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Differentiating *C. difficile* Colitis from *C. difficile* Colonization in Ulcerative Colitis – A role for Procalcitonin?

Andrew R. Reinink[*], **Julajak Limsrivilai**[§], **Bethany Reutemann**[⌘], **Tristan Feierabend**[⌘], **Emily Briggs**[§], **Krishna Rao**[‡], and **Peter D.R. Higgins**[§]

[*]Minneapolis Veterans Affairs Medical Center and University of Minnesota

[‡]Division of Infectious Disease, Department of Internal Medicine, University of Michigan & Veterans Affairs Ann Arbor Healthcare System

[§]Division of Gastroenterology, Department of Internal Medicine, University of Michigan

[⌘]Internal Medicine Residency Program, Department of Internal Medicine, University of Michigan

Abstract

Background/Aims—*Clostridium difficile* infection (CDI) frequently complicates ulcerative colitis (UC) and can mimic disease flare. Differentiating UC flare from CDI remains a clinical challenge, particularly due to *C. difficile* colonization. Procalcitonin (PCT) is a serum biomarker for bacterial infections. We hypothesized that PCT would differentiate acute CDI from UC flare and *C. difficile* colonization.

Methods—A single-center prospective cohort study was conducted from 2013 to 2016. All UC patients with a stool sample for *C. difficile* testing were eligible. 117 patients were enrolled, while 20 were excluded. Chart review was performed.

Results—Among 27 patients with CDI, median PCT was 60.7 (range 26–560.6) pg/ml, while among 90 patients without CDI, median PCT was 56.7 (25.1–2252) pg/ml ($P=0.9$). Fourteen patients with CDI responded completely to *C. difficile* treatment (CDI-R), while eight patients did not and were diagnosed with UC flare (CDI-NR). For CDI-R median PCT was 104.5 (26.3–560.6), compared to 40.3 (26.0–116.3) for CDI-NR ($P=0.036$).

Conclusions—In UC patients presenting with diarrhea, serum PCT was not significantly higher in UC patients with positive *C. difficile* testing. However, procalcitonin was significantly elevated in CDI-R vs. CDI-NR, suggesting that procalcitonin may have utility in making this discrimination.

Corresponding Author Contact Information: Andrew R. Reinink, Minneapolis Veterans Affairs Medical Center, Mail Stop 111D, 1 Veterans Drive, Minneapolis, MN 55417, United States of America, Phone: 612-467-4651, Fax: 612-725-2248, Andrew.Reinink@va.gov.

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Conception and design: PH, KR
Data acquisition: PH, JL, KR, AR, EB, BR, TF
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Keywords

Ulcerative Colitis; *Clostridium difficile*; Procalcitonin; Diagnosis

Introduction

C. difficile infection (CDI) is a toxin-mediated disease caused by a Gram-negative, spore-forming bacillus, and is responsible for more than 400,000 cases of infectious colitis in the US each year[1]. CDI frequently complicates the course of Ulcerative Colitis (UC)[2]. Clinical diagnosis of CDI in the setting of UC is difficult, however, as its symptoms can easily be confused with an acute flare of UC[2]. In addition, the recent adoption of PCR-based *C. difficile* assays has increased test sensitivity at the cost of detecting a significant number of colonized cases, where *C. difficile* is merely a bystander to active UC[3,4]. Thus, there is an urgent need for better tools to differentiate CDI and UC flare, particularly in the case of a positive *C. difficile* PCR. We hypothesized that procalcitonin (PCT)—a serum biomarker that for other infections has demonstrated sensitivity and specificity for bacterial infection[5]—would be elevated in acute CDI, but not in a UC flare or *C. difficile* colonization, enabling more rapid and accurate treatment decisions.

In patients with diarrhea and recent antibiotic exposure, and without other intestinal pathologies, the clinical dilemma while awaiting a *C. difficile* test result is primarily whether one should empirically start antibiotics to cover CDI. In UC, however, there is an added layer of complexity. The symptoms of CDI largely overlap with those of an acute UC flare, for which the treatment of choice would be immunosuppression. Standard UC flare treatment would begin with corticosteroids, progressing to anti-TNF medications or calcineurin inhibitors in the right clinical setting[2]. Treatments that increase immunosuppression are relatively contraindicated in the setting of untreated CDI[6]. Waiting to start immunosuppression in a severe UC flare can increase the morbidity of the disease, and the time it can take to exclude CDI as a cause of intensifying symptoms may be an explanation for the worsened long-term outcomes in UC patients who experience CDI[7].

