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Original Article

Clinical characterization and risk factors of *Clostridium difficile* infection in elderly patients in a Chinese hospital

Zhang Lihua*, Dong Danfeng*, Jiang Cen, Wang Xuefeng, Peng Yibing

Department of Laboratory Medicine, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

* Both authors contributed equally to this work.

Abstract

Introduction: *Clostridium difficile* is a common cause of nosocomial diarrhea, especially in elderly patients. This study aimed to analyze the clinical features and assess the risk factors associated with *Clostridium difficile* infection (CDI) in elderly hospitalized patients.

Methodology: A retrospective case-control study was conducted among elderly hospitalized patients (> 60 years of age) in a Chinese tertiary hospital between 2010 and 2013. Fifty-two CDI patients and 150 randomly selected non-CDI patients were included in the study. Clinical features of CDI and non-CDI patients were compared by appropriate statistical tests. Logistic regression analyses were performed on a series of factors to determine the risk factors for CDI among the elderly hospitalized patients.

Results: The elderly CDI patients showed higher leukocyte counts, lower serum albumin levels, longer duration of hospital stay, and higher mortality compared to the non-CDI patients. The proportion of patients admitted to the intensive care unit or exposed to gastric acid suppressants was also significantly different ($p < 0.05$) between the two groups. Multivariate analysis indicated that serum creatinine (OR 1.004; 95% CI 1.001–1.008), surgical intervention (OR 6.132; 95% CI 2.594–14.493), the number of comorbidities (OR 2.573; 95% CI 1.353–4.892), gastrointestinal disease (OR 4.670; 95% CI 2.002–10.895), and antibiotic use (OR 6.718; 95% CI 2.846–15.859) were independently associated with CDI.

Conclusions: This study revealed several risk factors for CDI among elderly hospitalized patients. These findings will increase the knowledge concerning this disease and provide information regarding the control and prevention of CDI in the elderly.

Key words: *Clostridium difficile* infection; elderly; risk factors; epidemiology.

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Introduction

Clostridium difficile has become one of the most common pathogenic causes of hospital-acquired diarrhea since the appearance of the first report on this pathogen in the late 1970s. The clinical manifestations of *Clostridium difficile* infection (CDI) vary from mild diarrhea to serious complications such as pseudomembranous colitis and toxic megacolon [1]. The last decade witnessed a great change in the epidemiology of CDI throughout the world, especially in Europe and North America [2]. Meanwhile, increases in the incidence of this disease also occurred in some Asian countries [3,4]. The high recurrence rate, mortality, and broad geographical distribution of this disease have aroused increasing levels of concern among medical workers.

The pathogenic strains of *C. difficile* secrete two main toxins, toxin A and toxin B, which mediate *C. difficile*-associated colitis and diarrhea [5]. The genes encoding toxin A (*tcdA*) and toxin B (*tcdB*) are located in the pathogenicity locus, and the expressions of *tcdA* and *tcdB* are negatively regulated by the *tcdC* gene. The epidemic hypervirulent strain, designated as PCR ribotype 027, has partial deletions in *tcdC* that may contribute to the hyperproduction of toxins A and B and thus cause severe disease [6,7].

It has been hypothesized that constant use of antibiotics may lead to significant reductions in the normal intestinal flora that allow *C. difficile* to colonize and possibly cause disease [8]. CDI contributes to the increases in the morbidity and mortality of elderly patients with different underlying diseases whose intestinal flora have been disrupted by the prior use of antibiotics. Elderly patients are well recognized as a high-risk population for CDI because their immunosenescence, high exposure to antibiotics, and frequent or prolonged hospitalizations increase the

opportunities for hosts to come into contact with the pathogen [9,10].

In recent years, researchers have sought to determine the risk factors for CDI. Studies of this topic have been carried out in different countries [11-13]. However, few reports have focused on CDI in China. We conducted a case-control study among elderly hospitalized patients in a Chinese tertiary hospital to determine if there are any relationships between patients' clinical characteristics and their CDI status. We aimed to assess the risk factors that are associated with CDI in elderly hospitalized patients to provide a basis for the control and prevention of *C. difficile*-associated diseases in this population.

