

C -reactive protein and albumin ratio for the diagnosis of complicated appendicitis in children

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Abstract

Background: No reliably specific marker for complicated appendicitis has been identified. Serum C-reactive protein (CRP) increases and albumin (ALB) decreases in patients with inflammation and infection. C-reactive protein and albumin ratio (CRP/ALB ratio) has been found associated with neonatal septicemia, inflammatory bowel disease and pancreatitis. However, its value in the diagnosis of complicated appendicitis has not been studied. The aim of this study was to evaluate the value of CRP/ALB ratio for predicting complicated appendicitis in children.

Methods: A retrospective study of 232 children with acute appendicitis was conducted with assessment of age, gender, weight, symptom duration, albumin and blood routine indexes. According to intraoperative findings and postoperative pathological results, patients were divided into the simple appendicitis group (127 cases) and complicated appendicitis group (105 cases). SPSS version 17 was used to analyse the data.

Results: Of the 232 patients, 118 (50.9%) were male and 114 (49.1%) were female. The age range was 1 to 15 years, the mean age of the patients was 8.30 ± 3.25 years. The CRP/ALB ratio was higher in complicated appendicitis compared with simple appendicitis ($p < 0.05$). Logistic regression analysis showed that mononuclear cell (MC), CRP, procalcitonin (PCT) and CRP/ALB ratio were independent risk factors for complicated appendicitis in children. Receiver operating characteristic (ROC) curve analysis showed that the area under the curve (AUC) of CRP/ALB ratio was higher than MC, PCT and CRP (0.946 vs 0.619 vs 0.843 vs 0.906). CRP/ALB ratio > 1.43 was found to be a significant marker in predicting complicated appendicitis with 91.4 % sensitivity and 90.6 % specificity. Compared with CRP/ALB ratio < 1.43 , patients with CRP/ALB ratio > 1.43 had a 102.22 times higher chance of complicated appendicitis (95% CI: 41.322 - 252.874).

Conclusion: The CRP/ALB ratio is a novel and promising indicator to predict complicated appendicitis in children before operation which is easy-to-measure and repeatable. Therefore, CRP/ALB ratio can provide a reference for the choice of surgical treatment for acute appendicitis in children.

Background

Acute appendicitis (AA) is the most common surgical disease in children requiring acute abdominal surgery, and its incidence is reported to be increasing^[1]. According to the symptoms, Pediatric Appendicitis Score (PAS), Computed tomography, ultrasound and blood tests, it is not difficult to diagnose AA, but it is difficult to confirm the type of appendicitis (simple or complicated appendicitis)^[2]. The standard clinical treatment for pediatric AA is appendectomy, but recent studies have shown that partial AA, especially simple AA, may be better treated with antibiotics than surgery^[3]. Determining the optimum algorithm for diagnostic procedure in complicated AA may not only reduce the number of unnecessary operations, but also the frequency of complications, and may contribute significantly to reducing the cost of treating patients with acute abdominal conditions.

Serum C-reactive protein (CRP) is a positive acute phase reactant synthesized by the liver and its level in the blood increases within hours in response to inflammation and infection^[4]. It is frequently used in infection and inflammation follow-up due to its short half-life, easy measurement and close relationship with prognosis of the disease. It can be used for diagnosis, treatment follow-up and mortality prediction especially in inflammatory cases.

Albumin is a negative acute phase reactant synthesized by the liver and its level in the blood decreases during inflammation. In previous studies, albumin was shown to be associated with inflammation severity, disease prognosis and mortality^[5]. The reason for this is the close relationship between inflammation and malnutrition.

The CRP/albumin ratio is a new inflammation-based prognostic score and it is correlated to the inflammation severity^[6]. In recent years, there have been many studies showed that CRP/ALB ratio can indicate the degree of inflammation and prognosis in neonatal septicemia, inflammatory bowel disease and pancreatitis. ALB and CRP are routine test indexes at the time of admission, which have better universality and simplicity in clinical practice. However, there is no study available in the literature which investigates the relationship of this marker with complicated AA. The present study investigated the predictive significance of the CRP/ALB ratio for predicting complicated appendicitis in children, so as to provide a reference for selecting appropriate treatment.

