ORIGINAL ARTICLE

Retrospective Study

Determination of surgical priorities in appendicitis based on the probability of undetected appendiceal perforation

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Abstract

AIM: To identify risk factors of actual appendiceal perforation when computed tomography (CT) scans suggest nonperforated appendicitis and accordingly determine surgical priority.

METHODS: We collected database of 1362 patients who underwent an appendectomy for acute appendicitis between 2006 and 2013. A single radiologist selected 1236 patients whose CT scans were suggestive of nonperforated appendicitis. Patients were divided into 2 groups: actual nonperforation group and actual perforation group according to intraoperative and pathologic features. Comparison of the 2 groups were made using binary logistic regression.

RESULTS: Of 1236 patients, 90 (7.3%) were found to have actual appendiceal perforation. Four risk factors related with actual appendiceal perforation were identified: body temperature $\geq$ 37.6 ℃ (HR = 1.912, 95%CI: 1.161-3.149; P = 0.011), out-of-hospital symptom duration $\geq$ 72 h (HR = 2.454, 95%CI: 1.292-4.662; P = 0.006), age $\geq$ 35 years (HR = 3.358, 95%CI: 1.968-5.728; P < 0.001), and appendiceal diameter on CT scan $\geq$ 8 mm (HR = 4.294, 95%CI: 1.034-17.832; P = 0.045). Actual appendiceal perforation group showed longer operation time, later initiation of diet, longer use of parenteral narcotics, longer hospital stay, and higher incidence of postoperative complications (P < 0.05).

CONCLUSION: We proposed here new criteria to select patients with adverse clinical outcomes after appendectomy among the patients with radiologically nonperforated appendicitis. Surgical appendectomy outcomes could be improved by determining the surgical priority according to our criteria.

Key words: Appendicitis; Appendiceal perforation; Operative priority; Prognosis; Practice guideline

Core tip: This study analyzed surgical outcomes of 1236 patients whose computed tomography (CT) scans were suggestive of nonperforated appendicitis, and showed in-hospital gross perforation rate was very low (7.3%) and it was predicted by several factors: body temperature $\geq$ 37.6 ℃, out-of-hospital symptom

duration $\geq$ 7 d, age $\geq$ 35 years, and appendiceal diameter on CT scan $\geq$ 8 mm. Therefore, determining operative priority based on risk factors of in-hospital perforation is expected to improve surgical outcomes by reducing perforation rates.

INTRODUCTION

Appendicitis is the most frequently encountered surgical emergency worldwide, and early app-endectomy has been advocated as the therapeutic gold standard to avoid complications. Patients with appendicitis present to the hospital at any time of day or night. However, appendectomies are not performed evenly at all times. A report indicated that although 41% of patients visited the emergency room between 11 PM and 8 AM, only 6% of operations were performed during that period, showing inconsistent durations between the patient visit and operative timing[1]. Besides the hospital visiting hour, appendectomy timing is inconsistently determined by various factors. Therefore, guidelines for the optimal timing of appendicitis are necessary.

The incidence of appendiceal perforation has been reported to range from 17% to 32%[2-6]. Appendiceal perforation dramatically increases morbidity in terms of extended treatment with antibiotics, greater risk of complications, and longer hospital stays[3,7-9]. Surgical priority of grossly perforated appendicitis is not as high as imminent perforation because gross contamination has already occurred. However, cases of microperforated or nonperforated appendicitis should be treated promptly according to the surgical priority, which should be determined based on the risk of gross perforation.

Abdominal computed tomography (CT) scan is widely used for predicting both the presence of appendicitis and its perforation. However, in a study, CT was found to have a low sensitivity (62%) in predicting appendiceal perforation[10]. This could mean that a considerable number of patients with perforated appendicitis could be incorrectly diagnosed radiologically as nonperforated. However, these patients require prompt operation because they are at the risk of progression to gross conta-mination.

In this study, of the patients with radiologically nonperforated appendicitis, we selected patients with actual perforation evidenced by the operative and pathologic features. We then showed here these patients manifested adverse clinical outcomes. Finally, we intended to determine risk factors that could be useful in predicting actual perforation based on the clinical criteria in patients whose CT scans suggested nonperforated appendicitis.

