Outcomes of *Clostridioides difficile* infection in adult cancer and non-cancer patients hospitalised in a tertiary hospital: a prospective cohort study

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ABSTRACT

Background *Clostridioides difficile* infection (CDI) is one of the most common healthcare-associated (HA) infections. Cancer patients, particularly haemato-oncological patients, have an increased risk for CDI due to more risk factors compared with non-cancer patients. The aim of this study was to investigate differences in outcomes associated with HA CDI in patients with solid and haematological malignancies compared with patients with no underlying malignant disease in a tertiary healthcare centre in Serbia.

Methods A prospective cohort study was conducted including adult patients diagnosed with an initial episode of HA CDI. Their demographic and clinical characteristics associated with risk factors for CDI were documented. Outcomes such as all-cause 30-day mortality, cure of infection, diarrhoea relaps and recurrence of disease were followed. Patients were assigned to cancer and non-cancer groups. Within the cancer group, patients were divided into the solid tumour subgroup and haematological malignancy subgroup.

Results During a 7-year period, HA CDI was observed in 28 (5.1%) patients with haematological malignancy, 101 (18.3%) patients with solid tumours and 424 (76.7%) non-cancer patients. Older age (OR 1.04, 95% CI 1.02 to 1.07, p<0.001), admission to the intensive care unit (ICU) (OR 2.61, 95% CI 1.37 to 4.95, p=0.003), mechanical ventilation (OR 5.19, 95% CI 2.78 to 9.71, p<0.001) and use of antibiotics prior to CDI (OR 1.04, 95% CI 1.02 to 1.06, p=0.02) were associated with increased mortality. Compared with patients with solid tumours, patients with haematological malignancy were younger (65 vs 57 years, p=0.015), did not require ICU admission (25.0% vs 0%) or mechanical ventilation (8.9% vs 0%) and were treated longer with antibiotics prior to CDI (14 vs 24 days, p=0.002).

Conclusions Patients with haematological malignancy were exposed to different risk factors for CDI associated with mortality compared with patients with solid tumours and non-cancer patients. Older age, ICU stay and mechanical ventilation, but not presence or type of cancer, predicted the all-cause 30-day mortality.

INTRODUCTION

Clostridioides difficile infection (CDI) is a common healthcare-associated (HA) infection and the leading cause of infectious diarrhoea in hospitalised patients.[1 2] Risk factors for CDI include previous exposure to antibiotics (especially fluoroquinolones, cephalosporins, monobactams, carbapenems and clindamycin), older age, the use of proton pump inhibitors (PPI), the use of feeding tubes, surgery, prolonged hospitalisation and others.[2–7] Cancer patients have an increased risk for CDI since they are usually exposed to more risk factors compared with non-cancer patients.[2 7] The frequency of CDI in cancer patients has been shown to be 7% compared with 1–2% in non-cancer patients.[8 9] Also, the incidence of CDI has been reported to be 2.5 times more frequent in patients with haematological malignancies compared with patients with solid tumours.[2 10] Treatment outcomes may also differ between cancer and non-cancer patients. It was shown that the recurrence rate of CDI was 15–30% in the general population, but some authors reported a higher recurrence in patients with cancer compared with non-cancer patients.[9 11] Moreover, higher recurrence and mortality rates were reported in patients with haematological malignancies.[12 13] This led to further investigations of the severity of illness and the assumption that patients with active malignancy may have a more severe clinical CDI and may require more intensified treatment compared with non-cancer patients.[14] Currently, the severity of CDI can be assessed using different scoring systems and commonly the CDI is classified as severe if leukocytosis with a white blood cell count of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL is present.[15] However, in immunocompromised cancer patients it is more difficult to establish the severity of CDI because of neutropenia.

Metronidazole monotherapy has been the recommended treatment for non-severe CDI, but the latest recommendations favour the use of oral vancomycin in Serbia.[14–16] In severe illness, vancomycin monotherapy as well as the combination of metronidazole and vancomycin have been used.[13 17]

The characteristics of CDI in patients with cancer have been described, but there are limited data comparing treatment outcomes in cancer and non-cancer patients.[10 18–20] The aim of this study was to investigate all-cause 30-day mortality associated with CDI in patients with solid and haematological

malignancies versus patients with no underlying malignancy in a tertiary healthcare centre in Serbia.

