Original Article

Clinical predictors of gangrenous appendicitis: elevated total bilirubin level and computed tomography scan findings

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Aim: Patients with gangrenous appendicitis usually require emergency surgery. Preoperative diagnosis of gangrenous appendicitis is clinically important but not always straightforward. We undertook this study to identify preoperative predictors of gangrenous appendicitis.

Methods: This was a single-center case–control study. We identified 162 patients who underwent appendectomy between September 2011 and August 2014 after the diagnosis of acute appendicitis was established. We identified laboratory parameters and computed tomography (CT) scan findings predictive of histologically or surgically diagnosed gangrenous appendicitis by univariable and multivariable analyses.

Results: Of 146 study patients, gangrenous appendicitis was confirmed in 102. Univariable analysis showed that two laboratory factors (C-reactive protein []and total bilirubin [T-Bil]) and three CT scan findings were significant predictors for gangrenous appendicitis. Multivariable analysis showed that T-Bil and two CT scan findings (appendicolith and fat stranding around the appendix) were independent predictors. The combination of "T-Bil ≥ 1.0 mg/dL or appendicolith" was able to predict gangrenous appendicitis with a sensitivity of 90.5%, positive predictive value of 80.4%, and accuracy of 77.8%. The combination of "T-Bil ≥ 1.0 mg/dL or fat stranding around the appendix" was able to predict gangrenous appendicitis with a sensitivity of 98.9%, positive predictive value of 76.4%, and accuracy of 71.9%.

Conclusion: These combinations of laboratory and CT scan findings could be valuable as predictors of gangrenous appendicitis.

Key words: Appendectomy, appendicitis, appendicolith, bilirubin, gangrenous appendicitis

INTRODUCTION

ACUTE APPENDICITIS IS a common cause of acute abdominal pain, and patients with gangrenous appendicitis usually require emergency surgery.[1] A delay in diagnosis or treatment could result in perforation, which can be associated with increased postoperative morbidity and prolonged hospital stay, whereas non-gangrenous appendicitis does not always require surgery and can be treated non-operatively in selected patients with antibiotics.[2–5] Thus, the preoperative diagnosis of gangrenous appendicitis is of great clinical importance. To predict the presence of gangrenous appendicitis, various methods have been reported, including clinical symptoms/signs, laboratory parameters, imaging studies, and a combination of these.[6–10] We reviewed preoperative findings and analyzed them to identify the best predictors of gangrenous appendicitis. We considered both blood tests and imaging findings to be important and therefore targeted these markers in this study.

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PATIENTS AND METHODS

THIS WAS A retrospective, single-center, case–control study. From the hospital database, we identified 162 patients with a histological diagnosis of acute appendicitis

who underwent appendectomy between September 2011 and August 2014 at Tokyo Metropolitan Tama Medical Center (Tokyo, Japan). Patients with an abscess were excluded because we first treat such patients with antibiotics and drainage.[11] The appendectomies were carried out by open laparotomy or using a laparoscopic approach. These patients were categorized as "gangrenous" or "non-gangrenous" based on the histological or surgical diagnosis. "Gangrenous" appendicitis was defined as histologically gangrenous or the presence of a perforated appendix during surgery. Others were classified as "non-gangrenous" appendicitis. Informed consent was waived for this study due to its retrospective nature. Thus, we here targeted patients with histologically confirmed appendicitis and not those with suspicious appendicitis.

Exclusion criteria were patients: (i) with histologically proven neoplasms of the appendix or the colon, or with other synchronous neoplasms, (ii) who received antibiotic treatment before they were referred to our hospital, (iii) with liver disease (viral hepatitis, autoimmune hepatitis, liver cirrhosis, or hepatocellular carcinoma), (iv) with a history of alcohol abuse, (v) with insufficient data, or (vi) age <15 years.

