



C-reactive Protein as a Potential Effective Predictor of Perforated Appendicitis in Pediatric Patients

Chia-Wei Chang¹, Shyi-Jou Chen¹, Der-Shiun Wang¹, Chih-Hsiung Hsu², Wan-Fu Hsu¹

¹Department of Pediatrics, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan,

²School of Public Health, National Defense Medical Center, Taipei, Taiwan

Background: Surgical intervention is important for acute appendicitis. Perforated appendicitis leads to more complications and is more difficult to manage. Studies differentiating ruptured from nonruptured appendicitis are controversial. **Aim:** Early identification of perforated appendicitis is important for first-line medical practitioners. Our study aimed to provide more indicators to evaluate the risk of perforation before surgery. **Methods:** This retrospective study included 116 patients who underwent an appendectomy at the Tri-Service General Hospital between 2014 and 2018 with pathological diagnosis. Based on the surgical records, the patients were classified into two groups: simple (nonperforation) and complicated (perforation). **Results:** The patients (68 boys, 48 girls) were all under 18 years of age. Simple appendicitis was diagnosed in 87 patients and perforated appendicitis in 29 patients. Analysis revealed significant differences in blood C-reactive protein (CRP) levels between the two groups. The highest Youden's index was at a CRP level of 1.755 mg/dL. Positive findings were obtained for suppurative change as well as chylous ascites. **Conclusion:** Elevated CRP level was found to be a useful biomarker in predicting perforated appendicitis, excluding other general factors in pediatric patients. Suppurative change and chylous ascites could serve as indicators for the possibility of perforation during surgery.

Key words: Perforated appendicitis, pediatric, C-reactive protein, appendix

INTRODUCTION

Acute appendicitis is one of the most common acute abdominal diseases encountered in pediatric emergency departments. Without timely diagnosis and surgical intervention, severe complications such as peritonitis, bowel perforation, and bowel gangrene may develop, resulting in more severe therapeutic complications.¹ Therefore, to improve the diagnosis, several diagnostic strategies have been established to differentiate between acute appendicitis and other abdominal conditions.² The Alvarado score is one of the most commonly used scoring systems to diagnose acute appendicitis, which includes vital signs, clinical symptoms, and blood test reports. However, its accuracy is limited;³ therefore, other parameters are important to help first-line health care providers make a more appropriate identification.

Acute appendicitis is caused by a series of inflammatory processes, starting from obstruction. As time progresses, if the

cause of obstruction persists, the appendix becomes swollen, ischemic, and ruptures, which may induce intra-abdominal infection.^{4,5} The exact time of perforation is unclear but is generally regarded as a high-risk factor for peritonitis if not intervened on time. Therefore, the possibility of perforation is crucial for pediatric clinicians. In addition, perforation of the appendix may complicate management during and after surgery.⁶ Therefore, obtaining adequate information before surgery would help establish therapeutic plans.

In practice, besides history taking and physical examinations, we usually perform blood tests, sonography, computed tomography (CT), or magnetic resonance imaging (MRI) for suspected appendicitis cases. Although sonography and CT can provide fast and accurate information on perforation of the appendix, sonography is highly operator dependent, and CT is not recommended for pediatric patients for initial diagnosis

Received: November 27, 2021; Revised: March 10, 2022;

Accepted: March 14, 2022; Published: May 03, 2022

Corresponding Author: Dr. Wan-Fu Hsu, Department of Pediatrics, Tri-Service General Hospital, National Defense Medical Center, No. 325, Sec. 2, Chenggong Rd., Neihsu Dist., Taipei 11490, Taiwan. Tel: +886-2-8792-3311; Fax: 0422-2594400. E-mail: jowfhsu@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Chang CW, Chen SJ, Wang DS, Hsu CH, Hsu WF. C-reactive protein as a potential effective predictor of perforated appendicitis in pediatric patients. J Med Sci 2023;43:51-5.

Perforated appendicitis predictor in children

because of the high dosage of radiation.⁷ On the other hand, MRI is recommended in pediatric groups but requires a longer time, possible need of sedative agents, and is not readily available considering the current medical resources.⁸ There are further limitations to applying these diagnostic tools to pediatric patients, including patient cooperation. Therefore, we prefer blood test results as the first objective measure, apart from physical examinations and history taking, to assess the need for additional imaging studies.

