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Delirium and other clinical factors with *Clostridium difficile* infection that predict mortality in hospitalized patients

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Abstract

Background—*Clostridium difficile* infection (CDI) severity has increased, especially among hospitalized elderly. We evaluated clinical factors to predict mortality following CDI.

Methods—We collected data from inpatients diagnosed with CDI at US academic medical center (HSR-IRB# 13630). We evaluated age, Charlson comorbidity index (CCI), admission from a long-term care facility (LTCF), intensive care unit (ICU) at time of diagnosis, white blood cell count (WBC), blood urea nitrogen (BUN), low body mass index (BMI), and delirium as possible predictors. A parsimonious predictive model was chosen using Akaike information criterion (AIC) and a best subsets model selection algorithm. Area under the ROC curve was used to assess the model's comparative; with AIC as selection criterion for all subsets to measure fit and control for over-fitting.

Results—From 362 subjects, the selected model included CCI, WBC, BUN, ICU, and delirium. The logistic regression coefficients were converted to a points scale and calibrated so that each unit on the CCI contributed 2 points, ICU contributed 5, unit of WBC (natural log scale) contributed 3, unit of BUN contributed 5, and delirium contributed 11.

Discussion—Our model shows substantial ability to predict short term mortality in patients hospitalized with CDI.

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Conclusion—Patients who were diagnosed in the ICU and developed delirium are at highest risk for dying within 30 days of CDI diagnosis.

Keywords

Clostridium difficile infection; predictive model; nosocomial infections; hospitalized patients; delirium

INTRODUCTION

Clostridium difficile (*C. difficile*) is an anaerobic bacterium that is one of the most common causes of antibiotic associated diarrhea and the main cause of healthcare onset infectious diarrhea (1–6). The incidence and severity of *C. difficile* infection (CDI) have increased dramatically in the past decade; with reported mortality rates over 15% in hospital epidemics (7–16). Elderly patients, especially those hospitalized with antibiotic exposure or in long-term care facilities (LTCF), have the greatest risk for infection and highest mortality rate (4–8;12–14;16).

C. difficile causes a toxin mediated intestinal inflammatory infection. The clinical manifestations of CDI can vary from asymptomatic carriage or mild self-resolving diarrhea to profuse diarrhea with pseudomembranous colitis, sepsis, and death. Current models to define severe CDI lack either sensitivity or specificity (17–19). There is no validated tool at CDI diagnosis to predict poor outcome (17;18). In this study, we evaluated clinical factors (demographics, co-morbidities, medications, laboratory values, and acute cognitive change) at CDI diagnosis. We present our findings to establish an evidence-based bedside tool that will allow clinicians to quickly identify hospitalized patients at highest risk of death following CDI.

METHODS

Hospitalized Cohort

IRB approval was obtained (HSR-IRB #13607). Sequential inpatients at our US academic hospital clinically diagnosed with CDI (May 2010–August 2011) were identified in the UVA Clinical Microbiology Laboratory once tested positive for via PCR for toxin B gene (BD GeneOhm™ Cdiff Assay, Becton, Dickinson and Company, Franklin Lakes, NJ or Xpert *C. difficile*, Cepheid, Sunnyvale, CA) based on manufactures instructions (20). Vital signs, laboratory values, and co-morbidities were obtained from the hospital electronic medical record. Most extreme value within 24 hours of CDI diagnosis was recorded. The Charlson comorbidity index was calculated for each subject from co-morbidities (21). Data was obtained by members of the research team and spot-checking and discrepancy resolution was done by the principle investigator. Delirium was identified retrospectively from medical record when acute cognitive change was cited by the clinical treatment team in medical record on the day of CDI diagnosis. Body-Mass index (BMI) used normative cut-offs for underweight (18.5 kg/m²) (22). Each subject was contacted via telephone for consent at 1month and, once consent was obtained, a semi-structured interview was

performed with subject, surrogate, or facility staff to record outcomes. The medical record and state death registry was also reviewed for 30 day mortality.

