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Two Markers For The Prediction of Acute Complicated Appendicitis In Children: Total Serum Bilirubin And C-Reactive Protein

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ABSTRACT

Objective: *Clinical diagnosis of appendicitis is still challenging, as many of its symptoms may be nonspecific and the presentation may be variable, especially in young children. This study aims to investigate the effectiveness of total serum bilirubin (TSB) and C-reactive protein (CRP) in predicting complicated appendicitis.*

Methods: *In this study, the records of 220 patients who underwent appendectomy with the pre-diagnosis of acute appendicitis in our clinic between January-2020 and August-2021 were retrospectively reviewed. Age, gender, and CRP and TSB levels of the patients were recorded. The patients were divided into two groups according to the postoperative histopathology as acute complicated appendicitis (Group-1) and acute non-complicated appendicitis (Group-2). There were 72 patients in Group-1 and 148 patients in Group-2.*
Results: *TSB levels were high in 75% of patients in group 1 and 19% of patients in group 2. While the CRP level increased in 90% of the patients in the 1st group, it increased in 34% of the 2nd group. While the mean TSB levels were 1.16 ± 0.90 mg/dL in Group-1, they were 0.56 ± 0.35 mg/ dL in Group-2. The mean value of CRP was 77.8 ± 59.5 mg/dL and 22.9 ± 14.20 mg/dL, respectively. CRP and TSB levels were statistically significantly higher in patients with acute complicated appendicitis.*
Conclusion: *Because they are cheap, simple and readily available in almost every laboratory, CRP and TSB can be used as a clinical marker to support the diagnosis in patients with clinically suspected acute complicated appendicitis.*

Keywords: *Acute complicated appendicitis, Total serum bilirubin, C-reactive protein*

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Introduction

Acute appendicitis is the most common cause of abdominal pain requiring surgery in children. Clinical diagnosis is still challenging, given that many symptoms of appendicitis may be nonspecific and the presentation may be variable, especially in young children [1,2].

The negative appendectomy and complicated appendicitis rate can be reduced using clinical examination, laboratory test, imaging and scoring systems in patients with acute appendicitis [3]. The negative appendectomy rate is between 28-57% in children younger than 12 years of age and even higher in children younger than two years of age [4,5]. Complicated appendicitis, on the other hand, may cause higher morbidity, long-term antibiotic therapy, increased hospitalization, and higher treatment costs [6,7].

Although many inflammatory markers are used for the diagnosis of acute complicated appendicitis, there is still no specific biomarker. It has been reported that high C-reactive protein (CRP) is an important marker in differentiating acute complicated appendicitis [5,8]. Total serum bilirubin (TSB), which has recently been accepted as a marker in diagnosing complicated appendicitis, also increases in infectious diseases involving organs other than the liver [9]. Although some studies have reported a relationship between higher TSB levels and complicated appendicitis in children [10,11], in some studies, it has been reported that high TSB alone is not associated with complicated appendicitis [13,14].

The present study aims to investigate the effectiveness of TSB and CRP in predicting complicated appendicitis.

Methods

This retrospective study was conducted in the Department of Pediatric Surgery at the University of Health Sciences Diyarbakır Gazi Yaşargil Training and Research Hospital between January 2020 and August 2021. The records of 313 patients younger than 18 years who underwent appendectomy were obtained from the hospital electronic medical information system and were retrospectively examined.

Of the 313 patients, 93 (29.7%) were excluded from this study for the following reasons: Acute or chronic infectious disease, hematological disease, heart failure, liver disease, the use of anticoagulants or steroids, cholelithiasis, acquired or congenital biliary disease and determination of a histopathologically normal appendix following appendectomy (n=63).

The patient's gender, age and preoperative laboratory markers (CRP and TSB) were recorded. Normal values were defined as: TSB ≤ 1.0 mg/dL, CRP ≤ 2.0 mg/dL. Surgery reports and histopathology reports of the patients were reviewed. Negative appendectomy rates were determined. The patients were divided into two groups as complicated appendicitis (Group-1) and uncomplicated appendicitis (Group-2) according to postoperative histopathology. For both groups, the specificity, sensitivity, positive predictive value and negative predictive value of TSB and CRP were calculated.

