

ORIGINAL ARTICLE

Diagnostic Value of Serum Procalcitonin in Appendicitis in Infants and Young Children: Retrospective Cohort Study

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SUMMARY

Background: An increasing number of studies have indicated that uncomplicated acute appendicitis can be cured with antibiotics alone. Reducing the hazards of appendicitis in infants and young children is a priority problem. It is necessary to search for potential biomarkers for early diagnosis of appendicitis in infants and young children.

Methods: A retrospective cohort study, including 366 infants and young children treated in the pediatric surgery department, was conducted. Complete blood count, C-reactive protein, and procalcitonin were measured at admission and 24 hours after operation.

Results: The median of PCT, CRP, and WBC in the acute appendicitis group and other diseases group were 1.20, 0.11 - 4.06; 16.50, 0.81 - 76.21; 13.51, 7.53 - 26.30 and 0.03, 0.01 - 0.13; 3.35, 0.92 - 6.33; 14.34, 8.84 - 17.23 at the admission, respectively. PCT and CRP were found higher in the acute appendicitis group than that in other abdominal pain diseases group ($p < 0.05$). WBC is not a specific indicator for identifying acute appendicitis and other abdominal pain diseases ($p > 0.05$). In different acute appendicitis cases, PCT and CRP significantly increased in complicated appendicitis ($p < 0.05$). Data showed that WBC mildly increased in complicated appendicitis compared to acute simple appendicitis ($p < 0.05$). ROC curves showed that PCT was a specific indicator for identifying acute appendicitis and other abdominal pain diseases, $AUC_{PCT} = 1.000$ (95% CI, 0.999 - 1.000). The median of antibiotic treatment is 4.0 d (95% CI 3.0 - 5.0) in acute appendicitis with PCT results versus 7.0 d (95% CI 5.0 - 9.0) in acute appendicitis without PCT result.

Conclusions: PCT shows a high diagnostic ability for appendicitis in infants and young children at admission and assists pediatricians in management of pediatric appendicitis. The combination of these biomarkers is highly recommended. Further studies are needed to confirm our findings.

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KEY WORDS

procalcitonin, appendicitis, infants, young children, antibiotic

LIST OF ABBREVIATIONS

PCT - procalcitonin
ROC - receiver operating characteristic
AUC - area under the curve
CRP - C-reactive protein
WBC - white blood cell

INTRODUCTION

Appendicitis is one of the most common diseases of abdominal pain in infants and young children [1]. The main treatment for patients suffering from appendicitis remains surgery either by laparoscopic or by open approach. Although appendectomy is considered effective, there are still short- or long-term complications. The overall morbidity rate of complication is 5 - 30%, with higher rates in cases of complicated appendicitis [2]. The mortality rate of acute appendicitis in infants and young children has declined in past years, but accurate diagnosis remains suboptimal, especially in infants and young children. A delay in diagnosis and treatment results in an increased hospital length of stay, perforation rate, post-operative morbidity, and mortality. Patients are characterized by an acute inflammatory process, approximately 16.5% of appendicitis leads to perforation, progresses to gangrene, abscess formation, or peritonitis, i.e., complicated appendicitis, which may lead to post-surgical complications, higher costs and even death [3]. Infants and young children suffering from appendicitis often present non-specific signs such as lethargy, anorexia, and irritability. Non-specific signs always lead to a high misdiagnosis rate. Notably, it is crucial to diagnose acute appendicitis in infants and young children early and to discriminate complicated and uncomplicated appendicitis for initiating preemptive therapy.

Overall, the initial misdiagnosis rates of acute appendicitis range from 70% to 100% in infants and young children [4]. The accuracy of acute appendicitis could be improved by using computerized tomography, ultrasound, and magnetic resonance image. However, it remains limited due to the increase in cost, radiation exposure risk, lifetime risk of cancer, and lack of universal availability [5]. Biomarkers of infection such as white blood cells (WBC), C-reactive protein (CRP), and procalcitonin (PCT) have been shown to be a guide for the diagnostic process of infection.

PCT, one of biomarkers of infection, is the prohormone of calcitonin, which has been discovered to have potential diagnostic value and accuracy in infection diseases [6]. Studies show that PCT production is induced by two mechanisms, by inflammatory mediators such as interleukin-1, interleukin-6, tumor necrosis factor-alpha and directly by lipopolysaccharides and bacterial endotoxins [7]. The role of PCT in the diagnosis of acute appendicitis in infants and young children is still inconclusive. We conducted this study to evaluate the diagnostic value of PCT for acute appendicitis in infants and young children.

