The use of the ratio of C-reactive protein to albumin for the diagnosis of complicated appendicitis in children

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Abstract

Background: No reliably specific marker for complicated appendicitis has been identified. The ratio of serum C-reactive protein (CRP) to albumin (ALB) (CRP/ALB ratio) is a new inflammation-based prognostic score that is associated with the severity of inflammation. However, its value in the diagnosis of complicated appendicitis has not been studied. The aim of this study was to evaluate the predictive value of the CRP/ALB ratio for the diagnosis of complicated appendicitis in children. Methods: A retrospective study of 232 children with acute appendicitis was conducted with assessments of age, sex, symptom duration, albumin and routine blood indexes on admission. According to intraoperative findings and postoperative pathological results, patients were divided into a simple appendicitis group (127 patients) and a complicated appendicitis group (105 patients). 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 CRP/ALB ratio was higher in complicated appendicitis than in simple appendicitis ($p<0.05$). Logistic regression analysis showed that higher levels of mononuclear cell count (MC), CRP, procalcitonin (PCT) and CRP/ALB ratio were independent risk factors for complicated appendicitis in children. Receiver operating characteristic curve analysis showed that the area under the curve of the CRP/ALB ratio (0.946) was larger than that of MC (0.619), CRP (0.906) and PCT (0.843). A CRP/ALB ratio >1.43 was found to be a significant marker in the prediction of complicated appendicitis, with 91.4% sensitivity and 90.6% specificity. Patients with a CRP/ALB ratio >1.43 had a 102.22 times higher chance of having complicated appendicitis (95% CI: 41.322 - 252.874) than those with a CRP/ALB ratio ≤1.43. Conclusion: The admission CRP/ALB ratio was significantly higher in children with acute complicated appendicitis. The CRP/ALB ratio is a novel but promising haematological marker that aids in the differentiation of acute complicated and simple appendicitis.

Background

Acute appendicitis (AA) is the most common surgical disease in children, and its incidence is reported to be increasing[1]. The diagnosis of acute appendicitis has a classic clinical appearance in only one-third of all patients. Clinical appearance in younger children is often atypical, and misdiagnosis in this age group is not rare, which can lead to an increased rate of perforation[2]. Clinical presentation, Pediatric Appendicitis Score (PAS), ALVARADO score, computed tomography, ultrasound and blood tests may be helpful in the diagnosis of AA, but it is difficult to confirm the type of appendicitis (simple or complicated appendicitis)[3-5]. Being able to diagnose uncomplicated vs. complicated appendicitis allows the surgeon to choose the best surgical approach, ranging from antibiotics and delayed appendectomy to laparotomy[6]. Perforated appendicitis after surgery requires antibiotic monotherapy or combination therapy[7]. The determination of the optimum algorithm for diagnostic procedures in complicated AA may reduce not only 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. There are tools to determine the severity of AA (abdominal ultrasound and computed tomography)[8]; nevertheless, these tools may be limited in some centres, e.g., owing to technicians who cannot give a

final report or a lack of personnel to carry them out. Consequently, serological methods to estimate complicated appendicitis are currently of interest.

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[9]. Albumin (ALB) is a negative acute phase reactant synthesized by the liver, and its level in the blood decreases during inflammation, which is associated with inflammation severity, disease prognosis and mortality[10]. The ratio of CRP to ALB (CRP/ALB ratio) is a new inflammation-based prognostic score that is correlated with inflammation severity[11]. In recent years, many studies have shown that the CRP/ALB ratio can indicate the degree of inflammation and prognosis in neonatal septicaemia, inflammatory bowel disease and pancreatitis[9, 12]. Moreover, the CRP/ALB ratio is used as a prognostic factor for many malignancies, such as hepatocellular carcinoma and nasopharyngeal carcinoma[13, 14].

However, there is no study available that investigates the relationship of this marker with complicated appendicitis. The present study investigated the predictive significance of the CRP/ALB ratio for the diagnosis of complicated appendicitis in children.

Methods

This retrospective study was approved by the institutional review board of the hospital (IRB number L202001). We hypothesized that the value of the CRP/ALB ratio is different between complicated and simple appendicitis. Our primary goal was to evaluate the predictive value of the CRP/ALB ratio for complicated appendicitis in children. The secondary goal was to determine the best cut-off point for the CRP/ALB ratio for the diagnosis of complicated appendicitis.

