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Original Article

Impact of the COVID-19 pandemic on the incidence of healthcare facility-onset *Clostridioides difficile* infection in hospitalized patients with sepsis: Interrupted time series analysis using Japanese Diagnosis Procedure Combination data

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A B S T R A C T

Objectives: Healthcare facility-onset *Clostridioides difficile* infection (HO-CDI) is a major nosocomial infection associated with high mortality and healthcare costs. We aimed to determine if HO-CDI incidence decreased due to the COVID-19 pandemic. We hypothesized that the pandemic decreased HO-CDI as healthcare workers became more diligent in handwashing and sanitization.
Methods: In this retrospective cohort study, adult patients with sepsis hospitalized in general wards from January 2018 to February 2021 were identified using a nationwide Japanese administrative database. Patients were divided into two groups according to the hospitalization date (before and after the first declaration of a state of emergency). The primary outcome was a change in the level of the HO-CDI monthly incidence ratio (per 10000 patient-days).
Results: Of the 49,156 eligible hospitalizations for sepsis, 41,870 were before and 7,283 were after the first state of emergency declaration. Interrupted time-series (ITS) analysis showed no significant difference in the HO-CDI incidence ratio after Japan's first state of emergency declaration (level change −1.0, 95% confidence interval (CI) −8.6 to 6.6, p = 0.8, slope change 0.06, 95% CI -0.17 to 0.3, p = 0.6). The overall HO-CDI incidence ratio was 3.86/10000 patient-days (interquartile range 2.97 −4.53); higher incidence existed in subgroups with older adults or a lower Barthel index at admission.
Conclusions: No significant change in HO-CDI incidence was observed in patients with sepsis hospitalized in general wards before and after Japan's first state of emergency declaration. Our study revealed that HO-CDI in general wards in Japan had been consistently decreasing since before the COVID-19 pandemic.

1. Introduction

Clostridioides difficile (*C. difficile*) is a spore-forming anaerobic gram-positive bacillus that is associated with nosocomial diarrhea. It is estimated that there were more than 450,000 cases of *C. difficile* infection (CDI) and approximately 29,000 *C. difficile*-associated deaths in the United States in 2011 [1]. Furthermore, the number of cases and deaths is increasing, with an estimated annual medical cost of approximately $150 million [2,3]. The incidence of CDI in recent years in Japan is unknown, as no nationwide CDI surveillance has been conducted. Based on a population-based study conducted in nine Tokyo hospitals, it is estimated that CDI occurs in more than 57,000 hospitalized cases per year in individuals over 50 years old in Japan [4]. *C. difficile* enters the human body via fecal-oral transmission through contact with healthcare workers, contaminated environments, or medical devices, and colonizes by forming spores. It has been reported that 3−18% of inpatients in acute care hospitals and 4−20% of residents in healthcare facilities have *C. difficile* [5,6], which progresses to symptomatic diarrhea following exposure to antimicrobial agents or antiulcer drugs [7].

Abbreviations: (HO-CDI), healthcare facility-onset *Clostridioides difficile* infection; (COVID-19), coronavirus disease 2019; DPC, Diagnosis Procedure Combination; (EIA), enzyme immunoassay; (PPE), personal protective equipment; (ICU), intensive care units; (ITS), interrupted time-series; (MDV), Medical Data Vision Co.,; (MRSA), methicillin-resistant *Staphylococcus aureus*; (NAAT), nucleic acid amplification test.

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The coronavirus disease 2019 (COVID-19) pandemic is ongoing, with the first case diagnosed in Wuhan, China, in 2019. Since January 2020, multiple cases have been confirmed throughout Japan, and the government has announced states of emergency in response to the pandemic. Although the number of patients is less compared to the United States and some European countries, more than 900,000 patients have been reported, and in Japan, more than 15,000 people have died as of July 2021 [8]. The healthcare workers have enforced wearing masks, hand hygiene, and environmental sanitization to prevent infection. In addition, the visits of patients' families were restricted in many medical facilities and nursing homes. The impact of these infection control measures on various types of nosocomial infections is controversial. While some reports indicate that these infection control measures have resulted in an overall decrease in nosocomial infections, others show an increase in some infections, such as catheter-related bloodstream infections [9,10]. Although several single-center observational studies have been reported, it is unclear whether the pandemic reduced healthcare facility-onset CDI (HO-CDI) [11–13].

