevalence around the world, causing serious morbidity and mortality. Its clinical picture can vary widely, from asymptomatic carriage to sepsis and mortality (Gerding et al., 1995). FOBT is an inexpensive and easily accessible test that can be used in GIS malignancies, GIS bleeding, inflammatory and infective bowel pathologies (Feldman et al., 2016). In our center, 16642 FOBTs were applied to adult patients between the years 2005 and 2020. 2330 FOBT results (14%) were positive. Between the years 2005 and 2020, the number of patients with *C. difficile* toxin A-B positive was 266.

FOBT was examined in 180 of CDI patients and 77 of them were found to be positive. As a result, CDI was detected in 77 of 2330 patients who were positive for FOBT. In other words, CDI was detected in 3.3% of FOBT positive patients. There is no study investigating the relationship between CDI and FOBT in the Turkish and English literature, so our findings could not be compared.

Determination of mortality rate and factors affecting mortality in CDI is decisive for the prognosis. In the study conducted in Canada, one-year mortality in CDI was found to be 37%; in another study, the 180-day mortality was found to be 5.7% (Pépin et al., 2005; Dubberke et al., 2008). In the study conducted by Shorr et al., involving an elderly patient population, it was reported that 30-day mortality was 10% and one-year mortality was 19% (Shorr et al., 2016). In the study conducted by Nanwa et al., it was reported that one-year mortality was determined as 13% (Nanwa et al., 2017). In the study conducted in Asian pacific countries, 60-day mortality in CDI patients was found to be 5.2% (Collins et al., 2020). In the study conducted in Taiwan, 30-day mortality was found to be 23.4%; and the presence of malignancy, high glucose level, 1.5-fold increase in serum creatinine were determined as independent risk factors affecting mortality (Chiang et al., 2019). Chopra et al. found that, the presence of a history of malignancy or organ transplant, a history of hospitalization in the last 60 days, long-term antibiotherapy, presence of nasogastric tube or parenteral nutrition and rectal enema were found as risk factors determining the 30-day mortality (Chopra et al., 2016). In our study, the 30-day mortality rate of the CDI patients was found to be 10.2%. A significant relationship was found between 30-day mortality and the age, FOBT results, hospitalizations of the patients. Patients with advanced age (> 65), negative FOBT result and a history of hospitalization in the last 14 days before CDI detection had a more mortal prognosis. Although our data are similar to the literature, there is no study in the literature investigating the relationship between FOBT and mortality in CDI. Not knowing the comorbid diseases of the patients and the drugs they used is seen as the deficiency of the study in interpreting this result. Unlike other studies mentioned above, our study concluded that advanced age affects mortality.

PME is a clinical picture characterized by leukocytosis, diarrhea, high fever and abdominal pain, in which pseudomembranes that can settle in the bowel, most frequently in the rectosigmoid region, as a result of inflammation caused by *C. difficile* toxins in the intestinal mucosa. Pseudomembranes appear as small, yellowish-white raised plaques or nodules (Tedesco et al., 1974). Toxic megacolon is a rare clinical picture of CDI that causes dilatation in the intestinal segments and systemic toxicity with severe morbidity and mortality. In one study, four of 207 patients with a diagnosis of CDI (1.9%) had PME (Musher et al., 2005). In the study conducted in Asia-Pacific countries, the incidence of toxic megacolon in CDI patients was found to be 0.2% (Collins et al., 2020), while this rate was found to be 0.4% and 3% in other studies (Berman et al., 2008; Earhart, 2008). In our study, it was observed that six patients (2.2%) developed PME and two patients (0.8%) developed toxic megacolon. In this sense, our data are similar to the literature.

CDI patients are known to have a recurrence rate of 20–35% (Neemann and Freifeld, 2017). In the study conducted in Asia Pacific countries, the recurrence rate in CDI patients was found to be 9.1%. Continuing to use antibiotics, using antacids and advanced age are known as risk factors for the development of recurrent CDI (Kılıç, 2013; Collins et al., 2020). The recurrence rate in our study was found to be 5.2%. Unlike the literature, no significant relationship was found between age and the development of recurrence. A statistically significant relationship was found between recurrence and FOBT positivity, presence of PME.

In conclusion; both the frequency and the severity of CDI have recently increased all over the world and it has become an important health problem. There are well-defined risk factors for the disease and it is important for clinicians to evaluate patients based on these risk factors. We believe that the data documented in this study are important because these data reveal both the clinical characteristics of patients with CDI in our region and their relationship with FOBT, which is a common test. Our findings need to be supported by new studies to be planned with a large patient population

Conflict of interest

All authors declare no conflict of interest regarding this manuscript.

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No competing financial interests exist.

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