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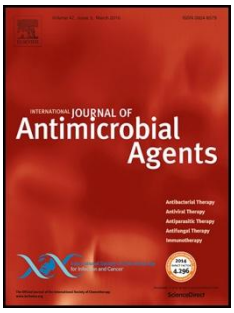

Title: Prediction of recurrent *clostridium difficile* infection at the bedside: the GEIH-CDI score

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Prediction of recurrent *Clostridium difficile* infection at the bedside: the GEIH-CDI score

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Running title: Prediction tool for recurrent CDI

Highlights:

- Based on data from a large cohort of patients, a clinical tool for prediction of recurrent CDI has been developed.
- The tool makes it possible to identify a subgroup of patients with a high probability of recurrence, thus enabling clinicians to select patients for new and expensive therapies that reduce the risk of recurrence

Abstract

Recurrence of *Clostridium difficile* infection (CDI) has major consequences for both patients and the health system. The ability to predict which patients are at an increased risk of recurrent CDI makes it possible to select candidates for therapy with new drugs and therapies (including fecal microbiota transplantation) that have proven to reduce the incidence of recurrence of CDI. Our objective was to develop a clinical prediction tool, the GEIH-CDI score, to determine the risk of recurrence of CDI. Predictors of recurrence of CDI were investigated using logistic regression in a prospective cohort of 274 patients diagnosed with CDI. The model was calibrated using the Hosmer-Lemeshow test. The tool comprises 4 factors: age (70-79 years and ≥80 years), history of CDI during the previous year, direct detection of toxin in stool, and persistence of diarrhea on the fifth day of treatment. The functioning of the GEIH-CDI score was validated in a prospective cohort of 183 patients. The area under the ROC curve was 0.72 (0.65 – 0.79). Application of the tool makes it possible to select patients at high risk (>50%) of recurrence and patients with low risk (<10%) of recurrence. GEIH-CDI score may be useful for clinicians treating patients with CDI.

Keywords: *Clostridium difficile*, recurrence, clinical prediction tool

Introduction

Clostridium difficile is the main cause of antibiotic-associated diarrhea and one of the main causes of health care–associated infection.[1,2] Around 85% of the patients diagnosed with *Clostridium difficile* infection (CDI) respond well to antibiotic therapy.[3] However, the disease recurs in at least 20% of patients during the weeks immediately following completion of treatment. [3,4] The impact of recurrence of CDI was recently reported after it was shown to be associated with higher costs and increased mortality. [5-7] Recurrence is associated with persistence of spores, an insufficient immune response, and loss of the diversity of gut microbiota.[4] Many studies have identified risk factors for recurrence,[8] although clinical decision making cannot be based merely on knowing whether or not a patient is at a greater risk of an event. Rather, it would be interesting to predict the real risk of the event by taking into account relevant factors and the interactions between them. Such information could be obtained using clinical prediction tools.[9]

More clinical tools have been developed for prediction of death or complicated disease course (colectomy, admission to intensive care) than for prediction of recurrence.[10] However, interest in such tools is limited because of the lack of new drugs and strategies that significantly reduce the risk of complications of CDI and death. In contrast, prediction of recurrence would help physicians to better select candidates for new expensive treatments

and fecal microbiota transplantation that have been shown to significantly reduce the frequency of recurrence of CDI.[11-13]. Furthermore, prediction tools would enable earlier diagnosis and treatment of recurrence thanks to closer follow-up and increased access to health care for patients at greater risk of recurrence. Finally, prediction tools could be used to improve the design of future clinical trials in this disease.

Most studies on clinical tools for prediction of recurrence of CDI are methodologically deficient or difficult to apply in clinical practice.[10] The objective of our study was to develop a simple clinical prediction tool that is easy to apply in daily clinical practice and could thus enable us to identify patients who are at a high risk of recurrence of CDI.