Statistical analysis

Statistical analysis was performed using IBM SPSS 21.0 software. The measured variables were presented as mean ± standard deviation, and categorical variables were presented as number (n) and percentage (%). Both groups were compared using the chi-square test. Logistic regression analysis was performed for independent variables. The results were examined within a 95% confidence interval, and a value of $p < 0.05$ was considered statistically significant.

Results

A total of 220 patients who underwent an appendectomy in our clinic were included in the present study. The definitive diagnosis of acute appendicitis was made histopathologically in all patients. Negative appendectomy rate was 20% (n=63). Acute complicated appendicitis was detected in 72 patients (32%) who participated in this study. One hundred forty-eight patients (68%) were described as acute non-complicated appendicitis. Of the patients, 129 (59%) were male and 91 (41%) were female, with a mean age of 10.91 ± 3.55 in the complicated appendicitis group and 11.83 ± 3.82 in the non-complicated appendicitis group. There was no significant difference between the groups regarding age ($p > 0.05$).

Table 1. Laboratory data of TSB and CRP according to groups

	Non-complicated appendicitis (n=148)				*Complicated appendicitis (n=72)*				*p*-value
	Mean	SD	Min	Max	Mean	SD	Min	Max	
TSB (mg/dL)	0,56	0,35	0,31	1,07	1,16	0,90	0,44	3,03	< 0,05
CRP (mg/dL)	22,90	14,20	2,00	108,00	77,80	59,50	2,00	203,20	< 0,005

Tablo 2. Distributions of bilirubin levels

TSB	*Total Patient (n= 220)*			
	Non-complicated appendicitis (n=148)		*Complicated appendicitis (n=72)*	
	n	%	n	%
> 1,00 mg/dL	28	19	54	75
≤ 1,00 mg/dL	120	81	18	25
Total	148	100	72	100

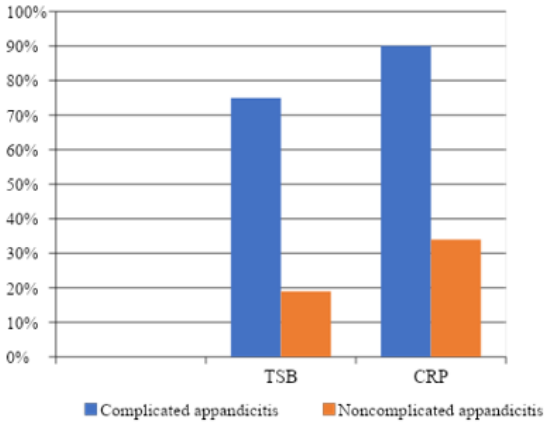
Mean TSB levels were 1.16 ± 0.90 mg/dL in patients with complicated appendicitis and 0.56 ± 0.35 mg/dL in patients with non-complicated appendicitis. The mean value of CRP was 77.8 ± 59.5 mg/dL and 22.9 ± 14.20 mg/dL, respectively. The laboratory data of the patients included in the study are presented in Table 1. The increase in TSB and CRP levels was statistically significantly higher in patients in group 1 ($p < 0.05$).

TSB value was high in 82 of 220 patients who underwent appendectomy. TSB was high in 54 (75%) of 72 patients with complicated appendicitis, while it was elevated in 28 (19%) of 148 patients with non-complicated appendicitis (Table 2). TSB levels were statistically significantly higher in patients with acute complicated appendicitis ($P < 0.05$). The CRP value increased in 65 (90%) patients with complicated appendicitis, while it increased in 50 (34%) patients with non-complicated appendicitis. The elevation of CRP levels was statistically significant, being more significant in patients with complicated appendicitis ($P < 0.005$). While the specificity of TSB was higher, the sensitivity of the CRP value was higher. The specificity, sensitivity, positive predictive value and negative predictive values of both laboratory parameters are shown in Table 3. Percentage distributions of CRP and TSB levels in both groups are shown in Figure 1. The correlation of the increase in CRP and TSB levels in the complicated appendicitis group was determined by logistic regression analysis ($p=0.003$).

