Clostridium difficile Severity and Outcome at a North of Portugal Healthcare Facility

Severidade e Prognóstico da Infeção por Clostridium difficile num Hospital do Norte de Portugal

ARTIGO ORIGINAL

João BARBOSA-MARTINS✉[1,2], Joana MENDONÇA[1,2], Carolina CARVALHO[2], Helena SARMENTO[1], Paula MOTA[3], Camila COUTINHO[2], Jorge COTTER[1]

Acta Med Port 2022 Apr;35(4):279-285 ▪ https://doi.org/10.20344/amp.16357

ABSTRACT

Introduction: *Clostridium difficile* infection has been increasingly reported, with a significant healthcare burden and important morbi-mortality. This study aimed to characterize and describe the severity and outcomes of this event at a Portuguese hospital.

Material and Methods: We conducted a retrospective analysis, by clinical record review, of all confirmed cases diagnosed in a hospital in the North of Portugal, between January 2013 and December 2018. We included those who were non-pregnant and at least 18 years old.

Results: Fifty-seven cases occurred, mostly in females and aged patients; 33.3% were healthcare facility-outset, while 31.6% were community-associated. Regarding severity, 43.9% had non-severe, while 29.8% severe and 21.0% fulminant presentations, the latter with the need of admission. Exposure to antibiotics occurred in 68.4%, while to proton-pump inhibitors in 57.9%. Risk factors for severe disease were female gender, chronic renal disease, and high neutrophil-lymphocyte ratio. Moreover, renal disease and a higher ratio were associated with fulminant disease. Thirty-day all-cause mortality was found in 15.8% while 90-day in 28.1%. Risk factors for 30-day mortality were renal disease, higher Charlson score, and higher neutrophil-lymphocyte ratio. Risk factors for 90-day mortality were advanced age, previous antibiotic exposure, higher Charlson score, and higher neutrophil-lymphocyte ratio.

Conclusion: Data concerning *Clostridium difficile* infection severity and prognosis in Portugal is scarce, and future studies should focus on this important topic.

Keywords: Clostridioides difficile; Clostridium Infections/diagnosis; Clostridium Infections/epidemiology; Risk Factors; Severity of Illness Index; Treatment Outcome

RESUMO

Introdução: A infeção por *Clostridium difficile* tem aumentado, com importante morbimortalidade e impacto nos sistemas de saúde. Este estudo procurou caracterizar e descrever a severidade e prognóstico desta infeção, na nossa instituição.

Material e Métodos: Realizou-se uma análise retrospetiva dos casos confirmados ocorridos entre janeiro de 2013 e dezembro de 2018, num hospital do Norte de Portugal. Recorreu-se à análise de processo clínico e foram incluídos doentes sem gravidez em curso e com pelo menos 18 anos.

Resultados: Verificaram-se 57 casos, a maioria em mulheres e idosos, sendo que 33,3% tiveram origem em instituições de saúde e 31,6% na comunidade. Nesta amostra, 43,9% tiveram doença não severa, 29,8% severa e 21,0% fulminante, estes com necessidade de internamento. A toma prévia de antibióticos ocorreu em 68,4%, e de inibidores da bomba de protões em 57,9%. O sexo feminino relacionou-se com doença severa, enquanto que a doença renal crónica e um elevado rácio neutrófilos-linfócitos se relacionaram com doença severa e fulminante. A mortalidade aos 30 dias verificou-se em 15,8% e associou-se a doença renal e elevação do *score* de Charlson e do rácio neutrófilos-linfócitos. A mortalidade aos 90 dias ocorreu em 28,1%, associada a idade avançada, toma de antibióticos e elevação do *score* e do rácio.

Conclusão: Em Portugal, são escassos os dados sobre a severidade e prognóstico desta infeção, pelo que são necessários mais estudos nacionais.

Palavras-chave: Clostridioides difficile; Fatores de Risco; Índice de Gravidade de Doença; Infeção por Clostridium difficile/diagnóstico; Infeção por Clostridium difficile/epidemiologia; Resultado do Tratamento

INTRODUCTION

Clostridium difficile is a toxin-producing Gram-positive anaerobe bacillus capable of infecting the gastrointestinal tract, causing a diverse spectrum of conditions, from asymptomatic colonization or mild diarrhea to fulminant life-threatening colitis.[1,2] Despite being one of the major causes of nosocomial infectious diarrhea, community-acquired *Clostridium difficile* infection (CDI) has been increasingly reported.[3] CDI carries a high economic burden with an estimated cost of €3 billion per year in the European Union and a deep impact on patients' quality of life.[4] Risk factors associated with CDI include the use of antibiotics, advanced age, prior comorbidities, previous hospitalization, use of a nasogastric catheter, gastrointestinal surgery, and use of proton-pump inhibitors (PPI).[1,5] Identifying individuals at higher risk of developing CDI, particularly in its most severe or fulminant forms, and prompt the early start of antimicrobial treatment, is of utmost importance to prevent adverse outcomes.[6] Conventionally, leukocytosis, elevated

