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The epidemiology of healthcare acquired Clostridioides difficile associated diarrhea in a healthcare facility in Saudi Arabia

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Abstract
Background: Clostridium difficile-associated diarrhea (CDAD) is the most frequent cause of nosocomial infectious diarrhea and can result in conditions ranging from mild diarrhea to toxic megacolon and pseudomembranous colitis. Aim of the study: Reducing the occurrence of clostridium difficile-associated diarrhea (CDAD) in King Fahad Medical City and improve its outcome. Methods: A retrospective analysis was conducted, and data were collected from medical records of male and female patients aged > 14 years with positive NAAT results for C. difficile toxin genes and clinical signs and symptoms in King Fahad Medical City, Riyadh, from Jan 2021 to Dec 2022 were included in the study while patients with diarrhea due to chronic CDIs, previous surgeries, and patients with incomplete records were excluded to assess the prevalence, risk factors, recurrence, and complications of CDAD.
Results: Antibiotics and proton-pump inhibitors were the commonest risk factors for Clostridium difficile infection (86.2%) for each. Most of the studied group (91.7%) had diarrhea as the main symptom while hypotension was the commonest complication of Clostridium difficile infection, (30.3%). The older patients, the presence of malignancy, previous antibiotics, previous PPI, shock, and occurrence of relapse were statistically significantly associated with mortality due to Clostridium difficile infection (p-value 0.002, 0.01, 0.01, 0.001 &0.004) respectively.
Conclusion: Older age, antibiotics, PPIs, and the presence of malignancy were risk factors for Health-care acquired infection Clostridium difficile-associated diarrhea for adults hospitalized for more than 2 calendar days after admission (Health-care acquired infection) in King Fahad Medical City.
Keywords: Clostridium difficile-associated diarrhea, risk factors, the outcome.

INTRODUCTION

The most common cause of nosocomial infectious diarrhea is Clostridium difficile. Patients in hospitals were at risk for diarrhea brought on by C. difficile. Adults with various hospital stays have different risk factors for Clostridium difficile -associated diarrhea (CDAD), and various preventive interventions should be taken into account (Hung et al., 2021). Clostridium difficile infection is caused by the gram-positive, spore-forming anaerobic bacterium Clostridium difficile (Al Alawi et al., 2020). It was initially identified in 1935 as a part of the typical intestinal flora of developing neonates (Althaqafia et al., 2022). Two endotoxins, toxin A (TcdA) and toxin B

(TcdB), are responsible for C. difficile's pathogenicity. These toxins primarily damage the target cells' cytoskeletal framework and tight junctions, which ultimately results in cell death. Although cardiac, renal, and neurological impairments are also known to occur, intestinal disease has been reported to be the most frequently reported symptom of Clostridium difficile infections (CDIs) (Al Alawi et al., 2020).

The most frequent risk factors for C. difficile diarrhoea are old age, immunocompromised state, and gastric acid suppressant use, particularly use of proton pump inhibitors (PPIs). Adults who have undergone previous intestinal surgery, have serious underlying gastrointestinal diseases like colon cancer or inflammatory bowel disease, or take antidepressants like mirtazapine and fluoxetine are also thought to be at a higher risk of developing C. difficile diarrhoea. However, in 2017 there were 145 cases per 100,000 people (Guh et al., 2020).

The gold standard for diagnosing CDIs is conventional culture and toxigenic culture methods (by isolating the bacterial cells and looking for toxins). They call for lengthy processing times, resources like appropriate testing media, and skilled technicians. Commercially available enzyme immunoassays (EIAs) have gained popularity and are simple to use, but their sensitivity is low (Obaid & Alhifany, 2020). Given that up to 21% of hospitalised patients have asymptomatic colonisation with C. difficile, the main drawback of this single-step method is that it may identify genes encoding the toxin rather than the actual toxins, which could result in an overdiagnosis of CDIs (Guh et al., 2020). Contrarily, the two-step algorithm for the detection of CDIs uses EIAs to detect toxins and then the NAAT to confirm any positive results (Wong et al., 2017). Therefore, the most accurate method for CDIs diagnosis was recommended by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) as a multi-step protocol using glutamate dehydrogenase (GDH) antigen/toxin A/B combined with NAAT (McDonald et al., 2018).

The likelihood of contamination and false-positive results was reduced in laboratories that used multiplex systems, such as the GeneXpert® PCR assay, which used a closed cartridge-based system for nucleic acid extraction, amplification, and detection. By focusing on the gene tcdC, which increases toxin production and pathogenicity in C. difficile strains, including the hypervirulent RT027 strain, GeneXpert® PCR assay can identify the majority of C. difficile strains. (Obaid & Alhifany, 2020).

Few studies have reported on the prevalence and risk factors of CDI in Saudi Arabia, and the information is scarce so this study is performed to assess risk factors that can enable us to perform effective preventive measures.

Research Question: What are the prevalence rate and risk factors of Clostridium difficile-associated diarrhea (CDAD) in King Fahad Medical City?

Aim of the study: Reducing the occurrence of clostridium difficile-associated diarrhea (CDAD) in King Fahad Medical City and improving its outcome.

Objectives:

General objectives;

1- To estimate the prevalence rate of Clostridium difficile-associated diarrhea (CDAD) in King Fahad Medical City.

2- To determine the risk factors of Clostridium difficile-associated diarrhea (CDAD) in King Fahad Medical City.

Specific objectives:

3- To assess the factors affecting the outcome of Clostridium difficile-associated diarrhea (CDAD) in King Fahad Medical City. All medical records of male and female patients

aged > 14 years with positive NAAT results for C. difficile toxin genes between Jan 2021 and Dec 2022 were included in the study while patients with diarrhea due to chronic CDIs, previous surgeries, and patients with incomplete records were excluded.

