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Original Article

Treatment outcomes and risk factors for severity and mortality in *Clostridioides difficile* infection: a single-center study in Thailand

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Abstract

Introduction: *Clostridioides difficile* often causes hospital-acquired diarrhea, leading to unfavorable treatment outcomes. This study investigates CDI treatment outcomes and factors affecting severity and mortality at a university hospital in Thailand.

Methodology: A retrospective study was conducted from June 2019 to December 2021. The primary endpoints were treatment outcomes with a 95% CI. Univariable and multivariable Cox regression analyses determined risk factors for severe CDI and 30-day mortality.

Results: Of 187 patients receiving a diagnosis of and receiving treatment for CDI, 103 patients (55.8%) presented non-severe CDI, and 84 patients (44.2%) had severe CDI. The 30-day mortality rate of CDI was 24.1%, which was significantly higher in the severe group (36.9 vs. 13.6%, $p \leq 0.001$). Multivariable analysis revealed the independent risk factor for severe CDI was chronic kidney disease (aOR 15.16, 95% CI 6.3, 36.48), and risk factors for all-cause mortality at 30 days were ICU admission (aOR 3.56, 95%CI 1.48, 8.56) and carbapenem exposure (aOR 2.79, 95% CI 1.17, 6.68).

Conclusions: This study demonstrated high mortality rates and a significant incidence of refractory and recurrent infections in the severe CDI group. Chronic kidney disease was an independent risk factor for severe CDI. ICU admission and carbapenem exposure were independent risk factors for all-cause mortality.

Key words: *Clostridoides difficile*; *Clostridoides difficile* infection; treatment outcome; mortality; severity; Thailand

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Introduction

Clostridioides difficile infection (CDI) is a frequent cause of hospital-acquired diarrhea, contributing to the global healthcare burden. Incidence rates vary by region, ranging from 1.99 to 8.00 per 10,000 patient days [1,2]. The mortality rate was significant among patients with CDI, ranging from 9 to 38%, with higher mortality observed among recurrent CDI cases [3]. This led to increased healthcare resource use and associated costs [4,5].

C. difficile is a strictly anaerobic, spore-forming, Gram positive bacillus. The pathophysiology of CDI involves toxin production only occurring in pathogenic strains containing the pathogenicity locus (PaLoc). Under normal circumstances, with balanced intestinal flora, the bacteria do not produce toxins [6]. Among certain hosts, disruption of balance may occur, and toxin production can occur, leading to CDI. *C. difficile* toxin can be categorized into two classes - binary and nonbinary. Binary toxin is the main substance in the pathophysiology of CDI and comprises two types of toxins. Toxin A (TcdA) and toxin B (TcdB) are clostridial glycosylating toxins inhibiting cytoskeletal function in enterocytes, leading to necrosis and potential pseudomembranous colitis [6]. *C. difficile*, particularly the North American pulsed field gel electrophoresis type 1 (NAP1) strain, has also been reported as a predictor for the severity and mortality of CDI [7].

CDI can present a range of symptoms - from asymptomatic carrier to intestinal infection, and extra-gastrointestinal infection. The symptoms can be severe and lead to death. With a variety of presentations and bacteriology of pathogenicity, the diagnosis and treatment of CDI are challenging [6,8]. Other than diagnostic issues, treatment of CDI is arduous due to variations in severity, association with antibiotic use, as well as spore formation resulting in difficulty in eradication and infection control. These all affect the quality of care and treatment outcomes of patients with CDI [6,8].

In Thailand, several reports have demonstrated that CDI is the most common cause of in-hospital diarrhea, with prevalence ranging from 12.3 to 24%, depending