C. difficile is resistant to alcohol hygiene; therefore, guidelines recommend aggressive handwashing with soap and running water to prevent transmission [14,15]. Contrarily, a systematic review concludes that hand hygiene alone is not enough; therefore, whether handwashing and hand hygiene can reduce the incidence of HO-CDI is still controversial [16]. Our hypotheses were as follows: (a) HO-CDI was decreased because healthcare workers were becoming more concerned about contracting COVID-19 infection and being more proactive in handwashing than before the pandemic, and (b) The impact of handwashing alone may be evaluated by focusing on patients in general wards, where we can assume that there was little change in contact precautions, including personal protective equipment (PPE) and environmental cleaning, from pre-pandemic levels. This study aimed to learn how to effectively control the spread of *C. difficile*.

2. Materials and methods

2.1. Study design and data source

We conducted a retrospective cohort study using the Japanese Diagnosis Procedure Combination (DPC) database provided by Medical Data Vision Co. Ltd (MDV; Tokyo, Japan). DPC is a Japanese lump-sum payment system for acute-care hospital inpatients in which provider reimbursement is calculated by grouping patients according to DPC categories [17]. The MDV database is a hospital-based billing database collecting data from all insurance types and contains fully anonymized outpatients, inpatients, and DPC data. As of September 2021, the MDV database included more than 38 million patients and 23% of acute care hospitals in Japan [18]. This database has been used for similar epidemiological studies [7,19]. The database contains patients' demographic data (age and sex), medical and pharmacy billing data, clinical diagnoses coded using the International Classification of Diseases 10th revision (ICD-10), and medical procedures coded using Japanese classification codes and medical billing codes. This database contains only a small portion of physiological or laboratory data governed independently of other data under contract with each institution [18]. Moreover, the results of laboratory tests included in the database are limited to selected blood tests. Therefore, we can identify that a CDI laboratory test had been ordered but cannot know whether the test result was positive. This study was conducted using the same dataset as another clinical research study [20]. The Kyoto University Graduate School and Faculty of Medicine Ethics Committee approved the study protocol (R3145).

2.2. Study population

We identified patients with sepsis who were 18 years or older and were hospitalized in general wards between January 2018 and February 2021. We focused on patients with sepsis because we were interested in the patient population that was exposed to antimicrobial agents for some bacterial infection, which is one of the risks for developing HO-CDI, and did not experience significant changes in the population's overall risk before and during the pandemic. In this study, we defined the patients who met the following criteria as patients with sepsis. First, patients with the diagnosis of both infection (ICD-10 codes A039, A021, A207, A217, A227, A239, A241, A267, A280, A282, A327, A392, A393, A394, A400, A401, A402, A403, A408, A409, A410, A411, A412, A413, A414, A415, A418, A419, A427, B007, B377, J189, J440, N390) and organ dysfunction (ICD-10 codes J960, J969, J80, R092, R570, R571, R578, R579, I951, I959, N170, N171, N172, N178, N179, K720, K729, K763, F050, F059, G931, G934, G938, D695, D696, D65) were identified using the ICD-10 codes which were partially modified from ICD-9 codes used in the previous validation study [21] (Supplementary Table 1). These diagnoses were identified from the database as main diagnosis, diagnosis at admission, diagnosis with the first or second highest medical costs, or comorbidity at admission. Second, patients in whom intravenous antibiotics were used within two days of hospitalization. If a patient was hospitalized more than once, we counted each hospitalization as a single hospitalization.

