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Retrospective Analysis of *Clostridioides difficile* infection Rates in Hospitalized Patients during COVID-19 Pandemic. A Unicenter Study in Reus, Spain

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Abstract: Background: *Clostridioides difficile* infections (CDI) vary in severity from mild diarrhea to life-threatening conditions like pseudomembranous colitis or toxic megacolon, often leading to sepsis and death. The COVID-19 pandemic prompted changes in healthcare practices, potentially affecting CDI incidence, though reported data are inconclusive. We studied factors influencing CDI incidence and outcomes at a university hospital throughout the COVID-19 pandemic years. **Methods:** We conducted a retrospective study on all adult hospitalized CDI cases from January 1, 2020, to December 31, 2022. We collected demographic information, comorbid conditions, and concurrent infections. **Results:** While overall CDI and COVID-19 rates decreased in 2022, a notable increase in CDI infections was observed among oncological patients and those undergoing some aggressive treatments, such as colon or gastroscopies. The prevalence of comorbidities remained unmodified, and there were declines in prior gastrointestinal surgeries and proton pump inhibitor prescriptions. Factors associated with patient fatality or prolonged hospitalization included older age, cancer, chronic kidney disease, higher Charlson and McCabe indices, elevated C-reactive protein, and low albumin concentrations. **Conclusion:** Our study shows the evolving landscape of CDI during the COVID-19 pandemic and emphasizes the impact of delayed diagnoses and treatments exacerbated by telemedicine adoption. Identified risk factors for CDI-related mortality or prolonged hospital stays underscore the importance of targeted interventions in high-risk populations.

Keywords: cancer; clostridioides difficile; COVID-19; infectious diseases; pandemic; risk factors

1. Introduction

Clostridioides difficile is an anaerobic, Gram-positive, spore-forming bacillus that can proliferate in the intestinal lumen and stands as the primary etiological agent of nosocomial diarrhea [1,2]. The pathogenic spectrum of this microorganism gives rise to a variety of illnesses collectively termed *C. difficile* infections (CDI), ranging from uncomplicated diarrhea to severe conditions like pseudomembranous colitis and toxic megacolon, with potential outcomes including sepsis and fatality [3]. CDI represents an enduring and significant global public health concern, typically arising after disturbances in the normal gut microbiota caused by antibiotic usage [4]. Recent reports have

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documented an upsurge in CDI in Spain and other Western countries, attributed to heightened clinical suspicion and enhanced diagnostic sensitivity [5]. According to the VINCat registry (a program of the Health Service of the Autonomous Community of Catalonia that establishes a unified surveillance system for nosocomial infections), the incidence rate increased from 2.20 cases per 10,000 hospital stays in 2011 to 3.41 in 2016 [6,7]. This escalation held statistical significance across all CDI categories, including nosocomial, healthcare-related, and community-acquired. Furthermore, there has been a noteworthy surge in the rate of hospitalizations attributed to CDI, escalating from 3.9 cases per 100,000 persons in 2003 to 12.9 in 2013-2015 [7]. The main risk factors for CDI are antibiotic use, advanced age, environmental contamination, and comorbidities such as gastrointestinal diseases or immunodeficiency [8,9].

The coronavirus disease 2019 (COVID-19) outbreak prompted an extensive reorganization of healthcare services worldwide, with a significant dependence on robust infection prevention and control measures, including stringent adherence to hand hygiene and proper utilization of personal protective equipment. Theoretically, this heightened emphasis on prevention practices may have positively influenced the incidence of CDI and other hospital-acquired infections. Conversely, reallocating resources and efforts towards managing COVID-19 and an upsurge in antibiotic consumption for treating pneumonia and respiratory conditions associated with the virus might have produced a contrary effect [6]. The reported findings are inconclusive, with the majority indicating either no impact or a decrease in CDI rates during the initial wave of COVID-19 [10–16]. Nevertheless, as the pandemic evolved, so too could its impact on CDI incidence. The clinical characteristics of patients with COVID-19 and the treatments received have undergone enormous changes in recent years. While the initial wave of the pandemic witnessed stringent closures, restricted hospital activities, and a notable lack of population protection, recent times have seen a widespread implementation of effective vaccines, well-established medical protocols, more effective treatments, and shorter hospital stays [17–19]. These advancements make it probable that the impact on the incidence of CDI will vary across different pandemic years. As such, we conducted a study to examine the factors influencing the incidence and outcomes of CDI within a university hospital in Reus, Spain, throughout the COVID-19 pandemic years.