1. Internal Medicine Department. Hospital da Senhora da Oliveira. Guimarães. Portugal.
2. Medical Oncology Department. Hospital da Senhora da Oliveira. Guimarães. Portugal.
3. Clinical Pathology Department. Hospital da Senhora da Oliveira. Guimarães. Portugal.
✉ **Autor correspondente:** João Barbosa Martins. joaomartinsmed@gmail.com

Recebido/*Received*: 05/05/2021 - **Aceite/*Accepted*:** 15/07/2021 - **Publicado *Online*/*Published Online*:** 14/02/2022 - **Publicado/*Published*:** 01/04/2022

serum creatinine, hypoalbuminemia, and older age were associated with severe complications and a more severe outcome.[7] Likewise, other studies have also reported that associated comorbidities such as malignancy and chronic renal disease (CRD), antibiotic use, or presenting symptoms, are important severity predictors.[7] Inflammatory markers, such as neutrophil-lymphocyte ratio (NLR), that are already associated with a worse prognosis in other conditions, have also been associated with the severity and worse outcomes in CDI patients.[8] Nevertheless, more consistent predictors are needed, as the performance of these markers remains unsatisfactory. Portuguese CDI epidemiological data concerning incidence, risk factors, severity, and outcome is scarce,[9] and therefore, more national studies are needed. The aim of this study was to determine the presence of risk factors, severity, and outcomes of CDI in our hospital population between 2013 and 2018.

MATERIAL AND METHODS

Study design

We conducted a single-center, retrospective and observational study between January 2013 and December 2018 at Hospital Senhora da Oliveira – Guimarães, located in the North of Portugal. The subjects were all consecutive adult (aged ≥ 18 years) and non-pregnant patients who had a confirmed diagnosis of CDI by a stool test. The study protocol was approved by our institution's Ethics Committee.

Definitions

CDI diagnosis was defined by the presence of diarrhea and a positive *C. difficile* stool test. The origin of CDI was defined as[10,11]: (1) Healthcare facility-onset (HO) – outset at least 48 hours after healthcare facility admission; (2) Community-associated (CA) – outpatient setting or within 48 hours after healthcare admission and no history of healthcare facility discharge in the previous 12 weeks. (3) Community-onset, healthcare facility–associated (CO-HCFA) – outpatient setting or within 48 hours of admission to healthcare when the patient had been discharged from a healthcare facility within the previous four weeks. (4) Community-associated, indeterminate cases (CA–IND) – outpatient setting or within 48 hours of admission to healthcare when the patient had been discharged from a healthcare facility within the previous 4 – 12 weeks. Patients with CDI were classified as having either non-severe, severe or fulminant disease based on the 2018 Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) CDI guidelines.[5] A severe initial episode was defined as the presence of leukocytosis with a white blood cell (WBC) count of ≥ 15.0 x 10^3/uL or a serum creatinine level of ≥ 1.5 mg/dL. Fulminant initial episode was defined as the presence of hypotension or shock, ileus or megacolon.[5] If these data were unavailable, severity was classified as indeterminate. The outcome was defined as all-cause mortality at 30 and 90 days.[11,12] Recurrence was considered if the number of days after a previous episode of positive CDI was > 14 and ≤ 56 days (2 - 8 weeks).[11] NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.[8]

Variables

Data were collected from patient's clinical records. The parameters collected included demographic, comorbid medical conditions, origin of acquisition of CDI, laboratory test results, exposure in the previous 30 days to antimicrobials, PPI, chemotherapy, nasogastric catheter, and major gastrointestinal surgery, SHEA/IDSA severity criteria, and outcomes.

Microbiological tests

Patients with a positive stool result for *C. difficile* were identified by the Microbiology Laboratory of the Clinical Pathology Department. Before 2014, *C. difficile* toxins A and B detection were performed using the enzyme immunoassay (EIA) Techlab® C. DIFF QUIK CHEK COMPLETE® and after that, confirmed by PCR using the Xpert *C. difficile* kit®.