MATERIALS AND METHODS

Study design and data collection

This study was a retrospective analysis of patients who underwent operations for acute appendicitis at the Department of Surgery of Daejeon St. Mary's Hospital, the Catholic University of Korea, between January 2006 and December 2013. Daejeon St. Mary's Hospital is a teaching community hospital with residents on call and supervised by attending surgeons. The study was approved by the ethics committee of Daejeon St. Mary's Hospital, the Catholic University of Korea (IRB code: DC13RISI0004). The data were gathered from the electronic medical records.

Patients who underwent appendectomy with the impression of nonperforated appendicitis based on preoperative CT scan were the object of our study (Figure 1). During the aforementioned period, 1886 patients underwent operations for appendicitis treatment. Of these, we first excluded the patients who underwent procedures other than simple appendectomy, such as resection of a part of small or large intestine (n = 25). We then excluded patients who underwent appendectomy $\geq$ 3 d after initial presentation (n = 21). In addition, we excluded patients who did not receive a preoperative CT scan (n = 478). Consequently, 1362 patients remained who received CT scan and thereafter underwent appendectomy. The following step was to differentiate between nonperforated and perforated appendicitis based on the preoperative CT scans. We used an evidence-based definition of perforated appendicitis after a thorough review of the literature; the CT feature of appendiceal perforation was defined as the presence of a hole in the appendix or a fecalith in the abdomen[10,11]. CT images were re-evaluated by one radiologist (G. Park) with $\geq$ 10 years of experience in abdominal imaging. To avoid selection bias, the radiologist was not given information about the patient's final diagnosis. The radiologist was provided the CT images in a random sequence created by Picture Archiving and Communication System software (PACS, Maroview, Infinitt, Seoul, Korea) in stack mode. After re-evaluation of CT images, 1236 patients were selected whose CT scan did not suggest a appendiceal perforation. We then divided this patient population into 2 groups: patients with actual appendiceal perforation and those without actual perforation (control group) according to the intraoperative and pathologic features. Thereafter, we investigated whether there were differences in
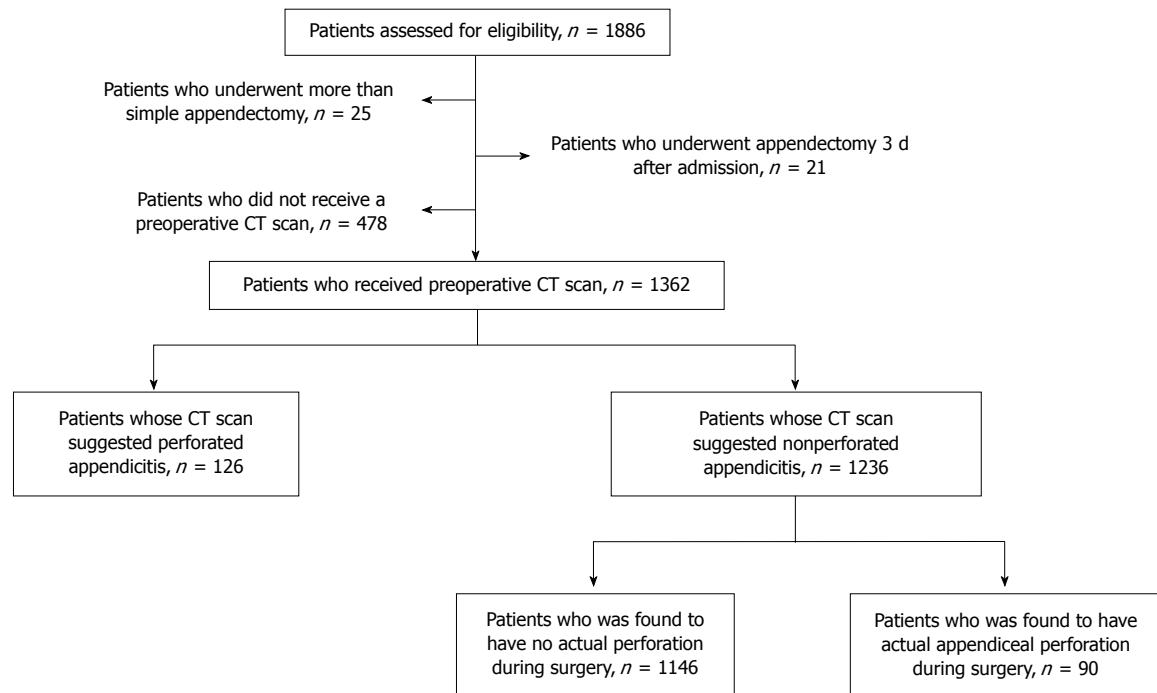
Patients assessed for eligibility, *n* = 1886

