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【 ORIGINAL ARTICLE 】

Clinical Usefulness of the "MN Criteria" - the *Clostridioides difficile* Infection Severity Scoring System - in the Japanese Setting

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Abstract:

Objective The severity of *Clostridioides difficile* infection (CDI) is an important prognostic factor. The "MN criteria," proposed in Japan in 2017, attempted to remedy the shortfalls in the reported guidelines proposed globally to determine CDI severity. We therefore assessed the accuracy of the MN criteria and validated the important factors associated with predicting CDI severity.

Methods Sixty-six CDI cases were investigated retrospectively at a Japanese University Hospital from January 2015 to December 2018. The fulminant cases were screened out, and the non-fulminant cases were classified according to their severity stages using the nine variables included in the MN criteria. Clinical events, such as death within 28 days, colectomy, and admission to the intensive care unit, were evaluated. First, the sensitivity and specificity of the MN criteria for predicting clinical events were determined. The relationships between clinical events and the explanatory variables were then evaluated through univariate and multivariate analyses.

Results The screening of the fulminant cases and classification of the non-fulminant cases into mild/moderate and severe/super severe cases resulted in a sensitivity of 1.00 and a specificity of 0.89. Univariate and multivariate analyses revealed a significant association of the serum albumin (Alb) level as well as white blood cell (WBC) count with clinical events.

Conclusion The findings provide evidence supporting the accuracy of the MN criteria in predicting CDI severity and show that the Alb and WBC are important variables in predicting CDI severity.

Key words: MN criteria, *Clostridioides difficile*, *Clostridioides difficile* infection, severity scoring system

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Introduction

Clostridioides difficile infection (CDI) is one of the most common causes of healthcare-associated infections in adults (1, 2). If unrecognized or untreated, CDI can be fatal and, in severe cases, may necessitate interventions, such as surgical treatments and hospitalization in the intensive care unit (ICU). Therefore, several guidelines to assess the severity of CDI by combining clinical data, laboratory data, and image data have been reported (3-7).

The first major guidelines to be published were the Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) guidelines in 2010 (3), followed by the American College of Gastroenterology (ACG) in 2013 (4), the European Society of Clini-

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Table 1. The MN Criteria: the Severity Scoring System for *Clostridioides difficile* Infection (9).

	0	1	2	3
Age (years)	<65	≥65	-	-
Abdominal pain or distension	No	Yes	-	-
BT (°C)	<37	37-37.4	37.5-38.4	≥38.5
Diarrhea (Bristol scale ≥5)	0-2 (hematochezia+1)	3-9 (hematochezia+1)	≥10 (hematochezia+1)	-
WBC (/μL)	<12,000	12,000-14,999	15,000-19,999	≥20,000
eGFR (mL/min/1.73 m^2)	≥80	50-79	30-49	<30 or dialysis
Alb (g/dL)	≥3.0	2.5-2.9	2.0-2.4	<2.0
Image findings ・Intestinal dilation ・Intestinal wall thickening ・Adipose tissue invasion around the intestinal tract ・Ascites that cannot be explained by other causes ・Pseudomembranes	No	-	Yes	-

Severity stages are determined by the total score, as described below.
Mild: ≤4 points; moderate: 5-9 points; severe: 10-13 points; super severe: ≥14 points.
However, the cases with hypotension, shock, ileus, or toxic megacolon are classified as fulminant.
BT: body temperature, WBC: white blood cell, eGFR: estimated glomerular filtration rate, Alb: serum albumin

cal Microbiology and Infectious Diseases (ESCMID) in 2014 (5), the World Society of Emergency Surgery (WSES) in 2015 (6), and the Australasian Society for Infectious Diseases (ASID) in 2016 (7). These guidelines list several factors for diagnosing CDI, and the severity detection following these guidelines is simple and applicable for clinical use; however, cases with at least one of the factors of body temperature (BT) ≥38.5°C, white blood cell (WBC) count ≥15,000/μL, and serum creatinine level (SCr) ≥1.5× base line occasionally result in a misdiagnosis of mild CDI as severe.