Statistical Analysis

Predictive model—All statistical analysis was done with R version 3.1.1 (23). We identified 9 clinically obtained potential predictors of interest (age, admission from a long-term care facility (LTCF), Charlson comorbidity index score, peripheral white blood cell count (WBC), low BMI ($< 18.5 \text{ kg/m}^2$), serum albumin, blood urea nitrogen (BUN), diagnosed in intensive care unit (ICU), antibiotic use at time of diagnosis, and delirium). BUN was selected to reflect the acute changes seen with dehydration instead of assessing for underlying chronic kidney disease, which is accounted for in the Charlson co-morbidity index. Wilcoxon rank sum test was used to determine significance. A parsimonious predictive model was chosen using an all subsets selection algorithm (24) with AIC (25) as the model selection criterion. The model was directly calculated from the retained variables. The area under the Receiver Operating Characteristic (ROC) curve (AUC) was used to assess the predictive ability of the model. We used bootstrap model validation to assess the optimism in the AUC (26).

Points Scale—The logistic regression coefficients were converted to a points scale calibrated by scaling the regression coefficients to make 1 point on the Charlson scale equivalent to 2 points and rounding the remaining coefficients to the nearest integer.

RESULTS

Enrolled hospitalized cohort

There were 1,022 patients screened from fecal samples that tested positive for *C. difficile* in the clinical microbiology laboratory. Of these, 591 were not inpatients, 29 had chronic diarrhea, and 40 were < 18 years old. We enrolled the 362 hospitalized adult subjects who did not have chronic diarrhea and followed them for 30 days after CDI diagnosis or until death. Subjects in our cohort had a median age of 63.5 years (interquartile range (IQR) 51.6, 72.9) and Charlson comorbidity score of 5 points (IQR 3, 7). In our cohort, 17% of subjects ($n=61$) died within 30 days of CDI diagnosis, see Table I.

In addition to the predictors considered above, we also considered serum albumin. Since this lab test was only performed for 87% of subject in our cohort, it was excluded from further consideration. Additionally, 100% of subject who died were on antibiotics at the time of CDI diagnosis, making it impossible to estimate an associated odds; it was therefore excluded from the model. Therefore, the predictive model was directly calculated from the 5 retained variables: Charlson score, ICU at diagnosis, WBC, BUN, and delirium (Table II).

The area under the ROC curve is 0.804 (Figure 1). The regression coefficients and their standard errors are shown in Table II. The bootstrap estimate of optimism was -0.034 ; suggesting that this model applied to a novel cohort is expected to have a AUC of 0.770.

Points Scale

The calibration of the regression coefficients into a points scale is shown in Table II. With this model, a 1 point corresponds to approximately an 11% increase in the odds of death within 30 days (Figure 1).

The points score is almost as effective in determining survival, as compared to the raw logistic regression model, as shown by the nearly identical ROC curves (Figure 2). In our 30 day predictive model, delirium was the factor most strongly predictive of death following CDI.

DISCUSSION

We propose a model of clinical factors that can predict 30 day mortality following CDI in hospitalized patients. With 5 simple, low or no cost clinical factors known at CDI diagnosis (WBC, BUN, Charlson score, location at diagnosis, and delirium), clinicians can use this tool to enhance the early recognition of high risk patients with CDI, implement a more intensive treatment regimen, and aid in the decision for earlier surgical consultation. Likewise, this model can provide an evidence-based, objective definition for severe CDI that could be used in future research studies or clinical guidelines to define severe CDI.

There have been multiple recent studies that have identified univariate risk factors associated with poor outcome following CDI (17–19). Zar, et al. published a scoring system to define severe CDI (≥ 2 points) and determined that patients with severe CDI had better outcomes on oral vancomycin, as compared to metronidazole, and has since served as the basis for treatment guidelines (5). Additionally, in 2011, Fujitani, et al. evaluated eight clinical scales, including the scoring system published by Zar, et al., to determine the predictive value of each. They found the Hines VA Index most predictive of severe CDI (κ -score, 0.69 [95% confidence interval, 0.59–0.83]) (17–19;27). This index utilized clinical factors (fever, abnormal radiology, blood pressure and peripheral white blood cell count) to correlate with higher disease severity. However, neither severity index provided evidence to support the weighting of each factor.

A unique variable identified as a highly significant predictive variable for 30-day mortality is delirium. Delirium is under-recognized, under-diagnosed, and under-reported in hospitalized patients (28–30). Although we did not perform systematic or objective assessments to verify all cases of delirium in this study, regression analysis estimated the highest point for this variable. This observation is clinically relevant because previous studies have shown that hospitalized patients with delirium have worse outcomes (28–30). However, the role of delirium in predicting severe outcomes from CDI has not been reported. Moreover, the causes of delirium are multi-factorial and often reversible (28–30). Its detection early on may indicate the need to identify reversible etiologies, which when addressed promptly, may potentially improve outcome.

