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Effectiveness of Antibiotics for Uncomplicated Diverticulitis: A Retrospective Investigation Using a Nationwide Database in Japan

Rintaro Moroi[a] Kunio Tarasawa[b] Hiroshi Nagai[a] Yusuke Shimoyama[a] Takeo Naito[a] Hisashi Shiga[a] Shin Hamada[a] Yoichi Kakuta[a] Kiyohide Fushimi[c] Kenji Fujimori[b] Yoshitaka Kinouchi[a] Atsushi Masamune[a]

[a]Division of Gastroenterology, Tohoku University Hospital, Sendai, Japan; [b]Department of Health Administration and Policy, Tohoku University Graduate School of Medicine, Sendai, Japan; [c]Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Bunkyo, Japan

Keywords
Diverticulitis · Antibiotics · Big data

Abstract
Introduction: The efficacy of antibiotics for diverticulitis without abscess or peritonitis (uncomplicated diverticulitis) is controversial. We aimed to investigate the effectiveness of antibiotics for uncomplicated diverticulitis. ***Methods:*** We collected admission data for patients with acute uncomplicated diverticulitis using a nationwide database. We divided eligible admissions into two groups according to antibiotic initiation within 2 days after admission (antibiotic group vs. nonantibiotic group). We conducted propensity score matching and compared the rates of surgery (intestinal resection and stoma creation), in-hospital death, and medical costs between the groups. We also performed multivariate analysis to identify the clinical factors that affect surgery. ***Results:*** We enrolled 131,936 admissions; among these, we obtained 6,061 pairs after propensity score matching. Rates of both intestinal resection and stoma creation in the antibiotic group were lower than those in the nonantibiotic group (0.61 vs. 3.09%, $p < 0.0001$, and 0.08 vs. 0.26%, $p = 0.027$, respectively). Median costs in the antibiotic group were higher than those in the nonantibiotic group (315,820 JPY vs. 300,175 JPY, $p < 0.0001$, respectively). Multivariate analysis showed that non-initiation of antibiotics within 2 days after admission was a clinical factor that increased the risk of intestinal resection (odds ratio [OR] = 5.19, 95% confidence interval [CI]: 4.38–6.16, $p < 0.0001$) and stoma creation (OR = 2.68, 95% CI: 1.53–4.70, $p = 0.0006$). ***Conclusion:*** Our results indicated that antibiotics for uncomplicated diverticulitis expected to have moderate to severe disease activity may reduce the risk of intestinal resection and stoma creation. Further investigations are warranted.

Introduction

Diverticulitis is one of the most frequent intestinal diseases in clinical practice. A population-based study from the UK reported that the incidence rates of diverticulitis in 2005 were increased 2.28-fold compared with those in 1990 [1].

Rintaro Moroi and Kunio Tarasawa contributed equally to this work.

karger@karger.com
www.karger.com/dig

Correspondence to:
Rintaro Moroi, rinta@med.tohoku.ac.jp

Although the number of patients with diverticula is increasing in Japan [2, 3], whether the trend in the number of patients with diverticulitis in Japan is also increasing remains unclear. Clarifying the trend in the number of diverticulitis cases is essential in clinical practice.

Some patients with diverticulitis present with accompanying abdominal abscess or peritonitis (complicated diverticulitis), and surgical intervention is needed in such cases. Most patients with diverticulitis do not have abdominal abscess or peritonitis and usually require conservative therapy. However, the need for antibiotics in diverticulitis without abdominal abscess or peritonitis (uncomplicated diverticulitis) remains controversial. Two randomized trials reported that the surgery rate and complication rate in uncomplicated diverticulitis did not differ between antibiotic and nonantibiotic groups [4, 5]. However, those studies included a relatively small number (several hundred) of participants. Investigating the need for antibiotics in uncomplicated diverticulitis with a large number of participants is essential to guide clinical practice.

We have previously reported several studies using the Diagnosis Procedure Combination (DPC) nationwide database [6–14]. Use of the DPC, which contains a large amount of admission data, can facilitate clarification regarding the clinical practice of diverticulitis and evaluation of the efficacy of antibiotics. The aim of this study was to evaluate the effectiveness of antibiotics for uncomplicated diverticulitis and to clarify current clinical practice of diverticulitis in Japan.

