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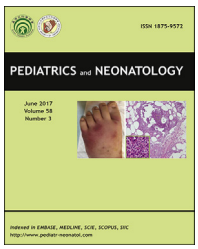

ORIGINAL ARTICLE

Risk Factors for Prolonged Hospitalization in Pediatric Appendicitis Patients with Medical Treatment

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Key Words
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Background: With effective antibiotics against enteric flora and computed tomography-guided drainage for abscesses, the initial use of nonoperative therapy for children with appendicitis has increased both in recent reports and at our hospital. However, it has been reported that these patients have a relatively longer hospital stay and that their treatment is more expensive than those who undergo aggressive surgical intervention.
Methods: This was a retrospective cohort study based in a single medical center. A systemic chart review was conducted to identify risk factors for prolonged hospitalization in pediatric appendicitis patients not initially undergoing surgical treatment. Patient demographics, clinical symptoms, duration of symptoms, laboratory findings, imaging findings, complications, and length of hospital stay were analyzed. Logistic regression analysis was used to identify significant predictors of prolonged hospitalization ($\geq$15 days) and readmission.
Results: One hundred and twenty-five patients were recruited in this study, of whom 53 (42.4%) had prolonged hospitalization. The values of serum C-reactive protein (CRP) were significantly higher in patients with prolonged hospitalization compared with those without prolonged hospitalization (203 $\pm$ 108.6 mg/L vs. 140 $\pm$ 93.0 mg/L, $p = 0.001$). Risk factors of prolonged hospitalization were serum CRP >150 mg/L (35/53 vs. 28/72, $p = 0.001$), abscess formation (38/53 vs. 35/72, $p = 0.008$), and multiple abscesses (10/53 vs. 1/72, $p = 0.001$). Under multivariate analysis, CRP >150 mg/L (odds ratio = 1.004, $p = 0.0334$) and multiple abscesses (odds ratio = 8.788, $p = 0.044$) were two independent predictors for prolonged hospitalization.

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Conclusion: Marked elevation of serum CRP (>150 mg/L) and multiple abscesses are two independent risk factors for prolonged hospitalization in children with appendicitis who are initially treated nonoperatively.

1. Introduction

Appendicitis is one of the most common causes of acute abdomen in children.[1–3] Patients who are diagnosed early and undergo an appendectomy before perforation have a good outcome.[4,5] However, it is difficult to diagnose in young children because its clinical manifestations may be atypical and many patients have perforated appendicitis when diagnosed.[6–8] Appendiceal perforation occurs frequently in younger children with a longer duration of clinical symptoms. The rates of perforation vary by age, but are reportedly between 20% and 76%.[6–11]

In children with atypical presentations, ultrasonography (US) is recommended as a first-line imaging tool by the American College of Radiology.[12] Increased use of US alone or US with computed tomography (CT) for children's appendicitis is associated with lower negative appendectomy and misdiagnosis rates.[13]

Patients with perforated appendicitis or an uncertain diagnosis may initially be treated nonoperatively. Appropriate and effective antibiotic therapy against enteric flora and CT-guided drainage of abscesses increased the success rate of nonoperative treatment.[14,15] Most pediatric surgeons use the absence of fever, resolution of abdominal pain, normalization of white blood cell (WBC) count, and tolerance of a regular diet as indicators for discontinuation of postoperative intravenous antibiotics.[14,16] However, there is limited evidence as to the optimum duration of antibiotic therapy for children's appendicitis when they are not initially treated using surgery. Some patients have a poor response to antibiotic treatment, along with persistent symptoms, prolonged hospitalization, recurrent admission, and large abscesses that require image-guided drainage.

In this study, we identified the risk factors for prolonged hospitalization of children with appendicitis who were initially treated nonoperatively.

2. Methods

A 5-year retrospective chart review of pediatric patients with appendicitis was conducted. Consecutive patients who were aged <18 years and underwent regular follow-up visits for appendicitis at our hospital between January 1, 2009 and December 31, 2013 were enrolled into this study. Only those who received antibiotic treatment without initial surgical intervention were included. Children with underlying organic disease or who were receiving antibiotic treatment before admission to our hospital were excluded.