Furthermore, although the *C. difficile* PCR assay has excellent performance characteristics, the laboratory test alone cannot differentiate between infection and asymptomatic colonization[8]. This becomes even more problematic in UC, where a higher prevalence of colonization with *C. difficile* exists and the symptoms of UC flare and CDI have considerable overlap[9–11]. Therefore, a reliable surrogate marker for CDI has clear value in the UC population.

The aim of our trial was to study the role PCT may play as such a marker. We sought to compare the procalcitonin levels of UC patients with new-onset or worsening diarrhea, hypothesizing that PCT, but not traditional biomarkers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or white blood cell (WBC) count, would discriminate between *C. difficile* positive and negative groups. Furthermore, we hypothesized that among UC patients with a positive *C. difficile* assay, higher PCT levels would discriminate between those who would and would not improve with antibiotic treatment, implying that their presentation was caused by a UC flare with asymptomatic *C. difficile* colonization.

Methods

Sample testing and clinical epidemiology

The University of Michigan institutional review board approved this study. Our design was a single center, prospective cohort study. From July 2013 to August 2016, we obtained notifications from the University of Michigan clinical laboratory of any adult, inpatient or outpatient, with a previous diagnosis of UC (by International Classification of Diseases, Ninth Revision code) who submitted a stool sample for *C. difficile* testing. After manually verifying the UC diagnosis through chart review, we included all patients who had a serum sample suitable for PCT testing collected concurrently with stool samples. We excluded patients who were status-post a total colectomy or who were diagnosed with another infection, as this could also increase PCT and decrease the specificity of our analysis. Serum PCT measurement was performed with a polystyrene, antibody-coated, bead-based assay (R&D Systems, Inc., Minneapolis, MN) run on a Luminex® 200™ (Luminex Corporation, Austin, TX) dual laser detection system.

At the discretion of the treating medical team, *C. difficile* testing was performed on stools using the C. DIFF QUIK CHEK COMPLETE® test (Techlab, Inc., Blacksburg, VA) for *C. difficile* glutamate dehydrogenase (GDH) and toxins A or B by enzyme immunoassay (EIA). All samples discordant by EIA testing (GDH^{+}/$toxin^{-}$) were subjected to analysis for the *tcdB* gene by real-time PCR (BD GeneOhm™ Cdiff Assay; BD, Franklin Lakes, New Jersey).

The data warehouse query included the age of patient at testing, date of *C. difficile* sample, and date of serum sample, to which our study coordinator added the results of *C. difficile* and PCT testing. Our investigators (AR, JL, EB, BR, TF) then performed manual review in the university's electronic medical record systems to obtain information on sex, verification of UC diagnosis and phenotype, concomitant steroids, immunomodulators, anti-tumor necrosis factor agents, history of CDI, recent exposure to antibiotics, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell (WBC) count, admission hemoglobin, and minimum serum albumin. We followed the clinical course to see whether any non-CDI infections were diagnosed, and whether treatment for a UC flare was initiated.

Statistical analysis

After performing data cleaning and calculating descriptive statistics including measures of central tendency and spread, the data with symmetrical distributions were presented as mean and standard deviation (SD); the data with skewedness were presented as median, range, and interquartile range (IQR). Categorical data were presented as percentages. To compare between the CDI and no-CDI groups, unpaired t-tests were used for the symmetrically-distributed continuous data, and either log transformation followed by a t-test (if transformation restored a normal distribution) or Wilcoxon rank sum test was used for the data with asymmetrical distribution. The Chi-square test was used to compare the categorical data. A second, pre-planned analysis sub-classified the CDI-positive patients by whether they responded to anti- *C. difficile* antibiotics (CDI-R) vs. whether they did not respond

(CDI-NR). In all cases the non-responders were treated with initiation or intensification of immunosuppression, making their response to antibiotics a proxy for whether their symptoms were due to a 'true' CDI vs. a due to a UC flare with a 'false-positive' *C. difficile* assay. We then examined biomarker differences between the two groups. A two-sided *P* value of <0.05 was considered statistically significant for all analyses.

