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The clinical value of IMA and SCUBE1 in the diagnosis of acute appendicitis in children

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ABSTRACT

Objectives. This study aims to show the clinical value of ischemia-modified albumin (IMA) and Signal Peptide, Complementary C1r/C1s, Uegf and Bmp1–Epidermal Growth Factor Like Domain Containing 1 (SCUBE1) protein in pediatric appendicitis. *Methods*. Eighty-one pediatric patients hospitalized in the pediatric surgery ward with acute appendicitis and a control group of 62 pediatric patients with unspecific abdominal pain were included in this prospective case-control study. Thirty-nine patients whose pathology specimens confirmed acute appendicitis made up the final appendicitis group. *Results*. Patients with appendicitis had higher IMA ($p<0.001$) and SCUBE1 ($p<0.001$) levels than the control group. In receiver operating characteristic (ROC) analysis, areas under the curve (AUC) were 0.991 (sensitivity=97.4%, specifity=100%, positive likelihood ratio (+LR) infinity, negative likelihood ratio (-LR)=0.03, positive predictive values (+PV)=100%, negative predictive value (-PV)=98.3% for IMA and 0.803 (sensitivity = 89.7%, specificity =64.5%, +LR=2.53, -LR=0.16, +PV=61.4%, -PV=90.9%) for SCUBE1. *Conclusions*. The present study shows that IMA may be a reliable marker for a more accurate diagnosis of appendicitis. SCUBE1 can be used to exclude diagnosis if used in combination with other laboratory and clinical data.

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Introduction

Acute appendicitis (AA) is one of the common surgical emergencies in children. The lifetime risk of developing appendicitis is 7-8%, with higher incidences at younger ages [1]. During decision-making process for appendectomy, anamnesis, physical examination, laboratory tests, imaging methods, and clinical decision rules such as Alvarado score are used [2]. However, clinical symptoms, physical examination findings, and radiological characteristics are specific neither for the grade of the disease nor for perforation. In addition, radiological tests have their limitations such as accessibility, high costs, and radiation exposure, especially in the pediatric population. In a recent study that reviewed pediatric literature, the negative appendectomy rates have varied greatly, from 1% to 40% [3].

Many biomarkers have been studied in the diagnosis of acute appendicitis, such as White blood cell (WBC) count, Absolute neutrophil count (ANC), C-reactive protein (CRP), Erythrocyte Sedimentation Reaction, Tumor Necrosis Alpha, Alpha 1-Glycoprotein, leukocyte elastase complex, Interleukins, granulocyte colony-stimulating factor, tissue inhibitor metalloproteinase-1, serum amyloid A, plasma calprotectin, D-Dimer, and procalcitonin. However, none of these tests have been proved to be precise enough in diagnosing acute appendicitis individually [2,4].

Ischemia modified albumin (IMA) has recently become a prominent molecule regarding the role of ischemia in the pathophysiology of appendicitis. Hypoxia, acidosis, free radical damage, and membrane degradation cause a structural change in albumin. IMA is a marker formed after damage in the N-terminal region of albumin. The altered N-terminus can no longer bind transition metals, such as cobalt. The causes of the increases in IMA have been shown to be endothelial or extracellular hypoxia, acidosis, and free oxygen radicals [5]. IMA is a well-known

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biomarker of ischemia in other diseases, including stroke, acute mesenteric ischemia, and acute coronary syndrome [6-9]. It is also an indicator of oxidative stress, which plays an essential role in the pathogenesis of AA [10-12].

Studies have investigated the diagnostic value of mean platelet volume (MPV) and platelet distribution width (PDW) in acute appendicitis [13]. Signal Peptide, Complementary C1r/C1s, Uegf, and Bmp1-Epidermal Growth Factor Like Domain Containing 1 (SCUBE1) protein is a biomarker that is released from the platelet surface as a result of platelet aggregation. Elevations is SCUBE1 levels have been demonstrated in acute coronary syndrome, ovarian torsion, acute appendicitis, ischemic stroke, and acute mesenteric stroke [14-17].

The study's primary aim was to compare IMA and SCUBE1 values between pediatric patients with pathologically confirmed acute appendicitis and nonspecific abdominal pain.

Materials and Methods

Patient Selection

The study was approved by the Clinical Researches Ethics Committee (2017/108). Eighty-one patients admitted to our hospital's Emergency Department (ED) with abdominal pain and were hospitalized in our pediatric surgery wards with the presumptive diagnosis of AA after anamnesis, physical examination, laboratory tests, and ultrasonography was included in the study. Ten patients were excluded from the study due to missing laboratory tests. Fifty-four of the hospitalized patients were operated. Thirty-nine patients whose pathology results confirmed acute appendicitis were included in the study.