Patients who had CDI at the time of hospitalization were excluded and were defined as those with the diagnosis of CDI at admission (ICD-10 code A047) or those treated with antimicrobials for CDI within three days after hospitalization. Specific antimicrobial agents for CDI include oral vancomycin, oral or intravenous metronidazole, oral fidaxomicin, or intravenous bezlotoxumab, all covered by insurance for CDI treatment in Japan. In this study, patients with COVID-19 (ICD-10 code U071) at the time of hospitalization and patients admitted to the intensive care unit during hospitalization were also excluded to focus on practice in general wards, which were less affected by the COVID-19 pandemic.

The primary outcome was a change in the level of the monthly incidence ratio of HO-CDI (as per 10,000 patient-days). In this study, HO-CDI was defined as patients who received antimicrobials for CDI covered by insurance in Japan (oral vancomycin, oral or intravenous metronidazole, oral fidaxomicin, or intravenous bezlotoxumab) on the day or the day after the CDI laboratory test implementation and cases that occurred after the fourth day of hospitalization [14]. The definition of CDI laboratory test in this study was the implementation of either the enzyme immunoassay (EIA) or nucleic acid amplification test (NAAT) or both. The Barthel index was calculated based on the activities of daily living scores recorded in the DPC database. The cumulative score of the Barthel index ranges from 0 to 100 points, with 0 indicating bedridden patients and 100 indicating completely independent patients.

2.3. Statistical analysis

Categorical and ordinal variables were summarized as numbers and percentages, continuous variables as mean and standard deviation if normally distributed, and as median and interquartile range (IQR) if not normally distributed.

Interrupted time-series (ITS) analysis is one method to evaluate the effectiveness of population-level health interventions [22]. Instead of a simple before-and-after comparison, the treatment effect is estimated using the past as a control group. A segmented regression approach is used to test the effect of a treatment on the outcome of interest using an appropriately defined impact model. One of the method's strengths is that they are generally unaffected by confounding variables, including unknown and unmeasured variables, by following a single population. Nevertheless, ITS can be affected by rapidly changing time-varying confounding factors. Other events that occur simultaneously with the intervention and may affect the outcome may act as time-varying confounders.

We described the monthly incidence ratio of HO-CDI as per 10000 patient-days. ITS analyses have been performed to assess whether the incidence ratio of HO-CDI was associated with the COVID-19 pandemic. The magnitude of associations was estimated by the level change and slope change in the incidence ratio of HO-CDI before and after the COVID-19 pandemic. Change level and slope were modeled using the linear regression model: dependent variables were the incidence ratio of HO-CDI; independent variables were an indicator representing before and after the COVID-19, the time elapsed since the study start date, and the time elapsed since the COVID-19 pandemic. In this study, the COVID-19 pandemic was defined as starting from May 2020, because the Japanese government announced the first declaration of a state of emergency on April 7, 2020 [23].

We performed subgroup analyses for age (<85 years, ≥85 years) and Barthel index at hospitalization. For sensitivity analysis, we performed ITS analyses with the following changes in the definition of HO-CDI in this study: (a) a patient who received antimicrobials for CDI on the day of CDI laboratory test implementation, and (b) a patient who received antimicrobials for CDI within four days of the CDI laboratory test implementation. We also performed ITS analyses by the change in the interrupted period to the following time points for sensitivity analyses: (c) March 2020 (the first peak in Japan), (d) January 2020 (the first confirmed case of COVID-19 in Japan) [24].