Patients who underwent more than simple appendectomy, *n* = 25

Patients who underwent appendectomy 3 d after admission, *n* = 21

Patients who did not receive a preoperative CT scan, *n* = 478

Patients who received preoperative CT scan, *n* = 1362

Patients whose CT scan suggested perforated appendicitis, *n* = 126

Patients whose CT scan suggested nonperforated appendicitis, *n* = 1236

Patients who was found to have no actual perforation during surgery, *n* = 1146

Patients who was found to have actual appendiceal perforation during surgery, *n* = 90

Figure 1 Patient selection and allocation in this study. CT: Computed tomography.

Definitions and terminology

Actual appendiceal perforation was defined (1) when an appendicolith was detected outside the appendix; (2) when pus or abscess fluid was evidenced around appendix with disruption of appendiceal wall continuity in the initial operative field without manipulation; or (3) when pus or abscess fluid was evidenced around appendix during surgery and the pathologic diagnosis indicated gangrenous appendicitis or periappendiceal abscess.

Out-of-hospital delay was defined as the time interval between development of initial symptom and the visit to hospital. Time to incision was defined as the time interval between arrival to the hospital and the performance of surgical incision. Comorbidities were assessed with the Charlson comorbidity index[12]. Postoperative complications were classified as described by Clavien[13]. whereby grade 1 represents deviation from the normal postoperative course without the need of pharmacological or any other intervention; grade 2 represents the requirement of pharmacological treatment; grade 3 represents surgical, endoscopic, or radiological intervention; and grade 4 represents a life-threatening complication requiring intensive care unit management. Of the postoperative complications, renal dysfunction was defined as postoperative serum creatinine $\geq$ 1.5 mg/dL in patients who had normal renal function preoperatively. Hepatitis was defined as postoperative serum ALT (alanine transaminase) $\geq$ 50 IU/L in patients who showed normal preoperative liver function. Hyperamylasemia was defined as postoperative serum amylase $\geq$ 160 IU/L in patients whose levels were within the normal range preoperatively.

Operative technique

The initial series of this study included patients who had undergone open appendectomy. Soon after, laparoscopic appendectomy with three ports became the norm in the treatment of acute appendicitis. Thereafter, we introduced the single-port laparoscopic surgery (SPLS) for appendectomy in March 2009. Since then, the SPLS replaced the conventional 3-port procedure. The umbilicus was the most typically used incision site, and a vertical incision with a length ranging from 1.5-2.5 cm was most often used. We frequently used commercially ready-made single ports, such as the OCTO port (Dalim Medical Co., Korea) and the Glove port (Sejong Medical Co., Korea). Peritoneal irrigation with copious amounts of saline was performed under direct visualization in all the procedures, and Jackson-Pratt drains were used as needed.

Perioperative management

We implemented a standardized perioperative protocol. For all patients with appendicitis, the initial step at the emergency department includes prompt intravenous hydration using crystalloid fluids and intravenous antibiotics (cefotetan 1.0 g). Because cefotetan is administered according to a 24-h dosing schedule, it was administered at the emergency department and not at a specific time before the incision. Thereafter,

starting on the first postoperative day, intravenous cefotetan (usually 1.0 g, maximum dose 2.0 g) was usually administered for 1 to 2 d, or longer if needed. All patients with appendiceal perforation received intravenous metronidazole 50 mg/kg coadministration (maximum dose 2 g). Antibiotic change or dosage adjustments were considered when there was no improvement of the clinical parameters, such as body temperature or leukocyte count. All Patients were allowed a clear liquid diet upon returning to the ward, and the diet was advanced as tolerated. Patients received intravenous ketorolac 0.1 mg/kg as needed for pain. Patients were discharged when tolerating a regular diet. At discharge, oral antibiotics (cefaclor or cefcapene) were prescribed for a 3-d period only to the patients with perforated appendicitis.

