[Prediction of Clostridium Difficile Infection Recurrence and Risk-Based Heterogeneity of Treatment Effect of Vnacomycin vs Fidaxomicin]

A thesis submitted by

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Abstract

Despite successful therapy for *Clostridium Difficile* Infection (CDI), a significant number of patients will experience a recurrence. We aimed to develop a predictive model for recurrent CDI and to compare the efficacy of fidaxomicin and vancomycin in different risk groups. We included patients enrolled in two phase 3 clinical trials, comparing the efficacy and safety of fidaxomicin vs vancomycin in the treatment of CDI. Using logistic regression, we developed a predictive model for CDI recurrence, including significant predictors as well as established risk factors for recurrence. Patients were divided into tertiles based on their predicted probability of CDI recurrence. We compared the efficacy of fidaxomicin versus vancomycin within each risk tertile. The total number of patients was 794 patients. 150 patients (19%) experienced CDI recurrence by day 28. The following variables were included in the model for CDI recurrence: age>40 years (OR 1.27; p= 0.47), low creatinine clearance (OR 0.99; p= 0.06), low serum albumin (OR 0.89; p= 0.46), urinary tract infection (UTI) within one month prior to CDI (OR 1.61; p= 0.05), CDI in the past 3 months (OR 1.73; p= 0.02) and history of cardiovascular disease (OR 1.68; p= 0.02). Use of acid lowering agents was protective for CDI recurrence (OR 0.60; p= 0.01). Calibration and discrimination of the model were good (c-statistic=0.66 and a non-significant p-value for the Hosmer-Lemeshow test). While there was no risk-by-treatment interaction on the odds ratio scale, there was substantial variation in the absolute risk reduction across risk groups (absolute risk reduction was 17.1%, 14.6% and 2.1% in the high, intermediate and low risk groups respectively). CDI recurrence can be predicted on the basis of easily obtainable clinical factors at the time of initial presentation. Targeting fidaxomicin therapy to patients at higher risk of recurrence may be a worthwhile clinical strategy.

Acknowledgements

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Table 1: Demographics and baseline characteristics stratified by CDI recurrence

Patient characteristic	**CDI Recurrence (N=150) (%)**	**No Recurrence (N=644) (%)**
Age > 40	136 (90.7)	534 (82.9)
Gender (Male)	62 (41)	256 (40)
Race (Caucasian)	139 (93)	574 (89)
Hospitalized (vs. Outpatient)	88 (59)	356 (55)
Severe CDI*	59 (39)	232(36)
Number of bowel movements at time of diagnosis >= 10	49 (33)	179 (28)
History of CDI within the past 3 months	35 (23)	93 (14)
History of UTI within the past month	33 (22)	86 (13.4)
History of lower respiratory tract infection within the past month	27 (18)	80 (12.4)
Use of acid lowering agents at time of diagnosis	69 (46)	325 (50.5)
Comorbid condition		
Cardiovascular disease*	74 (49)	203 (32)
Diabetes mellitus	37 (25)	135 (21)
Liver disease*	20 (13)	58 (9)
Baseline laboratory values		
Creatinine Clearance Rate ml/min (mean) (sd)	78.40 (43.04)	92.71(45.61)
Serum albumin g/l (mean) (SD)	3.02 (0.72)	3.15 (0.69)
WBC (mean) (sd)	10.57 (5.79)	9.90 (5.57)
Treatment arm		
Fidaxomicin	51 (34)	340 (52)
Vancomycin	99 (66)	304 (47)

*Cardiovascular disease: History of coronary artery disease, valvular disease or heart failure
*Liver disease: Active hepatitis B or C, cirrhosis, liver transplant
*Severe CDI: WBC >150000 /mm^3 and Creatinine > 1.5 mg/dl

Table 2: Univariate analysis

Variable	OR	95% CI	P value
Age > 40	1.02	(1.01,1.03)	0.003
Male gender	0.93	(0.65, 1.34)	0.71
NAP 1 strain	1.83	(1.14, 2.92)	0.01
Number of bowel movements at time of diagnosis >= 10	1.26	(0.86, 1.84)	0.24
BMI	0.99	(0.97, 1.02)	0.68
Severe CDI	1.15	(0.79, 1.65)	0.46
Hospitalized (vs. Outpatient)	0.87	(0.61, 1.25)	0.46
History of CDI in past 3 months	1.80	(1.15, 2.77)	0.01
History of UTI within the past month	1.83	(1.16, 2.84)	0.008
Lower respiratory tract infection in the past month	1.55	(0.95, 2.47)	0.07
Use of acid lowering agents at time of diagnosis	0.84	(0.59, 1.19)	0.32
Creatinine Clearance Rate ml/min	0.99	(0.99, 1)	0.0003
Serum Albumin g/l	0.76	(1.01, 1.69)	0.04
WBC	1.02	(0.99, 1.05)	0.22
History of cardiovascular disease	2.11	(1.47, 3.03)	<0.0001
History of liver disease	1.55	(0.88, 2.63)	0.11
Diabetes mellitus	1.23	(0.81, 1.86)	0.32

