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# Analysis of Recurrence Management in Patients Who Underwent Nonsurgical Treatment for Acute Appendicitis

Tsung-Jung Liang, MD, Shiuh-Inn Liu, MD, PhD, Chung-Yu Tsai, MD, Chi-Hsiang Kang, MD, Wei-Chun Huang, MD, PhD, Hong-Tai Chang, MD, and I-Shu Chen, MD

**Abstract:** The recurrence rate for acute appendicitis treated nonoperatively varies between studies. Few studies have adequately evaluated the management of these patients when appendicitis recurs. We aimed to explore the recurrence rate and management of patients with acute appendicitis that were first treated nonoperatively.

We identified patients in the Taiwan National Health Insurance Research Database who were hospitalized due to acute appendicitis for the first time between 2000 and 2010 and received nonsurgical treatment. The recurrence and its management were recorded. Data were analyzed to access the risk factors for recurrence and factors that influenced the management of recurrent appendicitis.

Among the 239,821 patients hospitalized with acute appendicitis for the first time, 12,235 (5.1%) patients were managed nonoperatively. Of these, 864 (7.1%) had a recurrence during a median follow-up of 6.5 years. Appendectomy was performed by an open and laparoscopic approach in 483 (55.9%) and 258 (29.9%) patients, respectively. The remaining 123 (14.2%) patients were again treated nonsurgically. Recurrence was independently associated with young age, male sex, percutaneous abscess drainage, and medical center admission by multivariable analysis. In addition, age <18, a (CCI) <2, medical center admission, and a longer time to recurrence were correlated with using laparoscopy to treat recurrence. Neither type of appendicitis, percutaneous abscess drainage, nor length of first time hospital stay had an influence on the selection of surgical approach.

In conclusion, a laparoscopic appendectomy can be performed in recurrent appendicitis cases, and its application may not be related to previous appendicitis severity.

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**Abbreviations:** CCI = Charlson Comorbidity Index, CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases Ninth Edition Clinical Modification, IQR = interquartile range, LA = laparoscopic

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From the Division of General Surgery (T-JL, S-IL, C-YT, C-HK, H-TC, I-SC), Department of Surgery, Kaohsiung Veterans General Hospital, Kaohsiung; School of Medicine (S-IL, W-CH, H-TC), National Yang-Ming University, Taipei; and Critical Care Center and Cardiovascular Medical Center (W-CH), Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan.

Correspondence: I-Shu Chen, Division of General Surgery, Department of Surgery, Kaohsiung Veterans General Hospital, No. 386, Dazhong 1st Rd, Zuoying District, Kaohsiung 81362, Taiwan (e-mail: nugaticc@gmail.com).

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appendectomy, NHIRD = National Health Insurance Research Database, OA = open appendectomy, OR = odd ratio.

## INTRODUCTION

Several studies have evaluated the outcomes of patients with acute appendicitis who were first treated nonoperatively.<sup>1–3</sup> The reported recurrence rates vary widely from 5% to 37%.<sup>4</sup> Some authors have also suggested that there is a risk of potentially missing a diagnosis for the patients treated nonoperatively because there is no surgical exploration and therefore no specimens retrieved for pathologic examination.<sup>5,6</sup> These debates led to an argument of whether an interval appendectomy should be performed.<sup>4,7</sup> Because the number of patients with recurrent appendicitis enrolled in most previous studies was small,<sup>8</sup> no strong evidence can be provided, and no concrete suggestions can be made. Therefore, these debates remain unresolved.

Laparoscopic appendectomy (LA) is currently widely applied for the treatment of acute appendicitis. It has the benefits of a decreased wound infection rate, shorter hospital stay, and better diagnostic power, especially in women of childbearing age.<sup>9,10</sup> However, when it comes to recurrent appendicitis, some wonder if LA is an appropriate treatment for a repeatedly inflamed appendix in conjunction with the probable dense adhesions surrounding it. Despite these concerns, LA has been utilized in complicated appendicitis<sup>11</sup> and some support its use in interval appendectomies.<sup>7</sup> However, the feasibility of LA in the management of recurrent appendicitis remains unclear.