Logistic regression analysis was performed to find a combination of parameters that could differentiate between UC with CDI vs. UC without CDI, as well as between CDI-R vs. CDI-NR. The parameters with significant correlations with other parameters (Pearson correlation coefficient, $r \geq .5$) were identified by construction of a correlation matrix, and were selectively excluded from analyses. The predictive models including the non-correlated, significant parameters based on logistic regression results were built. The backward selection method was used to select predictors in the final multivariate model. The areas under the receiver operating characteristic (ROC) curve (AuROC) of each model were reported. Data analysis was performed with STATA 12 (Stata Corp, College Station, TX), R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., North Carolina, US).

Results

137 total patients were enrolled: 65 outpatients and 72 inpatients. Of the 20 excluded patients, 18 were diagnosed with infections other than CDI that hadn't been detected on initial enrollment, one had a different direct PCR test for *C. difficile* and was negative for GDH/toxin on our standard multistep testing protocol, and one was completely asymptomatic. Of the remaining 117 patients, 62 were outpatients and 55 were inpatients. In the 27 patients with CDI, 11 were inpatients. Descriptive characteristics of the study cohort stratified by CDI status, including age, sex, inpatient status, concomitant UC medications, prior CDI, and recent antibiotic use are presented in Table 1, and differed only in the likelihood of having had a prior CDI – 59% of those who were eventually diagnosed with CDI had a previous CDI, while only 14% of the *C. difficile* – negative group had a prior CDI (P<0.01).

Procalcitonin

Serum PCT was measured in all 117 patients. In the 27 patients with CDI, the median was 60.7 pg/ml (range 26.0–560.6, interquartile range [IQR] = 31.7–116.3). In the 90 patients without CDI, the median PCT was 56.7 pg/ml (25.1– 2252, IQR = 40.3–82.5). (Figure 1). The levels were not statistically different between the two groups (P=0.79). The area under the receiver operator characteristic curve (AUC) for this comparison was 0.51 (95% confidence interval [CI] 0.42–0.60).

Other inflammatory markers

We also looked at differences in CRP and serum WBC count between the groups with and without CDI. For CRP, the median was 0.9 mg/dl (0.05–15.4, IQR = 0.3–5.3) for the CDI group and 1.2 (0.1–22.6, IQR = 0.4–4.3) for the no-CDI group. The difference was not statistically significant (P=0.82). For maximum WBC count, the mean was 9490 ±3130 cells/μl for the CDI group and 9030 ±5510 cells/μl for the no-CDI group. The difference in mean WBC count of 460 cells/μl was not significant (95% CI −1211 to 2131, P=0.68).

Inflammatory markers and response to antibiotic treatment

While PCT did not discriminate between those with and without a positive stool test for *C. difficile*, it did differentiate those patients who would or would not respond to antibiotic therapy alone. Of the 27 patients with UC and a positive *C. difficile* assay, five were treated concurrently for a UC flare and CDI. The remaining 22 were started solely antibiotics to cover *C. difficile*—that is, the treating physicians' initial impressions were that the presentation of these patients was solely due to CDI. 19 of these patients were treated with standard-dose oral vancomycin, while three of them received metronidazole. Of these 22 patients, 14 responded (CDI-R) completely to treatment, and needed no changes in therapy for their UC, while eight did not respond (CDI-NR) to treatment, and were subsequently treated for a UC flare with symptom improvement. The median PCT for the CDI-R group was 105.3 (range 26.3–560.6, IQR = 32.4–190.5), while for the CDI-NR group it was 40.3 (range 26.0–116.3, IQR = 29.0–60.3), P=0.036 for the log-transformed PCT values. (Figure 1) The area under the receiver operator characteristic curve (AUC) for this comparison was 0.71 (95% CI 0.5–0.93). (Figure 2a) Neither initial antibiotic choice (vancomycin vs. metronidazole) nor mode of laboratory diagnosis (positive GDH and toxin EIA vs. positive GDH EIA, negative toxin EIA, positive toxin PCR) differentiated CDI-R from CDI-NR. (Chi-squared NS for both)

Multivariable Logistic Regression

For the distinction between the CDI and no-CDI groups, no covariates met our threshold to be included in a multivariate model. For the CDI-R vs. CDI-NR distinction, our model combined procalcitonin with WBC and HGB, obtaining an AUC of 0.86 (95% CI 0.7–1). (Figure 2b)