METHODS

Study design, patients and definitions

We conducted a prospective study including adult patients (≥18 years) diagnosed with an initial episode of CDI from 2011 to 2017 at the Military Medical Academy (MMA), Belgrade (Serbia), a 1200-bed teaching hospital of the University of Defence. Our tertiary healthcare centre comprises 27 departments and, when there is suspicion of CDI, testing is performed and positive results are immediately reported to medical doctors specialised in infectious diseases and healthcare epidemiology. The infectious diseases specialist evaluates best treatment options (metronidazole or vancomycin or combination of both antibiotics). The healthcare epidemiologist evaluates the origin, risk factors and outcomes of the infection. Reviewing the clinical chart information on patient characteristics, risk factors related to healthcare were collected. We gathered data on the following variables: intrinsic factors (existing at admission), sex, age, malignancy and factors related to healthcare including previous hospitalisation in other hospitals, previous infections, ICU admission, duration of treatment in ICU, mechanical ventilation, nasogastric tubes, use of histamine-2-receptor antagonists (H_2RAs), PPIs, chemotherapy and antibiotics (number, type and duration of antibiotic usage). Data about the length of stay (LOS) in hospital, first recurrence of CDI, readmission to MMA, deaths within 30 days of CDI diagnosis and in-hospital mortality were also recorded.

A CDI case was defined as any hospitalised patient with laboratory confirmation of a positive toxin assay of *C. difficile* associated with diarrhoea (≥3 daily in a 24-hour period with no other recognised cause) or visualisation of pseudomembranes on sigmoidoscopy, colonoscopy, or histopathologic analysis on day 3 or later following admission to MMA (day 1).[15 21 22] We also included all patients readmitted to MMA. Readmission to MMA was defined as readmitted patients who did not have a CDI during their index admission to hospital but had onset of symptoms within 4 weeks of discharge from MMA.[23] Microbiological testing was performed at the Institute of Medical Microbiology at the MMA. Enzyme immunoassay kits for *C. difficile* toxins A and B were used (Vidas, BioMérieux, *C. difficile* toxins A&B (CDAB)).

First CDI recurrence was defined as a return of symptoms associated with a repeated positive test within 15–56 days after the initial diagnosis.[21] Patients with community-associated CDI and HA CDI acquired in another hospital were excluded from the study. Patients hospitalised for any non-cancer illness who developed initial HA CDI were assigned to the non-cancer group, whereas those who developed initial HA CDI with underlying malignancy were assigned to the cancer group which was divided into the haematological malignancy and solid malignancy subgroups. The Ethics Committee of the MMA approved the research protocol (MF VMA 05/20–22).

Statistical analysis

Data analyses were performed with SPSS version 25.0 (SPSS, Chicago, Illinois, USA). The results were expressed as mean±SD or as count and percentage (categorical data). The χ^2 test or Fisher exact test were used for categorical variables. For continuous variables with normal distribution, mean values were compared using the Student t-test. For non-parametric continuous variables the Mann–Whitney U test was used. All statistical tests were two-tailored and significance was set at $p<0.05$. If more than two groups were compared, the Kruskal–Wallis test was used. Risk factors independently associated with all-cause 30-day mortality (multivariable logistic regression anlysis) were identified by stepwise logistic regression analysis out of variables selected by univariable logistic regression analysis, with a limit for entering and removing categorical variables from the model at 0.05.

RESULTS

During 7 years we registered 836 patients with laboratory proven CDI. Among them, 183 patients acquired infection in community or in another hospital and were not included in the study. There were 553 patients undergoing in-hospital treatment at MMA who developed initial HA CDI and were included in the study, of which 424 were non-cancer patients and 129 were cancer patients. Patient characteristics are shown in table 1.

We found no statistically significant difference for all-cause 30-day mortality between cancer and non-cancer patients with CDI. Also, both groups received similar treatment for CDI, since 55.8% of cancer patients and 57.8% of non-cancer patients were treated with metronidazole or vancomycin monotherapy. Significantly more patients with cancer than non-cancer patients were treated with antibiotics prior to CDI (OR 0.45, 95% CI 0.20 to 0.98, p=0.004), but there was no significant difference in the number or type of administered antibiotics between the groups. We investigated the use of PPIs and H_2RAs as risk factors for CDI development and found no difference in exposure to these drugs between cancer and non-cancer patients. Cancer patients were younger (OR 0.98, 95% CI 0.97 to 0.99, p=0.006), more frequently male (OR 1.62, 95% CI 1.08 to 2.43, p=0.02) and had a higher prevalence of previous hospitalisations (OR 1.94, 95% CI 1.30 to 2.89, p=0.001) compared with the non-cancer group.