Laboratory data and histological findings of the excised appendixes were retrieved. The most recent laboratory data within 24 hours before surgery were used for analysis. We also investigated the enhanced abdominal computed tomography (CT) scan findings obtained at our hospital; CT scan findings from other hospitals were excluded because different CT scanner settings rendered their comparison difficult. All CT scans in this study were obtained using the same scanner in the emergency room. A single surgeon (I.N.) evaluated all preoperative CT images. We adopted the maximum diameter as the diameter of the appendix. An appendicolith was defined as any calcified concentration within the appendix, regardless of the size. Fat stranding around the appendix was defined as fat tissue with partial high attenuation on CT.

Statistical analysis

JMP software (version 11.1.1; SAS Institute, Cary, NC, USA) was used for statistical analysis. Data were expressed as the median and interquartile range. In univariable analyses, the χ^2-test or Fisher's exact test was used for categorical variables between groups, and continuous variables were compared using the Mann–Whitney *U*-test. Multivariable logistic regression analyses were undertaken to identify factors that were associated with the diagnosis of gangrenous appendicitis. Diagnostic accuracy was evaluated by creating receiver operating characteristic curves. We identified appropriate cut-off values and calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value for each set with an area under the curve >0.60. All analyses were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

OF 162 PATIENTS who underwent an appendectomy, 16 were excluded: two had an appendix neoplasm, 10 received antibiotic treatment before referral to our hospital, and four had insufficient data. No patients had liver disease or a history of alcohol abuse. After exclusions, 146 remained, of whom 102 patients were histologically or surgically confirmed to have gangrenous, and 44 patients diagnosed with non-gangrenous, appendicitis. Based on this, patients were categorized into the "gangrenous" and "non-gangrenous" groups.

Preoperative laboratory studies

Table 1 shows the characteristics of patients in the gangrenous and non-gangrenous groups. Patients in the gangrenous group had significantly elevated serum C-reactive protein (CRP) and total bilirubin (T-Bil) levels, and a significantly lower albumin level (Table 1). A multivariable logistic regression analysis indicated that T-Bil was the only factor that showed a significant association with the diagnosis of gangrenous appendicitis (odds ratio [OR], 3.04; 95% confidence interval [CI], 0.98–9.48) (Table 1). The receiver operating characteristic curve showed the cut-off value of T-Bil at 1.00 mg/dL. The area under the curve for T-Bil was 0.71 (Fig. 1).

Preoperative CT scan findings

Of the 146 patients reviewed, enhanced CT scan was undertaken for 138 patients (94.5%). We compared the following three findings between the two groups using univariable analyses: the maximum diameter of the appendix, presence of an appendicolith, and fat stranding around the appendix, all of which were previously reported to be associated with the severity of appendicitis.[12,13] Patients in the gangrenous group had a larger appendiceal diameter and were more likely to have appendicoliths and fat-stranding. These three factors were significant on univariable analyses (Table 2). We then undertook a multivariable logistic regression analysis and found that presence of an appendicolith (OR, 2.97;

Table 1. Preoperative parameters and the severity of appendicitis

	Univariable analysis			Multivariable analysis		
	Gangrenous	Non-gangrenous	*P*-value	Odds ratio	95% CI	*P*-value
Age, years (*N* = 146)	44 (32.0–57.0)	36 (23.3–51.3)	0.0225	1.01	0.98–1.04	0.6372
Female gender, *n* (%) (*N* = 146)	49 (48.0)	16 (36.4)	0.1256	1.66	0.56–4.91	0.3532
WBC ($\times 10^3/\mu L$) (*N* = 146)	14.2 (11.6–16.9)	14.2 (10.4–17.0)	0.6102	1.00	0.99–1.00	0.1359
CRP (mg/dL) (*N* = 146)	6.90 (2.59–13.36)	0.53 (0.13–3.87)	<0.0001	1.08	0.98–1.20	0.1139
T-Bil (mg/dL) (*N* = 145)	1.15 (0.80–1.50)	0.70 (0.53–1.00)	0.0001	3.04	0.98–9.48	0.0415
Alb (g/dL) (*N* = 139)	4.20 (3.70–4.50)	4.30 (4.10–5.00)	0.0016	0.38	0.12–1.22	0.0927

Alb, albumin; CI, confidence interval; CRP, C-reactive protein; T-Bil, total bilirubin; WBC, white blood cell.

