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

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Research article

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Abstract

Background: No reliably specific marker for complicated appendicitis has been identified. Serum C-reactive protein (CRP) and albumin (ALB) ratio (CRP/ALB ratio) has been a new inflammation-based prognostic score which 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 CRP/ALB ratio for complicated appendicitis in children.

Methods: A retrospective study of 232 children with acute appendicitis was conducted with assessment of age, gender, symptom duration, albumin and blood routine indexes on admission. 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 CRP/ALB ratio was higher in complicated appendicitis compared with simple appendicitis ($p<0.05$). Logistic regression analysis showed that the 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 CRP/ALB ratio (0.946) was was bigger than MC (0.619), CRP (0.906) and PCT (0.843). CRP/ALB ratio >1.43 was found to be a significant marker in predicting complicatedappendicitis 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: Admission CRP/ALB ratio was significantly higher in children with acute complicated appendicitis. It is a novel but promising hematological marker that aids 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 classic clinical appearance only in one third of all patients. Clinical appearance in the 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 diagnose of AA, but it is difficult to confirm the type of appendicitis (simple or complicated appendicitis)[3-5]. Been 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 mono or combination therapy[7]. 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.There are tools to determine the severity of AA (abdominal ultrasound and computed tomography)[8]; nevertheless, this tools may be limited in some centers e.g. technicians that can not give a final report or lack of personnel to carry them out. Consequently, serological methods to estimate the 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 was associated with inflammation severity, disease prognosis and mortality[10]. The CRP and ALB ratio (CRP/ALB ratio) is a new inflammation-based prognostic score and it is correlated to the inflammation severity[11]. 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[9, 12]. What's more, CRP/ALB ratio is used as prognostic factor of many malignancies, such as hepatocellular carcinoma, nasopharyngeal carcinoma[13, 14].

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

Methods

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

Settings and children

We reviewed the files of AA patients in the pediatric surgery department 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 not been treated with antibiotics or other anti-inflammatory drugs before admission. Patients with inflammatory diseases (such as pneumonia, cholecystitis), chronic wasting diseases (such as tuberculosis, malnutrition and tumor) 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 following study.

Study design

The characteristics of subjects including age, gender, intraoperative observation, postoperative pathological results and symptom duration (SD) were abstracted from inpatient medical records. The

data of white blood cell count (WBC), neutrophils count (NEUT), percentage of neutrophils (PN), lymphocytes count (LYMPH), CRP, platelet count (PLT), procalcitonin (PCT), mononuclear cell count (MC) and ALB tested on admission (within 2 hours) in 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[15].

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 ± standard deviation and values without normal distribution were presented as medians and interquartile ranges. 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 test was 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, area under the curve (AUC). The Youden index method was used to find the best cut-off point of the CRP/ALB ratio for 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

Patients Characteristics

We included 232 patients in our study-114 females (49.1 %), 118 males (50.9%). The mean age was 8.30±3.25 years (1-15 years). Among them, 105 cases (45.3%) were complicated appendicitis and 127 cases (54.7 %) were 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 ($r=0.22$; $P=0.001$), 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) and ALB (r=-0.345; P<0.001) levels.

Independent risk factors

Significant 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. And the 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 of complicated appendicitis, while ALB (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. When the CRP/ALB ratio was 1.43, the Youden index was the largest (0.82). Respectively, the AUC of PCT, CRP, MC and ALB were 0.843, 0.906, 0.619 and 0.239 (Figure. 1). 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 odds ratio of 4.53. CRP/ALB ratio showed a clearly better diagnostic performance of complicated appendicitis compared to CRP, PCT, MC and ALB (Table. 3).

According to the best cut-off point of CRP/ALB ratio 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 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)

