

Hyperbilirubinemia as a predictor of severity of acute appendicitis

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Abstract

Objective: This study aimed to investigate the clinical significance of preoperative hyperbilirubinemia in Japanese patients and to assess its clinical potential as a predictor of the severity of acute appendicitis.

Methods: We studied 318 patients with appendicitis who underwent appendectomy between July 2010 and June 2017. We analyzed preoperative data including age, sex, white blood cell count, C-reactive protein (CRP) level, fever, peritoneal irritation signs, and serum total bilirubin level as potential risk factors for complicated (perforated or gangrenous) appendicitis, using multivariate analysis.

Results: Complicated appendicitis was significantly more frequent in patients with hyperbilirubinemia (>1.1 mg/dL), high CRP level (>0.5 mg/dL), positive peritoneal irritation signs, and fever ($>37.3^{\circ}\text{C}$). Multivariate analysis revealed older age (>64 years), hyperbilirubinemia, high CRP level, and fever (odds ratios 3.36, 1.75, 7.61, and 2.43, respectively) as risk factors for complicated appendicitis. Multivariate analysis also identified hyperbilirubinemia, high CRP level, and fever (odds ratios 1.99, 5.90, and 2.72, respectively) as risk factors for complicated appendicitis among patients aged <65 years.

Conclusions: Hyperbilirubinemia, high CRP level, and fever may be useful predictors of the severity of acute appendicitis, with hyperbilirubinemia being especially useful among patients aged <65 years.

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Keywords

Acute appendicitis, complicated appendicitis, gangrenous appendicitis, hyperbilirubinemia, perforated appendicitis, C-reactive protein, fever, age

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Introduction

Acute appendicitis is one of the most common abdominal emergencies requiring emergency surgery, and appendectomy is the most frequently performed emergency operation worldwide.^{1,2} Various scoring systems, such as the Alvarado score, have been suggested for appendicitis, based on clinical features, physical examination, and laboratory data.³ However, the classical symptoms and signs of appendicitis may sometimes be absent, making it difficult to reach a definite diagnosis.⁴ Given that the delayed diagnosis and treatment of severe appendicitis is associated with increased risks of perforation and postoperative morbidity, mortality, and hospital stay, there is an urgent need for a predictor of the severity of acute appendicitis.⁵

Hyperbilirubinemia not caused by liver dysfunction or biliary obstruction can be observed in cases of acute appendicitis. Although some studies have reported on the usefulness of hyperbilirubinemia for assessing acute appendicitis,^{4,6–10} its clinical value remains controversial. We therefore aimed to investigate the clinical significance of preoperative hyperbilirubinemia in Japanese patients and to assess its value as a predictor of the severity of acute appendicitis.

Patients and methods

In this retrospective cohort, single-institution study, we evaluated 318 patients with pathologically diagnosed appendicitis who underwent appendectomy at our institution

between July 2010 and June 2017. Preoperative patient data included age, sex, white blood cell (WBC) count, C-reactive protein (CRP) level, fever, peritoneal irritation signs, and serum total bilirubin level.

The 318 patients were divided into two groups based on the pathological grade of acute appendicitis used in Japan:¹¹ complicated appendicitis (perforated or gangrenous appendicitis) and simple appendicitis (phlegmonous or catarrhal appendicitis). We compared preoperative clinical factors between these two groups and analyzed the risk factors for complicated appendicitis by multivariate analysis.

We set cut-off scores for WBC count, CRP level, fever, and total serum bilirubin level at 11,000/ μ L, 0.5 mg/dL, 37.3°C, and 1.1 mg/dL, respectively, based on previous reports.^{3,7,8}

Statistical analysis

Statistical analysis was carried out using PASW Statistics for Windows, Version 18 (SPSS Inc., Chicago, IL, USA). Clinicopathological characteristics were compared between the two groups using χ^2 or *t*-tests. Multivariate analysis was carried out by binomial logistic analyses, with adjustments for variables significant in univariate analysis. Statistical significance was defined as $P < 0.05$.

Ethical considerations

The study protocol was approved by the Institutional Review Board of the

Table 1. Characteristics and preoperative parameters in patients with complicated (perforated or gangrenous) and simple (phlegmonous or catarrhal) appendicitis.

