



Predictive factors of perforated appendicitis: Impact of the C-reactive protein level



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ABSTRACT

Background: Perforated appendicitis without an associated abscess necessitates emergency surgery. However, it is difficult to predict the presence of perforation before surgery, and the predictive factors are still unclear. Our purposes were to characterize a patient population with perforated appendicitis without an associated abscess to identify the preoperative predictive factors of appendiceal perforation.

Methods: We retrospectively identified 150 patients who underwent appendectomy for acute appendicitis at our institution from June 2018 to November 2020. Logistic regression analysis was performed to analyze the concurrent effects of various factors on the prevalence of perforated appendicitis.

Results: Forty (29%) of 150 patients had appendiceal perforation detected intraoperatively. Of these 40 patients, only 19 had appendiceal perforation detected on preoperative computed tomography. Multivariable analysis found that a higher C-reactive protein level, higher total bilirubin level, and the presence of an appendiceal fecalith were independent predictive factors for appendicitis with perforation.

Conclusion: Our analysis suggests that the presence of an appendiceal fecalith, a total bilirubin level of more than 21.38 $\mu\text{mol/L}$, and a C-reactive protein level of more than $3.0 \times 10^4 \mu\text{g/L}$ are predictive factors of perforated appendicitis.

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INTRODUCTION

Although acute appendicitis is one of the most common diseases that can potentially be cured by nonoperative treatment, most patients with acute appendicitis need surgical treatment and sometimes emergency surgery. One of the reasons that appendicitis requires emergency surgery is perforation, as this increases the risk of complications [1]. Studies have reported the factors related to perforation risk in children, including the white blood cell count, C-reactive protein (CRP) level, timing of admission, and ascites [2,3]. Additionally, age and surgery delay are risk factors for in-hospital appendiceal perforation [4]. However, the predictive factors of perforation at the time of admission and the emergency surgical indications remain unclear. The present study aimed to examine the predictive factors for perforated appendicitis based on the condition at the time of admission.

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MATERIALS AND METHODS

This retrospective cohort study analyzed data from the database of surgery for appendicitis of Nagano Municipal Hospital and was approved by the ethics committee of our hospital. Our hospital is located in Nagano City, Japan, which has a population of 378,000. About 1,130 abdominal operations are performed in our hospital per year, and about 13,000 patients are seen at our emergency department per year.

A total of 150 consecutive patients aged 5 to 92 years underwent appendectomy for acute appendicitis from June 2018 to November 2020 and were potentially eligible for study inclusion. Patients who underwent interval appendectomy were excluded from the analysis. Patients who had gangrenous appendicitis with an associated abscess were treated with percutaneous drainage and antibiotics without surgery and were excluded from this study. Collected data included perforation status, age, sex, BMI, white blood cell count, CRP level, duration of symptoms, timing from onset to admission, and timing from admission to surgery. All these data (including CRP level) were routinely collected at the time of admission. Postoperative complications classified as Clavien–Dindo grade I or higher were recorded. The diagnosis of appendicitis was confirmed using computed tomography (CT) or

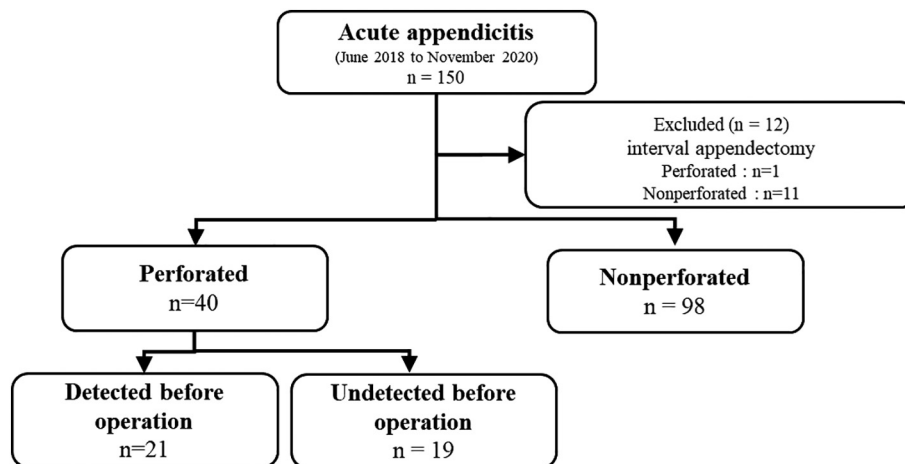


Fig 1. Flowchart of patient selection.

