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Original Article

Predictors of Perforated Acute Appendicitis: a Retrospective Study from a Single Institution

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Key Words
Perforated acute appendicitis;
C-reactive protein;
Abdominal computed tomography

Abbreviations
OR, odds ratio;
CI, confidence interval;
CT, computed tomography;
CRP, C-reactive protein;
SD, standard deviation

Purpose. Prompt appendectomy has long been the standard of treatment for acute appendicitis, due to the risk of progression and subsequent post-operative complications. This study aimed to identify independent predictors of acute complicated appendicitis.
Methods. Data were obtained from a retrospective database that recorded all appendicitis cases at the Chi-Mei Medical Center Data. There were 480 consecutive patients undergoing appendectomy for suspected acute appendicitis between January and December 2010. Two patient groups, without perforation (N = 332) and with perforation (N = 92), were analyzed to compare clinical characteristics, hospital stay, and post-operative complications.
Results. Ninety-two patients with appendiceal perforation and 332 patients with simple appendicitis were confirmed pathologically. The overall perforation rate of appendicitis was 21.70% (92/424), and the negative appendectomy rate was 11.67% (56/480). Univariate and multivariate logistic regression analysis identified 2 independent factors associated with appendiceal perforation, the duration of abdominal pain for over 3 days (odds ratio (OR): 3.03, 95% confidence interval (CI): 1.62-5.65, $p < 0.001$) and a C-reactive protein level over 30 mg/dl (OR: 5.38, 95% CI: 2.52-11.50, $p < 0.001$).
Conclusions. Computed tomography (CT) scanning has been shown to be highly accurate for diagnosing appendicitis, but it has not been specifically evaluated for perforated appendicitis. Combining the results of higher C-reactive protein levels obtained in the emergency department and patient delay are the predominant factors determining the incidence of complicated appendicitis.
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Appendectomy is a safe procedure for uncomplicated acute appendicitis. However, perforation makes surgical intervention for appendicitis more difficult and results in more complications. Identifying the predictors of appendiceal perforation before surgery may reduce the impact on the patient and prevent possible subsequent sequelae. Previous studies proposed that perforated acute appendicitis could be asso-

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ciated with personal history and underlying diseases, laboratory examinations, imaging studies, and the delay that occurs from the onset of abdominal pain to surgical intervention. This study aimed to determine which of these parameters are independent predictive factors of acute complicated appendicitis.

Patients and Methods

Patients in this study were recruited from the Chi-Mei medical center, which is a tertiary surgical referral centre. We have collected all patients who were diagnosed as suspected acute appendicitis between January and December 2010 (N = 509) in our hospital. Twenty-nine patients sustained complicated appendicitis confirmed in the ER by abdominal CT scans. Therefore, about 5.7% of the patients with complicated appendicitis underwent initial conservative treatment. The records of patients who underwent either laparoscopic or open appendectomy for presumed acute appendicitis were retrieved from the hospital database. All those who had appendectomy performed on a non-emergency basis or as a part of other surgical procedures (eg right hemicolectomy for carcinoma of the cecum and incidental appendectomy) were excluded. The records of 480 patients were retrieved in this retrospective study and all the medical notes, operative records, and pathology reports were reviewed. The diagnosis of acute appendicitis was confirmed if there was infiltration with polymorphs in the muscularis propria of the appendix. Perforation was confirmed pathologically and defined as an inflamed appendix with evidence of macroscopic perforation, rather than surgical or imaging findings. Periappendicitis, fibrous obliteration, and serositis were regarded as negative appendectomies.

We divided the variables into 4 categories (Table 1), including personal history and comorbidities, laboratory examinations, imaging studies, and time delay. For personal history and comorbidities, we recorded age, gender, fever, tachycardia, hypertensive cardiovascular disease, diabetes mellitus, and history of abdominal surgery. We obtained laboratory results, including WBC counts and C-reactive protein levels, in the emergency room, with a cutoff point based on clinical experience and previous reports. The abdominal CT was not routinely used but, instead, it was arranged by clinician decision. In our hospital, we did not have a strict protocol for arranging for abdominal tomography in the diagnosis of acute appendicitis. Abdominal CT would be considered for patients with diffuse peritonitis, atypical presentations, a longer history of the abdominal pain, or unknown abdominal pathogenesis after extensive investigations such as gynecologic consultations. Both patient delay and in- hospital delay were included when calculating the delay. The patient delay was defined as the duration of abdominal pain before presentation. In-hospital delay was defined as the time elapsing between presentation to the emergency room and to the operation room. Intra-abdominal drains were placed for the presence of diffuse peritonitis, turbid or purulent ascites, or perforated or unhealthy base of appendix during operation. In wounds that were not protected well or were contaminated, a subcutaneous drain was left in place.