	Complicated appendicitis (n = 134)	Simple appendicitis (n = 184)	P value
Age (years)	52.4	39.6	0.019
Sex (male:female)	66:68	70:114	0.046
WBC	12,661/ μ L	11,545/ μ L	0.067
	>11,000/ μ L	81 (44.0%)	0.202
CRP	9.87 mg/dL	3.04 mg/dL	<0.001
	>0.5 mg/dL	118 (64.1%)	<0.001
T-Bil	1.18 mg/dL	1.03 mg/dL	0.07
	>1.1 mg/dL	62 (33.7%)	0.014
Fever	75 (56.0%)	58 (31.5%)	<0.001
Peritoneal irritation signs	92 (68.7%)	102 (55.4%)	0.017

Values given as mean values. CRP, C-reactive protein; WBC, white blood cell; T-Bil, total bilirubin.

National Hospital Organization Fukuyama Medical Center (Hiroshima, Japan). All study procedures were performed in accordance with the guidelines of the Declaration of Helsinki, and all study subjects gave written informed consent to participate.

Results

The mean age of the patients was 45.0 (range, 14–94) years, and 136 of the patients were male. The mean WBC count was 12,015/ μ L (range, 1000–35,300/ μ L), mean CRP level was 5.92 (range, 0–39.2) mg/dL, and mean serum total bilirubin level was 1.1 (range, 0.3–4.5) mg/dL. Thirty-seven patients (11.6%) had perforated appendicitis, 97 (30.5%) had gangrenous, 148 (46.5%) had phlegmonous, and 36 (11.3%) had catarrhal appendicitis. Moreover, 179 patients (56.3%) had high WBC counts (>11,000/ μ L), 245 (77.0%) had high CRP levels (>0.5 mg/dL), 125 (39.3%) had hyperbilirubinemia (>1.1 mg/dL), 133 (41.8%) had fever (>37.3°C), and 194 (61.0%) had positive peritoneal irritation signs.

Complicated appendicitis was significantly more frequent in older patients

($P=0.019$), patients with hyperbilirubinemia ($P=0.014$), high CRP level ($P<0.001$), positive peritoneal irritation signs ($P=0.017$), and fever ($P<0.001$) (Table 1). Multivariate analysis revealed older age (>64 years) ($P<0.001$), high CRP level ($P<0.001$), hyperbilirubinemia ($P<0.038$), and fever ($P=0.001$) as risk factors for complicated appendicitis (Table 2).

Among younger patients (age <65 years), complicated appendicitis was significantly more common in patients with hyperbilirubinemia ($P=0.003$), high CRP level ($P<0.001$), positive peritoneal irritation signs ($P=0.034$), and fever ($P<0.001$) (Table 3). Multivariate analysis identified hyperbilirubinemia ($P=0.017$), high CRP level ($P<0.001$), and fever ($P=0.001$) as risk factors for complicated appendicitis in these patients (Table 4).

Discussion

Acute appendicitis is a common cause of abdominal pain in the emergency department, with a prevalence of 7–22 per 10,000 people.^{12,13} Although simple appendicitis (phlegmonous or catarrhal) can be

Table 2. Univariate and multivariate analyses in all patients.

	Univariate analysis		Multivariate analysis	
	OR	95% CI	OR	95% CI
Age (>64 years)	3.42	1.908–6.138	3.36	1.74–6.48
Male sex	0.633	0.403–0.993		
High CRP (>0.5 mg/dL)	10.148	4.477–23.004	7.61	3.257–17.757
Hyperbilirubinemia (>1.1 mg/dL)	1.771	1.121–2.798	1.75	1.031–2.959
Fever (>37.3°C)	2.762	1.741–4.381	2.43	1.449–4.057
Peritoneal irritation signs	1.761	1.104–2.808		

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

Table 3. Characteristics and preoperative parameters in younger patients (<65 years) with complicated and simple appendicitis.

	Complicated appendicitis (n = 93)	Simple appendicitis (n = 163)	P value	
Age (years)	41.4	34.9	0.066	
Sex (male:female)	43 : 50	63 : 100	0.236	
WBC	13,278/ μ L	11,821/ μ L	0.290	
	>11,000/ μ L	62 (66.7%)	91 (55.8%)	0.089
CRP	9.34 mg/dL	2.79 mg/dL	<0.001	
	>0.5 mg/dL	86 (92.5%)	103 (63.2%)	<0.001
T-Bil	1.24 mg/dL	1.04 mg/dL	0.10	
	>1.1 mg/dL	50 (53.8%)	57 (35.0%)	0.003
Fever	>37.3°C	55 (59.1%)	51 (31.3%)	<0.001
Peritoneal irritation sign	65 (69.9%)	92 (56.4%)	0.034	

Values given as mean values. CRP, C-reactive protein; T-Bil, total bilirubin; WBC, white blood cell.