Table 3. Accuracy of TSB and CRP as a marker in diagnosing complicated appendicitis

	TSB	**CRP**
Sensitivity	75%	90%
Specificity	81%	66%
PPV	66%	56%
NPV	87%	93%

Figure 1. Percentage Distributions of Laboratory Values



Discussion

The main cause of acute appendicitis is luminal obstruction of the appendix [15]. Obstruction causes include fecalitis, lymphoid tissue hypertrophy, tumors and intestinal parasites. The main organisms found in the appendix are Escherichia Coli and Bacteroides Fragilis [16,17]. With bacterial translocation caused by the obstruction of the appendix lumen, endotoxins and cytokines (such as IL-6, TNF-alpha) reach the liver parenchyma directly or via the portal vein. This situation, which results in the disruption of bilirubin excretion from the bile canaliculi, may lead to an increase in TSB levels [17].

Although acute appendicitis is a disease with a high prevalence in the normal population, the diagnosis is still challenging. Emergency surgeries may result in negative appendectomy. The negative appendectomy rate has been reported to be 15-25% in the pediatric population [18]. In our

study, the negative appendectomy rate was 20%, which is consistent with the literature. Delay in treatment causes complications, such as gangrenous, changes and perforation in the appendix. The acute complicated appendicitis rate in children has been reported to be 23-53% [19]. In our study, the complicated appendicitis rate was 32%, which is consistent with previously published studies.

The findings suggest that there is a relationship between increased TSB level and acute appendicitis and its complications [20,21]. The risk of perforation increases threefold in patients with TSB levels higher than 1 mg/dL [12].

It has been suggested to use TSB elevation as a diagnostic tool for appendiceal perforation and severe intra-abdominal infection leading to sepsis [22]. In our study, TSB levels were high in patients with perforated appendicitis. In some studies, it has been stated that increased TSB levels alone cannot be used in the differential diagnosis of complicated appendicitis [13,14,23]. The results of our study suggest that increased TSB level together with physical examination findings supporting appendicitis may predict perforated appendicitis in patients with right lower quadrant pain without liver disease.

CRP levels are higher in patients with complicated appendicitis compared to acute appendicitis [5,24-28]. In our study, the CRP value was higher in patients with complicated appendicitis, consistent with the literature. Our results support that patients with complicated appendicitis have more inflammation and higher serum CRP levels. The CRP level is used to support clinical data in making an operation decision [26-28]. It is stated that CRP elevation is an important marker in differentiating complicated appendicitis [5,8]. The CRP value increases more in children with high inflammatory response, such as complicated appendicitis [24,25]. In a published study, [29] it was stated that CRP elevation was superior to TSB elevation in the estimation of complicated appendicitis. In our study, it was observed that there was a correlation between CRP and TSB elevation in complicated appendicitis. Our results showed that the increase of CRP and TSB was not superior to each other in the differential diagnosis of complicated appendicitis. We think that the elevation of CRP and TSB may support complicated appendicitis.

Limitations of the study are that it is single-centered and retrospective. TSB and CRP are inexpensive, simple, and readily available in any laboratory. TSB and CRP can be used as clinical markers to support the diagnosis in patients with suspected complicated appendicitis. Multicenter prospective studies with larger patient populations are needed to confirm the diagnostic value of TSB and CRP in the differential diagnosis of complicated appendicitis.

Declarations

Funding: There is no financial support and sponsorship

Conflicts of interest/Competing interests: The authors declare that there is no conflict of interest.

Ethics approval: The Ethics Committee for Clinical Research in the University of Health Sciences Diyarbakır Gazi Yaşargil Training and Research Hospital (2021/953).

Availability of data and material: All data of the study is available for re-assessment.

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