MATERIALS AND METHODS

Patients

A retrospective evaluation was done of the clinical records of patients who had been tested WBC, CRP, and PCT in the Department of Pediatric Surgery, Maternity and Child Healthcare Hospital of Anyang, Anyang City, Henan Province, China, from January 1, 2016, to November 30, 2019. The inclusion criteria are age \leq 3 years, neonate born after 34 weeks of gestation, suspected early acute appendicitis, and needed antibiotic therapy. The suspected early acute appendicitis was based on clinical symptoms and signs, physical exam findings, ultrasound, and/or laboratory outcomes proposed by clinical practice [8]. We collected and analyzed the clinical and laboratory data. The diagnosis of simple acute appendicitis and complicated appendicitis was based on current medical records and was subsequently cross-validated according to clinical practice consensus [8,9].

Blood analysis

The WBC analysis was carried out on a Sysmex automated hematology analyzer XN 2000. The serum was used for PCT and CRP analysis in this study. PCT and CRP analysis kits were purchased from Medical System Biotechnology Co., LTD, Ningbo, Zhejiang, China. PCT and CRP measurements were obtained before initiation of antibiotic treatment in infants and young children suspected of acute appendicitis and that in the control group using Siemens ADVIA 1800 chemistry system. The usable checkout limit of CRP is 0.1 mg/L. The usable detection limit of PCT is 0.01 ng/mL. The variation coefficient of PCT concentration 0.03 ng/mL is less than 6%.

Statistics

SPSS 19.0 was used to perform the statistical analyses. The categorical variables were described by percentage and frequency. One-way analysis of variance was performed for comparison analysis. Comparison of continuous variables was analyzed by Mann-Whitney U test. $p < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Baseline results

Three hundred and sixty-six infants and young children who were hospitalized due to pain in the right lower abdomen from January 1, 2016, to November 30, 2019, were screened. Twenty-seven cases were excluded, 22 cases of incomplete data and 5 cases of treatment transfer. Patients were treated with antibiotics due to suspected acute appendicitis. One hundred and twenty-six children were finally diagnosed as other diseases, including 77 cases of acute gastroenteritis, 19 cases of acute nonspecific mesenteric lymphadenitis, 28 cases of

Table 1. Baseline characteristics of patients.

	Acute simple appendicitis (n = 61)	Acute suppurative appendicitis (n = 33)	Perforated acute appendicitis (n = 22)	Periappendiceal abscess (n = 17)	Other diseases (n = 126)	Acute appendicitis without PCT (n = 80)
Gender						
Male	35/61 (57.4%)	18/33 (54.5%)	12/22 (54.5%)	10/17 (58.8%)	66/126 (52.4%)	43/80 (53.8%)
Female	26/61 (42.6%)	15/33 (45.5%)	10/22 (45.5%)	7/17 (41.2%)	60/126 (47.6%)	37/80 (46.2%)
Birth weight, kg	3.6 (3.1 - 4.3)	3.3 (3.2 - 3.9)	3.4 (2.7 - 4.0)	3.4 (3.0 - 3.7)	3.3 (2.9 - 4.1)	3.3 (2.9 - 4.0)
Birth length, cm	51 (48 - 54)	51 (47 - 54)	50 (47 - 53)	51 (47 - 53)	50 (47 - 52)	50 (46 - 52)
Gestational age, week	38 (36 - 40)	38 (36 - 40)	38 (35 - 40)	38 (37 - 40)	38 (36 - 40)	38 (36 - 40)
Delivery type						
Caesarean birth	25/61 (41.0%)	13/33 (39.4%)	10/22 (45.5%)	8/17 (47.1%)	51/126 (40.5%)	39/80 (48.8%)
Vaginal birth	36/61 (59.0%)	20/33 (60.6%)	12/22 (54.5%)	9/17 (52.9%)	75/126 (59.5%)	41/80 (51.2%)
Age, year	2.6 (0.9 - 2.9)	2.7 (1.0 - 3.0)	2.6 (1.0 - 2.9)	2.5 (0.9 - 3.0)	2.4 (0.9 - 3.0)	2.4 (0.9 - 2.9)
Height, cm	89.0 (68.0 - 98.0)	86.0 (71.5 - 96.5)	87.0 (72.0 - 97.0)	91.0 (69.5 - 99.5)	94.5 (71.0 - 96.5)	94.4 (70.2 - 96.9)
Weight, kg *	14.2 (7.9 - 15.9)	13.5 (8.1 - 14.9)	13.1 (8.2 - 16.9)	14.4 (8.0 - 17.1)	15.5 (7.9 - 15.9)	15.5 (7.3 - 16.6)
Respiratory frequency, time/minute *	28 (25 - 39)	30 (26 - 39)	34 (29 - 40)	35 (29 - 40)	28 (26 - 35)	28 (25 - 38)
Temperature, °C	38.4 (37.0 - 39.0)	38.0 (37.2 - 39.0)	38.5 (37.5 - 39.0)	38.6 (37.5 - 39.5)	38.5 (37.6 - 39.5)	38.2 (36.9 - 39.1)
Pulse, time/minute	124 (105 - 132)	126 (108 - 135)	127 (110 - 135)	127 (110 - 135)	120 (102 - 130)	128 (106 - 140)