Statistical analysis

Differences in categorical variables such as clinical features, severity criteria, and mortality were assessed using χ^2 with Yates correction or Fisher exact tests, when appropriate. Normality was assessed by the Shapiro-Wilk test, and continuous variables were expressed as median ± interquartile range (IQR). Then, Kruskal-Wallis adjusted to Bonferroni correction or Mann–Whitney U tests were performed to compare independent groups. All tests were 2-tailed, and a P value lesser than 0.05 was considered statistically significant. All analyses were conducted using IBM SPSS® Statistics.

RESULTS

A total of 858 patients were tested for *C. difficile* during the study period. Only 823 were included for further analysis, and 57 (6.9%) fulfilled CDI criteria (Fig. 1). Of CDI subjects, seven (12.3%) did not require hospital admission, while the remaining 50 (87.7%) did. From a total of 103 545 inpatients admitted during the study period, the incidence was 0.48 cases per 1000 inpatients admitted.

Clinical features

The median age of CDI patients was 76.0 years (interquartile range, IQR, 21.0), and at least 44 patients (77.2%) were older than 65 years. In terms of gender, 34 (59.6%) were females while 23 (40.4%) were males. Nineteen cases (33.3%) were HO (median age 80.0 years), 18 (31.6%) were CA (median age 70.0 years), 11 (19.3%) were CO-HCFA (median age 79.0 years) and (15.8%) were CA-IND (median age 72.0 years) (Table 1). The median Charlson comorbidity index score was 5.0 (IQR 4.0). Hypertension was the most common comorbidity present in 36 (63.2%) of cases, followed by diabetes in 19 (33.3%) subjects (Table 1).

As for CDI severity, cases were distributed as follows: 25 (43.9%) fulfilled criteria for non-severe, 17 (29.8%) for

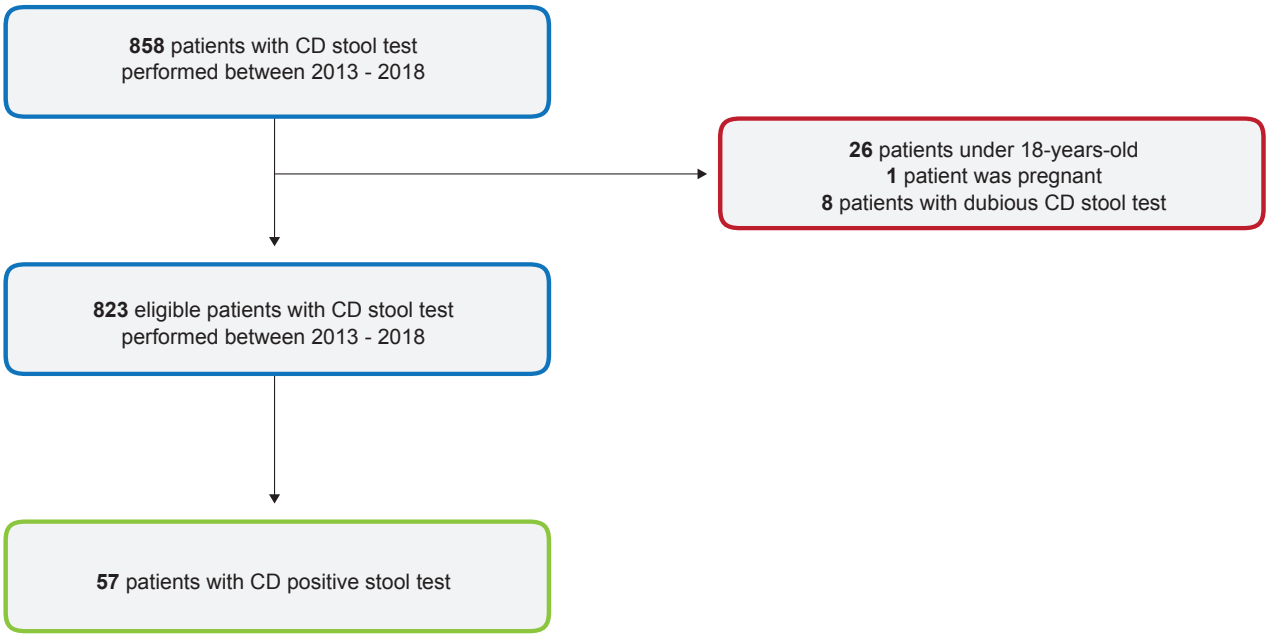

Figure 1 – Diagram of study patients with *Clostridium difficile* stool test performed between 2013 - 2018
CD: *Clostridium difficile*

severe, 12 (21.0%) for fulminant, and three (5.3%) were of indeterminate severity (due to missing laboratory data).