The control group consisted of 62 pediatric patients who applied to the ED with unspecific abdominal pain within the study period, for who the diagnosis of acute appendicitis was excluded by anamnesis, physical examination, laboratory tests, and ultrasonography.

The informed consent form was taken from the individuals and their families in the study and control groups.

Collection and storage of blood samples

Venous blood samples taken from the patients routinely during emergency service admissions were taken into anticoagulant-free biochemistry tubes under CLSI GP41-A6 guidelines. Blood samples for serum were centrifuged at 4000 rpm for 10 minutes after coagulation was completed. After the centrifuge, routine tests requested from the patients were studied immediately and the excess serum samples were kept at -80 ºC until the study day.

Biochemistry and hemogram measurement

Serum biochemistry parameters were studied in the Abbott Architect c16000 autoanalyzer which makes spectrophotometric measurement by using commercial kits. Hemogram was studied from complete blood by using flow cytometry method in Sysmex XN-1000 autoanalyzer.

Serum IMA Determination study protocol

Ischemia modified albumin (IMA) determination was made according to cobalt-albumin binding (CAB) method. According to this method, 3 µL 0.5% CoCl2x6H2O and 131.8 µL of NaH2PO4 with 7.4 of 75 mM pH were put on 40 µL serum sample and vortexed and left for incubation at room temperature for 10 minutes. Following incubation, 5.2 µL and 20 µL 0.9 % NaCl from 7.5 mg/mL DTT was added on the samples and left for incubation for 2 minutes. Water was put instead of DTT as blind sample. The results were read at 470 nm and given as absorbance.

SCUBE 1 Determination ELISA Kits Study Protocol

Serum SCUBE1 was measured with sandwich immunoassay (Enzyme-Linked Immunosorbent Assay (ELISA)) method. Commercially purchased Human SCUBE 1 (cat no: E-EL-H5405) ELISA kits were used in analyses.

Evaluation of pathological preparations

In our study, all of the preparations were evaluated and reported by a senior faculty pathologist blinded to test results. According to pathology results, appendicitis groups were classified as acute appendicitis - Stage 1, acute suppurative appendicitis - Stage 2, acute gangrenous appendicitis - Stage 3 and perforated acute gangrenous appendicitis - Stage 4.

Statistical Analysis

The normal distribution of continuous data was tested with the Kolmogorov Smirnov test, Histogram, and Q-Q plots. Parametric data were reported as mean (X) and standard deviation (SD), nonparametric data were reported as median and interquartile range [IQR (25%-75%)], and categorical variables were reported as number and frequency (%).

Student t test was used to analyze continuous variables as in the comparison of IMA and SCUBE1 levels between pathologically confirmed acute appendicitis and healthy control groups. Pearson's Chi-square test was used to compare categorical variables. Receiver operating characteristic (ROC) curve analysis was conducted for continuous variables and the areas under the curve (AUC) were calculated.

Cut-off points were determined using the Youden index and diagnostic value criteria were calculated with 95% confidence intervals. Significance was accepted as $p < 0.05$ in statistical analysis. All analyses were made with R based Jamovi statistical program (version 1.1.5.0; https://jamovi.org) and Statistical Package for Social Sciences (SPSS version 26).

Results

In this study, 69.2% (n=27) of the patients in the appendicitis group and 51.6% (n=32) of the patients in the control group were male. The mean age of the appendicitis group was 11.5±4.2 years, while the mean age of the control group was 10.8±3.9 years. Age and gender were not significantly different between the appendicitis group and the control group (p=0.398). Table 1 shows the comparison of demographic data and laboratory data between the patients in the appendicitis group and the patients in the control group.

Table 1. Comparison of demographics and laboratory data between the appendicitis and the control groups

Variables		n	Mean	±SD	p value
Age	Appendicitis	39	11.5	4.2	0.398
	Control	62	10.8	3.9	
	Total	101	11.1	4.1	
Gender (Male)	Appendicitis	27	69.2%	-	0.080
	Control	32	51.6%	-	
WBC (cells /mm^3)	Appendicitis	39	16458.7	5181.9	<0.001
	Control	60	8106.5	1527.6	
ANC (cells /mm^3)	Appendicitis	39	12531.9	5522.1	<0.001
	Control	60	4150.5	1332.5	
IMA (AbsU)	Appendicitis	39	0.86	0.09	<0.001
	Control	57	0.57	0.06	
SCUBE1 (ng/ml)	Appendicitis	39	25.46	8.59	<0.001
	Control	62	14.68	8.88	

WBC: White Blood Count, ***ANC:*** Absolute Neutrophil Count, ***IMA:*** Ischemia-modified Albumin, ***SCUBE1:*** Signal Peptide, Complementary C1r / C1s. Uegf and Bmp1 - Epidermal Growth Factor Like Domain Containing 1 protein, ± ***SD:*** Standard Deviation

The data of 39 patients whose pathological examinations were compatible with acute appendicitis were determined as 15 (27.8%) patients Stage 1, 20 (37.0%) patients Stage 2, 2 (3.7%) patients Stage 3, and 2 (3.7%) patients Stage 4. IMA and SCUBE1 measurements of the appendicitis group were significantly higher than those of the control group (p<0.001). The diagnostic values of statistically significant parameters were evaluated using ROC analysis. In the appendicitis group, AUC was above 0.900 for WBC, ANC, and IMA and above 0.800 for SCUBE1. ROC curves for laboratory data are given in Figure 1.