The diagnosis of appendicitis was based on clinical symptoms with positive diagnostic imaging (an abdominal US and/or CT scan). After the diagnosis of appendicitis was made, broad-spectrum intravenous antibiotic treatment was administered. At our hospital, the routine first-line intravenous antibiotics for acute appendicitis were ampicillin or a first-generation cephalosporin, plus gentamicin and metronidazole. Second-line parenteral antibiotic regimens contained a third-generation cephalosporin. Imipenem or piperacillin–tazobactam was used for advanced conditions. After discharge, amoxicillin–clavulanate was the routinely prescribed oral antibiotic.

The pediatrician routinely consulted the pediatric surgeon regarding the possibility of surgical intervention in patients with clinical presentations and imaging findings consistent with appendicitis. Following our government's case payment regulation for pediatric patients receiving operation for acute appendicitis, the pediatric surgeon routinely performed the operation in cases of nonperforated, early-perforated (duration of clinical symptoms < 2–3 days), or advanced appendicitis with clinically ill-appearing or critical complications (intractable abdominal pain, unstable vital signs, and bowel obstruction). Antibiotics were administered orally (augmentin or cafepime) once the fever and abdominal pain had resolved, the WBC count was normal, and a regular diet could be tolerated. Upgraded antibiotics and/or CT-guided drainage for abscesses was used if the patient had persistent fever, abdominal pain, nausea, or vomiting. The indications for discharge of the patients included well-tolerated solid foods, normal bowel habits, absence of fever and dehydration, and resolution of abdominal pain, ileus, and leukocytosis. After discharge from the hospital, oral antibiotics were still administered until the resolution of intestinal ileus and intra-abdominal abscess. The pediatric surgeon performed the interval laparoscopic appendectomy in those patients who had complete resolution of clinical symptoms, and negative features for local ileus and residual abscess on abdominal US.

To identify the risk factors for prolonged hospitalization in pediatric appendicitis patients initially undergoing nonoperative treatment, the cutoff value of 15 days for the length of hospital stay (LOS) used for analysis was based on a mean LOS of 15.4 days in the enrolled patients. The enrolled patients were divided into two groups for analysis. Patients in Group 1 had a LOS of <15 days (no prolonged hospitalization), while those in Group 2 had a LOS of ≥15 days (prolonged hospitalization). The demographics and clinical characteristics evaluated included age, sex, clinical symptoms, duration of fever, use of parenteral nutrition, complications, adverse events, and LOS. The blood tests for hemogram [hemoglobin, WBC count and its percentage of immature neutrophil count

(bands), electrolytes (sodium and potassium), and C-reactive protein (CRP)] at admission, and initial imaging findings were analyzed. Metabolic acidosis was also evaluated when blood gas examination was performed.

Fever was defined as a body temperature of more than 38°C according to an ear thermometer; severe dehydration was defined as palpitation or hypotension according to the Advanced Paediatric Life Support guidebook and accepted fluid challenge. Serum CRP was considered to be elevated if higher than 5 mg/L. Hyponatremia, hypernatremia, hypokalemia, and hyperkalemia were defined as a blood sodium level of <130 mEq/L, >150 mEq/L, <3.5 mEq/L, and >5 mEq/L, respectively.

The use of CT-guided drainage and parenteral nutrition, complications, adverse events, and subsequent interval appendectomy were compared between the groups. The relationship between LOS and the following factors was evaluated: demographics, clinical characteristics, laboratory findings (leukocytosis, neutropenia, percentage of bands in WBC, anemia, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, and serum CRP), and imaging findings (phlegmon, abscess formation, multiple abscesses, and appendicolith). A cutoff value was assessed based on the neighboring values of mean data for each laboratory parameter and size of abscess, to allow precise determination of statistically significant values. Independent predictors for prolonged hospitalization were determined through statistical analysis.