C-reactive protein (CRP) is an acute inflammatory protein that promotes leukocyte, complement, and cytokine migration to regions of inflammation and infection.⁹ However, evidence proving the association between blood test results and the perforation of appendices remains controversial.^{10,11} Therefore, we conducted a retrospective study to evaluate whether CRP level could be a useful inflammatory marker to predict perforation of the appendicitis.

MATERIALS AND METHODS

Between 2014 and 2018, medical records of all patients under 18 years of age who were diagnosed with acute appendicitis and underwent surgery at the Tri-Service General Hospital were retrieved for further evaluation. We retrospectively collected information such as age, sex, white blood cell (WBC) count, neutrophil count, and CRP level of patients who underwent appendectomy after surgical and pathological diagnosis of acute appendicitis. In addition, data of symptoms and signs such as fever peak, abdominal pain, nausea, vomiting, and diarrhea were collected.

When acute appendicitis was suspected clinically, the patients received surgical intervention within 24 h after the last blood sample collection. Enrolled patients were categorized into two groups based on their surgical records: simple (nonperforation) and complicated (perforation). Surgical records of all patients enrolled were collected and analyzed.

The Mann–Whitney *U* test or Student's *t*-test was performed for continuous variables such as age, leukocyte count, neutrophil count, and CRP level between the two groups. The Chi-square test was performed for categorical variables. To estimate the predictive value of CRP, receiver operating characteristic (ROC) curves were constructed, and the areas under the ROC curves were assessed. A two-tailed $P < 0.05$ was considered statistically significant. Statistical analyses for this study were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA).

IRB approval information

The study was approved by the Institutional Ethics Review Board of Tri-Service General Hospital (C202005186), and

the requirement for informed consent was waived due to the retrospective design of the study.

RESULTS

A total of 137 patients were enrolled in our study. Of these, 8 were excluded due to incomplete records, and 13 were excluded as a result of a negative pathological diagnosis of appendicitis. Finally, 87 patients in the simple group and 29 patients in the complicated group were included for the analysis [Figure 1].

Age and sex distributions were analyzed, and no difference was found between the two groups [Table 1]. In blood tests, the CRP level showed significant differences between the simple and complicated groups ($P < 0.05$) [Table 2]. The highest Youden index was at a CRP level of 1.755 mg/dL, with a sensitivity of 0.828 and specificity of 0.575 [Figure 2]. The leukocyte and neutrophil percentages did not differ significantly between the two groups [Table 2]. There were no differences in any symptoms or signs between the two groups [Table 1]. Regarding surgical findings, both suppurative change and chylous ascites in the appendix showed analytical significance ($P < 0.05$ for both) [Table 2].

Table 1: Patient characteristics, symptoms, and signs of each group

	Simple Group (n=87), n (%)	Complicated Group (n=29), n (%)	<i>P</i>
Gender (male)	51 (58.6)	17 (58.6)	1.00
Age (years)	12.9 (±3.48)	13.2 (±3.45)	0.75
Fever (>38°C)	25 (28.7)	10 (34.5)	0.17
Fever (>39°C)	8 (9.2)	2 (6.9)	0.21
RLQ abdomen pain	86 (98.9)	29 (100)	1.00
Nausea	64 (73.6)	21 (72.4)	1.00
Vomiting	47 (54)	15 (51.7)	0.83
Diarrhea	15 (17.2)	8 (27.6)	0.28

Data are shown as n (%) or mean (±SD). RLQ=Right lower quadrant, SD=Standard deviation

