Observational Study

Medicine®

OPEN

Preoperative assessment of complicated appendicitis through stress reaction and clinical manifestations

Chun-Bo Kang[a], Wen-Qiang Li[a], Jian-Wei Zheng[a], Xiao-Wei Li[a], Da-Peng Lin[a], Xiu-Feng Chen[a], De-Zhong Wang[a], Nan Yao[a], Xue-Kai Liu[b], Jun Qu[a,*]

Abstract

This study assessed the severity of the disease through the preoperative clinical manifestations and inflammatory reaction indicators of acute appendicitis, and established a score table to predict complicated appendicitis (CA).

The clinical data of 238 patients with acute appendicitis in our hospital were retrospectively analyzed, which included 18 patients with acute simple appendicitis (7.6%), 170 patients with acute purulent appendicitis (72.0%), and 48 patients with acute gangrene and perforation (20.3%). The clinical manifestations and inflammatory reaction indicators were analyzed by univariate logistic regression. Multivariate logistic regression analysis was performed to screen out the independent risk factors of CA. The β coefficients of independent risk factors entering the multivariate model were assigned by rounding, and the total score was the sum of values of all factors. Finally, verification and analysis were performed for the predictive model, and the operating characteristic curve (ROC) curve was drawn. Then, the area under the curve (AUC) was compared with the THRIVE scale, and the Hosmer–Lemeshow method was used to evaluate whether the model fitted well.

The multivariate logistic regression analysis of independent risk factors was performed, and the values were rounded to the variable assignment based on the β coefficient values. The plotted ROC and AUC was calculated as 0.857 ($P < .001$). Using the Hosmer–Lemeshow method, the X^2-value was 12.430, suggesting that the prediction model fitted well.

The scoring system can quickly determine whether this is a CA, allowing for an earlier and correct diagnosis and treatment. Furthermore, the scoring system was convenient, economical, and affordable. Moreover, it is easy to popularized and promote.

Abbreviations: AUC = area under the curve, CA = complicated appendicitis, NLR = neutrophil-to-lymphocyte ratio, ROC = operating characteristic curve, PCT = procalcitonin, UA = uncomplicated appendicitis, WBC = white blood cell.

Keywords: clinical manifestations, complicated appendicitis, predictive assessment, stress reaction

1. Introduction

Acute appendicitis is the most common surgical acute abdominal disease, and its lifetime incidence is approximately 7% to 9%.[1] According to clinical features and pathological anatomy changes, it is divided into acute simple appendicitis, acute purulent appendicitis, acute gangrenous or perforated appendicitis, and periappendiceal abscess. In present literatures, the first 2 types of pathology have often been called uncomplicated appendicitis (UA), and the latter two have been called complicated appendicitis (CA) or progressive appendicitis. CA accounts for 20% to 30% of acute appendicitis cases,[2,3] while UA accounts for 68% to 90% of cases in children.[1,4] CA is defined as irreversible appendicitis in some articles, because CA (acute gangrenous or perforated appendicitis) is difficult to cure by conservative treatment.[5] According epidemiology, immunology, and pathology data, some scholars have consider that appendicitis is not necessarily a progressive disease, and they considered that CA and UA are different diseases developed by different causes.[6–8] The results of the bacterial culture of ascites and fluid in the appendiceal cavity of these 2 types of appendicitis patients were significantly different. Furthermore, there was a higher positive rate of culture in CA.[9] Particularly for gram positive cocci and anaerobic bacteria, the positive rates for CA were 51.6% and 67.7%, respectively, while the positive rates for UA were 23.1% and 42.3%, respectively.[10] This was because the periappendiceal abscess often needs to be conservatively treated, such as the introduction of antibiotics or catheter drainage,[11] which is different from the treatment for acute gangrenous or perforated appendicitis.[12] In the present study, patients with periappendiceal abscess were excluded and not discussed for CA. This was because the CA in the present study refers to acute gangrenous appendicitis or perforated appendicitis. Hence, emergency surgery should be performed to avoid

Editor: Goran Augustin.