Patients and methods

Patient selection

Patients were prospectively included in the derivation cohort between July 2014 and February 2015 from 14 Spanish hospitals belonging to the Grupo de Estudio de Infección Hospitalaria (GEIH [*Nosocomial Infection Study Group*]) of the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC [*Spanish Society of Infectious Diseases and Clinical Microbiology*]). In order to be included in the study, patients had to have symptomatic CDI (defined as ≥3 loose stools in 24 hours), ileus, or pseudomembranous colitis confirmed microbiologically using free toxin testing of stool (immunoassay), the nucleic acid amplification test (NAAT), or culture of toxigenic *C. difficile*. Patients expected to die (in opinion of the investigator) during the following days were excluded, as were patients for whom follow-up and data collection were likely to be problematic, patients already participating in clinical trials, and patients who had received fidaxomicin since the onset of their disease.

Data collection

Patients were followed at 4 visits (baseline and 7-10 days after the initiation of treatment, and at 1 and 2 months after completion of treatment). The data collected at the baseline visit were demographic data, history, degree of dependence, clinical presentation, need for hospitalization, severity of CDI, time since onset of symptoms, and method of diagnosis. At the second visit, the data collected were treatment received, time until resolution of diarrhea, place of treatment, and therapy with antibiotics and proton pump inhibitors. At visits 3 and 4, we verified whether the disease had recurred and whether recurrence had been documented using microbiological techniques. Patients were seen in the hospital or

interviewed by telephone if they were not hospitalized. When it was not possible to obtain reliable data by telephoning the patient or his/her carers, we retrieved data from hospital information systems and public health network. All the participating centers had access to an online database.

Measurement of outcome

Recurrence was defined using the criteria applied in the case definition. Recurrence was also defined as reappearance of symptoms suggestive of CDI that resolved with vancomycin, metronidazole, or fidaxomicin if a new sample had not been sent to the laboratory. In contrast, if a sample sent to the laboratory was negative for toxigenic *C. difficile* despite a response to specific treatment for CDI, then reappearance of diarrhea was not considered a recurrence. Patients whose disease recurred were not readmitted to the derivation cohort, although clinical data on new episodes were collected. The importance of avoiding the overdiagnosis of recurrence was emphasized to the investigators.

Data are expressed as mean (standard deviation) and absolute and relative frequencies as appropriate. The *t* test and Mann-Whitney test were used to compare continuous variables and the chi-square test was used for categorical variables.

Derivation cohort

We performed a logistic regression model to estimate a predictive model for recurrence. Candidate predictors were selected from those that were significant in the univariate analysis and those selected by investigators based on the medical literature and clinical practice.

We used a parsimonious backward approach to investigate combinations of variables for inclusion in our final model (with $p \leq 0.05$ as an initial criterion for statistical significance). We then computed the points for each predictive variable's risk categories as the rounded value of the quotient resulting from dividing the coefficient of each category by the lowest coefficient. The simplicity of this scoring system allows a patient's risk to be estimated without using a calculator. The GEIH-CDI score was calculated for each patient based on a sum of individual points of each predictive variable included in the final model.

Discrimination for prediction of the event was estimated using the area under the ROC curve. The model was calibrated using the Hosmer-Lemeshow test for logistic regression.

The sensitivity, specificity, and likelihood ratios of the model were calculated for different cutoffs. The accuracy of the model was also calculated by dividing the sum of the true positives and negatives by the total population.

Validation cohort

The GEIH-CDI score was tested using a validation cohort. A new prospective cohort was recruited from 16 hospitals of the GEIH (12 of which had participated in the derivation cohort) between September 2015 and February 2016. The researchers collected a set of variables from the patients without knowing the results of the model from the derivation cohort (although the coordinating center had full knowledge of the results). The same inclusion criteria and definitions of CDI were applied.

All analyses were performed using Stata 14.1 for Windows.