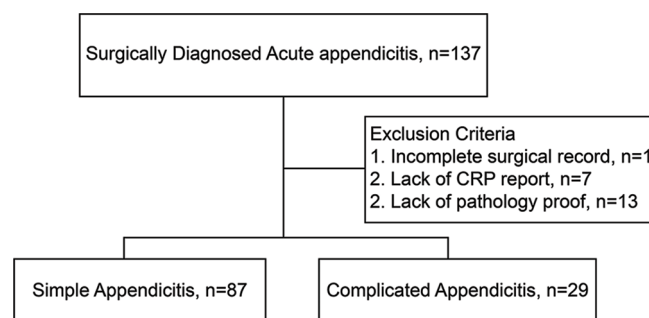


Figure 1: Flow chart shows selection of patients for analysis

Table 2: Blood test and surgical findings of each group

	Simple Group (n=87)	Complicated Group (n=29)	P
Blood tests			
WBC (/mm ³)	15929.0 (±4414.5)	15735.3 (±5523.7)	0.85
Neutrophil (%)	82.69 (±9.01)	80.98 (±12)	0.56
CRP (mg/dL)	3.93 (±7.29)	7.41 (±6.5)	0.02
Surgical findings, n (%)			
Suppurative change	54 (62.1)	24 (82.8)	0.04
Chylous fluid	25 (28.7)	21 (72.4)	<0.01

Data are shown as n (%) or mean (±SD). WBC=White blood cell, CRP=C-reactive protein, SD=Standard deviation

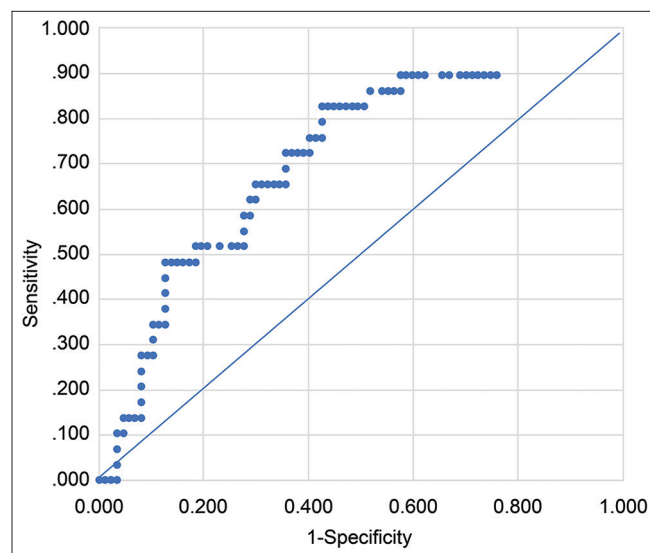


Figure 2: The chart shows that the receiver operating characteristic curve and area under the curve area was 0.75 with a standard deviation of 0.053. The highest Youden index was 1.402 at C-reactive protein level 1.755 mg/dl, sensitivity 0.828, and specificity 0.575

DISCUSSION

Laboratory data collected from pediatric patients diagnosed with acute appendicitis through pathological confirmation at the time of arrival at the emergency department were analyzed. The data revealed significant differences in CRP levels between patients with ruptured and nonruptured acute appendicitis. This finding implies that among patients with highly suspected acute appendicitis, the risk of the perforated appendix is related to the CRP level, irrespective of sex, age, onset time, fever, or other gastrointestinal symptoms. In clinical practice, this finding may help physicians who initially encounter patients with highly suspected acute appendicitis in clinically differentiating ruptured appendix by evaluating CRP level.

Previous studies have shown that among inflammatory markers, WBC count, procalcitonin level, and CRP level

could play different roles in predicting the overall diagnosis of appendicitis among pediatric patients,^{11,12} with CRP being a more sensitive marker.¹² In contrast, leukocyte count, neutrophil count, procalcitonin level, and CRP level can also help differentiate patients with complicated appendicitis from those with simple appendicitis. Among the markers, procalcitonin level was found to be more specific than leukocyte count and CRP level in diagnosing ruptured appendicitis; however, its sensitivity is the opposite.¹¹⁻¹³ Meanwhile, another study showed that CRP plays no role in diagnosing acute appendicitis.¹⁰ Regarding this controversial issue, CRP levels in the simple and complicated groups reached statistical significance in our study, implying that we could predict the risk of ruptured acute appendicitis based on elevated CRP levels. These results may provide surgeons with more information before surgery and allow for better preparation, hopefully offering a useful indication to pediatric health-care providers.

