

Development of Risk Assessment Model for *Clostridioides Difficile* Infection In Hospitalized Patients at Udon Thani Hospital

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ABSTRACT

Introduction: Antibiotic-associated diarrhea (AAD) has been an adverse event in patients with antibiotic use and more than 25% of AAD was associated with *Clostridioides difficile* infection (CDI). The incidence of CDI was increasing worldwide along with problems in treatment, but the data of CDI in Thailand was limited including the incidence and the risk factors for the infection. **Methods** This study was retrospective descriptive study. Relevant data in electronic medication records of hospitalized patients with CDI diagnosis between 1 October 2016 and 30 September 2019 at Udon Thani Hospital were reviewed and collected. Descriptive statistics were used for analyzing patients' demographic data and univariate and multivariate analysis were used for analyzing the factors associated with CDI and developing the risk score model for CDI assessment. **Results** Of 124,061 patients admitted at Udon Thani hospital, 87 adults were diagnosed with CDI (incidence rate was 0.041% per admission or 0.4 case/1,000 patient admissions). Patients had an average age of 60.91 ± 14.53 years, and an average BMI of 21.57 ± 3.54 kg/m². Most of patients with CDI were admitted to the medical ward (78.05%). From the multivariable analysis, only 4 factors showed statistical significance in multiple logistic regression and the equation presented as $CDI = -5.128 + 2.958 [\text{Hypoalbuminemia}] + 0.989 [\text{Cardiovascular diseases}] + 1.449 [\text{Respiratory infections}] + 1.158 [\text{Number of anti-infectives} \geq 4 \text{ items}]$. **Conclusion** This risk assessment model may be a useful assessment tool for predicting CDI in patients with high-risk and needs closely monitoring during hospitalization.

Keywords: Antibiotic-associated diarrhea, *Clostridioides difficile*, Risk assessment model

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Introduction

Antibiotic-associated diarrhea (AAD) has been reported in more than 35% of patients with antibiotic use and more than 25% of this disease was associated with *Clostridioides difficile* (formerly *Clostridium difficile*) infection (CDI). [1] The incidence of CDI was increasing worldwide along with increasing in resistance to antimicrobials for treating CDI contributed to treatment failure and spread in hospitalized patients. [2] The clinical manifestations of patients with CDI range from mild to severe diarrhea and may lead to death. Therefore, this infection is important for healthcare system because of its high mortality and morbidity and increased healthcare expenses. [2] In 2015, an incidence of 500,000 cases and 30,000 deaths (6%) was reported in United State. In addition, it was found that the infections in 83,000 cases (20%) were recurrent infections. [3] CDI is an important complication for inpatients rather than outpatients. From the systematic reviews and meta-analysis studies, intrinsic factors contributing to initial episode of CDI were patients' characteristics such as underlying diseases, age, etc. Extrinsic factors contributing to initial episode of CDI were drug uses such as antacids, antibiotics, etc. For recurrent infection, the affected factors may be intrinsic factors including elderly, diabetes mellitus, renal impairment, and CDI severity. Extrinsic factor for recurrent CDI was the use of risky medication before diagnosing, after diagnosing, during treatment and after treatment. [4-9] However, the data of CDI incidence in Thailand was limited including data about the risk factors, the outcome of treatment, and the mortality or morbidity of patients with CDI. This study was aimed to determine the incidence of CDI and the risk factors related to CDI in hospitalized patients. Then, the tool for predicting CDI occurrence could be developed from this study to assess the chance of CDI in all hospitalized patients with CDI risk factors. Then, a physician can make some decisions such as ordering a laboratory stool toxin test or starting CDI therapy in patient with nosocomial diarrhea. In addition, infection control and prevention should be conducted intensively such as restriction of unnecessary antibiotic use.

Methodology

Study design and setting

The study was a retrospective descriptive study and performed as a case-control study in Udon Thani Hospital, an excellence centre hospital in the north-eastern region of Thailand, with approximately 1,100 beds. The hospital is a referral center for patients in That Health Region 8, covering 7 surrounding provinces. Study protocol permission by the Ethic Committee for Human Research, Khon Kean University (No. HE632056) and Udon Thani Hospital (No. I028/2563).