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). We calculated descriptive statistics for demographics, clinical symptoms, physical findings, laboratory data, and imaging findings. Continuous variables are expressed as the mean ± the standard deviation. For univariate analysis, the Chi-square test with Fisher's exact test and Student *t* test were used to assess the significance of categorical and numerical variables, respectively. A *p* value of <0.05 was considered statistically significant. Simple and multiple logistic regression models were applied to determine risk factors for prolonged hospitalization.

This study was approved by the local institutional review board (CGMH 103-1842B).

3. Results

An algorithm of patient inclusion and classification is shown in Figure 1. A total of 953 children were diagnosed with acute appendicitis, 809 patients received appendectomy, and 144 patients were treated nonoperatively. Of the 144 patients treated nonoperatively, a total of 19 cases who were treated with the use of antibiotics before admission to our hospital were excluded. Among the 19 excluded cases, 10 were transferred from other hospitals and nine had been treated with antibiotics at a local medical department. A total of 125 patients were finally enrolled into this study. Forty-six (36.8%) patients underwent abdominal US, 13 (10.4%) underwent a CT scan, and 64 (51.2%) underwent both procedures as the initial diagnostic imaging studies.

Seventy-two patients (57.6%) responded well to treatment and were discharged within 15 days (Group 1), and 53 patients (42.4%) had a poor response to medical treatment

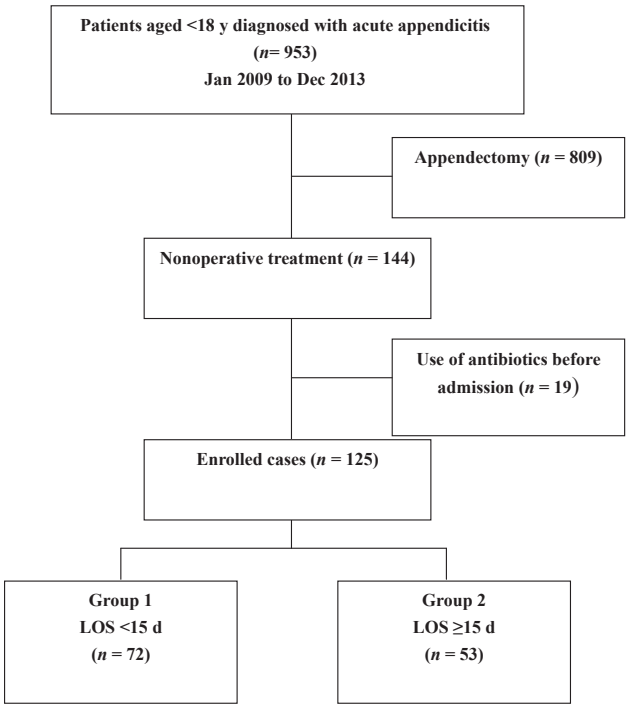

Figure 1 Algorithm of patient inclusion and classification. LOS = length of hospital stay.

and a LOS of ≥15 days (Group 2). The patient demographics, clinical characteristics, and LOS of both groups are summarized in Table 1. The mean LOS in Groups 1 and 2 was 11 ± 2.6 days and 21 ± 6.1 days, respectively. After univariate analysis, there were no significant differences in age, gender, clinical presentation, or duration of symptoms between the two groups.

Group 2 patients had a significantly higher mean serum CRP value than Group 1 patients (203 ± 108.6 mg/L vs. 140 ± 93.0 mg/L, $p = 0.001$). There were no significant differences with respect to leukocytosis, anemia, or electrolyte imbalance between the groups (Table 2).

Table 1 Demographics, clinical symptoms, and length of hospital stay (LOS).