The purpose of this study was to explore the recurrence rate and subsequent management of patients with acute appendicitis who were treated nonoperatively for their first occurrence. We used nationwide, population-based administrative claims data to ensure there were sufficient patients with appendicitis recurrence for analysis.

## METHODS

### Patients and Study Design

This study analyzed administrative claims data obtained from the Taiwan National Health Insurance Research Database (NHIRD) from 1996 to 2012. The accuracy of the NHIRD in diagnosis, drug prescriptions, comorbidities, invasive procedures, and in-hospital mortality has been validated in cardiovascular disease and stroke.<sup>12–14</sup> This study's population comprised all patients who were hospitalized with a primary diagnosis of acute appendicitis [International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) code 540.0, 540.1 and 540.9] for the first time between January 2000 and December 2010 and received nonsurgical treatment. Nonsurgical treatment was defined as no procedure code indicating appendectomy (ICD-9-CM code: 47.0, 47.01, and 47.09)

in the claim data of this index hospitalization. Patients were excluded if their first appendicitis admission occurred in 2011 or 2012 to ensure that all participants were followed for at least 2 years. Patients were excluded if they were ever hospitalized due to appendicitis or received an appendectomy between January 1996 and December 1999 (N=983). Therefore, enrolled patients were known to have at least 4 years free of disease prior to the index admission. This study was approved by the Human Research Committee of Kaohsiung Veterans General Hospital.

## RECURRENCE

Recurrence was defined as readmission with a primary diagnosis of acute appendicitis after the index hospitalization. Thus, patients without a record of rehospitalization during the study period were considered “nonrecurrence.” Patients were also viewed as nonrecurrence if the primary diagnosis of a rehospitalization was not appendicitis. Readmissions within the first 3 months after the index hospitalization were excluded because some authors suggest that early readmission reflects initial treatment failure rather than recurrence.<sup>15</sup> In addition, some patients could be scheduled for an interval appendectomy within 6 to 12 weeks after the initial nonoperative treatment.<sup>16</sup> Therefore, without these exclusion criteria, the recurrence rate would have been overestimated.

Patients with recurrence were categorized into 3 groups based on the treatments they received [nonoperative treatment, LA, or open appendectomy (OA)]. For those treated nonoperatively again, attention was paid to detect if they developed another recurrence. All patients were followed until death or the end of 2012.

## Statistical Analysis

The factors that were possibly related to recurrence were assessed by univariate analysis using a Cox regression. Variables that appeared to be significantly associated with recurrence were entered into the stepwise Cox proportional hazards model. Recurrence-free survival time was calculated from the time of index hospitalization to recurrence, death, or December 31, 2012, whichever came first. To determine the predictive factors for using a laparoscopic approach (ICD-9-CM code: 47.01) to treat recurrent appendicitis, a logistic regression model was used. Factors analyzed for their influences included age, sex, Charlson Comorbidity Index (CCI), type of appendicitis (generalized peritonitis, peritoneal abscess, no abscess, or peritonitis), receiving percutaneous abscess drainage (ICD-9-CM code: 54.91), hospital level (medical center, regional hospital, district hospital), and length of hospital stay. Comparisons between groups were assessed using a  $\chi^2$  or Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables. Hospital costs were converted from New Taiwan dollars to US dollars by using the average exchange rate during the study period (30.5:1).

Analyses were conducted using IBM SPSS version 20 (IBM Corp, Armonk, NY) and SAS 9.4 (SAS Institute Inc, Cary, NC). A difference was considered statistically significant if 95% confidence interval (CI) did not overlap and *P* was <0.05.