Population and sample

The population were all hospitalized patients aged over 18 years admitted in Udon Thani Hospital between 1 October 2016 to 30 September 2019. Patients in case group were adult patients with CDI diagnosis (ICD10 code A047 and positive stool *C. difficile* toxin assay or radiographs or computer tomography showed ileus or megacolon). Patients with incomplete data, negative *C. difficile* toxin, CDI

before admission, or referral to other hospitals were excluded from the study. Patients in the control group were adult patients without CDI diagnosis. Cases and controls with a ratio of 1 : 5 were used in this study. The sample size was calculated using Sample Size Calculator (UCSF CTSI) based on the formula for multiple logistic regression, providing the odd ratio (OR) of 1.57 identified from a previous meta-analysis in hospital acquired *C. difficile* infection associated with antibiotics. [10] A two-sided test statistic was determined with an α significance level of 0.05, a 80% predictive power at the β level of 0.20, and the proportion of cases versus the control of 1 : 5. The calculation indicated satisfactory sample sizes of 49 and 195 for the cases and control, respectively. However, all CDI patients during 1 October 2016 to 30 September 2019 would be recruited into the case group and patients without CDI during that time would be sampling systematically into the control group until reach 5 times of the case number.

Data collection

All data composed of demographic data and clinical data during hospitalization was reviewed and collected from electronic medication records. Demographic data including sex, age, body mass index, surgical history, social history (cigarette smoking and alcoholic drinking), underlying diseases, co-infections, medication uses duration 3 month before CDI, CDI history and admission history within 3 months. All of these parameters were interested variables from previous studied. [4-9] Clinical data during hospitalization including chief complaint, date of CDI diagnosis, serum albumin, white blood cell count, renal function test, and length of stay (before CDI diagnosis) were also reviewed and collected to confirm CDI and severity of infection.

Data analysis

Data from patients with and without CDI were summarized and compared. Descriptive statistics were used for analyzing the categorical and continuous variables and expressed as absolute (n) with relative (%) frequency and mean with standard deviation (SD), respectively. Univariable analysis was used for analyzing the factor associated with CDI, composed of Chi-square for nominal scale data and Mann-Whitney U-test for ordinal scale data and statistical significance (p-value) at <0.05. Then, the multicollinearity test and selection variable to multiple logistic regression that was variance Inflation Factor (VIF) <10 or Tolerance >0.1 means was not multicollinearity. The factors with statistically significant related with CDI were analyzed again to find their relationship using Stepwise logistic regression method. P-value for entry (pe) and p-value for remove (pr) of the factors in the equation were set at 0.05 and 0.1, respectively. Then, a risk assessment model was developed. All statistical analysis was carried out using STATA software, version 14.0.

Results

1. Patients' characteristics

During the study period, 124,061 patients were admitted in Udon Thani Hospital and 87 adult patients were diagnosed with CDI. Incidence rate was 0.041% per admission or 0.4 case/1,000 patient admissions. Five patients were excluded because 2 patients had unavailable or incomplete data, 1 patient had CDI before admission and 2 patient was referred to another hospital so that only 82 patients participated in this study. Male patient was slightly more than female patient (53.66% and 46.34%). The average age was 60.91 ± 14.53 years, and the average BMI was 21.57 ± 3.54 kg/m². Over 90% of patients with CDI denied cigarette smoking and alcoholic drinking. Some patients had a history of surgery (21.95%) and a history hospital admission within 3 months (41.46%). On CDI diagnosis day, the average eGFR of patients was 56.00 ± 40.97 mL/min. Most of them had eGFR ≤ 60 mL/min (56.10%) and had hypoalbuminemia (93.9%). For the control group, 401 patients were selected and participated in the study. The details of patients' characteristics are shown in Table 1.

Table 1 Patients' characteristics

Characteristic	Number of participants (%)		p-value
	CDI (n = 82)	Non-CDI (n = 401)	
Sex			
Male	44 (53.66)	213 (53.12)	0.929
Female	38 (46.34)	188 (46.88)	
Age (years)			
<30	4 (4.88)	64 (15.96)	0.009
30 – 60	30 (36.59)	179 (44.64)	0.180
>60	48 (58.54)	158 (39.40)	0.001
Body mass index (kg/m ²)			
Underweight (<18.5)	15 (18.29)	48 (11.97)	0.121
Healthy (18.5 ≤ BMI <25)	53 (64.63)	246 (61.35)	0.576
Overweight (25 ≤ BMI <30)	13 (15.85)	77 (19.20)	0.478
Obese (BMI ≥ 30)	1 (1.22)	30 (7.48)	0.035
Cigarette smoking	5 (6.1)	82 (20.45)	0.004
Alcoholic drinking	6 (7.32)	92 (22.94)	0.001
History of GI surgery	18 (21.95)	32 (7.98)	<0.001
History of admit (3 month)	34 (41.46)	63 (15.71)	<0.001
eGFR (mL/min/1.73 mm ²)			
<30	33 (40.24)	41 (10.22)	<0.001
30 – 60	13 (15.85)	56 (13.97)	0.656

Table 1 Patients' characteristics (Cont.)