To address these shortfalls, a more subdivided scoring system called the "MN criteria" was proposed as the first Japanese CDI severity scoring system in 2017. These criteria were introduced in the Japanese Clinical Practice Guidelines to manage *Clostridioides* (*Clostridium*) *difficile* infections (8). The MN criteria are based on nine categorical variables: age, abdominal pain/distension, BT, diarrhea count, hematochezia, WBC, estimated glomerular filtration rate (eGFR), serum albumin (Alb) level, and image findings; each variable is scored on a 3-point scale, as shown in Table 1 (9). These criteria were developed in line with the previous severity diagnosis systems while taking into account Japan's current medical situation, such as raising the age standard, owing to Japan's super-aging societal status (10). However, there are only few reports on the accuracy of the MN criteria, and the categorical variables used by the MN criteria have not been fully validated to detect severe cases in Japanese medical facilities.

Therefore, in the present study, we examined the potential of the MN criteria to predict the risk of severity in CDI patients and determine the important explanatory variables for the prediction.

Materials and Methods

Ethical approval

This clinical trial was approved by the Clinical Trial Management Center of Nagoya City University (NCU) Hospital and complied with the Declaration of Helsinki. The option to opt out was clearly defined and was always available to patients by presenting this information on the website.

Study design and patients

This retrospective study was conducted at the NCU Hospital (Aichi, Japan) from January 1, 2015, to December 31, 2018. Patients with CDI [toxin-positive stool test using the rapid membrane enzyme immunoassay performed with the commercially available C. DIFF QUIK CHEK COMPLETE kit (Abbott, Chicago, USA) and a clinical diagnosis] were recruited. Patients under 18 years old, outpatients, and patients with recurrent CDI were excluded. Recurrence of CDI was indicated by toxin positivity or treatment with antibiotics against *C. difficile* (oral fidaxomicin, oral vancomycin, or either parenteral or oral metronidazole) within eight weeks prior to the enrollment. Patients' clinical data were obtained on the first day of antibiotic treatment against *C. difficile*. If data were not available on the first day of treatment, laboratory data measured on the day before and the computed tomography (CT) or X-ray images obtained within the period from the onset of CDI to the third day after the start of treatment were used.

The primary outcome was defined as clinical events, such as developmental colectomy, admission to the ICU, or death within 28 days from the first day of antibiotic treatment against *C. difficile*. In brief, CDI cases with hypotension or shock, ileus, or toxic megacolon were screened out as fulmi-

nant; non-fulminant cases were scored according to the MN criteria and classified into four severity stages. Hypotension or shock was judged when one of the following criteria was met: (A) systolic blood pressure was ≤90 mmHg; (B) normal systolic blood pressure ≥150 mmHg and blood pressure decreased by ≥60 mmHg from normal; or (C) normal systolic blood pressure ≤110 mmHg and blood pressure decreased by ≤20 mmHg from normal. Furthermore, shock was defined when three or more of the following criteria were satisfied: (a) a heart rate of ≥100 beats per min; (b) weak pulse; (c) delayed refilling of claw bed capillaries; (d) disturbance of consciousness; (e) oliguria/anuria; or (f) pallor and cold sweat or fever with a temperature of ≥39°C. Next, we analyzed the impact of fulminant screening or classification of the non-fulminant cases as mild/moderate and severe/super severe on the incidence of clinical events. Finally, the relationship between the nine explanatory variables and the clinical events was evaluated through univariate and multivariate analyses.