Materials and Methods

DPC Data System

The DPC database is a medical claims database for inpatient and acute-care hospitals in Japan. In 2018, the database covered approximately 83% of acute-care beds in 1,730 hospitals [15]. There are six distinct categories of diagnosis in the DPC database: “main diagnosis,” “main disease triggering admission,” “most resource-consuming diagnosis,” “second most resource-consuming diagnosis,” “comorbidities at admission,” and “complications after admission.” Furthermore, the database contains patient demographics (including sex, age, body mass index [BMI], smoking history, and Charlson Comorbidity Index [CCI]), procedures (surgery and administration of antibiotics), hospital type (academic hospital or other), medical costs, length of hospital stay, and condition at discharge (death or other). The validity of disease names for diverticulitis and other diseases using International Classification of Diseases Tenth Revision (ICD-10) codes was confirmed [16, 17].

Extraction of Eligible Admissions and Data Collection

We collected administrative claims data for all patients admitted to and subsequently discharged from more than 1,100 DPC-participating hospitals for diverticulitis, from April 2012 through March 2022. Diverticulitis was identified using ICD-10 code K573 or K574 for the main disease triggering admission or using ICD-10 code K572, K573, K574, or K575 for the most resource-consuming diagnosis. We subsequently selected eligible admissions containing the word “diverticulitis” in the disease name. We excluded entries for suspected cases of diverticulitis containing the word “suspicious.” We also excluded cases containing the words “abscess,” “peritonitis,” and “perforation” related to comorbidities at admission. We eventually extracted patient admissions for diverticulitis in which computed tomography (CT) was performed within 2 days after admission to only select urgent admissions (Fig. 1).

We also collected the following data on patient admissions from the DPC database: patient age, sex, BMI, smoking history, and CCI [18]; hospital type (academic hospital or other); patient condition at discharge (in-hospital death); medical costs (available data from 2012 to 2021); length of hospital stay; and surgery (intestinal resection and stoma creation). Information regarding the administration of antibiotics was also collected.

Statistical Analysis

We divided the eligible patient admissions with and without initiation of antibiotics within 2 days after admission into an antibiotic group and a nonantibiotic group, respectively. We also classified the enrolled patient admissions into five categories according to age (≤49 years, 50–59 years, 60–69 years, 70–79 years, ≥80 years) and into three categories according to BMI (underweight: <18.5 kg/m^2, normal weight: 18.5–24.9 kg/m^2, overweight: >25.0 kg/m^2) according to the World Health Organization classification [19]. We investigated the clinical practice of diverticulitis by clarifying the actual state of antibiotics for diverticulitis.

We conducted propensity score matching analysis to evaluate the impact of antibiotics on the clinical course of diverticulitis. We used the following variables for propensity score matching: sex, age, and BMI categories, as described above; CCI; smoking history (categorized using the Brinkman index [BI] [20]); and hospital type. We subsequently compared antibiotic and nonantibiotic groups using rates of intestinal resection, stoma creation, and in-hospital death using χ^2 tests and the length of hospitalization and medical costs during the hospital stay using Wilcoxon’s signed-rank test. We also performed multivariate logistic regression analysis using data both before and after propensity score matching to identify clinical factors that affect intestinal resection and stoma creation.

The threshold for statistical significance was set at $p < 0.05$. All analyses were performed using JMP Pro16 software (SAS Institute, Tokyo, Japan). We calculated the C-statistics and standardized differences for each variable described above in propensity score matching.

Results

Background of Study Population

We finally included 131,936 eligible admissions in this study; 125,875 were assigned to the antibiotic group and the remaining 6,061 to the nonantibiotic