2. Materials and Methods

We conducted a retrospective study on all hospitalized CDI cases in our hospital, from January 1, 2020, to December 31, 2022. The facility, belonging to the Hospital Network for Public Use in the Autonomous Community of Catalonia, Spain, accommodates 367 beds dedicated to hospitalization and an Intensive Care Unit with 20 beds. As a general hospital, it serves a population exceeding 175,000 inhabitants, encompassing primary care facilities and elderly residences in the region. Additionally, the hospital assumes the role of a referral center for the disciplines of Oncology and Radiotherapy, catering to the entirety of the Tarragona province, with approximately 550,000 inhabitants.

The sole inclusion criterion was being a hospitalized patient aged 18 years or older, treated in any hospital department, and meeting the CDI case definition specified below. We excluded asymptomatic patients, even if they were carriers of a toxin-producing strain. We also excluded patients with a previous history of CDI or those admitted to palliative care units. We documented demographic information, comorbid conditions, and concurrent acute or chronic infections. The research staff manually collected the clinical and demographic data from the computerized medical records, with team members reviewing the records individually. The McCabe score, which indicates clinical prognosis [20], and the Charlson index, utilized for categorizing patient comorbidities [21], were recorded.

In this report, we use the following definitions:

CDI case: Patient with diarrhea defined as > 3 unformed stools in 24 consecutive hours or less, or toxic megacolon with no other known cause, who has (1) a positive laboratory result for toxin A or B in stool samples or isolation of a toxin-producing strain in stool or detection by molecular

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techniques of a toxin-producing strain; (2) endoscopic, surgical or histological examination that confirms the diagnosis of pseudomembranous colitis.

Nosocomial CDI: CDI identified > 48 h after admission and before discharge.

CDI associated with the health system: CDI beginning in the community or the first 48 hours from admission, identified in patients who have been discharged from a health center (hospital, residence, or social health center) ≤ 4 weeks before the onset of symptoms.

Community-acquired CDI: CDI that begins in the community or within the first 48 hours of admission, identified in patients with no history of admission to a healthcare facility or who have been discharged > 4 weeks before the onset of symptoms.

CDI diagnosis followed the algorithm endorsed by the European Society of Clinical Microbiology and Infectious Diseases [22]. CDI was confirmed with a positive result for both the immunochromatographic detections of glutamate dehydrogenase and toxins A/B (MonlabTest®, Monlab S.L., Cornellà, Spain). Additionally, CDI diagnosis was confirmed in cases where one of the previous results was negative, but a positive result emerged through molecular detection methods. SARS-CoV-2 infection was confirmed by antigen test or reverse transcription-polymerase chain reaction, as previously reported [23].

Data are shown as medians and interquartile ranges or as numbers and percentages. Statistical comparisons between any two groups were done with the Mann-Whitney U test (quantitative variables) or the χ^2 test (categorical variables). Statistical significance was set at $p \leq 0.05$. All calculations were made using the SPSS 25.0 statistical package (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Differential Clinical Characteristics of CDI across Three Years of COVID-19 Pandemics

Table 1 shows the ratio of patients admitted for CDI or COVID-19 in our hospital on the total number of admissions and stays, broken down according to the three years of study. A decrease in the incidence of CDI and COVID-19 per 1,000 admissions was observed in 2022 compared to previous years. The clinical characteristics of the patients are shown in Table 2. Age and sex distribution did not show any major variations. In 2022, the number of patients admitted to the Oncology department significantly rose. Some patients experienced remarkably longer stays in 2021 compared to 2020 or 2022, although differences did not reach statistical significance. No substantial changes were identified in the prevalence of comorbidities. The number of patients with a history of gastrointestinal surgery and those with prescribed proton pump inhibitors declined. Conversely, the number of patients treated with colon or gastroscopy procedures increased in 2021 and stabilized in 2022. In oncological patients, no changes were observed in the type of cancer, its extent, or the therapeutic interventions applied. The ratio of patients with a Charlson index >5 was lower in 2021, and there were no differences in the McCabe index, laboratory results, recurrence rates, or mortality between the observed periods.

Fifty-eight patients were prescribed a single antibiotic, while 68 received a combination of two or more. The predominant antibiotics administered were cephalosporins (49 cases), penicillins and their derivatives (46 cases), monobactams (30 cases), quinolones (25 cases), and linezolid (23 cases).