Statistical analyses

Statistical analyses were performed using the R statistical software program, version 4.0.2. R packages "psych" and "Hmisc" were used for descriptive statistics, such as the median and interquartile range (IQR). Outliers were detected using the Grubbs' test function available in the R package "outliers." The Shapiro-Wilk test and Q-Q plot were applied to determine the normality of each numerical variable. Statistical significance was assessed by means of the two-sample *t*-test, Mann-Whitney U test, or Fisher's exact test using the original R functions or the package "MASS." In terms of the Fisher's exact test, odd ratios (ORs) and 95% confidence intervals (CIs) were calculated, with a p value <0.05 considered statistically significant. In addition, for the parametric variables, statistical significance was set at a p value <0.05. Regarding the univariate analysis, Cramér's V coefficient was used to determine the correlation between clinical events and the categorical variables classified by the MN criteria, as shown in Table 1. Two-way cross tabulation and the above-mentioned analyses were carried out using the R package "gmodels" and "lsr," respectively. The rank correlation ratio was calculated using the following equation: square root of the Kruskal-Wallis chi-squared divided by the degree of freedom. The Kruskal-Wallis rank sum test was performed using the original R package "stats". The correlation ratio was calculated using means of the R package 'heplots' and expressed as eta-squared (η^2). For the multivariate analysis, the second method of quantification (quantification II), as described by Tanaka (11), was used to calculate the category scores and contribution rates of the categorical variables. This method is applicable for small sample sizes. The R source code was provided by Professor Shigenobu Aoki of Gunma University and downloaded from the following website: http://aoki2.si.gunma-u.ac.jp/R/src/qt2.R, encoding="euc-jp".

Results

Disposition of CDI cases according to the MN criteria

In this study, 66 CDI cases were examined; the disposition of the cases is shown in Fig. 1. Ten cases characterized by shock or hypotension, ileus, or toxic megacolon were screened as fulminant cases. In the remaining 56 non-fulminant cases, severity was scored based on data pertaining to the 9 variables. All data were able to be obtained in 22 cases and classified into 4 severity stages: mild [≤4 points (n=6)], moderate [5-9 points (n=11)], severe [10-13 points (n=5)], and super severe [≥14 points (n=0)].

Impact of fulminant screening on the incidence of clinical events

The characteristics and outcomes of the 66 CDI cases [fulminant cases (n=10), non-fulminant cases (n=56)] are shown in Table 2. There was no marked difference in gender between them; however, the patients in the fulminant category were older than those in the non-fulminant category (p =0.001). Clinical events occurred in 5 [4 deaths and 1 colectomy/ICU admission (the same patient)] of the 10 fulminant cases and 5 (5 deaths) of the 56 non-fulminant cases. This indicates a higher risk of clinical events in the fulminant category than in the non-fulminant category [OR of 9.62 (95% CI, 1.64-61.43); p=0.005].

The clinical event-free survival depicted by the Kaplan-Meier curve is shown in Fig. 2A. Clinical events were more likely to occur earlier and with greater incidence in the fulminant cases [median, 2 days (IQR, 2-3 days)] than in the non-fulminant cases [median, 10 days (IQR, 7-21 days)].

Impact of mild/moderate and severe/super severe classification on the incidence of clinical events

The characteristics and outcomes of the 22 non-fulminant cases [mild/moderate cases (n=17), severe/super severe cases (n=5)] are shown in Table 3. The cases were categorized based on a previous study (12). There were no marked differences in gender or age between them. Clinical events occurred in 3 of the 5 severe/super severe cases and 0 of the 17 mild/moderate cases. This indicates a higher risk of clinical events in the severe/super severe category than in the mild/moderate category (OR, not estimated; p=0.006). Classification performed using the MN criteria resulted in a sensitivity of 1.00 and a specificity of 0.89.

The clinical event-free survival depicted by the Kaplan-Meier curve is shown in Fig. 2B. Clinical events occurred early to late [median, 10 days (IQR, 6-16.5 days)], and the incidence tended to be high in the severe/super severe cases. All 3 cases in which clinical events occurred had 11 points, the highest MN score in this study.

