Risk prediction for 30-day mortality among patients with *Clostridium difficile* infections: a retrospective cohort study

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**Abstract**

**Background:** Current guidelines have unsatisfied performance in predicting severe outcomes after *Clostridium difficile* infection (CDI). Our objectives were to develop a risk prediction model for 30-day mortality and to examine its performance among inpatients with CDI.

**Methods:** This retrospective cohort study was conducted at China Medical University Hospital, a 2111-bed tertiary medical center in central Taiwan. We included adult inpatients who had a first positive *C. difficile* culture or toxin assay and had diarrhea as the study population. The main exposure of interest was the biochemical profiles of white blood cell count, serum creatinine (Scr), estimated glomerular filtration rate, blood urea nitrogen (BUN), serum albumin, and glucose. The primary outcome was the 30-day all-cause mortality and the secondary outcome was the length of stay in the intensive care units (ICU) following CDI. A multivariable Cox model and a logistic regression model were developed using clinically relevant and statistically significant variables for 30-day mortality and for length of ICU stay, respectively. A risk scoring system was established by standardizing the coefficients. We compared the performance of our models and the guidelines.

**Results:** Of 401 patients, 23.4% died within 30 days. In the multivariable model, malignancy (hazard ratio [HR] = 1.95), ≥ 1.5-fold rise in Scr (HR = 2.27), BUN-to-Scr ratio > 20 (HR = 2.04), and increased glucose (≥ 193 vs < 142 mg/dL, HR = 2.18) were significant predictors of 30-day mortality. For patients who survived the first 30 days of CDI, BUN-to-Scr ratio > 20 (Odds ratio [OR] = 4.01) was the only significant predictor for prolonged (> 9 days) length of ICU stay following CDI. The Harrell’s c statistic of our Cox model for 30-day mortality (0.727) was significantly superior to those of SHEA-IDSA 2010 (0.645), SHEA-IDSA 2018 (0.591), and ECSMID (0.650). Similarly, the conventional c statistic of our logistic regression model for prolonged ICU stay (0.737) was significantly superior to that of the guidelines (SHEA-IDSA 2010, c = 0.600; SHEA-IDSA 2018, c = 0.634; ESCMID, c = 0.645). Our risk prediction scoring system for 30-day mortality correctly reclassified 20.7, 32.1, and 47.9% of patients, respectively.

**Conclusions:** Our model that included novel biomarkers of BUN-to-Scr ratio and glucose have a higher predictive performance of 30-day mortality and prolonged ICU stay following CDI than do the guidelines.

**Keywords:** *Clostridium difficile* infection, Mortality, ICU stay, Glucose, BUN-to-Scr ratio

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Background

Clostridium difficile infection (CDI) is a critical healthcare-associated infection and accounts for 20–30% of antibiotic-associated diarrhea [1, 2]. The Antibiotic Resistance Threats in the United States report prioritized C. difficile as an urgent threat because it spreads rapidly and is naturally resistant to many antimicrobials used to treat other infections [3].

Predicting patients with CDI who are at risk of developing severe complications can guide appropriate treatment and follow-up, and in turn, prevent adverse outcomes [4, 5]. SHEA-IDSA 2010 and SHEA-IDSA 2018 clinical practice guidelines for treating CDI recommend using vancomycin or fidaxomicin to treat initial severe CDI [6, 7]. Two published studies provided evidence that, as high as 31.2–38% of severe CDI and 56–65% of severe-complicate CDI were under-treated [4, 5]. Compared with patients who were treated appropriately, those who were under-treated (according to SHEA-IDSA 2010 guideline) [6] were more likely to have adverse outcomes of all-cause mortality (Crowell’s: 7.2% vs 15.0%; Patel’s: 12.9% vs 43.5%), CDI-related mortality (Crowell’s: 3.8% vs 7.7%; Patel’s: 8.9% vs 21.7%), prolonged CDI-related hospital length of stay (Crowell’s: mean 7.5 days vs 9.4 days), or CDI-related ICU transfer (Patel’s: 4.8% vs 17.4%) [4, 5]. When patients were stratified by severity (defined by SHEA-IDSA 2010 guideline) [6], patients with severe CDI who were under-treated experienced more complications than those who were appropriately treated (death: 20% vs 18.5% for severe CDI; ICU transfer: 20% vs 7.4% for severe CDI), although these findings were not statistically significant [5]. Therefore, identification of potentially severe cases of CDI could provide evidence for appropriate treatment and lead to better patient outcomes.

Conventionally, marked leukocytosis, acute rise in serum creatinine (SCr), hypoalbuminemia, and older age are considered to be prognostic factors of severe complications (ie, intensive care unit [ICU] admission, colectomy, or death), according to guidelines developed by the Society for Healthcare Epidemiology of America and the Infectious Disease Society of America (SHEA-IDSA) in 2010 and 2018 and guidelines developed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in 2014 [6–8]. Although these indicators reasonably represent the underlying interactions between infection, immune-inflammatory responses, and malnutrition, their performance in predicting CDI severity is unsatisfactory [7, 9].