Cut-off values for IMA and SCUBE1 were calculated from the respective ROC curves. The cut-off value of 0.69 AbsU for IMA had a sensitivity of 97.4% and a specificity of 100% (AUC=0.991; 95% CI=0.973-1.000; p<0.001). For SCUBE1, the cut-off value of 15.94 ng/ml had a sensitivity of 89.7% and a specificity of 64.5% (AUC=0.803; 95% CI=0.716-0.890; p<0.001). While a 98.3% (89.1-99.7) negative predictive value was found for IMA, this rate was 90.9% (78.3-97.5) for SCUBE1, 95.2% (86.7-99.0) for WBC, and 93.7% (84.5-98.2) for ANC. Table 2 shows areas under the curve (AUC), cut-off values, sensitivities, specificities, positive predictive values (+PV), negative predictive values (-PV), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and p values in the prediction of AA.

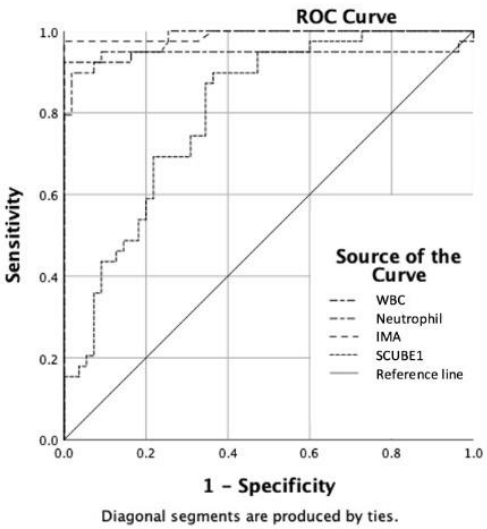

Figure 1. Receiver operating characteristic (ROC) curve analyses of important parameters for the diagnosis of appendicitis (WBC, ANC, IMA and SCUBE1)

Table 2. Diagnostic accuracy metrics of WBC, ANC, IMA, and SCUBE1 in diagnosis of acute appendicitis

Metric	WBC	ANC	IMA	SCUBE1
AUC ±SE (95% CI)	0.985±0.010 (0.965-1.000)	0.942±0.035 (0.873-1.00)	0.991±0.009 (0.973-1.000)	0.803±0.044 (0.716-0.890)
Cut off value	10760 cells/mm³	6960 cells /mm³	0.69 AbsU	15.94 ng/ml
Sensitivity (95 % CI)	92.3 (79.1-98.4)	89.7 (75.8-97.1)	97.4 (86.5-99.9)	89.7 (75.8-97.1)
Specificity (95 % Cl)	100.0 (94-100)	98.3 (91.1-99.9)	100.0 (93.73-100)	64.5 (51.3-76.3)
+PV (95 % *Cl*)	100.0 (90.3-100)	97.2 (85.5-99.9)	100.0 (90.1-100)	61.4 (47.6-74.0)
-PV (95 % Cl)	95.2 (86.7-99.0)	93.7 (84.5-98.2)	98.3 (89.1-99.7)	90.9 (78.3-97.5)
+LR (95 % Cl)	Inf	53.8 (7.69-377.1)	Inf	2.53 (1.78-3.6)
-LR (95 % Cl)	0.08 (0.03-0.24)	0.10 (0.04-0.25)	0.03 (0-0.21)	0.16 (0.06-0.41)
Accuracy (95 % Cl)	96.9 (91.4- 99.4)	94.9 (88.6-98.3)	98.9 (94.3-99.9)	74.3 (64.6-82.4)
p value [a]	< 0.001	< 0.001	< 0.001	< 0.001

WBC: White Blood Count, ***ANC:*** Absolute Neutrophil Count, ***IMA:*** Ischemia-modified Albumin, ***SCUBE1:*** Signal Peptide, Complementary C1r / C1s, Uegf and Bmp1 (CUB)- Epidermal Growth Factor (EGF) Like Domain Containing 1 protein, ***AUC:*** Area Under Curve, ***CI:*** Confidence Interval, ***LR:*** Likelihood Ratios, ***PV:*** Predictive Values, ***İnf:*** İnfinity, a: The values in groups were calculated by using ROC curve.

Discussion

Appendicitis is an important cause of abdominal pain in children however misdiagnosis rates are high despite diagnostic advances [3].