Statistical analysis

Numeric data were presented as mean and standard deviation or as median and range. Continuous variables were analyzed using the independent t-test, whereas proportions were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. For variables with a non-normal distribution, Wilcoxon rank sum tests were utilized to examine differences in central tendency. Binary logistic regression was used to assess the risk of in-hospital perforation while controlling for other independent variables. All P values were 2-tailed. Statistical analysis was performed using SPSS ver. 15.0 (SPSS Inc., Chicago, IL). Statistical significance was accepted for P values < 0.05.

RESULTS

Patient characteristics

Of the total 1236 patients whose CT scans suggested nonperforated appendicitis, 1146 (92.7%) were proven to have nonperforated appendicitis and 90 (7.3%) were proven to have actual perforated appendicitis. There were 612 men and 624 women. The median patient age was 37 (range, 15-93) years. The median body mass index was 22.6 (15.1-44.1) kg/m². Median time to incision was 373 (48-4285) min. There were differences between the mean and median values of time-to-incision to some extent. While the mean time-to-incision was 534 ± 498 min, the median time-to-incision was 373 (48-4285) min. These results could be attributed to the small number of patients who were operated with a long delay, which translated into a deviation of the mean values to the right. Overall, there were 6 (0.5%) open appendectomies, 932 (75.4%) multi-port laparoscopic appendectomies, and 298 (24.1%) single-port laparoscopic appendectomies.

Table 1 shows the comparison of patient demographic and baseline characteristics between the two groups. We found that both groups had differences in age, body temperature, serum neutrophil fraction,

and appendiceal diameter on CT scan. Patients with actual appendiceal perforation were older (> 35 years of age, 80% *vs* 53.1%, P < 0.001) and had a body temperature > 37.7 ºC (28.9% *vs* 15.8%, P < 0.05), neutrophil fraction > 65% (88.9% *vs* 79.7%, P < 0.05), and appendiceal diameter > 8 mm (97.8% *vs* 88.7%, P < 0.05). Both groups were similar with respect to sex, body mass index, comorbidity, and out-of-hospital delay. We were also unable to identify a significant difference in time-to-incision [534.6 ± 498.9 min (nonperforation group) *vs* 521.2 ± 487.4 min (actual perforation group), not significant].

Identification of factors related with actual appendiceal perforation

To identify independent factors related with actual appendiceal perforation, consequent multivariate analysis was performed using preoperative variables (Table 2). By multivariate analysis, we identified independent factors related with actual appendiceal perforation, including body temperature (< 37.6 ℃ *vs* ≥ 37.6 ℃), out-of-hospital delay (< 72 h *vs* ≥ 72 h), age (< 35 years *vs* ≥ 35 years), and appendiceal diameter (< 8 mm *vs* ≥ 8 mm). Using these 4 risk factors related with actual appendiceal perforation, we further stratified patients into 3 groups: low-risk (risk factor: 0-1), intermediate-risk (risk factors: 2), and high-risk group (risk factors: 3-4) (Table 3). The probability of actual appendiceal perforation increased 4.8 times in the intermediate-risk group and 10.7 times in the high-risk group compared to the control group (low-risk group).

Clinical outcomes of patients with actual perforation who were diagnosed as having nonperforation on CT scan

To determine the effects of actual appendiceal perforation in patients whose initial CT scans suggested nonperforated appendicitis, intraoperative and postoperative variables were compared (Table 4). There were no differences in operative methods between both groups. However, the actual perforation group had a longer operation time (71.2 ± 30.1 min *vs* 61.1 ± 24.4 min, P < 0.001) and higher incidence of drain insertion (23.3% *vs* 9.2%, P < 0.001). Furthermore, the actual perforation group had delayed postoperative recovery, which was evidenced by a later initiation of free oral fluids, solid diet, longer use of parenteral narcotics, and longer hospital stay (P < 0.05). However, readmission rates were comparable between the two groups.

We then classified postoperative complications according to Clavien's proposal (Table 5). The actual perforation group had higher incidence of grade 2 (14.4% *vs* 8.2%, P = 0.051), grade 3 (7.8% *vs* 1.2%, P < 0.001), and total number of complications (22.2% *vs* 9.9%, P < 0.05). The difference in the complication rates was more marked for grade 3

Table 1 Patient demographics and baseline preoperative characteristics of patients whose initial computed tomography scans suggested nonperforated appendicitis *n* (%)