Other severity indices that included comorbidities (eg, malignancy and renal disease) [10, 11], symptoms (eg, fever, hypotension, septic shock, pseudomembranous colitis, and ascites) [12–14], or antibiotic utilization [15, 16] as severity predictors have been reported to improve risk assessment of CDI severity in inpatients or ICU settings [17]. However, subjective measures, different outcomes (ie, mortality, colectomy, ICU admission, recurrence, or cure rate), and inconsistent CDI diagnostic criteria (eg, without information of diarrhea status) [9, 18], compromise the comparability and generalizability of the previous findings [17]. From a pathophysiologic perspective, dehydration, a warning sign of severe diarrhea and subsequent hemodynamic instability, should certainly be considered but has never been evaluated as a risk predictor for severe CDI. Blood urea nitrogen (BUN)-to-SCr ratio, which can quantify dehydration and distinguish pre renal kidney injury from intrinsic kidney disease, is a potential predictor for severe CDI.

To address the aforementioned gaps, we conducted this study to develop a new risk prediction model incorporating comorbidities, markers of infection, renal function, dehydration, and serum glucose to predict the risk of 30-day mortality, and to compare the predictive performance of our model and existing guidelines among adult patients with symptomatic CDI.

Methods

Data source

This retrospective cohort study was conducted at China Medical University Hospital (CMUH), a 2111-bed tertiary medical center in Taiwan. The data source was the CMUH–Clinical Research Data Repository (CRDR), which accumulates the single unified views of 2,660,472 patients who had sought care at CMUH between 2003 and 2016. The Institutional Review Board of CMUH approved this study (105-REC3–068 & 107-REC2–016).

Study population

Our study included all patients who had first-time positive results of C. difficile toxin assay or culture at CMUH between January 1, 2012, and December 31, 2016. The index date was the date when the specimen of positive C. difficile result was obtained. We excluded patients who 1) were aged younger than 20 years, 2) were not admitted, or 3) did not have diarrhea (at least 3 loose stools per day or loose stools for at least 3 days during hospitalization) [14, 19]. Data were pulled from the CMUH–CRDR, except for diarrhea status, which was manually reviewed using medical records. The mortality data were obtained by linking to the National Cause of Death Database. Our study population comprised 401 adult inpatients who had incident symptomatic CDI (Fig. 1).

Covariables and outcomes

C. difficile testing was performed in inpatients at physicians’ discretion, except that universal screening was performed in patients who were admitted to the medical ICU during the period between January 1, 2014, and February 28, 2015. Methods of C. difficile testing were presented in Additional file 1: Methods. The main
exposure of interest was the biochemical profiles of white blood cell count (WBC), SCr, estimated glomerular filtration rate (eGFR) through CKD-EPI equation [20], BUN, serum albumin, and glucose that were measured within −30 to −3 days of the index date (baseline) or measured within ±3 days of the index date (index). The definitions of variables are listed in Additional file 1: Figure S1. The primary outcome of interest was the 30-day all-cause mortality following the index CDI and the secondary outcome of interest was the length of ICU stay following CDI (for patients who survived the first 30 days of CDI).

Severity predictors from guidelines

Previous guidelines have provided certain severity predictors for identifying severe cases of CDI. The SHEA-IDSA 2010 criteria for a severe CDI are outlined as follows: having a WBC of ≥15,000 cells/μL or a 1.5-fold relative increase in SCr (compared with premorbid level) [6]. The SHEA-IDSA 2018 criteria are presented as follows: having a WBC of ≥15,000 cells/μL or an index SCr of ≥1.5 mg/dL (133 μM) [7]. The ESCMID 2014 criteria are outlined as follows: being aged ≥65 years, having a WBC of ≥15,000 cells/μL, a serum albumin level of < 3.0 g/dL, or a SCr level of ≥1.5 mg/dL (133 μM) or a 1.5-fold relative increase in SCr [8].

Statistical analyses

Continuous variables are presented as medians and interquartile ranges (IQR) and were analyzed using the Wilcoxon rank-sum test. Categorical variables are presented as frequency and proportions (%) and were analyzed using a chi-square test or Fisher’s exact test. All analyses were 2 sided, and the significance level was set to 0.05.

To develop the risk prediction model for 30-day mortality, variables that were significantly associated with 30-day mortality in the univariable analyses (i.e., P < 0.05) and that were clinically relevant were considered in the multivariable Cox proportional hazard model. We categorized the included variables in the multivariable model in the subsequent risk score development. Because of the high proportion of missing values for laboratory tests, we performed multiple imputation using an iterative Markov chain Monte Carlo procedure with 20 imputations and 100 iterations [21]. We used the original data and the data from multiple imputations in separate Cox models for 30-day mortality and in separate logistic regression models for prolonged (> 9 days) post-CDI length of ICU stay. We
compared the performance of our risk prediction model with that of the guidelines by using discrimination measure of Harrell’s c statistic for Cox models [22] or conventional c statistic for logistic regression models.