Table 1. Incidence rate of CDI and COVID-19 by total stays and admitted patients.

Variable	2020	2021	2022	*p* value[1]	*p* value[2]	*p* value[3]
Total stays of adult patients	80,611	87,167	92,594	-	-	-
Total admissions of adult patients	11,299	12,158	14,391	-	-	-
Total number of CDI patients	75	65	69	-	-	-
Total admissions of COVID-19 patients	829	867	841	-	-	-
Rate CDI / 10,000 stays	9.30	7.46	7.45	0.190	0.180	0.993
Rate CDI / 1,000 admissions	6.64	5.35	4.79	0.199	0.049	0.527

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Rate COVID-19 / 10,000 stays	102.84	99.46	90.83	0.489	0.010	0.059
Rate COVID-19 / 1,000 admissions	73.37	71.31	58.44	0.543	< 0.001	< 0.001

[1] Comparing 2020 and 2021; [2] Comparing 2020 and 2022; [3] Comparing 2021 and 2022; The infection rates were determined by dividing the number of cases by the total number of stays or admissions, and then multiplying by 10,000 in the first case and by 1,000 in the second. CDI: *Clostridioides difficile* infection. Statistical significance was calculated by the χ^2 test.

Table 2. Patient clinical and demographic characteristics.

Variable	2020 n = 75	2021 n = 65	2022 n = 69	*p* value[1]	*p* value[2]	*p* value[3]
Age	65.6 (16.4)	64.6 (17.4)	64.3 (21.4)	0.704	0.922	0.762
Male sex	39 (52.0)	22 (33.8)	33 (47.8)	0.031	0.617	0.100
Department of admission						
Internal Medicine	16 (21.3)	15 (23.1)	13 (18.8)	0.804	0.709	0.546
Emergency	32 (42.7)	23 (35.4)	30 (43.5)	0.378	0.921	0.220
Surgery	10 (13.3)	8 (12.3)	4 (5.8)	0.856	0.127	0.187
Intensive Care Unit	5 (6.7)	5 (7.7)	4 (5.8)	0.814	0.829	0.661
Oncology	6 (8.0)	6 (9.2)	15 (21.7)	0.795	0.019	0.046
Outpatient clinics	3 (4.0)	6 (9.2)	2 (2.9)	0.208	0.718	0.222
Other	3 (4.0)	2 (3.1)	1 (1.4)	0.769	0.352	0.524
CDI origin						
Nosocomial	24 (32.0)	19 (29.2)	22 (31.9)	0.723	0.988	0.739
Associated with health system	12 (16.0)	9 (13.8)	11 (15.9)	0.721	0.992	0.733
Community-acquired	39 (52.0)	37 (56.9)	36 (52.2)	0.559	0.983	0.581
Days of admission in ward						
Total days	12.7 (14.2)	22.0 (33.4)	13.9 (17.6)	0.458	0.594	0.265
Days pre-CDI	5.1 (7.7)	6.5 (11.0)	4.5 (9.3)	0.513	0.313	0.104
Days post-CDI	7.6 (11.5)	15.6 (27.3)	9.4 (12.0)	0.250	0.797	0.437
Comorbidities						
COVID-19	6 (8.0)	8 (12.3)	3 (4.3)	0.397	0.366	0.093
Diabetes mellitus	26 (34.7)	18 (27.7)	18 (26.1)	0.375	0.264	0.834
Chronic kidney disease	19 (25.3)	11 (16.9)	18 (26.1)	0.226	0.918	0.198
Chronic lung disease	11 (14.7)	5 (7.7)	3 (4.3)	0.196	0.037	0.414
Intestinal bowel disease	3 (4.0)	4 (6.2)	1 (1.4)	0.560	0.352	0.151
Gastric disease	24 (32.0)	17 (26.2)	25 (36.2)	0.448	0.592	0.209
Rheumatic disease	2 (2.7)	8 (12.3)	8 (11.6)	0.027	0.303	0.899
Cancer	19 (25.3)	12 (18.5)	21 (30.4)	0.606	0.404	0.110
Cancer type						
Lung	1 (1.3)	1 (1.5)	2 (2.9)	0.553	0.749	0.743
Breast	2 (2.7)	1 (1.5)	3 (4.3)			
Gastric	1 (1.3)	1 (1.5)	0 (0.0)			
Colorectal	3 (4.0)	3 (4.6)	3 (4.3)			
Kidney	0 (0.0)	0 (0.0)	1 (1.4)			
Bladder	1 (1.3)	0 (0.0)	0 (0.0)			
Gynecologic	4 (5.3)	1 (1.5)	3 (4.3)			
Blood	3 (4.0)	2 (3.1)	2 (2.9)			
Pancreas	0 (0.0)	2 (3.1)	3 (4.3)			