Of the 150 patients with acute appendicitis, 12 were excluded because they underwent interval appendectomy. Therefore, the study cohort comprised 138 patients with perforated or nonperforated appendicitis. Among the patients with perforated appendicitis, the perforation was detected preoperatively on CT in 21 patients but could not be detected on CT in 19 patients.

ultrasonography in most patients. The images were examined by an experienced radiologist who used them to make a definitive preoperative diagnosis. The presence of an appendicolith, appendiceal diameter, and ascites were noted on imaging. Appendicitis was diagnosed on imaging when the appendiceal diameter was greater than 6 mm; the diagnosis was supported by the presence of appendiceal wall thickening, fat stranding around the appendix, and free fluid. The standard treatment approach for acute appendicitis was laparoscopic appendectomy within 1 day of admission, and patients received intravenous antibiotics while waiting for surgery. Before the attainment of informed consent, patients were informed about the option of nonoperative management with antibiotics and the risks and benefits of both operative and nonoperative treatment.

The patients were divided into the perforated and nonperforated groups based on the intraoperative findings. Differences between the perforated and nonperforated groups were determined using the Mann–Whitney *U* test for the averages of continuous variables and the χ^2 test and Fisher exact test for categorical variables. Spearman rank

correlation was used to determine the relationship between perforation and the patient background data and condition. Unadjusted logistic regression analysis was conducted to determine the association between individual predictors and perforation. Baseline variables with $P < .05$ in univariate analysis were included in the multivariable model. All statistical analyses were conducted using IBM SPSS version 26.

RESULTS

Of the 150 patients who underwent appendectomy for acute appendicitis, 12 patients who underwent interval appendectomy were excluded. Intraoperative findings revealed perforation in 40 patients (29%). Of the 40 patients with perforated appendicitis, 19 were thought to have nonperforated appendicitis on preoperative CT (Fig 1).

Differences between the perforated and nonperforated groups are shown in Table 1. Compared with patients without perforation, patients with perforated appendicitis were more likely to be older ($P < .001$) and to have a high CRP level ($P < .001$), hyperbilirubinemia ($P < .001$), an appendiceal fecalith ($p = 0.001$), and a longer postoperative hospital stay ($P < .001$). However, the time from admission to operation and the complication rate did not significantly differ between the 2 groups ($P = .282$ and $P = .087$, respectively).

Table 2 shows the details of the complications. The incidence of Clavien–Dindo grade II and III complications did not significantly differ between the 2 groups, but the incidence of postoperative abscess formation was significantly higher in the perforated group than the nonperforated group ($P = .025$).

Table 1
Patient characteristics

	Perforated appendicitis group (n = 40)	Nonperforated appendicitis group (n = 98)	P value
Age	64.5 (43.5–80.5)	38.5 (19.0–57.0)	<.001
Male sex, n (%)	24 (60)	48 (49)	.264
Body mass index	22.0 (19.1–23.5)	20.3 (18.0–23.0)	.055
Onset to admission ≥ 24 h, n (%)	34 (85)	37 (38)	<.001
Admission to operation, h	6.0 (4.0–16.0)	8.5 (5.0–15.0)	.282
White blood cell count	13,100 (9,070–16,050)	13,750 (11,100–15,700)	.341
CRP level	8.76 (4.82–19.83)	0.89 (0.08–3.59)	<.001
Total bilirubin	22.2 (15.4–27.0)	15.4 (10.3–18.8)	<.001
Tenderness, n (%)	16 (40)	32 (33)	.56
Ascites, n (%)	26 (65)	53 (54)	.345
Appendiceal diameter	13 (10–14)	11 (9–13)	.003
Fecalith, n (%)	28 (70)	38 (39)	.001
Operation time, min	74.5 (57.5–92.0)	41.0 (34.0–60.0)	<.001
Days before discharge	7 (5–11)	3 (2–4)	<.001
Complications, n (%)	14 (35)	21 (21)	.087

Age, body mass index, white blood cell count, CRP level, total bilirubin, appendiceal diameter, operation time, and days before discharge are presented as median (interquartile range). CRP, C-reactive protein.