To develop the risk prediction scores, we assigned each independent variable a risk point, which was derived by dividing the beta regression coefficient of each variable by the smallest absolute coefficient and rounding off the quotient to the nearest integer [23]. A severity score was calculated for each patient by summing up the risk points corresponding to the risk factors. We then divided the study population into 2 groups on the basis of their severity scores (< 29 vs ≥29). We compared the performance of our risk prediction scoring system with that of the guidelines by using the reclassification measure of net reclassification index (NRI) [24].

Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) software. All analyses were 2 sided, and the significance level was set to 0.05.

Results
Description of patients with C. difficile infections
Of 401 inpatients with CDI, the mean age was 68.2 years, 59.1% were men, and 59.3% had documented fever (Table 1). Positive C. difficile toxin test results were detected in 54.1% of the patients and positive culture results were found in the remaining patients. The median hospital stay was 25 days, 52.9% were admitted to the ICU, and 23.4% died within 30 days after the index CDI.

Characteristics associated with 30-day mortality
Patient who died within 30 days following their CDI were more likely to be older (mean age: 72.5 vs 66.9 years), have malignancies (eg, leukemia and lymphoma; 53.2% vs 33.9%), have fever (70.2% vs 56.2%), and have higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores among patients admitted to ICU prior to CDI (median 18 vs 15), compared with those who survived within 30 days (Table 1).

The biochemical profiles significantly differed between patients who died and those who survived, except for the baseline eGFR. Patients who died had higher levels of WBC (median 13,700 vs 11,700 cells/µL), an increased likelihood of having an SCr level 1.5-fold higher than their premorbid level (55.4% vs 27.8%), higher levels of BUN (median 41.0 vs 25.0 mg/dL), an increased likelihood of having a BUN-to-SCr ratio of > 20 (69.4% vs 40.8%), lower levels of albumin (median 2.35 vs 2.60 g/dL), and higher levels of glucose (median 192 vs 158 mg/dL).

Risk prediction model for 30-day mortality
To develop the risk prediction model, we included age > 65 years, malignancy history, index WBC in tertiles, 1.5-fold rise in SCr, albumin < 2.5 g/dL, BUN-to-SCr ratio > 20, and glucose in tertiles in a Cox model (Fig. 2). The results obtained for the original and imputed data were similar. Malignancy (hazard ratio [HR] = 1.95; 95% confidence interval [CI] = 1.28, 2.95), rise in SCr (HR = 2.27, 95% CI = 1.44, 3.95), BUN-to-SCr ratio > 20 (HR = 2.04, 95% CI = 1.28, 3.24), and glucose level ≥193 mg/dL (reference: < 142 mg/dL, HR = 2.18, 95% CI = 1.17, 4.05) were significantly associated with 30-day mortality when imputed data were used. The discrimination performance of our model (Harrell’s c statistic = 0.727; 95% CI = 0.672, 0.782) was significantly superior to that of the model using severity indicators stated in the SHEA-IDSA 2010 (c statistic = 0.645; 95% CI = 0.588, 0.702), SHEA-IDSA 2018 (c statistic = 0.591; 95% CI = 0.537, 0.644), and the ESCMID guidelines (c statistic = 0.650; 95% CI = 0.594, 0.711) (Table 2).

Risk prediction scoring system for 30-day mortality
To develop a risk prediction scoring system, we assigned each risk predictor a risk point (Table 3). Patients with a risk score of ≥29 were considered to be at a higher risk (10% or higher) of 30-day mortality. Compared with the SHEA-IDSA 2010, SHEA-IDSA 2018, and ESCMID guidelines, our scoring system reclassified 20.7, 32.1, and 47.9% of the CDI patients into the correct risk category, respectively (Additional file 1: Table S1).

Risk prediction model for prolonged length of ICU stay following CDI
Of 307 patients who survived the first 30 days following CDI, the mean length of ICU stay following CDI was 9.8 days (median: 0 days; interquartile range, 0–9 days). We used the 3rd quartile (9 days) as the cut-off for prolonged post-CDI length of ICU stay in the multivariable logistic regression analysis.

We evaluated the performance of our risk prediction model in predicting post-CDI length of ICU stay > 9 days (Table 4). BUN-to-SCr ratio was the only significant and strong predictor for prolonged length of ICU stay following CDI (imputed data: adjusted OR, 4.01; 95% CI, 2.19–7.33). The discrimination performance of our prediction model was moderate (imputed data: c statistic, 0.737; 95% CI, 0.671–0.804), and was superior to the discrimination performance of SHEA-IDSA 2010 (c statistic, 0.600; 95% CI, 0.527–0.673), SHEA-IDSA 2018 (c statistic, 0.634; 95% CI, 0.564–0.704), and ESCMID (c statistic, 0.645; 95% CI, 0.573–0.718) (Table 5).