The statistical significance level was set at two-sided $p < 0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC), except for the ITS analyses, which were performed in R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Overall, 69,226 hospitalizations of patients with sepsis were identified between April 2018 and February 2021. Of these hospitalizations, 20,070 met the exclusion criteria. Finally, 49,156 eligible hospitalizations were included in the analysis. These patients were divided into two groups based on whether each patient's admission date was before or after the first declaration of a state of emergency in Japan (April 7, 2020): before the declaration (n = 41,870) and after the declaration (n = 7,286) (Fig. 1). Table 1 shows the included patients' baseline characteristics, infection source, medications used within two days of hospitalization, and clinical outcomes. There were no significant differences in baseline characteristics of patients, the incidence proportion of HO-CDI and CDI laboratory tests, length of hospital stay, and overall in-hospital deaths. All the CDI laboratory tests we identified were EIAs. There were some differences in the sources of infection and the medications used after hospitalizations. After the first declaration of a state of emergency, the use of carbapenems, anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drugs, and antiulcer drugs increased. At the same time, the proportion of respiratory infections decreased compared to before the first declaration of a state of emergency.

ITS analysis showed no significant difference in the incidence ratio of HO-CDI after the first declaration of a state of emergency (level change −1.0, 95% confidence interval (CI) −8.6 to 6.6, p = 0.8, slope change 0.06, 95% CI -0.17 to 0.3, p = 0.6). (Fig. 2). Sensitivity analyses with the different interrupted periods and subgroup analyses in older adult patients and patients with a low Barthel index also showed no significant changes (Table 2). Table 3 shows the incidence ratio of HO-CDI overall and in each subgroup. The overall incidence ratio of HO-CDI was 3.86/10000 patient-days (IQR 2.97–4.53), with a higher incidence in the subgroups with older adults or lower Barthel index at hospitalization.

4. Discussion

In this retrospective cohort study of patients with sepsis, we investigated the impact of the COVID-19 pandemic on the incidence of HO-CDI in general wards in Japanese hospitals. There were no differences in patients' background, length of hospital stay, or incidence proportion of in-hospital deaths, CDI, or CDI laboratory tests before and after Japan's first declaration of a state of emergency. However, there were some differences in the source of infection and medications used. ITS analysis showed no significant level or slope changes in HO-CDI incidence in the general wards. Sensitivity analyses with different interrupted periods and subgroup analysis by age and Barthel index at hospitalization also showed no significant difference in ITS analysis.

Several retrospective studies have investigated the impact of the COVID-19 pandemic on the incidence of HO-CDI. However, most of them were only small studies, and the results were inconsistent depending on the setting where each study was conducted, including whether ICU patients or COVID-19 patients were

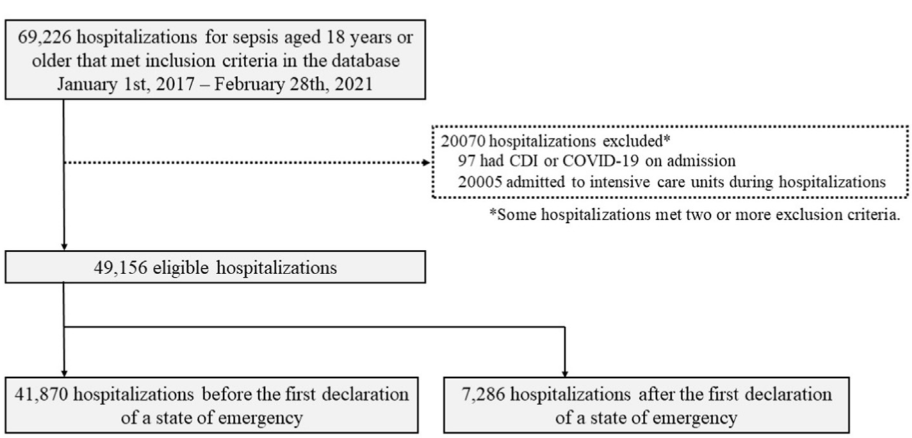

Fig. 1. Study flow diagram
COVID-19, coronavirus disease 2019.

Table 1
Baseline characteristics of patients.