Results

During the study period (July 2014 to February 2015), a total of 581 cases of CDI were recorded in the derivation cohort. Of these, 263 were excluded for various reasons: difficulties affecting the researchers (eg, vacations, workload) in 100 cases, refusal of informed consent or impossibility of obtaining it in 58 cases, difficulties with follow-up in 55 cases, probable death during the following days in 25 patients, and other situations in 25 cases. Therefore, the final sample included 318 patients. Of these, patients were excluded because they died before 30 days (22 cases), were participating in clinical trials (15 cases), received fidaxomicin after inclusion (4 cases), and were lost to follow-up or had insufficient data (3 cases). The remaining 274 patients were identified based on detection of toxin in stool in 152 cases, NAAT in 116 cases, and culture in only 6 cases. Mean (SD) age was 67.1 (19.0) years, 55% of patients were women, and 29 (10.6%) had had at least 1 other episode of CDI during the previous year. Recurrence of CDI during follow-up was recorded in 70 cases (25.6%, 63 diagnosed using microbiological techniques and 7 by response to treatment) (Figure 1). A single recurrence was recorded in 51 patients, 2 recurrences in 13 patients, 3 recurrences in 5 patients, and 4 recurrences in 1 patient.

Predictive model

We compared variables in patients who experienced recurrence with those who did not (Table 1). We started with a maximum model comprising the variables age, sex, positive toxin result, dependence according to the Katz index, previous episodes of CDI, underlying disease (analyzed using a composite variable that included presence of heart failure, kidney disease, diabetes, cancer, or immunosuppression), maximum temperature at the time of diagnosis, and persistence of diarrhea after 5 days of antibiotic treatment for CDI. The final

model included the following variables: age (<70 years [0 points], 70-79 years [1 point], and ≥80 years [2 points]), history of CDI during the previous year (2 points), persistence of diarrhea on the fifth day of treatment (2 points), and positive result in direct detection of toxin in stool (1 point) (table 2, Figure 2). The points for each variable were added, so that the GEIH-CDI score ranged from 0 to 7 points, with higher scores indicating a greater risk of recurrence

The score was calculated for each of the patients included in the cohort, and the scores were compared with the risk of recurrence observed for each score level. A greater risk was observed for the higher score ranges (Figure 3). The area under the ROC curve was 0.73 (0.66 – 0.80) for the original model and 0.72 (0.65 – 0.79) for simplified model and the Hosmer-Lemeshow goodness-of-fit test p value was 0.704.

With a cutoff of 4 points, sensitivity was 48.6% and specificity was 84.2%. With a cutoff of 2 points, sensitivity reached 91.4%, although specificity fell to 34.5%. The positive and negative likelihood ratio of the model was 3.08 and 0.61, respectively, and accuracy was 0.75.

Given that some patients in the derivation cohort died before recurrence and, therefore, were excluded, we performed a sensitivity analysis including these cases. The results obtained were identical, with an area under the ROC curve of 0.71 (0.64 – 0.78). Also, because the free toxin test was not done in fifty-one patients of the derivation cohort we performed a sensitive analysis excluding these patients. Again, the performance of the model showed no changes: area under the ROC curve of 0.74 (0.67 - 0.81).

The validation cohort included 183 patients whose demographic characteristics were similar to those of the derivation cohort. Mean age was 67.3 (19.0) years, 53% of patients were women, and 9.8% had had an episode of CDI during the previous year. The number of patients with recurrences was very similar to that in the derivation cohort (25.1%). The results of applying the model in the validation cohort with the derivation cohort can be seen in Figure 3. The accuracy of the model was similar (0.77). With the same cutoff of 4 points, sensitivity reached 50% and specificity 86%, whereas the area under the ROC curve was 0.75 (0.67 – 0.83). Finally, Table 3 summarizes the functioning of the predictive model including both cohorts. A composite score based on 3 ranges makes it possible to select a low-risk group (0-1 points; 29.9% of patients; risk of recurrence, 8.8%), an intermediate-risk group (2-3 points; 46.4% of patients; risk of recurrence, 22.3%), and a high-risk group (≥4 points; 23.9% of cases; risk of recurrence, 52.8%). The accuracy of the model applied to both cohorts was 0.76.