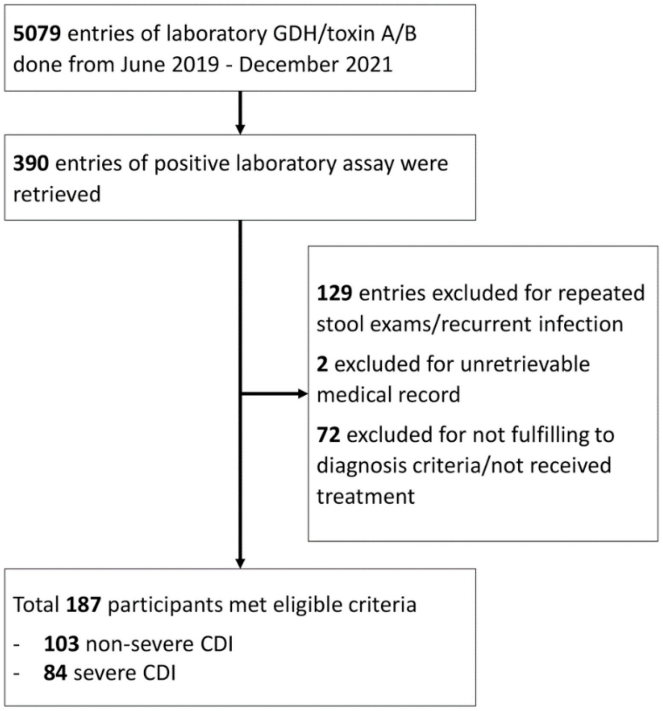
on the diagnostic tools used in the studies [9,10]. The clinical outcomes of CDI treatment in Thailand from 2002 to 2005, during which metronidazole was the most commonly used agent for treating CDI, revealed a response rate of 66.7% and a mortality rate of 37.5% [11]. This study exhibited a lower response rate and higher mortality for CDI compared with other studies performed in the USA and Canada [12]. In 2017, the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) published new clinical practice guidelines for CDI among adults and children, recommending vancomycin as the first-line therapy for CDI regardless of severity [13]. Therefore, very limited studies are available concerning the clinical outcomes and factors influencing the severity and mortality of CDI in Thailand, particularly in the era when vancomycin is recommended as the first-line therapy. This study aimed to investigate the treatment outcomes of patients with CDI and the factors affecting the severity and mortality of CDI in a single-center university hospital in Thailand.

Methodology

Study setting and population

This study constitutes a single-center, retrospective study conducted at Phramongkutklao Hospital, a 1200-bed teaching hospital in Bangkok, Thailand, between June 2019 and December 2021. All patients, aged 20 and over, receiving a diagnosis of and receiving treatment for CDI, were enrolled in the study. Criteria for diagnosis of CDI included patients passing three or more unformed stools within 24 hours that could not be explained by other etiologies and revealing positive results for stool GDH and/or toxin A/B [13]. Patients were excluded if medical records were missing/unretrievable, or participants did not receive treatment for CDI. For patients receiving multiple diagnoses of CDI, only data from the first diagnosis were included in the study.

Figure 1. Participant enrollment.



This study, using the rapid immunochromatographic point of care test, detected both Glutamate Dehydrogenase (GDH) and *C. Difficile* toxins A and B (SIMPLE GDH-Toxin®, OPERON S.A. Immunodiagnostics, Zaragoza, Spain).

All eligible patient's data were collected using medical chart review. All entries of GDH and stool toxin A/B positive assays were retrieved. After the diagnosis of CDI was confirmed, the patient's data were collected. Baseline characteristics of age, sex, BMI, and department of admission were collected. Data about underlying diseases, any infection 30 days before diagnosing CDI, and antibiotics received before diagnosing CDI were collected to identify factors associated with severe CDI and 30-day mortality. For severity classification, creatinine level (Cr) and white blood cell count were collected. Characteristics for fulminant CDI - hypotension, ileus, megacolon, and multi-organ failure were also collected. Patients were classified in the severe CDI group if the creatinine level at diagnosis exceeded 1.5 mg/dL, or the WBC count exceeded 15,000 cells/μL, or the patient indicated any signs of fulminant CDI according to the guideline developed by the IDSA and the SHEA in 2017 [13].

Study outcomes

Primary outcomes comprised the final treatment result and the all-cause mortality rate at 30 and 90 days in patients with CDI. Secondary outcomes were risk factors for severe CDI, and risk factors for mortality at 30 days using univariate and multivariate analysis.

The treatment outcomes were collected and classified into four categories described below.