Discussion

Despite recent advances in laboratory diagnosis of *C. difficile*, differentiating CDI from a UC flare remains the rate-limiting step in the evaluation and treatment of patients with UC who present with diarrhea, abdominal pain, and other symptoms compatible with both conditions. In this setting, an inexpensive, rapid, point-of-care test that could serve as a surrogate marker would have clear value, aiding clinicians in rapid treatment decisions. Current widely-used surrogate markers, however, have performance characteristics that prevent them from being useful in this scenario. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly-used markers of systemic inflammation. These are both consistently elevated in infectious gastroenteritis, including CDI, as well as in systemic autoinflammatory conditions such as UC, and are unable to discriminate between the two conditions[12]. Markers of luminal intestinal inflammation likewise lack specificity. Fecal leukocytes and fecal occult blood can be found in both UC and CDI. Fecal lactoferrin and calprotectin are likewise nonspecific, with the added issues of higher cost and longer turnaround time than the *C. difficile* assay itself.

In other situations where quickly differentiating a bacterial infection from a similarly-presenting viral or noninfectious process is critical, PCT has shown usefulness, and is gaining wider acceptance. For example, in patients presenting to the emergency department with dyspnea, PCT has great value in discriminating bacterial pneumonia from congestive heart failure[13]. Similarly, in critical-care medicine, algorithms utilizing procalcitonin to differentiate infectious from noninfectious illnesses and to guide antibiotic therapy in sepsis have proven to improve treatment decisions and reduce antibiotic overuse[5]. Previous studies have found procalcitonin to maintain a high sensitivity for infectious complications despite the presence of concomitant autoimmune disease, though this has not been widely studied[14,15].

Our study set out to investigate whether PCT could differentiate an active *C. difficile* infection from a flare of Ulcerative Colitis. To fill this role, however, PCT would need to be reliably elevated in CDI, and not in UC. In our study, we only saw this difference when comparing CDI treatment responders to CDI treatment non-responders, rather than with all CDI+ to CDI− patients. This may reflect the diagnostic uncertainty inherent in *C. difficile* testing, where positive PCR tests cannot distinguish colonization from true infection, but response to CDI therapy acts as a reasonable surrogate marker for "true CDI." As expected, none of the traditional biomarkers of inflammation alone did any better at discriminating CDI from UC flares, as ESR, CRP, and WBC count were similarly elevated in both populations.

The other question of note is why PCT was elevated in so many of the UC patients who were negative for CDI. In early literature, PCT was reported to be elevated in self-limited colitis, but not in UC[16]. However, in a subsequent study assessing PCT as a potential disease activity marker in IBD, PCT was found to be both elevated and proportional to severity in both Crohn's and UC[17,18]. Most recently, a study showed that PCT levels in patients with severe UC were significantly higher than those in patients with mild or moderate UC, who themselves were indistinguishable by PCT from healthy controls[19].

Compared to other autoimmune disorders that have been shown to not elevate PCT, how is UC, particularly severe UC, different? We can only speculate, but a likely mechanism relates to the dysfunction of the colonic mucosal barrier in an ulcerated, inflamed colon. This barrier dysfunction exposes more bacterial antigens to the systemic circulation, which, while not an infection, could well trigger the inflammatory cascade of which procalcitonin is a byproduct.

In the mixed population described in this study, it does not appear that procalcitonin is suitable for our intended goal, discriminating an acute UC flare from all cases of CDI. It may, however, associate with CDI patients that ultimately respond to antimicrobials and, thus, have "true CDI" as opposed to colonization. Further study is warranted as to how PCT can best be incorporated into IBD treatment algorithms, and describing more fully the endoscopic and pathophysiologic correlates of elevated PCT levels.