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Bile ducts	0 (0.0)	1 (1.5)	1 (1.4)			
Liver	1 (1.3)	0 (0.0)	1 (1.4)			
Other	3 (4.0)	0 (0.0)	2 (2.9)			
Cancer extension						
Localized	4 (5.3)	3 (4.7)	8 (11.6)	0.793	0.586	0.417
Metastasic	12 (16.0)	7 (10.8)	10 (14.5)			
Unknown	3 (4.0)	2 (3.1)	2 (2.9)			
Cancer therapy						
Chemotherapy	9 (12.0)	6 (9.2)	12 (17.4)	0.407	0.573	0.338
Immunotherapy	5 (6.7)	2 (3.1)	5 (7.2)	0.552	0.848	0.337
Radiation therapy	1 (1.3)	0 (0.0)	3 (4.3)	0.644	0.165	0.069
Treatments						
Immunosuppressive treatment	17 (22.7)	12 (18.5)	20 (29.0)	0.540	0.386	0.153
Previous GI surgery	21 (28.0)	9 (13.8)	1 (1.4)	0.042	< 0.001	0.006
Colonoscopy	0 (0.0)	6 (9.2)	2 (2.9)	0.007	0.138	0.122
Gastroscopy	5 (6.7)	12 (18.5)	8 (11.6)	0.033	0.303	0.265
H3PCDI	19 (25.3)	21 (32.3)	27 (39.1)	0.446	0.143	0.410
H6PCDI	21 (28.0)	21 (32.3)	30 (43.5)	0.615	0.060	0.183
AB3PCDI	47 (62.7)	42 (64.6)	37 (53.6)	0.811	0.271	0.196
PPI	64 (85.3)	35 (53.8)	34 (49.3)	< 0.001	< 0.001	0.564
Charlson index						
Index > 5	32 (42.7)	16 (24.6)	28 (40.6)	0.024	0.799	0.049
McCabe score						
Rapidly fatal disease	15 (20.0)	13 (20.0)	19 (27.5)	1.000	0.287	0.306
Ultimately fatal disease	23 (30.7)	16 (24.6)	14 (20.3)	0.425	0.154	0.548
Non-fatal disease	37 (49.3)	36 (55.4)	35 (50.7)	0.474	0.867	0.589
Laboratory analyses						
Leukocytes, x 10^9/L	10,736 (5,711)	11,091 (7,875)	13,947 (12,966)	0.644	0.193	0.125
Albumin, g/dL	3.3 (0.8)	3.2 (1.0)	3.2 (0.7)	0.526	0.499	0.666
C-reactive protein, mg/L	9.8 (10.3)	8.2 (10.3)	9.4 (8.8)	0.230	0.645	0.064
Outcomes						
Recurrences	8 (10.7)	7 (10.8)	5 (7.2)	0.984	0.474	0.475
Deceased	10 (13.3)	6 (9.2)	11 (15.9)	0.447	0.658	0.243

[1] Comparing 2020 and 2021; [2] Comparing 2020 and 2022; [3] Comparing 2021 and 2022; Days pre-CDI is the number of days of admission before *Clostridioides difficile* diagnosis; Days post-CDI is the number of days of admission after *Clostridioides difficile* diagnosis; AB3PCDI: Antibiotics 3 months prior to CDI; CDI: Clostridioides difficile infection; GI: Gastrointestinal; H3PCDI: Hospitalization 3 months prior to CDI; H6PCDI: Hospitalization 6 months prior to CDI; PPI: Proton pump inhibitors. The results of qualitative variables are shown as numbers and percentages, and statistical significance was calculated by the $\chi 2$ test. The results of quantitative variables are shown as medians and interquartile ranges, and statistical significance was calculated by the Mann-Whitney U test. Statistical analysis of cancer types has been done globally due to the low number of cases of each individual cancer.