Settings and children

We reviewed the files of AA patients in the paediatric surgery department of Tianjin Children's Hospital from September 2018 to May 2019. The cases of a total of 263 patients were retrieved initially, all of which were confirmed to be AA by intraoperative findings and postoperative pathological results. The patients had not been treated with antibiotics or other anti-inflammatory drugs before admission. Patients with inflammatory diseases (such as pneumonia and cholecystitis), chronic wasting diseases (such as tuberculosis, malnutrition and tumours) and those who had acute onset of chronic appendicitis were excluded from the study. Thus, 31 patients were excluded, and 232 subjects were enrolled for the following study.

Study design

The characteristics of subjects, including age, sex, intraoperative observation, postoperative pathological results and symptom duration (SD), were extracted from inpatient medical records. The white blood cell count (WBC), neutrophil count (NEUT), percentage of neutrophils (PN), lymphocyte count (LYMPH), CRP,

platelet count (PLT), procalcitonin (PCT), mononuclear cell count (MC) and ALB data tested on admission (within 2 hours) in venous blood samples were collected.

The children were divided into a complicated appendicitis group (105 patients) and a simple appendicitis group (127 patients) according to the following diagnostic code. Simple appendicitis was diagnosed on the basis of (1) intraoperative findings: inflamed appendix without signs of gangrene, perforation, purulent fluid, phlegmon, or intra-abdominal abscess and (2) histopathological examination confirming the diagnosis of appendicitis without necrosis or perforation. Complicated appendicitis was diagnosed on the basis of (1) intraoperative findings: signs of a gangrenous appendix with or without perforation, intra-abdominal abscess, appendix contained phlegmon 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[15].

Statistical analysis

Excel software was used for data entry, and Statistical Package for Social Sciences (SPSS) software was used for statistical assessments. The normal distribution of the data was evaluated with the Shapiro-Wilk test. Values with normal distribution are presented as the mean ± the standard deviation (mean ± SD), and values without normal distribution are presented as medians and interquartile ranges. Categorical variables are presented as numbers and percentages. Numerical values in the simple appendicitis group and the complicated appendicitis group were compared using Student's t test and the Mann-Whitney U test. The chi-squared test was used to compare categorical data. Univariable analysis was utilized 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 and the area under the curve (AUC). The Youden index method was used to find the best cut-off point of the CRP/ALB ratio for the diagnosis of complicated appendicitis. In statistical analysis, a $P<0.05$ with 95% confidence interval (95% CI) and 5% margin of error was considered statistically significant.

Results

Patient characteristics

We included 232 patients in our study: 114 females (49.1%) and 118 males (50.9%). The mean age was 8.30±3.25 years (1-15 years). Among them, 105 patients (45.3%) had complicated appendicitis, and 127 patients (54.7%) had simple appendicitis. The range of SD before operation was 0.2 to 30 days.

CRP/ALB ratio

The CRP/ALB ratio had a positive correlation with SD (P=0.001), WBC (P=0.002), CRP (P<0.001), MC (P=0.022), PN (P=0.019), and PCT (P<0.001) and a negative correlation with age (P=0.016) and ALB

(P<0.001) levels.

Independent risk factors

Significantly influenced factors were included in the backward stepwise regression analysis (Tables 1-2). In the univariate analysis, age (P=0.005), SD (P<0.001), ALB (P<0.001), WBC (P=0.006), NEUT (P=0.004), PN (P=0.152), MC (P=0.002), LYMPH (P=0.03), CRP (P<0.001), PCT (P<0.001) and CRP/ALB ratio (P<0.001) were associated with the type of AA. Higher levels of MC (P=0.03), PCT (P=0.002), CRP (P=0.046) and CRP/ALB ratio (P=0.001) were independent risk factors for complicated appendicitis, while ALB (P=0.019) was a protective factor. An increase in the CRP/ALB ratio of 1 unit resulted in an increase in the risk of complicated appendicitis by 8.209 times.

ROC curve analysis of the CRP/ALB ratio

ROC curve analysis of the CRP/ALB ratio resulted in an AUC of 0.946. When the CRP/ALB ratio was 1.43, the Youden index was the largest (0.82). The AUCs of PCT, CRP, MC and ALB were 0.843, 0.906, 0.619 and 0.239, respectively (Figure 1). The predictive values of the 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 CRP/ALB ratios, with an odds ratio of 4.53. The CRP/ALB ratio showed a clearly better predictive performance for the diagnosis of complicated appendicitis than CRP, PCT, MC and ALB (Table 3).