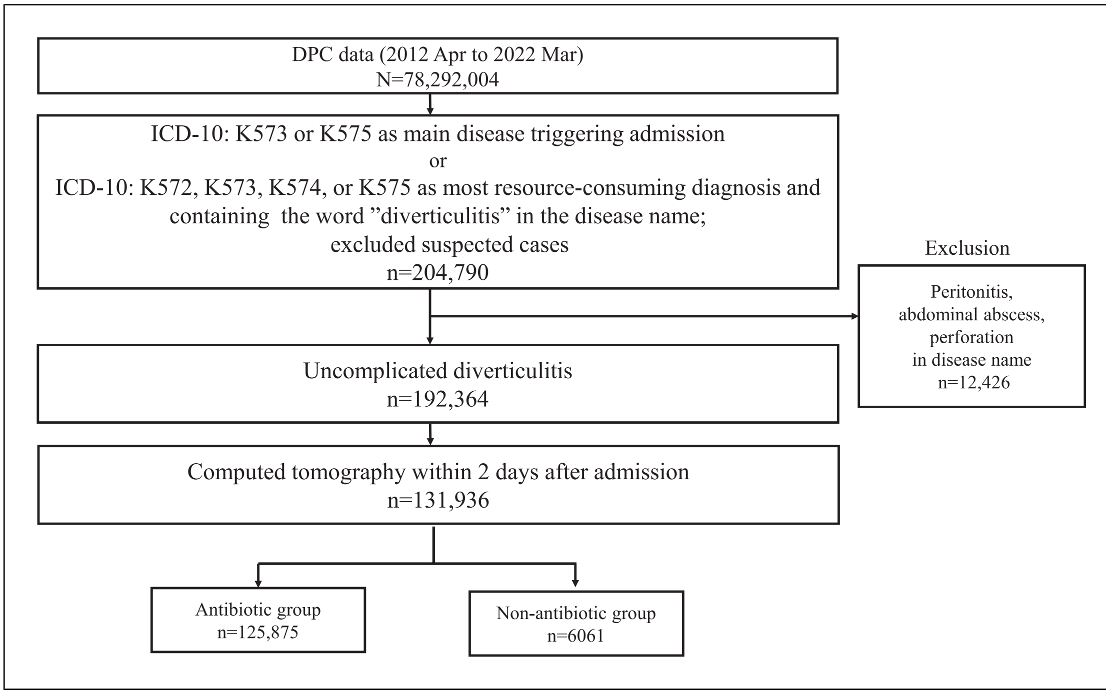

Fig. 1. Study flowchart. Eligible admissions were extracted from the database as per this flowchart. DPC, Diagnosis Procedure Combination; ICD-10, International Classification of Diseases Tenth Revision.

group (Fig. 1). After propensity score matching, 6,061 pairs of patient admissions were selected. The C-statistic was 0.70, and the standardized difference for each variable was <0.1. The characteristics of the study population are summarized in Table 1. The characteristics of both groups were similar after propensity score matching.

Descriptive Analysis of Diverticulitis

Details of antibiotics use are summarized in Figure 2. Second-generation cephalosporins were the most-used antibiotics (42.2%) in the treatment of diverticulitis, followed by third-generation cephalosporins (17.4%) and quinolones (15.2%).

Comparison of Clinical Outcomes between Antibiotic and Nonantibiotic Groups

Table 2 shows the results of comparisons of the clinical outcomes between the antibiotic and nonantibiotic groups after propensity score matching. The occurrence of surgery and stoma creation in the antibiotic group was significantly lower than that in the nonantibiotic group (0.61 vs. 3.09%, $p < 0.0001$, and 0.08 vs. 0.26, $p < 0.0001$, respectively). The rates of in-hospital death did not differ between the antibiotic and nonantibiotic groups (0.33 vs. 0.31%, $p = 1.00$). In contrast, medical costs in the antibiotic group were higher than those in the nonantibiotic group (315,820 JPY vs. 300,175 JPY; $p < 0.0001$).

Multivariate Analysis of Surgery and Stoma Creation

The results of multivariate analysis using the data before propensity score matching for the association between clinical factors and surgery (intestinal resection and stoma creation) are summarized in Table 3. In multivariate analysis, non-initiation of antibiotics within 2 days after admission was identified as a clinical factor that increased the risk of surgery (odds ratio [OR] = 5.19, 95% confidence interval [CI]: 4.38–6.16, $p < 0.0001$) and stoma creation (OR = 2.68, 95% CI: 1.53–4.70, $p = 0.0006$).

Table 4 shows the results of multivariate analysis using the data after propensity score matching for the association between clinical factors and surgery. This multivariate analysis also revealed that non-initiation of antibiotics within 2 days after admission was identified as a clinical factor that increased the risk of surgery (OR = 5.26, 95% CI: 3.68–7.50, $p < 0.0001$) and stoma creation (OR = 3.24, 95% CI: 1.19–8.87, $p = 0.022$).