Table 1 shows our sample demographic characteristics and comorbidities set according to disease severity classification. Older subjects were more likely to have fulminant disease (median 79.0 *vs* 66.0; $p = 0.051$) when compared to non-severe. Moreover, females seemed to have more severe disease when compared to males (76.5 *vs* 23.5%; $p = 0.044$). A background of CRD was associated with more severe disease (35.3 *vs* 4.0; $p = 0.012$) and also with fulminant disease when compared to non-severe (33.3 *vs* 4.0; $p = 0.030$). No significant differences were found when comparing fulminant to severe CDI in CRD patients. Higher NLR was associated with severe (median 10.9 *vs* 3.6; $p < 0.0001$) and fulminant disease (6.0 *vs* 3.6; $p = 0.004$) when compared to non-severe. No significant differences in NLR were found between severe and fulminant disease forms (10.9 *vs* 6.0; $p = 1.000$).

Table 2 shows our sample exposures according to their disease severity. In terms of CDI risk factors, 39 (68.4%) had previous antibiotic exposure, 33 (57.9%) had a history of prior PPI intake, and 9 (15.8%) had a nasogastric catheter placed in the previous 30 days. None of the previous exposures were associated with CDI severity.

Outcome

The 30-day all-cause mortality after CDI diagnosis was verified in nine (15.8%) patients, while 90-day all-cause mortality was verified in 16 (28.1%) (Table 3). Recurrence was reported in 8 (14.0%) cases. CDI severity did not correlate with all-cause mortality or recurrence (Table 3).

Ninety-day all-cause mortality was higher in patients older than 65 years old ($p = 0.012$), and, likewise, advanced age was significantly reported in patients with increased 90-day mortality (84.0 *vs* 72.0 years; $p = 0.004$) (Table 4).

Higher Charlson index score was associated with increased 30-day (median 5.0 *vs* 7.0; $p = 0.028$) and 90-day all-cause mortality (median 5.0 *vs* 6.0; $p = 0.015$) (Table 4). Furthermore, CRD was associated with the worst outcome at 30-days (55.6 *vs* 44.4%; $p = 0.009$) (Table 4). Higher NLR was likewise associated with CDI 30-day (median 8.5 *vs* 4.8; $p = 0.020$) and 90-day overall mortality (median 7.4 *vs* 4.6; $p = 0.009$). The use of any antibiotic on the 30 days before CDI was associated with higher 90-day overall mortality (93.8 *vs* 6.2%; $p = 0.024$) (Table 5). No association was found between any studied variable and CDI recurrence.

DISCUSSION

CDI is a challenging public health issue, so the characterization of the local population, the description of risk factors, and the identification of new prognostic markers are a continuous demand. Epidemiological data about CDI in Portugal remains limited. The EUCLID study revealed, for the Portuguese participating institutions, differences between the reported rates (2.9 and 3.0 per 10 000 patient bed-days, in 2011-2012 and 2012-2013, respectively) and the corresponding measured rates (19.3 and 14.7 per 10 000 patient bed-days, according to the winter and summer sampling, respectively) of CDI-positive samples.[13] Nevertheless, the Portuguese CDI measured rates were nearly similar to the European mean values. Here we found an incidence of 0.48 cases per 1000 inpatients which was lower than described by another Portuguese study (8.05 cases per 1000 inpatients).[9] Nevertheless, we considered all adult, non-pregnant inpatients admitted during the study period, and not only the ones admitted to the Internal Medicine ward. When compared to other Portuguese studies, the median age of our sample was similar, and, likewise, most of our patients