Discussion

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

Acute appendicitis remains a clinical diagnosis with laboratory and radiological test as an auxiliary diagnostic method. Since AA has a rate of been complicated of approximately 40%, different methods for predicting complicated appendicitis have been tested with inconsistent results. Radiological tests and ultrasonography prove to have an approximately 20% of false negative complicated appendicitis. The use of common serum biomarkers are uprising, such as PCT, CRP, WBC, fibrinogen and total bilirubin[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 aids the differentiation of acute complicated and simple appendicitis. In a meta-analysis evaluating the diagnostic value of serum markers on 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 diagnosing appendicitis. However, the differences of CRP between simple and complicated appendicitis were noticeable in children who are 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. CRP/ALB ratio has been used in several cohort studies as a surrogate for the CRP in assessing the severity of 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, 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 for AA[18, 22]. Studies suggested that different treatment strategies should be selected according to the type of AA: simple appendicitis should be the preferred antibiotic conservative treatment, while complicated appendicitis requires appendectomy in most cases[6, 15]. Children 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[23]. Therefore, 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 and antibiotic resuscitation prior to surgical intervention. Admission CRP/ALB ratio could guide preoperative (or postoperative) antibiotic selection and predict prognosis, referred the best cut-off point of CRP/ALB ratio 1.43. Although appendicitis protocols vary widely among centres, children with simple appendicitis typically receive a single antibiotic preoperatively and may even not receive postoperative treatment and get discharge home relatively soon[16]. Conversely, children with a complicated appendicitis recognised on admission typically receive a combination of more antibiotics, undergo operative treatment, and continue antibiotic therapy postoperatively. Hence, identification of predictive indicators for the complicated appendicitis is essential.

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

Conclusion

In conclusion, our study shows that on admission, the levels of MC, PCT, CRP and CRP/ALB ratios may help the clinician predict the occurrence of complicated appendicitis in children, and the CRP/ALB ratio had better predictive value for complicated appendicitis than others. Specifically, compared with CRP/ALB ratio =<1.43, patients with CRP/ALB ratio >1.43 had a 102.22 times higher chance of complicated appendicitis. CRP/ALB ratio, as a routine hematological marker, has better universality and simplicity, and can be an 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.

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

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Not applicable.

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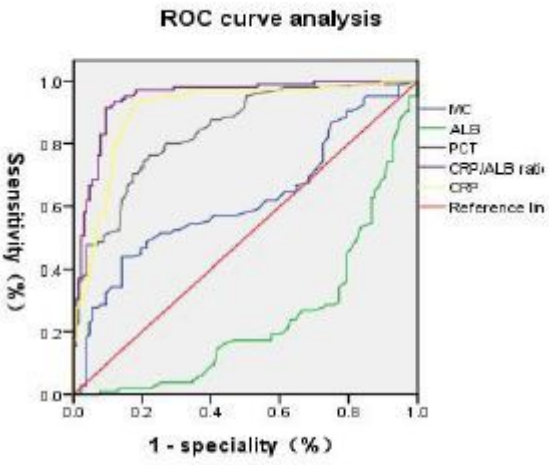
Tables

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.

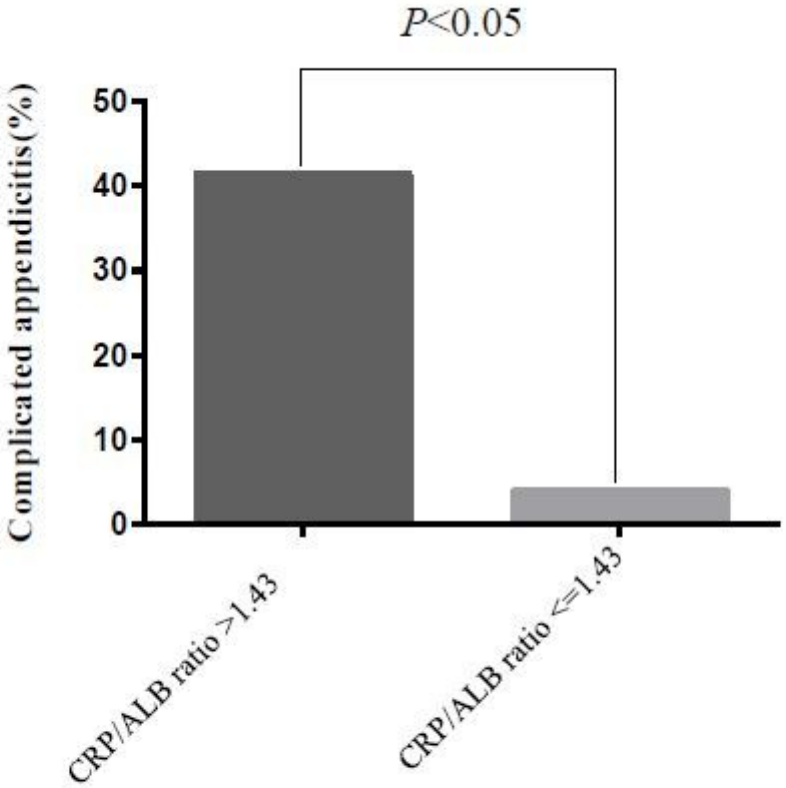


Fig 2. Diagnostic rate on the best cut-off point of CRP/ALB ratio

Figure 2

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

Supplementary Files

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