LITERATURE REVIEW

Background: The most common cause of nosocomial infectious diarrhea is Clostridium difficile-associated diarrhea (CDAD), which can cause anything from mild diarrhea to toxic megacolon and pseudomembranous colitis. A retrospective analysis of 174,903 elderly patients who had CDAD codes revealed that CDAD was linked to a higher risk of death, a new transfer to a long-term care facility, and a new transfer to a short-term skilled nursing facility. In France, the total additional costs for national insurance were estimated to be €85 million (US $93,243,725), and the average additional cost for hospital stays due to CDAD was €8295 (US $9099). CDAD is a significant infection control issue because it is frequently spread in healthcare settings by healthcare personnel. (Hung et al., 2021)

Risk factors: It is known that more than 40 risk factors contribute to the disease's onset. Age, sex, ethnicity, and comorbidities are examples of host-related traits that are well-known risk factors (Al Alawi et al., 2020). Antibiotic exposure, previous hospitalization, the use of feeding tubes, gastrointestinal surgery, and the use of proton-pump inhibitors are additional risk factors for CDAD (PPIs). The majority of antibiotic exposure classes, notably third-generation cephalosporins, clindamycin, or fluoroquinolones, have been associated with CDAD. (Lin et al., 2015). Heinlen and Ballard (2010) discovered that the ability of Clostridium difficile to produce toxin A (TcdA) and toxin B (TcdB), which are pro-inflammatory and cytotoxic toxins causing serious damage in the large intestine, contributes to its pathogenicity. (Azab et al., 2017)

Prevalence: The prevalence of illness is affected by several factors, as research conducted in 2011 to evaluate the incidence across 34 counties in 10 geographic areas of the United States revealed that the incidence was higher among people over 65, women, and people of European descent (Eze et al., 2017). Studies have revealed a changing pattern in the patient populations most frequently affected, with a rise in C. difficile infections among younger patients and those who have never taken antibiotics before (Chitnis et al., 2013). Of the patients with C. difficile, about 83,000 experienced at least one recurrence, and 29,000 passed away within 30 days of the initial diagnosis. Misuse of antibiotics makes patients more susceptible to C. difficile infections. Over 50% of hospitalised patients will receive an antibiotic while they are there, and 30% to 50% of antibiotic prescriptions are unnecessary or incorrect. Over the course of five years, the CDC projects that medical expenses could be reduced by up to $3.8 billion. (Mada & Alam, 2023)

Epidemiology: More people are becoming aware of the prevalence of C. difficile-associated diarrhea (CDAD). CDI prevalence was estimated to be around 2.4 and 1.7 per 10000 patients in Saudi Arabia's tertiary healthcare facilities in 2007 and 2008, respectively (Shajan et al., 2014).

According to estimates, the prevalence rates in South Asia and the Middle East are 10.5% and 11.1%, respectively, and they range from 23.8% in Kuwait to 8-10% in Jordan (Aljafel et al., 2020).

In England, there was a 61% decrease in CDI incidence between 2007 and 2010, according to recent research, suggesting that the incidence of CDIs may be decreasing in some locations. This decline could have been brought on by a change in the dominance of epidemic strains (ribotype 027), the successful implementation of preventative and control measures, or a combination of these factors. (Althaqafi et al., 2022)

Mode of transmission: The organism is transmitted among humans via the fecal-oral route. When the organism transforms into its spore state, it is challenging to get rid of alcohol-based and other conventional surface cleaners. (Woods et al., 2021)

Clinical features: Toxic strains of C. difficile can cause a wide range of illnesses, from asymptomatic infection or mild diarrhea to severe illness that can cause toxic megacolon, multisystem organ failure, and even death. After the first day of antibiotic use or up to six weeks after the end of an antibiotic course, CDI symptoms may appear. Diarrhea without other systemic symptoms and mild abdominal pain and cramps are considered symptoms of mild disease. Frequent diarrhea, abdominal distension, abdominal pain, fever, tachycardia, and/or oliguria are symptoms of moderate disease. Occult bleeding, renal failure with oliguria, hemodynamic instability requiring vasopressor support, or cardiopulmonary failure requiring mechanical ventilation are all symptoms of severe or fulminant disease. The first warning sign could be a decline in diarrhea caused by a colonic muscle tone. (Woods et al., 2021)

Prevention: Vaccination is an excellent preventative strategy for CDI, as it can control or reduce the infiltration of C. difficile pathogens into the gut epithelium and/or damage to the healthy gut microbiome. Bezlotoxumab has been approved for the prevention of CDI recurrence, but once the patient has excreted it, they are no longer protected. (Gonzales-Luna et al., 2023)

Of course, the best prevention is to limit the use of antibiotics. However, bacterial diseases require the use of antibiotics as a treatment. Preventive measures include reducing the frequency and length of antimicrobial treatments, reducing the use of other drugs like proton pump inhibitors linked to C. diff disease, and reducing the number of antibiotics. The single most significant risk factor is acknowledged to be exposure to antibiotics. Almost all antimicrobials raise the possibility of getting C. diff disease. Programs for antibiotic stewardship will improve this strategy. (Dinleyici & Vandenplas, 2019).

A good hand hygiene routine and contact avoidance are advised. It has also been demonstrated that cleaning with chlorine-containing products or other spore-destroying agents is effective. (Dinleyici & Vandenplas, 2019).