Methodology

Patient characteristics

The discharge summaries of all elderly hospitalized patients (> 60 years of age) at Ruijin Hospital (Shanghai, China) between December 2010 and May 2013 involved in this study were retrospectively reviewed. Demographics, clinical features, and in-hospital medications for each inpatient were collected from the patients' medical records for further analysis. Patient demographics included age, gender, and area one lived in (urban or rural). The clinical features included temperature, laboratory results (leukocyte count, serum albumin level, and serum creatinine level), ileus, surgical intervention (in the previous six months), intensive care unit (ICU) admission, duration of hospital stay, mortality, and comorbidities. Laboratory results were measured at the CDI diagnosis for the case patients, and for the controls, they were measured on admission. Comorbidities were divided into the following ten categories: gastrointestinal disease, liver disease, gall bladder, biliary tract or pancreatic disease, respiratory disease, cardiovascular disease, renal disease, neurological disease, hematologic or immunologic disorder, malignancy, and metabolic disorder. Moreover, patients' in-hospital medications (including antibiotics, gastric acid suppressants, and chemotherapy) in the two months prior to the CDI diagnosis for case patients and two months prior to admission for controls were also recorded.

This study was approved by the ethics committee of Ruijin Hospital. Patients' informed consent was not required by the review board because this study did not interfere with the patients.

Case definitions and control patients

The diagnoses of CDI were based on a combination of clinical and laboratory findings. CDI was defined as the presence of diarrhea and a stool test that was positive for the toxigenic *C. difficile* [14]. Diarrhea was defined as the passage of three or more unformed stools within 24 hours. The presence of *C. difficile* toxins A and B in the feces was detected by enzyme-linked fluorescence assay (ELFA) with a VIDAS automatic analyzer (Biomerieux, Marcy-l'Etoile, France). The epidemiological associations of CDI were divided into three types: healthcare facility-associated cases (*i.e.*, the symptoms developed after 48 hours of admission or within 4 weeks after discharge from a healthcare facility), community-associated cases (*i.e.*, the patient had not been admitted to a healthcare facility in the previous 12 weeks), and cases of indeterminate association (*i.e.*, the symptoms occurred between 4 and 12 weeks after discharge from a healthcare facility) [15].

The control group was composed of 150 patients who were randomly selected from among all the elderly patients (> 60 years of age) admitted to the hospital during the study period and had no known history of CDI.

Statistical analyses

The results are expressed as medians and quartiles for continuous variables and as frequencies and percentages for categorical variables. To examine differences in the demographics, clinical characteristics, and in-hospital medications between the CDI patients and the controls, the Wilcoxon rank-sum test was used for continuous data because these data were not normally distributed, and the Chi-square test or Fisher's exact test were used for categorical data where appropriate. Univariate and multivariate analyses were performed on a number of factors to assess whether those factors were relevant to CDI status. Statistically non-significant variables ($p > 0.05$) were removed from the multivariate logistic regression model in a stepwise manner. Odds ratios (ORs) with 95% confidence intervals (95% CIs) are presented for the logistic regression analyses.

Statistical assessments were two-tailed, and a probability level of < 0.05 was considered significant. All analyses were performed with SAS, version 8.1.

Table 1. Characteristics of CDI patients and controls

Characteristic	CDI patients (n = 52)	Controls (n = 150)	P value
Age (years)	73.5 (64.5–82)	72 (65–78)	0.289
Female gender	17 (32.7)	49 (32.7)	0.997
Area patient lives in			
Urban	51 (98.1)	147 (98.0)	1.000
Rural	1 (1.9)	3 (2.0)	
Clinical features			
Fever (≥ 38°C)	13 (25.0)	12 (8.0)	0.001*
Leukocyte count (10^9/L)	7.5 (5.2–10.7)	6.1 (4.7–7.8)	0.012*
Leukocyte count ≥ 15×10^9/L	5 (9.6)	4 (2.7)	0.051
Serum albumin (g/L)	29 (27–34.5)	34 (30–37)	0.001*
Serum creatinine (μmol/L)	69 (56.5–101.5)	72 (61–91)	0.678
Serum creatinine rise > 50%	8 (15.4)	5 (3.3)	0.005*
Ileus	5 (9.6)	4 (2.7)	0.051
Surgical intervention in previous six months	30 (57.7)	42 (28.0)	0.0001*
ICU admission [a]	16 (30.8)	13 (8.7)	< 0.0001*
Duration of hospital stay (days)	18 (11.5–29)	11 (7–17)	< 0.0001*
Mortality	9 (17.3)	4 (2.7)	0.0002*
No. of comorbidities [b]			
1–2	11 (21.1)	76 (50.7)	
3–4	29 (55.8)	65 (43.3)	< 0.0001*
≥ 5	12 (23.1)	9 (6.0)	
Comorbidities by category			
Gastrointestinal disease	24 (46.2)	24 (16.0)	< 0.0001*
Liver disease	11 (21.2)	23 (15.3)	0.334
Gall bladder, biliary tract or pancreatic disease	5 (9.6)	14 (9.3)	1.000
Respiratory disease	17 (32.7)	31 (20.7)	0.079
Cardiovascular disease	32 (61.5)	85 (56.7)	0.540
Renal disease	9 (17.3)	20 (13.3)	0.481
Neurological disease	14 (26.9)	25 (16.7)	0.106
Hematologic or immunologic disorder	7 (13.5)	16 (10.7)	0.585
Malignancy	12 (23.1)	31 (20.7)	0.714
Metabolic disorder	15 (28.9)	30 (20.0)	0.187
Medications			
Antibiotic	35 (67.3)	46 (30.7)	< 0.0001*
Cephalosporin	24 (46.2)	34 (22.7)	0.001*
Fluoroquinolone	9 (17.3)	5 (3.3)	0.002*
Carbapenem	10 (19.2)	10 (6.7)	0.009*
β-lactam/β-lactamase inhibitor compound	9 (17.3)	7 (4.7)	0.007*
Gastric acid suppressant [c]	25 (48.1)	39 (26.0)	0.003*
Chemotherapy	11 (21.2)	18 (12.0)	0.105

