Predictors of severe outcomes associated with *Clostridium difficile* infection in patients with inflammatory bowel disease

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SUMMARY

Background
The increasing incidence of *Clostridium difficile* (C. difficile) infection (CDI) among patients with inflammatory bowel disease is well recognised. However, most studies have focused on demonstrating that CDI is associated with adverse outcomes in IBD patients. Few have attempted to identify predictors of severe outcomes associated with CDI among IBD patients.

Aim
To identify clinical and laboratory factors that predict severe outcomes associated with CDI in IBD patients.

Methods
From a multi-institution EMR database, we identified all hospitalised patients with at least one diagnosis code for *C. difficile* from among those with a diagnosis of Crohn’s disease or ulcerative colitis. Our primary outcome was time to total colectomy or death with follow-up censored at 180 days after CDI. Cox proportional hazards models were used to identify predictors of the primary outcome from among demographic, disease-related, laboratory and medication variables.

Results
A total of 294 patients with CDI-IBD were included in our study. Of these, 58 patients (20%) met our primary outcome (45 deaths, 13 colectomy) at a median of 31 days. On multivariate analysis, serum albumin <3 g/dL (HR 5.75, 95% CI 1.34–24.56), haemoglobin below 9 g/dL (HR 5.29, 95% CI 1.58–17.69) and creatinine above 1.5 mg/dL (HR 1.98, 95% CI 1.04–3.79) were independent predictors of our primary outcome. Examining laboratory parameters as continuous variables or shortening our primary outcome to include events within 90 days yielded similar results.

Conclusion
Serum albumin below 3 g/dL, haemoglobin below 9 g/dL and serum creatinine above 1.5 mg/dL were independent predictors of severe outcomes in hospitalised IBD patients with *Clostridium difficile* infection.

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INTRODUCTION
There has been a recent increase in the incidence and severity of *Clostridium difficile* infection (CDI).\(^1\)\(^-\)\(^4\) Such infections account for an estimated $750 million–$3.2 billion in healthcare costs.\(^5\) While CDI was traditionally linked to antibiotic use or healthcare contact, recent research has identified several new at-risk groups.\(^6\) One such group includes patients with underlying inflammatory bowel disease (IBD).\(^7\)\(^-\)\(^12\) The incidence of CDI among hospitalised IBD patients increased from 1% in 1998 to 3% in 2007 with an increase in disease severity.\(^13\) CDI in IBD patients has also been associated with a significant increase in need for colectomy and even mortality with an effect that can persist up to 1 year after the primary infection.\(^14\)\(^-\)\(^16\) However, while a wealth of literature supports this adverse impact of CDI on IBD patients, few have attempted to identify prognostic factors that determine prognostic factors determining severe outcomes associated with CDI in the IBD cohort.

Indeed, there is an important need for such stratification by severity as existing treatment options vary in their comparative effectiveness in mild and severe disease. Metronidazole and vancomycin have traditionally been the agents of choice for treatment of CDI.\(^1\)\(^-\)\(^17\)\(^-\)\(^19\) Early guidelines suggested that most primary infections should be treated with metronidazole with vancomycin reserved for recurrent disease or those unable to tolerate metronidazole, in part due to the cost of vancomycin and concern for spread of vancomycin-resistant bacteria.\(^17\)\(^,\)\(^18\)\(^,\)\(^20\)\(^-\)\(^23\)

However, previous studies have demonstrated that while the two agents have comparable efficacy in mild disease, metronidazole is associated with a much greater treatment failure rate in those with severe CDI.\(^24\) Such comparative effectiveness studies in IBD patients are lacking. Retrospective series have reported their experience with both therapies.\(^25\) However, the absence of measures to objectively stratify severity of CDI in IBD patients influences interpretation and generalisability of such results.

We performed this study with the aim of identifying clinical and laboratory factors that predict severe outcomes associated with CDI in IBD patients. Identification of such factors would allow for the development of a quantitative severity score that can be used to inform comparative effectiveness studies and prospective trials of CDI therapy in IBD patients.