Althaqafi et al., 2022 performed a retrospective cohort study in the Western region of Saudi Arabia at a tertiary medical facility and reported 237 of the 2611 patients who underwent NAAT for C. difficile toxin genes during the two years (October 2018 to October 2020) had CDI. Consequently, the prevalence of CDI was 9.1% among the study's participants. Over 50% of the participants in the study were men (52.74%). Ninety-three percent of the patients were hospitalized. At the time of CDI diagnosis, the average body temperature was 37.23 ±0.81 ^{0}C. Althaqafi et al., 2022 demonstrated the risk factors connected to the emergence of a CDI. 74.30% of the patients used antibiotics, and the most common delivery method was intravenous (IV) (92.10%). The majority of patients (67.50%) used acid suppressants before the infection started, 46% of patients had cancer, and only 6.30% of patients had previously undergone gastrointestinal surgery. The frequency of CDI recurrence was 13.90%. The study participants were given prescriptions for several broad-spectrum antibiotics. The most widely used broad-spectrum antibiotic was piperacillin-tazobactam (used by 38.8% of the patients), followed by meropenem.

Choi et al., 2022 enrolled a total of 5,337 adult CDI patients, and 828 (15.5%) of them were determined to have severe CDI. The maximum body temperature, platelet count, eosinophil count, oxygen saturation, Glasgow Coma Scale, serum albumin, and respiratory rate were the top variables that the machine learning models chose. The SOFA score, white blood cell (WBC) count, serum albumin level, and ventilator use were all significantly associated with severe CDI after propensity score matching (P 0.001 for all). Patients with severe CDI were distinguished from

those without severe CDI using the log-rank test when their SOFA score was 4. More CDI patients with ribotype 018 strains than ribotype 014/020 patients used fluoroquinolones (P 0.001). The SOFA score was a clinical predictor of severe CDI even after propensity score matching analysis had adjusted for other factors. We also showed that the PCR ribotype in CDI patients may be related to the use of fluoroquinolones in hospital settings.

Another study was performed in a tertiary healthcare facility in Riyadh, Saudi Arabia by Alzouby et al., 2020 who reported a total of 106 episodes of CDI were found among 59 patients during the six-month surveillance period, accounting for 137,230 patient-days. Among the patients, men made up more than half of the studied group (n/N = 34/59; 58%) while women made up 42% (n/N = 25/59). According to NHSN definitions, out of the 106 episodes, 58% (n = 61) were new (incident) cases, 12% (n = 13) were recurrent cases, and 30% (n = 32) were duplicate cases. Cases that were duplicates were not included in the analysis. The majority of the new cases (n/N = 43/61; 70%) were healthcare onset (HO), then community-onset (CO) (21%), and community-onset healthcare-associated cases (8%). (CO-HAI). Only HA and CO-HAI were taken into account when calculating the incidence of CDI, which was 3.5 per 10,000 patient days.

Furthermore, in a general hospital in Saudi Arabia Al-Tawfiq et al., 2021 performed a study on Clostridioides difficile-associated disease epidemiology among patients and reported that among the 10,995 stool samples tested, there were a total of 577 distinct episodes of CDAD, or 5.2%, with an annual positivity rate ranging from 0.9% to 11.8%. Among all CDAD cases, there were 230 (39.9%) cases with community involvement, 105 (18.2%) with community-onset and healthcare facility involvement, and 242 (42%) with healthcare facility involvement and community involvement (HCFO-HCFAD). From 17% in 2001 to 20% in 2018 of all cases, there was a trend towards more community onset-healthcare facility-associated disease cases, while there was a trend towards fewer community-associated CDAD cases from 85% to 50% over time. The HCFO-HCFAD percentages, however, remained largely constant. From 2001 to 2018, the rate of HCFO-HCFAD per 1,000 patient days increased from 0.009 to 0.22. Al-Tawfiq et al., 2021 concluded that all tested samples had a CDAD prevalence of 5.15 percent, indicating a sizable amount of CDAD that is community-associated. The results are consistent with data from developed nations and call for additional research on the risk factors for community-associated CDAD.

Additionally, Obaid & Alhifany, 2020 reported that in Saudi Arabia, the incidence rate of CDI was studied in a small number of healthcare facilities. Published studies' single-center settings, which lack institutional protocols for detecting, screening, and managing CDIs, were their foundation. Comprehensive reporting of laboratory findings and clinical data is lacking in published literature. Additionally, they discovered numerous inconsistencies in the reported numbers in other studies, and the reported statistical records for incidence rates for some studies did not adhere to the IDSA guidelines. Therefore, for improved CDI detection and management as well as accurate epidemiological data reporting on a national level, they advise the implementation of a unified testing and screening algorithm that combines clinical symptoms with multi-step testing (GDH plus toxin and NAAT) and susceptibility results of C. difficile isolated strains to antibiotics.

Miqdad et al., 2023 reported patients with C. difficle infections, of which 12 (52.2%) were female and 11 (47.8%) were male. The patients were 58.3 years old on average (SD: 21.5); 13 (56.5%) were under 65 and 10 were over 65. Only four patients were comorbidity-free, and 19 (82.6%) patients had a number of comorbidities. Importantly, in 47.8% of the patients, hypertension was the most prevalent comorbidity. Furthermore, patients who stayed in the hospital

for less than four days and those who stayed for more than four days, respectively, had mean ages of 49.08 (19.7) and 68.36 (19.5), respectively, (P =.028), which had a significant impact on the hospital's length of stay.

Al Alawi et al., 2020 reported that the five-year prevalence of C difficile infection was 6.8%. The mean (SD) age was 56 (18), and men (53.5%) were more likely to be infected than women (46.5%). The use of broad-spectrum antibiotics and proton-pump inhibitors (PPI) were the most prevalent risk factors. PPIs and broad-spectrum antibiotic exposure overlapped by 56.6%. The type of PPI (P=.254) or antibiotic (P=.789) used did not statistically differ from the onset of C difficile infection.