- Incomplete treatment was defined as patients receiving a diagnosis of CDI but receiving treatment for less than ten days [13].
- Remission was defined as patients receiving a diagnosis of CDI, receiving treatment for at least ten days, and resolution of diarrhea at the end of treatment without CDI recurrence [13].
- Persistent diarrhea was defined as patients

receiving a diagnosis of CDI, receiving treatment for at least ten days, but still presenting diarrhea (three or more times of unformed stool within 24 hours) at the end of therapy [13,14].

- Recurrent infection was defined as an episode of symptom onset and a positive assay result following an episode with a positive assay result in the previous two to eight weeks [13].

Statistical analysis

Data from published studies of mortality in CDI in Singapore revealed mortality of severe CDI at 24.5% and non-severe CDI at 7.4% [15]. Given a two-sided *p* at 5% and power at 90%, the calculated number of participants needed was 83 for each group.

Table 1. Baseline demographics and clinical characteristics.

	Total (n = 187)	Severe (n = 84)	Non-Severe (n = 103)	*p*
Age	69.02 ± 17.43	72.95 ± 15.29	65.82 ± 18.47	**0.005**
Sex				
Male	102 (54.5%)	45 (53.6%)	57 (55.3%)	0.809
Female	85 (45.5%)	39 (46.4%)	46 (44.7%)	
Department				
Internal medicine	125 (66.8%)	63 (75%)	62 (60.2%)	0.109
Surgical	48 (25.7%)	14 (16.7%)	34 (33%)	
Orthopedics surgery	2 (1.1%)	0 (0%)	2 (1.9%)	
Obstetrics and Gynecology	3 (1.6%)	2 (2.4%)	1 (1%)	
Otolaryngology	3 (1.6%)	1 (1.2%)	2 (1.9%)	
Observe unit	5 (2.7%)	3 (3.6%)	2 (1.9%)	
PM & R	1 (0.5%)	1 (1.2%)	0 (0%)	
BMI	22.08 ± 3.78	22.45 ± 3.87	21.78 ± 3.7	0.255
ICU admission	52 (27.8%)	34 (40.5%)	18 (17.5%)	**< 0.001**
Underlying diseases				
HIV	3 (1.6%)	0 (0%)	3 (2.9%)	0.115
Diabetes mellitus	75 (40.1%)	42 (50%)	33 (32%)	**0.013**
Hematologic malignancy	37 (19.8%)	17 (20.2%)	20 (19.4%)	0.889
Post-transplantation	7 (3.7%)	2 (2.4%)	5 (4.9%)	0.375
Active solid malignancy	45 (24.1%)	16 (19%)	29 (28.2%)	0.147
Autoimmune disease	13 (7%)	3 (3.6%)	10 (9.7%)	0.101
Chronic kidney disease	62 (33.2%)	52 (61.9%)	10 (9.7%)	**< 0.001**
Liver cirrhosis	14 (7.5%)	10 (11.9%)	4 (3.9%)	**0.038**
Chronic lung disease	10 (5.3%)	5 (6%)	5 (4.9%)	0.74
Prior infection				
None	23 (12.3%)	7 (8.3%)	16 (15.5%)	0.136
Urinary tract	47 (25.1%)	22 (26.2%)	25 (24.3%)	0.764
Intra-abdominal	55 (29.4%)	28 (33.3%)	27 (26.2%)	0.288
Respiratory system	39 (20.9%)	22 (26.2%)	17 (16.5%)	0.105
Bloodstream infection	43 (23%)	22 (26.2%)	21 (20.4%)	0.348
Musculoskeletal system	12 (6.4%)	6 (7.1%)	6 (5.8%)	0.715
Skin and soft tissue	22 (11.8%)	10 (11.9%)	12 (11.7%)	0.957
Nervous system	4 (2.1%)	2 (2.4%)	2 (1.9%)	0.836
Prior antibiotic exposures				
None	21 (11.2%)	7 (8.3%)	14 (13.6%)	0.257
Penicillin	51 (27.3%)	22 (26.2%)	29 (28.2%)	0.764
Cephalosporins	71 (38%)	28 (33.3%)	43 (41.7%)	0.238
Carbapenem	95 (50.8%)	52 (61.9%)	43 (41.7%)	**0.006**
Vancomycin	26 (13.9%)	16 (19%)	10 (9.7%)	0.066
Fluoroquinolone	14 (7.5%)	7 (8.3%)	7 (6.8%)	0.691
Phosphonic acid	6 (3.2%)	4 (4.8%)	2 (1.9%)	0.276
Glycylglycine	7 (3.7%)	5 (6%)	2 (1.9%)	0.151
Aminoglycoside	5 (2.7%)	4 (4.8%)	1 (1%)	0.11
Metronidazole	19 (10.2%)	6 (7.1%)	13 (12.6%)	0.217
Macrolide	10 (5.3%)	4 (4.8%)	6 (5.8%)	0.748
Polymyxins	20 (10.7%)	15 (17.9%)	5 (4.9%)	**0.004**
Severity assessment				
Albumin	2.79 ± 0.64	2.71 ± 0.63	2.87 ± 0.64	0.098
CRP[#]	69.57 ± 64.3	130.86 ± 67.91	49.14 ± 51.51	0.051
Lactate	2.78 ± 4.94	3.59 ± 6.2	1.52 ± 0.65	**0.015**
Treatment				
Metronidazole	90 (48.1%)	17 (20.2%)	73 (70.9%)	**< 0.001**
Vancomycin	72 (38.5%)	43 (52.4%)	29 (28.2%)	**0.001**
Vancomycin plus metronidazole	25 (13.4%)	24 (28.6%)	1 (1%)	**< 0.001**
Surgical intervention	0 (0%)	0 (0%)	0 (0%)	N/A