Table 4. Univariate and multivariate analyses in younger patients (<65 years).

	Univariate analysis		Multivariate analysis	
	OR	95% CI	OR	95% CI
High CRP (<0.5 mg/dL)	7.157	3.11–16.47	5.90	2.494–13.976
Hyperbilirubinemia (<1.1 mg/dL)	2.214	1.31–3.73	1.99	1.13–3.502
Fever (>37.3°C)	3.179	1.872–5.398	2.72	1.543–4.782
Peritoneal irritation signs	1.792	1.043–3.076		

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

cured by appendectomy, complicated appendicitis (perforated or gangrenous) may cause complications such as bacterial peritonitis, urinary disorders, small bowel

obstruction, or intra-abdominal abscess formation. These complications may become life-threatening, thus highlighting the need for a correct diagnosis and early

treatment.^{5,6} However, the varied symptom patterns mean that it may be difficult to reach a definite diagnosis and, especially in asymptomatic cases, most physicians are required to carry out observation and re-evaluation, resulting in prolonged hospital stay and delayed definitive treatment, potentially leading to perforation.⁹ Despite the increase in diagnostic modalities such as ultrasonography and computed tomography, the rates of appendicitis misdiagnosis (15%) and appendiceal rupture have remained constant.¹⁴

The association between hyperbilirubinemia and appendicitis has been examined over the last decade. Hyperbilirubinemia occurs in systemic infections from various disease, including general peritonitis and sepsis,^{15,16} and several mechanisms leading to hyperbilirubinemia in systemic infection have been described. Several bacterial infections have been demonstrated to induce cholestasis,¹⁶⁻¹⁸ and *Escherichia coli* and *Bacteroides fragilis* are most common primary causative organisms of appendicitis.⁷ *E. coli* endotoxins cause dose-dependent cholestasis,¹⁹ and *E. coli* can also cause erythrocyte hemolysis, which increases the bilirubin load.²⁰ Furthermore, severe inflammation, as in complicated appendicitis, can cause edema of the intestine and intestinal hypomotility, which can also induce cholestasis in patients with complicated appendicitis. These mechanisms may thus lead to hyperbilirubinemia in cases of acute appendicitis.

Hyperbilirubinemia has previously been reported as a predictive factor of appendicitis. Svinc et al.¹⁰ reported that hyperbilirubinemia (>1.0 mg/dL) and high neutrophil-to-lymphocyte ratio (>4.8) were significantly associated with perforated appendicitis among 3392 cases (odds ratios 2.6 and 2.6, respectively). Furthermore, Eren et al.⁶ found that high CRP (>0.5 mg/dL) and hyperbilirubinemia (>1.2 mg/dL) were associated with

gangrenous or perforated appendicitis in a study of 162 patients. In Japan, Nomura et al.⁷ identified hyperbilirubinemia as a risk factor for gangrenous appendicitis among 410 patients (odds ratio 1.7919).

In the present study, multivariate analysis identified older age, high CRP level, hyperbilirubinemia, and fever as risk factors for complicated appendicitis overall, while hyperbilirubinemia, high CRP level, and fever were risk factors for complicated appendicitis in younger patients. Previous studies have not focused on younger patients; however, systemic functional reserve is more frequently lacking in older patients, potentially leading to many false-positives, and hyperbilirubinemia may thus be a more useful indicator in younger compared with older patients.

Furthermore, it may be difficult to obtain a complete anamnesis in the emergency department, with a high possibility of passing over the patient's present history. Changes in serum bilirubin level cannot be known at the first visit; however, older people are more likely to have primary hyperbilirubinemia than younger people, also suggesting that hyperbilirubinemia may be a more useful indicator in younger patients.

Regarding high CRP levels, Eren et al.⁶ reported that this was an important marker for predicting gangrenous or perforated appendicitis. Because complicated appendicitis is associated with more severe inflammation than simple appendicitis, high CRP levels may thus also be an important predictive factor for complicated appendicitis.

Nomura et al.⁷ also identified older age as a predictor of gangrenous appendicitis. Patients become increasingly immunologically compromised with age, and inflammation thus tends to be more severe in older compared with younger patients. This may explain why older age was also a significant

predictive factor for complicated appendicitis.

This study had several limitations. All the study patients underwent appendectomy and we did not investigate patients who received conservative treatment. Furthermore, it was a retrospective, single-institution study with a small sample size.

In conclusion, hyperbilirubinemia, high CRP level, and fever may be useful predictors of the severity of acute appendicitis, with hyperbilirubinemia being more useful among patients aged <65 years compared with older patients.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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