Data are median (Inter Quartile Range) or n/total (%). * p < 0.05.

intussusception in children, and 2 cases of right-sided pneumonia. One hundred and thirty-three cases of acute appendicitis included 61 cases of acute simple appendicitis, 33 cases of acute suppurative appendicitis, 22 cases of perforated acute appendicitis, and 17 cases of periappendiceal abscess. Eighty patients were diagnosed as acute appendicitis but were treated with antibiotics with no PCT value, as shown in Figure 1. Baseline characteristics of patients in each group are shown in Table 1.

PCT, CRP, and WBC levels in acute appendicitis and other diseases group

In this study, the control group consisted of 126 children with abdominal pain on the right who were finally diagnosed as other diseases. The median of PCT, CRP, and WBC in acute appendicitis group and other diseases group were 1.20, 0.11 - 4.06; 16.50, 0.81 - 76.21; 13.51, 7.53 - 26.30 and 0.03, 0.01 - 0.13; 3.35, 0.92 - 6.33;

14.34, 8.84 - 17.23 at admission, respectively. The data show that WBC is not a specific indicator for identifying acute appendicitis and other abdominal pain diseases (p > 0.05) (Figure 2A). However, PCT and CRP were found higher in the acute appendicitis group than that in the control group (p < 0.05) (Figure 2B and C).

PCT, CRP, and WBC levels in different types of acute appendicitis

In this study, 133 cases of acute appendicitis included 61 cases of acute simple appendicitis (group I), 33 cases of acute suppurative appendicitis (group II), 22 cases of perforated acute appendicitis (group III), and 17 cases of periappendiceal abscess (group IV). The clinical data of these groups were compared to each other. The median and range of PCT, CRP, and WBC were respectively 0.86, 0.11 - 1.30; 8.24, 0.81 - 43.45; and 11.35, 2.30 - 19.90 for acute simple appendicitis, 1.12, 0.31 - 2.67; 8.11, 0.85 - 52.82; and 14.45, 4.79 - 18.34 for acute

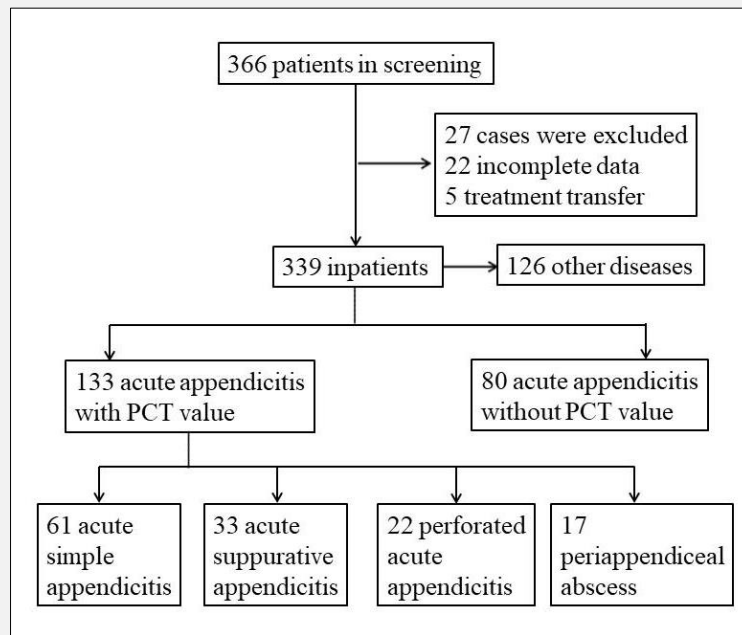


Figure 1. The flow diagram of the present study.