Discussion

Our study confirms that one-quarter of patients diagnosed with CDI and treated in a hospital experience a subsequent episode during the 2 months following completion of treatment. Even after excluding patients who have had a previous episode, we found that this proportion reached 21.2%. Our clinical prediction tool makes it possible to identify a high-risk population that could benefit from recently marketed or forthcoming treatments that have proven to reduce the risk of recurrence [11,12] but whose cost is very high and limits widespread administration,[14,15], as well fecal microbiota transplantation.

Several models for prediction of recurrence of CDI have been investigated; however, these have not been consolidated in clinical practice owing to their limitations. The accuracy reported by D'Agostino et al.[16] was somewhat lower than that found in our study, although this was not validated externally. In addition, the model was obtained from a cohort comprising patients participating in pivotal clinical trials of fidaxomicin, thus likely implying major biases. Hu et al.[17] reported details of their model, which included age, severity (measured according to the Horn index), and creatinine. However, the number of patients included in the validation cohort was small and the proportion of recurrences very different from that observed in the derivation cohort, in which it seems reasonable to suspect bias, given that the frequency of recurrence reached 50%. One recent study did not specifically consider recurrence as an outcome measure but included it within a broader category known as "complicated CDI". Furthermore, prediction depended on a specific laboratory test.[18] Finally, other attempts were affected by poor accuracy or could not be applied in clinical practice.[19-21]

The main strengths of our prediction tool are the size of the derivation cohort, the fact that patients were recruited from several centers, the low probability of inclusion bias (since the recurrence rate corresponds with that reported in the literature), the low number of losses to follow-up, and confirmation of the model in a validation cohort. Furthermore, the tool can be applied at the bedside without the need for laboratory tests other than routine diagnostic tests. Advanced age,[8] a history of previous episodes, [22] and direct detection of toxin in stool (compared with cases diagnosed using NAAT)[23] are known risk factors for recurrence. This last fact supports the policy of including toxin immunoassay in the diagnostic algorithm as it has been recently recommended.[24] Patients with negative toxin detection diagnosed by NAAT could have fewer recurrences due to a lower toxin and a bacterial burden but also due to an earlier detection and treatment of the disease. [23]Persistence of diarrhea has not been reported to be a risk factor for recurrence, probably because almost all studies on risk factors for recurrence of CDI have been retrospective and this information was not available. This variable is not present at diagnosis. However, in our opinion, it allows for more dynamic management that is compatible with routine clinical practice. For example, new treatments with monoclonal antibodies against *C. difficile* toxins are administered during the course of treatment with *C. difficile*–specific antibiotics.[12]

Interestingly our predictive tool can identify some patients on first episode of CDI having higher risk of CDI recurrence than some patients on the second episode.

Our study is subject to a series of limitations. The accuracy of the model is not very high; therefore, with a high cutoff, sensitivity is low. Nevertheless, the cutoff can be modified depending on how the model is to be applied. The laboratory methods were not

homogeneous due to the multicenter design of the study. In fact in some patients the free toxin test in feces was not performed. However the model performed well after excluding these patients. It could also be argued that patients diagnosed by positive NAAT but negative direct toxin tests could be merely colonized. Nevertheless, only symptomatic patients were accepted to have CDI or CDI recurrence and this was emphasized to investigators. The study was restricted to Spain, and many of the centers that participated in the derivation cohort also participated in the validation cohort. Finally, the variable time to resolution of diarrhea may not always be fully consistent or objective, since the fact that patients can experience changes in their intestinal rhythm can make it difficult to identify on which day diarrhea resolved. Greater accuracy might be obtained by combining this model with specific biomarkers of CDI.[25,26]

In summary, prediction of recurrence of CDI is increasingly important owing to its potential role in the management of patients and in decisions on therapy.[27]The prediction tool we propose may be useful for clinicians treating patients with CDI.