Statistics

Continuous data were described by the mean and standard deviation, and comparisons between the groups were performed by using the two-sample t-test. Categorical data were presented by count and percentage, and were compared by using the Chi-square or Fisher's exact test, as appropriate. To explore the effects of predictors on appendiceal perforation, multivariable binary logistic regression analyses were conducted. Patients' demographic and clinical factors were gathered in the first model, and treatment-related factors were then appended in the second model.

A p-value of less than 0.05 was considered as being statistically significant. Data analyses were performed by using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Fifty-six patients were found to have a normal ap-

Table 1. Characteristics of 424 appendicitis patients in the two groups

Variables	Non-perforated appendicitis* (n = 332)	Perforated appendicitis* (n = 92)	*p*-value
Personal history and comorbidity			
Age -years	35.98 ± 17.99	38.03 ± 21.82	0.409
≦ 8	7 (2.1%)	4 (4.4%)	0.029
9-64	303 (91.3%)	75 (81.5%)	
≧ 65	22 (6.6%)	13 (14.1%)	
Gender			
Male	195 (58.7%)	59 (64.1%)	0.350
Female	137 (41.3%)	33 (35.9%)	
Fever	9 (2.7%)	3 (3.3%)	0.729
Tachycardia	104 (31.3%)	42 (45.7%)	0.010
Comorbidity			
Abdomen surgery history	27 (8.1%)	7 (7.6%)	0.870
Diabetes mellitus	13 (3.9%)	10 (10.9%)	0.009
Hypertensive cardiovascular disease	35 (10.6%)	14 (15.2%)	0.215
Laboratory examinations			
White-cell count — $1 \times 10^3/mm^3$	13.78 ± 4.04	14.78 ± 5.48	0.105
C-reactive protein[c] — mg/dl	26.09 ± 41.23	72.55 ± 68.38	< 0.001
< 5 mg/dl	103 (32.9%)	11 (12.5%)	< 0.001
5-30 mg/dl	131 (41.9%)	16 (18.2%)	
≧ 30 mg/dl	79 (25.2%)	61 (69.3%)	
CT study	133 (40.1%)	54 (58.7%)	< 0.001
Time delay			
Patients delay (days)	1.70 ± 0.94	2.80 ± 2.53	< 0.001
< 3 days	292 (88.0%)	60 (65.2%)	< 0.001
≧ 3 days	40 (12.0%)	32 (34.8%)	
In hospital delay (hours)	8.82 ± 4.58	9.25 ± 5.19	0.471

* Values are expressed as mean ± SD for continuous variables and as number (%) for categorical variables.

pendix, 92 patients had appendiceal perforation, and 332 patients with simple appendicitis were pathologically confirmed. The overall perforation rate of appendicitis was 21.70% (92/424), and the negative appendectomy rate was 11.67% (56/480). The perforation rates in patients less than 8 year-old, 9-64 year-old, and older than 65 years were 4.4%, 81.5%, and 14.1%, respectively ($p = 0.029$) (Table 1). No gender predominance was found between the two groups ($p = 0.350$). Fever was present in 2.7% of the patients from the non-perforated appendicitis group and in 3.3% of those from the perforated appendicitis group, but this difference was not statistically significant ($p = 0.729$). Tachycardia was associated with rupture ($p = 0.010$). Comorbidities, including hypertensive cardiovascular disease, and a history of previous abdominal surgeries, were similar in the two groups, except for the fact that more patients in the appendiceal perforation group had diabetes mellitus (10.9% vs. 3.9%, $p = 0.009$). No significant differences were found in the white cell count in either of the two groups ($p = 0.105$). The CRP level was significantly different among the 2 groups (72.55 ± 68.38 mg/dl for the perforation group and 26.09 ± 41.23 mg/dl for the non-perforation group, $p < 0.001$). The perforation rate was also associated with increased CRP levels. Patients with C-reactive protein levels over 30 mg/dl had a perforation rate of 69.3%, those with 5-30 mg/dl had a perforation rate of 18.2%, and those with less than 5 mg/dl had a perforation rate of 12.5 %, $p < 0.001$. Comparing patients who had perforated appendicitis with those who did not, we found that more patients in the appendiceal perforation group had pre-operative CT (58.7% vs. 40.1%, $p = 0.001$). The mean duration of abdominal pain was 1.70 ± 0.94 days for the non- perforation group and 2.80 ± 2.53