Table 2
Postoperative complications

	Perforated appendicitis group (n = 40)	Nonperforated appendicitis group (n = 98)	P value
Complications, n (%)	14 (35)	21 (21)	.087
Clavien–Dindo Grade II	7 (18)	11 (11)	.234
Clavien–Dindo Grade over III	4 (10)	4 (4)	.229
SSI	4 (10)	9 (9)	1
Abscess	5 (13)	1 (1)	.025
Anatomical leakage	1 (3)	1 (1)	.497
Gastrointestinal injury	0 (0)	2 (2)	1
Ileus	3 (8)	4 (4)	.413
Others	4 (10)	4 (4)	.229

SSI, surgical site infection.

Table 3
Uni- and multivariate analyses results

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.036	1.018–1.054	<.001			
Male sex	0.64	0.303–1.350	.241			
Body mass index	1.06	0.979–1.148	.152			
Onset to admission ≥ 24 h	8.577	3.277–22.447	<.001			
White blood cell count	1	1.000–1.001	.434			
CRP level	1.208	1.122–1.301	<.001	1.187	1.098–1.282	<.001
Total bilirubin	5.649	2.376–13.431	<.001	3.184	1.206–8.407	.019
Tenderness	1.271	0.592–2.727	.538			
Ascites	1.472	0.684–3.164	.323			
Appendiceal diameter	1.229	1.073–1.407	.03			
Fecalith	3.561	1.616–7.850	.002	3.439	1.265–9.349	.016

OR, odds ratio; 95% CI, 95% confidence interval; CRP, C-reactive protein.

The univariate logistic analysis results are shown in Table 3. Because age and timing to admission from onset were correlated with the CRP level, age and timing to admission from onset were excluded from the multivariate logistic analysis. The receiver operating characteristic curve analysis suggested that the ideal cutoff CRP level and total bilirubin level for identifying appendiceal perforation were $3.0 \times 10^4 \mu\text{g/L}$ and $21.38 \mu\text{mol/L}$, respectively (Fig 2). The cutoff CRP value resulted in a sensitivity of 95.5%, specificity of 64.7%, and negative predictive value (NPV) of 98.7%. The cutoff total bilirubin value resulted in a sensitivity of 55.5%, specificity of 80.6%, and NPV of 81.4%. Patients with acute appendicitis with both a fecalith and a high CRP level had a significantly higher perforation rate than those with either or neither (2.4% vs 25% vs 73%, $P = .013$).

Differences between the group of patients with perforated appendicitis detected on preoperative CT and those with perforated appendicitis undetected on preoperative CT are shown in Table 4. The CRP level was the only factor that significantly differed between the 2 groups ($P < .001$).

Table 4
Characteristics of the patients with perforated appendicitis that was detected on CT versus those with perforated appendicitis that was not detected on CT