Table 1 – Demographics, clinical and laboratory data of CDI cases by severity

Characteristics	Overall n = 57 (100.0%)	Non-severe n = 25 (43.9%)	Severe n = 17 (29.8%)	Fulminant n = 12 (21.0%)	Indeterminate n = 3 (5.3%)	*p*
Age (years), median (IQR)	76.0 (21.0)	66.0 (33.5)	81.0 (23.5)	79.0 (18.0)	79.0 (8.0§)	0.021[a]; 0.088[b]; 0.051[c]; 1.000[d]
≥ 65, n (%)	44 (77.2)	17 (68.0)	13 (76.5)	11 (91.7)	3 (100.0)	0.303[a]
Gender, n (%)						
Male	23 (40.4)	15 (60.0)	4 (23.5)	3 (25.0)	1 (33.3)	**0.036[a]; 0.044[b]**; 0.100[c]; 1.000[d]
Female	34 (59.6)	10 (40.0)	13 (76.5)	9 (75.0)	2 (66.7)	
Charlson score, median (IQR)	5.0 (4.0)	4.0 (5.0)	5.0 (2.5)	6.0 (3.8)	6.0 (1.0§)	0.026[a]; 0.098[b]; 0.063[c]; 1.000[d]
Comorbidities, n (%)						
Cardiovascular disease	4 (7.0)	3 (12.0)	1 (5.9)	0 (0.0)	0 (0.0)	0.548[a]
Cerebrovascular disease	14 (24.6)	5 (20.0)	3 (17.6)	4 (33.3)	2 (66.7)	0.634[a]
Congestive heart failure	8 (14.0)	2 (8.0)	3 (17.6)	3 (25.0)	0 (0.0)	0.332[a]
Dementia	6 (10.5)	2 (8.0)	1 (5.9)	3 (25.0)	0 (0.0)	0.329[a]
Diabetes	19 (33.3)	7 (28.0)	6 (35.3)	3 (25.0)	3 (100.0)	0.860[a]
Hypertension	36 (63.2)	12 (48.0)	14 (82.4)	7 (58.3)	3 (100.0)	0.076[a]; 0.054[b]; 0.812[c]; 0.218[d]
Inflammatory bowel disease	6 (10.5)	4 (16.0)	1 (5.9)	0 (0.0)	1 (33.3)	0.421[a]
Liver disease	2 (3.5)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0.141[a]
Malignant neoplasia history	13 (22.8)	6 (24.0)	5 (29.4)	2 (16.7)	0 (0.0)	0.848[a]
Chronic renal disease	11 (19.3)	1 (4.0)	6 (35.3)	4 (33.3)	0 (0.0)	**0.012[a]; 0.012[b]; 0.030[c]**; 1.000[d]
Setting, n (%)						
HO	19 (33.3)	8 (32.0)	7 (41.2)	3 (25.0)	1 (33.3)	0.288[a]
CA	18 (31.6)	11 (44.0)	4 (23.5)	2 (16.7)	1 (33.3)	
CO-HCFA	11 (19.3)	2 (8.0)	3 (17.6)	5 (41.7)	1 (33.3)	
CA–IND	9 (15.8)	4 (16.0)	3 (17.6)	2 (16.7)	0 (0.0)	
Serum						
NLR, median (IQR)	5.3 (6.9)*	3.6 (2.7)	10.9 (11.7)	6.0 (18.3)	-*	**< 0.0001[a]; < 0.0001[b]; 0.004[c]**; 1.000[d]

[a]: comparison across three groups (Non-severe, severe, fulminant); [b]: non-severe versus severe; [c]: non-severe versus fulminant; [d]: severe versus fulminant; *: 3 values were missing on information; §: range
CDI: *Clostridium difficile* infection; IQR: interquartile range; HO: healthcare facility-onset; CA: community-associated; CO-HCFA: community-onset, healthcare facility–associated; CA-IND: community-associated, indeterminate cases; NLR: neutrophil-lymphocyte ratio

Table 2 – Exposures of CDI cases by severity

Predisposing factors	Overall n = 57 (100.0%)	Non-severe n = 25 (43.9%)	Severe n = 17 (29.8%)	Fulminant n = 12 (21.0%)	Indeterminate n = 3 (5.3%)	*p*
Exposure 30 days before CDI, n (%)						
Any antibiotic	39 (68.4)	15 (60.0)	14 (82.4)	9 (75.0)	1 (33.3)	0.267[a]
Chemotherapy	2 (3.5)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0.141[a]
Proton pump inhibitor	33 (57.9)	11 (44.0)	11 (64.7)	10 (83.3)	1 (33.3)	0.064[a]; 0.315[b]; 0.057[c]; 0.408[d]
Nasogastric catheter	9 (15.8)	2 (8.0)	3 (17.6)	3 (25.0)	1 (33.3)	0.332[a]
Major gastrointestinal surgery	1 (1.8)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000[a]

[a]: comparison across three groups (Non-severe, severe, fulminant); [b]: non-severe versus severe; [c]: non-severe versus fulminant; [d]: severe versus fulminant.
CDI: *Clostridium difficile* infection

were older than 65 years.[14–16] Like in other studies, we also found an increasing number of cases in females.[9,16–18] In our sample, even though most cases were HO-CDI, the number of CA-CDI cases was marginally different, indicating that CA-CDI represents an important proportion of this concerning condition. Similarly, other Portuguese authors

also found a growing number of CA-CDI cases compared to the previous years.[9,14] As such, future studies should be performed to explore possible community epidemiological measures. As for other risk factors for CDI, most of the well-known ones were also present in our population. The median Charlson Index score was lower than expected; however, this might be because patients with inflammatory bowel disease were younger and have few comorbidities. In our sample, previous exposure to antibiotics[16,17] and PPI were lower than reported by others.[15] The different results may