Table 3: Model 1 (Without *Clostridium difficile* strain). Total sample size used to develop the model = 794

Variable	OR	95% CI	P value
Age >40	1.27	(0.68, 2.48)	0.47
Creatinine Clearance Rate ml/min	0.99	(0.99, 1)	0.06
Serum Albumin g/l	0.89	(0.66, 1.21)	0.46
History of CDI within the past 3 months	1.73	(1.08, 2.67)	0.02
History of UTI within the past month	1.61	(1.01, 2.58)	0.05
Use of acid lowering agents at time of diagnosis	0.60	(0.42, 0.93)	0.01
Cardiovascular disease	1.68	(1.11, 2.57)	0.02

Table 4: Model 2 (With *Clostridium difficile* strain). Total sample size used to develop the model =794

Variable	OR	95% CI	P value
Age >40	1.27	(0.67, 2.48)	0.47
Creatinine Clearance Rate ml/min	0.99	(0.99, 1)	0.06
Serum Albumin g/l	0.95	(0.69, 1.30)	0.73
History of CDI within the past 3 months	1.68	(1.05, 2.60)	0.03
History of UTI within the past month	1.60	(0.99, 2.57)	0.05
Use of acid lowering agents at time of diagnosis	0.59	(0.41, 0.92)	0.01
Cardiovascular disease	1.57	(1.03, 2.43)	0.04
NAP1 strain	1.51	(0.90, 2.59)	0.13

Table 5: Comparison between vancomycin and fidaxomicin in different risk groups

Risk category	Recurrence		P value
	Fidaxomicin	Vancomycin	
Low	8.8%	10.9%	0.60
Intermediate	12%	26.6%	0.003
High	18.5%	35.6%	0.002

Table 6: Net reclassification improvement

Without strain	**With strain**		
Risk Category	Low	Intermediate	high
low	245 (25 recurrence)	24 (4 recurrence)	0
intermediate	30 (6 recurrence)	201 (35 recurrence)	36 (8 recurrence)
high	0	27(4 recurrence)	231 (68 recurrence)

Table7: Key characteristic in patients without strain data compared to patients with available data

Some of the key characteristic in patients without strain data compared to patients with available data			
Patient Characteristic	**Strain data available n= 583 (%)**	**Strain data not available n=211 (%)**	**P value**
Age (mean) (SD)	60.37 (18)	62.06 (16.75)	0.23
History of CDI within the past 3 months	96 (16.5)	32 (15.2)	0.66
History of UTI within the past month	91 (15.6)	28 (13.3)	0.41
History of lower respiratory tract infection within the past month	79 (13.6)	28 (13.3)	0.92
Use of acid lowering agents at time of diagnosis	270 (46.3)	124 (58.8)	0.002
Cardiovascular disease	191 (32.8)	86 (40.8)	0.04
Diabetes mellitus	117 (20.07)	55 (26.1)	0.07
Liver disease	54 (9.3)	24 (11.4)	0.38
Creatinine Clearance Rate ml/min (mean) (SD)	88.5 (44.77)	94.60 (47.23)	0.12
Serum albumin g/l (mean) (SD)	3.1 (0.7)	3.1 (0.7)	0.12
Fidaxomicin arm	293 (50.3)	98 (46.4)	0.34
CDI Recurrence	117 (20.1)	33 (15.6)	0.16

Table8: Frequency of missing variables

	Number of subjects	Percentage
WBC	**87**	**11%**
CDI strain	**211**	**27%**
Albumin	**48**	**6%**
Creatinine clearance	**32**	**4%**

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Figure1: Consort diagram of the flow from two RCTs