Table 1. Comparison of clinical characteristics of the study population before and after propensity score matching

	Before propensity score matching, total *N* = 131,936			After propensity score matching, total *N* = 12,122			
	nonantibiotic group, *n* = 6,061	antibiotic group, *n* = 125,875	*p* value	nonantibiotic group, *n* = 6,061	antibiotic group, *n* = 6,061	*p* value	standardized difference
Sex (male/female)	3,145/2,916	70,001/55,874	<**0.0001**	3,145/2,916	3,152/2,909	0.91	0.0023
Mean age (SD), years	65.8 (18.1)	52.5 (17.5)	<**0.0001**	65.8 (18.1)	65.4 (18.0)	0.27	
Age categories, years			<**0.0001**			1.00	
≥80	1,643	9,892		1,643	1,643		0
70–79	1,342	14,159		1,342	1,342		0
60–69	1,036	18,741		1,036	1,037		0.00044
50–59	821	24,548		821	820		0.00048
≤49	1,219	58,535		1,219	1,219		
Mean BMI (SD), kg/m^2	22.9 (4.1)	23.1 (4.9)	**0.0078**	22.9 (4.1)	23.0 (8.9)	0.63	
BMI categories			<**0.0001**			1.00	
Overweight (>25.0 kg/m^2)	1,451	76,277		1,451	1,452		0.00039
Normal range (18.5–24.9 kg/m^2)	3,636	32,644		3,636	3,638		0.00067
Underweight (<18.5 kg/m^2)	544	10,187		544	547		0.0017
CCI score			<**0.0001**			1.00	
0	3,954	99,853		3,954	3,953		0.00035
1	1,251	16,805		1,251	1,252		0.00041
2	856	9,217		856	856		0
BI			<**0.0001**			1.00	
BI <400	4,288	90,371		4,288	4,291		0.0011
400 ≤ BI < 600	365	9,336		365	362		0.0021
600 ≤ BI < 1,200	556	10,929		556	558		0.0014
1,200 ≤ BI	189	2,575		189	184		0.0048
Academic hospital (yes/no)	257/5,804	6,063/119,812	**0.039**	257/5,804	257/5,804	1.00	0

C-statistic: 0.70. SD, standard difference; BMI, body mass index; BI, Brinkman index.

Discussion

Our analysis after propensity score matching demonstrated that antibiotics use could reduce the risk of intestinal resection and stoma creation for uncomplicated diverticulitis. Multivariate analysis using data before propensity score matching also showed that nonantibiotic therapy was a clinical factor that increased the risk of intestinal resection and stoma creation. Second- and third-generation cephalosporins were the most common antibiotics administered for diverticulitis in Japan.

The efficacy of antibiotic therapy for uncomplicated diverticulitis is controversial. Two randomized controlled trials reported no differences in the time to recovery, hospital stay, complicated diverticulitis, and sigmoid resection between groups receiving antibiotics or conservative therapy [4, 5]. Two guidelines for diverticular diseases from Germany and the European Society of Coloproctology recommend that antibiotic therapy need not be prescribed routinely [21, 22]. In contrast, the guideline of the Japanese Gastroenterological Association states that antibiotic therapy is considered acceptable in present clinical practice because no studies have been conducted in Japan [23]. Our study included a high volume of patient admissions and showed that initiation of antibiotic therapy within 2 days after admission could reduce the risk of intestinal resection and stoma creation. Both analyses after propensity score matching and a multivariate analysis showed the same result. To our best knowledge, this is the first study to report the clinical efficacy of antibiotics for uncomplicated