Declarations

Funding: This study was carried out by internal funding

Competing Interests: JC has received consultancy and speaking fees from Astellas Pharma and MSD.

CHC has received speaking fees from Astellas Pharma.

JGA has received consultancy and speaking fees from MSD.

MS has received consultancy and speaking fees from Astellas Pharma and MSD

Ethical Approval: Local ethics committees approved the study

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Fig 1. Flow chart of cases (derivation cohort)

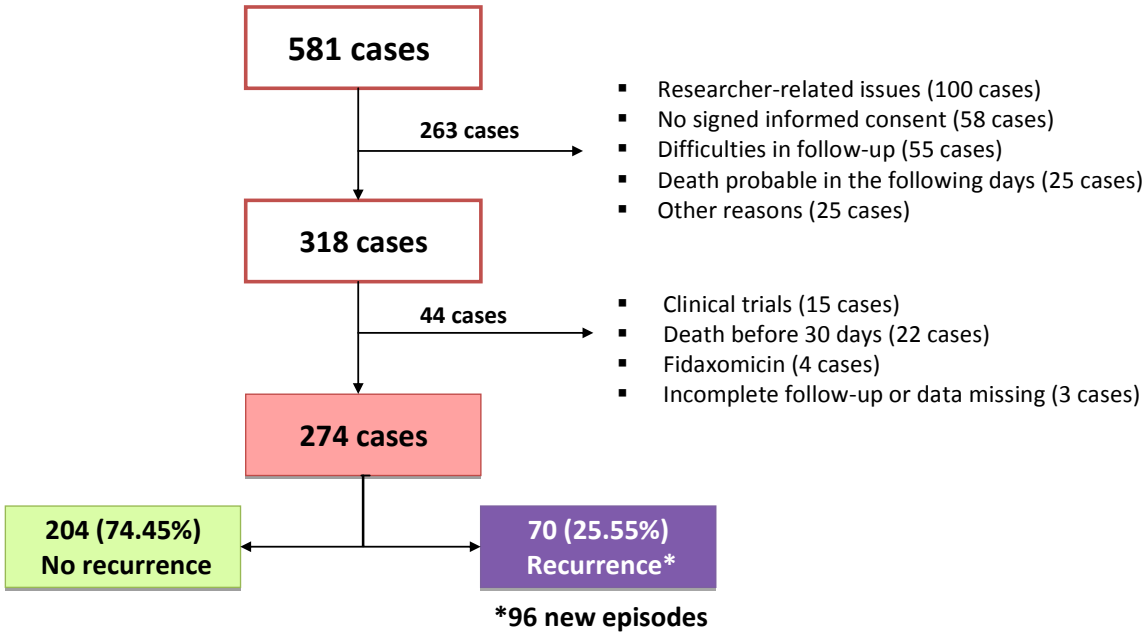

Fig 2. GEIH-CDI score

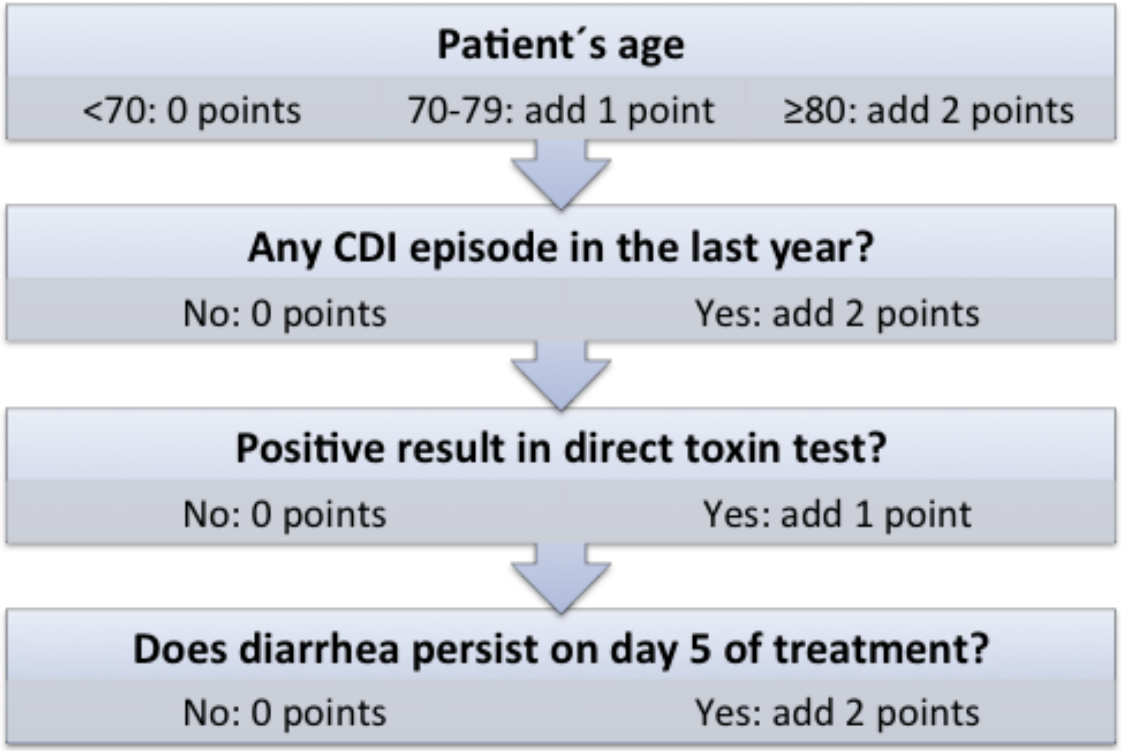

Fig 3. Risk of recurrence and GEIH-CDI score. Black bars: derivation cohort; grey bars: validation cohort