Hung et al., 2021 reported 451 patients were enrolled in total. Malignancy (odds ratio [OR] 7.15, 95% confidence interval [CI] 1.82-28.09; P = 0.005), prior cephalosporin therapy (odds ratio [OR] 10.8, 95% confidence interval [CI] 1.3-93.9; P = 0.03), and proton pump inhibitor (PPI) therapy (odds ratio [OR] 7.1, 95% confidence interval [CI] 2.1-24.7; P = 0.002) were independently related to CDAD. However, malignancy (OR 14.0, 95% CI 1.6-124.9; P = 0.02) and underlying diabetes mellitus (OR 20.5, 95% CI 2.9-144.9; P = 0.002) were independent risk factors of CDAD in 9 (4.2%) patients who developed CDAD later (15-30 days' hospital stay) and 207 patients with longer hospitalisation (15-30 days) but without CDAD.

Finally, this study's findings will give decision-makers the chance to assess Saudi Arabia's infection control services and programs for patients, identify any gaps, and suggest areas for improvement.

METHODS

A. Setting and Design: This is a retrospective analysis of patients who were positive for C. difficile toxin genes by NAAT presented after 2 calendar days of admission(to ensure C. difficile is a hospital-acquired infection this is the definition of CD-HAIs according to NHSN Criteria) Polage, et al., (2020).in King Fahad Medical City, a city that included 4 tertiary medical hospitals and 4 specialist centers with a total capacity of 1200 beds in Riyadh, during the period from Jan 2021 to Dec 2022 to examine the respective risk factors of CDAD for adults hospitalized for more than 2 calendar days after admission. The IRB of KFMC, Riyadh, KSA, approved the study (Protocol number 22-566E, registration number H-01-R-012).

B. Data Collection: Demographic characteristics such as age and sex and risk factors included antibiotics received prior to diarrhea, PPI, ward of admission (medical, surgical, ICU & CCU, and others), and presence of malignancy together with clinical data including comorbid conditions, investigations including WBCs, RBCs, and platelets count and outcomes such as mortality rate were gathered from the medical records.

C. Data Analysis and Management: All medical records of male and female patients aged > 14 years with positive NAAT results for C. difficile toxin genes and clinical signs and symptoms between Jan 2021 and Dec 2022 were included in the study while patients with diarrhea due to chronic CDIs, previous surgeries and patients with incomplete records were excluded.

The primary outcome was the assessment of C difficile infection in King Fahad Medical City, while the risk factors, the outcome such as mortality rate, and factors affecting the outcome were secondary outcomes.

D. ANDefinition Clostridium difficile-associated diarrhea 2 loose stools within at least a 2-day period and diagnosed by documented diarrhea plus positive laboratory confirmation for C. difficile toxin A/B.

The data were collected in a secured spreadsheet where accessed only by the researcher. Data analysis was done, using the Statistical Package for the Social Sciences, version 25 (IBM, 2017) When appropriate, quantitative data were presented as mean and standard deviations (SD), or median and range. Categorical variables were labeled with their absolute frequencies. For categorical data, The Chi-square and Fischer Exact tests were used for categorical variables to compare the studied groups when possible. Binary logistic regression was used to determine factors related to mortality due to clostridium difficile infection. A P-value <0.05 was considered statistically significant and a P-value <0.001 was considered highly statistically significant

RESULTS

Out of 118 patients with diarrhea collected from the record, 109 cases were included in the study as clostridium difficile-associated diarrhea while 9 were excluded because of incomplete records or CDI. The average age of the studied group was 52.27 years ranging from 14 to 94 years; about half were males (52.3%) and (47.7%) were females. (93.6%) were Saudi while (6.4%) were non-Saudi, about three-fourths (70.6%) were attributed to non-critical hospital sites and most of them (91.7%) had co-morbidities as shown in table (1).

Table (1); Socio-demographic characteristics;

Variables	Frequency (no=109)
Age (years)	
Mean ± SD	52.27± 21.7
Median	60
(range)	(14-94)
Sex	
Male	57 (52.3%)
Female	52 (47.7%)
Nationality	
Saudi	102 (93.6%)
Non-Saudi	7 (6.4%)
Location of attribution	
Adult ward	22 (20.2%)
Cardiac ward	8 (7.3%)
CCU	13 (11.9%)
ICU	5 (4.6%)
Medical ward	5 (4.6%)
Surgical ward	9 (8.3%)
Neuro-surgical care unit	5 (4.6%)
Post-natal ward	4 (3.7%)
Epilepsy Monitoring Unit (EMU)	1 (0.9%)
Main Hospital wards	28 (25.7%)
Rehab ward	4 (3.7%)
Pediatric Ward	1 (0.9%)
Gyne Oncology	2 (1.8%)
High-risk ward	2 (1.8%)
Hospital site	
Critical	32 (29.4%)
Non-critical	77 (70.6%)
Co-morbidities^	
No	9 (8.3%)
Yes	100 (91.7%)

Data presented as Mean ± SD, Median (range), or, number (percentage).
Co-morbidities^ such as hypertension, D.M,. and arthritis.

Table (2) illustrates that the average duration of hospital stay among the studied group was 66.5 days ranging from 6 to 423 days. The average WBCs, RBCs, and platelets counts were 9.25, 3.3, and 226.7 with (33.9%, 91.7%, and 15.6%) of the studied group leucocytosis, low RBCs count, and erythrocytopenia respectively. Regarding risk factors for Clostridium difficile infection, antibiotics, and PPI were the commonest ones (86.2%) for each one followed by malignancy (39.4%), chemotherapy (35.8%), and others (55.0%), and previous GIT surgery was the least risk factor in the studied group (14.7%). Most of the studied group (91.7%) had diarrhea as the main symptom followed by abdominal pain (66.1%) and then fever (15.6%).