Discussion
This is the first epidemiological study to investigate predictors for the severe outcome of CDI in Asia [25]. Our risk prediction model included age > 65 years, malignancy history, WBC in tertiles, 1.5-fold rise in SCr,
Table 1 Baseline demographic and clinical characteristics of adult inpatients with *Clostridium difficile* infections (CDI)

| Variablesa | Total (N = 401) | 30-Day Mortality | p-valuea |
|------------|-----------------|------------------|----------|
|            | Died (N = 94)   | Did not die (N = 307) |         |
| Age at index date, years | | | |
| Mean (standard deviation) | 68.2 15.8 | 72.5 13.2 | 66.9 16.4 | 0.001b |
| ≥ 65 years old | 234 58.4% | 63 67.0% | 171 55.7% | 0.051 |
| Male | 237 59.1% | 59 62.8% | 178 58.0% | 0.409 |
| Comorbidity within 1 year priorc | | | |
| Diabetes mellitus | 201 50.1% | 50 53.2% | 151 49.2% | 0.497 |
| Renal disease | 158 39.4% | 35 37.2% | 123 40.1% | 0.623 |
| Inflammatory bowel disease | 6 1.5% | 1 1.1% | 5 1.6% | 0.372b |
| Malignancy | 154 38.4% | 50 53.2% | 104 33.9% | 0.001 |
| Hospital admission within 90 days prior | 182 45.4% | 49 52.1% | 133 43.3% | 0.134 |
| Antibiotic use within 30 days prior | | | |
| Cephalosporins | 170 42.4% | 39 41.5% | 131 42.7% | 0.839 |
| Fluoroquinolones | 81 20.2% | 20 21.3% | 61 19.9% | 0.766 |
| Carbapenems | 100 24.9% | 25 26.6% | 75 24.4% | 0.671 |
| Anti-peptic ulcer agentsd | 296 73.8% | 68 72.3% | 228 74.3% | 0.710 |
| APACHE II score prior to CDIe | 15.0 (10.0, 20.0) | 18.0 (11.0, 21.0) | 15.0 (10.0, 20.0) | 0.036 |
| Fever (≥38 °C) at index CDI | 223 59.3% | 59 70.2% | 164 56.2% | 0.021 |
| Anti-diarrhea medicationsf | 225 56.1% | 51 54.3% | 174 56.7% | 0.679 |
| Stool routine | | | |
| Presence of mucus | 52 15.6% | 10 14.1% | 42 16.0% | 0.689 |
| Positive for red blood cell | 121 36.3% | 26 36.6% | 95 36.3% | 0.955 |
| Positive for WBC | 115 34.5% | 24 33.8% | 91 34.7% | 0.884 |
| C. difficile toxin or culture | | | |
| Toxin testg | 217 54.1% | 49 52.1% | 168 54.7% | 0.659 |
| Culture only | 184 45.9% | 45 47.9% | 139 45.3% | 0.007 |
| Biochemical profiles at index CDIh | | | |
| White blood cell count (WBC), cells/mm³ | 12,000 (8,300, 17,100) | 13,700 (8,600, 20,900) | 11,700 (8,100, 16,400) | 0.014 |
| First tertile: < 9440 | 129 33.0% | 27 28.7% | 102 34.3% | 0.017 |
| Second tertile: 9440 to < 14,600 | 126 32.2% | 23 24.5% | 103 34.7% | 0.017 |
| Third tertile: ≥ 14,600 | 136 34.8% | 44 46.8% | 92 31.0% | 0.017 |
| WBC > 15,000 | 126 32.2% | 41 43.6% | 85 28.6% | 0.017 |
| Serum creatinine (Scr), mg/dL | | | |
| Premorbid Scr² | 1.01 (0.67, 2.05) | 0.97 (0.60, 1.56) | 1.03 (0.69, 2.30) | 0.392 |
| Index Scr² | 1.41 (0.81, 3.74) | 1.64 (0.90, 3.66) | 1.34 (0.76, 3.82) | 0.224 |
| Rise in Scr level | | | |
| ≥ 1.5-fold | 113 34.9% | 46 55.4% | 67 27.8% | < 0.001 |
| ≥ 1.5045 mg/dL | 56 17.3% | 19 22.9% | 37 15.4% | 0.1172 |
| ≥ 1.5-fold or ≥ 1.5045 mg/dL | 123 38.0% | 48 57.8% | 75 31.1% | < 0.001 |
| eGFR (CKD-EPI), ml/min/1.73m² | 51.4 (17.3, 91.0) | 47.3 (16.7, 88.3) | 52.5 (17.6, 92.5) | 0.623 |
| BUN, mg/dL | 29.0 (14.0, 60.0) | 41.0 (21.0, 85.0) | 25.0 (13.0, 52.5) | < 0.001 |
| First tertile: < 17 | 110 30.8% | 14 16.5% | 96 35.3% | 0.004 |
| Second tertile: 17 to < 44 | 121 33.9% | 33 38.8% | 88 32.4% | 0.004 |
| Third tertile: ≥ 44 | 126 35.3% | 38 44.7% | 88 32.4% | 0.004 |
Table 1  Baseline demographic and clinical characteristics of adult inpatients with *Clostridium difficile* infections (CDI) (Continued)