In our analysis, we attempted to determine the most sensitive cut-off point of CRP level for differentiating ruptured appendicitis. Based on the ROC curve and calculation of the Youden index, we obtained a value of 1.755 mg/dl [Figure 2]. A comparison between the simple and complicated groups revealed that the cut-off value was lower than the mean CRP level in both groups. The most likely cause of this result may be the small sample size; a larger database might provide stronger evidence for better suggestions on clinical application. Despite these results, we can still conclude that the possibility of a ruptured appendix in patients with suspected appendicitis with elevated CRP levels is higher than that in patients with normal CRP levels.

Several studies have analyzed the time factor for distinguishing ruptured acute appendicitis. One study showed that the time 48 h after the onset of initial symptoms such as abdominal pain, fever, and gastrointestinal discomfort was positively related to ruptured appendicitis.⁴ Another study revealed that different CRP levels could indicate perforated appendicitis on different days after the onset of initial signs of discomfort, with statistical significance.¹⁴ Although evidence supports that CRP levels are positively correlated with onset time in predicting perforated appendix, it is sometimes challenging to determine the definite onset time of symptoms and signs in pediatric patients. Another study analyzed CRP levels 6 h before and after surgery to distinguish acute appendicitis from perforated appendicitis based on elevated CRP levels in pediatric patients.¹⁵ Even though the findings were significant, repeated blood sampling in a short period is not feasible in pediatric patients because the procedure would cause significant stress to the patients. In our study, we collected the data without considering the time factor, which

Perforated appendicitis predictor in children

provides a simpler CRP level to differentiate patients who were highly suspected of having acute appendicitis with or without perforation before surgery. Blood tests were performed regardless of the onset time of symptoms and signs, which is more general and easier for clinicians to apply to patients.

In the analysis of WBC count, we found no evidence of perforated appendicitis from leukocytosis. Previous studies have revealed that WBC count is positively related to appendicitis.^{11,14} However, regarding the diagnosis of ruptured appendicitis, the previous findings remain controversial. Most studies concluded that the combination of leukocytosis and elevated CRP levels could help differentiate complicated appendicitis from simple appendicitis more accurately.⁶ Another study reported that elevated CRP levels were more sensitive than leukocytosis in perforated appendicitis. In predicting complicated appendicitis, more evidence is needed to confirm the role of WBC counts. We expect that our ongoing study design will provide stronger evidence.

Abdominal tenderness occurred in almost all patients with acute appendicitis. In contrast, past reviews showed that abdominal tenderness was not helpful in differentiating the diagnosis in children at the acute stage, which may be related to poor specificity of physical examination in the pediatric group.¹¹

Signs and symptoms of complicated appendicitis are nonspecific and difficult to distinguish.⁶ Among the history and physical examination findings mentioned in past studies, peritoneal signs are most correlated with ruptured appendicitis.^{4,6} Similar to other symptoms and signs, fever, nausea, vomiting, and diarrhea could not provide solid information on ruptured appendicitis in our analysis and other studies.^{6,11}

Another point of view is that complicated appendicitis has a stronger relationship with intra-abdominal abscess, wound infection, and postoperative ileus than simple appendicitis.⁶ We found that the appearance of the appendix with both suppurative change and chylous ascites were significantly different between the two groups. The complications mentioned above were also closely related to the perforated appendix; thus, we could be aware of the severe condition based on the preoperative high CRP level.

The limitations of our research include the fact that the study population was small; the inclusion of more cases might help reach higher statistical efficacy. Second, our retrospective study did not include other inflammatory markers, such as procalcitonin. In addition, patients who did not undergo surgery were not enrolled in our study, considering the lack of pathologic proof of definite appendicitis. Despite few pediatric patients not undergoing surgery in our hospital due to strong suspicion of acute appendicitis, there is a study showing that

nonoperative treatment is also a choice in uncomplicated appendicitis patients,^{16,17} which may have led to selection bias in our study. Finally, because of the high availability of medical resources in our country, the patients may have received medical interventions before our examinations, which was unclear. Although the previous interventions may have had different effects on our study, we analyzed the data without considering this possibility, and the results still reached statistical significance. Currently, we are conducting research with a new study design, attempting to prospectively analyze larger groups with more detailed information to obtain stronger evidence with higher sensitivity and specificity.