Methods

Settings and children

We reviewed the files of AA patients in the minimally invasive surgery of Tianjin children Hospital from September 2018 to May 2019. A total of 263 patients were retrieved initially, and all of whom were confirmed by intraoperative findings and postoperative pathological results. The patients had complete clinical data and not treated by antibiotics or other anti-inflammatory drugs were included. And who met the listed criteria were excluded: (1) combine with inflammatory diseases, such as pneumonia, cholecystitis; (2) chronic wasting diseases, such as tuberculosis, malnutrition and tumor; (3) chronic appendicitis and acute onset of chronic appendicitis. Thus, 31 patients were excluded and 232 subjects were enrolled for following study.

Study design

The characteristics of subjects including age, gender, weight, intraoperative observation, postoperative pathological results and symptom duration(SD) were abstracted from inpatient medical records. The data of white blood cell (WBC), neutrophils (NEUT), percentage of neutrophils (PN), lymphocytes (LYMPH), CRP, platelets (PLT), procalcitonin (PCT), mononuclear cell (MC) and ALB tested in preoperative venous blood samples were collected.

The children were divided into complicated appendicitis group (105 cases) and simple appendicitis group (127 cases) according to the following diagnostic code. Simple appendicitis is diagnosed on the basis of (1) intraoperative findings: inflamed appendix without signs of gangrene, perforation, purulent fluid, contained phlegmone, or intra-abdominal abscess and (2) histopathological examination confirming the diagnosis of appendicitis without necrosis or perforation. complicated appendicitis is diagnosed on the basis of (1) intraoperative findings: signs of a gangrenous appendix with or without perforation, intra-abdominal abscess, appendicular contained phlegmone, or purulent free fluid and (2) histopathology confirming the diagnosis based on extensive necrotic tissue in the muscular layer of the appendix or signs of perforation^[7].

Statistical analysis

Excel software was used to data entry, Statistical Package for Social Sciences (SPSS) softwares were used for statistical assessments. The normal distribution of the data was evaluated with the Shapiro-Wilk test. Values with normal distribution were presented as mean \pm standard deviation and values without normal distribution were presented as median (range). Categorical variables were presented as numbers and percentages. Numerical values in the simple appendicitis group and the complicated appendicitis group were compared using the Student's t test and the Mann-Whitney U test. Chi-square (X^2) test and Fisher's exact test were used in comparison of categorical data. Univariable analysis was utilized in order to determine the effects of potential factors on complicated appendicitis. Significant factors were included in the stepwise multivariate Logistic regression model and independent predictors were identified. The diagnostic discrimination of independent predictors in complicated appendicitis was examined with ROC curve analysis. The Youden index method was used in order to determine the prediction point of the CRP/ALB ratio for complicated appendicitis. In statistical analysis, a $P < 0.05$ with 95% confidence interval and 5% margin of error was considered statistically significant.

Results

Patients Characteristics

The study population consisted of 232 patients, 114 females (49.1 %) and 118 males (50.9%). Among them, 105 cases (45.3%) were complicated appendicitis and 127 cases (54.7 %) were simple appendicitis. The symptom duration before operation was 0.2-30 days.

CRP/ALB ratio

The CRP/ALB ratio had a positive correlation with SD ($r=0.22$, $P=0.001$), WBC ($r=0.206$, $P=0.002$), CRP ($r=0.899$, $P < 0.001$), MC ($r=0.15$, $P=0.022$), PN ($r=0.154$; $P=0.019$), PCT ($r=0.327$; $P < 0.001$), and a negative correlation with age ($r=-0.159$; $P=0.016$), ALB ($r=-0.345$, $P < 0.001$) levels (Table 1).