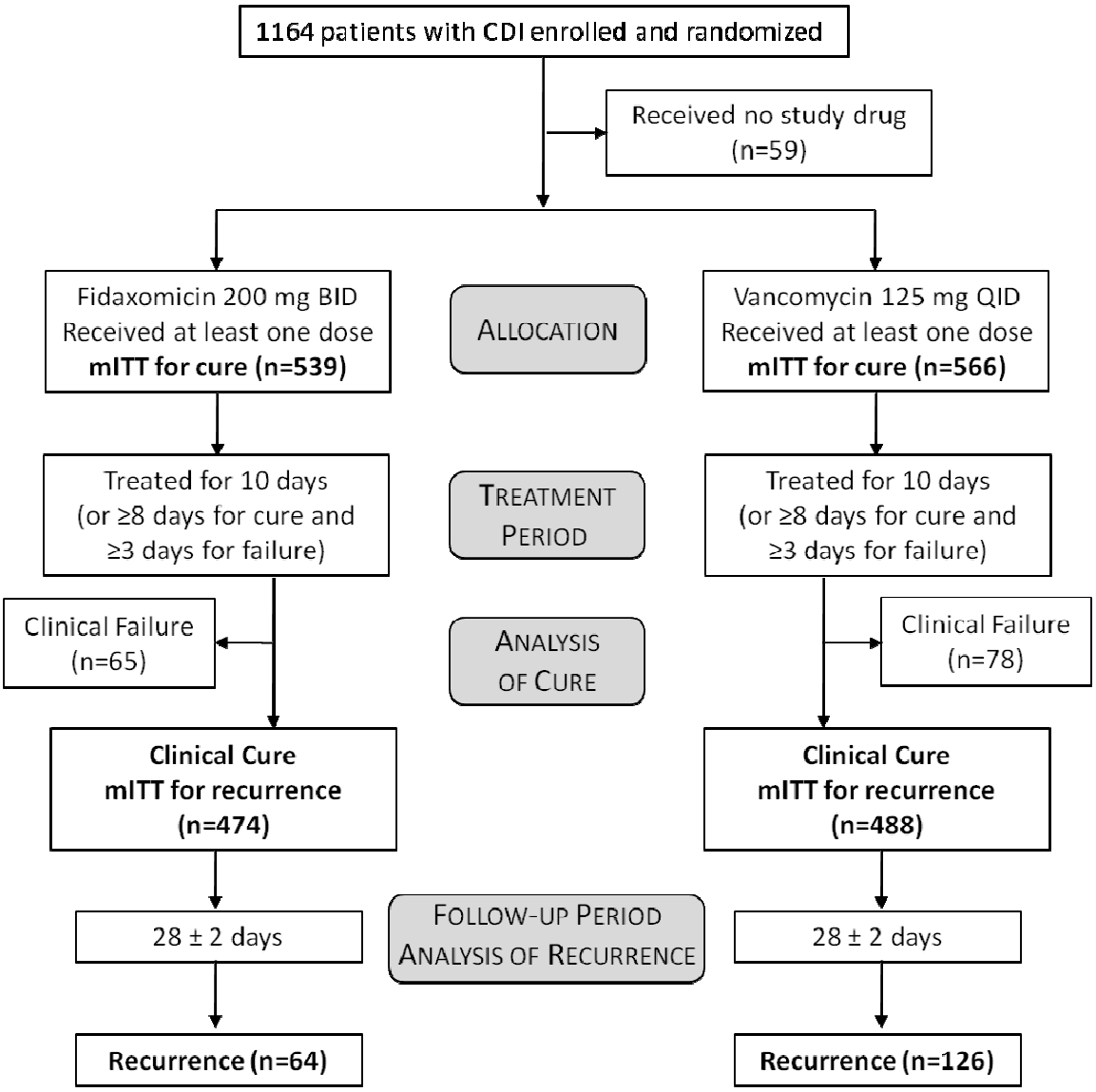
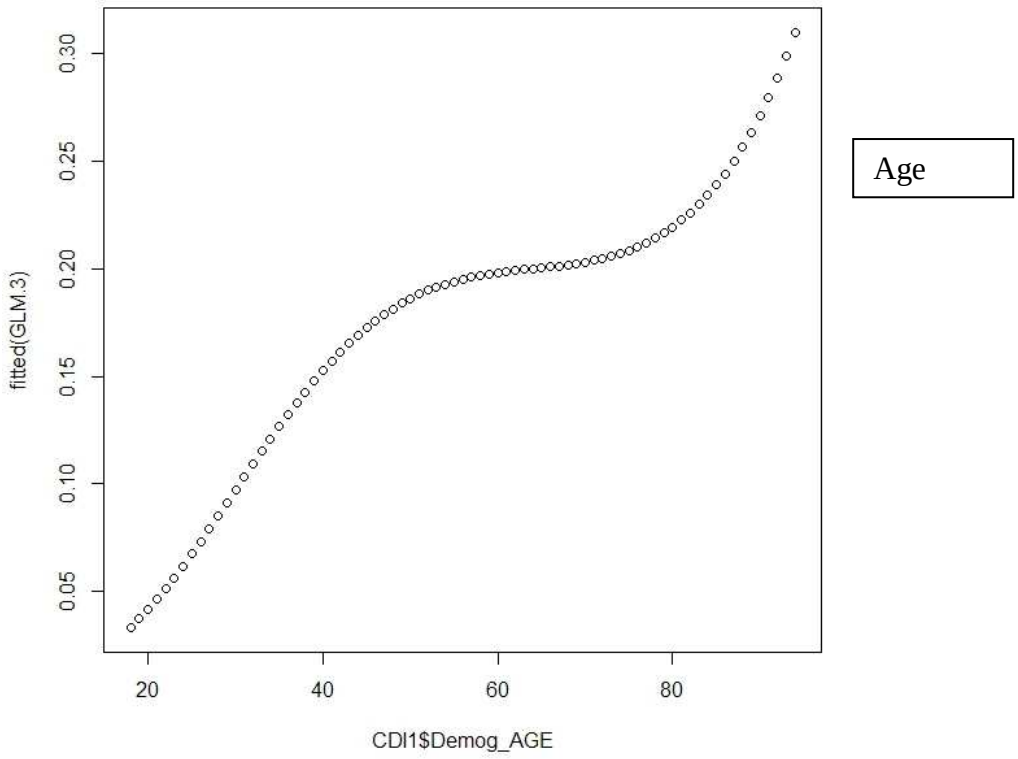
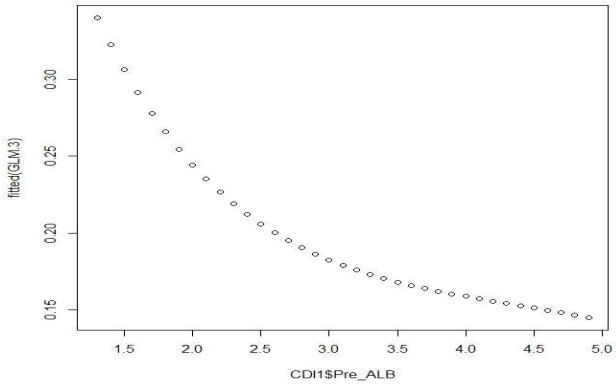
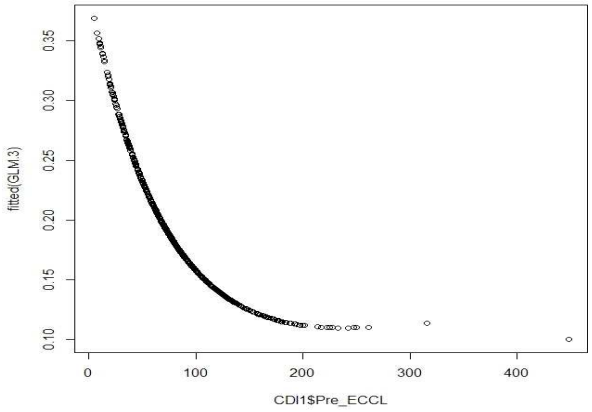