	All patients (n = 1236)	No actual appendiceal perforation (n = 1146)	Actual appendiceal perforation (n = 90)	P value
Age (yr)				< 0.001
15-35	556 (45.0)	538 (46.9)	18 (20.0)	
35-65	515 (41.7)	471 (41.1)	44 (48.9)	
≥ 65	165 (13.3)	137 (12.0)	28 (31.1)	
Sex				0.125
Men	612 (49.5)	560 (91.5)	586 (93.9)	
Women	624 (50.5)	52 (8.5)	38 (6.1)	
Body-mass index (kg/m^2)				0.186
< 20	255 (20.6)	239 (20.9)	16 (17.8)	
20-25	673 (54.4)	627 (54.7)	46 (51.1)	
≥ 25	308 (25.0)	280 (24.4)	28 (31.1)	
Comorbidity				0.097
Charlson index = 0	1142 (92.4)	1063 (92.8)	79 (87.8)	
Charlson index > 0	94 (7.6)	83 (7.2)	11 (12.2)	
Out-of-hospital delay[1]				0.118
< 72 h	874 (70.7)	817 (71.3)	57 (63.3)	
≥ 72 h	362 (29.3)	329 (28.7)	33 (36.7)	
Body temperature (℃)				0.003
< 37.6	1029 (83.3)	965 (84.2)	64 (71.1)	
≥ 37.6	207 (16.7)	181 (15.8)	26 (28.9)	
Presenting symptom				0.640
Abdominal pain	1209 (97.8)	1121 (97.8)	88 (97.8)	
Nausea, vomiting	14 (1.1)	13 (1.2)	1 (1.1)	
Fever/chill	12 (1.0)	12 (1.0)	0 (0.0)	
Indigestion	1 (0.1)	0 (0.0)	1 (1.1)	
Lab. findings, median (range)				
WBC count (× 10^3/mm^3)	12.0 (1.9-28.7)	11.9 (1.9-28.4)	13.8 (4.3-28.7)	0.128
Platelet count (× 10^3/mm^3)	222 (82-587)	223 (82-857)	215 (93-503)	0.102
Neutrophil fraction				0.038
< 65%	244 (19.7)	234 (20.4)	10 (11.1)	
≥ 65%	992 (80.3)	912 (79.6)	80 (88.9)	
Appendix diameter (CT scan)				0.004
< 8 mm	131 (10.6)	129 (11.3)	2 (2.2)	
≥ 8 mm	1105 (89.4)	1017 (88.7)	88 (97.8)	
Presence of appendicolith (CT scan)				0.502
No	1086 (87.9)	1009 (88.0)	77 (85.6)	
Yes	150 (12.1)	137 (12.0)	13 (14.4)	
Time-to-incision (min)[2]				0.860
mean ± SD	534 ± 498	535 ± 499	521 ± 487	
Median (range)	373 (48-4285)	373 (48-4285)	362 (70-3194)	

[1]Out-of-hospital delay was defined as the time interval between development of initial symptom and the visit to hospital; [2]Time-to-incision was defined as the time interval between arrival to the hospital and making incision for operation. CT: Computed tomography; SD: Standard deviation; WBC: White blood cells.

Table 2 Multivariate analysis of factors affecting actual appendiceal perforation

	Hazard ratio	95%CI	P value
Body temperature (℃)			0.011
< 37.6 (standard)	1		
≥ 37.6	1.912	1.161-3.149	
Out-of-hospital delay (h)			0.006
< 72 (standard)	1		
≥ 72	2.454	1.292-4.662	
Age (yr)			< 0.001
< 35 (standard)	1		
≥ 35	3.358	1.968-5.728	
Appendiceal diameter on CT scan(mm)			0.045
< 8 (standard)	1		
≥ 8	4.294	1.034-17.832	

CT: Computed tomography.

complications. Grade 3 complications were observed in 1.2% of patients in the control group and 7.8% in the actual perforation group. We experienced 21 reoperations in this study: 14 and 7 in the control and actual perforation groups, respectively. All grade 3 complications in both groups resulted in reoperation, possibly owing to our propensity to adopt a more rapid and definitive management; therefore, the actual perforation group also had a significantly higher reoperation rate (P < 0.001). Regardless of perforation, intra-abdominal abscess (n = 14) was the leading cause of reoperation, and intestinal obstruction (n = 6) was the second.