This study was supported by College Research Project of Aerospace Center Hospital (No.YN201429).

All authors have contributed significantly to the manuscript and declare that the work is original and has not been submitted or published elsewhere. None of the authors have any financial disclosure or conflict of interest.

[a] Department of General Surgery, [b] Department of Laboratory, Aerospace Center Hospital, Beijing, China.

[*] Correspondence: Jun Qu, Department of General Surgery, Aerospace Center Hospital, No.15 of Yuquan Road, Haidian District, Beijing 100049, China (e-mail: qujun1821@163.com).

Medicine (2019) 98:23(e15768)

Received: 13 December 2018 / Received in final form: 20 February 2019 / Accepted: 30 April 2019

http://dx.doi.org/10.1097/MD.0000000000015768

sepsis and septic shock, and increased mortality.[13] In choosing the optimal treatment, it is particularly important to determine whether it is a CA as soon as possible, especially when choosing a conservative treatment. The present study mainly focused on patients diagnosed with acute appendicitis, and established a preoperative prediction score through clinical manifestations and stress response indicators, in order to determine whether these patients have CA (acute gangrenous or perforated appendicitis) or UA, timely providing optimal treatment according to the condition. In this way, it would benefit the performance of prognosis risk assessments for CA patients, thereby reducing the risk of adverse prognosis. The report is presented, as follows.

2. Material and methods

2.1. Study setting and study population

During the period of June 2015 to November 2017, the Department of General Surgery of our hospital admitted 339 patients with acute appendicitis. Among them, 101 patients who did not meet the inclusion criteria or did not sign the experimental informed consent were excluded. Therefore, the present clinical study included a total of 238 eligible patients who provided a signed informed consent. Based on the clinical symptoms and signs before surgery, and combined with the raja isteri pengiran anak saleha appendicitis scoring system,[14] all patients received an appendectomy surgery after clear diagnosis. Among these patients, 2 patients were diagnosed with mucinous adenocarcinoma of the appendix after surgery, and were operated again and excluded from the group. Among the 236 patients enrolled in the present study, 133 (56.4%) patients were men and 103 (43.6%) were women, and their age ranged within 18 to 79 years old. Furthermore, among these 236 patients, 180 (76.3%) patients had migratory pain to the right lower quadrant on admission, 51 (21.6%) patients had right lower quadrant or lower abdominal pain, and 5 (2.1%) patients had upper abdominal pain. The mean duration of abdominal pain on admission was 26 ± 7 hours, in which nausea occurred in 87 (36.9%) patients, vomiting occurred in 39 (16.5%) patients, and fever occurred in 114 (48.3%) patients. Preoperative physical examination revealed that 90 (38.1%) patients had localized peritonitis and 146 (61.9%) patients had diffuse peritonitis. Postoperative pathological findings revealed that 18 (7.6%) patients had acute appendicitis, 170 (72.0%) patients had acute purulent appendicitis, and 48 (20.3%) patients had acute gangrenous appendicitis. Furthermore, 88 (37.3%) patients had appendix feces, while 148 (62.7%) patients had non-appendix fecal stones.

2.2. Methods

Routine examinations conducted for all patients before surgery: blood routine, urine routine, 4 blood coagulation, blood biochemistry, high-sensitivity C-reactive protein (hsCRP), procalcitonin (PCT), serum combination 1, the determination of lymphocyte subsets, x-ray, electrocardiogram, and abdominal ultrasonography. The neutrophil-to-lymphocyte ratio (NLR) was calculated based on the number of neutrophils (N) and lymphocytes (L) in blood. The study was approved by the Ethics Committee of the Aerospace Center Hospital. The written informed consent was obtained from all participants. If there were no surgical contraindications, laparoscopic appendectomy (204 patients, 86.4%), or open appendectomy (32 patients) were operated using a Storz laparoscopic camera system and a 5.0 mm 30° lens under endotracheal intubation combined anesthesia. Preliminary exploration was performed after entering the abdomen, and routine appendectomy was performed after a clear diagnosis. According to the intraoperative abdominal infection, it was determine whether the abdominal drainage tube would be placed, and the resected specimen was routinely sent for pathological examination. At 6 hours after anesthesia, drinking was immediately allowed and solid food can be given when the patient could drink with no signs of postoperative ileus. The patients were also treated with semi-recumbent, anti-infective, and symptomatic support.