METHODS

Data source and study population
Our study included all eligible patients from a multi-institutional electronic medical record (EMR) database during the period January 1998–June 2010. The two primary hospitals included within our cohort are both large (over 750 beds each) referral hospitals, using a common, shared institutional EMR. Eligible subjects included all adult patients with an International Classification of Diseases, 9th Edition, clinical modification (ICD-9-CM) diagnosis code for *C. difficile* infection (ICD-9-CM 008.45) with a concomitant diagnosis code for Crohn’s disease (ICD-9-CM 555.x) or ulcerative colitis (UC) (ICD-9-CM 556.x). As patients who require hospitalisation associated with their CDI are at the highest risk for an adverse outcome, we restricted our analysis to such patients with an in-patient diagnosis code of CDI. We required that the first date with a diagnosis code for Crohn’s disease or UC precede the first date associated with diagnosis of CDI. Patients with a diagnosis date of CDI prior to their first recorded date of IBD were excluded. In addition, patients who had undergone a total or partial colectomy prior to the diagnosis of CDI or had a diagnosis of colon cancer were excluded. The primary outcome for our study was time to total colectomy (ICD-9-CM 45.8) within 180 days of first diagnosis of CDI. Also included as our primary outcome was time to death. All analysis was censored at 180 days after CDI diagnosis. Patients who did not accrue the composite primary outcome were censored at 180 days.

Variables
Demographic variables included age, race and gender. Co-morbidity was adjusted for using the Elixhauser index, a validated and widely used measure of general co-morbidity in hospitalised patients.\(^26\) Type of IBD was determined by the presence of diagnosis codes for Crohn’s disease or UC. We examined the occurrence of an IBD hospitalisation prior to CDI by the presence of one or more in-patient codes for Crohn’s disease or UC prior to the index date of CDI. Medication use was ascertained as the presence of codes for steroids, 5-aminosalicylates (5-ASA), immunomodulators (azathioprine, mercaptopurine, methotrexate), or biological anti-TNF agents (infliximab, adalimumab) within 30 days after or at any time prior to the diagnosis of CDI. In a sensitivity analysis, we restricted medication use to the occurrence of medication codes within 30 days prior to diagnosis of CDI. We included six specific laboratory parameters – albumin, haemoglobin, creatinine, white blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). For albumin and haemoglobin, we included the lowest value within 60 days prior to the date of diagnosis of CDI. For the other four laboratory...
parameters, we included the highest value within the same time period as above. Dichotomous cut-offs for the laboratory values were selected based on prior literature supporting the clinical relevance of those thresholds in severe IBD colitis or CDI. 27, 28

Statistical analysis
All analyses were carried out using STATA 11.1 (StataCorp, College Station, TX, USA). Continuous variables were summarised using means and standard deviation, with use of medians and inter-quartile ranges when there was significant skew in distribution. Dichotomous variables were summarised using proportions and compared using the chi-squared tests. Our primary outcome was time to colectomy or death. Cox proportion hazards models were constructed for each of the variables included to examine their association with the primary outcome by estimating hazard ratios (HR) and 95% confidence intervals (95% CI). Multivariate Cox models adjusting for potential confounders were used to identify the independent predictors. All P-values <0.05 were considered statistically significant. The Institutional Review Board of Brigham and Women’s Hospital and Partners Healthcare System approved this study.

RESULTS
A total of 294 patients met the criteria for inclusion in our study. The median age was 58 years (mean 57 years) (Table 1). Of these patients, 205 had a diagnosis code for UC (70%) while the remaining had Crohn’s disease. Just over half the population had a prior in-patient hospitalisation code for Crohn’s disease or UC (n = 166; 57%). A total of 102 patients had codes for 5-ASA drugs (35%), while 68 had immunomodulators (23%) and 25 had been exposed to anti-TNF therapy (9%). Half the patients had used steroids (n = 153; 52%).