Within the cancer group, 28 patients had haematologic malignancy whereas solid tumours were present in 101 patients. In the subgroup of patients with haematological malignancy established diagnoses were: acute lymphoblastic leukaemia (7%), acute myeloid leukaemia (32%), non-Hodgkin's lymphoma (36%), Hodgkin's lymphoma (4%) and multiple myeloma (21%). The most common solid malignancies were pulmonary tumours (28%) followed by urological (18%), gastrointestinal (11%), nephrological (9%), hepatic (8%), pancreatic (8%), breast (6%) head and neck (4%) and other tumours (8%). We observed a variety of differences between the haematological malignancy and solid tumour subgroups, as shown in table 2. In the haematological malignancy subgroup, 79% of patients were on chemotherapy whereas in the solid tumour subgroup only 15% of patients had received chemotherapy at the time of CDI onset (OR 21.01, 95% CI 7.31 to 61.45, p<0.001).

Patients with haematological malignancy were younger (OR 0.96, 95% CI 0.93 to 1.00, p=0.015) and less likely to have surgery during hospitalisation than those in the solid tumour subgroup (OR 0.12, 95% CI 0.04 to 0.37, p<0.001). They were not admitted to the ICU, had no nasogastric tubes or mechanical ventilation. However, patients with haematological malignancy received a larger number of antibiotics prior to CDI (OR 1.72, 95% CI 1.18 to 2.50, p=0.005) and had a prolonged antibiotic treatment (OR 1.04, 95% CI 1.01 to 1.08, p=0.002). They were also administered PPIs more frequently (OR 2.74, 95% CI 1.16 to 6.49, p=0.022) and the number of days of hospitalisation prior to CDI was significantly higher (OR 1.02, 95% CI 1.00 to 1.04, p=0.04).

Table 1 Comparison of demographics, clinical characteristics and outcome in cancer and non-cancer patients with CDI

Variables	Cancer (n=129)	Non-cancer (n=424)	OR (95% CI)	P value
Age (years)	63.59±13.98	67.93±15.39	0.98 (0.97 to 0.99)	0.006
Age ≥65 years	59 (45.7%)	285 (67.21%)	0.41 (0.28 to 0.61)	<0.001
Male sex	82 (63.6%)	220 (51.9%)	1.62 (1.08 to 2.43)	0.020
Previous hospitalisation	75 (58.1%)	177 (41.7%)	1.94 (1.30 to 2.89)	0.001
Surgery	61 (47.3%)	205 (48.3%)	0.96 (0.65 to 1.42)	0.832
Intensive care unit	26 (20.2%)	100 (23.6%)	0.82 (0.50 to 1.33)	0.416
Diabetes	13 (10.0%)	75 (17.7%)	0.52 (0.28 to 0.57)	0.039
Nasogastric tube	12 (9.3%)	48 (11.3%)	0.80 (0.41 to 1.56)	0.519
Mechanical ventilation	9 (7.0%)	74 (17.5%)	0.35 (0.17 to 0.33)	0.004
Received AB prior to CDI	118 (91.5%)	407 (96.0%)	0.45 (0.20 to 0.98)	0.004
Fluoroqinolones	16 (12.4%)	85 (20.0%)	0.56 (0.32 to 1.00)	0.051
Cephalosporins second generation	24 (18.6%)	101 (23.8%)	0.73 (0.44 to 1.20)	0.215
Cephalosporins third generation	73 (17.2%)	236 (55.6%)	1.04 (0.70 to 1.55)	0.852
Aminoglycosides	28 (21.7%)	61 (14.4%)	1.65 (1.00 to 2.72)	0.048
Carbapenems	26 (20.2%)	89 (21.0%)	0.95 (0.58 to 1.42)	0.838
Macrolides	4 (3.1%)	15 (3.5%)	0.87 (0.28 to 2.68)	0.811
Penicillins	10 (7.8%)	42 (9.9%)	0.76 (0.37 to 1.57)	0.463
Glycopeptides	5 (3.9%)	31 (7.3%)	0.51 (0.19 to 1.34)	0.166
Sulfonamides	11 (8.5%)	30 (7.1%)	1.22 (0.60 to 2.52)	0.582
Clindamycin	0 (0%)	9 (2.1%)	NA	NA
Fosfomycin	0 (0%)	2 (0.5%)	NA	NA
Collistin	0 (0%)	6 (1.4%)	NA	NA
Linezolid	1 (0.8%)	3 (0.7%)	NA	NA
Rifampicin	1 (0.8%)	2 (0.5%)	NA	NA
Tigecyclin	0 (0%)	2 (0.5%)	NA	NA
H_2 receptor antagonists	54 (41.9%)	166 (39.2%)	1.12 (0.75 to 1.67)	0.582
Proton pump inhibitors	41 (31.2%)	121 (28.5%)	1.17 (0.76 to 1.79)	0.478
Days of hospitalisation prior to CDI	21.09±18.77	19.08±18.04	1.00 (0.99 to 1.02)	0.336
Monotherapy metronidazole	60 (46.5%)	194 (45.8%)	1.03 (0.69 to 1.53)	0.880
Monotherapy vancomycin	12 (9.3%)	51 (12.0%)	0.75 (0.39 to 1.45)	0.394
Monotherapy total	72 (55.8%)	245 (57.8%)	0.92 (9.62 to 1.37)	0.692
Combination treatment	54 (41.9%)	170 (40.1%)	1.08 (0.72 to 1.61)	0.720
Metronidazole treatment (days)	7.41±4.10	7.72±5.11	1.01 (0.95 to 1.08)	0.678
Vancomycin treatment (days)	7.58±4.14	7.68±3.52	1.00 (0.85 to 1.20)	0.929
Combination treatment (days)	10.02±5.83	10.04±5.79	1.00 (0.95 to 1.06)	0.980
Length of stay	38.33±24.47	38.54±31.33	1.00 (0.99 to 1.00)	0.332
All-cause 30-day mortality	22 (17.1%)	92 (21.7%)	0.74 (0.44 to 1.24)	0.254
Recurrence	5 (3.9%)	22 (5.2%)	0.74 (0.27 to 1.99)	0.545