Another unique variable we evaluated was admission from LTCF. As we have previously published, residents from LTCF may be at increased risk for *C. difficile* acquisition, as well as specifically ribotype 027, due to physical frailty, increased healthcare exposure, and live

in closer contact as compared to patients in the community (31). Additionally, LTCF residents may have worse CDI due to less diversity and therefore, decreased effectiveness of their microbiome due to a narrower diet and higher rates of antibiotic use (32).

Our study has several limitations. First, we excluded the use of antibiotics for this model since all of the patients who died were on antibiotics, antibiotics are strongly associated with death, but we are statistically unable to quantify the size of the effect. Additionally, a limitation of this study is the retrospective identification of subjects with delirium, based on notation in the medical record. In this study, we did not perform systematic or objective assessments to verify all cases of delirium. However, this study presents a novel association and hypothesis for further investigation. The use of delirium as a poor prognostic indicator needs to be evaluated in prospective studies with objective, validated assessments, such as the Confusion Assessment Method (33). Further investigation is needed to move beyond an association and begin to further understand the connection between inflammation and cognitive and functional decline (7;9;12;34;35). Indeed, we have previously shown that undetected intestinal inflammation is common among nursing home residents independent of diarrhea (36). Whether intestinal inflammation has a role in cognitive and functional decline during CDI is unknown. Further limitation of our proposed predictive models include it's being based on clinical factors; there may be additional benefit to include potential fecal biomarkers of bacterial characteristics or inflammatory response. Therefore, we are working to determine the predictive benefit of analyzing fecal biomarkers for mortality and relapse. Since this study did not have a control group of *C. difficile* negative subjects; we are unable to determine if our findings are specific to patients with CDI. Additionally, a potential limitation of the applicability of this model is the need for calculating the natural log for WBC and BUN in this model. However, this is can be overcome at the bedside using the scientific calculators included standard with most smartphones and handheld computing devices that might enable targeted attention to alterable risk factors.

Conclusion

In our cohort study of hospitalized patients with CDI, patients who were admitted from a long-term care facility, diagnosed in the intensive care unit, and developed delirium were at highest risk for dying within 30 days of CDI diagnosis.

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Highlights

- Goal: predict 30 day mortality for inpatients with *C. difficile* infection (CDI)
- Predictive factors: Charlson Co-morbidity Index (CCI), WBC, BUN, ICU, and delirium
- Weighted risk: delirium=11; ICU=5; unit of CCI=2, unit of WBC=3, unit of BUN= 5
- Delirium and ICU carry the highest risk mortality risk within 30 days of CDI

Figure 1.
Point scale and probability of death following hospitalization with CDI

Figure 2.
ROC Curves for Logistic Regression and Points Scale

Table I

Cohort Demographics

	Cohort	Alive (n=301)	Died (n=61)	P Value
Age in years (median, IQR)	63.5 (51.6, 72.9)	61.8 (50,72.5)	69.4 (60.9,75.4)	0.001
WBC	11 (6.8, 16.6)	10.2 (6.6,15.7)	13.3 (8.2, 21.3)	0.015
Charlson comorbidity score	5 (3, 7)	4 (3, 6)	7 (5, 9)	<.001
Serum albumin (n=164)	2.9 (2.5, 3.4)	3.0 (2.5, 3.5)	2.6 (2.2, 2.9)	<.001
BUN	21 (11, 35)	18 (10, 33)	31 (21, 53)	<.001
BMI	25.5 (22.3, 33)	25.9 (22.3, 33.1)	25.3 (22.2, 32.7)	0.545
Admitted from LTCF (%)	94 (26.0)	68 (22.6)	26 (42.6)	0.002

Table II**Predictive Model**

The mortality risk associated with each variable was calibrated from the regression coefficients into a points scale listed below

	Coefficients	Standard Error	z value	Pr(> z)	Points
Intercept [*]	-5.765	0.881	-6.545	5.94e-11	NA
Charlson score [*]	0.205	0.057	3.632	0.000	2
ln(WBC)	0.316	0.203	1.562	0.118	3
ln(BUN) [†]	0.490	0.232	2.109	0.035	5
Diagnosed in ICU	0.495	0.232	1.470	0.141	5
Delirium [*]	1.079	0.320	3.369	0.001	11

^{*} p<0.001;

[†] p<0.010