According to the best cut-off point of the CRP/ALB ratio of 1.43, a CRP/ALB ratio >1.43 was found in 95.1% of patients with complicated appendicitis and in 6.3% of those with simple appendicitis (P<0.001). Compared with a CRP/ALB ratio ≤1.43, patients with CRP/ALB ratio >1.43 had a 102.22 times higher chance of having complicated appendicitis (95% CI: 41.322 - 252.874).

Discussion

In this retrospective study, we found that MC, PCT, CRP, ALB and the CRP/ALB ratio on admission were independently associated with complicated appendicitis. Regarding prediction, the CRP/ALB ratio could identify children at high risk for complicated appendicitis, with a specificity of 90.6%, better than that of other haematological markers, and a high negative predictive value of 92.7%. In addition, the predictive value of the CRP/ALB ratio was better than that of CRP, which was the best haematological indicator reported by previous studies[15-17].

Acute appendicitis remains a clinical diagnosis with laboratory and radiological tests as auxiliary diagnostic methods. Since AA has a complication rate of approximately 40%, different methods for the prediction of complicated appendicitis have been tested with inconsistent results. Radiological tests and ultrasonography have been proven to have a false-negative rate of approximately 20% in the prediction of complicated appendicitis. The use of common serum biomarkers, such as PCT, CRP, WBC, fibrinogen and total bilirubin, is increasing[8]. The majority of studies have focused on the efficacy of the standard serum markers in the diagnosis of acute appendicitis and concluded that an elevation of CRP, PCT and WBC can

support the diagnosis of complicated appendicitis in children[16]. Caruso[18] et al. found that admission CRP is more accurate than PCT, WBC and PN to aid in the differentiation of acute complicated and simple appendicitis. In a meta-analysis evaluating the diagnostic value of serum markers in 1011 patients with perforated or non-perforated appendicitis, CRP was found to have the best discriminative capability[19]. Similarly, our study showed that CRP was found to have better discriminative capability than PCT and WBC in the diagnosis of appendicitis. However, the differences in CRP between simple and complicated appendicitis were noticeable in children between 5 and 17 years of age but not in those younger than 5[16]. Cordemans[20] et al. found that in the inflammatory response, due to the role of inflammatory mediators, increased capillary permeability leads to ALB leakage. The CRP/ALB ratio has been used in several cohort studies as a surrogate for CRP in assessments of the severity of the inflammatory response[9, 12, 21]. In our current clinical practice, CRP increases and ALB decreases in children with AA. As an alternative novel indicator of inflammation, the CRP/ALB ratio showed a good correlation with CRP and could have better predictive value for complicated appendicitis.

Recently, several trials have focused on the non-operative treatment of AA[18, 22]. Studies have suggested that different treatment strategies should be selected according to the type of AA: conservative antibiotic treatment should be the preferred treatment for simple appendicitis, while complicated appendicitis requires appendectomy in most cases[6, 15]. A child's appendix is not a non-functional organ left in the body. The appendix is 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[23]. Therefore, children with AA with a CRP/ALB ratio ≤1.43 may avoid unnecessary appendectomy.

Furthermore, discrimination between simple and complicated appendicitis is important, as it may guide appropriate intravenous fluid resuscitation and antibiotic administration prior to surgical intervention. The CRP/ALB ratio upon admission could guide preoperative (or postoperative) antibiotic selection and predict prognosis, with the best cut-off point of the CRP/ALB ratio being 1.43. Although appendicitis protocols vary widely among centres, children with simple appendicitis typically receive a single antibiotic preoperatively, may not even receive postoperative treatment and may be discharged home relatively soon[16]. Conversely, children with complicated appendicitis recognized on admission typically receive a combination of more antibiotics, undergo operative treatment, and continue antibiotic therapy postoperatively. Hence, the identification of predictive indicators for complicated appendicitis is essential.

It should be noted that the present study was limited by its retrospective design, which meant that not all data were available, especially data on initial symptoms and temperature. Furthermore, because the study was conducted in the paediatric surgery department of one hospital and the cohort was relatively small, its results should be regarded with caution. In addition, the impact of the CRP/ALB ratio on outcomes was not investigated, and the usefulness of the CRP/ALB ratio for the determination of the response to definitive treatment was not examined.