Independent risk factors

Significant influenced factors were included in the backward stepwise regression analysis (Tables 2-3). In the univariate analysis, age ($Z=-2.833, P=0.005$), SD ($Z=-4.467, P<0.001$), ALB ($t=7.592, P<0.001$), WBC ($Z=-2.773, P=0.006$), NEUT ($Z=-2.899, P=0.004$), PN ($Z=-1.433, P=0.152$), MC ($Z=-3.123, P=0.002$), LYMPH ($Z=-2.168, P=0.03$), CRP ($Z=-10.65, P<0.001$), PCT ($Z=-8.893, P<0.001$) and CRP/ALB ratio ($Z=-11.681, P<0.001$) were associated with the type of AA. MC (OR=3.511, 95%CI:1.126-10.949, $P=0.03$), PCT (OR=4.202, 95%CI: 1.695-10.414, $P=0.002$), CRP (OR=1.029, 1.029, 95%CI: 1.001-1.058, $P=0.046$) and CRP/ALB ratio (OR=8.209, 95%CI: 2.419-27.865, $P=0.001$) were independent risk factors of complicated appendicitis, while ALB (OR=0.803, 95%CI:0.668-0.965, $P=0.019$) were protective factors. An increase of 1 unit in the CRP/ALB ratio resulted in an increase of 8.209 times in complicated appendicitis risk.

ROC curve analysis of CRP/ALB ratio

ROC curve analysis of CRP/ALB ratio resulted in an AUC of 0.946 (95%CI:0.916-0.975) (Figure. 1). When the CRP/ALB ratio was 0.906, the approximate den index was the largest (0.82). Respectively, the ROC curves of PCT, CRP, MC and ALB were 0.843 (95%CI:0.793-0.892), 0.906 (95%CI:0.866-0.947), 0.619 (95%CI:0.545-0.694) and 0.239 (95%CI:0.177-0.301). The predictive values of CRP/ALB ratio were: 91.4 % sensitivity, 90.6 % specificity, 79.3 % PPV and 92.7 % NPV. There was an association between complicated appendicitis and higher levels of CRP/ALB ratio with an OR of 4.53 (95%CI:1.902-10.788). CRP/ALB ratio showed a clearly better diagnostic performance of complicated appendicitis compared to CRP, PCT and ALB (Table. 4).

According to the best cut-off point of CRP/ALB ratio 1.43, when the CRP/ALB ratio >1.43 , the ratio of children diagnosed with complicated appendicitis was 41.38%, significantly higher than that ≤ 1.43 (41.38 % vs 3.88%, $\chi^2=155.256, P <0.05$) (Figure. 2), and the relative risk was 102.222 (95% CI:41.322 - 252.874) .

Discussion

Since McBurney first performed appendectomy for AA, appendectomy has become the classic and standard treatment. However, Recent studies suggested that different treatment strategies should be selected according to the type of AA (simple or complicated appendicitis) : simple appendicitis should be the preferred antibiotic conservative treatment, while complicated appendicitis requires appendectomy in most cases^[3, 7]. Statistics show that about 62–81% of children with AA are simple appendicitis^[8]. Children's appendix is not a non-functional organ left in the body. The appendix is not only a “storage pool” for the gut microbiota to balance the steady state of the proinflammatory and anti-inflammatory activities of the intestine; and the high content of lymphoid tissue (mainly lymphocyte CD8 + T cells) in the appendix plays an important role in the immune function of the body^[9]. Therefore, conservative treatment for children with simple appendicitis is beneficial to maintain intestinal homeostasis and immune system development. Surgeons should diagnose the type of AA accurately to avoid unnecessary appendectomy. This study explores the common laboratory indicators to determine more valuable and

simple predictors of complicated appendicitis in children, thus providing a reference for the choice of surgical treatment for children with acute appendicitis.

Inflammation is the defensive response of the body to various pathogens and tissue injury, and the timing of inflammatory reaction will release a variety of inflammatory mediators. CRP, discovered as a protein capable of precipitating the C-polysaccharide of *Streptococcus pneumoniae* and synthesized by hepatocytes, is the prototypical acute-phase reactant whose level in human serum can increase rapidly within 48 h after the onset of inflammation or tissue injury^[10]. Elevations in baseline CRP level are useful to gauge infection and tissue injury and to monitor progression of chronic diseases. CRP is now appreciated as a indicator of inflammation that widely used in the diagnosis and evaluation of inflammatory diseases. Most of the inflammatory diseases have acute and chronic consumption, while ALB can indirectly determine the degree of inflammation by reflecting the consumption degree of the body. Moreover, acute inflammatory injury incites a cascade of proinflammatory mediators leading to microcirculatory dysfunction, capillary leak, and distributive shock. Cordemans^[11] et al. found that in the inflammatory response, due to the role of inflammatory mediators, increased capillary permeability leads to ALB leakage, and capillary leak is closely related to increased CRP and decreased ALB. So, CRP/ALB ratio can be used as a biological marker to reflect microvascular permeability.