Numerical data are given as medians (interquartile range), and categorical data are described as frequencies (percentage).
* $P < 0.05$; [a] ICU: intensive care unit; [b] The variable "no. of comorbidities" was made categorical, and Cochran-Armitage trend test was used to analyze the difference in this variable between the two groups; [c] Proton pump inhibitors or histamine-2 blocker

Results

Patient population

Two hundred and two elderly hospitalized patients were involved in the study, and 52 of these patients met the criteria for the diagnosis of CDI. Of these 52 cases, 44 (84.6%) were healthcare facility-associated CDI, 5 (9.6%) were community-associated CDI, and the other 3 (5.8%) CDI cases had indeterminate associations. The CDI patients had a median age of 73.5 years (interquartile range [IQR], 64.5–82 years), and the control group consisted of 150 patients with a median age of 72 years (IQR, 65–78 years).

Clinical features

As shown in Table 1, the proportions of patients who had fevers when the disease occurred were significantly different between the CDI and control groups ($p < 0.05$). Moreover, increased leukocyte counts and decreased serum albumin levels were found to be associated with CDI ($p < 0.05$). Although the serum creatinine levels were only slightly different between the two groups, more patients in the case group than in the control group exhibited a > 50% rise in serum creatinine levels ($p < 0.05$). Five patients (9.6%) with CDI and four patients (2.7%) in the control group suffered from ileus, and this difference was not statistically significant ($p = 0.051$). Additionally, 57.7% of the CDI patients and 28.0% of the controls had undergone surgery in the previous six months ($p = 0.0001$). A much larger proportion of the CDI patients than the controls were admitted to the ICU (30.8% versus 8.7%, respectively, $p < 0.0001$). Hence, previous surgical interventions and ICU admissions during hospitalization may be highly relevant to CDI.

For the CDI patients, the median hospital stay duration was 18 days (IQR, 11.5–29 days), and five of these patients (9.6%) were in the hospital for more than 60 days. For the controls, the median hospital stay duration was 11 days (IQR, 7–17 days), and two (1.3%) of these patients stayed in the hospital for over 60 days. There was a statistically significant difference ($p < 0.0001$) between the CDI patients and controls in the duration of hospital stays (see Table 1). Additionally, a total of 13 patients died within the study period; 9 (17.3%) of these were in the CDI group, and only 4 (2.7%) were in the control group. In-hospital mortality was significantly higher among the CDI patients than among the controls ($p = 0.0002$).

Comorbidities

The patients' comorbidities were divided into 10 disease categories that are displayed in Table 1. There was a large difference in the number of comorbidities between the groups ($p < 0.0001$). The patients with CDI had more comorbidities than did the controls. The main underlying diseases of the CDI patients were cardiovascular diseases (61.5%), gastrointestinal