AB, antibiotics; CDI, *Clostridioides difficile* infection; NA, not applicable.

The duration of CDI treatment was longer in patients with haematological malignancy (OR 1.05, 95% CI 1.01 to 1.10, p=0.025) and they were less likely to receive monotherapy with metronidazole (OR 0.24, 95% CI 0.09 to 0.63, p=0.004) or monotherapy at all (OR 0.42, 95% CI 0.18 to 1.00, p=0.046).

Nevertheless, treatment outcomes such as all-cause 30-day mortality rate and recurrence of CDI during hospital stay were not different between the malignant disease patient subgroups.

We performed a univariate and multivariate analysis of the effect of patients' demographic, clinical and treatment characteristics on all-cause 30-day mortality following CDI and the results are shown in table 3. The presence and type of cancer as well as chemotherapy were not associated with all-cause 30-day mortality of patients with CDI. Predictive risk factors of all-cause 30-day mortality were older age, admission to ICU and the presence of mechanical ventilation as well as prolonged treatment with antibiotics prior to CDI. In contrast, patients who underwent surgery were less likely to have a fatal outcome considered as all-cause 30-day mortality (OR 0.50, 95% CI 0.29 to 0.88, p=0.015). When compared for predictive risk factors, there was a significant difference among patients with haematological malignancy, solid tumours and non-cancer patients (Kruskal–Wallis test, p<0.001). This difference remained significant between groups as well (Mann–Whitney U test, p<0.05).

Admission to ICU was comparable between patients with solid tumours and non-cancer patients (25.1% vs 23.6%), whereas our patients with haematological malignancy were not admitted to the ICU and were not on mechanical ventilation. Patients with solid tumours were less likely to be on mechanical ventilation than non-cancer patients (OR 0.46, 95% CI 0.22 to 0.96, p=0.034). Patients with haematological malignancy received longer treatment with antibiotics prior to CDI compared with solid tumour and non-cancer patients (p<0.05), but there was no difference in antibiotic treatment between solid tumour and non-cancer patients. Surgery was most frequently observed in patients with solid tumours (58.4%) followed by non-cancer patients (48.3%) and patients with haematological malignancy (14.3%). The difference between solid tumour and non-cancer patients was not significant whereas patients with haematological malignancy were less likely to undergo surgery compared with both patients with solid tumours (OR 0.12, 95% CI 0.04 to 0.47, p<0.001) and non-cancer patients (OR 0.18, 95% CI 0.06 to 0.52, p<0.001).