The median lowest haemoglobin proximate to the C. difficile diagnosis was 8.4 g/dL. Similarly, the median lowest albumin was 2.4 g/dL, while the highest creatinine and WBC count were 1.3 mg/dL and 16.2 cells/mm³ respectively. Only 117 patients had a recent C-reactive protein measured with a median of 43.4 mg/L, while the median ESR among 203 patients was 58 mm/h. A total of 58 patients (13 colectomy, 45 deaths) met our primary outcome of colectomy or death within 180 days (20%) at a median of 33 days after admission or C. difficile diagnosis.

Table 2 presents the results of the univariate analysis of predictors of colectomy or death. Age >65 years was associated with a two-fold increase in risk of death (HR 2.14, 95% CI 1.02–4.49) compared with age <50 years. Elixhauser co-morbidity score of 3 and higher was not associated with increased likelihood of our primary outcome (HR 1.35, 95% CI 0.35–5.19). A diagnosis of UC (HR 1.59, 95% CI 0.86–2.95) and prior hospitalisation (HR 1.29, 95% CI 0.76–2.19) were not associated with higher risk of colectomy or death. Among the laboratory parameters, albumin, haemoglobin and creatinine were all associated with our primary outcome. Compared with patients with albumin >3.0 g/dL, those with a lower albumin were more likely to meet our primary outcome (HR 9.63, 95% CI 2.35–39.51) (Figure 1a). Similarly, haemoglobin below 9 g/dL (HR 8.26, 95% CI 2.58–26.47) (Figure 1b) and creatinine above 1.5 mg/dL (HR 2.36, 95% CI 1.38–4.06) (Figure 1c) were also associated with our primary outcome. Elevated WBC count, platelet count, or markers of inflammation (ESR, CRP) were not associated with death or requiring colectomy. On multivariate analysis, adjusting for age, co-morbidity, IBD type and medications, three laboratory parameters met statistical significance and remained independent predictors of colectomy or death. They were serum albumin <3 g/dL (HR 5.75, 95% CI 1.34–24.56), haemoglobin below 9 g/dL (HR 5.29, 95% CI 1.58–17.69) and creatinine above 1.5 mg/dL (HR 1.98, 95% CI 1.04–3.79).

We also performed various sensitivity analyses. Modelling serum albumin as a continuous variable revealed a

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Age-group</td>
<td></td>
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<tr>
<td>19–50 years</td>
<td>78 (25.5)</td>
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<tr>
<td>50–65 years</td>
<td>79 (26.9)</td>
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<tr>
<td>66 years and older</td>
<td>137 (46.6)</td>
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<tr>
<td>Elixhauser co-morbidity</td>
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<tr>
<td>0–2</td>
<td>53 (18.0)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>241 (82.0)</td>
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<tr>
<td>IBD type</td>
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<tr>
<td>Ulcerative colitis</td>
<td>205 (69.7)</td>
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<tr>
<td>Crohn’s disease</td>
<td>89 (30.3)</td>
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<tr>
<td>Prior IBD-related hospitalisation</td>
<td>166 (56.5)</td>
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<tr>
<td>IBD-related medications</td>
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<tr>
<td>5-aminosalicylates</td>
<td>102 (34.7)</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>68 (23.1)</td>
</tr>
<tr>
<td>Biological anti-TNFs</td>
<td>25 (8.5)</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>153 (52.0)</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
</tr>
<tr>
<td>Albumin &lt;3 g/dL</td>
<td>190 (64.62)</td>
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<tr>
<td>Creatinine &gt;1.5 mg/dL</td>
<td>112 (38.1)</td>
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<tr>
<td>Haemoglobin &lt;9 g/dL</td>
<td>162 (55.1)</td>
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<tr>
<td>White blood cell count &gt;12 000/mm³</td>
<td>201 (68.4)</td>
</tr>
<tr>
<td>Platelet count &gt;450 000/mm³</td>
<td>137 (46.6)</td>
</tr>
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similar association between albumin and risk of colectomy or death. Each 1 g/dL increase in serum albumin was associated with a reduction in risk of colectomy or death by 60% (HR 0.41, 95% CI 0.28–0.60). The corresponding effect sizes for a 1 g/dL increase in haemoglobin and 1 mg/dL increase in serum creatinine were 0.60 (95% CI 0.47–0.76) and 1.08 (95% CI 1.02–1.14) respectively. Approximately 80% of our primary outcomes occurred within 90 days. Restricting our analysis to those who underwent colectomy or died within 90 days yielded similar results for serum albumin (HR 4.37, 95% CI 1.01–19.02), haemoglobin (HR 4.28, 95% CI 1.25–14.70) and creatinine (HR 2.61, 95% CI 1.25–5.45), while a diagnosis of UC showed a trend towards significance (HR 2.10, 95% CI 0.97–4.58). Examining only recent medication use (within 30 days of CDI diagnosis) yielded similar results in our univariate and multivariate models.
DISCUSSION