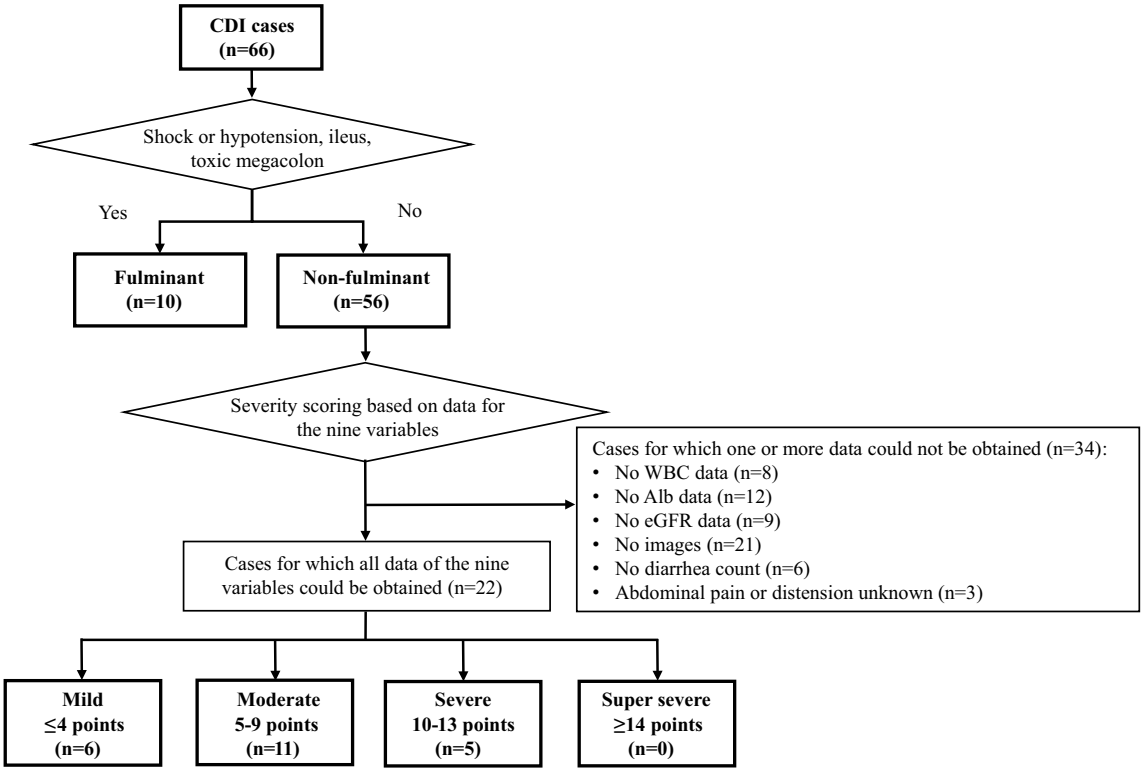

Figure 1. **Flow chart of the disposition of the cases included in this study according to the MN criteria. Alb: serum albumin; CDI: *Clostridioides difficile* infection; eGFR: estimated glomerular filtration rate; WBC: white blood cell**

Table 2. **Patient Characteristics for Fulminant and Non-fulminant Cases.**

Characteristic	Fulminant Number of cases (%) or median [IQR]		Non-fulminant Number of cases (%) or median [IQR]		p value
Number of patients	10		56		
Shock or hypotension	10	(100.0%)	0	(0.0%)	
Ileus	0	(0.0%)	0	(0.0%)	
Toxic megacolon	0	(0.0%)	0	(0.0%)	
Sex (male)	6	(60.0%)	32	(57.1%)	1.000
Age (years)	87	[79-88]	71	[56-80]	0.001*
Clinical events	5	(50.0%)	5	(8.9%)	0.005*
Death	4	(40.0%)	5	(8.9%)	0.024*
Colectomy	1#	(10.0%)	0	(0.0%)	0.152
Care in ICU	1#	(10.0%)	0	(0.0%)	0.152

*p<0.05 in Fisher's exact test or Mann-Whitney U test.

#Both clinical events occurred in the same patient.

ICU: intensive care unit, IQR: interquartile range

Relationship between the explanatory variables of the MN criteria and clinical events in the non-fulminant cases

A cross-tabulation of the 9 variables of the MN criteria and the incidence of clinical events in the 56 non-fulminant cases is shown in Table 4. There was a high tendency for clinical events to occur in cases with a lower Alb, higher WBC, lower eGFR, higher diarrhea count, presence of hematochezia, image findings, a lower BT, the absence of abdominal pain or distension, and age below 65 years old. In comparison to the allocation of the points in the MN criteria, which assigned high points for a higher BT, the presence of abdominal pain or distension, and an age of more than 65 years old, the opposite trend was observed.