In this retrospective study, elevated CRP levels were found to be a useful biomarker for predicting perforated acute appendicitis in highly suspected pediatric groups based on the clinical manifestations in general, regardless of the onset time, duration, and other gastroenteric symptoms. In contrast, suppurative change and chylous ascites could also indicate ruptured appendicitis, providing more indications to pediatric surgeons before completing the surgery.

CONCLUSION

Elevated CRP level was found to be a useful biomarker in predicting perforated appendicitis, excluding other general factors in pediatric patients. Suppurative change and chylous ascites could serve as indications for the possibility of perforation during surgery.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Howell EC, Dubina ED, Lee SL. Perforation risk in pediatric appendicitis: Assessment and management. *Pediatric Health Med Ther* 2018;9:135-45.
2. van Amstel P, Gorter RR, van der Lee JH, Cense HA, Bakx R, Heij HA. Ruling out appendicitis in children: Can we use clinical prediction rules? *J Gastrointest Surg* 2019;23:2027-48.
3. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, *et al.* Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World J Emerg Surg* 2020;15:27.
4. Gosain A, Williams RF, Blakely ML. Distinguishing acute from ruptured appendicitis preoperatively in the pediatric patient. *Adv Surg* 2010;44:73-85.

5. Schülin S, Schlichting N, Blod C, Opitz S, Suttkus A, Stingu CS, *et al.* The intra- and extraluminal appendiceal microbiome in pediatric patients: A comparative study. *Medicine (Baltimore)* 2017;96:e9518.
6. Almaramhy HH. Acute appendicitis in young children less than 5 years: Review article. *Ital J Pediatr* 2017;43:15.
7. Debnath J, George RA, Ravikumar R. Imaging in acute appendicitis: What, when, and why? *Med J Armed Forces India* 2017;73:74-9.
8. Imler D, Keller C, Sivasankar S, Wang NE, Vasanawala S, Bruzoni M, *et al.* Magnetic resonance imaging versus ultrasound as the initial imaging modality for pediatric and young adult patients with suspected appendicitis. *Acad Emerg Med* 2017;24:569-77.
9. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Front Immunol* 2018;9:754.
10. Kim E, Subhas G, Mittal VK, Golladay ES. C-reactive protein estimation does not improve accuracy in the diagnosis of acute appendicitis in pediatric patients. *Int J Surg* 2009;7:74-7.
11. Kwan KY, Nager AL. Diagnosing pediatric appendicitis: Usefulness of laboratory markers. *Am J Emerg Med* 2010;28:1009-15.
12. Yu CW, Juan LI, Wu MH, Shen CJ, Wu JY, Lee CC. Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis. *Br J Surg* 2013;100:322-9.
13. Cui W, Liu H, Ni H, Qin X, Zhu L. Diagnostic accuracy of procalcitonin for overall and complicated acute appendicitis in children: A meta-analysis. *Ital J Pediatr* 2019;45:78.
14. Wu HP, Chen CY, Kuo IT, Wu YK, Fu YC. Diagnostic values of a single serum biomarker at different time points compared with Alvarado score and imaging examinations in pediatric appendicitis. *J Surg Res* 2012;174:272-7.
15. Wu HP, Fu YC. Application with repeated serum biomarkers in pediatric appendicitis in clinical surgery. *Pediatr Surg Int* 2010;26:161-6.
16. Minneci PC, Hade EM, Lawrence AE, Sebastião YV, Saito JM, Mak GZ, *et al.* Association of nonoperative management using antibiotic therapy vs. laparoscopic appendectomy with treatment success and disability days in children with uncomplicated appendicitis. *JAMA* 2020;324:581-93.
17. Mosuka EM, Thilakarathne KN, Mansuri NM, Mann NK, Rizwan S, Mohamed AE, *et al.* A systematic review comparing nonoperative management to appendectomy for uncomplicated appendicitis in children. *Cureus* 2021;13:e18901.