There has been increasing recognition of the incidence and adverse impact of *C. difficile* infection in patients with IBD. However, most previous studies have focused on demonstrating that CDI itself is associated with adverse outcomes in IBD patients. None has identified factors predicting severe outcomes associated with CDI within the cohort of IBD patients. In this study, using a multi-institutional EMR, we demonstrate that among IBD patients hospitalised with CDI, a serum albumin below 3 g/dL, haemoglobin below 9 g/dL and creatinine >1.5 g/dL were independent predictors of severe outcomes and may carry prognostic significance in such patients.

One of the earliest studies to attempt to stratify severity of CDI was the study by Zar et al. In their trial comparing oral vancomycin with metronidazole, patients were classified as having severe disease in the presence of leucocytosis, age >60 years, low albumin, fever, or need for ICU admission. However, no information was provided on how these parameters were chosen for defining severe disease and the relative independent importance of each of the predictors. Lungulescu et al. identified elevated WBC count, presence of underlying malignancy, low serum albumin and elevated creatinine as predictors of severe disease in those with CDI, whereas Gujja et al. identified elevated WBC count and elevated creatinine as predictors of severe disease. However, none of the above severity criteria included patients with IBD.

We also identified several supportive laboratory parameters that may indicate an increased risk of severe outcomes associated with CDI in IBD patients. These include low albumin, low haemoglobin and elevated creatinine all of which were independent predictor of severe outcomes. These findings are consistent with the above studies examining predictors of severe CDI in the non-IBD population and extend the findings to an IBD cohort. In addition, our results are also consistent with previous studies that have demonstrated a prognostic value to both haemoglobin and serum albumin in determining outcomes of acute severe colitis. In a previous study aimed at defining a disease-specific severity score in UC, we identified that malnutrition and anaemia were strong predictors of requiring colectomy among hospitalised patients.

One key reason driving the need for stratifying severity of CDI in various cohorts is the variation in the efficacy of existing treatments for CDI based on disease severity. While vancomycin and, more recently, fidaxomycin, are the only drugs approved by the Food and Drug Administration (FDA) for the treatment of CDI, the costs associated with such therapies ($300–600 for one course of oral vancomycin) make metronidazole ($20) a more attractive option. However, the efficacy of metronidazole in comparison with vancomycin depends on the severity of the episode of CDI. A study by Zar et al. examined the comparative effectiveness of these two agents, stratifying by disease severity. In patients with mild disease, both metronidazole and vancomycin had similar efficacy (90% vs. 98%, *P* = 0.36). However, in patients classified as having severe disease, vancomycin had significantly superior efficacy in achieving disease cure (97% vs. 76%, *P* = 0.02). There have been no randomised controlled trials specifically comparing these two agents in IBD patients. Indeed, most studies of treatment efficacy in IBD have been retrospective with nonrandom allocation of treatments, often guided by severity of disease, and thus susceptible to bias stemming from confounding by indication. In a study examining recurrence of CDI, published only in abstract form so far, hospitalised IBD patients who received combined treatment with oral vancomycin and intravenous metronidazole had lower rates of disease recurrence than those who were treated with oral vancomycin alone, but no information was provided on the primary treatment efficacy with either regimen. A second treatment study examining the role of combined antibiotic-immunomodulator therapy found that the combination therapy was associated with higher likelihood of meeting the primary adverse outcome than use of antibiotics alone. In our present study, we did not find any association between immunosuppressive medication or steroid use and risk of colectomy or death at 180 days suggesting a need for further ongoing studies examining the role of such combined therapy in IBD patients.