## RESULTS

### Patient Demographics

A total of 239,821 patients hospitalized with acute appendicitis for the first time between 2000 and 2010 were identified

from the database. Of note, 71.4% of the patients were between 18 and 65-year old and 54.7% of the patients were men. Most of the patients (91.2%) were healthy with a CCI of 0. The type of appendicitis was coded as generalized peritonitis (19.1%), peritoneal abscess (6.2%), and no abscess or peritonitis (74.7%). For the initial management, 188,162 (78.5%) patients received OA while 39,415 (16.4%) patients received LA. The remaining 12,235 (5.1%) patients were treated nonoperatively (Figure 1).

### Recurrence and Its Predictors

Among the patients treated nonsurgically, 1427 (11.7%) were rehospitalized within 3 months (684, 452, and 291 patients in the first, second, and third months, respectively). Specifically, 864 (7.1%) patients developed disease recurrence in a median follow-up of 6.5 years [interquartile range (IQR): 3.8–9.4 years] (Figure 1). The median time to recurrence was 7.5 months (IQR: 4.4–19.8 months) and the mean time to recurrence was 16.8 months [standard deviation (SD): 22.8 months]. OA was performed in 483 patients (55.9%), LA in 258 patients (29.9%) and the remaining 123 patients (14.2%) were again treated without an operation. Second time recurrence was noted in 16 (13.0%) of these 123 patients. The median time to second recurrence was 4.9 months (IQR: 3.9–9.7 months). Appendectomies were performed by the open and laparoscopic approach in 10 (62.5%) and 1 (6.3%) patients, respectively. In 5 patients (31.2%), a nonoperative treatment was used; no in-hospital mortality was observed in these patients.

Table 1 shows a comparison between patients with and without disease recurrence. Using univariate and multivariable analyses, we found that recurrences were significantly associated with young age (Table 2). Specifically, relative to patients older than 65 years of age, an increased risk of recurrence was found in patients younger than 18-year old [hazard ratio (HR), 1.718; 95% CI, 1.371–2.154; *P* < 0.001], and those aged 18 to 65 years (HR, 1.274; 95% CI 1.041–1.560; *P* = 0.019). Male sex (HR, 1.168; 95% CI, 1.021–1.336; *P* = 0.024), having received percutaneous abscess drainage during the first appendicitis attack (HR, 1.869; 95% CI, 1.297–2.693; *P* = 0.001), and being hospitalized in a medical center (HR, 1.906; 95% CI, 1.662–2.187; *P* < 0.001) were also associated with a higher risk of appendicitis recurrence.

### Treatment Options for Recurrent Appendicitis

Table 3 shows the characteristics and management of the recurrent appendicitis. Age, CCI, type of appendicitis, and hospital level were significantly different between the 3 management groups (LA, OA, and nonoperative). Percutaneous abscess drainage was performed only in the nonoperative group (3.3%). The LA group had the longest time to recurrence, the shortest length of stay, and the highest hospital cost among the 3 treatment groups.

Results from multivariable logistic regression models showed that a CCI  $\geq 2$  was associated with a decreased likelihood of using a laparoscopic instead of a conventional open approach to treat recurrent appendicitis [odds ratio (OR), 0.095; 95% CI, 0.013–0.712; *P* = 0.022] (Table 4). In contrast, age <18 (OR, 2.644; 95% CI, 1.404–4.981; *P* = 0.003), medical center admission (OR, 1.653; 95% CI, 1.185–2.306; *P* = 0.003), and a longer time to recurrence (OR, 1.012; 95% CI, 1.005–1.019; *P* = 0.001) were independently associated with an increased likelihood of using a laparoscopic approach. Neither sex, type of appendicitis, previous percutaneous abscess