Table (2); Risk factors, CBC, and clinical picture among the studied group;

Variables	Frequency (no=109)
Duration of hospital stay (days) *Mean ± SD* *Median* *Range*	 66.5± 70.1 40 (6-423)
WBCs *Mean ± SD* *Median* *Range*	 9.25± 7.6 8.01 (0.06-34.6)
WBCs Low Normal High	 30 (27.5%) 42 (38.5%) 37 (33.9%)
RBCs *Mean ± SD* *Median* *Range*	 3.3± 0.57 3.28 (2.12-4.93)
RBCs Low Normal High	 100 (91.7%) 7 (6.4%) 2 (1.8%)
Platelets *Mean ± SD* *Median* *Range*	 226.7± 168.5 195 (9-1118)
Platelets Low Normal High	 17 (15.6%) 87 (79.8%) 5 (4.6%)
Malignancy	43 (39.4%)
Previous GIT surgery	16 (14.7%)
Antibiotics	94 (86.2%)
Chemotherapy	39 (35.8%)
PPI	94 (86.2%)
Others	60 (55.0%)
Fever	17 (15.6%)
Diarrhea	100 (91.7%)
Abdominal pain	72 (66.1%)
Others	79 (72.5%)

Data presented as number (percentage) or Mean ± SD, Median (range)

Regarding the complications of Clostridium difficile infection, hypotension was the commonest one (30.3%) followed by ileus and shock (22.0%) for each then relapse (14.7%) and toxic mega-colon (7.3%) as demonstrated in figure (1) while figure (2) showed that about two-thirds of the studied group showed spontaneous recovery (76 cases 69.7%), 6 cases (5.5%) had surgery and 27 cases (24.8%) died.

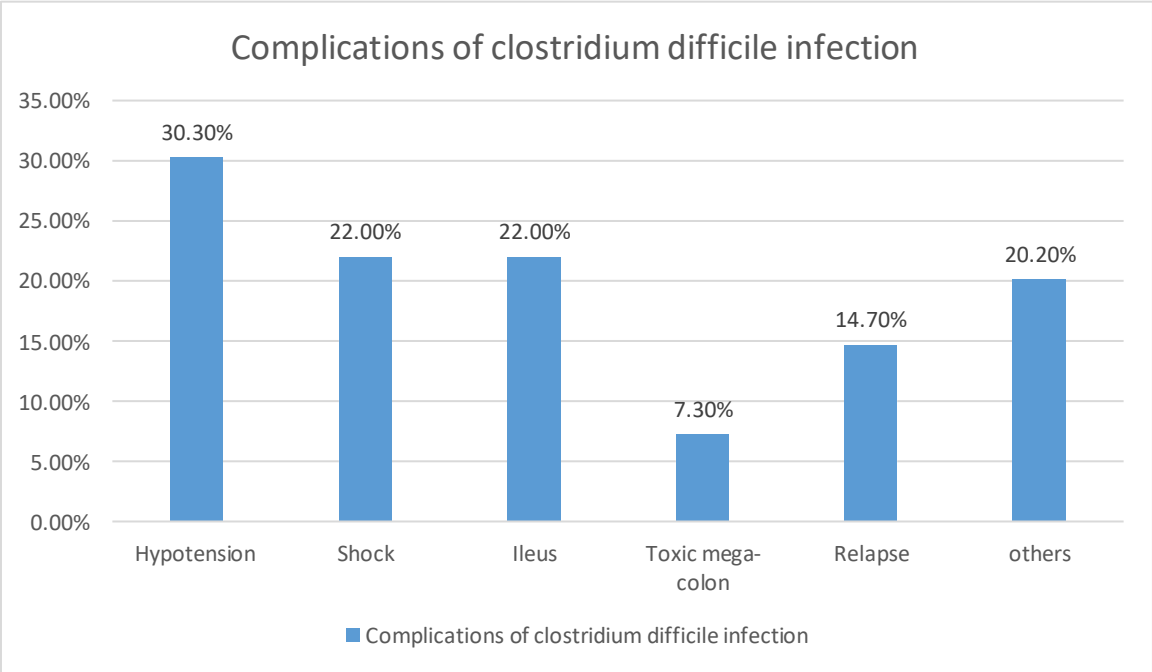

Fig (1); Complications of clostridium difficile infection among the studied group;

Table (3) showed that there was a statistically significant association between mortality due to Clostridium difficile infection and the patients' ages, presence of malignancy, previous antibiotics, previous PPI, shock, and occurrence of relapse; (37.7%) of the older age group, (37.2%) of the malignant patients, (28.4%) of patients receive antibiotics, (28.7%) of patients received PPI, (70.8%) of shocked patients and (56.3%) of patients with Clostridium difficile infection relapse died (P-value= 0.002*, 0.01*, 0.01*, 0.02*, 0.001**&0.004* respectively) while other variables weren't statistically significantly associated with the patient's survival after Clostridium difficile infection .