Table 2 Demographics, clinical characteristics and outcome in patients with haematological malignancy and CDI versus those with solid tumours and CDI

Variables	Haematological malignancy (n=28)	Solid tumour (n=101)	OR (95% CI)	P value
Age (years)	57.15±17.69	65.34±12.92	0.96 (0.93 to 1.00)	0.015
Age 65 years	11 (39.3%)	48 (47.5%)	0.71 (0.30 to 1.68)	0.439
Male sex	17 (60.7%)	65 (64.4%)	0.86 (0.36 to 2.02)	0.793
Previous hospitalisation	20 (71.4%)	55 (54.5%)	2.09 (0.84 to 5.19)	0.112
Surgery	2 (7.2%)	59 (58.4%)	0.05 (0.01 to 0.24)	<0.001
Intensive care unit	0 (0%)	26 (25.1%)	NA	NA
Nasogastric tube	0 (0%)	12 (11.9%)	NA	NA
Mechanical ventilation	0 (0%)	9 (8.9%)	NA	NA
Received AB prior to CDI	26 (92.6%)	92 (91.1%)	1.27 (0.26 to 6.25)	0.767
No of ABs prior to CDI	2.48±1.22	1.84±1.10	1.72 (1.18 to 2.50)	0.005
Fluoroqinolones	4 (14.3%)	12 (11.9%)	1.23 (0.36 to 4.17)	0.733
Cephalosporins second generation	4 (14.3%)	20 (19.8)%)	0.68 (0.21 to 2.17)	0.509
Cephalosporins third generation	10 (35.7%)	63 (62.4%)	0.034 (0.14 to 0.80)	0.014
Aminoglycosides	10 (35.7%)	18 (17.8%)	2.56 (1.01 to 6.47)	0.042
Carbapenems	7 (25.0%)	19 (18.8%)	1.44 (0.53 to 3.87)	0.470
Macrolides	0 (0%)	4 (4.0%)	NA	NA
Penicillins	5 (17.9%)	5 (5.0%)	4.17 (1.11 to 15.63)	0.024
Glycopeptides	1 (3.6%)	4 (4.0%)	NA	NA
Sulfonamides	7 (25.0%)	4 (4.0%)	8.08 (2.17 to 30.14)	<0.001
Linezolid	0 (0%)	1 (1.0%)	NA	NA
Rifampicin	0 (0%)	1 (1.0%)	NA	NA
AB treatment prior to CDI (days)	24.26±18.10	14.03±11.43	1.04 (1.01 to 1.08)	0.002
H_2 receptor antagonists	16 (57.1%)	38 (37.6%)	2.21 (0.95 to 5.17)	0.067
Proton pump inhibitors	14 (50.0%)	27 (26.7%)	2.74 (1.16 to 6.49)	0.022
Days of hospitalisation prior to CDI	27.63±21.70	19.30±17.60	1.02 (1.00 to 1.04)	0.040
Monotherapy metronidazole	6 (21.4%)	54 (53.5%)	0.24 (0.09 to 0.63)	0.004
Monotherapy vancomycin	5 (17.9%)	7 (6.9%)	3.03 (0.88 to 10.00)	0.080
Monotherapy total	11 (39.3%)	61 (60.4%)	0.42 (0.18 to 1.00)	0.046
Combination treatment	16 (57.1%)	38 (37.6%)	2.38 (1.00 to 5.56)	0.051
AB treatment of CDI (days)	15.99±9.65	11.25±8.13	1.05 (1.01 to 1.10)	0.025
Metronidazole treatment (days)	7.33±2.66	7.43±4.25	0.98 (0.85 to 1.13)	0.970
Vancomycin treatment (days)	10.20±5.40	5.71±1.50	1.49 (0.90 to 2.46)	0.119
Combination treatment (days)	10.69±4.52	9.74±6.29	1.03 (0.93 to 1.13)	0.583
Chemotherapy	22 (78.5%)	15 (14.9%)	21.01 (7.31 to 61.45)	<0.001
Length of stay	49.19±25.30	35.37±23.50	1.02 (1.00 to 1.04)	0.014
All-cause 30-day mortality	5 (17.9%)	17 (16.8%)	1.07 (0.36 to 3.22)	0.898
Recurrence	1 (3.6%)	4 (4.0%)	0.89 (0.10 to 8.37)	0.925

AB, antibiotics; CDI, *Clostridioides difficile* infection; NA, not applicable.

As expected, LOS was inversely related to all-cause 30-day mortality since death reduced the patients' in-hospital stay.

Because mechanical ventilation was associated with the highest risk of fatal outcome and was significantly more prevalent in non-cancer patients, we performed an all-cause 30-day mortality risk factor analysis without patients on mechanical ventilation. Nevertheless, there was still no significant difference in the all-cause 30-day mortality rate among patients with solid tumours and non-cancer patients. The fatal outcome was again associated with older age, ICU, surgery, antibiotic treatment prior to CDI and LOS.

DISCUSSION

This study provides information on the characteristics and outcomes of HA CDI in cancer and non-cancer patients treated in a tertiary care hospital. There were no differences in all-cause 30-day mortality during the hospital stay between cancer and non-cancer patients. Nevertheless, we found differences in demographic, clinical and treatment characteristics of patients with haematological malignancy, solid tumours and non-cancer patients.