Recently, series of studies have shown that CRP/ALB ratio can be used to judge the degree of inflammatory response and prognosis. Study have shown that CRP/ALB ratio is more comprehensive and valuable than CRP, PCT, or other indicators that can reflect the balance between the degree of acute inflammatory response and immunity of patients with severe pneumonia. Kaplan^[12] et al. studied the correlation between pancreatitis and CRP/ALB ratio, and found that CRP/ALB ratio was not only closely related to the pancreatitis grade (Atlanta grade) and the degree of inflammation, but also an independent risk factor affecting the prognosis. Furthermore, CRP/ALB ratio can be also used as a predictive factor for the prognosis of lung cancer^[6], sepsis in premature infants, and septic shock. The Inflammatory reaction and exudation around appendix in complicated appendicitis is more serious than that in simple appendicitis. In view of this, CRP/ALB ratio may be used to predict the type of AA (complicated appendicitis) by judging the degree of inflammatory response and exudation in children.

According to statistics, the incidence of AA in children is dominated by males, about 55% ~ 60%^[13]. In this study, 232 children with AA were also predominantly male (50.9%). AA often has acute consumption and inflammatory exudation around the appendix. When encountering acute inflammatory injury, the body produces an inflammatory emergency response that increases WBC, NP, CRP and PCT, which are positively correlated with the degree of inflammatory response. But ALB showed negative correlation with the degree of inflammation and inflammatory exudation around the abdominal cavity or appendix. Multivariable Logistic regression analysis showed that MC (OR = 3.511, 95%CI:1.126–10.949, P = 0.03), PCT (OR = 4.202, 95%CI: 1.695–10.414, P = 0.002), CRP (OR = 1.029, 95%CI:1.001–1.058, P = 0.046) and CRP/ALB ratio (OR = 8.209, 95% CI: 2.419–27.865, P = 0.001) were independent risk factors for complicated appendicitis (P < 0.05). ALB (OR = 4.53, 95%CI:1.902–10.788) was the protective factor (P <

0.05). Some studies have found that preoperative CRP, insufficient value to diagnose AA, can predict complicated appendicitis (especially perforated appendicitis) more accurately than other common serum tests (WBC, PN, PCT) by judged the degree of AA inflammation. In this way, CRP can provide an important reference for the choice of appendectomy^[7, 14, 15]. The odds ratio of CRP/ALB ratio was higher than that of MC, CRP and PCT (OR:4.53 vs 1.029 vs 1.276), indicated that it can predict complicated appendicitis with higher value by reflecting the degree of inflammation and inflammatory exudation.

In this study, ROC curve analysis showed that the AUC of CRP/ALB ratio was higher than that of MC, PCT, CRP and ALB, with more diagnostic value for complicated appendicitis .When the cut-off point of CRP/ALB ratio was 1.43, the youden index for predicting complicated appendicitis was the largest (0.82), the sensitivity and specificity were 91.4% and 90.6%, and the positive predictive value and negative predictive value were 79.3% and 92.7%. When the CRP/ALB ratio > 1.43, the risk of complicated appendicitis was 102.222 times higher than the CRP/ALB ratio = < 1.43, suggesting that AA with CRP/ALB ratio > 1.43 had a higher risk of complicated appendicitis and recommended appendectomy.

Conclusion

In summary, the MC, PCT, CRP and CRP/ALB ratios were the independent risk factors for complicated appendicitis in children, and the CRP/ALB ratio had better predictive value for complicated appendicitis than others. The risk of complicated appendicitis was significantly increased when the CRP/ALB ratio > 1.43, and appendectomy was preferred. CRP/ALB ratio, as a routine preoperative assay index, has better universality and simplicity, and can be an ideal and new predictor for children with complicated appendicitis. The limitations of our research include the retrospective nature, single-center, low population study, which may limit the diagnostic value of the CRP/ALB ratio.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Tianjin Children's Hospital institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to publication

Not applicable

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WF drafted the manuscript, QY analyzed and collected the data, XZ analyzed the data and drafted the manuscript, ML analyzed the data and drafted the manuscript, HC critically reviewed the manuscript.