Table (3); Relation between socio-demographic characteristics and survival among the studied group;

Variables	Survivors NO.=82 (%)	Non-survivors NO.=27 (%)	P-value	Odds ratio 95% CI
Age				4.2
<60 years (no.=56)	49 (87.5%)	7 (12.5%)	0.002*^	(1.61-11.16)
≥60 years (no=53)	33 (62.3%)	20 (37.7%)		
Sex				1.24
Male (no.=57)	44 (77.2%)	13 (22.8%)	0.61	(0.52-2.97)
Female (no.=52)	38 (73.1%)	14 (26.9%)		
Nationality				0.48
Saudi (no.=102)	76 (74.5%)	26 (25.5%)	0.5^^	(0.056-4.24)
Non-Saudi (no.=7)	6 (85.7%)	1 (14.3%)		
Hospital site				1.18
Critical (no.=77)	58 (75.3%)	19 (24.7%)	0.9^^	(0.39-2.64)
Non-critical (no.=32)	24 (75.0%)	8 (25.0%)		
Co-morbidities				1.16
No (no.=9)	7 (77.8%)	2 (22.2%)	0.8^^	(0.23-5.98)
Yes (no.=100)	75 (75.0%)	25 (25.0%)		
WBCs				
Low (no.=30)	23 (76.7%)	7 (23.3%)		----------
Normal (no.=42)	32 (76.2%)	10 (23.8%)	0.9^	
High (no.=37)	27 (73.0%)	10 (27.0%)		
RBCs				
Low (no.=100)	73 (73.0%)	27 (27.0%)	0.1^	--------
Normal (no.=7)	7 (100.0%)	0 (0.0%)		
High (no.=2)	2 (100.0%)	0 (0.0%)		
Platelets				
Low (no.=17)	10 (58.8%)	7 (41.2%)	0.2^	----------
Normal (no.=87)	68 (78.2%)	19 (21.8%)		
High (no.=5)	4 (80.0%)	1 (20.0%)		
Malignancy				2.96
No (no.=66)	55 (83.3%)	11 (16.7%)	0.01*^	(1.21-7.25)
Yes (no.=43)	27 (62.8%)	16 (37.2%)		
Previous GIT surgery				0.66
No (no.=93)	69 (74.2%)	24 (25.8%)	0.7^^	(0.17-2.5)
Yes (no.=16)	13 (81.2%)	3 (18.8%)		
Antibiotics				1.39
No (no.=14)	14 (100.0%)	0 (0.0%)	0.01*^^	(1.23-1.58)
Yes (no.=95)	68 (71.6%)	27 (28.4%)		
Chemotherapy				1.33
No (no.=70)	54 (77.1%)	16 (22.9%)	0.5^	(0.54-3.24)
Yes (no.=39)	28 (71.8%)	11 (28.2%)		
PPI				1.4
No (no.=15)	15 (100.0%)	0 (0.0%)	0.02*^^	(1.23-1.59)
Yes (no.=94)	69 (71.3%)	25 (28.7%)		

Fever No (no.=92) Yes (no.=17)	 70 (76.1%) 12 (70.6%)	 22 (23.9%) 5 (29.4%)	 0.6^	1.32 (0.42-4.18)
Diarrhea No (no.=9) Yes (no.=100)	 8 (88.9%) 74 (74.0%)	 22 (11.1%) 26 (26.0%)	 0.4^^	2.8 (0.33-23.6)
Abdominal pain No (no.=31) Yes (no.=78)	 25 (80.6%) 57 (73.1%)	 6 (19.4%) 21 (26.9%)	 0.2^	2.8 (0.33-23.6)
Hypotension No (no.=76) Yes (no.=33)	 61 (80.3%) 21 (63.6%)	 15 (19.7%) 12 (36.4%)	 0.06^	2.3 (0.94-5.75)
Shock No (no.=85) Yes (no.=24)	 75 (88.2%) 7 (29.2%)	 10 (11.8%) 17 (70.8%)	 0.001**	 18 (6.16-54.7)
Ileus No (no.=85) Yes (no.=24)	 66 (77.8%) 16 (66.7%)	 19 (22.4%) 8 (33.3%)	 0.3^	1.7 (0.64-4.67)
Toxic mega-colon No (no.=101) Yes (no.=8)	 78 (77.2%) 4 (50.0%)	 23 (22.8%) 4 (50.0%)	 0.1^^	3.39 (0.78-14.6)
Relapse No (no.=93) Yes (no.=16)	 75 (80.6%) 7 (43.8%)	 18 (19.4%) 9 (56.3%)	 0.004*	5.36 (1.76-16.3)

Univariate regression showed that older age group (95% CI 1.61 to 11.16), presence of malignancy (95% CI 1.21 to 7.25), antibiotics (95% CI 1.23 to 1.58), PPI treatment (95% CI 1.32 to 1.59), shock (95% CI 6.16 to 54.7) and Clostridium difficile infection relapse (95% CI 1.761 to 16.3) were the statistically significant predictors of patient mortality due to Clostridium difficile infection while in multivariate binary logistic regression, malignancy (95% CI 1.69 to 42.03), and shock (95% CI 7.45 to 223.2) were the only statistically significant predictors of patients' mortality due to Clostridium difficile infection as shown in table (4), Fig (2) .

Table (4); Univariate and multivariate analysis of the factors predicting death as an outcome of clostridium difficile among the studied group;

	Univariate analysis		Multivariate analysis	
Variables	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age ≥60 years	4.2 (1.61-11.16)	0.002*	 ---------	 ------
Malignancy	2.96 (1.21-7.25)	0.01*	8.4 (1.69-42.03)	 0.009*
Antibiotics	1.39 (1.23-1.58)	 0.01*	 ----------	 --------
PPI	1.4 (1.23-1.59)	 0.02*	 ----------	 --------
Shock	18 (6.16-54.7)	0.001**	40.7 (7.45-223.2)	 0.001**
Relapse	5.36 (1.76-16.3)	0.004*	 ----------	 ------

** Statistically significant difference (p<0.05), ** statistically highly significant difference (p<0.001), CI=Confidence Interval*