Figure2: Smoothed plot for age, albumin and creatinine clearance.



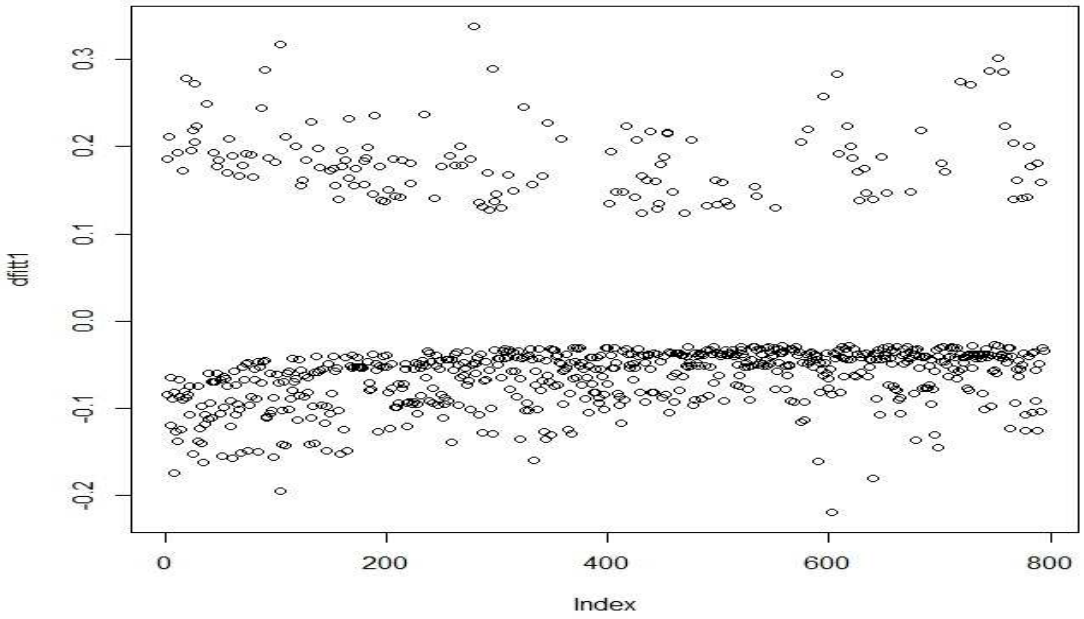


Serum albumin g/l (range 1.3-4.9)



Creatinine Clearance Rate ml/min (range 5-200)

