Performance of Published *Clostridium difficile* Severity Scoring Systems in an External Cohort

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BACKGROUND

OVERVIEW OF CDI

- *C. difficile* infection (CDI): leading cause of gastroenteritis-related death in USA
  - 453,000 infected per year
  - 35,000 deaths per year
  - Risk of complicated CDI (attributable ICU admission, colectomy, or death) is 7–15%

THE DILEMMA WITH NEW & ADVANCED TREATMENTS FOR CDI: WHO SHOULD GET THEM?

- Effective treatments exist to decrease risk of adverse outcomes but there are limitations:
  - Cost (monoclonals, fidaxomicin)
  - Invasiveness (loop ileostomy)
  - Cost/safety (fecal transplant)

THE HOPE OF PREDICTIVE MODELING

- Accurately predict adverse outcomes
- Applicable early after diagnosis
- Portable and validated
- Can be used to allocate treatments

PUBLISHED PREDICTIVE MODELS FOR CDI SEVERITY

- Overall poor performance when validated in a small external cohort (n=184) against complicated CDI (Fujitani et al, 2011)
- Best score by kappa: Hines VA but only 73% sensitive (Table 1)
- Other predictive modeling metrics such as net reclassification index (NRI) and area under the curve / discriminant function were not assessed

Table 1. Validation of CDI Severity Scores

Index	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Kappa score (95% CI)
Beth Israel	63.2	87.3	36.4	95.4	0.38 (0.24–0.52)
UPMC version 1	68.4	93.9	56.5	96.3	0.57 (0.43–0.71)
University of Calgary version 1	68.4	90.3	44.8	96.1	0.48 (0.34–0.62)
Hines VA	73.7	93.4	70.0	97.0	0.69 (0.54–0.83)
Modified University of Illinois	84.2	59.4	19.3	97.3	0.18 (0.08–0.27)
University of Calgary version 2	73.7	72.7	23.7	96.0	0.24 (0.13–0.36)
UPMC version 2	73.7	88.5	42.4	96.7	0.47 (0.33–0.61)
University of Temple	68.4	71.5	21.7	95.2	0.20 (0.09–0.32)

note. CI, confidence interval; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; UPMC, University of Pittsburgh Medical Center.

OBJECTIVE

Validate and assess CDI severity scoring systems in a large, external cohort using multiple metrics

METHODS

Literature search revealed nine scores with objective criteria

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Scores applied to pre-existing cohort of 1144 inpatients with CDI

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Assessed ability to predict primary outcome of complicated CDI

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Compared metrics: sensitivity, specificity, positive/negative predictive values, discriminant function (DF), and net reclassification index (NRI)

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Baseline score for NRI comparison was IDSA (Cohen et al., 2010): a 1.5-fold rise in creatinine above baseline [AKI] OR a white blood cell count [WBC] >15,000 cells/mm3

DEFINITIONS OF METRICS

	Disease Status (Truth)		
Results of Test	Positive	Negative	Total
Positive	a	b	a+b
Negative	c	d	c+d
Total	a+c	b+d	

Sensitivity = a / a+c
Specificity = d / b+d
Positive Predictive Value = a / a+b
Negative predictive value = d / c+d
Discriminant function = a+d / a+b+c+d
NRI=P(up|event)−P(down|event)
+P(down|nonevent)−P(up|nonevent)

RESULTS

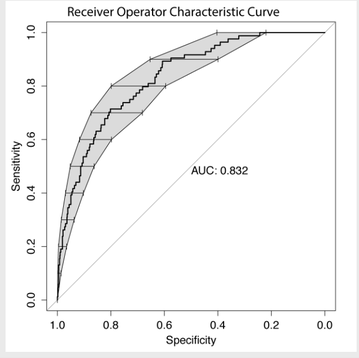
THE IN-HOUSE PREDICTIVE MODEL

Predictor	Severe *Clostridium difficile* Infection OR (95% CI)	*P* Value
Age (yr)	1.03 (1.01 –1.05)	<.001
Female gender	2.48 (1.45 –4.23)	.001
Healthcare-associated *Clostridium difficile* infection	. . .	. . .
Metastatic cancer	3.31 (1.41 –7.8)	.006
Congestive heart failure	. . .	. . .
Diabetes mellitus	. . .	. . .
Concurrent antibiotic use	4.49 (1.95 –10.3)	<.001
Systolic blood pressure (mm Hg)	0.97 (.96 –.98)	<.001
Mechanical ventilation	. . .	. . .
Creatinine >1.5 mg/dL	2.92 (1.77 –4.82)	<.001
Total bilirubin >1.2 mg/dL	2.48 (1.41 –4.35)	.002
White blood cell count (cells/μL)	1.03 (1.01 –1.04)	<.001

Rao et al, 2015

- Total 1144 cases of CDI
- 90 had a complicated CDI outcome (7.9%)
- In-house model: AUC of 0.83 (Figure 1)

Figure 1. In-house model ROC curve



Score	Predicted n (%)	Sens	Spec	PPV	NPV	DF
Gujja et al.	**120 (10.5)**	**0.36**	**0.98**	**0.27**	**0.94**	**0.67**
IDSA complicated	371 (32.4)	0.59	0.70	0.14	0.95	0.64
Na et al.	173 (15.1)	0.41	0.87	0.21	0.94	0.64
IDSA severe	381 (33.3)	0.58	0.68	0.14	0.95	0.63
Belmares et al.	152 (13.3)	0.37	0.89	0.22	0.94	0.63
Jardin et al.	345 (30.2)	0.52	0.71	0.14	0.95	0.62
Zar et al.	347 (30.3)	0.52	0.71	0.14	0.95	0.62
Lunglescu et al.	214 (18.7)	0.40	0.83	0.17	0.94	0.62
McEllistrem et al.	160 (14)	0.24	0.87	0.14	0.93	0.56

Score	Predicted n (%)	NRI (IDSA severe)	NRI (IDSA complicated)
Gujja et al.	**120 (10.5)**	**0.01**	-0.01
IDSA complicated	371 (32.4)	-0.02	N/A
Na et al.	**173 (15.1)**	**0.02**	0.00
IDSA severe	381 (33.3)	N/A	0.02
Belmares et al.	152 (13.3)	-0.01	-0.03
Jardin et al.	345 (30.2)	-0.03	-0.05
Zar et al.	347 (30.3)	-0.03	-0.05
Lunglescu et al.	214 (18.7)	-0.03	-0.06
McEllistrem et al.	160 (14)	-0.15	-0.17

CONCLUSIONS

- The in-house model had excellent performance with AUC = 0.83
- All of the published models evaluated performed poorly upon validation in our external cohort
- None significantly improved upon the IDSA guideline (Cohen et al., 2010) scores for severe and complicated CDI
- The relative ranking of the scores depended on the metric used to assess them
- Better scores are needed for severe CDI, and biomarkers may be required to improve performance

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