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ORIGINAL ARTICLE

Observational Study

Did the severe acute respiratory syndrome-coronavirus 2 pandemic cause an endemic *Clostridium difficile* infection?

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Abstract

BACKGROUND

Clostridium difficile infection (CDI) has increased in prevalence during the last years. The coronavirus disease 2019 (COVID-19) pandemic has negatively influenced patient outcomes. The majority of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2)-infected patients received antibiotics during hospitalization.

AIM

To analyze the factors that influenced CDI development after SARS-CoV-2 infection.

METHODS

Between March 2020 to December 2020, we performed a prospective observational study including 447 patients diagnosed with CDI who were admitted to our tertiary referral university hospital. The diagnosis of CDI was based on the presence of diarrhea (≥ 3 watery stools within 24 h) associated with *Clostridium difficile* toxins A or B. We excluded patients with other etiology of acute diarrhea.

RESULTS

Among the total 447 (12.5%) patients with CDI, most were male (54.3%) and mean age was 59.7 ± 10.8 years. Seventy-six (17.0%) had history of COVID-19, most being elderly (COVID-19: 62.6 ± 14.6 years *vs* non-COVID-19: 56.8 ± 17.6 years, P = 0.007), with history of alcohol consumption (43.4% *vs* 29.4%, P = 0.017), previous hospitalizations (81.6% *vs* 54.9%, P < 0.001) and antibiotic treatments (60.5% *vs*

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35.5%, $P < 0.001$), requiring higher doses of vancomycin and prone to recurrent disease (25.0% *vs* 13.1%, $P = 0.011$). Age over 60 years [odds ratio (OR): 2.591, 95% confidence interval (CI): 1.452-4.624, $P = 0.001$], urban residence (OR: 2.330, 95%CI: 1.286-4.221, $P = 0.005$), previous antibiotic treatments (OR: 1.909, 95%CI: 1.083-3.365, $P = 0.025$), previous hospitalizations (OR: 2.509, 95%CI: 1.263-4.986, $P = 0.009$) and alcohol consumption (OR: 2.550, 95%CI: 1.459-4.459, $P = 0.001$) were risk factors of CDI in COVID-19.

CONCLUSION
CDI risk is unrelated to history of SARS-CoV-2 infection. However, previous COVID-19 may necessitate higher doses of vancomycin for CDI.

Key Words: COVID-19 infection; *Clostridium difficile* infection; Risk factors; Antibiotic use; Pandemic; Recurrence

Core Tip: The coronavirus disease 2019 (COVID-19) pandemic was associated with an increased prevalence of *Clostridium difficile* (*C. difficile*) infections. Previous hospitalization and antibiotic treatment are known risk factors for *C. difficile* infection. Patients with a past history of COVID-19 infection, however, required higher doses of vancomycin and were more prone to developing recurrent disease. Rational antibiotic use should be implemented in all patients with COVID-19 infection. Diarrhea is a symptom of COVID-19 infection, which could delay the diagnosis of *C. difficile* infection. All the patients should be tested for *C. difficile* toxins A and B if watery diarrhea develops.

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INTRODUCTION

Since 1978, when *Clostridium difficile* (*C. difficile*) was found to be the cause of pseudomembranous colitis[1,2], numerous epidemiological data have shown that *C. difficile* infection (CDI) is the leading cause of nosocomial infectious diarrhea worldwide[3,4]. Indeed, it is one of the most common healthcare-associated infections[5]. Over the last two decades, there has been a dramatic worldwide increase in both incidence and severity of CDI[6]. In the United States, CDI causes about half a million infections and almost 30000 deaths annually[7]; in Europe, about 152905 people are infected with *C. difficile*, with an annual mortality above 8000 people[8,9]. The increased incidence of CDI, the risk of recurrence and difficult treatment in relapses are associated with high economic costs, which burdens the health system worldwide[1,2]. The prevention of CDI remains a significant concern for health systems, which are actively seeking to prevent outbreaks and maximize patient safety.