DISCUSSION

Although the presence of appendiceal perforation

Table 3 Risk estimation of developing actual appendiceal perforation

Groups	No. of risk factors[1]	Ratio of patients with perforation *vs* total population	Hazard ratio of perforation	95%CI	*P* value
Control group	0-1		1		
Intermediate risk group	2	52/581 (9.0%)	4.8	2.416-9.563	< 0.001
High risk group	3-4	28/156 (17.9%)	10.7	5.064-22.596	< 0.001

[1]The risk factors are (1) patient age $\geq$ 65 years; (2) body temperature $\geq$ 37.8 years; (3) body temperature $n \geq$ 8 mm; and (4) out-of-hospital symptom duration $\geq$ 72 h.

Table 4 Comparison of intraoperative and postoperative variables according to the presence of actual appendiceal perforation *n* (%)

	All patients (*n* = 1236)	No actual appendiceal perforation (*n* = 1146)	Actual appendiceal perforation (*n* = 90)	*P* value
Surgical technique				0.111
Open appendectomy	6 (0.5)	5 (0.5)	1 (1.1)	
Lap. appendectomy				
Multiport	930 (75.3)	857 (74.8)	73 (81.1)	
Single-port	299 (24.2)	283 (24.7)	16 (17.8)	
Operation time (min)				< 0.001
Mean ± SD	61.8 ± 25.0	61.1 ± 24.4	71.2 ± 30.1	
Median (range)	55 (15-230)	55.0 (15-230)	65.0 (35-200)	
Drain insertion				< 0.001
No	1110 (89.8)	1041 (90.8)	69 (76.7)	
Yes	126 (10.2)	105 (9.2)	21 (23.3)	
Duration prior free oral fluids				0.001
Mean ± SD	1.3 ± 0.7	1.2 ± 0.6	1.6 ± 0.6	
Median (range)	1 (1-7)	1 (1-7)	1 (1-6)	
Duration prior soft diet				< 0.001
Mean ± SD	1.5 ± 0.9	1.47 ± 0.9	1.92 ± 1.1	
Median (range)	1 (1-8)	1 (1-8)	2 (1-8)	
Dosage of analgesics				0.054
Mean ± SD	1.58 ± 3.8	1.48 ± 3.5	2.83 ± 6.5	
Median (range)	1 (0-70)	1 (0-70)	1 (0-50)	
Analgesics duration, median (d)				0.007
Mean ± SD	0.77 ± 1.8	0.72 ± 1.7	1.4 ± 2.2	
Median (range)	0.0 (0-42)	0.0 (0-42)	1 (0-15)	
Postoperative complications				
Severe complications (grade 3-4)	16 (1.3)	14 (1.2)	7 (7.8)	< 0.001
Total complications	94 (7.6)	113 (9.9)	20 (22.2)	0.014
Postoperative hospital stay (d)				< 0.001
Mean ± SD	4.02 ± 2.3	3.92 ± 2.3	5.2 ± 2.9	
Median (range)	4 (1-48)	3 (1-48)	4 (2-17)	
Readmissions				0.714
No	1210 (97.9)	1122 (97.9)	88 (97.8)	
Yes	26 (2.1)	24 (2.1)	2 (2.2)	

has a considerable effect on the prognosis of appendicitis, the diagnostic yield of appendiceal perforation by abdominal CT is considerably low. A previous study reported that CT had a sensitivity of 62% and specificity of 81% in predicting appendiceal perforation[10]. In the present study, 7.3% (90/1236) of patients with nonperforated appendicitis on CT images were found to have an actual perforation. Importantly, the patients in the actual perforation group definitely showed adverse clinical outcomes. Therefore, a prompt surgical intervention could improve surgical outcomes among such a patient population (Figure 2).

In our study, we attempted to find independent factors that could be useful in discriminating between actual nonperforation and actual perforation in patients diagnosed with nonperforation radiologically. Time-to-incision did not affect the perforation, which suggests a low possibility of in-hospital perforation. Notably, we found four independent factors that can be useful to determine the presence of appendiceal perforation: body temperature $\geq$ 37.6 ℃, out-of-hospital symptom duration $\geq$ 72 h, age $\geq$ 35 years, and appendiceal diameter on CT scan $\geq$ 8 mm. Based on the number of these risk factors, we were able to classify the patients into 3 groups: low-risk (risk factor: 0-1), intermediate risk (risk factors: 2), and high-risk (risk factors: 3-4) groups. The high-risk group had 10.7 times higher probability of actual perforation than the low-risk group.