Table 2. Risk factors for CDI in elderly patients

Variable	Univariate analysis		Multivariate analysis [a]	
	P value	OR (95% CI) [b]	P value	OR (95% CI)
Age	0.2337	1.024 (0.985–1.064)	-	-
Fever	0.0014	3.833 (1.620–9.071)	-	-
Leukocyte count	0.0193	1.072 (1.011–1.136)	-	-
Serum albumin	0.0110	0.932 (0.883–0.984)	-	-
Serum creatinine	0.0342	1.003 (1.000–1.006)	0.0118	1.004 (1.001–1.008)
Ileus	0.0368	3.883 (1.001–15.057)	-	-
Surgical intervention	0.0001	3.507 (1.821–6.754)	< 0.0001	6.132 (2.594–14.493)
ICU admission	< 0.0001	4.684 (2.066–10.621)	-	-
Duration of hospital stay	0.1028	1.006 (0.999–1.014)	-	-
No. of comorbidities [c]	< 0.0001	3.044 (1.809–5.120)	0.0040	2.573 (1.353–4.892)
Gastrointestinal disease	< 0.0001	4.500 (2.238–9.048)	0.0004	4.670 (2.002–10.895)
Antibiotic use	< 0.0001	4.655 (2.369–9.146)	< 0.0001	6.718 (2.846–15.859)
Cephalosporin	0.0013	2.924 (1.503–5.691)	-	-
Fluoroquinolone	0.0006	6.070 (1.932–19.073)	-	-
Carbapenem	0.0091	3.333 (1.300–8.550)	-	-
β-lactam/β-lactamase inhibitor compound	0.0037	4.276 (1.504–12.156)	-	-
Gastric acid suppressant	0.0033	2.635 (1.369–5.073)	-	-
Chemotherapy	0.1056	1.968 (0.860–4.503)	-	-

[a] A stepwise logistic regression model was used for multivariate analysis. Statistically non-significant variables ($p > 0.05$) were removed from the model;
[b] OR, odds ratio; 95% CI, 95% confidence interval; [c] The variable "no. of comorbidities" was made categorical.

diseases (46.2%), and respiratory diseases (32.7%); these diseases were present in 56.7%, 16.0%, and 20.7% of the controls, respectively. Most of the underlying diseases were not significantly associated with CDI status ($p > 0.05$), with the exception that the CDI patients seemed to be more likely to suffer from underlying gastrointestinal diseases ($p < 0.0001$).

Medications

Of the 52 patients with CDI, 35 (67.3%) had been exposed to antibiotics within the two months prior to the CDI diagnosis, whilst only 46 (30.7%) of the controls had been exposed to antibiotics during the two months prior to admission ($p < 0.0001$). The most commonly received antimicrobial agents among both groups were cephalosporins, and cephalosporin use was significantly different between the case and control groups ($p = 0.001$). Additionally, fluoroquinolones had been used by a greater proportion of the CDI patients than the non-CDI patients ($p = 0.002$). The usage of carbapenems and β-lactam/β-lactamase inhibitor compounds was also significantly different between the groups ($p = 0.009$ and 0.007, respectively). Other antibiotics that were administered to the patients are not shown in Table 1; these data were not subjected to statistical analysis due to the small numbers of patients who had received these antibiotics. The CDI patients had more exposure to gastric acid suppressants than did the controls ($p = 0.003$). The difference in the proportions of patients who had received chemotherapy did not reach statistical significance ($p = 0.105$).

Risk factors

Patient variables, including clinical characteristics and medications, were examined for associations with CDI. Univariate analysis identified a number of factors that were significantly associated with the patients' CDI status (see Table 2). Multivariate analysis was subsequently performed on these variables via a stepwise logistic regression model. As demonstrated in Table 2, the following risk factors included in the model were independently associated with CDI among elderly hospitalized patients ($p < 0.05$): serum creatinine (OR 1.004; 95% CI 1.001–1.008), surgical intervention (OR 6.132; 95% CI 2.594–14.493), the number of comorbidities (OR 2.573; 95% CI 1.353–4.892), gastrointestinal disease (OR 4.670; 95% CI 2.002–10.895), and antibiotic use (OR 6.718; 95% CI 2.846–15.859).

Discussion

CDI has long been regarded as a nosocomial disease, and its epidemiology has changed over the past two decades. In most cases, the acquisition of CDI is thought to occur during hospitalization. The increased incidence of CDI in healthcare facilities is most likely attributable to the high density of individuals who are prone to CDI, particularly elderly patients. Due to compromised immune statuses and various comorbidities that lead to poor underlying conditions, elderly hospitalized patients are believed to be at high risk for CDI. However, it has been recognized that a number of CDI cases are acquired outside healthcare settings. Reports on community-acquired CDI have revealed alarming trends among young people without nosocomial exposure and peripartum women [1]. Moreover, research has also focused on the incidence and severity of CDI in children [16,17]. According to the 2010 clinical practice guidelines of the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA), leukocytosis and increased serum creatinine levels are used to define the severity of CDI [14]. Our study showed that increased serum creatinine levels were independently associated with CDI in the elderly, which suggests that CDI patients may have renal dysfunction as a result of dehydration or inadequate renal perfusion caused by frequent diarrhea.