days for the appendiceal perforation group, and it was significantly different between the two groups ($p < 0.001$). The appendiceal perforation rate was significantly higher in the patients who had abdominal pain for over 3 days before presenting to the emergency department than in those with less than 3 days elapsing (34.8 % vs. 12.1 %, $p < 0.001$). The mean time between emergency department arrival and surgical intervention was 8.82 ± 4.58 hours for the non-perforation group and 9.25 ± 5.19 hours for the appendiceal perforation group; $p = 0.471$). The multivariate logistic regression analysis identified 2 independent predictors associated with appendiceal perforation, and those were the duration of abdominal pain for over 3 days (odds ratio (OR): 3.029, 95% confidence interval (CI): 1.624- 5.652, $p < 0.001$) and C-reactive protein levels over 30 mg/dl (OR: 5.378, 95% CI: 2.515-11.498, $p < 0.001$) (Table 2). The sensitivity and specificity of CRP was 66.3% and 76.2%, respectively.

More patients had intra-abdominal drainage placed in the perforation group than in the non-perforation group (75% vs. 24.7%, $p < 0.001$). As compared to patients in the non-perforation group, more patients from the perforation group had delayed wound closure (12.0% and 2.4 %, $p < 0.001$). The overall wound infection rate (classification as grade I surgical complications) was 8.25% (35/424). The wound infection rate was higher in perforation cases (19.6%) than in non-perforation cases (5.1%) ($p < 0.001$). The incidence of intra-abdominal abscesses (classification as grade II surgical complications) was 1.65%, and it was higher in perforation cases (4.4%) than in non-perforation cases (0.9%) ($p = 0.043$). There were no significant differences between the post-operative ileus and pulmonary complications between the two groups (1.5% vs. 3.3%, $p = 0.379$; 0.9% vs. 1.1, $p = 1.000$). Patients in the perforation group had longer hospital stays than those in the non-perforation group (6.15 ± 5.25 days and 3.52 ± 3.27 days, $p < 0.001$) (Table 3).

Discussion

Acute appendicitis occurs when the appendiceal lumen is obstructed, leading to fluid accumulation, luminal distention, inflammation and, finally, perforation.[1-4] Classic symptoms of appendicitis have been well described.[5] However, up to one third of the patients with acute appendicitis have atypical presentations.[6] Moreover, patients with alternative abdominal conditions may present with clinical findings indistinguishable from acute appendicitis.[7] Thus, although appendicitis traditionally has been a clinical diagnosis, many patients are found to have normal appendixes at surgery. The misdiagnosis of this acute condition has led to the inappropriate removal of a normal appendix in 8-30% of patients.[8]

Table 2. Multivariate logistic regression analysis of predictors

		OR	95% CI	*p*-value
Patient characteristics				
	Age-year			
	≦ 8 versus 9-64	0.980	0.249-3.856	0.976
	≧ 65 versus 9-64	2.339	0.978-5.593	0.056
Tachycardia	Yes versus No	1.229	0.691-2.185	0.483
Diabetes mellitus	Yes versus No	2.227	0.802-6.183	0.124
Time delay				
	patients delay			
	≧ 3 versus < 3 days	3.029	1.624-5.652	< 0.001
Laboratory examinations				
	C-reactive protein — mg/dl			
	5-30 versus < 5	0.965	0.419-2.226	0.934
	≧ 30 versus < 5	5.378	2.515-11.498	< 0.001

OR: odds ratio; CI: confidence interval.