There have been a number of controversies over the appropriate timing of appendectomy for acute

Table 5 Comparison of postoperative complications *n* (%)

	No actual appendiceal perforation (*n* = 1146)	Actual appendiceal perforation (*n* = 90)	*P* value
Grade 1, *n* (%)	5 (0.8)	0 (0.0)	1.000
Renal dysfunction	1	0	
Hepatitis	1	0	
Hyperamylasemia	3	0	
Grade 2, *n* (%)	94 (8.2)	13 (14.4)	0.051
Wound infection	72	8	
Urinary retention	11	1	
Delayed gastric emptying	6	2	
Pneumonia	2	0	
Pleural effusion	2	2	
Renal dysfunction	1	0	
Grade 3, *n* (%)	14 (1.2)	7 (7.8)	
Intra-abdominal abscess	9	5	
Intestinal obstruction (ileus)	4	2	
Intra-abdominal hemorrhage	1	0	
Severe complications (grade 3-4), *n* (%)	14 (1.2)	7 (7.8)	< 0.001
Total complications, *n* (%)	113 (9.9)	20 (22.2)	0.014

Postoperative complications were classified as described by Clavien: grade 1 = deviation from the normal postoperative course without the need for pharmacological or any other intervention; grade 2 = requiring pharmacological treatment with drugs; grade 3 = requiring surgical, endoscopic, or radiological intervention; and grade 4 = life-threatening complication requiring intensive care unit management.

[Surgical outcomes]

Within 3 d (median time span: 373 min)

Patients whose CT scan suggested nonperforated appendicitis, *n* = 1236

Admission   Operation

No actual perforation: 92.7% (*n* = 1146)

Actual appendiceal perforation: 7.3% (*n* = 90)
Risk factors
1: Body temperature ≥ 37.6 ℃
2: Out-of-hospital delay ≥ 72 h
3: Age ≥ 35 years
4: Appendiceal diameter on CT scan ≥ 8 mm
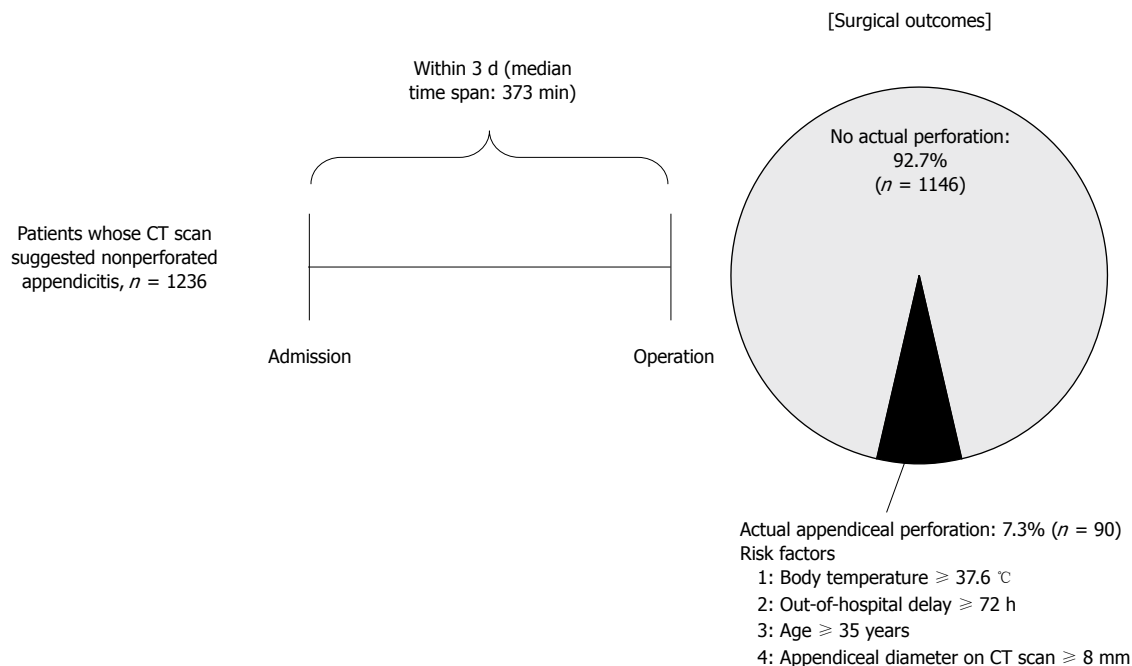
Figure 2 Outline of this study.

appendicitis. Proponents of prompt appendectomy emphasize the time dependency of pathologic grade and complication rates[14-18]. Ditillo *et al*[19] reported in an analysis of 1081 patients with acute appendicitis that the risk of developing advanced pathology and complications increased with time-to-treatment, favoring prompt appendectomy. In contrast, Kearney *et al*[4] reported that the stage of appendicitis was affected by out-of-hospital delay, but not by in-hospital delay. These differences may be attributed to variations in study design, patient characteristics, and inclusion/exclusion criteria.