2.3. Inclusion criteria

Based on the following criteria:

(1) The preoperative diagnosis was clearly acute appendicitis (according to preoperative clinical manifestations, laboratory tests, and imaging examinations);
(2) The patients and their families agreed and provided a signed informed consent;
(3) The preoperative examination revealed no significant organ dysfunction or other surgical contraindications;
(4) The age range was 18 to 80 years old.

2.3.1. Exclusion criteria.

(1) Patients with a diagnosis that did not meet the inclusion criteria;
(2) Patients who were >80 years old or <18 years old;
(3) Patients who have an important organ dysfunction, making the patient not suitable for general anesthesia appendectomy.
(4) Pregnant or lactating women;
(5) Patients with mental illness.

2.4. Evaluation index

Operation time, blood loss during the operation, fasting time out of the operation, bed rest time, hospital stay, mortality, incision infection rate, and the situation of using analgesics after the operation were observed. Incision infection was determined when the incision had purulent secretions or the incision secretion bacterial culture was positive.

2.5. Statistical methods

Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL). The measurement data were expressed as mean ± standard deviation ($\overline{X} \pm SD$) and (M, Q1–Q3) using independent samples t test. The cut-off value was calculated using Medcalc. Count data were expressed in percentage, and analyzed by X^2- test. If necessary, Yates continuity correction or Fisher exact test was performed. The primary study endpoint was acute gangrenous appendicitis confirmed after the operation or perforation appendicitis identified during the surgery. The logistic regression model was subsequently used for single factor and multivariate regression analysis, and in screening for independent risk factors. The area under the operating characteristic curve (ROC) was calculated using Medcalc software (Mariakerke, Belguim). The area under the ROC curve when it was >0.5 was the prognostic value. The closer it was to 1, the better the effect. The fitness of each model was evaluated

Table 1

Each numerical variable cut-off value of patients with acute appendicitis.

	Cut-off value	Sensitivity	Specificity	Youden Index	LR+	LR–
Abdominal pain score	7	41.67	74.47	16.13	1.63	0.78
Abdominal pain time, h	32	54.17	81.91	36.08	3.00	0.56
The highest temperature, °C	37.9	58.33	80.85	39.18	3.05	0.52
WBC ($\times 10^9$)	13.66	66.67	51.06	17.73	1.36	0.65
NE (%)	85.2	70.83	45.74	16.58	1.31	0.64
NLR	10.9	62.50	57.45	19.95	1.47	0.65
CRP, mg/L	66.1	83.33	72.34	55.67	3.01	0.23
PCT, ng/mL	0.48	54.17	75.53	29.70	2.21	0.61

LR+ = positive likelihood ratio, LR– = negative likelihood ratio, NE = neutrophil, NLR = neutrophil-to-lymphocyte ratio, PCT = procalcitonin, WBC = white blood cell.

using the Hosmer–Lemeshow goodness-fit test. The 2-sided test for significance level was set as $\alpha = 0.05$, and a P-value $<.05$ was considered statistically significant.

3. Results

Medcalc 15.8 was used to calculate the cut-off value, sensitivity, specificity, Youden index, and positive and negative likelihood ratio, and obtain the numerical variable node related to factors that are possibly associated with the severity of acute appendicitis patients. The obtained values are presented in Table 1. The cut-off value of the abdominal pain score was 7 while the abdominal pain duration was 32 hours. And the cut-off value of the highest body temperature, the peripheral white blood cell (WBC) count, neutrophil (NE%), NLR, CRP, and PCT were 37.9 °C, 13.66×10^9/L, 85.2%, 10.9, 66.1 mg/L, and 0.48 ng/mL, respectively.