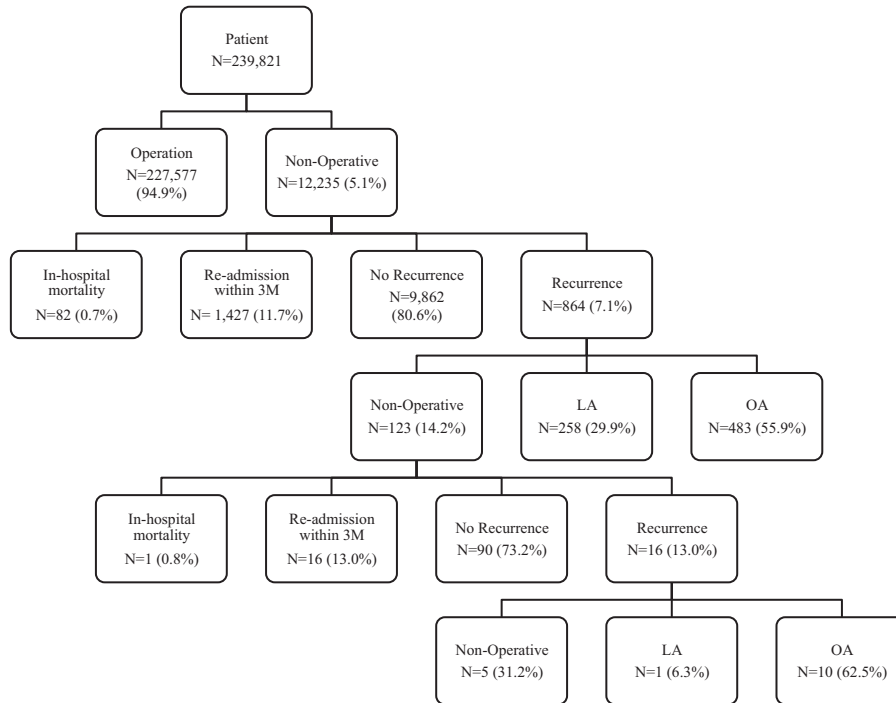


FIGURE 1. Flowchart of nonoperatively managed patients.

TABLE 1. Follow-Up for Nonsurgically Treated Appendicitis

Characteristic	No Recurrence (N = 9862)	Recurrence (N = 864)	P
Age, y			<0.001
<18	1858 (18.8%)	224 (25.9%)	
18–65	6205 (62.9%)	523 (60.5%)	
>65	1799 (18.2%)	117 (13.5%)	
Sex			0.012
Male	4956 (50.3%)	473 (54.7%)	
Female	4906 (49.7%)	391 (45.3%)	
Charlson Comorbidity Index			0.148
0	8259 (83.7%)	740 (85.6%)	
1	920 (9.3%)	79 (9.1%)	
≥2	683 (6.9%)	45 (5.2%)	
Type of appendicitis			<0.001
General peritonitis	2167 (22.0%)	167 (19.3%)	
Peritoneal abscess	2579 (26.1%)	286 (33.1%)	
No abscess or peritonitis	5116 (51.9%)	411 (47.6%)	
Percutaneous abscess drainage			<0.001
No	9684 (98.2%)	833 (96.4%)	
Yes	178 (1.8%)	31 (3.6%)	
Hospital level			<0.001
Medical center	3800 (38.5%)	477 (55.2%)	
Regional hospital	4228 (42.9%)	271 (31.4%)	
District hospital	1834 (18.6%)	116 (13.4%)	
Length of stay, d	7.1 (8.1)	6.9 (5.5)	0.016

Values are number of patients (%) or mean (standard deviation).