According to a univariate analysis, the correlation be-

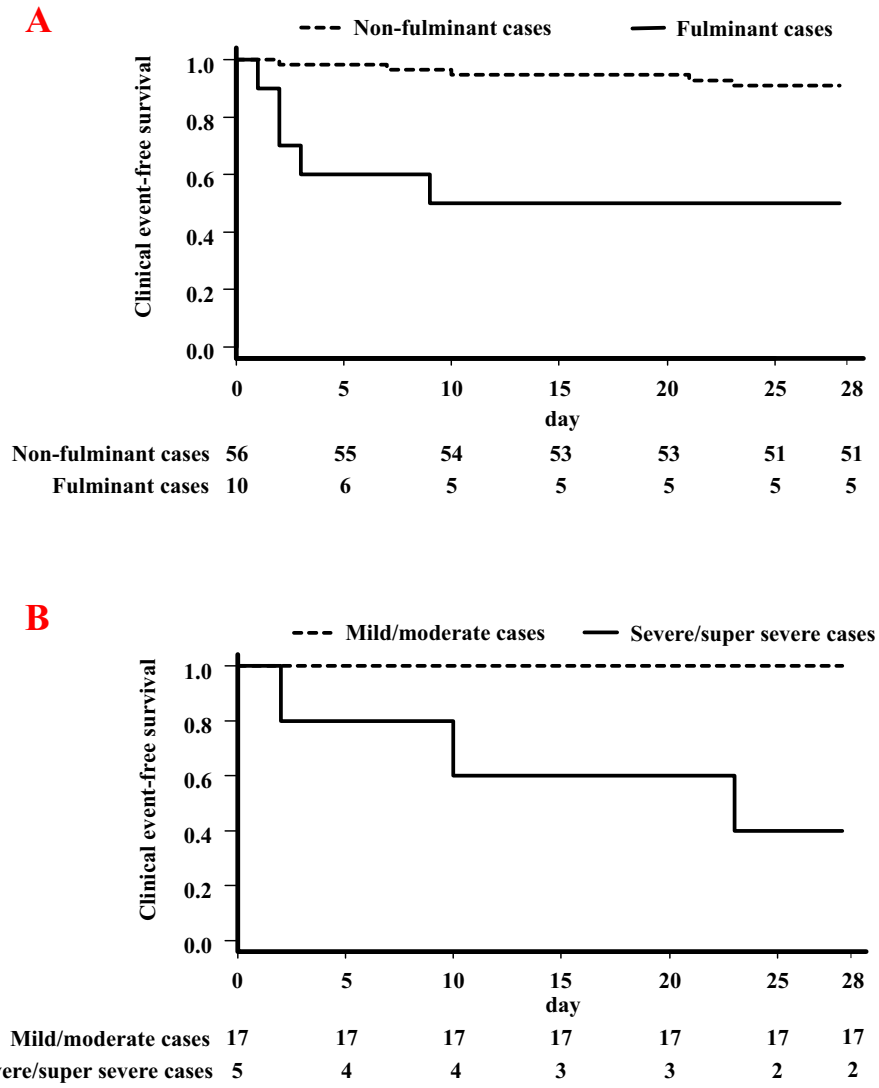

Figure 2. **Kaplan-Meier curve of the incidence of clinical events in the non-fulminant (n=56) and fulminant cases (n=10) and in the mild/moderate (n=17) and severe/super severe cases (n=5). (A) Clinical events were more likely to occur earlier and with greater incidence in the fulminant cases [median, 2 days (IQR, 2-3 days)] than in non-fulminant cases [median, 10 days (IQR, 7-21 days)]. (B) Clinical events occurred early to late [median, 10 days (IQR, 6-16.5 days)], and the incidence tended to be high in the severe/super severe cases.**

Table 3. **Patient Characteristics in Mild/Moderate and Severe/ Super Severe Cases.**