Numerous risk factors for CDI have been identified such as older age, previous exposure to antibiotics (ie, clindamycin, fluoroquinolones, cephalosporins, monobactams and carbapenems), the use of PPIs, chemotherapy, the use of nasogastric tube feeding and prolonged hospitalisation.[2–7 10 24]

Advanced age is recognised as a risk factor for CDI in cancer and non-cancer patients.[24] The age differed among our cohort, with patients with haematological malignancies being younger while non-cancer patients were older than patients with solid tumours, which is in line with some other studies.[12 18 25 26]

Antibiotic therapy is frequently administered in hospitals to treat infections or for prophylaxis. In our cohort, cancer patients were more exposed to antibiotic use than non-cancer patients, but the exposure was very high (>90%) in both groups. In contrast, the study by Larrainzar-Coghen *et al* showed similar exposure to antibiotics prior to CDI between cancer and non-cancer patients (82.7% and 86.7%, respectively).[18] The most frequently used antibiotics in our study were fluoroquinolones and cephalosporins of the second and third generation, but there was no difference in exposure between cancer and non-cancer patients. Nevertheless, patients with haematological malignancy

Table 3 Univariable and multivariable analysis of demographic, clinical and treatment characteristics for all-cause mortality within 30 days of CDI diagnosis

Variables	Univariable analysis OR (95% CI)	P value	Multivariable analysis OR (95% CI)	P value
Age	1.04 (1.02 to 1.06)	<0.001	1.04 (1.02 to 1.07)	<0.001
Age ≥65 years	2.46 (1.53 to 3.96)	<0.001		
Male sex	1.32 (0.87 to 2.00)	0.192		
Solid tumours	0.79 (0.45 to 1.39)	0.415		
Haematological malignancy	0.82 (0.30 to 2.21)	0.694		
Previous hospitalisation	0.94 (0.62 to 1.42)	0.768		
Surgery	0.54 (0.35 to 0.82)	0.004	0.50 (0.29 to 0.88)	0.015
Intensive care unit	2.98 (1.91 to 4.65)	<0.001	2.61 (1.37 to 4.95)	0.003
Nasogastric tube	5.20 (2.98 to 9.09)	<0.001		
Mechanical ventilation	7.23 (4.37 to 11.94)	<0.001	5.19 (2.78 to 9.71)	<0.001
Received AB prior to CDI	0.96 (0.38 to 2.43)	0.932		
No of ABs prior to CDI	0.88 (0.76 to 1.06)	0.168		
Fluoroqinolones	0.86 (0.50 to 1.49)	0.586		
Cephalosporins second generation	1.51 (0.95 to 2.41)	0.079		
Cephalosporins third generation	0.79 (0.52 to 1.20)	0.267		
Aminoglycosides	0.63 (0.34 to 1.15)	0.128		
Carbapenems	1.27 (0.76 to 2.13)	0.361		
Macrolides	0.47 (0.12 to 1.89)	0.289		
Penicillins	0.76 (0.36 to 1.60)	0.471		
Glycopeptides	0.84 (0.35 to 2.04)	0.705		
Sulfonamides	0.89 (0.39 to 2.03)	0.789		
Clindamycin	0.24 (0.02 to 3.17)	0.278		
Fosfomycin	1.00 (0.99 to 1.01)	0.999		
Colistin	17.29 (1.87 to 159.84)	0.012		
Linezolid	1.21 (0.11 to 13.23)	0.876		
Rifampicin	1.00 (0.99 to 1.01)	0.999		
Tigecyclin	8.88 (0.40 to 198.60)	0.168		
AB treatment prior to CDI (days)	1.02 (1.01 to 1.03)	0.016	1.04 (1.02 to 1.06)	0.020
H_2 receptor antagonists	0.16 (0.76 to 1.76)	0.487		
Proton pump inhibitors	1.07 (0.68 to 1.68)	0.763		
Days to CDI	1.00 (0.99 to 1.01)	0.972		
Monotherapy metronidazole	0.88 (0.58 to 1.33)	0.553		
Monotherapy vancomycin	1.22 (0.66 to 2.27)	0.531		
Monotherapy total	0.96 (0.63 to 1.45)	0.845		
Combination treatment	0.89 (0.58 to 1.35)	0.582		
Metronidazole treatment (days)	0.98 (0.93 to 1.03)	0.393		
Vancomycin treatment (days)	1.00 (0.92 to 1.08)	0.945		
Combination treatment (days)	1.00 (0.98 to 1.02)	0.990		
Length of stay	0.99 (0.98 to 0.99)	0.004	0.97 (0.96 to 0.99)	<0.001
Cancer	0.78 (0.47 to 1.30)	0.343		
Chemotherapy	0.77 (0.33 to 1.79)	0.543		
Recurrence	0.46 (0.14 to 1.56)	0.204		