Variables	Group 1 ($n = 72$) LOS <15 d	Group 2 ($n = 53$) LOS ≥15 d	*p*
Age (y)	10.0 ± 4.4	10.2 ± 3.8	0.822
Sex (% male)	55.6	50.9	0.609
Abdominal pain	100%	100%	NS
Fever	76.4%	77.4%	0.899
Vomiting	62.5%	68%	0.530
Diarrhea	38.9%	43.4%	0.612
Duration of symptoms (d)	4.3 ± 2.2	3.8 ± 2.2	0.259
LOS (d)	11.3 ± 2.6	21.1 ± 6.1	<0.001*

NS = not significant.

* Numerical data were analyzed using the Student *t* test and categorical data using the Chi-square test. A *p* value of <0.05 was considered to be statistically significant.

Table 2 Laboratory findings at admission.

Variables	Group 1 (n = 72) LOS <15 d	Group 2 (n = 53) LOS ≥15 d	p
Hemoglobin (g/dL)	12.8 ± 1.2	13.0 ± 1.3	0.452
Platelets (1000/L)	306 ± 93.3	286 ± 84.8	0.212
WBC (1000/L)	16.1 ± 6.6	16.3 ± 5.6	0.851
Leukocytosis, n (%)	50 (69.4)	37 (69.8)	0.965
Bands (%)	2.7	3.1	0.807
Neutrophil (%)	78.4	81.6	0.094
Hypernatremia, n (%)	0 (0)	0 (0)	NS
Hyponatremia, n (%)	0/44 (0)	3/38 (7.9)	0.058
Hyperkalemia, n (%)	0 (0)	0 (0)	NS
Hypokalemia, n (%)	10/44 (22.7)	4/38 (10.5)	0.143
CRP (mg/L)	140 ± 93.0	203 ± 108.6	0.001*

CRP = C-reactive protein; LOS = length of hospital stay; NS = not significant; WBC = white blood cells.
* Numerical data were analyzed using the Student t test and categorical data using the Chi-square test. A p value of <0.05 was considered to be statistically significant.

Furthermore, compared with Group 1 patients, Group 2 patients suffered more frequently from abscess formation (48.6% vs. 70.4%, p = 0.008) and multiple abscess formation (1.4% vs. 18.5%, p = 0.001). There was no significant difference in the rate of phlegmon formation, abscess size, or the presence of appendicolith between the groups (Table 3). Under Chi-square analysis, the patients with multiple abscesses had a significantly longer hospital stay than those with a single abscess (p = 0.013). Multivariate analysis identified that CRP >150 mg/L (odds ratio = 1.004, 95% confidence interval: 1–1.007, p = 0.0334) and multiple abscesses (odds ratio = 8.788, 95% confidence interval: 1.060–72.867, p = 0.044) were two independent predictors of prolonged hospitalization (Table 4).

As shown in Table 5, CT-guided drainage of abscesses, complications, or parenteral nutrition were not performed in Group 1, while in Group 2, 10 patients underwent CT-guided abscess drainage and 10 patients required parenteral nutrition, of whom one suffered from a catheter-related infection. Statistical analysis revealed that CT-guided abscess drainage, use of parenteral nutrition, and catheter-related infection after parenteral nutrition were associated with prolonged hospitalization (LOS ≥ 15 days; Table 5).

Table 3 Imaging findings at admission.

Variables	Group 1 (n = 72) LOS <15 days	Group 2 (n = 53) LOS ≥15 d	p
Phlegmon, n (%)	8 (11.1)	5 (9.4)	0.598
Any abscess, n (%)	35 (48.6)	38 (70.4)	0.008*
Single abscess, n (%)	34 (47.2)	28 (51.9)	0.514
Multiple abscesses, n (%)	1 (1.4)	10 (18.5)	0.001*
Abscess size (cm)	5.32 ± 1.8	5.85 ± 2.0	0.274
Appendicolith, n (%)	30 (42.3)	19 (36.5)	0.522

LOS = length of hospital stay.
* Numerical data were analyzed using the Student t test and categorical data using the Chi-square test. A p value of <0.05 was considered to be statistically significant.

Table 4 Predictors of prolonged hospitalization.