The coronavirus disease 2019 (COVID-19) pandemic in 2020 profoundly altered medical practice and introduced multiple challenges for gastroenterologists in approaching patients with digestive diseases, due to the many digestive and hepatic manifestations of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection. Frequently, residual and/or post-infection issues can alter the course of patients with digestive disorders (especially patients with inflammatory bowel disease, advanced liver disease, *etc*.). 2020 has certainly been a challenging year for gastroenterologists; in particular, this pandemic year has profoundly altered medical practice, and has brought multiple challenges in approaching patients with digestive diseases, given that many digestive and hepatic manifestations of SARS-CoV-2 infection, most often residual/post-infection, may alter the course of patients with

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digestive disorders (especially for patients with inflammatory bowel disease, advanced liver disease, *etc.*).

Diarrhea is one of the most common gastrointestinal symptoms in patients with COVID-19, showing a prevalence ranging from 11% to 17%[8,9]. SARS-CoV-2 can actively infect and replicate in the gastrointestinal tract through the angiotensin-converting enzyme 2 receptors disrupting the normal intestinal flora, leading to gastrointestinal symptoms, including diarrhea[9-15]. Before the COVID-19 pandemic the most common cause of diarrhea (excluding inflammation and organic intestinal lesions) was irritable bowel syndrome and functional disorders.

Patients with SARS-CoV-2 infection have numerous risk factors for CDI, including receipt of broad-spectrum antibiotic treatment, hospitalization, elderly age, and existence of multiple comorbidities or immunocompromised status. During the COVID-19 pandemic, many patients received antibiotic treatment, sometimes with no clear indication or as primary prophylaxis for pneumonia[12]. One study showed that 91% of COVID-19 patients received antibiotic treatment[14], but generally over 70% of COVID-19 patients were treated with broad-spectrum antibiotics (mostly respiratory quinolones) in order to treat or to prevent bacterial co-infections and super-infections [13,16,17]. We hypothesized that an increase in CDI incidence and recurrence occurred during the COVID-19 pandemic.

An Italian retrospective study during the COVID-19 pandemic found a significant decrease in the incidence of healthcare-associated CDI in 2020 compared to the previous 3 years (explained by increased pandemic precautions). However, other data showed that COVID-19 departments actually had a higher incidence of CDI compared to non-COVID-19 wards, but upon statistical analysis, the difference did not reach the threshold of significance[4,18].

Considering these contradictory data, the aim of this study was to assess the impact of the COVID-19 pandemic on the characteristics of CDI patients and to analyze the factors that influenced the incidence of CDI during the COVID-19 pandemic.

MATERIALS AND METHODS

Study population

We performed a prospective observational study including patients with CDI between March 2020 to December 2020. We analyzed data from this period because on March 1, 2020, the Clinical Hospital for Infectious Disease Iasi was declared a COVID-19 Unit, and as a result the Institute of Gastroenterology and Hepatology was designated the clinic to hospitalize patients with CDI. The diagnosis of CDI was based on the presence of diarrhea (≥ 3 watery stools within 24 h) associated with detection of *C. difficile* toxin A or B (by enzyme immunoassay) in stool samples[19]. Hospital-acquired CDI was defined as a stool sample positive for *C. difficile* toxin(s) at least 72 h after hospital admission. Each patient's stool was tested only once. We collected demographic data (sex, age, residence), clinical and laboratory parameters, use of antibiotics, information regarding previous hospitalizations, comorbidities, associated medication, previous COVID-19 infection, treatment of CDI, and discharge. CDI data (first episode/relapse and relapse number), length of hospital stay and mortality during admission were also analyzed. The treatment started with vancomycin 125 mg every 6 h, and therapeutic response was defined as the absence of diarrhea after at least 72 h of treatment. We have excluded patients with other etiologies of acute diarrhea.

The study was approved by the Local Medical Ethics Committee (No. 12 /2020/ March 15th, 2020). All patients provided written informed consent before study inclusion or further analysis.

Statistical analysis

Categorical variables were expressed as frequency and percentage. Continuous variables were expressed as mean ± standard variation for normally distributed continuous data. All data were normally distributed. Groups were compared using the χ^2 test for categorical variables and using the independent *t* test or Mann-Whitney *U* test for continuous variables (depending on data distribution). Univariate analysis was performed for each recorded data type. Variables with $P < 0.1$ in univariate analysis were included in the multivariate analysis (logistic regression). The odds ratio (OR) with 95% confidence interval (CI) was calculated for qualitative variables included in the logistic regression. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 20.0 software (IBM Corp., Armonk, NY, United

States).