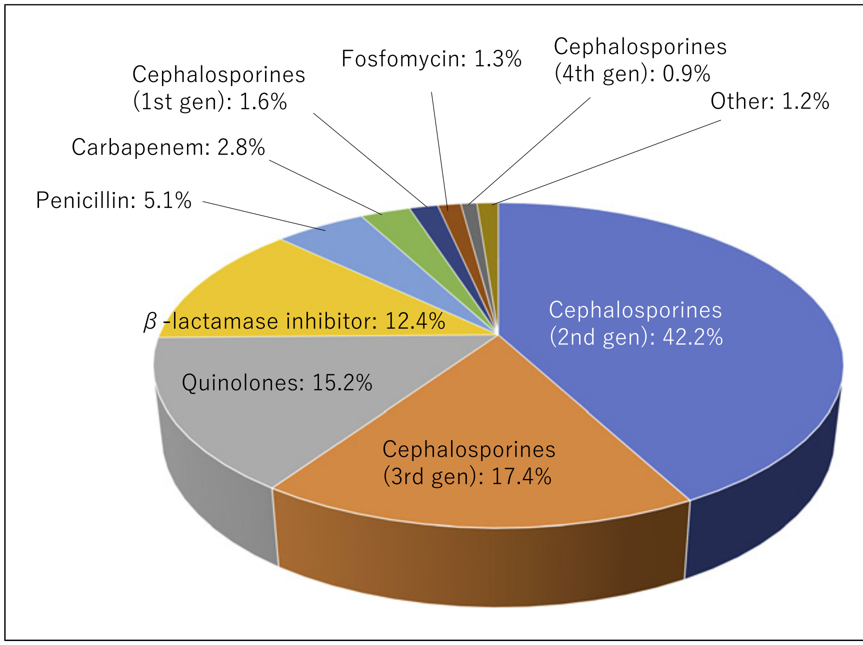

Fig. 2. Clinical practice of uncomplicated diverticulitis. Use rate of antibiotics for uncomplicated diverticulitis in Japan.

Table 2. Comparison of clinical outcomes between nonantibiotic and antibiotic groups

Clinical outcomes	After propensity score matching, total *N* = 12,122		
	nonantibiotic group (*n* = 6,061)	antibiotic group (*n* = 6,061)	*p* value
Intestinal resection, *n* (%)	187 (3.09)	37 (0.61)	<**0.0001***
Stoma creation, *n* (%)	16 (0.26)	5 (0.08)	**0.027***
In-hospital death, *n* (%)	19 (0.31)	20 (0.33)	1.00*
Median length of hospital stay (interquartile range), days	8 (5–11)	8 (6–10)	<**0.0001****
Median medical costs of hospital stay (interquartile range), JPY	300,175 (222,765–407,347.5)	315,820 (254,630–394,770)	<**0.0001****

*χ^2 test. **Median test.

diverticulitis. However, our study is retrospective, and several biases such as selection bias could exist, which we discuss below. Although there are some limitations, our study findings indicated that antibiotic therapy in the early phase after admission could be effective; therefore, antibiotic therapy for uncomplicated diverticulitis should be considered. We additionally conducted another propensity score matching to evaluate in more detail patients' background and eliminate confounding bias to the extent possible. Similar results in the clinical outcomes were observed (online suppl. Tables 1, 2; for all online suppl. material, see https://doi.org/10.1159/000534167).

The reason the results differed between the two previous randomized controlled trials and our data might be owing to differences in the number of participants in each study. The two previous randomized controlled trials included hundreds of participants. Although calculation of the required sample size was conducted in each study, the number of participants might have been too small to compare the rates of surgery and complication; those rates in the previous studies were very low (1.9–3.8%) [4, 5]. On the contrary, the DPC database includes so-called big data, with a large amount of admission data across Japan. Our analysis after propensity score matching

Table 3. Multivariate analysis of the association among clinical factors and surgery in the study population (before propensity score matching)*