[#] High frequency of missing data; only 12 entries have been recorded. BMI: body mass index; CRP: C-reactive protein; HIV: human immunodeficiency viruses; ICU: intensive care unit; PM & R: Physical Medicine and Rehabilitation.

Baseline characteristics were reported among all patients, patients with non-severe CDI, and severe CDI. Continuous data were reported as mean with standard deviation, while noncontinuous data were reported as number (percentage). Differences between baseline characteristics in both severity groups were calculated using the chi-square for non-continuous data and the independent t-test for continuous data. For factors contributing to disease severity and mortality at 30 days, selected characteristics were calculated for the odds ratio with univariable and multivariable analysis. Missing data were reported as missing and were not used in the analysis. For all analyses, a two-sided $p < 0.05$ was considered significant, and all statistical analyses were calculated using IBM SPSS, Version 27 (IBM Corp. Armonk, NY, USA).

Results

Baseline characteristics

From June 2019 to December 2021, 5,079 stool GDH and Toxin A/B tests were performed, resulting in 390 positive GDH and/or Toxin A/B tests. In all, 202 tests were excluded due to not fulfilling diagnostic criteria, not receiving treatment, repeated stool exams, recurrent infection, or unretrievable medical records (Figure 1). A total of 187 unique first-episode patients receiving a diagnosis of CDI and receiving treatment were enrolled, with 103 in the non-severe group and 84 in the severe group. The mean age was 69.02 ± 17.43 years, with patients having severe CDI being slightly older compared with those with non-severe CDI (72.95 ± 15.29 vs. 65.82 ± 18.47 years, $p = 0.005$). Both groups of patients were male-dominated. The patients were almost entirely admitted to the internal medicine (66.8%) and surgical wards (25.7%). Significantly higher rates of severe CDI occurred among patients admitted to the ICU (40.5 vs. 17.5%, $p < 0.001$). Also, a higher percentage of patients with diabetes mellitus, CKD, and liver cirrhosis were observed in the severe CDI group (Table 1).

Although most patients received a diagnosis of infections and were exposed to antibiotics before developing CDI, 12.3% of patients had CDI without prior infection or antibiotic exposure. Carbapenems and polymyxins exposure were higher among patients with severe CDI compared with the non-severe group (61.7 vs. 41.7%, $p = 0.006$; 17.9 vs. 4.9%, $p = 0.004$). No differences were observed in serum albumin or CRP levels between the two groups. However, serum lactate was significantly higher in the severe CDI group (3.59 ± 6.2 vs. 1.52 ± 0.65, $p = 0.015$) (Table 1).