Figure3: DFFIT Plot



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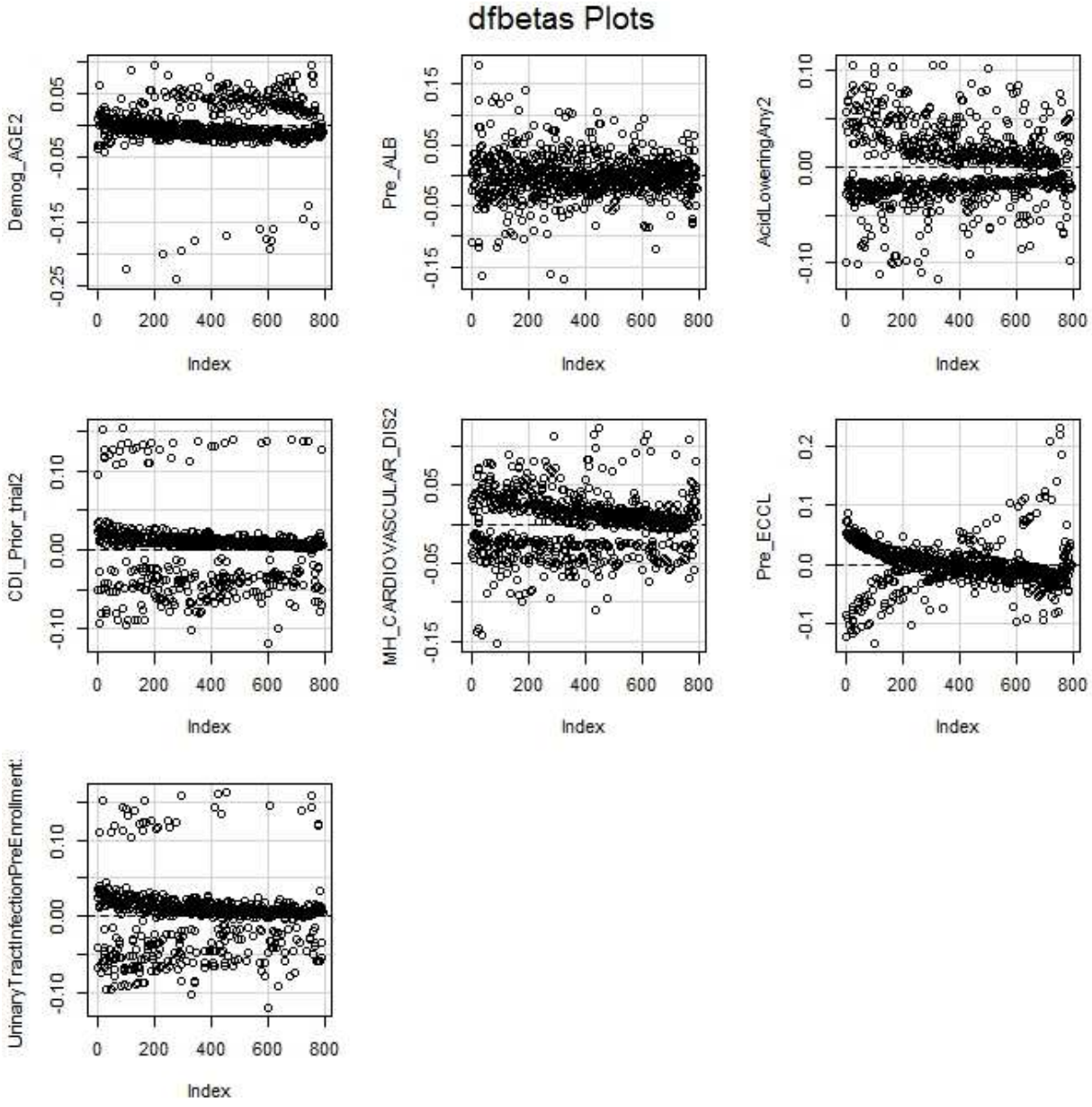
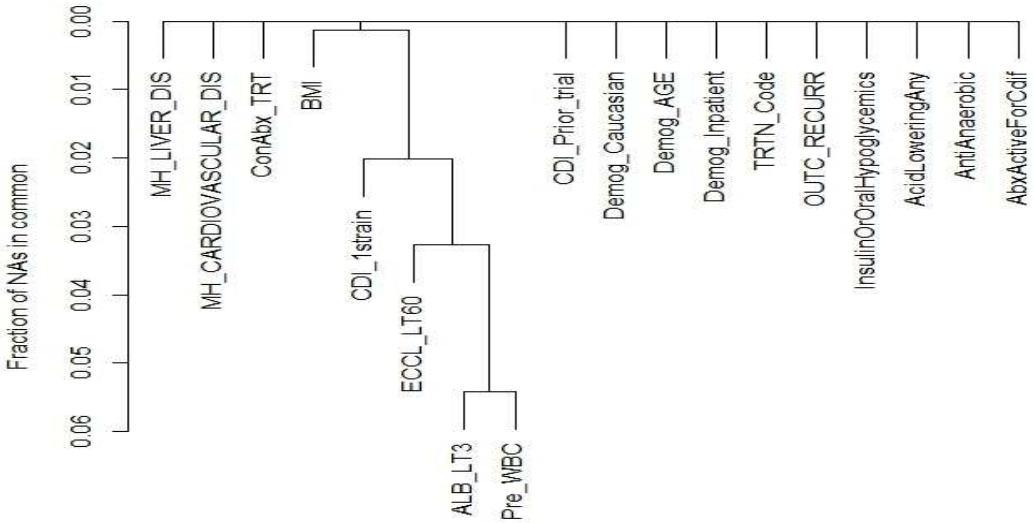


