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# Geriatric nutritional risk index as a risk-factor for *Clostridioides difficile* infection relapse in elderly Japanese patients

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## Abstract

**Objective:** Old age is a risk factor for *Clostridioides difficile* infection (CDI). As the world's aging population increases, identifying risk factors for CDI in elderly patients is a matter of urgency. This study examined the relationship between CDI relapse and nutritional status using the geriatric nutritional risk index (GNRI).

**Patients and Methods:** Between January 2016 and December 2021, 108 patients were diagnosed with CDI. Of the 108 patients, 19 were excluded because of younger age (<65 years), early death within 14 days of the initial CDI diagnosis, and insufficient data. The patients were divided into low- (<75) and high-GNRI groups (≥75) based on the receiver operating characteristic curve analysis. Variables associated with CDI relapse were also analyzed.

**Results:** The median GNRI scores in all patients and in the low- and high-GNRI groups were 74.9, 68.9, and 83.9, respectively. Of the 89 patients, 28 (31.8%) experienced a CDI relapse. The log-rank test showed a significantly better relapse-free survival (RFS) in the high GNRI group ($P$=0.002). Univariate analysis revealed that low GNRI ($P$=0.004), chronic kidney disease (CKD) ($P$=0.004), and beta-lactamase inhibitor administration before the initial diagnosis of CDI ($P$=0.025) were significantly correlated with RFS. Multivariate analysis revealed that low GNRI ($P$=0.008) and CKD ($P$=0.010) were independent prognostic factors for RFS.

**Conclusion:** Among elderly patients, a low GNRI was strongly associated with CDI relapse. Our study may help clinicians to consider therapeutic strategies for elderly patients with CDI.

**Key words:** *Clostridioides difficile* infection, elderly, relapse, nutritional status, geriatric nutritional risk index

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## Introduction

*Clostridioides difficile* infection (CDI) is a disease characterized by fever and diarrhea and accounts for 20–30% of antibiotic-associated diarrhea[1]. The estimated number of incident CDI cases reached 453,000, and that of deaths within 30 days of the initial diagnosis of CDI reached 29,300 based on data from the Center for Disease Control and Prevention of the United States in 2011[2]. Older age (>65 years) is an important risk factor for CDI[1, 3]. As the world's aging population increases, identifying risk factors for CDI in elderly patients has become an urgent matter.

Many recent studies have reported an association between nutritional status and various diseases. The geriatric nutritional risk index (GNRI) is a simple and objective tool that uses serum albumin levels and body mass index (BMI) to assess the nutritional status of older patients[4]. A low GNRI has been reported to be an adverse prognostic factor in patients with various diseases[5–8]. Additionally, a low GNRI is also suggested to be related to the severity or mortality of infectious diseases such as aspiration pneumonia[9] or coronavirus disease 2019[10]. The relationship between CDI and nutritional status, including serum albumin levels[1, 11] and BMI[12, 13], has also been reported. However, the relationship between CDI and the GNRI has not been re-

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ported. This study aimed to elucidate whether a low GNRI would influence CDI relapse.

## Patients and Methods

### Iwate Prefectural Senmaya Hospital

Iwate Prefectural Senmaya Hospital is located in a rural area in Japan. The hospital has 148 beds and provides both acute- and chronic-phase treatment in accordance with regional needs.

### Study design

The present study was conducted at a single institution. The requirement for written informed consent was waived because this was a retrospective observational study. The study protocol was approved by the ethics committee of Iwate Prefectural Senmaya Hospital (approval number: 4) and performed in accordance with the Declaration of Helsinki.

### Patients

Between January 2016 and December 2021, the total hospitalization, mean patient age, and length of hospital stay (LOS) in Iwate Prefectural Senmaya Hospital were 219,022, 79.4 years, and 21.0 days, respectively. During the same period, 108 patients with fever and diarrhea were diagnosed with CDI during hospitalization. Of the 108 patients, three were excluded because they were aged <65 years, 10 were excluded because of early death (within 14 days) after the initial diagnosis of CDI, and 6 were excluded because of insufficient data. Then, 89 patients were enrolled in this study (Figure 1). The diagnostic criteria for CDI were as follows: glutamate dehydrogenase antigen and toxin A/B were positive using a detection kit (C. DIFF QUIK CHEK COMPLETE®, Abbott Diagnostics Medical Co., Tokyo, Japan), and toxin A/B was negative using the kit, but the toxin B gene was positive using the nucleic acid amplification test.