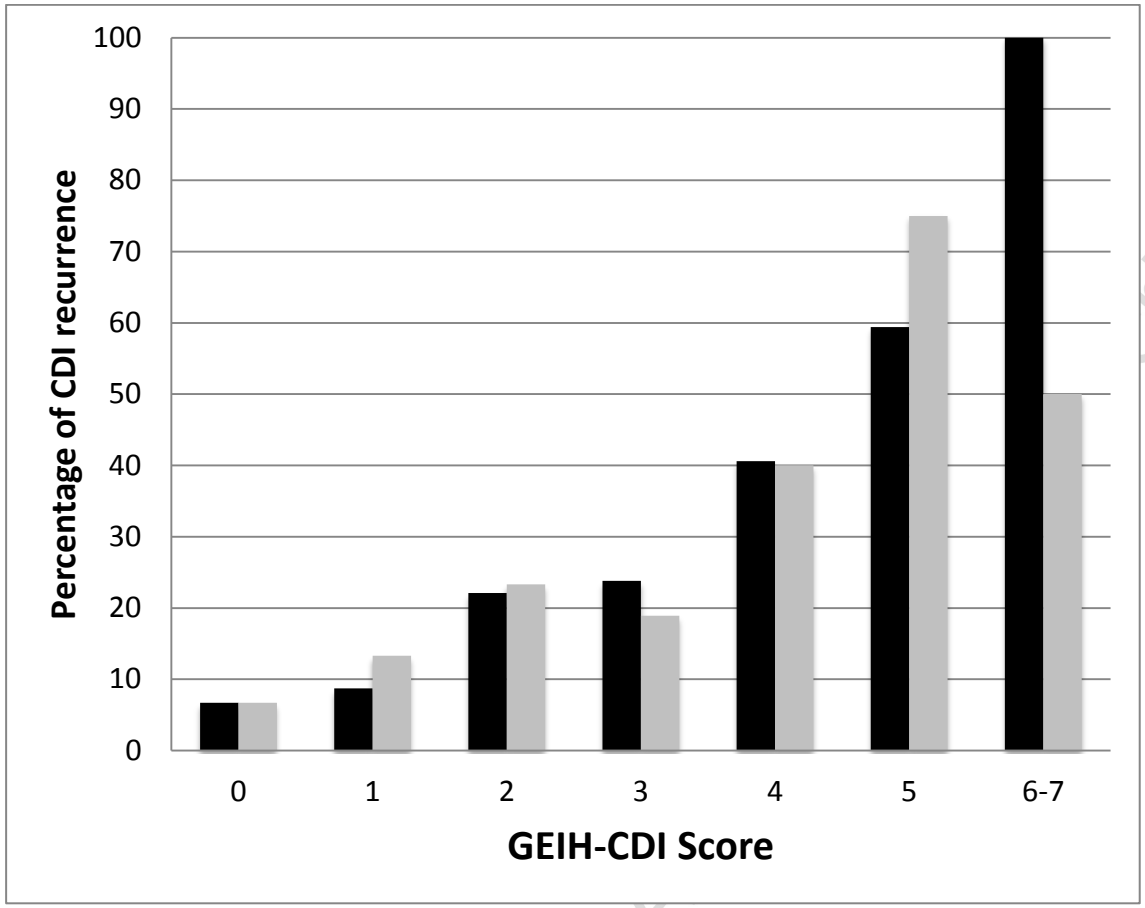

Table 1. Derivation cohort: comparison between patients with and without recurrence

Variable		No recurrence (204)	Recurrence (70)	p
Sex	Male (123)	98 (79.7)	25 (20.3)	0.074
	Female (151)	106 (70.2)	45 (29.8)	
Age	<70 (128)	104 (81.3)	24 (18.8)	0.015
	70-79 (51)	39 (76.5)	12 (23.5)	
	≥80 (95)	61 (64.2)	34 (35.8)	
Time to diagnosis since the onset of symptoms	<7 days (190)	148 (77.9)	42 (22.1)	0.037
	≥7 days (82)	54 (65.9)	28 (34.1)	
Previous episode	No (245)	189 (77.1)	56 (22.9)	0.003
	Yes (29)	15 (51.7)	14 (48.3)	
Type of episode[1]	Nosocomial (138)	102 (73.9)	36 (26.1)	0.979
	Health care–acquired (68)	51 (75.0)	17 (25.0)	
	Community-acquired (68)	51 (75.0)	17 (25.0)	
Temperature (maximum in the first 24 h)	<38 (203)	155 (76.4)	48 (23.6)	0.156
	≥38 (67)	45 (67.6)	22 (32.4)	
No. of bowel movements	Ileus (2)	2 (100)	0	0.408
	3 (56)	43 (76.8)	13 (23.2)	
	4-6 (127)	93 (73.2)	34 (26.8)	
	7-10 (52)	35 (67.3)	17 (32.7)	
	>10 (32)	27 (84.4)	5 (15.6)	

Direct detection of toxin in feces	Positive (152)	105 (69.1)	47 (30.9)	0.023
	Negative/not performed (122)	99 (81.1)	23 (18.9)	