3.2. Factors Related to Patient Fatality and Length of Hospital Stay

In Table 3, the characteristics of 27 deceased patients are compared to those of the survivors. The deceased individuals, on average, were older and showed a markedly higher frequency of admissions to the Oncology department. Regarding their comorbidities, they were more likely to suffer from chronic kidney disease or cancer than the survivors. Among the deceased patients with cancer, there was a notable prevalence of lung cancer or metastasis. Deceased patients had a higher

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frequency of prior hospital admissions. The Charlson and McCabe indices were consistently higher in this group. Additionally, elevated leukocyte and C-reactive protein concentrations were observed, while the albumin concentration was lower than in survivors.

Table 4 shows the characteristics of patients necessitating prolonged hospitalization, defined arbitrarily with a cut-off point set at five days, compared to those with shorter stays. Individuals requiring extended hospitalization were more frequently admitted to the Oncology department and exhibited a higher prevalence of diabetes mellitus or cancer. Among the subset of cancer patients, a higher occurrence of metastases was observed, coupled with a more frequent history of radiation therapy. The extended-stay patients consistently manifested elevated Charlson and McCabe indices, heightened serum C-reactive protein concentrations, and lower albumin concentrations than those with shorter stays.

Table 3. Risk factors for mortality of patients with CDI.

Variable	Survivors n = 182	Deceased n = 27	*p* value
Age	63.9 (18.8)	71.2 (13.9)	0.054
Male sex	80 (44.0)	14 (51.9)	0.442
Department			
Internal Medicine	38 (20.9)	6 (22.2)	0.873
Emergency	79 (43.4)	6 (22.2)	0.036
Surgery	22 (12.1)	0 (0.0)	0.056
Intensive Care	11 (6.0)	3 (11.1)	0.325
Oncology	16 (8.8)	11 (40.7)	< 0.001
Outpatient clinics	11 (6.0)	0 (0.0)	-
Other	5 (2.7)	1 (3.7)	0.781
CDI origin			
Nosocomial	53 (29.1)	12 (44.4)	0.108
Associated with health system	28 (15.4)	4 (14.8)	0.938
Community-acquired	101 (55.5)	11 (40.7)	0.151
Days of admission in ward			
Total days	15.8 (24.4)	17.4 (9.9)	0.740
Days pre-CDI	5.1 (9.5)	6.9 (8.0)	0.367
Days post-CDI	10.7 (19.3)	10.6 (9.5)	0.984
Comorbidities			
COVID-19	14 (7.7)	3 (11.1)	0.544
Diabetes mellitus	53 (29.1)	9 (33.3)	0.655
Chronic kidney disease	34 (1.6)	14 (51.9)	< 0.001
Chronic lung disease	15 (8.2)	4 (14.8)	0.268
Intestinal bowel disease	8 (4.4)	0 (0.0)	0.267
Gastric disease	56 (30.8)	10 (37.0)	0.513
Rheumatic disease	16 (8.8)	2 (7.4)	0.811
Cancer	31 (17.0)	11 (40.7)	0.007
Cancer type			
Lung	1 (0.5)	3 (11.1)	< 0.001
Breast	5 (2.7)	1 (3.7)	
Gastric	2 (1.1)	0 (0.0)	
Colorectal	8 (4.4)	1 (3.7)	
Kidney	0 (0.0)	1 (3.7)	
Bladder	0 (0.0)	1 (3.7)	
Gynecologic	7 (3.8)	1 (3.7)	
Blood	6 (3.3)	1 (3.7)	

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Pancreas	5 (2.7)	0 (0.0)	
Bile ducts	0 (0.0)	2 (7.4)	
Liver	2 (1.1)	0 (0.0)	
Other	2 (1.1)	3 (11.1)	
Cancer extension			
Localized	13 (7.1)	2 (7.4)	
Metastasic	18 (9.9)	11 (40.7)	< 0.001
Unknown	6 (3.3)	1 (3.7)	
Cancer therapy			
Chemotherapy	20 (11.0)	7 (25.9)	0.084
Immunotherapy	9 (4.9)	3 (11.1)	0.414
Radiation therapy	3 (1.6)	1 (3.7)	0.551
Treatments			
Immunosuppressive treatment	36 (19.8)	13 (48.1)	0.001
Previous GI surgery	28 (15.4)	3 (11.1)	0.560
Colonoscopy	4 (2.2)	4 (14.8)	0.001
Gastroscopy	20 (11.0)	5 (18.5)	0.261
H3PCDI	52 (28.6)	15 (55.5)	< 0.001
H6PCDI	57 (31.3)	15 (55.5)	0.008
AB3PCDI	107 (58.8)	19 (70.4)	0.251
PPI	111 (61.0)	22 (81.4)	0.116
Charlson index			
Index > 5	58 (31.9)	18 (66.7)	< 0.001
McCabe score			
Rapidly fatal disease	24 (13.2)	23 (85.2)	
Ultimately fatal disease	50 (27.5)	3 (11.1)	< 0.001
Non-fatal disease	107 (58.8)	1 (3.7)	
Laboratory analyses			
Leukocytes	11299 (6906)	15912 (18580)	0.016
Albumin	3.3 (0.8)	2.9 (0.6)	0.017
C-reactive protein	8.1 (8.8)	15.9 (12.9)	< 0.001
Outcomes			
Recurrences	18 (9.9)	2 (7.4)	0.682