Metronidazole was the most common treatment regimen for CDI in this cohort, followed by vancomycin, and then vancomycin plus metronidazole, with usage rates of 48.1, 38.5, and 13.4%, respectively. In the non-severe CDI group, 70.9% of patients were treated with metronidazole and 28.2% with vancomycin. In the severe CDI group, 52.4% of patients were treated with vancomycin, 28.6% with vancomycin plus metronidazole, and 20.2% with metronidazole. Vancomycin and the combination of vancomycin plus metronidazole were more commonly prescribed for patients with severe CDI. None of the patients received other surgical interventions (Table 1). None of the patients received fecal microbiota transplantation.

Primary outcomes

At the end of treatment, the outcomes demonstrated remission in 67.9%, persistent diarrhea in 11.2%, and recurrent infection in 11.2% of patients. A significantly higher percentage was found of treatment success (82.5 vs. 50%, $p < 0.001$), lower rate of recurrence (6.8 vs. 16.7%, $p = 0.031$), and lower rate of persistent diarrhea (5.8 vs. 17.9%, $p = 0.009$) among patients with non-severe CDI. The all-cause 30-day and 90-day mortality rates were 24.1 and 29.9%, respectively. A higher mortality was noted at 30 days (13.6 vs. 36.9%, $p < 0.001$) and 90 days (18.4 vs. 44%, $p < 0.001$) among patients with severe CDI compared with those with non-severe CDI (Table 2).

Risk factors for severe CDI

Univariable analysis revealed that statistically significant factors influencing the severity of CDI included age (OR 1.03, 95% CI: 1.01-1.04), ICU admission (OR 3.21, 95% CI: 1.64-6.27), underlying chronic kidney disease (OR 15.11, 95% CI: 6.88-33.2),

Table 2. Treatment outcomes and mortality at 30 and 90 days.

Result	Total (n = 187)	Severe (n = 84)	Non-Severe (n = 103)	*p*
Incomplete treatment	14 (7.5%)	10 (11.9%)	4 (3.9%)	**0.038**
Remission	127 (67.9%)	42 (50%)	85 (82.5%)	**< 0.001**
Persistent diarrhea	21 (11.2%)	15 (17.9%)	6 (5.8%)	**0.009**
Recurrent infection	21 (11.2%)	14 (16.7%)	7 (6.8%)	**0.031**
Mortality				
30-days mortality	45 (24.1%)	31 (36.9%)	14 (13.6%)	**< 0.001**
90-days mortality	56 (29.9%)	37 (44%)	19 (18.4%)	**< 0.001**

diabetes mellitus (OR 2.12, 95% CI: 1.17-3.85), and exposure to carbapenem (OR 2.27, 95% CI: 1.26-4.09) and polymyxin (OR 4.26, 95% CI: 1.48-12.27). Multivariable analysis demonstrated that underlying chronic kidney disease (adjusted OR 15.16, 95% CI: 6.3-36.48) was the only independent factor influencing the severity of CDI (Table 3).

Risk factors for mortality at 30 days

Univariable analysis revealed that statistically significant factors influencing the mortality of CDI included ICU admission (OR 5.75, 95% CI: 2.77 – 11.93), underlying chronic kidney disease (OR 2.11, 95% CI: 1.06 – 4.21), diabetes mellitus (OR 2.12, 95% CI: 1.17-3.85) and exposure to carbapenem (OR 4.12, 95% CI: 1.93 - 8.79). Multivariable analysis demonstrated that underlying ICU admission (adjusted OR 3.56, 95% CI: 1.48 – 8.56), and exposure to carbapenem (adjusted OR 2.79, 95% CI: 1.17 – 6.68) were independent factors influencing the severity of CDI (Table 4).

Discussion

Of 5079 entries of laboratory investigation for CDI in our cohort between June 2019 and December 2021, 390 entries were positive only accounting for 7.7% of all tests prescribed. Also, 201 of 390 positive entries were considered of no clinical importance due to repeated examination or not fulfilling the criteria of diagnosis.