Variables	Multivariate analysis	
	OR (95% CI)	p
CRP >150 mg/L	1.004 (1–1.007)	0.0334*
Any abscess, n (%)	1.857 (0.87–3.963)	0.1097
Multiple abscesses, n (%)	8.788 (1.060–72.867)	0.044*

CI = confidence interval; CRP = C-reactive protein; OR = odds ratio.
* A p value of <0.05 was considered to be statistically significant.

Table 5 Interventions and adverse events.

Variables	Group 1 (n = 72) LOS <15 d	Group 2 (n = 53) LOS ≥15 d	p
Image-guided drainage, n (%)	0 (0)	10 (18.5)	<0.001*
Parenteral nutrition, n (%)	0 (0)	10 (18.5)	<0.001*
Catheter-related infection, n (%)	0 (0)	1 (2)	<0.001*
Interval appendectomy (%)	69.4	77.4	0.326

LOS = length of hospital stay.
* Numerical data were analyzed using the Student t test and categorical data using the Chi-square test. A p value of <0.05 was considered to be statistically significant.

4. Discussion

The best treatment for perforated appendicitis in children is still under debate. Recent studies indicated that initial nonoperative treatment with a subsequent interval appendectomy was associated with significantly more adverse events and a prolonged time to normal activity compared with early appendectomy, and that it was also more expensive.[17,18] Initial nonoperative treatment for pediatric appendicitis became popular for a number of reasons. First, the patients' family members always request an accurate diagnosis before surgery and a negative appendectomy raises concerns. Furthermore, with effective antibiotics and CT-guided abscess drainage, the success rate of nonoperative management increased.[14,15] In our institution, the ratio of nonperforated to perforated appendicitis in pediatric patients was found to have changed very little based on the analysis of hospital data collected in recent years. However, the use of initial nonoperative treatment in these patients was found to have increased to 22% in 2013. This trend toward managing appendicitis conservatively may have been influenced by a change in how this treatment was reimbursed, following the government's policy of providing a fixed payment by diagnosis-related

groups in Taiwan. The mean duration of hospitalization (15 days) of our series is relatively longer than the LOS in previous studies. The reason for the longer LOS in our series may be because our institute is the only medical center (tertiary hospital) in a large city of more than 2 million people. Approximately one-third of the studied patients had been transferred from local hospitals or hospitals in neighboring cities. Compared with the patients with initial help at our outpatient or emergency department, most of the referred patients had a longer mean duration of symptoms due to delayed diagnosis of appendicitis. The majority of the referred cases had scattered turbid fluid collection or multiple abscesses. Following the government's case payment policy, the pediatric surgeon did not usually perform surgical intervention in these patients for the prevention of possible subsequent complications.

Initial nonoperative treatment for ruptured appendicitis includes intravenous fluid hydration, intravenous antibiotics, appropriate pain control, parenteral nutrition, and image-guided percutaneous drainage. To reduce inflammation before an interval appendectomy, broad-spectrum single- or double-agent therapy is thought to be as effective as triple-agent therapy, although this view is based on limited evidence.[14,19] The duration of intravenous antibiotic treatment is determined by clinical indicators, including fever, abdominal pain, bowel function, and WBC count.[14] An abscess was diagnosed when US showed a well-defined hypoechoic or heterogeneous lesion, or when a CT scan showed a well-defined lesion with ring enhancement.[15] It was recommended that patients with significant abscesses should be treated using image-guided (US or CT) drainage by aspiration or through placement of a catheter.[15] The previously reported success rate was around 74–84.2% in children with perforated appendicitis who were treated conservatively, and the median LOS was 6 days (range, 3–24 days).[19,20] In this retrospective study, we found that the mean LOS was around 14 days (range, 4–40 days), which was longer than that of previous reports, because our patients were not discharged with a central catheter for subsequent intravenous hydration or parenteral nutrition. None of our patients had fever, abdominal pain, or leukocytosis, and they all had satisfactory dietary intake and normal bowel movements. Therefore, the LOS in our study patients represents the complete control of acute infectious and inflammatory conditions for the treatment of appendicitis.