Days pre-CDI is the number of days of admission before *Clostridioides difficile* diagnosis; Days post-CDI is the number of days of admission after *Clostridioides difficile* diagnosis; AB3PCDI: Antibiotics 3 months prior to CDI; CDI: *Clostridioides difficile* infection; GI: Gastrointestinal; H3PCDI: Hospitalization 3 months prior to CDI; H6PCDI: Hospitalization 6 months prior to CDI; PPI: Proton pump inhibitors. The results of qualitative variables are shown as numbers and percentages, and statistical significance was calculated by the χ^2 test. The results of quantitative variables are shown as medians and interquartile ranges, and statistical significance was calculated by the Mann-Whitney *U* test. Statistical analysis of cancer types has been done globally due to the low number of cases of each individual cancer.

Table 4. Risk factors for prolonged hospital stays of patients with CDI.

Variable	Days Post-CDI ≤ 5 n = 111	Days Post-CDI > 5 n = 98	*p* value
Age	61.9 (18.6)	68.34 (17.6)	0.012
Male sex	47 (42.3)	47 (48.0)	0.415
Department of admission			
Internal Medicine	18 (16.2)	26 (26.5)	0.186
Emergency	57 (51.4)	28 (28.6)	< 0.001
Surgery	9 (8.1)	13 (13.3)	0.225

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Intensive Care	5 (4.5)	9 (9.2)	0.133
Oncology	9 (8.1)	18 (18.4)	0.027
Other	2 (1.8)	4 (4.1)	0.324
CDI origin			
Nosocomial	24 (21.6)	41 (41.8)	0.158
Associated with health system	13 (11.7)	19 (19.4)	0.124
Community-acquired	14 (12.6)	38 (38.8)	< 0.001
Days of admission in ward			
Total days	4.7 (7.0)	28.7 (27.9)	< 0.001
Days pre-CDI	3.0 (6.3)	8.0 (11.3)	< 0.001
Days post-CDI	1.7 (1.9)	20.9 (22.7)	< 0.001
Comorbidities			
COVID-19	8 (7.2)	9 (9.2)	0.602
Diabetes mellitus	24 (21.6)	38 (38.8)	0.007
Chronic kidney disease	20 (18.0)	28 (28.6)	0.070
Chronic lung disease	9 (8.1)	10 (10.2)	0.599
Intestinal bowel disease	5 (4.5)	3 (3.1)	0.587
Gastric disease	33 (29.7)	33 (33.7)	0.540
Rheumatic disease	7 (6.3)	11 (11.2)	0.206
Cancer	21 (18.9)	31 (31.6)	0.050
Cancer type			
Lung	1 (0.9)	3 (3.1)	0.241
Breast	3 (2.7)	3 (3.1)	
Gastric	0 (0.0)	2 (2.0)	
Colorectal	4 (3.6)	5 (5.1)	
Kidney	0 (0.0)	1 (1.0)	
Bladder	1 (0.9)	0 (0.0)	
Gynecologic	4 (3.6)	4 (4.1)	
Blood	5 (4.5)	2 (2.0)	
Pancreas	2 (1.8)	3 (3.1)	
Bile ducts	0 (0.0)	2 (2.0)	
Liver	0 (0.0)	2 (2.0)	
Other	1 (0.9)	4 (4.1)	
Cancer extension			
Localized	3 (2.7)	12 (12.2)	0.026
Metastasic	13 (11.7)	16 (16.3)	
Unknown	5 (4.5)	2 (2.0)	
Cancer therapy			
Chemotherapy	11 (9.9)	16 (16.3)	0.301
Immunotherapy	9 (8.1)	3 (3.1)	0.223
Radiation therapy	0 (0.0)	4 (4.1)	0.008
Treatments			
Immunosupressive treatment	19 (17.1)	30 (30.6)	0.022
Previous GI surgery	13 (11.7)	18 (18.4)	0.177
Colonoscopy	6 (5.4)	2 (2.0)	0.206
Gastroscopy	9 (8.1)	16 (16.3)	0.068
H3PCDI	27 (24.3)	40 (40.8)	0.019
H6PCDI	30 (27.0)	42 (42.9)	0.014
AB3PCDI	59 (53.2)	67 (68.4)	0.025
PPI	65 (58.6)	68 (69.4)	0.195
Charlson index			