	Overall	Before the declaration of a state of emergency	After the declaration of a state of emergency
	n = 49,156	n = 41,870 (85.2%)	n = 7,286 (14.8%)
Age (years), median (IQR)	82 (74.0–88.0)	82 (74.0–88.0)	83 (74.0–89.0)
Male sex, n (%)	27089 (55.1)	23089 (55.1)	4000 (54.9)
BMI (kg/m^2), median (IQR)	20.7 (18.0–23.5)	20.7 (18.0–23.5)	20.7 (18.0–23.5)
Barthel index, median (IQR)	20.0 (0.0–95.0)	25 (0.0–95.0)	10 (0.0–85.0)
Charlson Cormobidity Index			
0, n (%)	34748 (70.7)	29636 (70.8)	5112 (70.2)
1, n (%)	10485 (21.3)	8911 (21.3)	1574 (21.6)
2≦, n (%)	3923 (8.0)	3323 (7.9)	600 (8.2)
Source of infection			
Respiratory, n (%)	32155 (65.4)	28090 (67.1)	4065 (55.8)
Urinary tract, n (%)	13584 (27.6)	10934 (26.1)	2650 (36.4)
Hepatobiliary, n (%)	2384 (4.9)	1978 (4.7)	406 (5.6)
Skin and soft tissue, n (%)	1310 (2.7)	1111 (2.7)	199 (2.7)
Gastrointestinal, n (%)	1439 (2.9)	1218 (2.9)	221 (3.0)
Sepsis/septic shock, n (%)	4109 (8.4)	3437 (8.2)	672 (9.2)
Antibiotics			
Penicillin, n (%)	22117 (45.0)	19046 (45.5)	3071 (42.2)
Cephalosporin, n (%)	21360 (43.5)	18082 (43.2)	3278 (45.0)
Carbapenem, n (%)	7796 (15.9)	6478 (15.5)	1318 (18.9)
Quinolone, n (%)	2413 (4.9)	2085 (5.0)	328 (4.5)
Anti-MRSA drugs, n (%)	1385 (2.8)	1118 (2.7)	267 (3.6)
Aminoglycoside, n (%)	328 (0.7)	277 (0.7)	51 (0.7)
Antiulcer agents, n (%)	16752 (34.1)	14133 (33.8)	2619 (36.0)
HO-CDI, n (%)	509 (1.0%)	440 (1.0%)	69 (0.9%)
CDI laboratory tests, n (%)	4923 (10.0)	4209 (10.1)	714 (9.8)
Hospital length of stay, median (days), median (IQR)	17 (10.0–32.0)	17.0 (10.0–33.0)	17.0 (9.0–31.0)
Inhospital death, n (%)	10813 (22.0)	9178 (21.9)	1635 (22.4)

BMI, body mass index; MRSA, methicillin-resistant *Staphylococcus aureus*; HO-CDI, healthcare facility onset *Clostridioides difficile* infection; IQR, interquartile range.
The number of patients missing BMI: before the declaration 5947, after the declaration 1063.
The number of patients missing Barthel index: before the declaration 108, after the declaration 102.

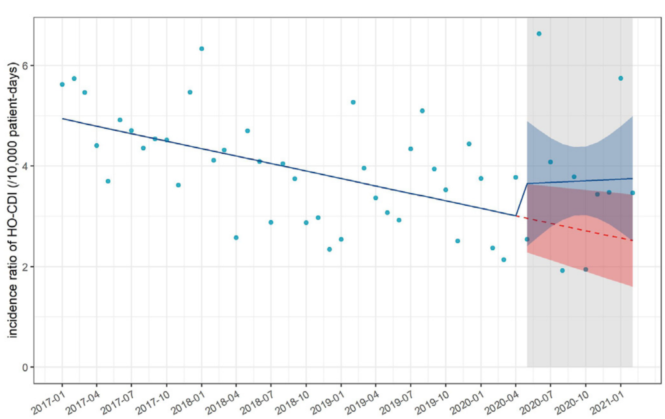

Fig. 2. Interrupted time-series analysis
The blue dots indicate the incidence of HO-CDI (/10000 patient-days) for each month. The blue line indicates the factual predicted trend based on a model (in the scenario with the first declaration of a state of emergency) and the dashed red line indicates the counterfactual predicted trend based on a model (in the scenario without the first declaration of a state of emergency). The blue and red areas after the interrupted period indicate 95% confidence intervals for the fact and counterfactual, respectively. HO-CDI, healthcare facility-onset *Clostridioides difficile* infection. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