| Variablesa | Total (N = 401) | 30-Day Mortality | p-valuea |
|------------|-----------------|------------------|----------|
|            | Died (N = 94)   | Did not die (N = 307) |
| BUN > 26   | 188             | 52.7%            | 55       | 64.7% | 133 | 48.9% | 0.011 |
| BUN-to-Scr ratio | 188 (12.2, 30.1) | 26.1 (17.6, 36.8) | 16.8 (11.1, 27.3) | < 0.001 |
| Index BUN-to-Scr > 20 | 170             | 47.6%            | 59       | 69.4% | 111 | 40.8% | < 0.001 |
| Albumin, g/dL | 2.50 (2.20, 2.90) | 2.35 (2.00, 2.80) | 2.60 (2.20, 3.00) | 0.003 |
| Albumin < 2.5 | 89              | 44.3%            | 33       | 56.9% | 56  | 39.2% | 0.022 |
| Albumin < 3 | 155             | 77.1%            | 50       | 86.2% | 105 | 73.4% | 0.051 |
| Serum glucose, mg/dL | 162 (129, 222) | 192 (151, 232) | 158 (127, 208) | 0.002 |
| First tertile: < 142 | 107             | 32.7%            | 13       | 16.9% | 94  | 37.6% | 0.001 |
| Second tertile: 142 to < 193 | 108 | 33.0% | 26 | 33.8% | 82 | 32.8% |
| Third tertile: ≥193 | 112             | 34.3%            | 38       | 49.4% | 74  | 29.6% |      |

Abbreviations: APACHE Acute Physiology and Chronic Health Evaluation, BUN blood urea nitrogen level, CDI *C. difficile* infections, CI confidence interval, eGFR estimated Glomerular filtration rate, HR hazard ratio, IQR interquartile range, SCr serum creatinine, WBC white blood cell count

*Continuous variables were presented as median and IQRs and analyzed using Wilcoxon rank-sum test, if not otherwise indicated. Categorical variables were presented as frequency and proportion (%) and analyzed using chi-square test, if not otherwise indicated. P-values that were < 0.05 are shown in bold.

Mean age and the proportion of inflammatory bowel disease were analyzed using two-sample t-test and Fisher’s exact test, respectively.

Diabetes mellitus was defined according to the patients’ ICD-9-CM diagnosis codes and the use of glucose-lowering agents. Renal disease, inflammatory bowel disease, and malignancy were defined using the ICD-9-CM diagnosis codes.

APACHE II score was only available for patients admitted to intensive care units (N = 211).

Use of anti-diarrhea medications or probiotics within 0 to 14 days of the index CDI.

Included 158 patients (39.4%) with positive toxin genes test and 59 patients (14.7%) with positive C. difficile toxin enzyme immunoassay test.

We obtained the maximum WBC, maximum index SCr, closest BUN, minimum albumin, and closest glucose values that were measured within −3 to +3 days of the index CDI.

For premorbid SCr, we obtained the minimum SCr that were measured within −30 to −4 days of the index CDI.

eGFR was estimated by CKD-EPI equation (Levey 2009).
albumin < 2.5 g/dL, BUN-to-SCr ratio > 20, and serum glucose in tertiles, where BUN-to-SCr ratio and glucose have not been indicated in prior studies. Our risk prediction model and risk prediction scoring system performed superior to current guidelines in predicting 30-day mortality and prolonged length of ICU stay following CDI.

Published guidelines in the US (SHEA-IDSA 2010 and 2018) [6, 7] and Europe (ESCMID 2014) [8] and recently developed severity indices, such as the Zar [26], Bauer [19], ATLAS [15], Velazquez-Gomez [14], or Gomez-Simmonds [27] scoring systems, have attempted to establish valid criteria for predicting the severity of CDI. Nonetheless, guidelines are based on expert opinions or systematic reviews and the definitions of severe CDI and its treatment outcomes evaluated in other studies have varied. For example, Zar et al. assessed both cure rate and relapse [26]; Bauer et al. evaluated treatment failure and recurrence [19]; and ATLAS evaluated cure rate, and its findings were validated in another cohort for mortality and colectomy [15, 28].

Increased levels of WBC (≥ 15,000 or 30,000 cells/μL) and rise in SCr (1.5-fold high than the premorbid level or absolute value of 1.5 mg/dL), which indicate immune reaction and renal function, are the most common markers between the aforementioned severity criteria [6, 7, 15, 19].