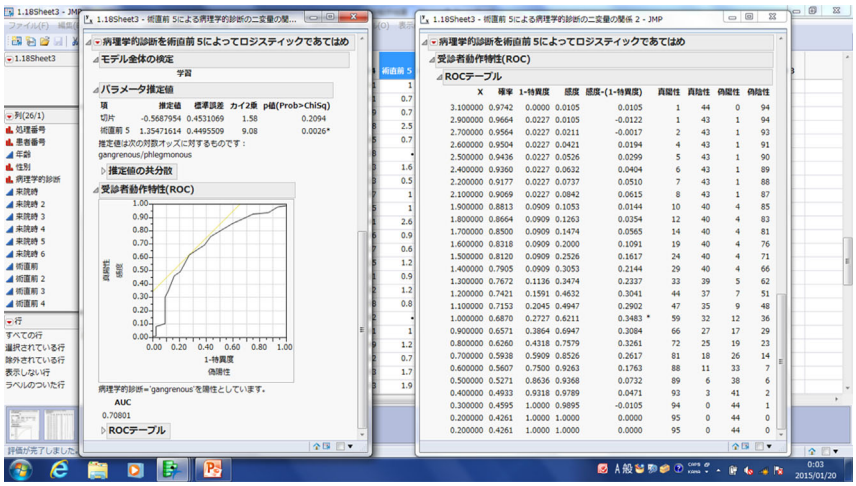

Fig. 1. Receiver operating characteristic curve analyses of total bilirubin level as a predictor of gangrenous appendicitis.

95% CI, 1.22–7.51) and fat stranding around the appendix (OR, 32.21; 95% CI, 5.32–634.91) were significantly related to gangrenous appendicitis (Table 2).

Combination of clinical indicators predicting gangrenous appendicitis

We combined "T-Bil ≥ 1.0 mg/dL" with "appendicolith" or "fat stranding around appendicitis," and analyzed the diagnostic accuracy. The combination of "T-Bil = >1.0 mg/dL or appendicolith" was able to predict gangrenous appendicitis with a sensitivity of 90.5%, PPV of 80.4%, and accuracy of 77.8%. The combination of "T-Bil = >1.0 mg/dL or fat stranding around the appendix" was able to predict gangrenous appendicitis with a sensitivity of 98.9%, PPV of 76.4%, and accuracy of 71.9% (Table 3).

DISCUSSION

IN ORDER TO preoperatively determine the severity of appendicitis, various factors have been proposed as useful diagnostic indicators, including clinical symptoms/signs, imaging findings, laboratory parameters such as white blood cell count (WBC), CRP level, procalcitonin, and fibrinogen, and various combinations of these parameters.[6–10] Total bilirubin has been reported to reflect the severity of acute appendicitis.[14] Potentially useful imaging studies include ultrasonography (US), CT scan, and magnetic resonance imaging. The appendicitis inflammatory response score and the Alvarado score, which are based on clinical symptoms/signs and laboratory parameters indicative of inflammation (WBC and/or CRP), are widely acknowledged.[6–8] Some other scoring systems also include US or CT scan findings.[15,16] However, the detection of the clinical signs often

Table 2. Preoperative computed tomography scan findings and the severity of appendicitis

	Univariable analysis			Multivariable analysis		
	Gangrenous	Non-gangrenous	*P*-value	Odds ratio	95% CI	*P*-value
Diameter of appendix, mm (n = 131)	13.4 (11.7–15.9)	12.4 (11.0–15.0)	0.0167	1.16	0.98–1.42	0.0930
Appendicolith (n = 136)						
Present	67	14	0.0002	2.97	1.22–7.51	0.0166
Absent	29	26				
Fat stranding around appendix (n = 136)						
Present	95	28	0.0001	32.21	5.32–634.91	<0.0001
Absent	1	12				

CI, confidence interval.