included [25]. A single-center descriptive survey in Italy showed fewer CDI cases in general wards in 2020 compared to 2017–2019 [11]. A report from a tertiary center in Spain during the pandemic peak from March to May 2020, when nearly all patients were isolated and healthcare workers always wore PPE, showed no significant change in antimicrobial use compared to the previous year. However, the number of patients with CDI complicated by COVID-19 decreased [12]. A single-center retrospective observational study at the Veterans Affairs Hospital in Ann Arbor used ITS analysis to evaluate the number of CDI laboratory tests and the incidence of CDI. After March 1, 2020, the first peak in their region, the number of tests was significantly lower than from January 2019 to March 2020. However, there was no significant change in the incidence of CDI [13]. Contrarily, a report of large surveys from a US multicenter study showed that CDI had decreased due to the pandemic. According to the survey on healthcare-associated infections reported by acute care hospitals to the National Healthcare Safety Network, the quarterly calculated standardized infection ratios of laboratory-identified CDI were lower in 2020 than in 2019 [10].

We hypothesized that the COVID-19 pandemic would have reduced HO-CDI through changes in handwashing among healthcare workers, but our ITS analysis showed no obvious impact. Although it is difficult to conclude in the setting of our study, where there was no direct information on handwashing, the following points were considered as possible interpretations or reasons for these findings. First, the pandemic may not have affected the incidence of HO-CDI. Although the pandemic might have affected handwashing among healthcare workers, the impact might not have been significant enough to reduce the incidence of HO-CDI. It is also possible that handwashing and hand hygiene have always been sufficiently thorough in Japan that we could not expect further improvement. It remains controversial whether there has been a change in hand hygiene compliance due to the pandemic. Some studies using automated hand hygiene monitoring systems reported that hand hygiene compliance improved with the pandemic, while others reported that it did not [26–28]. Moreover, no reports from Japan have investigated changes in hand hygiene compliance caused by the pandemic. Although we believed that the healthcare workers in the early stages of the pandemic in Japan

Table 2
Subgroup analysis and sensitivity analysis.

		Level change			Slope change		
	n	Estimates	95% CI	P value	Estimates	95% CI	P value
Subgroup analyses							
Age, years							
<85	28,735	−2.7	−14 to 8.9	0.6	0.08	−0.28 to 0.44	0.6
≥85	20,421	1.9	−12 to 15	0.8	0.01	−0.40 to 0.43	>0.9
Barthel index							
0 point	19,713	0.68	−15 to 17	>0.9	−0.01	−0.51 to 0.48	>0.9
< median (18 point)	24,135	4.3	−8.8 to 17	0.5	−0.12	−0.52 to 0.29	0.6
≥ median (18 point)	25,021	−8.9	−22 to 4.5	0.2	0.31	−0.10 to 0.72	0.14
Sensitivity analyses							
(a) patients who received CDI drugs on the day of CDI laboratory tests implementation	49,156	1.3	−4.8 to 7.3	0.7	−0.02	−0.21 to 0.16	0.8
(b) patients who received CDI drugs within four days of the CDI laboratory tests implementation	49,156	−0.69	−9.8 to 8.5	0.9	0.04	−0.25 to 0.32	0.8
(c) the interrupted period: March 2020	49,156	−0.80	−7.3 to 5.7	0.8	0.06	−0.15 to 0.26	0.6
(d) the interrupted period: January 2020	49,156	−3.7	−8.6 to 1.3	0.14	0.14	−0.02 to 0.30	0.095

CI, confidence interval; CDI, *Clostridioides difficile* infection.

Table 3
Incidence ratio of HO-CDI.