RESULTS

A total of 3562 patients were admitted to our tertiary hospital during the study period, of whom 447 (12.5%) were diagnosed with CDI. Most of the patients were male (243 patients, 54.3%). The mean age was 59.7 ± 10.8 years, and over half of the patients had previous hospitalizations (266 patients, 59.5%). Baseline characteristics of the patients included in the study are presented in Table 1.

Of all the patients included in the study, 76 (17.0%) had a history of COVID-19. All of the COVID-19 patients were diagnosed with healthcare-associated CDI. Nineteen patients (25.0%) had recurrent CDI. All patients with CDI were treated with vancomycin (125 mg) every 6 h orally. In patients with a history of COVID-19, 26 (34.2%) received an increased dose of vancomycin (250 mg every 6 h for 10 d) and 28 (36.8%) received a high dose of vancomycin (500 mg every 6 h) because they did not respond to the initial dose. In addition, 14 patients (18.4%) received vancomycin enemas. Two patients in the COVID-19 group received fidaxomycin, as they were non-responders to even the maximal doses of vancomycin. Seventeen patients from the COVID-19 group with recurrent CDI received the tapering vancomycin regimen. Compared with the COVID-19 group, the majority of patients with no history of COVID-19 and CDI (302 patients, 81.4%) responded to the conventional doses of vancomycin (125 mg every 6 h for 10 d), and none of these patients needed fidaxomycin.

There was no significant difference in gender and hospitalization days as well as for the inflammatory syndrome between patients with a past history of COVID-19 who developed CDI and those without a history of COVID-19 (Table 1). However, the patients with a history of COVID-19 and CDI had a higher mean age (62.6 ± 14.6 *vs* 56.8 ± 17.6, $P = 0.007$), previous antibiotic treatment (60.5% *vs* 35.5%, $P < 0.001$), previous hospitalizations (81.6% *vs* 54.9%, $P < 0.001$), were chronic alcohol consumers (43.4% *vs* 29.4%, $P = 0.017$) and were more prone to recurrent disease (25.0% *vs* 13.1%, $P = 0.011$). Thirty-one patients (6.9%) died during hospitalization. The mortality rate was similar in both groups (6.6% *vs* 7.0%, $P = 0.893$).

The results of the univariate and multivariate regression analyses are shown in Table 2. The multivariate analysis demonstrated that age more than 60-years-old (OR = 2.59, 95%CI: 1.452-4.624, $P = 0.001$), urban area residence (OR = 2.33, 95%CI: 1.286-4.221, $P = 0.005$), previous antibiotic treatments (OR = 1.90, 95%CI: 1.083-3.365, $P = 0.025$), previous hospitalizations (OR = 2.5, 95%CI: 1.263-4.986, $P = 0.009$) and chronic alcohol consumption (OR = 2.55, 95%CI: 1.459-4.459, $P = 0.001$) were risk factors for CDI development in patients with a history of COVID-19.

DISCUSSION

An increase in the number of CDI cases was expected during the COVID-19 pandemic due to the numerous risk factors of patients with COVID-19 (elderly, multiple comorbidities requiring immunosuppressive treatment, prolonged hospitalization that is frequently in intensive care units, and antibiotic treatment)[5,7,20-22]. Our results demonstrated that 12.5% of patients admitted to our tertiary hospital were diagnosed with CDI. More than half of our patients with CDI had previous hospitalizations, and 17.0% of them were previously hospitalized for COVID-19. We found that all of the COVID-19 patients were diagnosed with healthcare-associated CDI. Our results are completely different from those of an Italian retrospective study during the COVID-19 pandemic that found a significant decrease in the incidence of healthcare-associated CDI in 2020 compared to the previous 3 years[4]. The authors explained that the decrease of CDI was due to increased pandemic precautions.