Hypoalbuminemia (< 2.5 or < 3 mg/dL), a malnutrition albumin < 2.5 g/dL, BUN-to-SCr ratio > 20, and serum glucose in tertiles, where BUN-to-SCr ratio and glucose have not been indicated in prior studies. Our risk prediction model and risk prediction scoring system performed superior to current guidelines in predicting 30-day mortality and prolonged length of ICU stay following CDI.

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Hypoalbuminemia (< 2.5 or < 3 mg/dL), a malnutrition

### Table 2

| Variables | SHEA-IDSA (2010) | SHEA-IDSA (2018) | ESCMID (2014) |
|-----------|------------------|------------------|---------------|
|           | aHR (95% CI)     | p-value          | aHR (95% CI)  | p-value          | aHR (95% CI)  | p-value          |
| Age > 65 years old | 1.44 (0.84, 2.47) | 0.185            | 1.41 (0.91, 2.17) | 0.124 |
| WBC > 15,000 cells/mm³ | 1.43 (0.92, 2.24) | 0.113            | 1.69 (1.11, 2.56) | 0.013 |
| Rise in SCr ≥ 1.5-fold | 2.55 (1.64, 3.98) | < 0.0001         | 1.72 (1.13, 2.61) | 0.012 |
| SCr ≥ 1.5045 mg/dL | 1.27 (0.84, 1.93) | 0.265            | 1.35 (0.89, 2.04) | 0.157 |
| Rise in SCr ≥ 1.5-fold or ≥ 1.5045 mg/dL | 1.40 (0.77, 2.54) | 0.028            | 2.23 (1.37, 3.61) | 0.001 |
| Albumin < 3 g/dL | 1.60 (0.83, 3.10) | 0.053            | 1.91 (1.12, 3.27) | 0.018 |

### Table 3

| Variables | Regression coefficients (βs) | Risk point |
|-----------|------------------------------|------------|
| Age > 65 years old | 0.4179 | 4 |
| Malignancy | 0.6656 | 7 |
| WBC in tertiles, cells/mm³ | 0 | |
| First tertile: < 9440 | Reference | 0 |
| Second tertile: 9440 to < 14,600 | −0.2299 | −2 |
| Third tertile: ≥ 14,600 | 0.0930 | 1 |
| Rise in SCr ≥ 1.5-fold | 0.8212 | 9 |
| Albumin < 2.5 g/dL | 0.4226 | 5 |
| Glucose in tertiles, mg/dL | 0 | |
| First tertile: < 142 | Reference | 0 |
| Second tertile: 142 to < 193 | 0.4993 | 5 |
| Third tertile: ≥ 193 | 0.7784 | 8 |
| BUN-to-SCr ratio > 20 | 0.7119 | 8 |

Abbreviations: aHR adjusted hazard ratio, CDI C. difficile infections, CI confidence interval, SCr serum creatinine, WBC white blood cell count

*a* We included the variables in separate Cox proportional hazard models and evaluated the discrimination performance of these models using Harrell’s c statistic.

*b* The Society of Hospital Epidemiology of America (SHEA) and the Infectious Disease Society of America (IDSA) jointly published the clinical practice guidelines for CDI in 2010 and updated in 2018 (Cohen 2010; McDonald 2018).

*c* The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) published the treatment guideline for CDI in 2014 (Debast 2014).

*d* The discrimination performance of these models was significantly lower than that of our prediction model (Harrell’s c statistic = 0.727; 95% CI = 0.672, 0.782).

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| Albumin < 2.5 g/dL | 0.4226 | 5 |
| Glucose in tertiles, mg/dL | 0 | |
| First tertile: < 142 | Reference | 0 |
| Second tertile: 142 to < 193 | 0.4993 | 5 |
| Third tertile: ≥ 193 | 0.7784 | 8 |
| BUN-to-SCr ratio > 20 | 0.7119 | 8 |

Abbreviations: BUN blood urea nitrogen, SCr serum creatinine, WBC white blood cell count

*a* We assigned each variable a risk point by dividing the corresponding regression coefficient by the absolute smallest coefficient (i.e., 0.0930) and rounding it to the nearest integer.
marker, is another commonly marker for severe CDI [8, 14, 26, 27].

Other predictors of poor CDI outcomes that have been reported included: older age [26], systemic antibiotic use, underlying illnesses, altered mental status [14], physical findings (e.g., fever, hypotension [14], tachycardia [14], abdominal pain or distention, and septic shock [27]), pseudomembranous colitis [14, 26, 27], ICU admission [14, 26], toxic megacolon, and colectomy [27]. However, ICU admission and CDI-related complications should not be used as prognostic predictors because these events are outcomes of severe CDI.