Table 3 – Outcomes of CDI cases by severity

Outcomes	Overall n = 57 (100.0%)	Non-severe n = 25 (43.9%)	Severe n = 17 (29.8%)	Fulminant n = 12 (21.0%)	Indeterminate n = 3 (5.3%)	*p*
Recurrence, n (%)	8 (14.0)	2 (8.0)	4 (23.5)	1 (8.3)	1 (33.3)	0.296[a]
30-day all-cause mortality, n (%)	9 (15.8)	2 (8.0)	4 (23.5)	3 (25.0)	0 (0.0)	0.289[a]
90-day all-cause mortality, n (%)	16 (28.1)	5 (20.0)	7 (41.2)	4 (33.3)	0 (0.0)	0.317[a]

[a]: comparison across three groups (non-severe, severe, fulminant)
CDI: *Clostridium difficile* infection

Table 4 – Outcomes of CDI cases by demographics, clinical and laboratory data

Characteristics	Overall n = 57 (100.0%)	30-day all-cause mortality n = 9 (15.8%)	*p*	90-day all-cause mortality n = 16 (28.1%)	*p*	Recurrence n = 8 (14.0%)	*p*
Age (years), median (IQR)	76.0 (21.0)	75.0 (23.5) *vs* 79.0 (16.0)	0.105	72.0 (23.5) *vs* 84.0 (12.8)	**0.004**	76.0 (22.5) *vs* 80.5 (21.8)	0.565
≥ 65, n (%)	44 (77.2)	9 (100.0)	0.101	16 (100.0)	**0.012**	7 (87.5)	0.667
Gender, n (%)							
Male	23 (40.4)	2 (22.2)	0.288	5 (31.3)	0.566	4 (50.0)	0.702
Female	34 (59.6)	7 (77.8)		11 (68.8)		4 (50.0)	
Charlson score, median (IQR)	5.0 (4.0)	5.0 (3.8) *vs* 7.0 (3.0)	**0.028**	5.0 (4.5) *vs* 6.0 (3.8)	**0.015**	5.0 (4.0) *vs* 5.5 (4.5)	0.937
Comorbidities, n (%)							
Cardiovascular disease	4 (7.0)	0 (0.0)	1.000	0 (0.0)	0.568	2 (25.0)	0.090
Cerebrovascular disease	14 (24.6)	1 (11.1)	0.427	3 (18.8)	0.735	3 (37.5)	0.391
Congestive heart failure	8 (14.0)	3 (33.3)	0.103	4 (25.0)	0.202	2 (25.0)	0.311
Dementia	6 (10.5)	2 (22.2)	0.237	2 (12.5)	1.000	0 (0.0)	0.580
Diabetes	19 (33.3)	3 (33.3)	1.000	6 (37.5)	0.917	3 (37.5)	1.000
Hypertension	36 (63.2)	6 (66.7)	1.000	10 (62.5)	1.000	5 (62.5)	1.000
Inflammatory bowel disease	6 (10.5)	0 (0.0)	0.575	0 (0.0)	0.170	1 (12.5)	1.000
Liver disease	2 (3.5)	1 (11.1)	0.293	1 (6.3)	0.486	0 (0.0)	1.000
Malignant neoplasia history	13 (22.8)	2 (22.2)	1.000	4 (25.0)	1.000	1 (12.5)	0.667
Chronic renal disease	11 (19.3)	5 (55.6)	**0.009**	6 (37.5)	0.057	0 (0.0)	0.332
Setting, n (%)							
HO	19 (33.3)	5 (55.6)	0.033	9 (56.3)	0.087	2 (25.0)	0.762
CA	18 (31.6)	0 (0.0)		3 (18.8)		4 (50.0)	
CO-HCFA	11 (19.3)	1 (11.1)		1 (6.3)		1 (12.5)	
CA–IND	9 (15.8)	3 (33.3)		3 (18.8)		1 (12.5)	
Serum							
NLR, median (IQR)*	5.3 (6.9)	4.8 (5.3) *vs* 8.5 (12.7)	**0.020**	4.6 (4.5) *vs* 7.4 (11.6)	**0.009**	5.2 (7.0) *vs* 6.4 (6.3)	0.335

*: 3 values were missing on information
CDI: *Clostridium difficile* infection; IQR: interquartile range; HO: healthcare facility-onset; CA: community-associated; CO-HCFA: community-onset, healthcare facility–associated; CA-IND: community-associated, indeterminate cases; NLR: neutrophil-lymphocyte ratio

have to do with different periods of exposure considered before CDI (in our case, it may be lower). As for nasogastric catheters, our estimates were slightly higher compared to another Portuguese study.[19] Further studies with a larger sample size should be performed in order to assess the association between CDI and these risk factors reported in our population.