Characteristic	Mild/moderate Number of cases (%) or median [IQR]		Severe/super severe Number of cases (%) or median [IQR]		p value
Number of patients	17		5		
MN score	6	[4-8]	11	[10, 11]	0.001*
Sex (male)	10	(58.8%)	3	(60.0%)	1.000
Age (years)	74	[65-85]	72	[70-79]	0.942
Clinical events	0	(0.0%)	3	(60.0%)	0.006*
Death	0	(0.0%)	3	(60.0%)	0.006*
Colectomy	0	(0.0%)	0	(0.0%)	-
Care in ICU	0	(0.0%)	0	(0.0%)	-

*p<0.05 in Fisher's exact test or *t*-test

ICU: intensive care unit, IQR: interquartile range

Table 4. Cross-tabulation of the Explanatory Variables of the MN Criteria and Clinical Events in the 56 Non-fulminant Cases.

Variables	Category	Clinical event	No event	Number of cases
Alb (g/dL)	≥3.0	0%	100%	15
	2.5-2.9	0%	100%	14
	2.0-2.4	27%	73%	11
	<2.0	50%	50%	4
	ND	0%	100%	12
WBC (/μL)	<12,000	3%	97%	34
	12,000-14,999	25%	75%	8
	15,000-19,999	0%	100%	1
	≥20,000	40%	60%	5
	ND	0%	100%	8
eGFR (mL/min/1.73 m^2)	≥80	11%	89%	19
	50-79	7%	93%	15
	30-49	0%	100%	5
	<30 or dialysis	25%	75%	8
	ND	0%	100%	9
Diarrhea count	0-2	9%	91%	22
	3-9	8%	92%	25
	≥10	33%	67%	3
	ND	0%	100%	6
Hematochezia	No	6%	94%	50
	Yes	33%	67%	6
	ND	-	-	0
Image	No	0%	100%	12
	Yes	17%	83%	23
	ND	5%	95%	21
BT (°C)	<37	14%	86%	22
	37-37.4	7%	93%	15
	37.5-38.4	8%	92%	13
	≥38.5	0%	100%	6
	ND	-	-	0
Abdominal pain or distension	No	11%	89%	36
	Yes	0%	100%	17
	ND	33%	67%	3
Age (years)	<65	17%	83%	23
	≥65	3%	97%	33
	ND	-	-	0

Alb: serum albumin, WBC: white blood cell, eGFR: estimated glomerular filtration rate, BT: body temperature, ND: no data

tween the nine variables and the clinical events was estimated using the Cramér's V coefficient, as shown in Table 5. The 56 non-fulminant cases and 22 non-fulminant cases for which all data pertaining to the 9 variables could be obtained were analyzed. The correlated variables (Cramér's V>0.25) were Alb (Cramér's V=0.531) and WBC (Cramér's V=0.425) in the 56 non-fulminant cases; and Alb (Cramér's V=0.824), WBC (Cramér's V=0.797), diarrhea count (Cramér's V=0.551), eGFR (Cramér's V=0.464), and BT (Cramér's V=0.279) in the 22 non-fulminant cases. Upon an analysis of the confounding between variables (Cramér's V>0.5), the diarrhea count was suggested to be a confounding factor with the WBC (Cramér's V=0.560) and Alb (Cramér's V=0.510).

According to a multivariate analysis, except for the diarrhea count, the correlation between the four variables (Alb, WBC, eGFR, and BT) and clinical events was analyzed using quantification II, as shown in Fig. 3. Quantification II was performed with a high correlation ratio (η=0.962) and a high percentage of correct classification (95.5%) in the 22 non-fulminant cases. The contribution ratios of these variables were as follows: Alb, 44%; WBC, 38%; eGFR, 13%; and BT, 6%, and the partial correlation coefficients for these variables were 0.86, 0.83, 0.60, and 0.33, respectively.

Table 5. Cramér's V Coefficient for Correlations between the Explanatory Variables of the MN Criteria and Clinical Events.

Variables	Non-fulminant (n=56)	Non-fulminant cases for which all data of the nine variables could be obtained (n=22)
Alb	0.531*	0.824*
WBC	0.425*	0.797*
eGFR	0.234	0.464*
Diarrhea count	0.197	0.551*
Hematochezia	0.195	0.105
Image	0.165	0.129
BT	0.153	0.279*
Abdominal pain or distension	0.120	0.057
Age	0.037	<0.001

* Cramér's V coefficient >0.25.