Our severity predictive model had significantly higher discrimination power than did the existing guidelines in Table 4

| Variables | Crude OR (95% CI) | P-value | Logistic regression model - Original (N = 99) Adjusted OR (95% CI) | P-value | Logistic regression model - Imputed (N = 307) Adjusted OR (95% CI) | P-value |
|-----------|------------------|---------|-------------------------------------------------|---------|-----------------------------------------------------------------|---------|
| Age > 65 years old | 1.51 (0.88, 2.57) | 0.133 | 1.37 (0.56, 3.36) | 0.492 | 1.28 (0.72, 2.30) | 0.400 |
| Malignancy | 0.57 (0.32, 1.03) | 0.061 | 0.60 (0.23, 1.60) | 0.310 | 0.54 (0.29, 1.03) | 0.061 |
| WBC in tertiles, cells/mm³ | | | | | | |
| 1st tertile: < 9440 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | | | |
| 2nd tertile: 9440 to < 14,600 | 1.33 (0.68, 2.61) | 0.412 | 1.17 (0.37, 3.74) | 0.786 | 1.19 (0.57, 2.52) | 0.640 |
| 3rd tertile: ≥ 14,600 | 2.33 (1.21, 4.50) | 0.012 | 1.21 (0.36, 4.01) | 0.756 | 1.76 (0.84, 3.69) | 0.132 |
| Rise in SCr ≥ 1.5-fold | 1.48 (0.79, 2.76) | 0.217 | 2.40 (0.92, 6.26) | 0.073 | 1.34 (0.69, 2.59) | 0.393 |
| Albumin < 2.5 g/dL | 2.22 (1.08, 4.54) | 0.030 | 1.89 (0.72, 4.95) | 0.195 | 1.36 (0.66, 2.82) | 0.400 |
| BUN-to-SCr ratio > 20 | 4.74 (2.66, 8.46) | < 0.001 | 3.81 (1.51, 9.58) | 0.005 | 4.01 (2.19, 7.33) | < 0.001 |
| Glucose tertiles, mg/dL | | | | | | |
| 1st tertile: < 142 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | | | |
| 2nd tertile: 142 to < 193 | 1.61 (0.83, 3.12) | 0.161 | 1.41 (0.46, 4.33) | 0.545 | 1.28 (0.46, 3.93) | 0.480 |
| 3rd tertile: ≥ 193 | 1.57 (0.79, 3.11) | 0.194 | 0.87 (0.28, 2.72) | 0.812 | 0.54 (0.29, 1.03) | 0.618 |
| C statistic (95% CI) | 0.741 (0.639, 0.844) | | 0.737 (0.671, 0.804) | | | |

Abbreviations: BUN blood urea nitrogen, CI confidence interval, OR odds ratio, Ref reference, SCr serum creatinine, WBC white blood cell count

Table 5 Discrimination performance of published guidelines for prolonged (> 9 days) length of ICU stay following C. difficile infections (CDI) among adult inpatients with CDI who survived the first 30 days following CDI (N = 307)²

| Variables | SHEA-IDSA (2010)² | SHEA-IDSA (2018)² | ESCMID (2014)³ |
|-----------|------------------|------------------|----------------|
| Age > 65 years old | | | |
| WBC > 15,000 cells/mm³ | | | |
| Rise in SCr ≥ 1.5-fold | | | |
| SCr ≥ 1.5045 mg/dL | | | |
| Albumin < 3 g/dL | | | |
| C statistic (95% CI) | | | |

Abbreviations: aOR adjusted hazard ratio, CDI C. difficile infections, CI confidence interval, SCr serum creatinine, WBC white blood cell count

References:
1. The Society of Hospital Epidemiology of America (SHEA) and the Infectious Disease Society of America (IDSA) jointly published the clinical practice guidelines for CDI in 2010 and updated in 2018 (Cohen 2010; McDonald 2018).
2. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) published the treatment guideline for CDI in 2014 (Debast 2014).
3. The discrimination performance of these models was significantly lower than that of our prediction model (c statistic = 0.737; 95% CI = 0.671, 0.804).
predicting 30-day mortality. Our scoring system reclassified 21% (SHEA-IDSA 2010), 32% (SHEA-IDSA 2018), or 46% (ESCMID) of CDI patients into the correct risk category. Consistent with our findings, Stevens et al. showed that both the SHEA-IDSA 2010 and 2018 criteria had low discrimination power ($c = 0.582$ and 0.587) [9]. Further evaluation of these clinical guidelines in high-quality studies is required, which is also suggested by the latest SHEA-IDSA guidelines [7].

Other severity indices did not evaluate their performance in predicting prolonged length of ICU stay separately from other outcomes, but they used composite measure of mortality, ICU admission, or colectomy [18, 27, 29]. However, ICU admission may not be a reasonable outcome measure because many patients with CDI are already in the ICU at the time of CDI occurrence. In our study, we assessed the secondary outcome of prolonged length of ICU stay following CDI and used 9 days as the cut-off. The 9-day cut-off is the 75th quartile in the distribution in our study population and is also comparable to the length of ICU stay attributable to CDI reported in two prior studies [30, 31]. Zahar et al.’s assessed the morbidity and mortality attributable to ICU-acquired CDI and estimated that the increase in the ICU stay due to CDI was 8.0 ± 9.3 days, in comparison to the diarrheic population [30]. Dodek et al. also investigated the attributable ICU and hospital length of stay of ICU-acquired CDI and reported that median ICU days following CDI was 7 days (IQR, 3–14 days) [31]. Therefore, an ICU stay of more than 9 days is a clinically relevant outcome measure for patients with CDI. In addition, our risk prediction model can better identify patients at high risk of prolonged ICU stay following CDI than can the guidelines.