Disease severity was described in accordance with SHEA/IDSA 2018 guidelines.[5] There are other severity scores available[20]; however, the SHEA/IDSA guidelines have been widely used in several studies, and they have already been validated to agree with risk factors and outcomes.[11] CDI patients with an increased likelihood of severe outcomes may benefit from early interventions and aggressive treatment early in the course of disease. To the best of our knowledge, few Portuguese studies relied on severity criteria. Most of our cases presented non-severe disease, but their proportion was lower compared to other studies, which used an approach similar to ours, but included a larger sample.[11] Age is a known risk factor for CDI severity.[21,22] Our data corroborated these findings as aged subjects seem to have more severe presentations and 90-day mortality, particularly over 65 years old. Moreover, our analysis showed a higher proportion of females with severe disease. Nevertheless, the role of gender to severity and outcomes remains unclear.[23] As in our case, another Portuguese study did not find any association between sex and mortality.[16] A higher Charlson score was associated with a worse 30-day and 90-day prognosis in our sample. The comorbidity that seems to predict the worse prognosis was CRD, as it was associated with disease severity and 30-day mortality, corroborating previous data.[23] Antibiotic intake was associated with the worse 90-day outcomes, which is in agreement with other studies that suggested that some antibiotics classes may indeed be associated with disease severity.[23] Interestingly, a higher NLR seems to be positively associated with the likelihood of presenting severe disease and also with 30-day and 90-day increased all-cause mortality. This inflammatory marker is a simple and cheap indicator of subclinical inflammation and extension of the inflammatory process. It has been recently used as an inflammatory marker in chronic diseases and as a prognostic marker in malignancies and cardiovascular diseases.[8] Chaudhry *et al* described that elevated NLR is associated with CDI Intensive Care unit admission and mortality.[24] Also, Nsier *et al* showed that a higher NLR in CDI was associated with disease severity and mortality.[8] Future prospective studies are necessary to elucidate the potential role of this biomarker.

The limitations of our study are its retrospective nature, small sample size, methodological limitations (possible presence of confounders), and the reliance on review of clinical records. Clinical records could have been incomplete in terms of exposures or comorbidities. Regarding our analysis, we had a small sample size, and some confounding factors may not have been considered in the univariate analysis. Further large, multicentric, and prospective studies should be performed.

CONCLUSION

Our study describes CDI epidemiology at a Portuguese Hospital. Our data is consistent with previous reports that CDI seems to be more frequent in HO, although CA comprised an important proportion of cases. Reported risk factors for CDI such as antibiotics and PPI recent intake were present in our population. Charlson index, age, and NLR may constitute interesting predictors for CDI severity or outcomes and should be pursued for further validation. In clinical practice, early identification of subjects at risk for severe forms of CDI is essential. Therefore, further studies are required to improve risk factor stratification and to prompt the implementation of beneficial actions.

AUTHORS CONTRIBUTION

JBM: Draft of the paper and critical review. Contribution to the design of the work. Analysis and interpretation of data. Critical review and final approval of the version to be published.

JM: Contribution to the design and draft of the work. Analysis and interpretation of data. Critical review and final approval of the version to be published.

CC, HS, PM, CC, JC: Contribution to the design and draft of the work. Analysis and interpretation of data. Draft of the paper, critical review and final approval of the version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration issued by World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare that they followed the protocols in use at their working center regarding patient data publication.

COMPETING INTERESTS

The authors declare that there are no competing interests.

FUNDING SOURCES

No subsidies or grants contributed to this work.

REFERENCES

1. Loo VG, Bourgault AM, Poirier L, Lamothe F, Michaud S, Turgeon N, et al. Host and pathogen factors for Clostridium difficile infection and colonization. N Engl J Med. 2011;365:1693–703.
2. Rodríguez Garzotto A, Mérida García A, Muñoz Unceta N, Galera Lopez MM, Orellana-Miguel MÁ, Díaz-García CV, et al. Risk factors associated with Clostridium difficile infection in adult oncology patients. Support