Unsurprisingly, most of the patients were from the internal medicine and surgical wards where patients were more likely to have longer hospital stays, or underlying conditions associated with more frequent hospital visits compared with other departments. Similarly, patients admitted to the ICU usually presented severe diseases or underlying conditions and extended duration of the admission period. These patients also presented a higher probability of infections and antibiotic exposure, resulting in poor outcomes and

Table 3. Univariable and multivariable analysis for risk of severe CDI.

	Univariable		Multivariable	
	Crude OR 95%CI	***p***	**Adjusted OR 95%CI**	***p***
Age	1.03 (1.01, 1.04)	0.006*	1 (0.98, 1.03)	0.767
Sex				
Male	Reference	1		
Female	1.07 (0.6, 1.92)	0.809		
BMI	1.05 (0.97, 1.14)	0.254		
ICU	3.21 (1.64, 6.27)	0.001*	2.08 (0.78, 5.5)	0.141
Underlying diseases				
HIV	NA	1		
Diabetes mellitus	2.12 (1.17, 3.85)	0.013*	1.28 (0.6, 2.73)	0.520
Hematologic malignancy	1.05 (0.51, 2.17)	0.889		
Post-transplantation	0.48 (0.09, 2.53)	0.385		
Active solid malignancy	0.6 (0.3, 1.2)	0.149		
Autoimmune disease	0.34 (0.09, 1.29)	0.115		
Chronic kidney disease	15.11 (6.88, 33.2)	< 0.001*	15.16 (6.3, 36.48)	**< 0.001**
Liver cirrhosis	3.34 (1.01, 11.08)	0.048		
Chronic lung disease	1.24 (0.35, 4.44)	0.740		
Prior infection				
None	0.49 (0.19, 1.26)	0.142		
Urinary tract	1.11 (0.57, 2.15)	0.764		
Intra-abdominal	1.41 (0.75, 2.65)	0.289		
Respiratory system	1.8 (0.88, 3.66)	0.107		
Bloodstream infection	1.39 (0.7, 2.74)	0.349		
Musculoskeletal system	1.24 (0.39, 4.01)	0.715		
Skin and soft tissue	1.02 (0.42, 2.5)	0.957		
Nervous system	1.23 (0.17, 8.93)	0.837		
Prior antibiotic exposures				
None	0.58 (0.22, 1.51)	0.262		
Penicillin	0.91 (0.47, 1.73)	0.764		
Cephalosporins	0.7 (0.38, 1.27)	0.239		
Carbapenem	2.27 (1.26, 4.09)	0.006*	1.65 (0.73, 3.73)	0.229
Vancomycin	2.19 (0.94, 5.12)	0.071	0.84 (0.25, 2.8)	0.779
Fluoroquinolone	1.25 (0.42, 3.71)	0.692		
Fosfonic acid	2.52 (0.45, 14.14)	0.292		
Glycylglycine	3.2 (0.6, 16.91)	0.172		
Aminoglycoside	5.1 (0.56, 46.53)	0.149		
Nitroimidazole	0.53 (0.19, 1.47)	0.223		
Macrolide	0.81 (0.22, 2.96)	0.748		
Polymyxins	4.26 (1.48, 12.27)	0.007*	2.97 (0.77, 11.55)	0.115

* Statistically significant. HIV: human immunodeficiency viruses.

Table 4. Univariable and multivariable analysis for risk of mortality at 30 days.