Severity	Mild-moderate (201)	154 (76.6)	47 (23.4)	0.206
	Severe or complicated (71)	49 (69.0)	22 (31.0)	
Incontinence (fecal)	No (163)	131 (80.4)	32 (19.6)	0.005
	Yes (109)	71 (65.1)	38 (34.9)	
Comorbidities	Inflammatory bowel disease (15)	13 (86.7)	2 (13.3)	0.274
	Cancer (71)	53 (74.6)	18 (25.4)	0.915
	Immunosuppression[2] (64)	51 (79.7)	13 (20.3)	0.256
	Heart failure (48)	33 (68.1)	15 (31.9)	0.271
	Kidney disease (49)	34 (69.4)	15 (30.6)	0.398
	Diabetes (56)	44 (78.6)	12 (21.4)	0.370
	Dementia (32)	21 (65.6)	11 (34.4)	0.223
Laboratory	Leukocyte count (264)	11,299.8 (8603.5)	12,960.1 (8476.9)	0.172
	Creatinine (mg/L) (264)	1.2 (1.1)	1.2 (1.4)	0.874
	Proteins (g/L) (175)	5.7 (0.9)	5.5 (1.0)	0.096
	Albumin (g/L) (156)	3.0 (0.7)	3.0 (0.7)	0.840
	C-reactive protein (mg/L) (187)	60.8 (78.3)	82.8 (76.2)	0.094
Able to dress	Yes (186)	147 (79.0)	39 (21.1)	0.012
	No (88)	57 (64.8)	31 (35.2)	
Able to walk several blocks	Yes (179)	142 (79.3)	37 (20.7)	0.011
	No (95)	62 (65.3)	33 (34.7)	
Time until resolution of diarrhea	<5 days (159)	131 (82.4)	28 (17.6)	0.000
	≥5 days (124)	72 (63.2)	42 (36.8)	
Treatment	Metronidazole (152)	119 (78.3)	33 (22.7)	0.556