Conclusion

In conclusion, our study shows that on admission, the levels of MC, PCT, CRP and CRP/ALB ratios may help clinicians predict the occurrence of complicated appendicitis in children, and the CRP/ALB ratio had better predictive value for complicated appendicitis than other haematological markers. Specifically, patients with a CRP/ALB ratio >1.43 had a 102.22 times higher chance of complicated appendicitis than patients with a CRP/ALB ratio ≤1.43. The CRP/ALB ratio, as a routine haematological marker, has better universality and simplicity and can be a novel but promising predictor for complicated appendicitis in children.

Abbreviations

AA: acute appendicitis; CRP: C-reactive protein; ALB: albumin; PCT: procalcitonin; MC: mononuclear cell count; SD: symptom duration.

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 (approved number L202001) and with the 1964 Declaration of Helsinki 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.

Authors' contributions

WF drafted the manuscript, QY and XZ analysed and collected the data, ML analysed the data and drafted the manuscript, and HC critically reviewed the manuscript. All authors approved the final manuscript as submitted.

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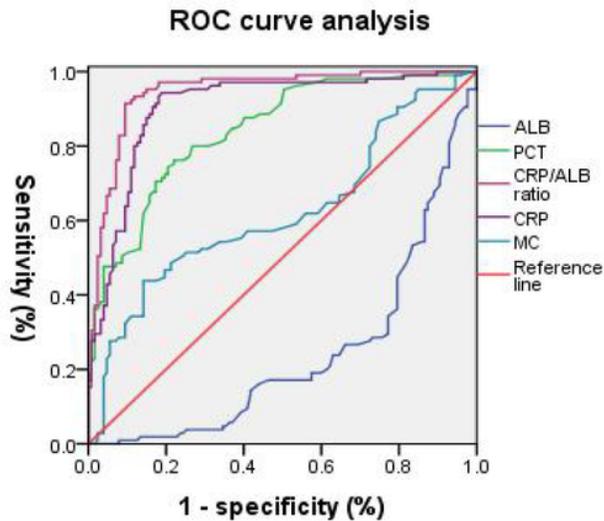
	AUC	SE	95 % CI
CRP/ALB ratio	0.946	0.015	0.916-0.975
PCT	0.843	0.025	0.793-0.892
CRP	0.906	0.021	0.866-0.947
MC	0.619	0.038	0.545-0.694
ALB	0.239	0.031	0.177-0.301

AUC: area under curve.

Figure 1

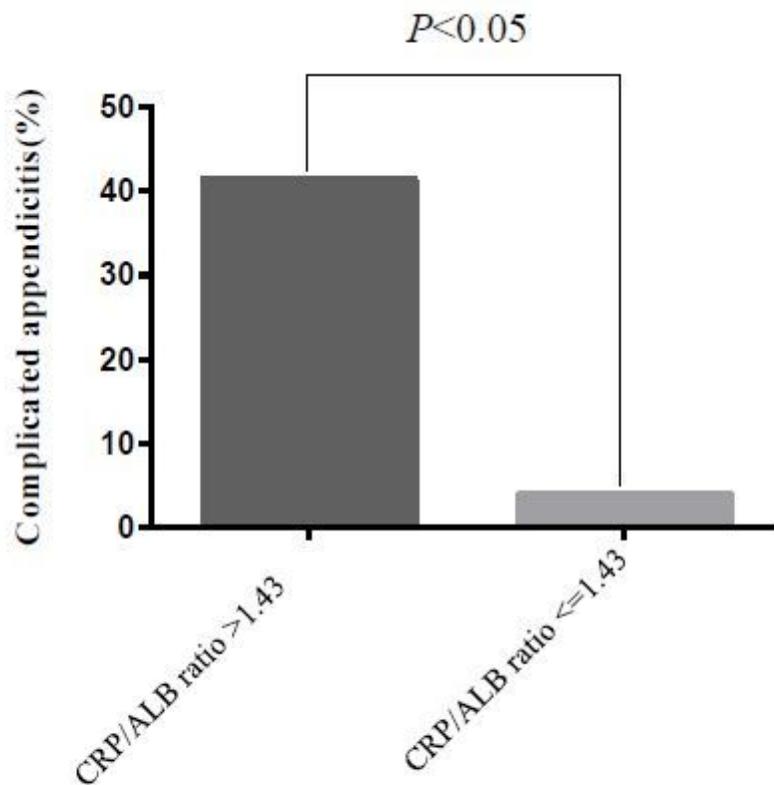Diagnostic assessment of independent predictors of complicated appendicitis with ROC curve analysis.

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

Supplementary Files

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