Figure5: pattern of missing data



List of abbreviations

CDI: Clostridium difficile infection

Introduction

Clostridium difficile infection (CDI) is a major cause of nosocomial and antibiotic associated diarrhea. The incidence of this infection is increasing in hospitals secondary to widespread use of broad spectrum antibiotics [1]. The annual estimated cost for CDI treatment in the United States is $3.2 billion dollars [2]. Despite successful therapy, about 15%–25% of patients will experience a recurrence of diarrhea in association with a positive stool test for *C difficile* [3-7]. Recurrent CDI has been associated with significant morbidity, mortality and economic health care burden [8-10]. Several therapeutic strategies have been proposed for management of recurrent CDI including prolonged use of antibiotics, probiotics and immunotherapy [5]. Despite this, management of recurrent CDI remains a substantial therapeutic challenge.

Several risk factors associated with CDI recurrence have been identified. These include age>65 years, low serum antibody concentration against toxin A, concomitant use of antibiotics, use of proton pump inhibitors, use of fluroquinolones, serum albumin <2.5 and renal failure [11-14]. A prediction rule for CDI recurrence has been published using 3 clinical risk factors, age>65 years, severe disease and additional antibiotic use after CDI therapy [15]. This model has not been widely used given the requirement of a subjective assessment (Horn's index) for disease severity, as well as the need to use post-treatment decision information in the prediction (i.e. future antibiotic use). It is also unclear how this risk score interacts with the various treatment options.

The current treatment regimens for CDI include metronidazole and vancomycin [16]. Fidaxomicin was recently approved for treatment of CDI. In clinical trials, fidaxomicin was non-inferior to vancomycin for treatment of CDI and was associated with fewer recurrences than vancomycin, 13% vs. 26% [17]. There is a significantly higher cost in using fidaxomicin compared to

vancomycin. Given the possible superiority of fidaxomicin compared to vancomycin in preventing recurrence, establishing specific clinical markers to predict recurrence of CDI may help clinicians justify use of fidaxomicin in patients with especially high risk of recurrence, while avoiding its use in those unlikely to recur.

Our aim is to develop a predictive model for CDI recurrence. We will use this model to stratify patients in the same cohort into different risk groups for recurrence and compare the efficacy of fidaxomicin versus vancomycin among different risk groups.

Materials and Methods

2.1 [Patient population]

Patients included in this study were enrolled in two phase 3 clinical trials, comparing the efficacy and safety of fidaxomicin vs. vancomycin in the treatment of CDI. These were prospective, multicenter, double-blind, randomized, parallel-group, noninferiority trials, which were conducted between May 2006 and December 2009. Patients were enrolled at sites in the United States, Canada, and Europe. Eligible patients were 16 years of age or older with a diagnosis of CDI, defined as presence of diarrhea (change in bowel habits with >3 unformed bowel movements in the 24 hours prior to randomization) and either C. difficile toxin A, B, or both in the stool within 48 hours of randomization. Patients could have received up to 4 doses but no more than 24 hours of vancomycin or metronidazole prior to randomization, and no doses of other potentially effective treatments for CDI. Patients with life-threatening or fulminant CDI, toxic megacolon, previous exposure to fidaxomicin, a history of ulcerative colitis or Crohn's disease, and >1 occurrence of CDI within 3 months of study start were excluded.

2.2 [Treatment allocation]

Patients received the study medication orally for 10 days using an every 6 hour regimen: fidaxomicin 200 mg every 12 hours with intervening matching placebo doses or vancomycin 125 mg every 6 hours. Patients were evaluated during the 10-day course of therapy for clinical cure or failure. If cured, patients were followed for 28 days after the last dose of study medication for recurrence.

2.3 [CDI Recurrence]

Patients who were cured of the initial CDI episode, remained in the study, and had end-of-study follow-up between days 36 and 40, were evaluated for recurrence. Clinical recurrence was defined as the reappearance of >3 diarrheal stools/24 hours within 4 weeks after stopping therapy, C. difficile toxin A and/or B in stool, and a need for retreatment for CDI.

2.4 [Variable selection and risk model development]

Data were checked for missing values. All predictors with missing values were identified. We performed multiple imputations as it has been shown to minimize bias in effect estimates compared to complete case analysis [18].

Since a specific *Clostridium difficile* strain (NAP1/BI/027) has shown to be associated with recurrence risk in prior studies, but is infrequently available for decision making clinically (and was not universally collected in our dataset), we constructed models with (Model 1) and without (Model 2) this variable, and assessed the incremental improvement in model performance [19].