The growing number of CDI cases is only one of many causes for concern. In recent years, one of the clinical challenges in patients with CDI is recurrent infection, which is often difficult to treat. Recurrent CDI is defined as an episode of CDI occurring within 8 wk of a previous episode[1,22], and it may be due to relapse of the previous CDI by the same strain or reinfection by a different strain[23]. About 15%-30% of CDI patients with an initial response to antimicrobial treatment have a risk of recurrence of the infection, and it is important to note that the risk of further recurrence significantly increases[1]. In our cohort, 19 patients (25.0%) had recurrent CDI.

Table 1 Baseline characteristics of the study groups, *n* (%)

Parameter	Past history COVID-19	Non-COVID-19	*P*
	n = 76	*n* = 371	
Age in yr, mean ± SD	62.6 ± 14.6	56.8 ± 17.6	0.007
Male	35 (46.1)	208 (56.1)	0.110
Country side	18 (23.7)	170 (45.8)	< 0.001
Hospitalization days, mean ± SD	8 (5)	9 (7)	0.094
Alcohol consumption	33 (43.4)	109 (29.4)	0.017
AB during hospitalization	29 (38.2)	154 (41.5)	0.588
Previous AB treatment	46 (60.5)	132 (35.5)	< 0.001
Comorbidities	65 (85.5)	348 (93.8)	0.013
Liver cirrhosis	17 (22.4)	158 (42.6)	0.001
IBD	3 (3.9)	31 (8.4)	0.187
DM	0	16 (4.3)	0.065
Malignancies	8 (10.5)	50 (13.5)	0.486
CKD	5 (6.6)	30 (8.1)	0.656
Previous hospitalizations	62 (81.6)	204 (54.9)	< 0.001
Recurrence	19 (25.0)	50 (13.1)	0.011
Leukocytes, mean ± SD	11320 (8843)	11560 (6650)	0.203
CRP, mean ± SD	2.53 (10.3)	2.52 (10.4)	0.103
Death	5 (6.6)	26 (7.0)	0.893

AB: Antibiotics; CKD: Chronic kidney disease; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; DM: Diabetes mellitus; IBD: Inflammatory bowel disease; SD: Standard deviation.

Table 2 Risk factors for *Clostridium difficile* infection after coronavirus disease 2019

	Univariate analysis			Multivariate analysis		
Parameter	OR	CI	*P*	OR	CI	*P*
Age > 60 yr	2.321	1.455-3.703	< 0.001	2.591	1.452-4.624	0.001
Urban area	1.935	1.273-2.940	0.001	2.330	1.286-4.221	0.005
Previous AB treatments	1.632	1.223-2.178	<0.001	1.909	1.083-3.365	0.025
Previous hospitalizations	2.444	1.503-3.947	< 0.001	2.509	1.263-4.986	0.009
Alcohol consumption	1.248	1.014-1.536	0.017	2.550	1.459-4.459	0.001

AB: Antibiotics; CI: Confidence interval; OR: Odds ratio.

There was no significant difference in gender and hospitalization days as well as for the existence of inflammatory syndrome between patients with a history of COVID-19 that developed CDI and those without a history of COVID-19. However, the patients with a history of COVID-19 and CDI were elderly, were from an urban area, had previous antibiotic use, and were chronic alcohol consumers.

Although the majority of the literature on the epidemiologic features of CDI is based on the association of antibiotic therapy and hospitalization settings[17,24-26], some other potential risk factors for CDI, such as advanced age, immunosuppression, comorbidities, chemotherapy, renal insufficiency, hypoalbuminemia, organ transplantation and use of proton pump inhibitors, have been identified to explain the increased incidence of CDI[7,21,27].

COVID-19 may present as acute diarrhea and abdominal pain. Even in these conditions, with symptoms suggestive for COVID-19, testing for *C. difficile* must be done every time because patients with SARS-CoV-2 infection are patients at high risk for CDI.

Although CDI can affect individuals of all ages, the elderly are recognized as high-risk for this infection[17,27]. Older patients represent a vulnerable population for CDI because they often have multiple comorbidities, have frequent and prolonged hospitalizations, receive broad-spectrum antibiotics, and have altered host defense against infections[27]. At the same time, COVID-19 seems to primarily affect elderly patients, patients who usually have severe forms of the disease, and patients who were frequently treated with antibiotics.