3.1. Single factor regression analysis

Factors that may be associated with the severity of acute appendicitis patients,[15] such as abdominal pain score, duration of abdominal pain, maximum body temperature, tenderness range (divided into 3 sections: <3, 4–6, and >7), the highest WBC count, NE (%), NLR, CRP, and PCT, were analyzed using the single-factor regression method. $P<.05$ means that the difference was statistically significant. The values are presented in Table 2.

3.2. Establishment of the multi-factor regression analysis and prediction model

For independent risk factors with statistical significance, a multivariate regression analysis was further performed using the method of Forward Wald, and $P<.05$ means that the difference was statistically significant. This was rounded to the variable assignment based on the β coefficient values. Hence, 1 point was given when the highest body temperature was >37.9 °C, the tenderness range was >3, peripheral blood WBC was $>13.66 \times 10^9$/L, and NLR was >10.9, while 3 points were given when CRP was >66.1 mg/L, and the total score was 7. Then, a prediction model was developed, as shown in Table 3.

3.3. Comparison of the validity and accuracy of the new prediction model

The patient ROC was drawn, and the area under the curve (AUC) was calculated. For the AUC, a value >0.5 was considered to have prognostic value, and the closer the value was to 1, the higher the accuracy. The AUC was compared with the sample Z-test. The AUC for this prediction model was 0.857 (95% CI: 0.806–0.908; $P<.001$), as shown in Fig. 1. When the Hosmer–Lemeshow method was used ($P>.05$), the value of X^2 was 12.430, suggesting that the prediction model fitted well.

Table 2

Single factor analysis of the related factors of complicated appendicitis.

						Exp (B) 95.0% CI	
	β	SE	Wald	Sig.	Exp (B)	Lower limit	Higher limit
Abdominal pain score	0.734	0.337	4.738	0.029	2.083	1.076	4.034
Abdominal pain time	1.678	0.346	23.489	0.000	5.353	2.716	10.550
The highest temperature	1.777	0.347	26.294	0.000	5.911	2.997	11.658
Tenderness range							
≤3			15.096	0.001			
4–6	1.268	0.558	5.160	0.023	3.554	1.190	10.614
≥7	1.373	0.386	12.649	0.000	3.949	1.852	8.417
Highest WBC	0.736	0.339	4.705	0.030	2.087	1.074	4.057
NE (%)	0.717	0.350	4.201	0.040	2.048	1.032	4.063
NLR	0.811	0.333	5.943	0.015	2.250	1.172	4.318
CRP	2.571	0.420	37.429	0.000	13.077	5.739	29.799
PCT	1.294	0.336	14.863	0.000	3.648	1.889	7.044

When P is <.05, it means difference has statistically significance.

NE = neutrophil, NLR = neutrophil-to-lymphocyte ratio, PCT = procalcitonin, SE = standard error, WBC = white blood cell.

Table 3

Establishment of multifactorial regression analysis and prediction model of risk factors for complicated appendicitis.

	Assignment	β	SE	Wald	Sig.	Exp (B)	Exp (B) 95.0% CI	
							Lower limit	Higher limit
The highest temperature	1	1.476	0.437	11.401	0.001	4.374	1.857	10.302
Tenderness range								
≤3	0			8.599	0.014			
4–6	1	1.426	0.673	4.491	0.034	4.164	1.113	15.574
≥7	1	1.232	0.517	5.671	0.017	3.427	1.244	9.445
Highest WBC	1	0.901	0.454	3.942	0.047	2.462	1.012	5.991
NLR	1	0.949	0.433	4.813	0.028	2.584	1.107	6.033
CRP	3	2.776	0.498	31.050	0.000	16.059	6.048	42.640

Total score is 7 points. $P < .05$ means difference has statistically significance.

CI = confidence interval, NLR = neutrophil-to-lymphocyte ratio, SE = standard error, WBC = white blood cell.