Clinical factors	Number of patients (before propensity score matching)	Intestinal resection			Stoma creation		
		OR	95% CI	*p* value	OR	95% CI	*p* value
Sex	Male: 73,146	Reference		<**0.0001**	Reference		0.82
	Female: 58,790	**0.63**	**0.55–0.73**		0.95	0.59–1.52	
Age categories	≥80 years: 11,535	1.06	0.15–1.39	81	**16.89**	**7.00–40.79**	<**0.0001**
	70–79 years: 15,501	**1.92**	**1.56–2.36**	<**0.0001**	**13.38**	**5.66–31.60**	<**0.0001**
	60–69 years: 19,777	**1.85**	**1.52–2.25**	<**0.0001**	**4.66**	**1.79–12.18**	**0.0017**
	50–59 years: 25,369	**1.63**	**1.35–1.98**	<**0.0001**	**4.46**	**1.77–11.26**	**0.0015**
	<50 years: 59,754	Reference			Reference		
BMI classification	Overweight: 34,095	0.82	0.70–0.97	0.18	0.60	0.33–1.11	0.10
	Normal: 79,863	Reference			Reference		
	Underweight: 10,731	1.52	1.22–1.89	0.40	1.37	0.71–2.64	0.35
BI	BI <400: 94,659	Reference			Reference		
	400 ≤ BI < 600: 9,701	1.06	0.82–1.37	0.64	**2.15**	**1.03–4.48**	**0.041**
	600 ≤ BI < 1,200: 11,485	**1.29**	**1.05–1.37**	**0.016**	0.97	0.44–2.13	0.94
	1,200 ≤ BI: 2,764	1.00	0.67–1.49	1.00	1.04	0.31–3.43	0.28
Academic hospital	Yes: 6,320	**1.68**	**1.31–2.14**	<**0.0001**	1.83	0.84–4.00	0.13
	No: 125,616	Reference			Reference		
CCI score	0: 103,807	Reference			Reference		
	1: 18,056	1.12	0.93–1.35	0.22	0.70	0.37–1.32	0.27
	≥2: 10,073	1.20	0.96–1.49	0.11	1.23	0.69–2.18	0.49
Initiation of antibiotics within 2 days after admission	Yes: 125,875	Reference		<**0.0001**	Reference		**0.0006**
	No: 6,061	**5.19**	**4.38–6.16**		**2.68**	**1.53–4.70**	

BMI, body mass index; CI, confidence interval. *Logistic regression analysis.

included over 6,000 admissions each in the antibiotic and nonantibiotic groups, making it easy to detect slight differences in the surgery rate between groups.

The rates of in-hospital death were not different between the antibiotic and nonantibiotic groups. A multicenter retrospective study reported that the rate of in-hospital death among patients with uncomplicated diverticulitis was 0.2% [24], which was similar to our result. The mortality rate owing to uncomplicated diverticulitis is expected to be very low. Therefore, antibiotic therapy might not affect the mortality rate in uncomplicated diverticulitis.

Our multivariate analysis revealed that older age was a clinical factor that increases the risk of stoma creation. Elderly patients are usually expected to have a worse general condition compared to younger patients and develop complications after surgery. Therefore, surgeons may be likely to select stoma creation for elderly patients in order to avoid anastomotic leakage. Another retrospective study also showed that older age was a risk factor that was associated with stoma creation [25].

The median duration of hospital stay and median medical costs differed between the two groups. Although the interquartile range in each group was slightly different, the length of hospital stay in each group was 8 days. We consider that differences in the duration of hospital stay may not have clinical importance. However, medical costs in the antibiotic group were higher than those in the nonantibiotic group, which might be owing to the cost of antibiotics. Although higher than the surgery rate in the antibiotic group, the surgery rate in the nonantibiotic group was only approximately 3%. Therefore, the higher surgery rate in the nonantibiotic group might not affect the overall medical costs.

This study has several limitations. First, the DPC database does not contain details of patients' clinical data or information including body temperature, laboratory data, and CT findings. Those data are useful to detect the severity and complications of diverticulitis and clinical course of diverticulitis. Therefore, we alternatively evaluated the rates of intestinal resection, stoma creation, and in-hospital death.

Table 4. Multivariate analysis of the association among clinical factors and stoma creation in the study population (after propensity score matching)*