Table 3. Comparison of clinical outcomes

	Non-perforated appendicitis* (n = 332)	Perforated appendicitis* (n = 92)	*p*-value
Operation method			
Mcburney incision	313 (94.3%)	73 (79.3%)	< 0.001
Midline laparotomy	5 (1.5%)	19 (20.7%)	
Mcburney incision conversion to midline	4 (1.2%)	0 (0.0%)	
Laparoscopic appendectomy	10 (3.0%)	0 (0.0%)	
Drainage in abdomen cavity	82 (24.7%)	69 (75%)	< 0.001
Drainage under the external oblique fascia	21 (6.3%)	7 (7.6%)	0.666
Delayed wound closure	8 (2.4%)	11 (12.0%)	< 0.001
Complication			
Wound infection	17 (5.1%)	18 (19.6%)	< 0.001
Intra-abdominal abscess	3 (0.9%)	4 (4.4%)	0.043
Ileus	5 (1.5%)	3 (3.3%)	0.379
Lung complication (atelectasis, pneumonia)	3 (0.9%)	1 (1.1%)	1.000
Length of stay	3.52 ± 3.27	6.15 ± 5.25	< 0.001

* Values are expressed as mean ± SD (standard deviation) for continuous variables and as number (%) for categorical variables.

A rate of unnecessary removals as high as 20% has been considered acceptable in the surgery literature.[9,10] However, negative laparotomy can be avoided in many patients if modern diagnostic methods are used to confirm or exclude acute appendicitis. During the past decade, CT has emerged as the dominant imaging method for evaluating adults with suspected appendicitis. The judicious use of CT imaging in patients with equivocal clinical presentations suspected of having appendicitis led to a significant improvement in the preoperative diagnosis. It resulted in a substantial decrease in the rate of negative appendectomies compared to previously published reports, without incurring an increase in the perforation rates. In US, the incidence of negative appendectomies has declined steadily over the past decade to approximately 8% in 2007.[11] We enrolled 480 patients in this retrospective study and the negative appendectomy rate was 11.67% (56/480). Only 193 patients (40.2%) underwent abdominal CT scans and were diagnosed with acute appendicitis by imaging findings. 287 patients (59.8%) were diagnosed with acute appendicitis based on clinical history, physical findings, and laboratory data. The negative appendectomy rate was 3.10% (6/193) in the CT scan group and 17.42% (50/287) in the non-CT group. Some investigators have attributed the declining rates of negative appendectomies at their centers to the increased use of CT scans.[12-15] With more use of abdominal CT scans for suspicious appendicitis cases, we might see a future decline in the rate of negative appendectomies. However, there was still an up to 22% perforation rate with the use of CT scans.[16] The optimal initial treatment for perforated appendicitis may be nonoperative. In our study, perforation of appendicitis was associated with a higher percentage of intra-abdominal drainage placement, risk of wound infections, delayed wound closures, intra-abdominal abscesses, and the length of hospitalization (Table 3). For this reason, it is important to be able to reliably distinguish between acute and perforated appendicitis. CT scans have been shown to be highly accurate for the diagnosis of appendicitis, but they have not been specifically evaluated for perforated appendicitis.

Extremes of ages have previously been demonstrated to be linked to the risk of perforation.[17,18] However, our own data demonstrated no significantly increased risk of perforation in pre-school children, old age groups, or female patients.

Laboratory data, including leukocytosis, segment neutrophil predominance, and the presence of band forms, have a high predictive power as combined diagnostic tests to detect appendicitis. Nevertheless, they are not specific enough to detect a ruptured appendicitis.[19-22] The C-reactive protein has been studied to increase the diagnostic rate of acute appendicitis.[23-25] In our study, we found that CRP was higher in ruptured appendicitis than in simple appendicitis (72.55 ± 68.38 vs. 26.09 ± 41.23 mg/dL, $p < 0.001$). In our study, patients had a 5.378 times higher risk of perforation than those with normal CRP levels, especially in cases where the C-reactive protein level was over 30 mg/dl in the emergency department. In other words, the level of CRP concentration is the only reliable laboratory test for the detection of appendiceal rupture and is positively related to the severity of acute appendicitis.

It has been demonstrated that CRP could differentiate children with non-perforated appendicitis from children with perforated appendicitis.[26] This observation has also been reported in adults.[27,28] In one study, an elevated CRP (> 5 mg/l) was measured in 98% of the patients in the acute appendicitis with perforation group, as compared to 72.5% in the non-perforation group. The author concluded that CRP is superior to bilirubin and WBC levels for anticipating perforation in acute appendicitis.[29] Thereafter, CRP levels are a reliable marker to predict perforated appendicitis.