### Data collection

We examined the data of all enrolled patients, including age, sex, body mass index (BMI), duration of hospitalization prior to the initial diagnosis of CDI, medical condition, antibiotics administered prior to the initial diagnosis of CDI. In addition, laboratory findings at initial diagnosis of CDI, severity of CDI, treatment for CDI, relapse of CDI, and length of hospital stay (LOS). This study defined chronic kidney disease (CKD) as a medical condition. CKD was diagnosed by a decreased estimated glomerular filtration rate (eGFR, <60 mL/min/1.73 $m^2$) for three or more months[14]. Leukocyte count, lymphocyte count, C-reactive protein (CRP) level, albumin level, and total cholesterol level were evaluated as laboratory parameters. The severity of CDI was assessed using the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) criteria 2018 as follows: non-severe was defined as leukocytosis with a leukocyte count of ≤15,000 × $10^3$ cells/μL and a serum creatinine level <1.5 mg/dL. Furthermore, severe was defined as leukocytosis with a leukocyte count of ≥15,000 ×$10^3$ cells/μL or a serum creatinine level >1.5 mg/dL; fulminant was defined as hypotension or shock, ileus, and megacolon[15]. CDI relapse was defined as CDI that occurred within 2–8 weeks of its initial onset[15].

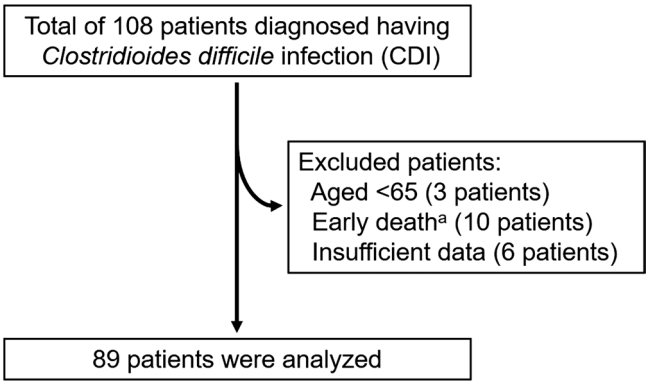


**Figure 1** Flow chart of enrolled patients in the present study. [a]Early death was defined as death within 14 days after the initial diagnosis of *Clostridioides difficile* infection (CDI).

### Calculating GNRI and setting cut-off of GNRI

GNRI during the initial CDI episode was also evaluated. Serum albumin level (g/dL) and BMI were used to calculate GNRI. The GNRI formula was as follows: GNRI = 14.89 × serum albumin (g/dL) + 41.7 × BMI (kg/$m^2$) / 22[4, 7].

The appropriate cut-off was set using receiver operating characteristic curve analysis (Figure 2). The area under the curve was 0.628 (95% confidence interval [CI]:0.499–0.757), and the most appropriate cut-off value was calculated to be 74.670. The sensitivity and specificity of the cut-off values were 0.714 and 0.607, respectively. We determined that the cut-off value of the GNRI was 75 and divided it into two groups: a low GNRI (GNRI <75) and a high GNRI group (GNRI ≥75).

### Statistical analysis

Data are presented as median (range) for continuous variables and number (%) for categorical variables. Statistical analysis was performed using the t-test or Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Relapse-free survival (RFS) was determined using the Kaplan–Meier method and analyzed using the log-rank test. Univariate and multivariate analyses with Cox proportional model was used to also analyze the risk factors associated with CDI relapse. All statistical analyses were performed using the EZR software (Jichi Medical