Acknowledgments

Not applicable.

Abbreviations

AA: Acute appendicitis; CRP/ALB ratio: C-reactive protein and albumin ratio

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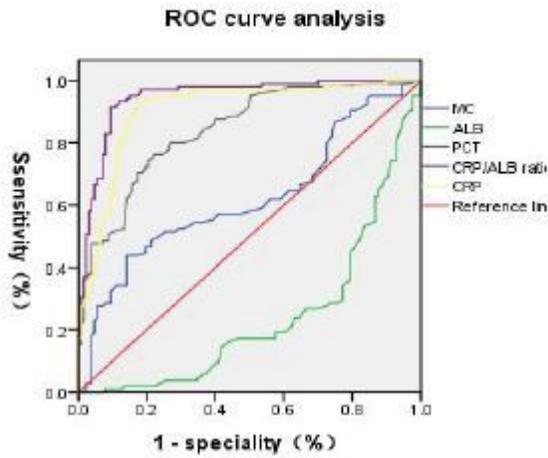
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Tables

Due to technical limitations, Tables 1, 2, 3, and 4 are only available as downloads in the supplemental files section

Figures



	AUC	SE	95 % CI
CRP/ALB ratio	0.946	0.015	0.916-0.975
PCT	0.843	0.025	0.793-0.892
CRP	0.906	0.021	0.866-0.947
MC	0.619	0.038	0.545-0.694
ALB	0.239	0.031	0.177-0.301

AUC:area under curve.

Fig. 1. Diagnostic assessment of independent predictors of complicated appendicitis with ROC curve analysis.

Figure 1

Diagnostic assessment of independent predictors of complicated appendicitis with ROC curve analysis.

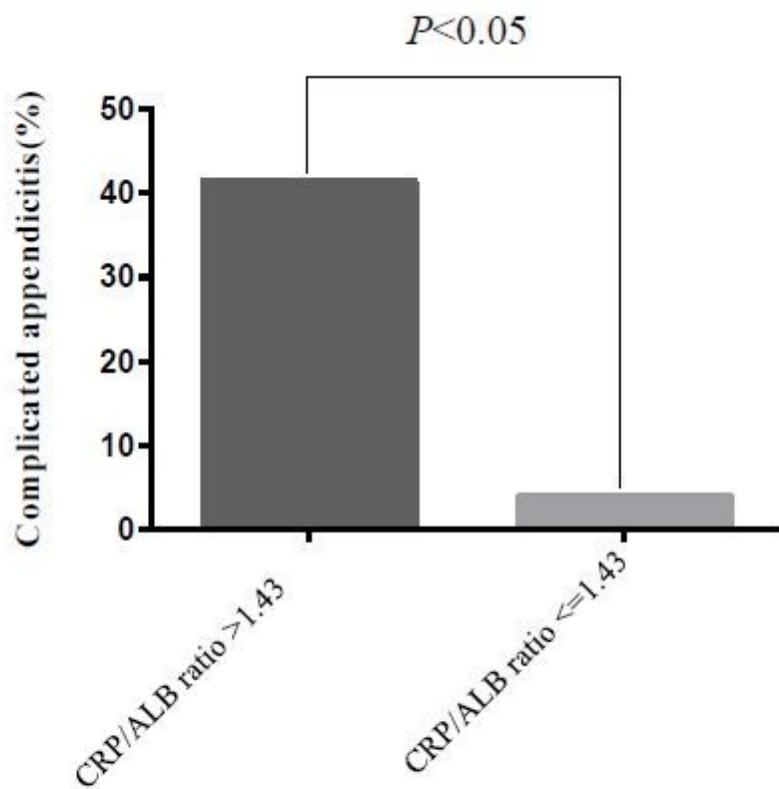


Fig 2. Diagnostic rate on the best cut-off point of CRP/ALB ratio

Figure 2

Diagnostic rate on the best cut off point of CRP/ALB ratio