Table 3. Combination of clinical indicators predicting gangrenous appendicitis

	Sn (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)
T-Bil ≥ 1.0 mg/dL or appendicolith	90.5	47.5	80.4	67.9	77.8
T-Bil ≥ 1.0 mg/dL and appendicolith	40.0	87.5	88.4	38.0	54.1
T-Bil ≥ 1.0 mg/dL or fat stranding around appendix	98.9	27.5	76.4	91.7	71.9
T-Bil ≥ 1.0 mg/dL and fat stranding around appendix	60.0	72.5	83.8	43.3	63.7

NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity; T-Bil, total bilirubin.

depends on the physician's experience and is subjective. Ultrasonography, which also depends on the examiners' skill and experience, is sometimes less objective and thus less reproducible than CT scan imaging. Magnetic resonance imaging is not always available as an emergency study. Thus, we focused on the usefulness of both laboratory parameters and CT scan findings.

Elevated T-Bil level has been reported to be a common finding in patients with appendicitis.[17] The mechanism leading to an elevated T-Bil level in patients with appendicitis is unclear. Previous studies have proposed that a bacterial infection might prevent smooth bile flow. In patients with sepsis, pro-inflammatory cytokines and nitric oxide, produced in response to infection, are believed to impair liver function and ductal bile formation.[18,19] These processes could contribute to T-Bil elevation in patients with gangrenous appendicitis.

The visualization of appendicoliths and fat stranding around the appendix on the CT scan were independent risk factors predictive of gangrenous appendicitis in the present study. Therefore, we analyzed the combinations of "T-Bil ≥ 1.0 mg/dL and/or appendicolith" and "T-Bil ≥ 1.0 mg/dL and/or fat strand around appendix." Whereas neither combination had a high specificity, the high sensitivity and robust PPV of both "T-Bil ≥ 1.0 mg/dL or appendicolith" and "T-Bil ≥ 1.0 mg/dL or fat strand around appendix" suggests their usefulness to prevent the misdiagnosis of gangrenous appendicitis.

Obtaining an enhanced abdominal CT scan is a routine procedure in most tertiary care hospitals in Japan. Previous studies reported that CT scan was useful for diagnosing the severity of appendicitis and for determining the treatment strategy.[20] This study reveals that the presence of fat stranding around the appendix is a strong indicator of gangrenous appendicitis; however, this finding is sometimes subtle and could be difficult to detect. In contrast, an appendicolith is easier to see even on a non-enhanced CT scan. Therefore, we propose the combination of an appendicolith on CT scan and elevated T-Bil to preoperatively establish the diagnosis of gangrenous appendicitis. These indicators are especially valuable for decision-making by non-abdominal surgeons when considering the need for surgery, such as in the emergency room, because they are based on clear objective parameters.

There are some limitations in this study. First, this study was based on a retrospective analysis of a

relatively small number of patients. Second, the study targeted patients >15 years of age and does not provide conclusions for younger patients. Moreover, the patients' condition could have changed between the time of obtaining the specimen for laboratory tests and operation, and data used in the present study might not accurately reflect the status at the time of surgery. Third, as described, this study targeted patients with histologically confirmed appendicitis and not those with suspicious appendicitis. In daily practice, we, intentionally or unintentionally, take two steps: diagnosing the condition as appendicitis and then diagnosing/considering its severity. The present effort targeted the second step. Thus, the present results might not be adapted to patients with suspicious appendicitis, for example, patients with acute lower right abdominal pain. We believe that symptoms/signs are very important to diagnose the condition in both (the first and second) steps. An incorporation of symptoms/signs into the presently proposed predictor could create some clinically useful marker to predict/diagnose gangrenous appendicitis among patients with suspicious appendicitis; this could be a future study target.

CONCLUSIONS

PREOPERATIVE ELEVATED T -Bil level and visualization of an appendicolith on CT scan could be useful clinical indicators to establish the diagnosis of gangrenous appendicitis. These two indicators are easily assessed and thus could be readily applicable in the evaluation of patients with presumed appendicitis.

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DISCLOSURE

APPROVAL OF THE research protocol: Approval to conduct this study was obtained from the ethics committee of Tokyo Metropolitan Tama Medical Center (Ethics Committee Approval Case Number 31-34).

Informed consent: N/A.

Registry and the registration no. of the study: N/A.

Animal studies: N/A.

Conflict of interest: None.

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