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Major article

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

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Background: *Clostridium difficile* infection (CDI) severity has increased, especially among hospitalized older adults. We evaluated clinical factors to predict mortality after CDI.

Methods: We collected data from inpatients diagnosed with CDI at a U.S. academic medical center (HSR-IRB#13630). We evaluated age, Charlson comorbidity index (CCI), whether patients were admitted from a long-term care facility, whether patients were in an intensive care unit (ICU) at the time of diagnosis, white blood cell count (WBC), blood urea nitrogen (BUN), low body mass index, and delirium as possible predictors. A parsimonious predictive model was chosen using the Akaike information criterion (AIC) and a best subsets model selection algorithm. The area under the receiver operating characteristic curve was used to assess the model's comparative, with the AIC as the selection criterion for all subsets to measure fit and control for overfitting.

Results: From the 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 admission contributed 5 points, each unit of WBC (natural log scale) contributed 3 points, each unit of BUN contributed 5 points, and delirium contributed 11 points.Our model shows substantial ability to predict short-term mortality in patients hospitalized with CDI.

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

Clostridium difficile is an anaerobic bacterium that is one of the most common causes of antibiotic-associated diarrhea and the main cause of health care–onset infectious diarrhea.[1-6] The incidence and severity of *C difficile* infection (CDI) have increased dramatically in the last decade, with reported mortality rates >15% in hospital epidemics.[7-16] Elderly patients, especially those hospitalized with antibiotic exposure or in long-term care facilities (LTCFs), have the greatest risk for infection and the 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, comorbidities, medications, laboratory values, and acute cognitive change) at CDI diagnosis. We present our findings to establish an

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evidence-based bedside tool that will allow clinicians to quickly identify hospitalized patients at the highest risk of death after CDI.

METHODS

Hospitalized cohort

Institutional review board approval was obtained (HSR-IRB #13607). Sequential inpatients at our U.S. academic hospital clinically diagnosed with CDI (May 2010-August 2011) were identified in the University of Virginia Clinical Microbiology Laboratory once they tested positive via polymerase chain reaction for toxin B gene (BD GeneOhm Cdiff Assay; BD Company, Franklin Lakes, NJ or Xpert C. difficile; Cepheid, Sunnyvale, CA), based on manufacturers' instructions.[20] Vital signs, laboratory values, and comorbidities were obtained from the hospital electronic medical record. The most extreme value within 24 hours of CDI diagnosis was recorded. The Charlson comorbidity index was calculated for each subject from comorbidities.[21] Data were obtained by members of the research team, and spot-checking and discrepancy resolution was done by the principal investigator. Delirium was identified retrospectively from medical records when acute cognitive change was cited by the clinical treatment team in medical records on the day of CDI diagnosis. Body mass index used normative cutoffs for underweight participants (18.5 kg/m^2).[22] Each subject was contacted via telephone for consent at 1 month, and once consent was obtained, a semistructured interview was performed with the subject, surrogate, or facility staff to record outcomes. The medical record and state death registry were also reviewed for 30-day mortality.

Statistical analysis

Predictive model

All statistical analysis was done with R version 3.1.1 (R Foundation for Statistical Computing; Vienna, Austria). We identified 9 clinically obtained potential predictors of interest (age, admission from an LTCF, Charlson comorbidity index score, peripheral white blood cell count [WBC], low body mass index [$\leq$18.5 kg/m^2], 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 comorbidity index. The Wilcoxon rank-sum test was used to determine significance. A parsimonious predictive model was chosen using an all subsets selection algorithm,[23] with Akaike information criterion[24] 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.[25]

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, 51.6-72.9) and a Charlson comorbidity index score of 5 points (interquartile range, 3-7). In our cohort, 17% of subjects (n = 61) died within 30 days of CDI diagnosis (Table 1).

Predictive model

In addition to the previously mentioned predictors, we also considered serum albumin. Because this laboratory test was only performed for 87% of subjects in our cohort, it was excluded from further consideration. Additionally, 100% of subjects 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 following 5 retained variables: Charlson score, ICU at diagnosis, WBC, BUN, and delirium (Table 2).

The AUC is 0.804 (Fig 1). The regression coefficients and their SEs are shown in Table 2. The bootstrap estimate of optimism was -0.034, suggesting that this model applied to a novel cohort is expected to have an AUC of 0.770.

Points scale

The calibration of the regression coefficients into a points scale is shown in Table 2. With this model, 1 point corresponds to an approximately 11% increase in the odds of death within 30 days (Fig 1).

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

DISCUSSION

We propose a model of clinical factors that can predict 30-day mortality after 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 after CDI.[17-19] Zar et al[17] published a scoring system to define severe CDI ($\geq$2 points) and determined that patients with severe CDI have better outcomes on oral vancomycin than metronidazole, and the system has since served as the basis for treatment guidelines.[5] Additionally, in 2011, Fujitani et al[18] evaluated 8 clinical scales, including the scoring system published by Zar et al, to determine the predictive value of each scale. They found the Hines VA Index most predictive of severe CDI (κ score, 0.69; 95% confidence interval, 0.59-0.83).[17-19,26] This index used clinical factors (fever, abnormal radiology, blood pressure, and peripheral WBC) 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 underrecognized, underdiagnosed, and underreported in hospitalized patients.[27-29] Although we did not perform systematic or objective