Alb: serum albumin, WBC: white blood cell, eGFR: estimated glomerular filtration rate, BT: body temperature

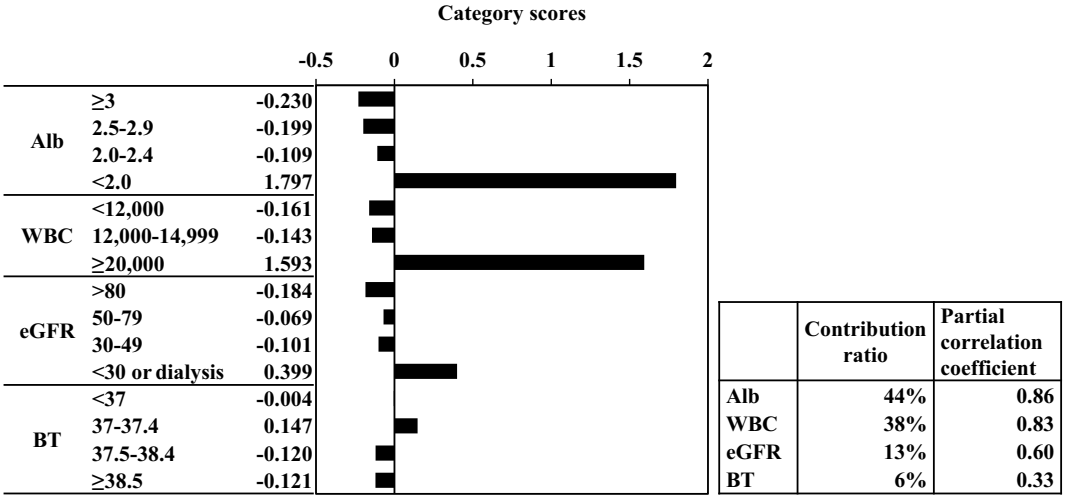

Figure 3. Correlation between the four explanatory variables and clinical events analyzed by quantification II. The contribution ratios of these variables were as follows: Alb, 44%; WBC, 38%; eGFR, 13%; and BT, 6%; the partial correlation coefficients for these variables were 0.86, 0.83, 0.60, and 0.33, respectively. Alb: serum albumin, BT: body temperature, eGFR: estimated glomerular filtration rate, WBC: white blood cell

Results of a post-hoc subgroup analysis of the relationship between the explanatory variables of the MN criteria and fulminant cases

The correlation between the nine variables and fulminant cases was estimated using the correlation ratio (eGFR, age, WBC, Alb, and BT), rank correlation ratio (diarrhea count), and Cramér's V coefficient (hematochezia, image, and abdominal pain or distension) in the 66 CDI cases. The following variables were correlated with fulminant cases: eGFR, 0.141; age, 0.121; WBC, 0.108; Alb, 0.103 (correlation ratio >0.1); diarrhea count, 0.203 (rank correlation ratio >0.2); and hematochezia, 0.365 (Cramér's V>0.25). BT (correlation ratio=0.007), images (Cramér's V=0.145), and abdominal pain or distension (Cramér's V=0.116) were not correlated with fulminant cases.

Discussion

Our analysis revealed that (1) the screening of fulminant cases and classification of non-fulminant cases into severity stages according to the MN criteria can accurately predict cases in which populations clinical events are likely to occur within 28 days, and (2) the Alb and WBC, which are included in the MN criteria, are highly correlated with clinical events.