Characteristic	Number of participants (%)		p-value
	CDI (n = 82)	Non-CDI (n = 401)	
>60	36 (43.90)	304 (75.81)	<0.001
Hypoalbuminemia (Alb <3.5 g/dL)	77 (93.90)	108 (26.93)	<0.001
Ward			
Medicine department	64 (78.05)	171 (42.64)	<0.001
Other departments	18 (21.95)	230 (57.36)	
Length of stay			
> 5 days	57 (69.51)*	167 (41.65)	<0.001
≤ 5 days	25 (30.49)*	234 (58.35)	

* From hospital admission to the occurrence of CDI

2. Medical conditions and medication use within 90 days

Most patients with CDI had infectious diseases. Respiratory tract infections were found in 67.07% of participants followed by sepsis (42.68%) and skin, soft-tissue and bone infections (26.83%). In contrast, some patients without CDI had infectious diseases. Skin, soft-tissue and bone infections were found in 18.45% of non-CDI participants, followed by gastrointestinal infections (13.97%) and respiratory tract infections (12.72%). For other medical conditions, more than half of patients with CDI had underlying diseases. Cardiovascular diseases were found in 70.73% of participants followed by chronic kidney disease (45.12%) and diabetes mellitus (42.68). In contrast, some patients without CDI had underlying diseases. However, cardiovascular diseases were found in 32.91% of participants followed by gastrointestinal diseases (18.95%) and respiratory diseases (15.96%). Other infectious diseases and medical conditions are listed in Table 2.

In patients with CDI, most of them had history of anti-infective agent use in previous 90 days. Cephalosporins were used in 84.15% of participants, followed by carbapenems (51.22%) and fluoroquinolones (34.15%). In patients without CDI, cephalosporins were used in 77.06% of participants, followed by penicillins (23.69%) and fluoroquinolones (15.21%) as shown in Table 2. For non-infective agents, proton pump inhibitors were commonly used in patients with CDI (67.07%) and without CDI (59.10%) followed by corticosteroids in 46.91% and 24.44% of participants, respectively.

Table 2 Medical conditions and medication

Medical conditions and medication	Number of participants (%)		p-value
	CDI (n = 82)	Non-CDI (n = 401)	
Infectious disease			
Respiratory infections	55 (67.07)	51 (12.72)	<0.001
Sepsis	35 (42.68)	34 (8.48)	<0.001
Skin, soft-tissue and bone	22 (26.83)	74 (18.45)	0.083
infections			
Urinary tract infections	15 (18.29)	27 (6.73)	0.001
Gastrointestinal infections	9 (10.98)	56 (13.97)	0.470
Infective endocarditis	2 (2.44)	3 (0.75)	0.168
CNS infections	2 (2.44)	4 (1.00)	0.283
Medical conditions			
Cardiovascular diseases	58 (70.73)	140 (34.91)	<0.001
Chronic kidney diseases	37 (45.12)	35 (8.73)	<0.001
Diabetes mellitus	35 (42.68)	63 (15.71)	<0.001
Anemia	31 (37.8)	53 (13.22)	<0.001
Gastrointestinal diseases	26 (31.71)	76 (18.95)	0.011
Acute kidney injury	23 (28.05)	17 (4.24)	<0.001
Cancer	15 (18.29)	39 (9.73)	0.027
Respiratory diseases	14 (17.07)	64 (15.96)	0.803
Neurological diseases	12 (14.63)	18 (4.49)	0.001
Immune diseases	9 (10.98)	16 (3.99)	0.013
Other	14 (17.07)	29 (7.23)	0.001
Anti-infective agent exposure			
High-risk antibiotics			
Cephalosporins	69 (84.15)	309 (77.06)	0.156
Fluoroquinolones	28 (34.15)	61 (15.21)	<0.001
Lincosamides	32 (39.02)	48 (11.97)	<0.001
Medium-risk antibiotics			
Penicillins	36 (43.90)	95 (23.69)	<0.001
β -lactam/lactamase inhibitors	30 (36.59)	52 (12.97)	<0.001
Macrolides	10 (12.16)	33 (8.23)	0.236
Low-risk antibiotics			
Carbapenems	42 (51.22)	53 (13.22)	<0.001
Nitroimidazoles	12 (14.63)	79 (19.70)	0.305

Table 2 Medical conditions and medication (Cont.)