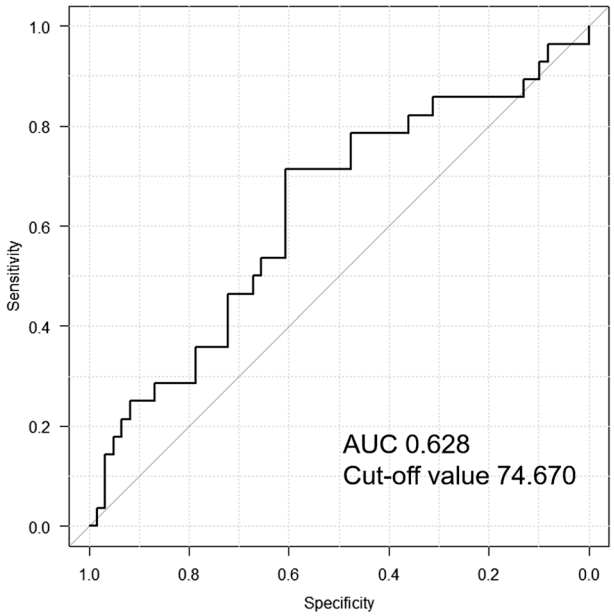


**Figure 2** ROC curve analysis. The most appropriate cut-off value was calculated at 74.670 with 0.714 sensitivity and 0.607 specificity. Based on the result, we determined that the cut-off value of GNRI was 75. ROC: receiver operating characteristic; GNRI: geriatric nutritional risk index.

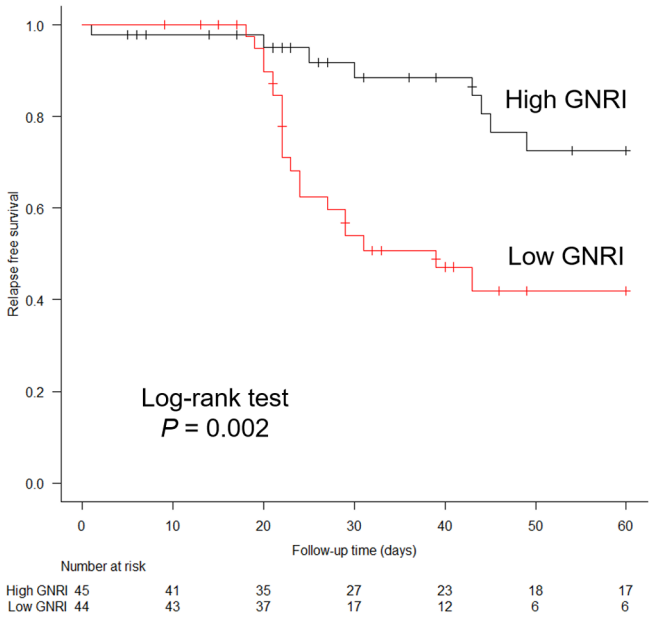


**Figure 3** Kaplan-Meier curves of RFS between the low- and high-GNRI groups. RFS in high GNRI group was significantly better than that in low GNRI group using log-rank analysis. RFS: relapse free survival; GNRI: geriatric nutritional risk index.

University Saitama Medical Center, Saitama, Japan). Statistical significance was set at $P<0.05$.

## Results

### Patient characteristics

Table 1 summarizes the patient characteristics. The median GNRI in all patients and in the low- and high-GNRI groups were 74.9, 68.9, and 83.9, respectively. In the low GNRI group, age was significantly higher ($P=0.009$), and LOS was longer ($P=0.003$) than in the high GNRI group. Body mass index (BMI) and serum albumin levels, which are components of the GNRI, were significantly lower in the low GNRI group than in the high GNRI group.

### Comparison of RFS between the low and high GNRI groups

Of the 89 patients, 28 (31.8%) experienced a CDI relapse. The recurrence rates in the low- and high-GNRI groups were 45.5% (20/44) and 17.8% (8/45), respectively. Figure 3 shows the Kaplan–Meier curves of RFS between the low- and high-GNRI groups. The log-rank test showed that RFS in the high GNRI group was significantly better than that in the low GNRI group ($P=0.002$).

### Univariate analysis for relapse CDI

Table 2 shows the univariate analysis for relapse CDI using Cox proportional hazard model. According to univariate analysis, low GNRI ($P=0.004$), patients with CKD ($P=0.004$), administration of beta-lactamase inhibitor, including ampicillin/sulbactam, piperacillin/tazobactam, and cefoperazone/sulbactam, prior to initial diagnosis of CDI ($P=0.025$), and serum albumin levels ($P=0.047$) were significantly correlated with RFS.

### Multivariate analysis for relapse CDI

Table 3 shows the multivariate analysis for relapse CDI. We determined the analysis variables by referring the univariate analysis and previous reports[1, 15, 16, 25, 26]. Cox proportional hazard model showed that low GNRI ($P=0.008$) and patients with CKD ($P=0.010$) were independent RFS prognostic factors.