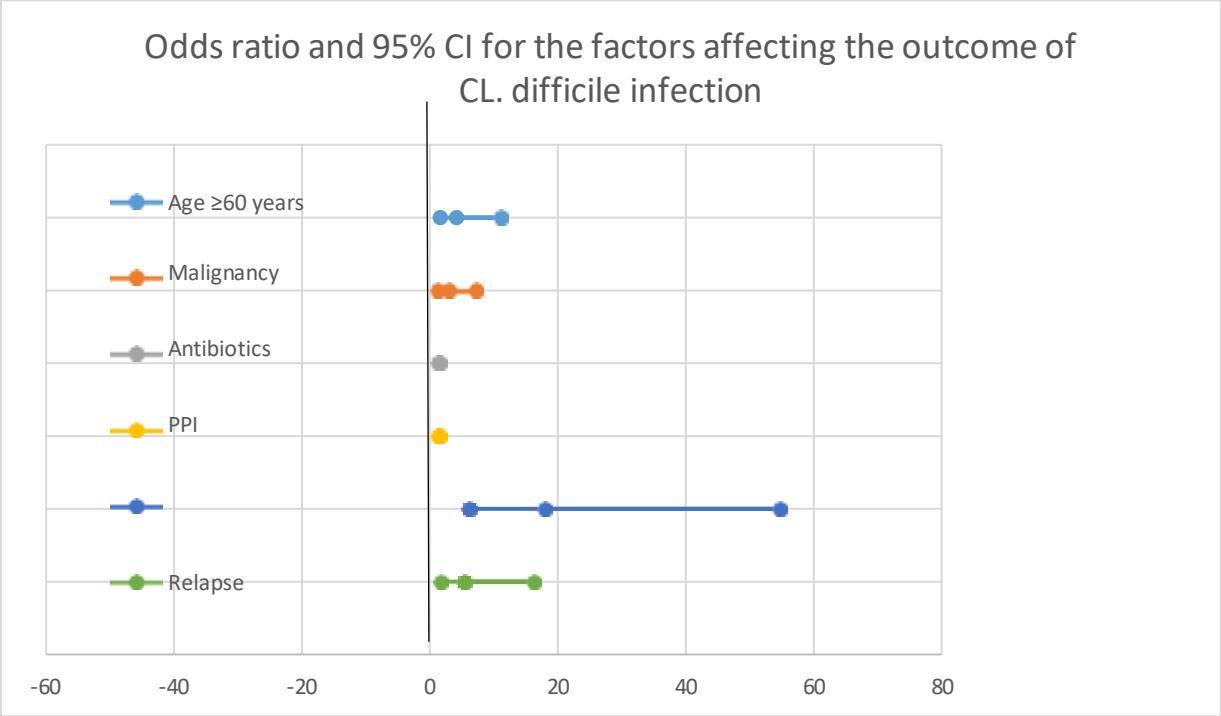

Fig (2); Funnel plot graph for the Odds ratio of the factors predicting death as an outcome of clostridium difficile among the studied group in univariate analysis.

DISCUSSION AND LIMITATIONS

Infection with Clostridium difficile is a serious public health concern and social burden. Our research will fill the gap about the prevalence rate and risk factors of Clostridium difficile-associated diarrhea (CDAD) in King Fahad Medical City, Riyadh, and will support important information. the results of this study will provide decision-makers with the opportunity to evaluate Saudi Arabia's patient infection control services and programs, identify any shortcomings, and recommend areas for improvement.

The average age of the studied group was 52.27 years ranging from 14 to 94 years; about half were males (52.3%) and (47.7%) were females. (93.6%) were Saudi while (6.4%) were non-Saudi, about three-fourths (70.6%) were attributed to non-critical hospital sites and most of them (91.7%) had co-morbidities. That was close to Al Alawi et al., 2020 who reported the mean (SD) age of the 129 patients that encountered inclusion criteria was 56 (18) years. Men reported (53.5%) of the patients (n=69). The majority of the cases were from non-ICU wards. Additionally, that was supported by Althaqafi et al., 2022 who reported the mean age was 56.86 (21) years, and the infection was more prevalent among men (52.74%) than among women (47.26%).

However, Hung et al., 2021 reported a mean age of CDAD was 76.5 ± 10.7. men gender counted 47.4 of the CDAD cases. Elderly people are disproportionately affected by CDI, which may be explained by the following risk factors: aging-related immune system impairment, increasing antibiotic consumption, and frequent contact with healthcare workers.

In our research, the average duration of hospital stay among the studied group was 66.5 days ranging from 6 to 423 days. The average WBCs, RBCs, and platelets counts were 9.25, 3.3, and 226.7 with (33.9%, 91.7%, and 15.6%) of the studied group leucocytosis, low RBCs count, and erythrocytopenia respectively. Regarding risk factors for Clostridium difficile infection, antibiotics, and PPI were the commonest ones (86.2%) for each one followed by malignancy (39.4%), chemotherapy (35.8%), and others (55.0%), and previous GIT surgery was the least risk factor in the studied group (14.7%). Most of the studied group (91.7%) had diarrhea as the main symptom followed by abdominal pain (66.1%) and then fever (15.6%). That was supported by Alzouby et al., 2020 who reported that Proton pump inhibitor use was the most frequent risk factor (92%), followed by prolonged antimicrobial therapy (>10 days) in the 90 days prior (77%) and protracted hospitalization for more than 3 weeks (75%). Other risk factors of significance included elderly patients >65 years of age (58%) and nasogastric tube feeding (58%), which were both defined as receiving more than three antibiotics within the previous 90 days (63%). Tazocin (n = 24), vancomycin (n = 21), imipenem (n = 15), meropenem (n = 14), and colistin (n = 9) were the most frequently used antibiotics.

However, Althaqafi et al., 2022 reported antibiotic use (74.68%) was the risk factor most frequently linked to CDI, followed by the recent use of acid-suppressants (67.50%), cancer (46%), and prior gastrointestinal surgery (6.30%).