According to the result of the receiver operating characteristic curve (ROC curve), a CRP level > 30 mg/dl shows the best predictive power in our series. In a prospective study, when the cutoff value of CRP was 76.7 mg/dl, its sensitivity for detecting acute perforated appendicitis was 75% and its specificity was 35%.[30] Our series showed that the sensitivity and specificity are 66.3% and 76.2%, respectively. Additionally, the sensitivity and specificity are significantly influenced by the cutoff level. Therefore, we still concluded that the CRP is the best available parameter for predicting acute perforated appendicitis, even though it does not have perfect sensitivity and specificity.

Our study revealed that patients with perforation had a significantly longer duration of the abdominal pain than patients with non-perforated appendicitis. Patients with abdominal pain for over 3 days had a 3.029 times higher risk of appendicieal perforation than those with abdominal pain for less than 3 days (Table 3). The influence of the time that elapsed between presentation to the emergency department and the operation outcome after appendectomy is controversial. Busch et al. concluded that an in-hospital delay of more than 12 hours was associated with a significantly higher frequency of perforated appendicitis and negatively influenced the outcomes after appendectomy.[31] However, Abou-Nukta et al. identified no statistically significant differences in the length of stay, operative time, or rate of complications between adult patients that underwent appendectomy between 12 and 24 hours as compared to those undergoing the procedure less than 12 hours after emergency department admission.[32] Furthermore, Ditillo et al. found that patient delays in presenting to the emergency department were more profoundly related to a worsening pathology than in-hospital delays.[33] Following the principle of performing prompt appendectomy, our patients all underwent appendectomy less than 24 hours after admission. This practice made in-hospital delay less significant as compared with the duration of the abdominal pain.

Combining the results of higher C reactive protein levels obtained in the emergency department and the patient delays at presentation are the predominant factors determining the incidence of complicated appendicitis, regardless of the in-hospital delay. This may explain why the perforation rate of acute appendicitis remained approximately 20%, even after the an intervention of negative appendectomy, produced by abdominal computed tomography, decreased.[34,35]

Conclusion

Operation for acute perforated appendicitis is associated with high morbidity. The increased risk of perforation appears to be related to delays in presentation and to CRP levels elevated > 30 mg/dl. Our findings should promote increased awareness in patients with clinically diagnosed acute appendicitis with abdominal pain > 3 days or CRP levels > 30 mg/dl, as they are likely to have an appendicular perforation.

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原　著

穿孔性急性闌尾炎的預測因子：一個單一機構的回顧性研究

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目的　因為急性闌尾炎的病程進展及後續術後併發症的風險，使得闌尾切除術一直是治療急性闌尾炎的標準。本研究的目的是找出複雜性急性闌尾炎的獨立預測因子。

方法　本研究回溯性蒐集在奇美醫學中心診斷為急性闌尾炎的病人資料。在 2010 年 1 月到 12 月間，480 名病人因急性闌尾炎接受闌尾切除手術。在兩組-非穿孔性案例 (n = 332) 和穿孔性案例 (n = 92)-進行分析，比較臨床特徵，住院時間和術後併發症。

結果　92 例穿孔性闌尾炎和 332 例單純性闌尾炎均經病理證實。整體闌尾炎穿孔率為 21.70% (92/424)，陰性闌尾切除率分別為 11.67% (56/480)。單變異和多變異回歸分析發現與穿孔性闌尾相關的兩個獨立因子；腹痛超過 3 天 (勝算比：3.03，95% 信賴區間 1.62-5.65，$p < 0.001$) 和 C-反應蛋白值超過 30 毫克/公升 (勝算比：5.38，95% 信賴區間：2.52-11.50，$p < 0.001$)。

結論　腹部電腦斷層掃描被證明可以非常準確的診斷闌尾炎，但對於穿孔性闌尾炎的特異性評估仍沒有結論。高 C-反應蛋白值及病人延遲就醫這兩項因素，是複雜闌尾炎的獨立預測因子。

關鍵詞　穿孔性急性闌尾炎、C-反應蛋白、腹部電腦斷層。