AB, antibiotics; CDI, *Clostridioides difficile* infection.

were less exposed to third generation cephalosporins prior to CDI. A large meta-analysis of studies in general hospital patients showed that all the aforementioned antibiotics may pose a similar risk for CDI.[24 27] There was no difference between cancer and non-cancer patients regarding the number of antibiotics used or the length of treatment. However, patients with haematological malignancy were treated with a larger number of antibiotics and for a longer period, in accordance with previous data.[18 28] The use of combinations of antibiotics for a prolonged time has been associated with an increased risk of CDI in cancer and non-cancer patients.[29–31]

PPIs and H_2RAs suppress gastric acid release and increase the gastric pH, which potentially reduces local bactericidal properties.[24] The use of PPIs was higher in patients with haematological malignancy than in patients with solid tumours, but overall there was no significant difference between cancer and non-cancer patients. Similar findings were reported by Larrainzar-Coghen *et al*.[18] A meta-analysis which included a large number of observational studies found that the risk of CDI was almost two times higher in PPI users than in non-users.[32]

Patients with haematological malignancy had a greater exposure to chemotherapy in our study than those with solid tumours (79% vs 15%). We observed a low frequency of chemotherapy in patients with solid tumours because the majority of these patients were admitted to the hospital for surgical removal of the tumour. Although chemotherapy has been associated with CDI, Fuereder *et al* showed that chemotherapy per se is not a risk factor for CDI in haemato-oncological patients. They concluded that antimicrobial therapy was a major risk factor observed independently from chemotherapy in the examined cohort.[26 33]

The patients with haematological malignancy in our cohort were predominantly medical patients who did not require admission to the ICU and, accordingly, mechanical ventilation and nasogastric tubes were not present in this patient subgroup.

In contrast, patients with solid tumours had similar frequencies of surgery, ICU stay and nasogastric tube to non-cancer patients, but mechanical ventilation was more frequent in non-cancer patients. ICU stay has been positively associated with CDI in trauma/surgery patients.[34 35] A study in a large cohort of intubated patients showed that prolonged mechanical ventilation was an independent predictor of HA CDI.[36]

Previous hospitalisation occurred more frequently in the cancer group and is in accordance with other findings.[18] Recurrent hospitalisation and prolonged LOS have been associated with the increased likelihood of exposure to *C. difficile*, but opposite results have also been reported.[37–39]

The treatment of CDI in cancer and non-cancer patients was similar and monotherapy with metronidazole or vancomycin was most common. Nevertheless, patients with haematological malignancy were less likely to receive monotherapy and more likely to have prolonged treatment of the CDI, indicating that the severity of illness might have been different in these patients. Larrainzar-Coghen *et al*[18] reported more frequent use of fidaxomicin in patients with haematological malignancy, and other authors have reported more frequent use of vancomycin and metronidazole in patients with cancer and severe disease.[8 17 18 40] Fidaxomicin was not prescribed in our population of patients since the drug was not marketed in Serbia during the study.

Increased LOS is a risk factor for the development and treatment outcomes of CDI.[41] There was no difference in LOS between cancer and non-cancer patients, but haemato-oncological patients had an increased LOS because of the hospitalisation time prior to CDI and the prolonged treatment of the infection. Increased LOS and increased mortality in the presence of CDI have been reported in patients with haematological malignancy.[42] Honda *et al* reported a median LOS of 41.5 days in a cohort of 126 CDI cases (17.5 days before and 18 days post-CDI diagnosis), which is comparable to our results in solid tumour and non-cancer patients.[43]

There was no difference in outcomes in terms of all-cause 30-day mortality or recurrence of illness during hospital stay between cancer and non-cancer patients in our study. Our mortality rate in cancer patients (17.1%) is in accordance with other studies reporting a range of 3–19.7%.[18 24 44] Non-cancer patients with CDI had a high mortality rate (21.7%), comparable to a Hungarian study in which 30-day mortality of 21.9% was reported.[45] However, other studies have reported lower mortality rates of 6.9–9.9% in non-cancer patients.[18 28] We observed low rates of disease recurrence (3.9–5.2%), which is similar to the results of Silva-Velazco *et al* (6.3–8.1%) but in contrast to 15–35% of patients reported in other studies.[16 24] However, our low recurrence rates may have been biased by the fact that patients were only followed up to hospital discharge and recurrence was registered only if they were re-admitted to the hospital for CDI.