## Discussion

We found that a low GNRI strongly influenced CDI relapse in elderly patients. The relationship between GNRI and various diseases, including solid tumors[5, 6], heart failure[7], and hemodialysis[8], has been reported. Similarly, a relationship between the GNRI and infectious diseases has been reported[9, 10]. However, the relationship between GNRI and CDI has not yet been reported, and we believe that this study is the first report on the relationship between low GNRI and CDI relapse in elderly patients.

**Table 1** Characteristics of analyzed patients in low and high GNRI groups

| Variable | All patients (n=89) | Low GNRI (n=44) | High GNRI (n=45) | *P*-value |
|---|---|---|---|---|
| GNRI | 74.9 (51.0–97.6) | 68.9 (51.0–74.7) | 83.9 (75.3–97.6) | <0.001* |
| Age, years | 88 (66–103) | 90 (73–103) | 87 (66–99) | 0.009* |
| Age category | | | | |
| 65–74 | 7 (7.9) | 1 (2.3) | 6 (13.3) | |
| 75–84 | 17 (19.1) | 8 (18.2) | 9 (20.0) | |
| 85–94 | 54 (60.7) | 28 (63.6) | 26 (57.8) | |
| 95 and over | 11 (12.4) | 7 (15.9) | 4 (8.9) | |
| Gender, Male/Female | 39/50 | 20/24 | 20/26 | 0.832 |
| BMI, kg/m$^2$ | 20.2 (14.4–32.6) | 17.8 (14.6–24.1) | 21.5 (14.4–32.6) | <0.001* |
| Duration of hospitalization prior to initial diagnosis of CDI, days | 22 (1–117) | 26 (1–117) | 20 (1–110) | 0.235 |
| Medical condition | | | | |
| Neurological disease | 52 (58.4) | 28 (63.6) | 24 (53.3) | 0.392 |
| Chronic kidney disease | 37 (41.6) | 16 (36.4) | 21 (46.7) | 0.392 |
| Malignancy | 16 (18.0) | 10 (22.7) | 6 (13.3) | 0.281 |
| Tube feeding | 15 (16.9) | 11 (25.0) | 4 (8.9) | 0.051 |
| History of gastrointestinal surgery | 14 (15.7) | 8 (18.2) | 6 (13.3) | 0.573 |
| Antibiotics prior to initial diagnosis of CDI | | | | |
| Ceftriaxone | 48 (53.9) | 23 (52.3) | 25 (55.6) | 0.833 |
| Ampicillin/Sulbactam | 23 (25.8) | 14 (31.8) | 9 (20.0) | 0.233 |
| Piperacillin/Tazobactam | 15 (16.9) | 10 (22.7) | 5 (11.1) | 0.167 |
| Cefoperazone/Sulbactam | 12 (13.5) | 7 (15.9) | 5 (11.1) | 0.550 |
| Levofloxacin | 11 (12.4) | 7 (15.9) | 4 (8.9) | 0.353 |
| Multiple antibiotics | 37 (41.6) | 22 (50.0) | 15 (33.3) | 0.135 |
| Severity of CDI, Mild/Severe/Fuluminant | 66/23/0 | 35/9/0 | 31/14/0 | 0.334 |
| Laboratory parameters | | | | |
| Leukocytes, ×10$^3$ cells/μL | 8.7 (1.0–38.0) | 9.3 (1.0–22.3) | 8.4 (2.6–38.0) | 0.990 |
| Lymphocytes, ×10$^3$ cells/μL | 1.0 (0.2–3.3) | 0.9 (0.2–3.3) | 1.0 (0.2–3.3) | 0.777 |
| CRP, mg/dL | 4.6 (0.2–36.5) | 4.6 (0.3–22.0) | 4.5 (0.2–36.5) | 0.705 |
| Albumin, g/dL | 2.5 (1.3–3.8) | 2.2 (1.3–2.9) | 2.9 (2.1–3.8) | <0.001* |
| Total cholesterol, mg/dL | 139.6 (71.5–270.0) | 139.2 (87.1–217.9) | 146.0 (71.5–270.0) | 0.987 |
| Treatment for CDI | | | | |
| Metronidazole | 70 (78.7) | 38 (86.4) | 32 (71.1) | 0.120 |
| Vancomycin | 19 (21.3) | 7 (15.9) | 12 (26.7) | 0.302 |
| Length of hospital stay, days | 66 (10–727) | 79(19–727) | 56 (10–220) | 0.003* |

*Parameters with *P*-value <0.05. Data are expressed as the median (range) or number (%). GNRI: geriatric nutritional risk index; BMI: body mass index; CDI: *Clostridium difficile* infection; CRP: C-reactive protein.