4. Discussion

Acute appendicitis is a common surgical acute abdominal condition. Appendectomy has long been considered as the optimal treatment for patients with acute appendicitis. However, in recent years, more and more attention has been given to conservative treatment. Furthermore, some literatures have suggested that UA can be treated safely and effectively through conservative treatment.[16–19] By comparing the observations and follow-ups, it was found that for UA, the complication of conservative treatment was significantly lower than that in the surgical treatment group.[20–22] However, in my opinion, appendectomy is still the preferred treatment for UA. Only when the patient is reluctant to undergo surgery or the patient's general condition is poor, combined with multiple organ failure and other surgical contraindications can we consider conservative treatment. CA can result in a variety of potentially serious complications, such as peritonitis, abdominal abscess, and paralytic intestinal obstruction,[23] and its surgical treatment should be performed as early as possible and adequately prepared before the operation, in order to reduce intraoperative and postoperative complications, and reduce mortality.[13,24] Particularly for elderly patients, they have less physiologic reserves and poorer nutritional status, as well as more postoperative complications and mortality, when compared with younger patients.[23] These fully illustrate the importance of immediately determining whether the patient has CA before the operation, in order to prevent the delayed timing of surgery due to complicated preoperative preparation or any affect on the prognosis of patients due to the choice non-surgical treatment. The study aims to identify whether it is CA as soon as possible after admission, so as to select the optimal treatment promptly, decrease unnecessary examinations and treatment, and reduce related complications.

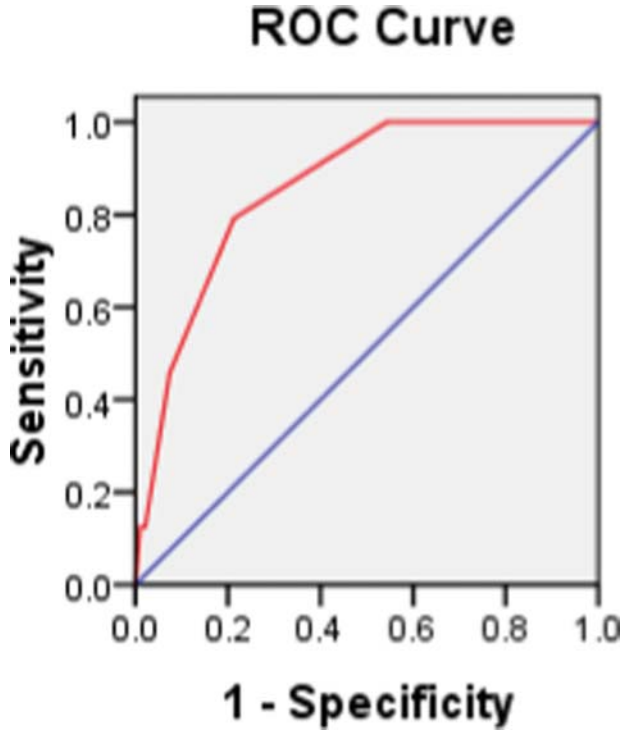

Figure 1. Validity and accuracy comparison of new prediction model. The AUC value is 0.857 (95% CI: 0.806–0.908), $P < .001$. AUC = area under the curve, CI = confidence interval.

There are some differences between UA and CA in clinical manifestations, laboratory tests, and imaging examinations. However, in order to avoid artificial subjective factors, the scoring system should be applied to objectively distinguish between UA and CA. At present, the scoring system for CA in literature is basically confined to the combination of clinical manifestations and imaging.[3,25] The following features were observed on abdominal ultrasound or CT: external gas of the appendiceal cavity, appendiceal fecalith, appendiceal wall strengthening defects, fluid around the appendix, intestinal obstruction, and so on. These features have high specificity, but express lower sensitivity and excessive variation, reducing the reliability of the score. It has been reported that ≥18% of CA may not exhibit the above typical imaging findings.[15,26] Therefore, in the choice of treatment options, these CA are easily mistaken for UA and conservative treatment would be chosen.[27] If this segment of patients chooses conservative treatment, there will be a higher failure rate or recurrence rate, or cause severe complications.[17,28] On the other hand, fluid around the appendix and appendiceal fecalith will both appear in UA. Increasing the diagnostic sensitivity of CA will be at the expense of reduced specificity.[3] At the same time, this will increase the false-positive diagnostic rate of CA, and lead this segment of UA patients to undergo appendectomy, which would add to their relevant expenses. Indeed, this has been traditionally considered as a safe and effective method of treating UA.[3] Although the proportion of conservative treatment based on diagnosis recommendations is not very high, and considering the high incidence of acute appendicitis, a considerable number of UA