	Perforated appendicitis on CT (n = 21)	Nonperforated appendicitis on CT (n = 19)	P value
Age	63.0 (43.5–84.5)	66.0 (43.0–78.0)	.39
Male sex, n (%)	12 (57)	12 (63)	.755
Body mass index	21.8 (20.1–23.5)	22.5 (19.0–23.7)	.942
Onset to admission ≥ 24 h, n (%)	19 (90)	15 (79)	.398
Admission to operation, h	6.0 (4.0–7.8)	12.0 (4.0–17.0)	.224
White blood cell count	15,200 (9,015–17,750)	11,800 (9,050–14,100)	.057
CRP level	18.08 (7.46–28.71)	4.84 (3.68–12.58)	<.001
Total bilirubin	23.9 (15.4–29.9)	22.2 (17.1–23.9)	.63
Tenderness, n (%)	7 (33)	9 (47)	.52
Ascites, n (%)	14 (67)	12 (63)	1
Appendiceal diameter, mm	13.0 (9.0–14.0)	14.0 (11.0–14.0)	.361
Fecalith, n (%)	14 (67)	14 (74)	.736
Operation time, min	73.0 (51.5–98.5)	75.0 (60.0–86.0)	.708
Days before discharge	7 (6.0–17.0)	6 (5.0–8.0)	.069
Complications, n (%)	9 (43)	5 (26)	.32

Age, body mass index, white blood cell count, CRP level, total bilirubin, appendiceal diameter, operation time, and days before discharge are presented as median (interquartile range). CRP, C-reactive protein.

DISCUSSION

This study analyzed a single-center database to investigate the predictive factors of acute appendicitis with perforation at the time of admission. The results showed that perforation was associated with the presence of an appendiceal fecalith and a high CRP level. Although the operation time and postoperative hospital stay were longer in the perforated group than the nonperforated group, the postoperative complications rate did not significantly differ between the 2 groups.

Previous studies have shown that an in-hospital delay of shorter than 24 hours before surgery for acute appendicitis is not associated with increased risks of postoperative complications [5–7]. However, some studies focusing on the risk factors for perforation or complicated appendicitis have reported a relationship between surgical delay and

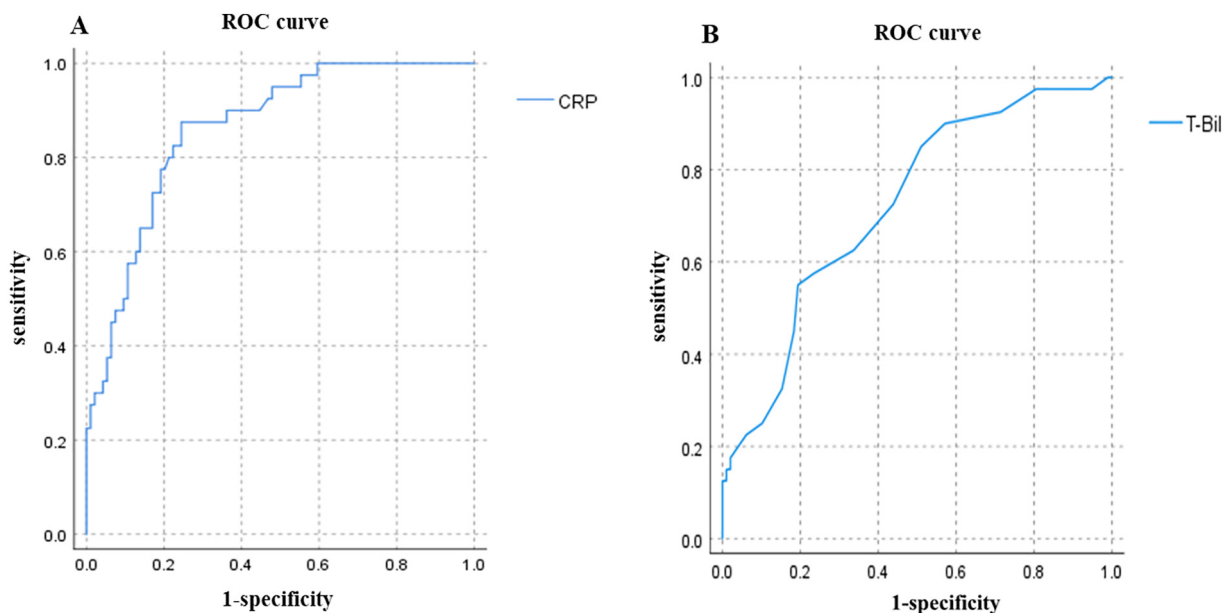


Fig 2. Receiver operating characteristics curves. A, At a cutoff value of $3.0 \times 10^4 \mu\text{g/L}$ for the C-reactive protein level, the area under the receiver operating characteristic curve (AUROC) is 0.862, sensitivity is 95.5%, and specificity is 64.7%. B, At a cutoff value of $21.38 \mu\text{mol/L}$ for the total bilirubin level, the AUROC is 0.723, sensitivity is 55.0%, and specificity is 80.6%.

perforation [3,5,8]. In addition, one recent retrospective cohort study reported that the in-hospital perforation risk of patients with acute appendicitis is not associated with the time to operation and antibiotic timing but is associated with age [4].