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Index > 5	29 (26.1)	47 (48.0)	0.001
McCabe score			
Rapidly fatal disease	19 (17.1)	28 (28.6)	< 0.001
Ultimately fatal disease	19 (17.1)	34 (34.7)	
Non-fatal disease	72 (64.9)	36 (36.7)	
Laboratory analyses			
Leukocytes	11,688 (10,109)	12,141 (8,454)	0.729
Albumin	3.6 (0.8)	2.9 (0.7)	< 0.001
C-reactive protein	6.8 (9.4)	11.8 (9.6)	< 0.001
Outcomes			
Recurrences	10 (9.0)	10 (10.2)	0.769
Deceased	10 (9.0)	17 (17.3)	0.073

Days post-CDI is the number of days of admission after Clostridioides difficile diagnosis; AB3PCDI: Antibiotics 3 months prior to CDI; CDI: Clostridioides difficile infection; GI: Gastrointestinal; H3PCDI: Hospitalization 3 months prior to CDI; H6PCDI: Hospitalization 6 months prior to CDI; PPI: Proton pump inhibitors. The results of qualitative variables are shown as numbers and percentages, and statistical significance was calculated by the $\chi 2$ test. The results of quantitative variables are shown as medians and interquartile ranges, and statistical significance was calculated by the Mann-Whitney U test. Statistical analysis of cancer types has been done globally due to the low number of cases of each individual cancer.

4. Discussion

This study identified distinct clinical characteristics among CDI patients throughout different phases of the COVID-19 outbreak. Hospital clinical practices have significantly differed over the three years of the pandemic. In 2020, there were widespread home confinements, postponed doctor visits, a surge in telemedicine usage, delays in diagnostics, a deficiency in effective anti-COVID-19 therapies, evident confusion within hospital and social environments, and a predominant focus on COVID-19 and the prevention of its nosocomial transmission. Transition characterized 2021, marked by the global rollout of effective vaccines, enhanced understanding and confidence regarding pandemic characteristics, and a gradual return to normal hospital activities. By the second half of 2022, the situation had essentially normalized, with a large portion of the population vaccinated and hospital and healthcare resembling pre-pandemic times [24–26]. Notably, infection prevention guidelines underwent substantial changes, incorporating universal masking. These alterations in routine clinical practice have necessarily influenced CDI features.

In 2022, we observed a decrease in the incidence of CDI that mirrored the decline in COVID-19 cases. We attribute this trend to the gradual normalization of clinical activities, which facilitated increased attention to other clinical scenarios alongside a reduction in severe COVID-19 cases. To our knowledge, these findings have not been previously reported. Previous studies aimed to elucidate the relationship between CDI and COVID-19, but variations in methodologies have resulted in inconclusive outcomes. Allegretti et al. [27] reported no increase in CDI rates among COVID-19 patients compared to non-COVID-19 cases. Similarly, Luo et al. [10] and Sinnathamby et al. [28] found no significant difference in CDI rates between the pre-pandemic and pandemic periods. Conversely, several authors [13,29,30] noted a reduction in CDI rates during the early stages of the outbreak compared to the pre-pandemic period. Most studies suggest no discernible increase in CDI during the initial phases of the pandemic [31]. However, our investigation reveals that CDI incidence declined alongside COVID-19 cases in the latter stages.

A striking trend within our cohort is the notable surge in infected oncological patients and those undergoing aggressive treatments, such as gastro or colonoscopies, in 2022 compared to previous years. In the initial two years of the pandemic, we witnessed a widespread transition to telemedicine and public advisories urging individuals to seek in-person medical care only when absolutely necessary. This precautionary stance led to delayed diagnoses and treatments for numerous conditions, including cancer [32]. In the United States, substantial declines have been documented across virtually all non-COVID-19-related healthcare interactions, encompassing emergency

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department visits [33], outpatient hospital visits [34], surgeries [35], and even myocardial infarctions [36]. Similarly, in Spain [37] and within our hospital, there was a notable decrease in non-urgent diagnoses and treatments during the pandemic's early years. The gradual return to standard medical practices likely explains the uptick in oncology patients and individuals undergoing procedures such as gastro or colonoscopies.