Traditionally, risk factors for CDI include advanced age, exposure to healthcare settings, and antibiotic use. Our study focusing on elderly hospitalized patients has validated the notion that prior use of antimicrobial agents is closely related to the occurrence of CDI. Cephalosporins (mainly third- and fourth-generation cephalosporins) were found to be the most frequently used antibiotics in both CDI patients and controls. Univariate analyses indicated that cephalosporins and fluoroquinolones were received more often by the CDI patients than by the controls, which is consistent with the results of a previous study that was conducted in Canada [7]. We also found that CDI patients had more exposure to carbapenems and β-lactam/β-lactamase inhibitor compounds. Research has suggested that broad-spectrum antibiotics strongly affect the survival of intestinal microflora and that the disturbance of normal flora increases the risk of CDI [18]. Fluoroquinolones have been identified as a prominent risk factor for this infection, and their frequent use has been associated with outbreaks of CDI that were caused by ribotype 027 strains [19,20]. It has been reported that patients with gastrointestinal

diseases are more likely to be infected with *C. difficile* [21], which is supported by our findings. We suggest that normal intestinal microflora and microenvironments are likely altered when people acquire gastrointestinal diseases and that these alterations facilitate the colonization and reproduction of certain pathogens such as *C. difficile*. In our study, multivariate analysis showed that surgical intervention (within six months) and the number of comorbidities were significantly associated with CDI in elderly hospitalized patients. These findings can be explained by the poorer underlying conditions and reduced immune functions of these potential CDI patients because *C. difficile* is an opportunistic pathogen. Furthermore, some authors have concluded that exposure to gastric acid suppressants, chemotherapy, immunosuppressive drugs, and nasogastric feeding may increase the risk of CDI [22-24]. Other studies have described the connection between the acquisition of CDI and the length of patients' hospital stays and have come to divergent conclusions [16,23,25].

Our study has several limitations. First, the sample size was relatively small, and the results derived from this single-centre study might not be representative of all hospitals in China due to patient heterogeneity across different institutions. To overcome this weakness, multicenter studies with larger populations should be performed in the future. Second, we recorded the use of antibiotics by these patients within the two months preceding the diagnoses of diseases but did not track antibiotic exposure prior to this period, which may also have affected the occurrence of CDI in these patients. Finally, we found that elderly patients with CDI exhibited higher mortality than did the controls; however, we could not determine whether these deaths were primarily caused by CDI or CDI was only a contributing factor. It is possible that sicker patients with more comorbidities would have worse clinical outcomes regardless of the presence of CDI.

Unlike in Western countries, little is known about *Clostridium difficile* infection in China [8]. Recent studies conducted in Chinese healthcare settings have mainly focused on the antimicrobial resistance of strains or the risk factors and molecular epidemiology of CDI [26-29]. Currently, there are no well-established diagnostic procedures for CDI in our country, due to a lack of clinical awareness. To our knowledge, laboratory methods to test for CDI, such as microbiologic identification, immunologic detection, or polymerase chain reaction (PCR)-based tests, are primarily used for research purposes nationwide. Therefore, more attention should be paid to *C. difficile*-associated diseases, and further studies should be performed to enrich our understanding of CDI in China.

Conclusions

Our study provided a comparison of the clinical features of CDI and non-CDI elderly hospitalized patients and revealed that elevated serum creatinine levels, previous surgical interventions, the number of comorbidities, gastrointestinal diseases, and exposure to antibiotics were significantly associated with CDI among elderly hospitalized patients. It is essential for medical workers to realize the importance of *C. difficile*-associated diseases in elderly patients because they are at a high risk for CDI, and their treatment is often complicated due to different comorbidities. Our findings underscore the need for a combination of antibiotic stewardship, staff training, surveillance of patients' conditions, and appropriate isolation precautions in the prevention and control of this disease in the elderly.

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Authors' contributions

Zhang Lihua participated in the study design, collected the data, performed the statistical analyses, and drafted the manuscript. Dong Danfeng participated in the design of the study and helped to draft the manuscript. Jiang Cen carried out the sample processing and participated in the data analyses. Wang Xuefeng was involved in the study design and coordination. Peng Yibing conceived of the study and helped to revise the manuscript. All authors have read and approved this final manuscript.

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Corresponding author

Peng Yibing, MD
Department of Laboratory Medicine,
Ruijin Hospital, Shanghai Jiaotong University School of Medicine
197 Ruijin No.2 Road
Shanghai 200025, China
Phone: +86 21 6437 0045
Fax: +86 21 6431 1744
Email: pyb9861@sohu.com

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