**TABLE 2.** Factors Associated With Recurrence After Nonsurgically Treated Appendicitis

	Univariate			Multivariate		
	HR	(95% CI)	P	HR	(95% CI)	P
Age, y						
<18	1.621	(1.296–2.028)	<0.001	1.718	(1.371–2.154)	<0.001
18–65	1.176	(0.962–1.437)	0.113	1.274	(1.041–1.560)	0.019
>65	1	(Reference)		1	(Reference)	
Sex						
Male	1.204	(1.053–1.376)	0.007	1.168	(1.021–1.336)	0.024
Female	1	(Reference)		1	(Reference)	
CCI						
<2	1	(Reference)				
≥2	0.869	(0.644–1.173)	0.359			
Peritonitis or abscess						
No	1	(Reference)		1	(Reference)	
Yes	1.236	(1.081–1.413)	0.002	1.094	(0.951–1.257)	0.209
Percutaneous abscess drainage						
No	1	(Reference)		1	(Reference)	
Yes	2.198	(1.536–3.147)	<0.001	1.869	(1.297–2.693)	0.001
Medical center						
No	1	(Reference)		1	(Reference)	
Yes	1.965	(1.719–2.247)	<0.001	1.906	(1.662–2.187)	<0.001
Length of stay, d	1.001	(0.992–1.010)	0.789			

CCI = Charlson Comorbidity Index; HR = hazard ratio.

drainage, nor the length of the first-time hospital stay had an impact on the selection of surgical approach for recurrent appendicitis.

## DISCUSSION

This study explored appendicitis recurrence and management in patients with acute appendicitis that were treated nonoperatively for their first occurrence. By using nationwide population-based claim data, we were able to retrieve a sufficient number of recurrent patients (N = 864) for analysis. We identified not only risk factors for recurrence, but also factors associated with using a laparoscopic approach to treat recurrent appendicitis. To our knowledge, the later part of the analysis has not been previously done in any other studies.

The recurrence rate for nonsurgically treated appendicitis in our study was 7.1%, which is comparable to the 7.4% (95% CI, 3.7–11.0) recurrence rate reported by Andersson and Petzold<sup>8</sup> in a meta-analysis that pooled 7 studies; 58 recurrences were detected in a total of 1061 enrolled patients. We also found that the recurrence rate almost doubled (from 7.1% to 13.0%) in patients who had already experienced 1 recurrence. For those who experienced 2 recurrences (N = 16), the second one developed faster than the first. The median time to recurrence was 9.7 months for the first recurrence and 4.9 months for the second (P = 0.026). Although there were no in-hospital mortalities during the management of the second recurrences, an appendectomy should be considered to prevent another episode of relapse in this group of patients due to their elevated incidence of recurrence.

In the present study, we found that young age, male sex, receiving percutaneous abscess drainage, and hospitalization in a medical center were independently associated with recurrent appendicitis. In comparison with previous studies, conflicting results in the factors associated with recurrent appendicitis were

observed. For example, Kaminski et al<sup>4</sup> reported that men were less likely to have recurrences than women, and that age, CCI, type of appendicitis, and percutaneous abscess drainage had no impact on recurrence. However, in a study published by McCutcheon et al,<sup>15</sup> age and hospital teaching status were significantly associated with recurrence. Sex was also associated with recurrence; males were more prone to have a disease recurrence than females. Therefore, our findings were consistent with McCutcheon et al in terms of sex and age.

Multivariable analysis found that age <18, CCI <2, medical center admission, and a longer time to recurrence were associated with using a laparoscopic approach to treat recurrent appendicitis. A longer time to recurrence may indicate a better resolution of previous inflammation and therefore make a laparoscopic approach more feasible. We also found that using a laparoscopic approach may not be related to the severity of the first appendicitis attack because type of appendicitis, previous percutaneous abscess drainage, and length of first-time hospital stay had no influence on the selection of surgical approach to treat patients with disease recurrence. In short, when determining the appropriate surgical approach for recurrent appendicitis, the patients' own condition (age and CCI) may have more of an effect than the severity of the previous insult. Therefore, recurrent appendicitis may be viewed as an entirely new episode of an old disease, especially if the time to relapse is longer.