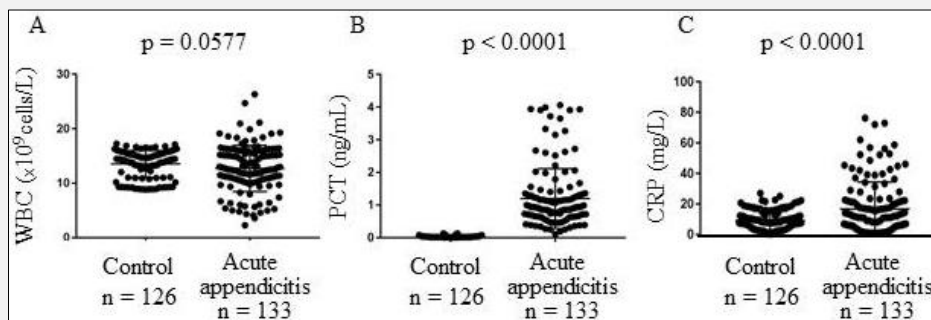


Figure 2. Comparison of infection biomarker levels in acute appendicitis group and control group.

WBC (A), PCT (B), and CRP (C) in acute appendicitis group (n = 133) and abdominal pain on right finally diagnosed as other diseases (n = 126).

suppurative appendicitis, 0.85, 0.19 - 3.72; 11.26, 0.85 - 62.05; and 15.10, 5.01 - 26.30 for perforated acute appendicitis, and 3.10, 0.97 - 4.06; 37.03, 1.52 - 76.21; and 15.74, 4.35 - 24.68 for periappendiceal abscess at the admission. As Figure 3A shown, WBC was not show a significant difference between group III and IV

($p > 0.05$). However, WBC was significantly higher in group III-IV vs. group I (< 0.05). There was no significant difference between group II and III in PCT and CRP levels ($p > 0.05$). When group II or III was compared with group I, there was a significant increase in PCT and CRP levels ($p < 0.05$). When group IV was