Additionally, Hung et al., 2021 reported that in terms of gender, age, the use of nasogastric tubes, and other underlying diseases, there were no differences (such as hypertension, prior stroke, chronic renal disease, congestive heart failure, malignancy, or liver cirrhosis). Additionally, ceftazidime or ceftriaxone exposure was higher in CDAD patients prior to the onset of CDAD (100% vs. 60.4%; P Z 0.01) than in patients receiving ceftriaxone during hospitalization. However, there were no differences between the groups in terms of prior use of fluoroquinolone, penicillin, carbapenem, glycopeptide, metronidazole, fosfomycin, H2-blocker, or steroids. The presence of underlying malignancy (OR 14.0; P Z 0.02) or diabetes mellitus (OR 20.5; P Z 0.002) was independently associated with CDAD among patients hospitalized for 15 to 30 days in the multivariate analysis.

In our study, regarding the complications of Clostridium difficile infection, hypotension was the commonest one (30.3%) followed by ileus and shock (22.0%) for each then relapse (14.7%) and toxic mega-colon (7.3%) and about two-thirds of the studied group showed spontaneous recovery (76 cases 69.7%), 6 cases (5.5%) had surgery and 27 cases (24.8%) died. That was supported by Althaqafi et al., 2022 who reported that complications were detected in the study population. Hypotension was the most commonly recorded complication (28.40%), followed by shock (17.20%), ileus (3.30%), and toxic megacolon (2.80%).

Our result revealed that there was a statistically significant association between mortality due to Clostridium difficile infection and the patients' ages, presence of malignancy, previous antibiotics, previous PPI, shock, and occurrence of relapse; (37.7%) of the older age group, (37.2%) of the malignant patients, (28.4%) of patients receive antibiotics, (28.7%) of patients received PPI, (70.8%) of shocked patients and (56.3%) of patients with Clostridium difficile infection relapse were died(P-value= 0.002*, 0.01*, 0.01*, 0.02*, 0.001**&0.004* respectively) while other variables weren't statistically significantly associated with the patient's survival after Clostridium difficile infection. That was supported by Czepiel et al., 2021 who reported eleven factors were found by multivariate logistic regression to collectively distinguish CDI deaths from controls. The most significant ones included advanced age, the presence of cancer, a higher Charlson Index, an increase in WBC (1000/L), CRP (100 mg/L), complications, and cognitive

impairment. The C-statistic for this model was 0.864, which indicates that it had a very high degree of discriminative accuracy. Selected parameters and the interval between a CDI diagnosis and death were evaluated for correlation. Death was significantly correlated with advanced age, higher WBC, neutrophil, CRP, or creatinine levels, the presence of cancer, cognitive impairment, and complications.

In our study, Univariate regression showed that older age group (95% CI 1.61 to 11.16), presence of malignancy (95% CI 1.21 to 7.25), antibiotics (95% CI 1.23 to 1.58), PPI treatment (95% CI 1.32 to 1.59), shock (95% CI 6.16 to 54.7) and Clostridium difficile infection relapse (95% CI 1.761 to 16.3) were the statistically significant predictors of patient mortality due to Clostridium difficile infection while in multivariate binary logistic regression, malignancy (95% CI 1.69 to 42.03), and shock (95% CI 7.45 to 223.2) were the only statistically significant predictors of patients' mortality due to Clostridium difficile infection.

To find risk factors for severe CDI, Choi et al., 2022 combined conditional logistic regression with univariate and multivariate analysis. After PS matching, the univariate analysis revealed seven independent variables to be significant predictors of severe CDI. Multivariate analysis was performed separately by the various models because the Sequential Organ Failure Assessment Score (SOFA score) at the time of CDI diagnosis and the increase in SOFA score by more than 2 points had multicollinearity. SOFA score is an objective, early obtainable value that is widely used to assess and/or predict a patient's prognosis in infectious disease research. SOFA is used as a measure of sepsis-related organ dysfunction, which can be identified as an acute change of two or more points in the total score. In multivariate analysis, severe CDI was associated with the SOFA score (adjusted odds ratio [aOR], 1.16; 95% confidence interval [CI], 1.11-1.20; P 0.001), maximum WBC count (aOR, 1.01; 95% CI, 1.00-1.02; P 0.001), minimum serum albumin (aOR, 0.65; 95% CI, 0.52-0.51; P 0.001), and ventilator use (aOR, 5. Even after accounting for other variables, it was discovered that increases of more than 2 points in SOFA scores were significantly associated with severe CDI in multivariate analysis (aOR, 2.29; 95% CI, 1.68-3.11; P 0.001). The strains' ribotypes weren't linked to severe CDI.

This study will provide actual information to the policymakers which assist them in making plans and taking appropriate action in this area and we recommend educational programs to increase awareness about preventive measures for Clostridium difficile infection.

A small number of patients. And Lack of previous research studies on the prevalence rate and risk factors of Clostridium difficile-associated diarrhea (CDAD) in King Fahad Medical City, Riyadh were the limitations of the study

CONCLUSIONS

Diarrhea was the most Common Clinical Feature of Clostridium difficile infection. Prolonged antimicrobial therapy and Proton pump inhibitor use were the most frequent risk factors. Hypotension was the commonest complication of CDI. Age ≥60 years, Malignancy, shock, and relapse were the most statistically significant predictors of patients' mortality due to CDI.

RECOMMENDATIONS

1. Reduce the number of CDI cases by using antibiotics and proton-pump inhibitors as needed
2. Multicenter studies are required to clarify the country's CDI burden
3. Taking contact isolation precautions in the patient's private room is recommended in any hospital policy to reduce C.diff-HAIs.
4. Important for patients to have knowledge and awareness of the appropriate use of antibiotics.

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