Medical conditions and medication	Number of participants (%)		p-value
	CDI (n = 82)	Non-CDI (n = 401)	
Glycopeptides	9 (10.98)	10 (2.49)	<0.001
Sulfonamide derivatives	6 (7.32)	5 (1.25)	0.001
Aminoglycosides	16 (19.51)	19 (4.74)	<0.001
Tetracyclines	3 (3.66)	11 (2.74)	0.639
Colistin	20 (24.39)	10 (2.49)	<0.001
Antivirals	12 (14.81)	18 (4.49)	<0.001
Anthelmintics	8 (9.88)	3 (0.75)	<0.001
Antitubercular agents	10 (12.35)	11 (2.74)	<0.001
Antifungals	10 (12.35)	3 (0.75)	<0.001
Non-infective agent exposure			
Proton pump inhibitors	55 (67.07)	237 (59.10)	0.139
Histamine ₂ antagonists	5 (6.10)	19 (4.74)	0.588
Antacids	5 (6.10)	4 (1.00)	0.033
Corticosteroids	38 (46.34)	98 (24.44)	<0.001
Immunosuppressive agents	10 (12.19)	9 (2.24)	<0.001
Anticancer agents	7 (8.53)	13 (3.24)	0.033
Number of all medication exposure			
≥ 5 items	58 (70.73)	77 (19.20)	<0.001
< 5 items	24 (29.27)	324 (80.80)	
Number of anti-infective agent exposure			
≥ 4 items	57 (69.51)	65 (16.21)	<0.001
< 4 items	25 (30.49)	336 (83.79)	

3. Factors associated with CDI and development of risk assessment model for *Clostridioides difficile* infection

Univariable analyses of the patient characteristics, medical conditions and medication uses, were performed between patients with and without CDI. Factors from patients' characteristics significant related to CDI composed of age > 60 years, length of hospital stay > 5 days, history of gastrointestinal surgery, history of hospital admission within 3 month and hypoalbuminemia. In contrast, obese (BMI over 30 kg/m²), and eGFR > 30 mL/min had decrease in risk of CDI. Cigarette smoker and alcoholic drinker had decrease in risk of CDI, too. Factors from medical conditions significant related to CDI were some infectious diseases composed of sepsis, respiratory infections, urinary tract infections and some medical conditions composed of cancer, cardiovascular diseases, diabetes mellitus, chronic kidney

disease, immune diseases, neurological diseases, gastrointestinal diseases, acute kidney injury, anemia. Factors from medication use significant related to CDI were found with most anti-infective agents except for Nitromidazoles, Macrolides and Tetracyclines and some of non- anti- infective agents including antacid, corticosteroids, immunosuppressive agents and anticancer agents.

All 42 factors were analysed and considered to be the risk factors to CDI with statistical significance except for obese (only 1 patient in CDI group) and social history (unreliable) were analysed together for finding their relationship with CDI using multivariable analysis with binary logistic regression. Risk factors with statistical significance ($p < 0.05$) were selected by stepwise logistic regression. The factor with highest odd ratio was hypoalbuminemia (OR 19.260; 95% CI: 7.276-50.979) followed by respiratory tract infection (OR 4.258; 95% CI: 2.145-8.452), anti-infective items ≥ 4 items (OR 3.182; 95% CI: 1.599-6.331) and cardiovascular disease (OR 2.687; 95% CI: 1.389-5.213). The final model composed of 4 factors included into the equation for CDI = $-5.128 + 2.958 [\text{Hypoalbuminemia}] + 0.989 [\text{Cardiovascular diseases}] + 1.449 [\text{Respiratory infections}] + 1.158 [\text{Number of anti-infective item} \geq 4 \text{ items}]$.

Table 3 Multivariable analysis of factors related to *Clostridioides difficile* infection by stepwise logistic regression analysis (N=483)

Variables	β - coefficient	Odds Ratio	95% confidence interval for Odds ratio		p-value
			Lower	Upper	
Hypoalbuminemia Alb < 3.5 g/dL	2.958	19.260	7.276	50.979	< 0.001
Cardiovascular diseases	0.989	2.687	1.389	5.213	< 0.005
Respiratory infections	1.449	4.258	2.145	8.452	< 0.001
Anti-infective items ≥ 4 items	1.158	3.182	1.599	6.331	0.001
Constant	-5.128	0.006	0.002	0.017	< 0.001