patients may avoid surgery. These patients, when successful treated, will be exempt from appendectomy. This would reduce their cost of treatment, improve their quality of life, and prevent complications associated with appendectomy.[22] It has been reported in literature that there is still a 0.2% incidence of appendix carcinoid pathology after appendectomy.[29] In the present study, 2 patients (0.84%) were diagnosed with appendix mucinous adenocarcinoma after surgery. Therefore, for acute appendicitis, non-surgical options should still be carefully considered.

At present, the preoperative assessment of using stress response indicators for CA were more confined to children with acute appendicitis,[12,30] but has been less reported in adults. The subject regards postoperative pathology as the standard. Adult patients were divided into 2 groups: UA, including acute simple appendicitis and acute purulent appendicitis; CA, including acute gangrenous and acute perforated appendicitis. The cut-off values related to the factors of CA were calculated by using Medcalc 15.8. This included the abdominal pain score, the duration of abdominal pain, the maximum body temperature, and the range of tenderness (3 segments: $\leq$3, 4–6, and $\geq$7), WBC count, NE (%), NLR, CRP, and PCT. All the above indicators were entered into the single-factor regression analysis, and it was found that there was a statistical significance in the results ($P < .05$). This prediction model is a scoring system derived from the coefficients of the predictors, allowing the maximum possible score to be 7 points, and higher scores were more likely associated with CA. Then, in the multivariate regression analysis, the differences in all the above indexes were statistically significant ($P < .05$), and the values were rounded to the meaningful indexes assignment, based on the β coefficient values. That is, 1 point was given when the highest body temperature was >37.9 °C, the tenderness range was >3, peripheral blood WBC was $>13.66 \times 10^9$/L and NLR was >10.9, while 3 points were given when CRP was >66.1 mg/L, and the total score was 7. The prediction model (ROC) was developed, and the AUC was calculated as 0.857. This suggests that the prediction model has good discriminating ability. This prediction model is a scoring system derived from the coefficients of the predictors. Hence, the maximum possible score is 7 points. Furthermore, higher scores were more likely to be associated with CA. In the present study, the CRP value was measured by hypersensitivity, and the sensitivity of CA was 83.33% and 72.34%, respectively, which was higher than that reported in a literature.[2] Therefore, hsCRP had the highest score of 3 in this prediction model, while the other indexes all had 1 point. Other stress indicators in a relevant literature presented with different types of reports.[2] For example, a WBC count of $>13.66 \times 10^9$/L in the present study was used as the meaningful index to distinguish complicated and UA. Its sensitivity and specificity were similar to those reported in literature (66.67% and 51.06%, respectively). In some studies,[30,31] the association of WBC counts with CRP alone did not improve diagnostic accuracy (AUC = 0.715). However, in the present study, the above indexes were combined with some clinical manifestations of patients, and the diagnosis of CA was significantly improved. The ACU value was 0.857, suggesting that this model has better discriminating ability.

The scoring system had 5 indicators based on the clinical manifestations and stress indicators in the present study, in which the included clinical data was easy to collect, such as the highest body temperature and abdominal tenderness range, in which both were obtained by general admission examinations. The experimental data contained in the prediction model was easy to collect without drawing additional blood, or the need for special equipment and reagents. This allows for the rapid collection of relevant results, such as peripheral blood WBC, NLR, and CRP. This prediction model does not include an imaging examination. Hence, there is no need to increase patient examination costs and the pain of moving patients. It is very convenient and practical.