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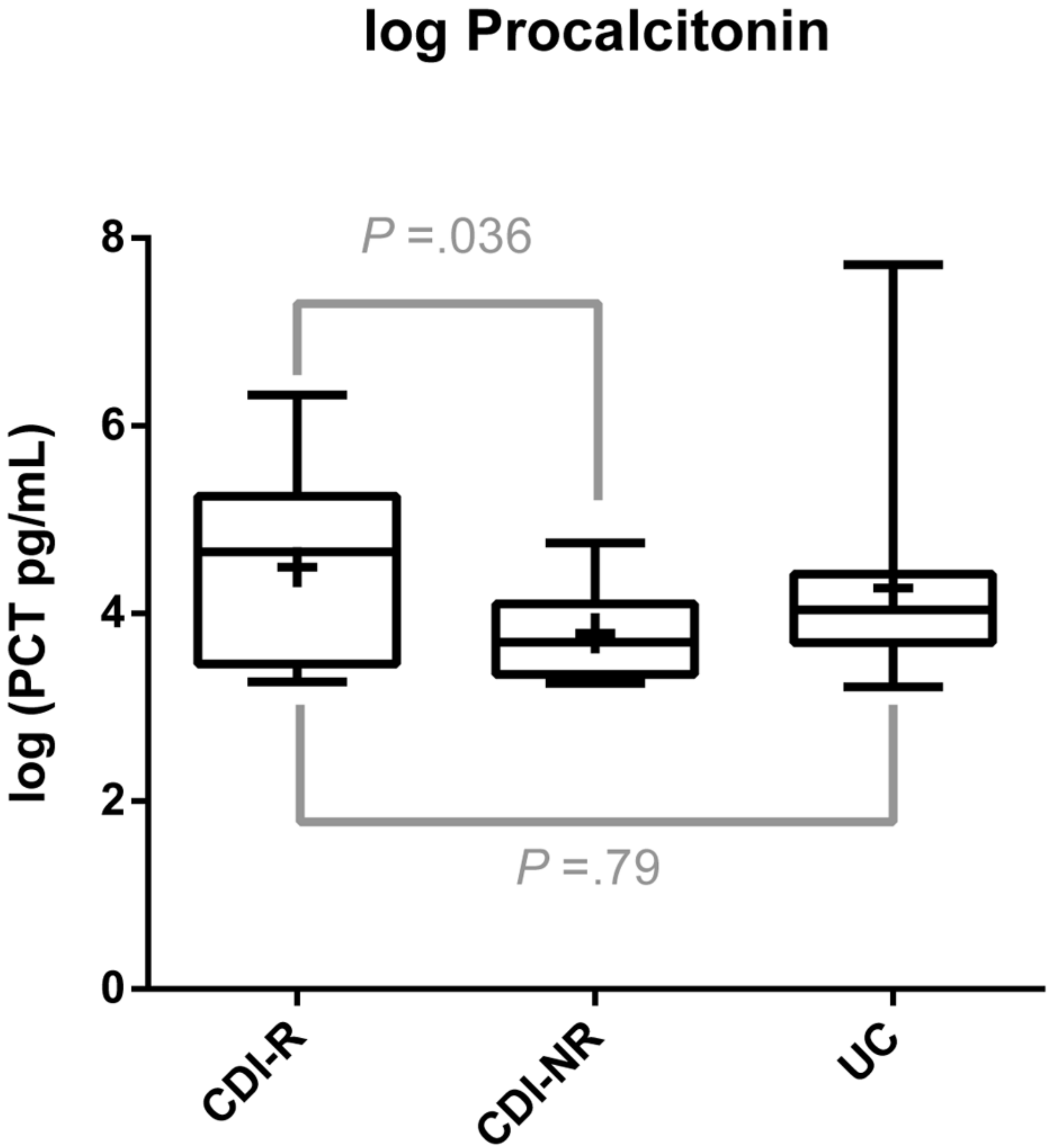
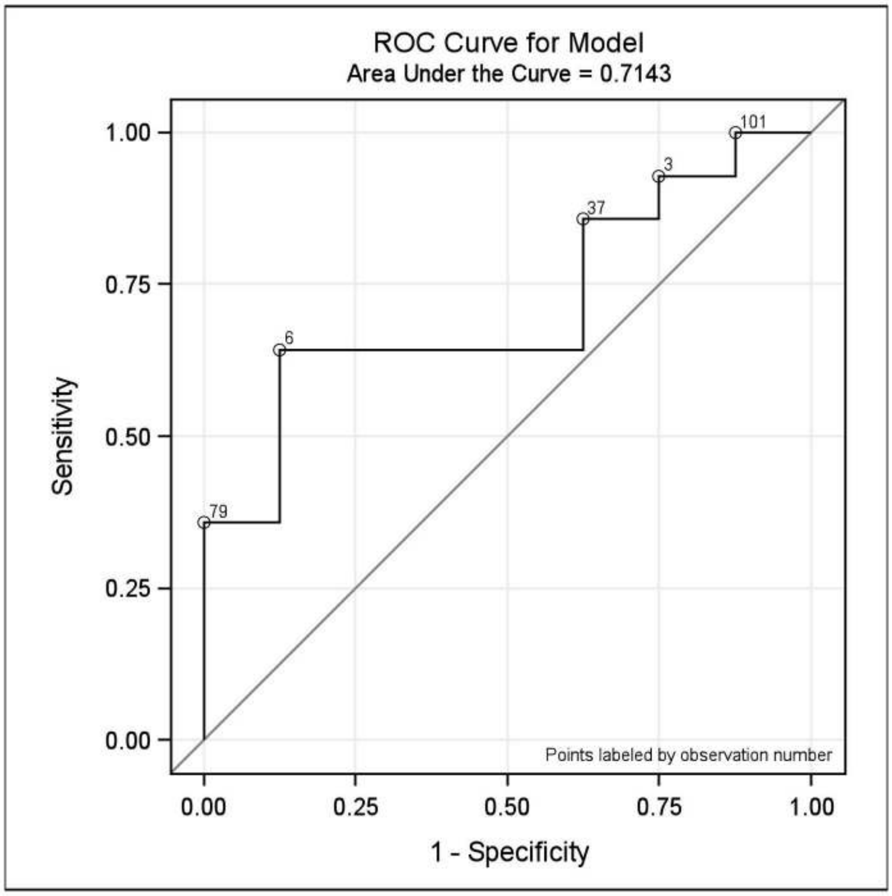