A comparison of LA versus OA in pediatric patients was done in 1 meta-analysis of 18 publications.<sup>17</sup> The pooled results of patients with complicated appendicitis showed that LA was associated with a reduced risk of wound infection and bowel obstruction, and a shorter hospital stay, but a higher risk of intra-abdominal abscess. This is in consistent with results seen in adult patients.<sup>9</sup> The adoption of LA in children with recurrent appendicitis (N = 96 in this study) may provide similar benefits to those seen for LA in adults. This may explain why pediatric

**TABLE 3.** Characteristics and Management of Recurrent Appendicitis

Characteristic	LA (N = 258)	OA (N = 483)	Nonoperative (N = 123)	P
Age, y				<0.001
<18	96 (37.2%)	112 (23.2%)	16 (13.0%)	
18–65	146 (56.6%)	308 (63.8%)	69 (56.1%)	
>65	16 (6.2%)	63 (13.0%)	38 (30.9%)	
Sex				0.663
Male	137 (53.1%)	271 (56.1%)	65 (52.8%)	
Female	121 (46.9%)	212 (43.9%)	58 (47.2%)	
CCI				
0	241 (93.4%)	412 (85.3%)	87 (70.7%)	<0.001
1	16 (6.2%)	42 (8.7%)	21 (17.1%)	
≥2	1 (0.4%)	29 (6.0%)	15 (12.2%)	
Type of appendicitis (2nd)				<0.001
Peritonitis	40 (15.5%)	115 (23.8%)	25 (20.3%)	
Abscess	63 (24.4%)	98 (20.3%)	47 (38.2%)	
No abscess or peritonitis	155 (60.1%)	270 (55.9%)	51 (41.5%)	
Percutaneous abscess drainage (2nd)				<0.001
No	258 (100%)	483 (100%)	119 (96.7%)	
Yes	0 (0%)	0 (0%)	4 (3.3%)	
Hospital level (2nd)				0.017
Medical center	167 (64.7%)	264 (54.7%)	73 (59.3%)	
Regional hospital	79 (30.6%)	183 (37.9%)	36 (29.3%)	
District hospital	12 (4.7%)	36 (7.5%)	14 (11.4%)	
Time to recur, min	20.2 (28.1)	15.4 (19.4)	17.9 (21.7)	0.019
1st length of stay, d	6.98 (5.48)	6.35 (5.17)	8.76 (6.30)	<0.001
2nd length of stay, d	4.24 (3.20)	5.02 (3.57)	8.23 (6.92)	<0.001
Hospital cost (2nd)	1286 (608)	1158 (581)	1143 (1141)	0.039
In-hospital mortality	0	0	0	

Values are number of patients (%) or mean (standard deviation).

1st = the first time hospitalization; 2nd = the second time hospitalization (the recurrent episode); CCI = Charlson Comorbidity Index; LA = laparoscopic appendectomy; OA = open appendectomy.

surgeons in Taiwan tend to use laparoscopy to treat recurrent appendicitis in patients less than 18 years of age. However, caution should be exercised owing to the likelihood of developing intra-abdominal abscesses, especially in young children with a small habitus and limited working space for laparoscopy. Some studies suggest that a well-trained surgeon and adequate laparoscopic peritoneal lavage is the key to reducing intra-abdominal abscess formation.<sup>18,19</sup>

Recently, many researchers have challenged the role of appendectomy as the gold standard for treating appendicitis; they argue that antibiotic treatment may have equivalent results to surgery.<sup>1,20</sup> Most studies have been performed in patients with only uncomplicated appendicitis. However, Hansson et al<sup>21</sup> conducted a randomized clinical trial aimed at unselected patients. They concluded that antibiotic therapy seems to be a feasible first-line treatment for acute appendicitis. With this trend, there could be more patients whose first case of appendicitis is treated nonsurgically. The prognoses and subsequent management of these patients deserve more attention.

Among our patients with recurrence, only 1 patient (0.8%) in the nonoperative group died during their hospitalization. For those who experienced 2 recurrences, no in-hospital mortality was observed. These results seem to imply that although appendicitis did recur, the severity of the disease may not get worse each time. Further studies are certainly needed to clarify this assertion.