There are several implications to our findings. Our demonstration of adverse prognostic impact of low serum albumin on CDI-associated outcomes in IBD patients supports that IBD patients who require hospitalisation for CDI and have such a risk factor or are malnourished be considered as having severe disease, and appropriately triaged to more aggressive upfront therapy with oral vancomycin (or potentially fidaxomicin) either alone or in combination with metronidazole. Supporting this practice is the superior efficacy of vancomycin in severe disease. While there has not been a head-to-head comparison of fidaxomicin with metronidazole, trials among patients with moderate-to-severe CDI have demonstrated comparable efficacy of fidaxomicin vs. oral...
vancomycin.35 Ambulatory patients, particularly those with no other adverse factors (such as older age, low albumin, anaemia, or elevated creatinine), may be appropriate for metronidazole as the initial therapy with treatment escalation in the setting of nonresponse. The appropriate handling of concomitant immunosuppressive therapy cannot be inferred from our analysis and merits further examination; however, we did not identify their use to be predictive of need for colectomy or death.

There are a few limitations to our study. First, we relied on use of administrative codes to define our eligible population. However, previous studies have demonstrated good accuracy with the use of ICD-9-CM codes to define CDI.36 In particular, as our codes were associated with in-patient stay, the accuracy of such codes is likely to be greater. Second, treatment allocation was nonrandom. As such, we could not examine the comparative effectiveness of vancomycin and metronidazole in treating patients with CDI. Third, as diagnosis codes in our database are not marked by primary or secondary positions, we could not differentiate CDI as the primary reason for hospitalisation from CDI acquired while in the hospital for an unrelated reason. We adjusted for comorbidity using the Elixhauser index to minimise the potential bias introduced through non-CDI co-morbidity. However, we acknowledge the possibility that prognostic factors in patients with quiescent IBD who contract CDI during an unrelated hospitalisation may differ from those with active disease who are hospitalised primarily for CDI. Further multi-centre studies with adequate numbers to separate out these two subgroups may be warranted. Fourth, we did not examine the effect of recurrent CDI in determining treatment outcomes. Nevertheless, we do not anticipate that the markers of severe disease would differ between primary and recurrent infections. Finally, both the major hospitals included under our multi-institutional EMR are major referral hospitals, although both have well established primary care practices. Thus, it is possible that our cohort may skew towards more severe disease. However, this would have enriched the frequency of occurrence of our primary outcomes, allowing for inclusion of more variables in our multivariate models.

Our study has several strengths. To our knowledge, it is one of the first studies examining the factors predicting severity of CDI among patients with IBD. The use of a multi-institutional cohort and availability of both laboratory and medication information confer greater strength to our findings than previous studies of CDI in IBD, which have been unable to adjust for those factors.

In conclusion, we demonstrate that low serum albumin is an independent predictor of severe outcomes associated with CDI in hospitalised IBD patients, while other demographic and laboratory parameters such as age and low haemoglobin may have prognostic significance, but were not independent predictors of colectomy or death. IBD patients who have these risk factors may require more aggressive upfront therapy directed against CDI, while ambulatory CDI-IBD patients with no adverse prognostic factors may be tried on an initial course of metronidazole therapy. There is an urgent need for prospective comparative effectiveness studies in IBD patients with stratification by disease severity.

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