GNRI is a simple and objective tool that can be used to assess nutritional status in elderly patients. Nutritional status is usually classified into four groups: major risk (GNRI <82), moderate risk (GNRI: 82–92), low risk (GNRI: 92–98), and no risk (GNRI >98)[4]. Most studies on the GNRI have used this classification[5, 6, 9, 10]. However, the GNRI values in the present study were lower than those reported previously. The median age of the study population was 88 years and the study population was completely different. Therefore, a new cut-off value was set for GNRI in accordance with our study population.

The GNRI has two components: serum albumin level and BMI. Albumin is a well-known predictive marker for CDI incidence, recurrence, and mortality. Among elderly patients, a low albumin level (≤2.5 g/dL) influences CDI mortality[1, 11]. Reports on the association between BMI and CDI are increasing. A recent meta-analysis suggested that high BMI may be a protective factor against CDI[12]. Furthermore, Suzuki *et al.* reported that low BMI (<18.5 kg/m$^2$) is a risk factor for CDI among older patients with pneumonia in Japan[13]. Therefore, the GNRI, calculated using serum albumin levels and BMI, can be a reasonable and strong tool for predicting the risk of CDI in elderly patients.

Older age (>65 years) is a known risk factor for CDI incidence, relapse, and mortality[1, 16]. Additionally, Linsky *et al.* reported that older age (>80 years) was a risk factor for CDI

**Table 2** Univariate analysis for relapse CDI using cox proportional hazard model

| Variable | HR (95% CI) | *P*-value |
|---|---|---|
| GNRI <75 | 3.388 (1.475–7.783) | 0.004* |
| Age, years | 1.047 (0.990–1.107) | 0.105 |
| Gender, Male | 0.541 (0.249–1.173) | 0.120 |
| BMI, kg/m$^2$ | 0.932 (0.833–1.043) | 0.218 |
| Duration of hospitalization prior to initial diagnosis of CDI, days | 0.995 (0.982–1.009) | 0.490 |
| Medical condition | | |
| Neurological disease | 2.034 (0.890–4.649) | 0.092 |
| Chronic kidney disease | 0.214 (0.074–0.617) | 0.004* |
| Malignancy | 0.792 (0.301–2.088) | 0.637 |
| Tube feeding | 1.300 (0.527–3.210) | 0.569 |
| History of gastrointestinal surgery | 0.248 (0.059–1.051) | 0.058 |
| Antibiotics prior to initial diagnosis of CDI | | |
| Ceftriaxone | 0.684 (0.325–1.439) | 0.317 |
| Levofloxacin | 1.960 (0.744–5.166) | 0.174 |
| Beta-lactamase inhibitor | 2.485 (1.123–5.498) | 0.025* |
| Multiple antibiotics | 1.456 (0.694–3.057) | 0.320 |
| Severe CDI | 0.800 (0.339–1.887) | 0.610 |
| Treatment for CDI | | |
| Metronidazole | 2.061 (0.7132–5.954) | 0.182 |
| Vancomycin | 0.5832 (0.221–1.539) | 0.276 |
| Laboratory parameters | | |
| Leukocytes, ×10$^3$ cells/μL | 1.000 (1.000–1.000) | 0.641 |
| Lymphocytes, ×10$^3$ cells/μL | 1.000 (0.999–1.000) | 0.282 |
| CRP, mg/dL | 1.018 (0.972–1.066) | 0.453 |
| Albumin, g/dL | 0.497 (0.249–0.991) | 0.047* |
| Total cholesterol, mg/dL | 1.004 (0.994–1.014) | 0.456 |

* Parameters with *P*-value <0.05. HR: hazard ratio; CI: confidence interval; GNRI: geriatric nutritional risk index; BMI: body mass index; CDI: *Clostridioides difficile* infection; CRP: C-reactive protein.