Figure 1.

Comparison of log-transformed procalcitonin levels among groups. We did not find a significant difference between the UC patients that did and did not have a positive *Clostridium* difficile assay (P= 0.79), but we did find a difference between CDI-R and CDI-NR groups (*P* =0.036). CDI-R, *Clostridium difficile* infection (in Ulcerative Colitis) with response to antibiotic therapy; CDI-NR, *Clostridium difficile* infection (in Ulcerative Colitis) without response to antibiotic therapy; UC, Ulcerative Colitis with negative *Clostridium difficile* testing.


ROC Curve for Model
Area Under the Curve = 0.7143
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00
79
6
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3
101
Points labeled by observation number

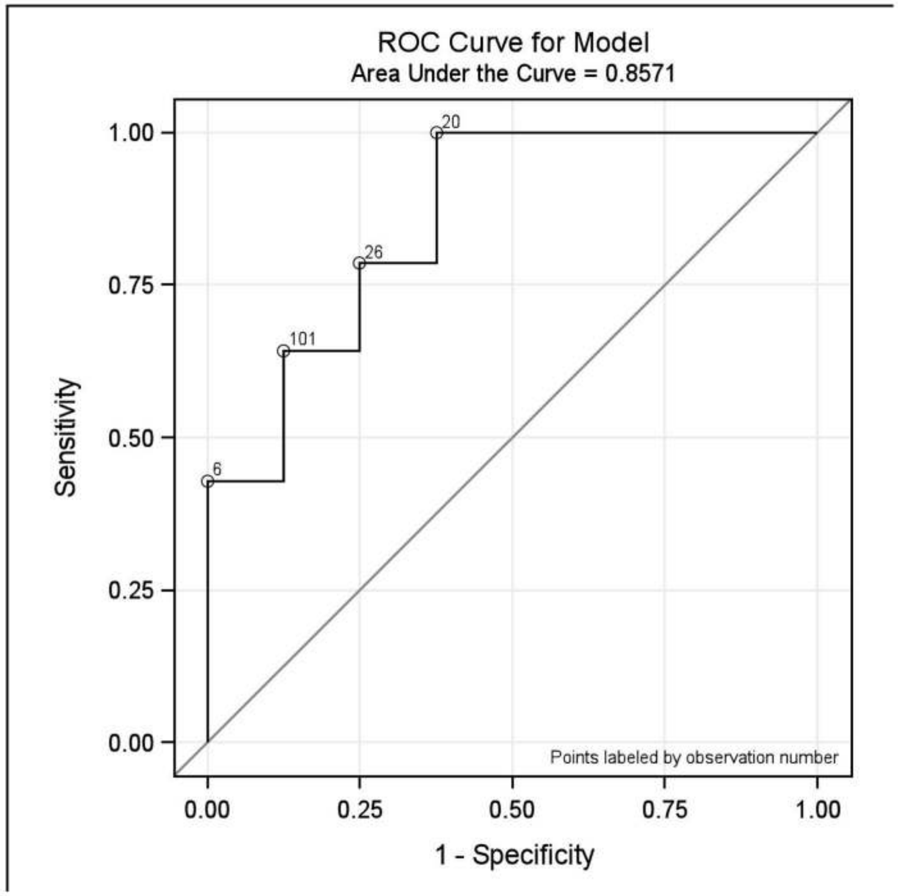

Figure 2.

Figure 2. a) Receiver-operator characteristic (ROC) curve for the ability of log-transformed procalcitonin values to differentiate CDI-R from CDI-NR. Area under the ROC curve is 0.71 (95% CI 0.5–0.93).

Figure 2. b) Receiver-operator characteristic (ROC) curve for the ability of a multivariable model that includes procalcitonin, Hemoglobin, and WBC count to differentiate CDI-R from CDI-NR. Area under the ROC curve is 0.86 (95% CI 0.7–1)

Table 1

Characteristics on presentation of the *C. difficile* positive and negative groups.

Characteristic	*C. difficile* Positive (+)			*C. difficile* Negative (−)	*P*
N	27			90	
Age	46.3 ± 21.3			42.1 ± 17.3	0.29
Male	0.48 (13)			0.49 (44)	0.93
Inpatient	0.41 (11)			0.49 (44)	0.46
5-ASA's	0.78 (21)			0.62 (56)	0.14