The scoring system is limited to the preoperative diagnosis of acute appendicitis. To a certain extent, it is able to quickly and accurately distinguish between CA and UA. The scoring system was evaluated in the present study. However, multicenter clinical data were also needed to verify and confirm the universal applicability of the scoring system. The scoring system established in the present study, which was entirely based on clinical manifestations and stress factors, was a complementary approach to imaging studies. The scoring method in the present study can prevent the shortcomings of imaging, such as the radiation of CT examinations, the subjectivity of readers, the increase in medical expenses, and the extension of diagnosis time. In particular, it can avoid the multiple moving and checking of patients with acute abdominal conditions, and reduce the patient's pain and danger.

5. Conclusion

In summary, the scoring system is convenient, economical, affordable, and easy to be popularized and promoted. In the present retrospective clinical study, the clinical data were still limited. Hence, there is a need to collect more clinical data and conduct further studies in experimental centers for further research and improvement.

Author contributions

Conceptualization: Wen-Qiang Li, Jian-Wei Zheng, Xiao-Wei Li, Da-Peng Lin.
Data curation: Wen-Qiang Li, Jian-Wei Zheng, Xiao-Wei Li, Da-Peng Lin.
Investigation: Wen-Qiang Li, Jian-Wei Zheng, Xiao-Wei Li, Da-Peng Lin.
Methodology: Xiu-Feng Chen, De-Zhong Wang, Nan Yao, Xue-Kai Liu.
Project administration: Jun Qu.
Resources: Wen-Qiang Li, Jian-Wei Zheng, Xiao-Wei Li, Da-Peng Lin.
Software: Xiu-Feng Chen, De-Zhong Wang, Nan Yao, Xue-Kai Liu.
Supervision: Jun Qu.
Validation: Jun Qu.
Visualization: Xiu-Feng Chen, De-Zhong Wang, Nan Yao, Xue-Kai Liu.
Writing – original draft: Chun-Bo Kang.
Writing – review & editing: Chun-Bo Kang.

References

[1] Anderson JE, Bickler SW, Chang DC, et al. Examining a common disease with unknown etiology: trends in epidemiology and surgical management of appendicitis in California, 1995-2009. World J Surg 2012;36:2787–94.
[2] Aydin OU, Soylu L, Dandin O, et al. Laboratory in complicated appendicitis prediction and predictive value of monitoring. Bratisl Lek Listy 2016;117:697–701.