Clinical factors	Number of patients (after propensity score matching)	Intestinal resection			Stoma creation		
		OR	95% CI	*p* value	OR	95% CI	*p* value
Sex	Male: 6,297	Reference		**0.076**	Reference		0.49
	Female: 5,825	**0.66**	**0.49–0.90**		1.39	0.54–3.60	
Age categories	≥80 years: 3,285	**0.46**	**0.28–0.75**	**0.0017**	6.31	0.75–53.09	0.090
	70–79 years: 2,684	0.92	0.61–1.39	0.69	2.77	0.30–25.91	0.37
	60–69 years: 2,073	1.07	0.71–1.63	0.75	1.91	0.17–21.65	0.60
	50–59 years: 1,641	1.31	0.86–2.00	0.20	3.83	0.39–37.58	0.25
	<50 years: 2,438	Reference			Reference		
BMI classification	Overweight: 2,903	**0.66**	**0.47–0.94**	**0.20**	0.85	0.27–2.64	0.78
	Normal: 7,274	Reference			Reference		
	Underweight: 1,091	**1.59**	**1.05–2.41**	**0.30**	1.51	0.48–4.72	0.48
BI	BI <400: 8,579	Reference			Reference		
	400 ≤ BI < 600: 727	1.03	0.60–1.77	0.91	**3.79**	**1.01–14.23**	**0.048**
	600 ≤ BI < 1,200: 1,114	1.28	0.84–1.96	0.25	1.34	0.28–6.51	0.71
	1,200 ≤ BI: 373	1.46	0.74–2.86	0.28	$1.1174e^{-6}$	0–	0.99
Academic hospital	Yes: 514	**3.3**	**2.19–4.98**	**< 0.0001**	2.73	0.62–12.03	0.18
	No: 11,608	Reference			Reference		
CCI score	0: 7,907	Reference			Reference		
	1: 2,503	1.01	0.71–1.44	0.97	0.86	0.23–3.25	0.82
	≥2: 1,712	0.96	0.63–1.47	0.85	**3.46**	**1.31–9.16**	**0.012**
Initiation of antibiotics within 2 days after admission	Yes: 6,061	Reference		**< 0.0001**	Reference		**0.022**
	No: 6,061	**5.26**	**3.68–7.50**		**3.24**	**1.19–8.87**	

BMI, body mass index; CI, confidence interval. *Logistic regression analysis.

The DPC database also does not contain the time of admission, only the date of admission. Therefore, we defined admissions with antibiotic administration within 2 days after admission as the antibiotic group. Similarly, we limited cases to those that received CT within 2 days after admission so as to only select urgent admissions owing to diverticulitis. The reason why patients in the nonantibiotic group were not administered antibiotics within 2 days after admission was unclear. Furthermore, the criteria of antibiotics use were also unclear on the DPC database. Second, several biases and confounding factors could exist even though we conducted propensity score matching and multivariate analysis. We excluded complicated cases containing the words "abscess," "peritonitis," and "perforation" in the descriptions of comorbidities at admission. However, there is a possibility that we did not completely eliminate those complications at admission. Furthermore, the DPC database contains only data of inpatients, not outpatients in other hospitals or clinics. Some patients with uncomplicated diverticulitis were conservatively treated without admission. Our data may not reflect all patients with uncomplicated diverticulitis, and selection bias might exist in this study. For the same reason, we were not able to collect the data of patients' background including past medical history and medications which improves the validity of comparison between antibiotic and nonantibiotic groups in this study. Third, the DPC database does not follow patients who are transferred to another hospital. Therefore, we calculated the number of admissions, not individuals. We cannot analyze the long-term prognosis and distinguish whether the admission is a first one or a recurrence for the same reason. Although our results from a large amount of database indicated that antibiotic administration for diverticulitis might improve the outcome, further prospective studies with an adequate number of participants are necessary to address the limitations in this study.

Conclusion

Antibiotic administration may improve the outcome of uncomplicated diverticulitis. However, there are several limitations in this study. Therefore, further prospective studies are needed to more precisely clarify the effectiveness of antibiotics and address the limitations in this study.

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Statement of Ethics

The study protocol was reviewed and approved by the Ethics Committee of the Tohoku University Graduate School of Medicine (2021-1-815). The need for informed consent was waived by the Ethics Committee of the Tohoku University Graduate School of Medicine.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R.M., K.T., H.N., Y.S., T.N., H.S., S.H., and Y. Kakuta contributed to the study conception and design. Material preparation, data collection, and analysis were performed by R.M., K.T., K. Fujimori, and K. Fushimi. The first draft of the manuscript was written by R.M. and revised critically by K.T., Y. Kinouchi, and A.M. All the authors read and approved the final version of the manuscript.

Data Availability Statement

Data cannot be shared with researchers who are not approved for access by the Japanese Ministry of Health, Labour and Welfare. Further inquiries can be directed to the corresponding author.

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