In our study, the time to operation did not significantly differ between patients with perforated versus nonperforated appendicitis, and both groups underwent appendectomy within 24 hours after admission. As expected, the postoperative complications rate did not significantly differ between the 2 groups, which could be the result of the optimal appendectomy procedure performed in our institution. However, the perforated group had a longer operation time and longer postoperative hospital stay than the nonperforated group; these factors might be disadvantages of perforation.

In the present study, the perforated group was significantly older than the nonperforated group, which supports the findings of other recent studies [4,9]. However, in our study, age was correlated with other factors, such as the time to admission and CRP level. Therefore, to detect more useful and clearer indicators of the need for emergency examination, we focused on the CRP level and established a cutoff value. Although previous studies of pediatric patients have reported that the white blood cell count, CRP level, time to admission, ascites, and tenderness are risk factors for perforated appendicitis [2,3], the white blood cell count, ascites, and tenderness were not associated with perforation in our study.

A recent study suggested that a delay of 24 hours or more between the onset of appendicitis and hospital admission is a risk factor for appendiceal perforation [6]. CRP is an inflammatory marker that is produced 12 to 24 hours after the onset of inflammation. Therefore, a high CRP level may be related to at least a 12-hour delay between onset and admission. CRP may be a more useful predictor of appendiceal perforation than the time from the onset, as the actual timing of the onset is sometimes unclear [10]. In addition, the present results support recent studies in showing that the presence of an appendiceal fecalith is a risk factor for perforation [3,11] and support a study showing that hyperbilirubinemia is a predictor of perforated appendicitis [12].

Although CT is widely used and has high sensitivity and specificity in diagnosing appendicitis, it is still difficult for a general practitioner to use CT to detect perforation at the time of admission in the emergency room. In our study, 19 perforated cases could not be detected on CT before surgery. This might reflect the occurrence of in-hospital perforation or misdiagnosis. Thus, the present study findings might be considerably helpful in predicting perforated appendicitis at the time of the first presentation.

Recent guidelines state that perforated appendicitis with an associated abscess can be treated with nonoperative management, while gangrenous appendicitis without an associated abscess and appendicitis with peritonitis require emergency surgery [13]. We suggest that clinicians should consider emergency surgery for patients who have an appendiceal fecalith, total bilirubin level of more than 21.38 $\mu\text{mol/L}$, and CRP level of more than $3.0 \times 10^4 \mu\text{g/L}$ without a drainable abscess on imaging or signs of peritonitis at the time of presentation.

Several limitations of this study should be acknowledged. First, this study was a retrospective, single-center study, which may increase the likelihood of a type I statistical error. The present findings require confirmation in a multicenter prospective study. Second, patients who received interval appendectomy or completely conservative treatment

were excluded from this study, and selection bias was likely to have occurred. Finally, this study could not show the definitive timing of the perforation (before hospital admission or in-hospital), as the diagnosis of perforation was based on the operative notes.

In conclusion, our analysis suggests that the presence of an appendiceal fecalith, a total bilirubin level of more than 21.38 $\mu\text{mol/L}$, and a CRP level of more than $3.0 \times 10^4 \mu\text{g/L}$ are independent predictors of perforated appendicitis. Although further evidence is required to confirm the present findings, these factors may be useful in judging the likelihood of perforation in the emergency room or outpatient department and in enabling clinicians to have a more informed discussion with patients about their treatment options.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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Ethics Approval

This study was approved by the ethics committee of our hospital.

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