Immunomodulators	0.30 (8)			0.27 (24)	0.79
Biologics	0.63 (17)			0.71 (63)	0.44
Prior CDI	0.59 (16)			0.14 (13)	**<0.01**
Recent antibiotics	0.26 (7)			0.12 (11)	0.08
Response to CDI treatment	Yes	No	Undetermined	NA	NA
	0.52 (14)	0.30 (8)	0.18 (5)		

Abbreviations: AZA: Azathioprine, 6-MP: 6-Mercaptopurine, MTX: Methotrexate, 5-ASA: 5-Aminosalicylates, CDI: *C. difficile* infection.

Table 2

Comparisons of inflammatory markers between UC patients with and without CDI, and of the subjects with CDI between those that did (CDI-R) and did not (CDI-NR) respond to antibiotic treatment. Values with approximately normal distributions are presented as mean (standard deviation), and those that are skewed with as median (lowest value – highest value). For skewed data, p-values are from t-tests on log-transformed data.

Inflammatory Marker (units)	UC with CDI (N=27)	UC without CDI (N=90)	*p*	CDI-R (N=14)	CDI-NR (N=8)	*p*
Procalcitonin (pg/ml)	60.7 (26.0–560.6)	56.7 (25.1–2252)	0.79	105.3 (26.3–560.6)	40.3 (26.0–116.3)	**0.0356**
Albumin (g/dl)	3.85 (0.52)	3.97 (0.61)	0.36	3.88 (0.60)	3.79 (0.53)	0.73
Creatinine (mg/dl)	0.79 (0.25)	0.84 (0.20)	0.36	0.81 (0.26)	0.73 (0.30)	0.36
C-Reactive Protein (mg/dl)	0.9 (0.05–15.4)	1.2 (0.1–22.6)	0.82	0.60 (0.1–9.2)	0.85 (0.1–7.5)	0.91
Hemoglobin (g/dl)	12.15 (1.67)	12.5 (2.14)	0.44	12.38 (1.82)	11.44 (1.17)	0.20
WBCs (Cells/μl)	9.03 (5.51)	9.49 (3.13)	0.68	10.23 (6.86)	7.19 (3.54)	0.26
Absolute Neutrophils (Cells/μl)	6.06 (4.52)	6.59 (3.45)	0.61	6.96 (5.45)	4.51 (3.35)	0.30
Platelets (Cells/μl)	302.6 (93.6)	352.3 (135.4)	**0.04**	295.7 (85.6)	268.4 (87.9)	0.48