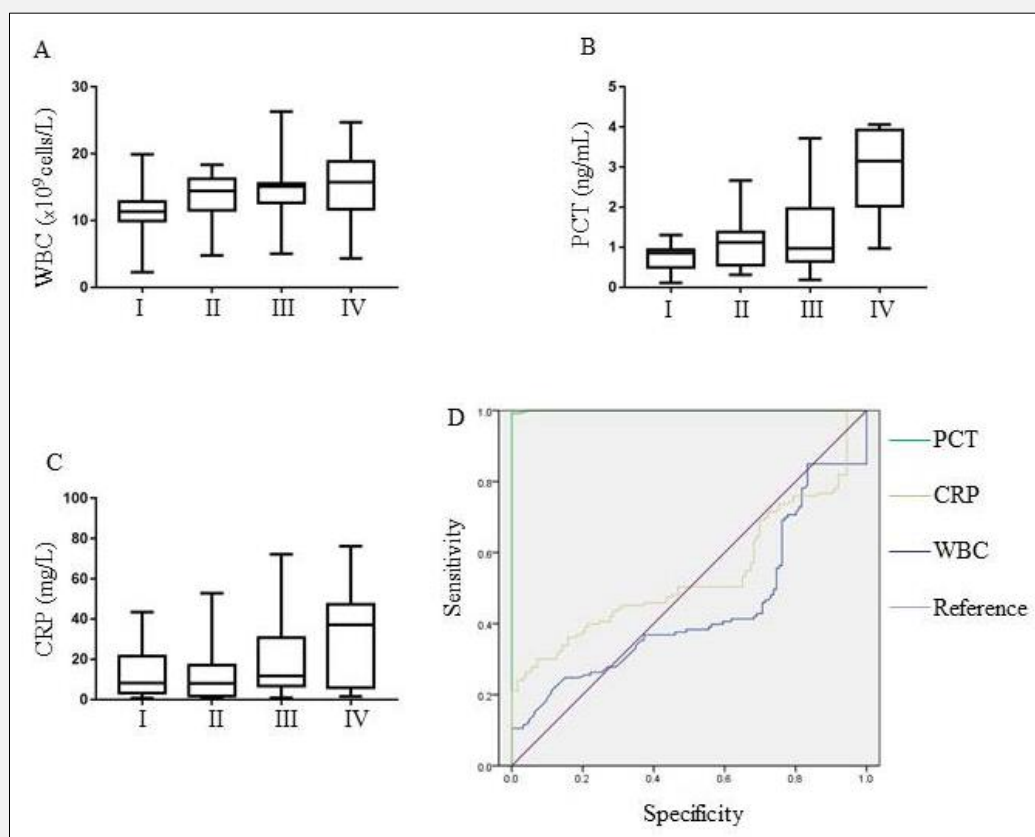


Figure 3. Infection biomarkers in different acute appendicitis.

I - acute simple appendicitis (n = 61), II - acute suppurative appendicitis (n = 33), III - perforated acute appendicitis (n = 22), IV - periappendiceal abscess (n = 17). WBC (A), PCT (B), and CRP (C) levels in different groups. (D) The diagnostic efficiency of biomarkers for acute appendicitis and other disease with pain in the right lower abdomen. Area under the ROC curve (AUC), WBC = 0.439 (95% CI, 0.367 - 0.510), PCT = 1.000 (95% CI, 0.999 - 1.000), CRP = 0.538 (95% CI, 0.466 - 0.610).

compared with group II or III, there was a significant increase in PCT and CRP levels ($p < 0.05$) (Figure 3B - C). Data suggest that PCT and CRP significantly increased in complicated appendicitis. In the receiver operating characteristic (ROC) curve, PCT was shown to be a good marker for differential diagnosis of acute appendicitis and other disease pain in the right lower abdomen (Figure 3D).

Using PCT to guide antibiotic treatment

When investigating the duration of antibiotic treatment in acute appendicitis with or without PCT results, we found that the duration of antibiotic treatment is significantly different in acute appendicitis with or without PCT result 24 hours after operation. The median of antibiotic treatment is 4.0 d (95% CI 3.0 - 5.0) in acute appendicitis with PCT result versus 7.0 d (95% CI 5.0 - 9.0) in acute appendicitis without PCT results (Fig-

ure 4). In the group without PCT results, physicians administered antibiotics according to clinical symptoms, WBC, CRP, and blood culture results. No death was found in this cohort study.

DISCUSSION

The appendix arises from the inferior tip of the cecum. It is a long, thin diverticulum. The average length of neonatal appendix is 4.5 cm [10]. The most common disease of the appendix is appendicitis which is common among all kinds of people. It is the most common atraumatic surgical abdominal disease in children aged 2 years or older. Due to imperfect language expression and other factors, infants with appendicitis are often misdiagnosed or diagnosis is delayed. Delay in diagnosing appendicitis increases the risk of perforation

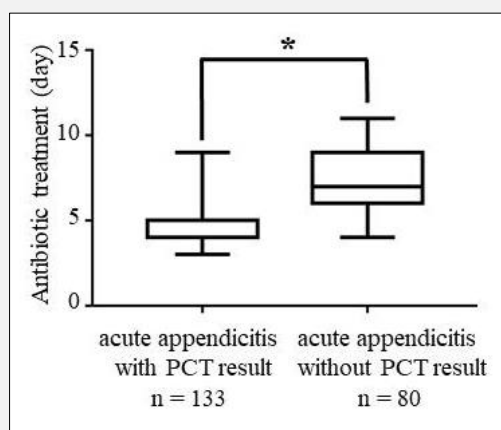


Figure 4. Antibiotic treatment time in acute appendicitis with or without PCT results.