For model development, we used easily obtainable baseline clinical characteristics we thought might be associated with CDI recurrence. The model was developed on both study arms to optimize power and to avoid bias in assessing heterogeneity of treatment effect across risk groups. We performed univariate analysis for several baseline characteristics including demographics, comorbidities, hospitalization status, laboratory values and concomitant use of antibiotics. Continuous predictors were checked for nonlinear associations. Covariates with a univariate p value less than 0.2 were included as candidate for the building of the multivariable predictive model, as were established risk factors for CDI recurrence, including age, serum albumin, creatinine clearance, NAP1 strain and use of acid lowering agents. A backward elimination was then performed until only variables with a p-value<0.05 were left in the model. All established risk factors were forced into the final model, regardless of statistical significance.

Model discrimination ability was evaluated using the concordance statistic. The Hosmer-Lemeshow test was used to evaluate goodness of fit. Net reclassification improvement (NRI) was used to compare the models with and without *clostridium difficile* strain. This method has been recommended to assess the incremental value of a specific marker on a prediction model [20].

Based on the predicted probabilities in Model 1, patients were ranked according to their recurrence risk and divided into 3 equally-sized strata. Within each risk stratum, we compared the effectiveness, measured as CDI recurrence within 4 weeks, of fidaxomicin vs vancomycin. We used R software for all statistical analysis.

Results

3.1 [Cohort description]

A total of 794 patients treated per protocol who were cured and followed for 28 days were included in our analysis. 150 patients (19%) had CDI recurrence by day 28 (Figure1). Demographics, clinical characteristics and laboratory values at baseline are illustrated in Table 1. CDI strain type was missing in 211 subjects (Table 8). Patients with missing strain data had similar baseline characteristics except history of cardiovascular disease and use of acid lowering agents were both higher in patients who did not have the strain typed (Table 7)

3.2 [CDI recurrence prediction model]

In the univariate analysis (Table 2), 9 variables had a p value <0.2 and were included in the multivariable analysis. There was a non linear association between age as a continuous predictor and CDI recurrence. Smoothed plots indicated it was well modeled as a binary variable where age greater than 40 increases the risk of recurrence (Figure 2). Model 1 (without the CDI strain variable) included 7 variables (Table 3) and had a C statistic of 0.65. Hosmer-Lemeshow p value was 0.77 which indicated a good model fit. The following variables were found to be predictive of CDI recurrence, age>40, low creatinine clearance, low serum albumin, history of CDI in the past three months, history of UTI in the past month and past medical history of cardiovascular disease. Use of acid lowering agents at the time of diagnosis was found to be protective for recurrence. Model 2 with the CDI strain variable included 8 variables (Table 4) and had a C statistic of 0.66. The effects of all established predictors of recurrence (including

creatinine clearance, age, serum albumin and NAP1 strain) all went in the anticipated direction and were retained in the model even when not statistically significant.

3.3 [Checking for interactions]

Based on prior studies on CDI recurrence risk factors, no significant interactions were suspected among the predictors in the final model. However, we checked for interaction between treatment and risk of CDI recurrence (tertiles). We performed type three test as follow:

```
GLM.1 <- glm(OUTC_RECURR ~ TRTN_Code +variable+TRTN_Code *variable,
  family=binomial(logit), data=CDI)
summary(GLM.1)
Anova(GLM.1,test="Wald",type=3)
```

Result:

```
> Anova(GLM.1,test="Wald",type=3)
Analysis of Deviance Table (Type III tests)
Response: OUTC_RECURR
                    Df   Chisq Pr(>Chisq)
(Intercept)          1 55.3515  1.008e-13 ***
TRTN_Code            1  0.3072     0.5794
variable             2 20.3124  3.884e-05 ***
TRTN_Code:variable   2  2.2632     0.3225
```

P value is 0.32 which means that there is no significant interaction between treatment and risk categories on odds ratio scale which implies substantial variation on the absolute risk scale.

3.4 [Checking for influence points]

To detect influence points we estimated changes in model fit or coefficients by removing an observation using DFFIT (change in global fit) and DFBETAS (change in individual coefficients). DFFIT plot shows two points that could be influential (>0.3) (Figure 3). We removed those points and re- ran the model but no change in estimate was observed. Thus we concluded there are no major influential points in our data. DFBETA plots also showing that there are no major influential points in each of the individual variables (Figure 4).

3.5 [Checking for Multicollinearity]

All the predictors in the final multivariable model were checked for multicollinearity. We used Variance Inflation Factor (VIF) to check if there is a high correlation between predictors.

```
> vif(glm1)
                          Demog_AGE2                        MH_LIVER_DIS2
                            1.174977                             1.034256
                   AcidLoweringAny2                   CDI_Prior_trial2
                            1.114194                             1.025386
              MH_CARDIOVASCULAR_DIS2                             Pre_ECCL
                            1.237917                             1.220528
UrinaryTractInfectionPreEnrollment2
                            1.052104
```

Variance Inflation Factor for all the variables in the model are around 1 which indicates that there is no major correlation between predictors.