**Table 3** Multivariate analysis for relapse CDI using cox proportional hazard model

| Variable | HR (95% CI) | *P*-value |
|---|---|---|
| GNRI <75 | 3.705 (1.411–9.728) | 0.008* |
| Age, years | 1.025 (0.964–1.091) | 0.429 |
| Chronic kidney disease | 0.224 (0.071–0.701) | 0.010* |
| Administration of beta-lactamase inhibitor prior to initial diagnosis of CDI | 1.864 (0.805–4.317) | 0.146 |
| Severe CDI | 1.613 (0.624–4.168) | 0.324 |
| Administration of MNZ for initial CDI | 1.184 (0.391–3.586) | 0.765 |

* Parameters with *P*-value <0.05. HR: hazard ratio; CI: confidence interval; GNRI: geriatric nutritional risk index; CDI: *Clostridium difficile* infection; MNZ: metronidazole.

relapse[16]. In the present study, prognostic factors associated with CDI relapse in elderly patients were analyzed. As stated above, the median age of our study population was 88 years, which was much higher than that reported in previous studies. Among elderly patients, age may be less relevant to CDI relapse.

However, it is uncertain whether CKD reduced the risk of CDI relapse in this study. CKD is also a well-known risk factor for CDI[17, 18]. We considered the following hypotheses: First, this was a single-institutional study in a Japanese rural area; therefore, selection bias may have affected this result. Second, most patients in this study were initially treated with metronidazole. Most metronidazole is metabolized by the liver; approximately 80% and 15% of the metabolites are eliminated via the urine and feces, respectively[19, 20]. Metabolites of metronidazole in the blood increased more among patients with renal failure than among healthy volunteers[21]. In patients with CKD, excretion of metronidazole metabolites via feces may increase because of the increased blood concentration of its metabolites. Thus, administration

of metronidazole for CDI may have a high therapeutic effect in patients with CKD. Third, serum creatinine level, which is used to calculate eGFR, is related to skeletal muscle mass[22]. Among elderly patients, skeletal muscle mass decreases with age[23], which leads to decreased serum creatine levels. Thus, the eGFR is often estimated to be higher than the actual value in elderly patients, and the number of patients diagnosed with CKD may decrease. The same can be said about CDI severity. CDI severity is categorized by leukocyte counts and serum creatinine levels according to the SHEA/ISDA guidelines 2018[15]. In the present study, many elderly patients with less skeletal muscle mass were classified into the non-severe group for the reasons mentioned above. These factors might have affected this study's results.

Oral antibiotics including metronidazole, vancomycin, and fidaxomicin are usually administered to treat CDI. Metronidazole is recommended as the first-choice treatment for initial non-severe CDI according to the Japanese Clinical Guidelines 2018[24]. Metronidazole is less expensive; however, it is recognized to have a higher risk of treatment failure or CDI relapse than other medications[25, 26]. Our study demonstrated that the administration of metronidazole for initial CDI tended to be related to CDI relapse. Conversely, vancomycin or fidaxomicin is the first-choice treatment for initial CDI, even if the patient is considered non-severe in the SHEA/ISDA guidelines 2018[15]. Additionally, the SHEA/IDSA guidelines 2021 recommended fidaxomicin as the first-choice treatment for initial CDI instead of vancomycin[27]. Fidaxomicin is an expensive drug but has some excellent characteristics. First, fidaxomicin is superior to metronidazole or vancomycin preventing CDI relapse[26, 28]. Second, *Clostridioides difficile* with resistance to fidaxomicin is rare[27, 29]. Third, fidaxomicin is a narrow-spectrum drug and there are no treatment indications other than CDI[27, 30]. Among older patients with low nutritional status, that is, among those with a high risk for relapse, vancomycin or fidaxomicin should be considered as the initial treatment for CDI.

This study had some limitations. First, this was a retrospective observational study conducted at a single institution. Accordingly, the analysis was performed with limited sample size. Second, our study population was much older than those in the previous reports, as stated above; therefore, this study had the possibility of selection bias. Third, most patients with CDI are treated with oral metronidazole. Vancomycin or fidaxomicin is mainly used as a treatment for CDI in the United States and European countries; thus, the treatment situation can differ greatly.

## Conclusion

We identified a strong relationship between nutritional status and CDI relapse in elderly patients in Japan. Our study may help clinicians to consider therapeutic strategies for elderly patients with CDI. The GNRI is a simple and strong tool to assess the nutritional status of elderly patients; administration of vancomycin or fidaxomicin, which has a lower risk of treatment failure or relapse of CDI than metronidazole, should be considered for patients with CDI with low GNRI.

**Conflicts of interest:** The authors declare that they have no competing interests.

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