Acute appendicitis with PCT result group, n = 133; Acute appendicitis without PCT result group, n = 80. * p < 0.05.

and complications. Complication and mortality rates are much higher in children and the elderly. Appendicitis is diagnosed in 1% - 8% of children with acute abdominal pain in emergency departments [1]. Appendiceal perforation is nearly universal in children 3 years or younger compared with less than 15% in adolescents [11]. Lymphoid follicle hyperplasia is the typical pathological change of appendicitis, often caused by fecaliths, foreign bodies, or parasites [12]. WBC count, C-reaction protein test, ultrasonography, nuclear medicine scans, and computed tomography have been used to evaluate children with suspected appendicitis in these years. Although imaging and biomarker tests are valuable adjuncts to history and examination, their limitations mean that clinical assessment is still the mainstay of diagnosis [13].

Increasing numbers of studies have indicated that uncomplicated acute appendicitis can be cured with antibiotics alone [9]. Irrational phenomena in the use of antibiotics were unsuitable opportunity for administration and extended time of drug use. Reducing the hazards of appendicitis in infants and young children is a priority problem. It is necessary to investigate for potential biomarkers for early diagnosis of appendicitis in infants and young children. In this study, we retrospectively evaluated 366 infants and young children treated in the pediatric surgery department. The white cell blood count, CRP, and PCT were classic biomarkers of inflammation [14]. The white blood cell count, CRP, and PCT were measured at the admission and 24 hours after operation in this study. The white blood cell count was used in auxiliary analysis diagnosis of all kinds of disease. In diseases related to inflammation, white blood cell count could be used to evaluate the severity of the

disease. But white blood cell count was not always an effective means in certain patients. A further analysis of different WBC count results would help in understanding the disease. Relying solely on white blood cell count to evaluate a disease is not conducive to accurate understanding of the disease. In this study, we observed that WBC did not show a significant difference between perforated acute appendicitis group and periappendiceal abscess group. However, WBC was significantly higher in perforated acute appendicitis and periappendiceal abscess group versus acute simple appendicitis group. The previous research indicated that the WBC could be used to predict both diagnosis and severity of appendicitis when analyzing the changes between neutrophils and lymphocytes.

The neutrophil-to-lymphocyte ratio (NLR) can predict acute appendicitis and distinguish between uncomplicated and complicated appendicitis [15]. WBC count, age, and duration of symptoms could be used to predict complicated appendicitis in children younger than 5 years of age with acute appendicitis. The model was mentioned as a promising method which aided in the differentiation of acute simple and complicated appendicitis [16]. As the research goes further, WBC count would be shown more and more accurate for clinical applications. CRP is a commonly assayed biomarker in diseases related to inflammation. However, CRP has two isoforms, one of which is produced locally in inflamed or damaged tissues. The other isoform is routinely produced in absence of inflammation and may have net anti-inflammatory effects [17]. CRP has an obviously wider application which is beyond inflammatory biomarker. Abnormal CRP results do not necessarily indicate inflammation progression. CRP is superi-

or to WBC in the differential diagnosis between uncomplicated and complex appendicitis [18]. In this study, our colleagues found that there were significantly increased CRP levels when compared to the acute suppurative appendicitis group or perforated acute appendicitis group with acute simple appendicitis group. When compared to the periappendiceal abscess group with acute suppurative appendicitis group or perforated acute appendicitis group, there was a significant increase in CRP levels. In the receiver operating characteristic (ROC) curve, CRP was shown to be superior to WBC for differential diagnosis of acute appendicitis and other disease pain in the right lower abdomen. Procalcitonin is a valuable biomarker that is generally elevated in bacterial infections. An increasing body of evidence supports the role of PCT to improve diagnosis of bacterial infections and to guide antibiotic therapy [19]. In this study, our colleague found that PCT was shown to be a good marker for differential diagnosis of acute appendicitis and other disease pain in the right lower abdomen. In the group without PCT results, physicians administered antibiotics according to clinical symptoms, WBC, CRP, and blood culture results. The median of antibiotic treatment in acute appendicitis with PCT results is 3 days less than acute appendicitis without PCT results.

The combination of several indicators will be more conducive to the assessment of disease status, prophylactic use of antibiotics, and control of antibiotic withdrawal time for postoperative infection. Prospective cohort studies will further enrich our conclusions.

CONCLUSION

CRP and PCT were superior to WBC for differential diagnosis of acute appendicitis and other disease pain in the right lower abdomen. PCT shows a high diagnostic ability for appendicitis in infants and young children at admission, and assists pediatricians in management of pediatric appendicitis. The combination of these biomarkers is highly recommended.

Declaration of Interest:

The authors declared that they have no conflicts of interest to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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