3.6 [Dealing with the missing data]

Data were checked for missing values. All predictors with missing values were identified. There were no missing values in outcome. We studied the pattern of missing values. Figure 5 illustrates the missing pattern. Subset of patients with missing strain variable also missing creatinine clearance and subset of those patients are missing serum albumin and WBC. We performed multiple imputations method as it has been shown to minimize bias in effect estimates compared to complete case analysis. We used 5 imputations in our analysis. Table 1 result was based on original dataset. Univariate analysis, model 1 and 2 were done on the imputed dataset.

3.7 [Incremental value of CDI strain]

Adding the CDI strain variable to the model had a small effect on the discrimination ability of the model (c statistic increased by 0.01). To further explore the usefulness of this predictor, we calculated the NRI in the extended model after adding the strain variable to the 7 predictors in model 1. Based on the predicted risk from model 1 we used 14% and 21% as cut offs (which defined risk tertiles) to calculate NRI (table 6). The improvement in reclassification for those with CDI recurrence was 0.01 ((12-11)/150), and those without recurrence 0.02 ((47-34)/644). Thus, the NRI was 0.03.

3.8 [Risk-based Heterogeneity of Treatment Effect]

Based on model 1 (without strain), the mean predicted probability for recurrence was 19% (SD 9.9%). Tertiles were created from the predicted probabilities and were labeled as low,

intermediate and high risk groups. Risk of CDI recurrence in the low risk group ranged from 5 to 14%, intermediate risk from 14 to 21% and high risk group from 21 to 55%.

While the interaction between treatment and risk tertiles was non-significant (p=0.32), indicating no significant diffrences. Given the substantial risk heterogeneity across these groups, there was substantial heterogeneity in the absolute benefit of fidaxomicin therapy. Absolute risk reduction was 17.1%, 14.6% and 2.1% in the high, intermediate and low risk groups respectively. Corresponding to a number needed to treat of 6, 7 and 50 respectively.

Discussion

We developed a prediction model for CDI recurrence using simple baseline clinical characteristics and laboratory values. The variables we used to construct this model are easily obtainable on routine medical practice. Using this model, we showed substantial benefit in using fidaxomicin in the high risk group. The benefit of fidaxomicin in the low risk group appears to be minimal since these patients are unlikely to have recurrence even when treated with vancomycin. The number needed to treat to prevent a single recurrence was almost 10-fold higher in the low risk tertile compared to the high risk tertile.

The risk factors that we included in the model for CDI recurrence are age > 40 years, renal impairment (measured as creatinine clearance), low serum albumin and history of CDI in the past three months. These risk factors were consistent with previously published studies [11-14]. We additionally identified UTI within one month prior to CDI to be predictive of recurrence. This could be a surrogate for a combination of specific host risk factors and exposure to specific types of antibiotics. Similarly, a past medical history of cardiovascular disease was also found to

be predictive for CDI recurrence, consistent with prior studies showing that comorbidities are associated with CDI recurrence. The only class of medications we found to be predictive for CDI recurrence was the use of any form of acid lowering agents. We found a protective association of using these medications at time of diagnosis.

NAP1 strain was associated with CDI epidemic in the last decade and has been shown to be associated with CDI recurrence in several studies. Although there are emerging technologies to detect the NAP1 strain, most laboratories do not have the capacity to do so. In our model, addition of the NAP1 strain did not improve the prediction (C statistic increase only by 0.01). Furthermore, adding the NAP1 strain to the model had a minimal net reclassification improvement. Therefore, the need for routine measurement of NAP1 is difficult to justify on the basis of recurrence prediction.

Our study has several strengths, including high quality demographic and baseline clinical characteristics and laboratory values collected prospectively from two RCTs. Furthermore, the sample size was large and appropriate to develop the prediction model. Additionally, the study populations were multicenter and multinational; therefore, the model is likely to be quite generalizable. Finally, embedding the predictive model directly in a clinical trial allowed us to estimate the relative effectiveness of fidaxomicin versus vancomycin across risk strata in an unbiased way, providing evidence of the potential usefulness of the model.

Limitations to our study include a short follow up duration (28 days). However, CDI recurrence usually occurs within the first 4 weeks after therapy. Additionally, independent validation of the model will provide a better assessment of the generalizability of the model, a pre-condition for its widespread use for decision making.

In conclusion, CDI recurrence can be predicted using simple clinical characteristics and laboratory values. Our model may aid in identifying patients who would have a substantial benefit from using fidaxomicin to prevent CDI recurrence. Conversely, low risk patients are highly unlikely to get incremental benefit from fidaxomicin compared to vancomycin.

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