The accuracy of the scoring system based on the MN criteria has also been analyzed in previous studies. Yamagishi et al. reported that classifying CDI cases into 2 groups - mild to moderate and severe to super severe, according to the MN criteria - resulted in a sensitivity of 0.40 and a specificity of 0.98 within a 28-day prognosis period and was superior to the Zar criteria (sensitivity of 0.24 and specific-

ity of 1.00) (12). They applied the scoring system while considering all cases, including the fulminant cases, as a single category. In the present study, screening the fulminant cases resulted in a sensitivity of 1.00 and specificity of 0.89 in the non-fulminant cases. We thus inferred that screening the fulminant cases would be able to improve the accuracy of predicting severe CDI cases. The IDSA/SHEA guideline 2021 also states that the "Definition of fulminant CDI is supported by: hypotension or shock, ileus, megacolon (13)", which is considered to be an internationally common fulminant discrimination method. Fulminant cases often require urgent attention; as noted in this study as well, there was a tendency for clinical events, such as colectomy, ICU admission, and death within 28 days, to occur earlier in fulminant cases than in non-fulminant cases, confirming the importance of screening for such cases.

As evident from several laboratory studies, the Alb, WBC, and SCr are major CDI mortality risk factors, similar to our findings; however, the association between these factors and death differs among reports. For example, Solomon et al. reported that a WBC over 20,000/μL and SCr over 1.5 mg/dL were major CDI mortality risk factors (14); in contrast, Wilson et al. reported that an Alb <2.5 g/dL but not the WBC or SCr was a major risk factor (15). These results suggest that although there is no unified opinion on the role of these factors, they are correlated with the severity of CDI. Competing effects between these factors or other characteristics of the patients, such as whether or not they are immunocompromised, may exist. Regarding variables other than the Alb and WBC, which had a strong correlation, the eGFR was shown to be weakly correlated, and the remaining variables were poorly or negatively correlated with clinical events in our study. We hypothesize that this discrepancy is due to the fact that, in the 66 CDI cases, the eGFR, age, and hematochezia were strongly correlated with fulminant cases, as observed in the post-hoc subgroup analysis. Because fulminant cases were screened first, it is possible that the effects of these variables were weak when it came to scoring only non-fulminant cases.

Several limitations associated with the present study warrant mention. First, the study was retrospective, and the sample size was small owing to the lack of data. Therefore, we conducted an analysis that was possible even with a small sample size and verified the usefulness of the MN criteria from various angles. The univariate analysis indicated that the Alb and WBC had a strong correlation with clinical events in the 56 non-fulminant cases and the 22 non-fulminant cases; furthermore, the multivariate analysis yielded the same result. Even with this sample size, we observed that the accuracy of the MN criteria is high and a difference exists in the strength of the contributions of these variables to clinical events. We therefore propose validating this finding using a large sample size. Second, this study was conducted before the methods of the *C. difficile* toxin test were improved. Currently, if a stool test presents both antigen-positive and toxin-negative results with a rapid membrane enzyme immunoassay, a nucleic acid amplification test is performed to detect the toxin gene. This study targeted only toxin-positive cases using the rapid membrane enzyme immunoassay. Therefore, the tests performed during the period of this study may have missed toxin-positive cases compared to the current technology, but it is unlikely that this affected the research results. Third, as in a previous report (12), there were no cases judged to be super severe, so the appropriateness of differentiating between severe and super severe cases could not be fully verified. The national guideline contains no description of super severe cases, and treatment methods are distinguished as mild, severe, relapse, and intractable (more than two instances of relapse) (8). This is one point where revisions have been proposed concerning the clinical application and further development of the MN criteria. Fourth, we did not evaluate the efficacy and safety of antimicrobial agents against *C. difficile*, as the purpose of our study was to examine the usefulness of the MN criteria. Fifth, since this study focused on the accuracy of the MN criteria and the analysis of factors associated with predicting CDI severity, we did not compare the MN criteria with other classifications. However, comparing our findings with other classifications is important for verifying the usefulness of the MN criteria. Thus, in the future, a new protocol should be established, and its advantages and limitations compared with other classifications should be verified.

In conclusion, the findings provide evidence supporting the accuracy of the MN criteria in predicting CDI severity and show that the Alb and WBC are important variables in predicting CDI severity. Our findings also suggest that the accuracy of the MN criteria may be able to be maintained and simplified. By furthering this discussion, more practical criteria for determining CDI severity may be able to be established.

The authors state that they have no Conflict of Interest (COI).

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