Notably, we identified BUN-to-SCr ratio and serum glucose as strong predictors of 30-day mortality. A BUN-to-SCr ratio of > 20 indicates dehydration and an early stage of kidney injury, which reasonably reflects the severity for CDI patients. In contrast, one previous study of 184 CDI patients did not find any association between a BUN-to-SCr ratio of ≥20 and severe outcomes (defined as any event of ICU admission, colectomy, or death within 30 days) [29]. Moreover, no prior study has found an association between increased baseline glucose level and increased mortality among CDI patients. Our study showed that diabetes at admission was not associated with 30-day mortality, but a serum glucose level of ≥193 mg/dL was (HR = 2.18; 95% CI = 1.17, 4.05). One study including 94 CDI patients identified that diabetes was associated with relapse of CDI (odds ratio [OR] = 2.7; 95% CI = 0.8–9.2) [32]. Another study including 247 CDI patients revealed that diabetes was an independent risk factor for recurrent CDI within 6 months (OR = 3.05; 95% CI = 1.84, 5.03) but that serum glucose level was not (median of 147 mg/dL for recurrent CDI and 146 mg/dL for nonrecurrent CDI) [33]. Blood glucose can influence the host immune-inflammatory response, such as macrophages, and affect the community structure of the gut microbiome, such as changing the ratio of nontoxicogenic to toxicogenic C. difficile [34]. Whether a hyperglycemic status in itself or through modification of a patient’s intestinal microbiome facilitates the growth of C. difficile warrants further investigation [34]. Both BUN-to-SCr ratio and serum glucose can be clinically modified and can serve as indicators to measure treatment optimization. Future research should clarify whether modifying these predictors can benefit patients with CDI.

Our study has several limitations. First, due to the retrospective design, the screening and diagnosis of CDI were not based on a standardized research protocol and certain variables of interest had missing values. However, we used extensive data—which were electronic medical records from the well-established CMUH–CRDR, expert adjudication of clinical presentation of CDI, and the National Cause of Death Dataset—, and multiple imputation method [21], to compensate for this limitation. Second, not all patients with CDI received molecular typing of C. difficile, which prevented us from differentiating toxicogenic versus nontoxicogenic strains for all CDI and evaluating the prognostic value of strain virulence. Nonetheless, our proposed risk model provides simple and readily available laboratory markers to triage patients with CDI and lower the action threshold to initiate optimization of fluid status and empirical antibiotic therapy.

Conclusions
Our proposed risk prediction model and scoring system performs more accurately in identifying potentially severe CDI than do existing guidelines. The newly identified clinical markers, namely BUN-to-SCr ratio and glucose, are readily available and also increase awareness of clinicians to optimize supportive care in patients with CDI. Future research should replicate our study in other populations. The infectious disease community should work toward consensus regarding the definition of severity and treatment response of CDI to support comparability of information and evidence-driven decision making for optimal CDI care.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s13756-019-0642-z.

Additional file 1. Supplementary method: Clostridium difficile testing; Figure S1. Time frames for the definition of covariates; Table S1. Net reclassification of risk prediction score and the published guidelines.

Abbreviations
APACHE: Acute Physiology and Chronic Health Evaluation; BUN: Blood urea nitrogen; CDI: Clostridium difficile infection; CI: Confidence interval; CMUH: China
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Medical University Hospital; CRDR: Clinical Research Data Repository; eGFR estimated Glomerular filtration rate; ESICMID: The European Society of Clinical Microbiology and Infectious Diseases; HR: Hazard ratio; ICU: Intensive care unit; IQR: Interquartile range; NRI: Net reclassification index; SCr: Serum creatinine; SHEA-IDSA: The Society for Healthcare Epidemiology of America and The Infectious Diseases Society of America; WBC: White blood cell

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Authors’ contributions
HYC designed the study, coordinated the data preparation, supervised the data analysis, and wrote a major part of this manuscript; HCH and CWC contributed to the data preparation and the data analysis; YCY contributed to the quality check of the database; YCC reviewed the electronic medical records to abstract the data of diarrhea, ICU status, and APACHE II score; NT and HSL provided the data of C. difficile culture and toxin tests and the clinical microbiology information; MWH contributed to the study design and critically edited the manuscript; CCK supervised the whole study and critically edited the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The minimal datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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The Institutional Review Board of CMUH approved this study (105-REC3-068 & 107-REC2-016) and the need for informed consents was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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