Therefore, further clarification of the optimal operation timing is required. Our results do not fully support either timing; rather, we support prompt appendectomy for the selected patients who have high-risk factors for actual perforation.

Appendicitis is largely initiated by the luminal obstruction by inspissated stool (fecalith or appendicolith) or lymphoid hyperplasia[20]. Luminal obstruction promotes bacterial overgrowth and increases mucus secretion, leading to intraluminal distention and wall pressure elevation. Subsequently, blood and lymphatic flow are impaired, and mucosal

ischemia follows. These events collectively lead to the progression of inflammation, such as gangrene and perforation. In our study, patients with actual perforation showed longer operation time, delayed initiation of postoperative diet, longer and higher doses of postoperative analgesics, higher incidences of postoperative complications, and a longer hospital stay. Therefore, performing appendectomy before its perforation is crucial in the treatment of appendicitis.

In conclusion, our study showed that actual appendiceal perforation occurred in 7.3% (90/1236) of the patients whose CT scans suggested nonperforated appendicitis. The actual perforation group showed inferior clinical outcomes. These patients require prompt operation because they are at the risk of progression to gross contamination. We detected four independent factors that can predict perforated appendicitis even though the CT scans of the patients suggest nonperforated appendicitis: body temperature $\geq 37.6\,^{\circ}\text{C}$, out-of-hospital symptom duration ≥ 72 h, age ≥ 35 years, and appendiceal diameter on CT scan ≥ 8 mm. We think that surgical outcomes of appendectomy could be improved by following our guidelines for the determination of surgical priority based on the sum of the risk factors.

COMMENTS

Background
Although the presence of appendiceal perforation has a considerable effect on the prognosis of appendicitis, the diagnostic yield of appendiceal perforation by abdominal computed tomography (CT) is considerably low. Therefore, clinicians frequently encounter patients have perforated appendicitis in the operation room, even though their preoperative CT scans suggested nonperforated appendicitis.

Research frontiers
Appendiceal perforation is an event provoking appendicitis progression from a local disease to an extensive or systemic disease. Therefore, it should be clearly characterized. To prevent or promptly manage it, the identification of risk factors related with appendiceal perforation is particularly important.

Innovations and breakthroughs
To improve the accuracy of CT scans in predicting perforated appendicitis, several CT features favoring perforated appendicitis have been proposed. However, improving predictability of perforated appendicitis using clinical manifestations has not been attempted. The authors herein proposed new criteria to select patients with adverse clinical outcomes after appendectomy among the patients with radiologically nonperforated appendicitis.

Applications
The authors have developed novel and simple criteria to predict actual perforated appendicitis in patients whose CT scans suggested nonperforated appendicitis: body temperature $\geq 37.6\,^{\circ}\text{C}$, out-of-hospital symptom duration ≥ 72 h, age ≥ 35 years, and appendiceal diameter on CT scan ≥ 8 mm. The authors were able to classify the patients into 3 groups based on the number of risk factors: low-risk (risk factor: 0-1), intermediate risk (risk factors: 2), and high-risk (risk factors: 3-4) groups. The high-risk group had 10.7 times higher probability of actual appendiceal perforation than the low-risk group. The authors criteria could be particularly advantageous in the determination of surgical priority or when encountered with indeterminate CT features for appendiceal perforation.

Peer-review
This is a good paper, with a very good and rigorous design, with clear definitions of variables and interesting information obtained from an absolutely

correct statistical analysis, bi and multivariate. Leaving apart minor corrections that may be easily remedied, it is born from a weak hypothesis and perhaps it must be otherwise designed and conceived. Information obtained from this design must be utilized as it is really interesting, and only a few reports have given such a good approximation to risk factors of perforated appendicitis in the presence of a normal CT.

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