The multivariate regression analysis in our study showed that older age, ICU stay, mechanical ventilation and prolonged antibiotic treatment prior to CDI were positive predictors of a fatal outcome. In contrast, surgery and LOS were associated with survival. Our study was comparable in methodology to the study by Larrainzar-Coghen *et al* but the results are only partially consistent.[18] They showed that age, solid malignancy, haematological neoplasm, previous hospital admission, parenteral feeding and fever predicted the all-cause 30-day mortality of CDI in their cohort.[18] However, a possible explanation for the discrepancy between the studies is that the mortality rate of their non-cancer patients was lower than ours (8.6% vs 21.7%) whereas the patients with cancer had similar mortality rates. Age has been reported as an independent predictor of mortality in other studies as well.[18 24 44] ICU stay and mechanical ventilation are consistent with patients being critically ill and having higher odds for a fatal outcome.[19] Larrainzar-Coghen *et al* reported previous hospitalisations to be predictive of higher mortality rates, arguing that this increases the risk of exposure to *C. difficile* spores and colonisation of the patients.[18] Furthermore, the disruption of the intestinal flora may enhance the damage of *C. difficile* toxins in the intestinal epithelium, and immunosuppressed patients may not be able to offer an adequate immunological response.[18] Similarly, the gastrointestinal flora is disrupted by the prolonged use of antibiotics, which we observed in patients with haematological malignancy.

Altogether, our data show that patients in our study were exposed to different CDI risk factors associated with mortality. Patients with haematological malignancy were younger, not associated with ICU and mechanical ventilation in contrast to solid tumour and non-cancer patients. However, they were exposed to prolonged treatment with antibiotics prior to CDI and were less likely to undergo surgery than solid tumour and non-cancer patients. In contrast, our results pointed out only age and mechanical ventilation as the difference between patients with solid tumours and non-cancer patients regarding mortality predictors. When adjusted for mechanical ventilation, all other parameters remained predictive of mortality and there were again no differences in mortality rates between patients with haematological malignancy, solid tumours and those without cancer.

Limitations of study

The present study has several limitations. It is a single-centre study and our data may not be generalised to other healthcare centres. Fidaxomicin was not available for our patients. Unfortunatelly, data concerning patients after discharge from the hospital were not available. Therefore, the frequency and impact

Key messages

What is already known on this subject

- *Clostridioides difficile* infection (CDI) is a common healthcare-associated infection and the leading cause of infectious diarrhoea in hospitalised patients. Risk factors so far associated with CDI include previous exposure to antibiotics (especially fluoroquinolones, cephalosporins, monobactams, carbapenems and clindamycin), older age, surgery and prolonged hospitalisation.
- Cancer patients have an increased risk for CDI since they are usually exposed to more risk factors compared with non-cancer patients. However, there are limited data comparing treatment outcomes in cancer and non-cancer patients.

What this study adds

- Risk factors for CDI associated with mortality were different between patients with haematological malignancy and those with solid tumours and non-cancer patients.
- Outcomes such as all-cause 30-day mortality rate and recurrence of CDI during hospital stay were similar between cancer (including haematological malignancy and solid tumours) and non-cancer patients.
- Older age, intensive care unit stay, mechanical ventilation and prolonged antibiotic treatment prior to CDI were positive predictors of a fatal outcome.

of post-discharge CDI, initial and recurrent, could be widely underestimated. Another major limitation was the lack of culture and molecular typing data.

However, the strengths of our study include its prospective cohort design, duration of 7 years and the 'real-life' study of the patient population.

CONCLUSIONS

From our 7-year cohort study it can be concluded that there was no difference in outcomes regarding all-cause 30-day mortality rate and recurrence of CDI during hospital stay between patients with cancer (including haematological malignancy and solid tumours) and non-cancer patients. However, patients with haematological malignancy were exposed to different risk factors for CDI associated with mortality compared with patients with solid tumours and non-cancer patients, and they were less likely to be treated with metronidazole monotherapy.

In our cohort, older age, prolonged antibiotic treatment prior to CDI, ICU stay and mechanical ventilation predicted the all-cause 30-day mortality.

Contributors SVK, BoM, AP and VŠ participated in the design of the study and interpretation of the data. BoM, VP, MM, DT and OT took part in acquisition of data. VD-S, BrM and SVK interpreted the data. SVK, BoM, AP and VŠ coordinated and helped to draft the manuscript. All authors have read and approved the final version of the manuscript.

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