We did not observe any major differences in the patients' comorbidities, whether the CDI was acquired within the hospital, another social health center, or the community, or in the majority of previous treatments and illnesses, as well as in the severity of their diseases measured by the Charlson and McCabe indices. However, some noteworthy trends are worth discussing despite failing to reach statistical significance. For instance, in 2022, a higher number of patients with previous admissions stood out despite receiving less antibiotic therapy. This data raises the question of whether there is horizontal transmission of spores during these admissions, indicating possible infection outbreaks [36]. Unfortunately, we were unable to pinpoint the cases in time and space. Another significant issue is the wide range of post-CDI admission days, particularly notable in 2021, where some patients had to be admitted for many weeks. This observation reflects the inherent shortcomings of telemedicine during 2020 and 2021 and the inevitable reality that hospital care was largely redirected towards COVID-19 cases.

It's noteworthy that the majority of CDI cases originate from the community and hospitals. This underscores the significance of adopting antimicrobial stewardship programs globally, as advocated by the World Health Organization [38]. Such programs aim to implement evidence-based guidelines for prescribing and administering antimicrobials, thereby mitigating drug misuse.

Our subsequent aim was to investigate the factors influencing mortality or extended hospital stays post-CDI. The factors were similar across both scenarios. These individuals were characterized by advanced age compared to those who survived, along with a higher prevalence of chronic kidney disease or cancer as concurrent ailments. Lung cancer or metastatic cancer featured prominently among their comorbidities. Consequently, they exhibited a more frequent history of immunosuppressive treatment and recent hospitalization within three months preceding the CDI diagnosis. The Charlson and McCabe indices indicated a more severe disease prognosis, while leukocyte count, albumin levels, and C-reactive protein were more altered. These findings underscore the significance of these parameters as potential indicators of heightened mortality risk or prolonged hospitalization in this patient population. Our findings conform to existing literature highlighting numerous risk factors associated with mortality from CDI, encompassing cancer, chronic kidney, cardiovascular, or liver diseases [39–42]. These comorbidities significantly influence the Charlson index, and it has been suggested that tailoring antibiotic treatment according to Charlson index severity may yield superior efficacy compared to strategies based on laboratory findings [43].

In conclusion, our study sheds light on the evolving landscape of CDI amidst the COVID-19 pandemic in a medium-sized public hospital in Western Europe. The shifts in clinical practices and healthcare utilization in 2022 were associated with decreased CDI and COVID-19 incidences. However, a striking trend emerged with a significant increase in CDI cases among oncological patients and those undergoing aggressive treatments, likely reflecting delayed diagnoses and treatments during the pandemic's earlier stages, exacerbated by the widespread adoption of telemedicine. The persistently low co-infection rates of C. difficile and COVID-19, alongside consistent patient comorbidities and disease severity indices, underscore the resilience of CDI dynamics amidst pandemic disruptions. Notably, advanced age, chronic kidney disease, and cancer emerged as key risk factors for mortality or prolonged hospital stays post-CDI, echoing existing literature.

As we navigate the aftermath of the pandemic, it is imperative to address the challenges posed by telemedicine in facilitating timely diagnoses and treatments, particularly for vulnerable populations. Targeted interventions and healthcare policies should prioritize early detection and management of CDI, especially among high-risk individuals, while considering tailored antibiotic treatments guided by comprehensive risk assessment tools such as the Charlson index. In this sense,

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creating profiles based on history, clinical, and analytical data can help identify patients with a higher mortality risk. Prioritizing treatments with very effective yet expensive drugs, such as fidaxomicin or bezlotoxumab, for these high-risk patients could significantly improve outcomes [5]. Additionally, our results highlight the importance of managing easily controllable risk factors, such as treatment with antibiotics or proton pump inhibitors and minimizing the length of hospital stays. An important lesson that can be drawn from this article is the imperative need to rule out CDI in cancer patients admitted with diarrhea, given the high risk of mortality. By integrating lessons learned from the pandemic experience, we can strive towards optimizing patient outcomes and healthcare delivery in the post-COVID era.

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