This study has several strengths. First, to our knowledge, this is the first study to evaluate the risk factors for prolonged hospitalization extensively in pediatric patients with early perforated appendicitis. We found no statistical differences in hemoglobin levels, platelet or WBC counts, or the percentage of bands or neutrophils between patients with prolonged hospitalization and those who left hospital within 15 days. These findings are in agreement with those of Nadler et al.[19] A study evaluating the effect of conservative management of complicated appendicitis in children by Kogut et al[21] found that nonresponders had a higher percent band count. A significantly higher mean serum CRP level was found in our patients with prolonged hospitalization. This would be expected as CRP is an acute-phase protein of hepatic origin that acts as a robust and independent diagnostic marker of severe bacterial infection in children with fever at initial presentation.[22] Early observational studies suggested that an elevated CRP level (>50 mg/L) was useful for identifying patients with a perforated appendix, and that it had a sensitivity of 76% and a specificity of 82%.[23] Another retrospective study also concluded that CRP was a potent and objective inflammatory marker that reflected pathological severity in appendicitis.[24] We found that a serum CRP value of >150 mg/dL was an independent predictor of prolonged hospitalization in pediatric appendicitis patients who were treated nonoperatively, a finding not previously been reported. In our experience, a significant elevation of serum CRP may indicate advanced appendicitis with progressive inflammation, and it may predict a poor response to medical treatment.

Nadler et al[19] reported that patients with a phlegmon on a CT scan had a favorable outcome and were less likely to require early surgical intervention. However, in our study, there was no significant association between the percentage of phlegmon formation and the LOS. Our analysis also showed that significantly more patients (70.4%) with prolonged hospitalization were found to have an abscess on initial abdominal US or CT scans compared with those without prolonged hospitalization (48.6%). Risk factors for abscess formation are not well understood, and the type of abscess that should be drained continues to be under debate. A retrospective review concluded that multiple intra-abdominal abscesses could be managed successfully by multiple image-guided drainage procedures, and the authors indicated that catheter placement should be performed if more than 3 cm of fluid had collected.[15] Only 10 patients in our study underwent image-guided drainage, while the others received antibiotic treatment without invasive procedures. In our experience, a simple abscess can be treated conservatively, regardless of its size, if patients have improving symptoms, although this might prolong the total hospital course. The presence of an appendicolith on CT or US has previously been identified as a risk factor for recurrent appendicitis,[25–27] although in our study, it was not associated with prolonged hospitalization.

Due to prolonged illness, 10 patients (all in Group 2) received parenteral nutrition for 3–18 days. One had a catheter-related infection requiring a further course of antibiotics. Recently, Castelló González et al[27] reported that there was an increased risk of recurrent appendicitis if symptoms persisted after the resolution of an inflammatory mass, or if more than 6 days were needed for its resolution.[27] However, the rate of readmission due to recurrent abdominal symptoms or fever was not significantly associated with LOS before the interval appendectomy (15.3–17%).

This study had some limitations. The study population was from a single medical center, and the results may be less generalizable than those from multicenter studies with a prospective observational design. A potential risk factor (underlying malnutrition) was not recorded or examined, which may affect the LOS.

In conclusion, a marked elevation of serum CRP on admission and abscess formation on initial abdominal US or CT scans are risk factors for prolonged hospitalization in children with appendicitis who are initially treated nonoperatively. CRP >150 mg/L and multiple abscesses are two independent predictors for prolonged hospitalization. On

the basis of the results of this study, we recommend early surgical drainage or aggressive CT drainage in patients with CRP >150 mg/L or multiple abscesses to shorten hospitalization as much as possible. These patients might benefit from early surgical intervention or image-guided drainage of the abscess, but further studies are needed for identification.

Conflicts of interest

All authors declare no potential, perceived, or real conflicts of interest, especially with respect to any financial arrangement with a company the product of which is discussed in this paper.

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