[3] Kim HY, Park JH, Lee YJ, et al. Systematic review and meta analysis of CT features for differentiating complicated and uncomplicated appendicitis. Radiology 2018;287:104–15.
[4] uptodatechina.com [Internet]. Beijing: UpToDate; 2017. Available at: https://www.uptodate.com/contents/search. Accessed February 4, 2010.
[5] Bhangu A, Søreide K, Di Saverio S, et al. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. Lancet 2015;386:1278–87.
[6] Livingston EH, Woodward WA, Sarosi GA, et al. Disconnect between incidence of nonperforated and perforated appendicitis: implications for pathophysiology and management. Ann Surg 2007;245:886–92.
[7] Andersson RE. The natural history and traditional management of appendicitis revisited: spontaneous resolution and predominance of prehospital perforations imply that a correct diagnosis is more important than an early diagnosis. World J Surg 2007;31:86–92.
[8] Rubér M, Andersson M, Petersson BF, et al. Systemic Th17-like cytokine pattern in gangrenous appendicitis but not in phlegmonous appendicitis. Surgery 2010;147:366–72.
[9] Jackson HT, Mongodin EF, Davenport KP, et al. Culture-independent evaluation of the appendix and rectum microbiomes in children with and without appendicitis. PLoS One 2014;9:e95414.
[10] García-Marín A, Pérez-López M, Martínez-Guerrero E, et al. Microbiologic analysis of complicated and uncomplicated acute appendicitis. Surg Infect (Larchmt) 2018;19:83–6.
[11] Zhang HL, Bai YZ, Zhou X, et al. Nonoperative management of appendiceal phlegmon or abscess with an appendicolith in children. J Gastrointest Surg 2013;17:766–70.
[12] Poudel R, Bhandari TR. Risk factors for complications in acute appendicitis among paediatric population. JNMA J Nepal Med Assoc 2017;56:145–8.
[13] Blakely ML, Williams R, Dassinger MS, et al. Early vs interval appendectomy for children with perforated appendicitis. Arch Surg 2011;146:660–5.
[14] Shuaib A, Shuaib A, Fakhra Z, et al. Evaluation of modified Alvarado scoring system and RIPASA scoring system as diagnostic tools of acute appendicitis. World J Emerg Med 2017;8:276–80.
[15] Atema JJ, van Rossem CC, Leeuwenburgh MM, et al. Scoring system to distinguish uncomplicated from complicated acute appendicitis. Br J Surg 2015;102:979–90.
[16] Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. JAMA 2015;313:2340–8.
[17] Sallinen V, Akl EA, You JJ, et al. Meta-analysis of antibiotics versus appendicectomy for non-perforated acute appendicitis. Br J Surg 2016;103:656–67.
[18] Harnoss JC, Zelienka I, Probst P, et al. Antibiotics versus surgical therapy for uncomplicated appendicitis: systematic review and meta-analysis of controlled trials (PROSPERO 2015 CRD42015016882). Ann Surg 2017;265:889–900.
[19] Steiner Z, Buklan G, Stackievicz R, et al. Conservative treatment in uncomplicated acute appendicitis: reassessment of practice safety. Eur J Pediatr 2017;176:521–7.
[20] Georgiou R, Eaton S, Stanton MP, et al. Efficacy and safety of nonoperative treatment for acute appendicitis: a meta-analysis. Pediatrics 2017;139:e20163003.
[21] Rollins KE, Varadhan KK, Neal KR, et al. Antibiotics versus appendicectomy for the treatment of uncomplicated acute appendicitis: an updated meta-analysis of randomised controlled trials. World J Surg 2016;40:2305–18.
[22] Knaapen M, van der Lee JH, Bakx R, et al. APAC collaborative study group. Initial non-operative management of uncomplicated appendicitis in children: a protocol for a multicentre randomised controlled trial (APAC trial). BMJ Open 2017;7:e018145.
[23] Wu TC, Lu Q, Huang ZY, et al. Efficacy of emergency laparoscopic appendectomy in treating complicated appendicitis for elderly patients. Saudi Med J 2017;38:1108–12.
[24] Cetinkaya E, Erdogan A, Akgul O, et al. High serum cancer antigen 125 level indicates perforation in acute appendicitis. Am J Emerg Med 2015;33:1465–7.
[25] Park JH. LOCAT Group. Diagnostic imaging utilization in cases of acute appendicitis: multi-center experience. J Korean Med Sci 2014;29:1308–16.
[26] Svensson JF, Patkova B, Almström M, et al. Nonoperative treatment with antibiotics versus surgery for acute nonperforated appendicitis in children: a pilot randomized controlled trial. Ann Surg 2015;261:67–71.
[27] Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. Lancet 2011;377:1573–9.
[28] Lee SL, Spence L, Mock K, et al. Expanding the inclusion criteria for nonoperative management of uncomplicated appendicitis: outcomes and cost. J Pediatr Surg 2018;53:42–7.
[29] Fallon SC, Hicks MJ, Carpenter JL, et al. Management of appendiceal carcinoid tumors in children. J Surg Res 2015;198:384–7.
[30] Kaiser M, Schroeckenfuchs M, Castellani C, et al. The diagnostic value of hepcidin to predict the presence and severity of appendicitis in children. J Surg Res 2018;222:102–7.
[31] Schellekens DH, Hulsewe KW, van Acker BA, et al. Evaluation of the diagnostic accuracy of plasma markers for early diagnosis in patients suspected for acute appendicitis. Acad Emerg Med 2013;20:703–10.