	Incidence ratio of HO-CDI(/10000 patients-days), median (IQR)
Overall	3.86 (2.97−4.53)
Age, years	
< 85	3.31 (2.52−4.59)
≥ 85	4.35 (3.23−5.22)
Barthel index	
0 point	4.21 (3.16−5.69)
< median (18 point)	4.12 (3.37−5.11)

HO-CDI, healthcare facility onset *Clostridioides difficile* infection; IQR, interquartile range.

were more diligent in their hand hygiene than before the pandemic, there may have been no actual change in hand hygiene compliance itself. Second, it is also possible that we could not detect the difference because the incidence of HO-CDI in Japan had been on a downward trend since before the pandemic. A previous DPC data study showed that hospitalizations related to CDI in Japan declined from 2009 to 2016 [29]. In our analysis after 2017, HO-CDI had consistently decreased regardless of the pandemic, and such a trend may be a result of the appropriate use of broad-spectrum antimicrobial agents becoming more widespread in Japan. Third, the ITS analysis assumptions may not be met in our study. Compared to before the pandemic, carbapenems were administered more frequently, and fewer patients had respiratory tract infections during the pandemic in our study. Using DPC data, Nagano et al. reported that hospitalizations for community-acquired pneumonia in Japan decreased by about 48% year on year, particularly for mild and moderate cases, suggesting that the characteristics of patients in general wards had changed slightly due to the pandemic [30]. These changes in the characteristics of the patients may have made the ITS analysis inappropriate.

Our study has several novelties. First, the use of a large database allowed us to perform ITS analyses on a large patient population. Second, we could focus on general wards less relevant to COVID-19. Contrarily, there are some limitations. First, the definition of HO-CDI used in this study may not be accurate since the database did not include the results of CDI laboratory tests. Vancomycin and metronidazole are also covered in Japan for enterocolitis other than CDI and anaerobic bacterial infections. Therefore, there remains a concern that this study's definition of HO-CDI does not accurately measure the occurrence of HO-CDI. However, a previous prospective study conducted to determine the exact number of HO-CDI in Japan reported the following: CDI incidence of 2.7−8.4/10000 patient-days in the non-ICU settings and an overall incidence of 5.7/10000 patient-days [31]. The median value of HO-CDI incidence in our study was 3.86 (IQR 2.97−4.53)/10000 patient-days. A simple comparison cannot be made because the studies were conducted with different populations. However, we considered that the measurement of HO-CDI incidence by our definition is not significantly dissociated from the real-world measurements. Second, the included patients may have been misclassified due to uncertainty in the validity of the adopted ICD-10 codes used as our eligibility criteria. These codes were partially modified versions of the ICD-9 codes used in the reference validation study, revealing that the sensitivity and specificity for sepsis in the non-ICU setting were 60% and 94.7%, respectively [21]. Our study attempted to improve the validity by adding intravenous antibiotics to the inclusion criteria. However, since there are no reports on diagnostic accuracy, the external validity of this study on the Japanese DPC database is unknown. The remaining uncertainty in septic patients included in our research is a significant limitation of this study.

5. Conclusions

In this study, ITS analysis using a nationwide Japanese database showed no significant change in the incidence of HO-CDI in general wards before and during the COVID-19 pandemic. HO-CDI in general wards in Japan had been consistently decreasing since before the pandemic.

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Declaration of competing interest

Koji Kawakami has received research funds from Eisai Co., Ltd., Kyowa Kirin Co., Ltd., Sumitomo Pharma Co., Ltd., Mitsubishi Corporation, and Real World Data Co., Ltd.; consulting fees from LEBER Inc., JMDC Inc., Shin Nippon Biomedical Laboratories Ltd., and Advanced Medical Care Inc.; executive compensation from Cancer Intelligence Care Systems, Inc.; honorarium from Mitsubishi Chemical Holdings Corporation, Mitsubishi Corporation, Pharma Business Academy, and Toppan Inc.; and holds stock in Real World Data Co., Ltd.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.anaerobe.2023.102693.

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