Care Cancer. 2015;23:1569–77.
3. Guh AY, Adkins SH, Li Q, Bulens SN, Farley MM, Smith Z, et al. Risk factors for community-associated Clostridium difficile infection in adults: a case-control study. Open Forum Infect Dis. 2017;4:1–8.
4. Boekhoud IM, Hornung BV, Sevilla E, Harmanus C, Bos-Sanders IM, Terveer EM, et al. Plasmid-mediated metronidazole resistance in Clostridioides difficile. Nat Commun. 2020;11:1–12.
5. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:987–94.
6. Thabit AK, Alsolami MH, Baghlaf NA, Alsharekh RM, Almazmumi HA, Alselami AS, et al. Comparison of three current Clostridioides difficile infection guidelines: IDSA/SHEA, ESCMID, and ACG guidelines. Infection. 2019;47:899–909.
7. Chiang HY, Huang HC, Chung CW, Yeh YC, Chen YC, Tien N, et al. Risk prediction for 30-day mortality among patients with Clostridium difficile infections: a retrospective cohort study. Antimicrob Resist Infect Control. 2019;8:1–11.
8. Nseir W, Khamisy-Farah R, Amara A, Farah R. The prognostic value of inflammatory markers in Clostridium difficile-associated diarrhea. Isr Med Assoc J. 2019;21:658–61.
9. Sintra S, Taveira F, Canha C, Carvalho A, Simão A. Epidemiology of Clostridium difficile infection in Portugal: experience at a tertiary care hospital. Eur J Intern Med. 2019;60:e11–3.
10. Russo EM, Kuntz J, Yu H, Smith J, Hauser RG, Halchenko Y, et al. Incidence of Clostridioides difficile infections among young and middle-aged adults: Veterans Health Administration. Infect Control Hosp Epidemiol. 2019;40:997–1005.
11. Pinzon MC, Buie R, Liou JI, Shirley DK, Evans CT, Ramanathan S, et al. Outcomes of community and healthcare-onset clostridium difficile infections. Clin Infect Dis. 2019;68:1343–50.
12. Wang MS, Evans CT, Rodriguez T, Gerding DN, Johnson S. Clostridium difficile infection and limitations of markers for severity in patients with hematologic malignancy. Infect Control Hosp Epidemiol. 2013;34:127–32.
13. Davies KA, Longshaw CM, Davis GL, Bouza E, Barbut F, Barna Z, et al. Underdiagnosis of Clostridium difficile across Europe: The European, multicentre, prospective, biannual, point-prevalence study of Clostridium difficile infection in hospitalised patients with diarrhoea (EUCLID). Lancet Infect Dis. 2014;14:1208–19.
14. Vieira AM, Machado MV, Lito L, Cristino JM, Fernandes A, Maldonado R, et al. Diarreia associada a Clostridium difficile num hospital central. GE Port J Gastroenterol. 2010;17:21–8.
15. Oleastro M, Coelho M, Gião M, Coutinho S, Mota S, Santos A, et al. Outbreak of Clostridium difficile PCR ribotype 027 - the recent experience of a regional hospital. BMC Infect Dis. 2014;14:1–9.
16. Correia L, Monteiro R, Alfaro T, Simão A, Carvalho A, Costa N. Doença associada ao Clostridium difficile – aumento dramático da incidência em doentes internados. Rev Soc Port Med Interna. 2012;19:61–8.
17. Silva JD, Veloso N, Godinho R, Rosa I, Gonçalves L, Medeiros I, et al. Diarreia associada ao Clostridium difficile - casuística de 8 anos. GE Port J Gastroenterol. 2012;19:284–9.
18. Santos A, Isidro J, Silva C, Boaventura L, Diogo J, Faustino A, et al. Molecular and epidemiologic study of Clostridium difficile reveals unusual heterogeneity in clinical strains circulating in different regions in Portugal. Clin Microbiol Infect. 2016;22:695–700.
19. Almeida N, Silva N, Parente F, Portela F, Gouveia H, Alexandrino B, et al. Colite pseudomembranosa: uma casuística de internamentos. GE Port J Gastroenterol. 2006;13:06–13.
20. Fehér C, Mensa J. A comparison of current guidelines of five international societies on Clostridium difficile infection management. Infect Dis Ther. 2016;5:207–30.
21. Patel UC, Wieczorkiewicz JT, Tuazon J. Evaluation of advanced age as a risk factor for severe Clostridium difficile infection. J Clin Gerontol Geriatr. 2016;7:12–6.
22. Abou Chakra CN, Pepin J, Sirard S, Valiquette L. Risk factors for recurrence, complications and mortality in Clostridium difficile infection: a systematic review. PLoS One. 2014;9:e98400.
23. Khanafer N, Barbut F, Eckert C, Perraud M, Demont C, Luxemburger C, et al. Factors predictive of severe Clostridium difficile infection depend on the definition used. Anaerobe. 2016;37:43–8.
24. Chaudhry AS, Azab BN, McGinn JT, Bloom SW. Neutrophil lymphocyte ratio vs total leukocyte count as a predictor of adverse outcomes in Clostridium difficile associated diarrhea (CDAD). J Am Coll Surg. 2015;221:e63.