Discussion

The incidence of CDI in hospitalized patients at Udon Thani Hospital in 3 years period was 0.041% per admission or 0.4 case/1,000 patient admissions which was higher than the 2010 nationwide CDI incidence of Thailand that reported 0.01% per admission or 0.1 case/1000 patient admissions. [11] The higher incidence of CDI in this study may be because Udon Thani Hospital is a tertiary care hospital. Most patients usually had various comorbidities or complicated infections and may receive potent antibiotics during hospitalization. This is supported by a higher percentage of infectious diseases found in patients with CDI than patients without CDI. Over 67% of patients with CDI in this study had infectious diseases. As the patients with various kinds of infections, they also had higher percentage of antibiotic exposure than patients without CDI. The most commonly exposed antibiotics in patients with CDI were cephalosporins (85.15%), followed by carbapenems (51.22%), and penicillins (43.90%) similar to study

by Ngamskulrungronj et al. [12] However, the incidence of CDI in this study was lower than 0.2% reported by Soontornpas *et al.* [13] Higher incidence may belong to different CDI toxin testing criteria. Stool examination for CDI toxin test was performed in patients suspected CDI without diarrhea in Srinagarind hospital meanwhile stool test for CDI toxin in Udon Thani Hospital was limited to patients suspected CDI with diarrhea.

The average age of patients with CDI was 60.9 years and 58.54% of patients aged over 60 years. Elderly patients usually had underlying diseases which may impair host immunity against infectious disease. [14] Co-morbidities commonly found in our participants were cardiovascular diseases (70.73%), chronic kidney disease (45.12%) and diabetes mellitus (46.28%) and some patients had many comorbidities similar to previous studies. [11] In contrast, patients without CDI had lower incidence of underlying disease but cardiovascular diseases were still the most commonly found comorbidity (32.91%) followed by gastrointestinal diseases (18.95%) and respiratory diseases (15.96%). Patients with CDI were usually admitted in medical ward (78.05%) because they required medicines for treating medical problems including anti-infectives for infectious diseases. Other wards usually supported patients who needed other medical procedures such as operations. Patients with CDI had lower eGFR and serum albumin than non-CDI patients. Both renal impairment and malnutrition may contribute to the impairment of immunity to prevent infection in patients with CDI. [15-16] For other medication use, proton pump inhibitors were used in 67.9% of patients with CDI. This drug group was reported as a possible risk factor for CDI. [17] They inhibit gastric acid secretion so that *C. difficile* can enter via the mouth to the stomach and increase the risk of infection. However, this drug group was not a significant risk factor in this study.

From univariable analysis, 42 factors showed statistically significantly related to CDI. There were 3 variables with p-value <0.05 in univariable analysis but were not included in multivariable analysis. Cigarette smoking and alcoholic drinking were not included because of unreliable data collection in electronic medication records. Obese was also not included because of only 1 patient with obese in CDI group. When these risk factors were tested for their correlation by binary logistic regression analysis, only 4 factors showed statistical significance composed of hypoalbuminemia, cardiovascular diseases, respiratory infections, and anti-infective items ≥ 4 items similar to previous study. [4,18] All of these factors are related to the impairment of human immunity. Protein is an important component in immune response so that the patients with protein malnutrition also have immune deficiency. [16] Use of these broad-spectrum antimicrobials may alter normal flora in gastrointestinal tract and cause overgrowth of *C. difficile* that contribute to the occurrence of CDI. [14] Moreover, 69.51% of patients with CDI had history of antibiotic exposure within 90 days for at least 4 items and increased the risk of CDI infection. Respiratory tract and cardiovascular system are vital organ so that dysfunction of these organ may also contribute to impairment of immunity. [19-20] There are a few articles about risk score tool for CDI but the variables in the model were different. For example, 2 factors were included in the model of a study

in primary care unit composed of the history of hospital admission and antibiotic use ≥ 5 items. [21] In a multicenter study, 12 variables were included in the model composed of age, history of admission, length of stay, and 8 comorbidities. [22] In this study, only 4 variables were related to CDI which overlapped with previous studies except for hypoalbuminemia. To develop the risk assessment model for CDI, stepwise logistic regression analysis was performed to formulate the equation. This equation can be used for predicting the occurrence of CDI. However, risk score model should be developed and tested for its' sensitivity and accuracy before practical use in real situation.

Limitations

There were some limitations of the study. Firstly, patients with nosocomial diarrhea were not routinely screened for *C. difficile* toxin, which may lead to underreporting of CDI. Secondly, this study was a retrospective study so that data collection for some variables yielded ambiguous information such as smoking, and alcohol consumption. Thirdly, the risk score model was not completely developed and tested in this study. Therefore, future study should concern about these aspects.

Conclusion

The incidence rate of CDI in Udon Thani Hospital was as low as 0.041% per admission or 0.4 case/1,000 patient admissions. There were only 4 factors significantly related to CDI and were included in the equation for predicting the occurrence of CDI. This risk assessment model may be useful for physicians to assess the chance of CDI in hospitalized patients and make some decisions such as sending stool toxin tests or starting CDI therapy.

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