	Vancomycin (76)	52 (68.4)	24 (31.6)	
	Metronidazole plus vancomycin (31)	22 (71.0)	9 (29.0)	
	Metronidazole followed by vancomycin (10)	7 (70.0)	3 (30.0)	
Continue on antibiotics (on day 7)	Yes (128)	96 (75.0)	32 (25.0)	0.955
	No (144)	107 (74.3)	37 (25.7)	
Continue on proton pump inhibitors (on day 7)	Yes (163)	131 (80.4)	32 (19.6)	0.017
	No (110)	67 (67.3)	33 (32.7)	

1. Nosocomial: CDI symptoms that were not present on the day of admission appear during hospitalization (at least 48 hours after admission) or within 3 days after discharge. Health care–associated: hospitalization in the last 3 months or living in a residence or periodic dialysis or IV ambulatory treatment or outpatient treatment. Community-acquired: all other cases
2. HIV infections with less than 200 CD4 cell count/mm^3 or treatment with immunosuppressive drugs

Table 2. Logistic model. Derivation cohort

	Coefficient	95% Confi.interval	Score
Constant	-2.7	-3.6 to -1.9	-
Age 70-79	0.49	0.35 - 1.33	1
Age ≥80	1.17	0.50 - 1.83	2
Toxin-positive	0.65	0.09 - 1.40	1
Previous episode	1.30	0.45 - 2.14	2
Diarrhea on day 5	1.18	0.58 - 1.78	2

Table 3. Risk of recurrence in the study population (derivation and validation cohorts) for different score values.

Derivation cohort (273)[1]					Validation cohort (182)[1]				Both cohorts (455)						
Score	**No recurrence**	**Recurrence**	**Cases (%)**	**Recurrence (%)**	**No recurrence**	**Recurrence**	**Cases (%)**	**Recurrence (%)**	**No recurrence**	**Recurrence**	**Cases (%)**	**Recurrence (%)**	**Composite score**	**Cases (%)**	**Recurrence (%)**
6-7	0	2	0.7	100	3	3	3.3	50	3	5	1.8	62.5			
5	13	19	11.7	59.4	4	12	8.8	75	17	31	10.5	64.6	4-7 (high risk)	23.7	52.8
4	19	13	11.7	40.6	12	8	11.0	40	31	21	11.4	40.4			
3	53	15	24.9	22.1	30	7	20.3	18.9	83	22	23.1	21.0	2-3 (intermediate risk)	46.4	22.3
2	48	15	23.1	23.8	33	10	23.6	23.3	81	25	23.3	23.6			
1	42	4	16.8	8.7	26	4	16.5	13.3	68	8	16.7	10.5	0-1 (low risk)	29.4	8.8
0	28	2	11.0	6.7	28	2	16.5	6.7	56	4	13.2	6.7			

1. One case in both the derivation cohort and the validation cohort was not included in the model because of lack of data for one of the variables included in the score.

1
2