The present study has several limitations. First, the possibility of a coding error is inherent in any study using claims data. Therefore, only patients whose primary diagnosis (first diagnostic code) was appendicitis were enrolled in this study. Of note, our main focus was patients with appendicitis recurrence. Therefore, recurrent patients needed to have 2 times of coding appendicitis listed in the primary diagnosis to be enrolled in our study. Therefore, this made the diagnoses more accurate and reliable. Second, despite the multivariate analysis conducted, some factors, such as laboratory parameters and symptoms on presentation, were not available for adjustment. Third, operative reports were not available in this study and therefore we could not determine if the subsequent appendectomy following the initial nonoperative treatment was for the management of disease recurrence or prescheduled as an interval appendectomy, which was usually performed between 6 and 12 weeks after the first hospitalization. To avoid enrollment of patients undergoing elective appendectomy and bias our results, we excluded readmission within the first 3 months. However, early recurrence might have been missed based on this definition of recurrence. Nevertheless, nearly half of the early readmissions (47.9%) happened within the first 1 month, which in McCutcheon's opinion, is considered more of an initial treatment failure rather than a recurrence.<sup>15</sup> The estimated recurrence rate would rise to 13.1% and 9.4% if we only excluded patients who were readmitted within the first 1 and 2 months, respectively. Fourth,



**TABLE 4.** Factors Associated With Using Laparoscopy Approach (Versus Open Approach) to Treat Recurrent Appendicitis

	Univariate			Multivariate		
	OR	(95% CI)	P	OR	(95% CI)	P
Age, y						
<18	3.375	(1.829–6.228)	<0.001	2.644	(1.404–4.981)	0.003
18–65	1.866	(1.042–3.344)	0.036	1.496	(0.817–2.740)	0.192
>65	1	(Reference)		1	(Reference)	
Sex						
Male	0.886	(0.654–1.200)	0.433			
Female	1	(Reference)				
CCI						
<2	1	(Reference)		1	(Reference)	
≥2	0.061	(0.008–0.450)	0.006	0.095	(0.013–0.712)	0.022
Peritonitis or abscess (1st)						
No	1	(Reference)				
Yes	1.130	(0.835–1.529)	0.429			
Peritonitis or abscess (2nd)						
No	1	(Reference)				
Yes	0.842	(0.620–1.145)	0.274			
Percutaneous abscess drainage (1st)						
No	1	(Reference)				
Yes	1.778	(0.823–3.841)	0.143			
Medical center (2nd)						
No	1	(Reference)		1	(Reference)	
Yes	1.522	(1.114–2.080)	0.008	1.653	(1.185–2.306)	0.003
1st length of stay, d	1.022	(0.994–1.052)	0.123			
Time to recur, min	1.009	(1.002–1.015)	0.007	1.012	(1.005–1.019)	0.001

1st = the first time hospitalization; 2nd = the second time hospitalization (the recurrent episode); CCI = Charlson Comorbidity Index; OR = odds ratio.

the nonoperative treatment was not standardized. The usage of antibiotics varied between hospitals and physicians, including differences in antibiotic regimen, duration, and access of administration (intravenous versus oral). The decision to use percutaneous drainage was also dependent on the individual surgeon's discretion rather than a consensus. Fifth, there is a trend of increasing use of laparoscopy for appendectomy in Taiwan. In 2004, only 9% of all appendectomies done in Taiwan were laparoscopic. However, the percentage increased every year; LA accounted for half of all appendectomies performed in 2010. Therefore, patients with recurrent appendicitis may have had their operation done laparoscopically partly due to the incremental use of LA in general.

In conclusion, recurrence is a rare event in patients with appendicitis that were treated nonsurgically at first occurrence. LA was performed in nearly one-third of patients with recurrent appendicitis and seemed to be feasible, with a shorter hospital stay but higher cost. Interestingly, application of LA may be associated more with a patient's own characteristics rather than the severity of prior appendicitis.

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