	Univariable		Multivariable	
	Crude OR 95%CI	***p***	**Adjusted OR 95%CI**	***p***
Age	1.02 (1, 1.04)	0.125	1.01 (0.99, 1.03)	0.400
Sex				
Male	Reference	1		
Female	0.58 (0.29, 1.17)	0.129		
BMI	1.01 (0.92, 1.11)	0.768		
ICU	5.75 (2.77, 11.93)	< 0.001*	3.56 (1.48, 8.56)	0.005*
Underlying diseases				
HIV	NA	1		
Diabetes mellitus	0.69 (0.34, 1.39)	0.295	0.44 (0.19, 1.01)	0.052
Hematologic malignancy	1.2 (0.53, 2.71)	0.669		
Post-transplantation	NA	1		
Active solid malignancy	0.89 (0.4, 1.99)	0.777		
Autoimmune disease	0.55 (0.12, 2.56)	0.442		
Chronic kidney disease	2.11 (1.06, 4.21)	0.033*	2.05 (0.88, 4.78)	0.098
Liver cirrhosis	1.82 (0.58, 5.74)	0.307		
Chronic lung disease	1.6 (0.38, 6.66)	0.522		
Prior infection				
None	0.26 (0.06, 1.17)	0.080		
Urinary tract	1.46 (0.7, 3.08)	0.314		
Intra-abdominal	0.73 (0.34, 1.57)	0.422		
Respiratory system	1.35 (0.61, 3.01)	0.457		
Bloodstream infection	1.49 (0.7, 3.19)	0.304		
Musculoskeletal system	1.04 (0.27, 4.02)	0.955		
Skin and soft tissue	0.45 (0.13, 1.62)	0.223		
Nervous system	NA	1		
Prior antibiotic exposures				
None	0.3 (0.07, 1.32)	0.111		
Penicillin	0.6 (0.27, 1.37)	0.225		
Cephalosporins	0.44 (0.21, 0.95)	0.036*		
Carbapenem	4.12 (1.93, 8.79)	< 0.001*	2.79 (1.17, 6.68)	0.021*
Vancomycin	2.21 (0.92, 5.31)	0.075	0.85 (0.27, 2.62)	0.774
Fluoroquinolone	0.5 (0.11, 2.31)	0.371	0.64 (0.13, 3.23)	0.592
Fosfonic acid	3.26 (0.63, 16.77)	0.157		
Glycylglycine	8.62 (1.61, 46.15)	0.012*		
Aminoglycoside	4.93 (0.8, 30.49)	0.086		
Nitroimidazole	0.16 (0.02, 1.27)	0.084		
Macrolide	0.33 (0.04, 2.69)	0.300		
Polymyxins	6 (2.27, 15.87)	< 0.001*	2.69 (0.83, 8.72)	0.098

HIV: human immunodeficiency viruses.

high mortality rates [16].

Treatment outcomes were better in non-severe CDI with a significantly higher rate of remission. In contrast, patients with severe CDI possessed a higher probability of persistent diarrhea and recurrent infection similar to prior studies [15,17]. However, it should also be noted that a high percentage of patients receiving a diagnosis of severe CDI could receive metronidazole therapy in this cohort which is not recommended by the current focused updated guidelines by the IDSA and the SHEA in 2021 [18].

Overall, the 30-day mortality of CDI in this present study was 24.1%. The overall 30-day mortality of CDI was higher in the severe group, 13.6% in the non-severe CDI group, and 36.9% in the severe CDI group. The mortality in this study was moderately higher than in several population-based studies in Europe and the USA, ranging from 8 to 19% [19,20]. Comparable to a study in Singapore, which is a country in the same region, the mortality of CDI was only 12.5%, lower than in this study [15]. Despite vancomycin being recommended as the first line treatment of CDI regardless of severity, metronidazole was prescribed in one-half of patients with CDI in this study [13,18]. Since 2000, comparable studies on CDI treatment have demonstrated that vancomycin is superior to metronidazole regarding both clinical cure and mortality rate [21-23]. This observation is probably because the present study revealed a high rate of treatment regimens that were not compliant with the standard recommended practice guidelines. Additionally, almost all the study participants had hospital-acquired CDI and were hospitalized, contributing to higher mortality compared with other studies. The *C. difficile* strain with different ribotypes was also considered to impact the severity of CDI. Ribotypes 027 and 014/020 were notably associated with recurrence, while ribotype 027 was observed to cause more prominent fever and leukocytosis [24]. Other strains, including ribotypes 014/020, 017, 056,

106, and 078/126, have also been reported to cause CDI with poor health outcomes [25]. However, ribotype testing was not routinely performed at our institution. According to the most recent molecular epidemiology study in Thailand, the five most prevalent ribotypes were 014/020, 010, 017, 039, and 009, which may imply the circulating *C. difficile* strains in Thailand [26].