Sandhu *et al*[28] collected data of several studies regarding concomitant antibiotic use in patients with COVID-19 in the United States. Most of these patients received empiric antibacterial therapy with either moxifloxacin, cefoperazone or azithromycin [29]. These antibiotics are known to be strongly associated with CDI, and the authors reported that CDI was due to the overuse of antibiotics in COVID-19 patients[28-31].

We found that chronic alcohol consumption was a risk factor for CDI after COVID-19 infection. Chronic alcohol consumption influences gut microbiota by decreasing the bacterial diversity and increasing intestinal permeability and systemic inflammation [32]. We found no other studies on the increased risk of CDI in chronic alcohol users, but we have two explanations for our result. The first is based upon the fact that almost 40% of our hospitalized patients had liver cirrhosis; the main etiology of which was alcoholism. The second is based upon the numerous data showing that during the pandemic alcohol consumption increased worldwide, sometimes to a worrisome degree[33].

Our study has some strengths and several limitations. This is the first prospective study that characterized CDI after SARS-CoV-2 infection. The identification of risk factors for CDI after COVID-19 highlights the importance of recognizing vulnerable groups, such as the elderly population and patients who consume alcohol. The limitations of our study are represented by the small sample of cases and the fact that our data came from a single-center care unit without information on the *C. difficile* strains. We do not yet have a definite explanation for the fact that patients with CDI after COVID-19 require higher doses of vancomycin.

CONCLUSION

We observed that patients with a history of COVID-19 and CDI were from an urban area, had a higher mean age, had previous antibiotic treatments and hospitalizations, were chronic alcohol consumers, and were more prone to recurrent disease. Also, escalating the doses of vancomycin to obtain the therapeutic effect was another feature of the patients studied. In these patients, the antibiotic treatment for COVID-19 should be personalized in order to diminish the risk of CDI. Further large studies are needed in order to establish if it is cost-effective to start CDI treatment with higher doses of vancomycin in patients with a past history of COVID-19.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) pandemic profoundly altered medical practice and has brought forth multiple challenges for gastroenterologists in handling of patients with digestive diseases, due to the many digestive and hepatic manifestations of COVID-19. Frequently, residual/post-infection issues can alter the course of patients with digestive disorders (especially patients with inflammatory bowel disease, advanced liver disease, *etc*.). *Clostridium difficile* infection (CDI) was also a challenge for gastroenterology during the COVID-19 pandemic.

Research motivation

Many patients diagnosed with COVID-19 have numerous risk factors for CDI, including broad-spectrum antibiotic treatment, hospitalization, elderly age, multiple comorbidities, and immunocompromised status.

Research objectives

The aim of this study was to analyze the factors that influenced CDI development after COVID-19.

Research methods

Between March 2020 to December 2020, we performed a prospective observational study including 447 patients diagnosed with CDI who had been admitted to our tertiary referral university hospital. The diagnosis of CDI was based on the presence of diarrhea (≥ 3 watery stools within 24 h) associated with *C. difficile* toxin A or B.

Research results

Most of the patients in our study were male (54.3%), and showed a mean age of 59.7 ± 10.8 years. Of all the patients included in the study, 76 (17.0%) had a history of COVID-19. The patients with a history of COVID-19 were more likely to be elderly, have a history of alcohol consumption and have previous hospitalizations and antibiotic treatments than the patients without a history of COVID-19. The patients with a history of COVID-19 also needed higher doses of vancomycin and were prone to recurrent disease. Age over 60 years, residence in an urban area, previous antibiotic treatment, and previous and current alcohol consumption were identified as risk factors for CDI development in patients with COVID-19.

Research conclusions

Hospitalizations, antibiotic use and alcohol consumption represent risk factors for CDI development in patients over 60-years-old from an urban area with a history of COVID-19. These patients were at higher risk of recurrence and needed higher doses of vancomycin for CDI treatment.

Research perspectives

Our study highlights the importance of judicious use of antibiotics and recognizing the patients at risk for developing CDI. Future research should focus on the management of patients with CDI after or during COVID-19 in order to improve the prognosis in these patients.

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