The severe CDI group showed a higher percentage of patients with diabetes mellitus, chronic kidney disease, and liver cirrhosis, likely due to the immune dysfunction linked to these conditions. This aligns with related studies demonstrating an association between diabetes mellitus and an increased incidence of CDI [27]. In contrast, conflicting data indicates the effect of liver cirrhosis on mortality [28]. However, in univariate and multivariate analysis, only patients with chronic kidney disease were found to exhibit a higher association with CDI severity. This is supported by published studies and multiple systematic reviews showing a higher prevalence of CDI among patients with chronic kidney disease as well as a higher prevalence of severe infection [29,30].

CDI has been associated with antibiotics exposure and, in this study, exposure to carbapenem and polymyxins contributed to higher crude odds in developing severe CDI in univariate analysis, not in the multivariate model. This contradicted the study of CDI in Singapore showing carbapenem exposure as an independent factor for severe CDI [15]. Additionally, according to the same study, CRP has been reported as an independent risk factor. However, due to the high amount of missing data in this study, the analysis cannot be made to demonstrate this association. Although CDI is usually associated with antibiotic use, a minority of the patients in this study developed CDI without any history of infection or antibiotic exposure according to medical records. No new discovery for community-acquired CDI has been reported to be associated with colonizer or among patients with certain risks such as advanced age, post-gastrointestinal procedure, or exposure to nonantibiotic medication such as proton pump inhibitors [15,31].

Even though many studies have linked advanced age and kidney injury to mortality, the trend was not been observed in this study. ICU admission and carbapenem exposure correlated to 30-day mortality in this present study. Currently, no studies identified ICU admission or antibiotics exposure as risk factors for death among patients with CDI; nevertheless, high mortality of patients developing CDI during ICU stay was observed whether CDI was the main cause of death [16,32].

This present study contributed a single-center analysis, which collects data from all patients with laboratory-confirmed CDI diagnoses receiving treatment over a specific period. Notably, it represents the most recent data available in Thailand.

Nevertheless, this current study encountered several limitations. Firstly, due to its observational retrospective nature, data were incomplete regarding clinical manifestations and laboratory findings, and some information may have been underreported. Consequently, unaccounted biases might have led to an underestimation of the true relationship between influencing factors and the mortality and severity of CDI. Secondly, as a tertiary care unit, the severity of the disease might have been overestimated. Thirdly, this study is based on experience from a single center in Thailand and highlights a lack of compliance with the guidelines, as 20.2% of severe CDI patients received metronidazole alone, which may have impacted the outcomes. Therefore, the findings, being less generalizable, should be carefully evaluated and compared with other cohorts. Geographic region, socioeconomic status, and the healthcare system of different countries might influence the study outcomes. Finally, genotyping data of *C. difficile* which some ribotypes may be associated with severe CDI and mortality, were not being performed in this study. A prospective, multicenter study, employing appropriate control of laboratory investigations and treatment, should be pursued for further investigation.

Conclusions

Our study highlights significant mortality rates and a frequent incidence of refractory and recurrent infections within the severe CDI group. Furthermore, chronic kidney disease emerged as an independent risk factor for severe CDI, underscoring the importance of monitoring this comorbidity among patients with CDI. Additionally, ICU admission and exposure to carbapenems were identified as independent risk factors for mortality, emphasizing the need for vigilant management strategies in these high-risk populations. These findings underscore the importance of early recognition and targeted interventions to improve outcomes among patients with severe CDI.

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Ethics Approval Statement
The Institutional Review Board, Royal Thai Army Medical Department provided approval for the study (approval number IRBRTA R139h/66_Exp). As the data were retrospective and de-identified, the Committee waived the requirement for informed consent.

Availability of data and materials
The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors contributions
Conceptualization, T.C, W.N., method, T.C, W.N.; data collection, T.C, W.N.; formal analysis, T.C, W.N.; writing—original draft preparation, T.C, W.N., supervision, W.N.; project administration, T.C, W.N. All authors contributed to manuscript writing and revision and agreed to submit the manuscript for publication. All authors meet the ICMJE authorship criteria.

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Conflict of interests
No conflict of interests is declared.

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