Previously, a large number of biomarkers have been examined as indicators of appendicitis. Phospholipase A2, serum amyloid A, interleukins, cytokines, bilirubin, procalcitonin, and D-dimer have been investigated for diagnosis, and the authors indicated their lower diagnostic accuracy [2,4,18].

Regardless of age, WBC and ANC are the most frequently used diagnostic laboratory tests in diagnosing appendicitis in children admitted to the ED with acute abdominal pain. An increased WBC count rises the likelihood of appendicitis; however, a normal WBC does not exclude the diagnosis [19]. While a normal WBC count has a 95.6% negative predictive value in children younger than four years of age, the negative predictive value for children between 4 and 12 years of age is 89.5%. The negative predictive value of a low or normal WBC count is 92% among adolescents [20]. In other studies, in which preoperative WBC and ANC values were examined in appendicitis cases, WBC and ANC levels were significantly higher when compared with control groups ($p<0.001$) [21,22]. In Sengul et al.'s study [23], AUC were 0.708 and 0.699, cut-off values of 10600 cells/mm³ and 8170 cells/mm³ were calculated with sensitivities of 72.2% and 70.7% and specificities of 60.0% and 73.3% for WBC and ANC, respectively. Sevinç et al. [24] analyzed 3.392 acute appendicitis cases and calculated a WBC cut-off value of 11.900 cells/mm3 (sensitivity 71.2%; specificity 67.2%).

In our study, mean WBC (cells/mm³) counts were 16458.7±5181.9 and 8106.5±1527.6 in the appendicitis group and control group ($p<0.001$). The following values were determined in the evaluation of the ROC curve for WBC in the prediction of appendicitis cases; Cut-off=10760 cells/mm³, AUC=0.985, sensitivity=92.3%, specificity=100%. Mean ANC (cells/mm³) values were 12531.9±5522.1 and 4150.5±1332.5 in the appendicitis and control group, respectively, and this difference between the groups was statistically significant ($p<0.001$). The following values were determined in the evaluation of the ROC curve for ANC in the prediction of appendicitis cases; Cut-off=6960 cells/mm³, AUC=0.942, sensitivity =89.7% and specificity=98.3%. In the present study, in parallel with the literature, WBC and ANC values in the appendicitis group were significantly higher compared with the control group.

Free radical damage in AA increases IMA levels which can be used in the diagnosis of appendicitis [5,11]. There are few studies in the literature evaluating IMA levels in appendicitis [10,25,26]. Yeniocak et al. [27], in their study, stated that serum IMA levels in patients who applied to the ED with the complaint of abdominal pain could be an indicator of surgery or a clue of complicated cases, especially in terms of acute appendicitis and ovarian pathologies.

In their study on 65 patients who underwent appendectomy and 30 control patients, Dumlu et al. [28] evaluated the two groups for IMA levels and found a mean IMA level of 0.64±0.09 AbsU in appendicitis cases and a mean level of 0.31±0.09 AbsU in controls ($p<0.001$). The studies conducted on IMA levels of pediatric patients are limited [11,12]. In a study by Nazik et al. [11], the mean IMA level was 0.56±0.1 AbsU in appendicitis cases and 0.33±0.1 AbsU in controls ($p<0.001$). In their ROC analysis, a cut-off of 0.445 AbsU was calculated; AUC was 0.99; sensitivity was 96.7% and specificity was 99.7%.

In our study, mean IMA values were 0.86±0.09 AbsU and 0.57±0.06 AbsU, in the appendicitis and the control group, respectively ($p<0.001$). For IMA, the calculated cut-off point was 0.69 AbsU; AUC was 0.991; sensitivity was 97.4%, and specificity was 100%. In the present study, the mean IMA value was significantly higher in appendicitis patients. Based on these findings, IMA may perform better than other inflammatory markers in predicting appendicitis cases.

The secondary aim of this study was to find out the value of SCUBE1 as a diagnostic marker in AA. SCUBE1 was initially shown to be an inflammatory marker and the only known source of SCUBE1 was endothelial cells. Tu et al. [29] showed higher secretion rates of SCUBE1 from activated platelets. In a study conducted by Sonmez et al. [17] on 47 adult AA patients and 43 controls, the difference between SCUBE1 levels in the patient and control groups was not statistically significant ($p=0.209$). However, SCUBE1 was significantly higher in the CRP positive group ($p=0.048$).

In our study, mean SCUBE1 values in the appendicitis and the control group were 25.46±8.59 ng/ml and 14.68±8.88 ng/ml, respectively, and this difference was statistically significant ($p<0.001$). For SCUBE1, the calculated cut-off point was 15.94 ng/ml, AUC was 0.803, sensitivity was 89.7%, specificity was 64.5%, positive LR was 2.53, and negative LR was 0.16. In the light of these data, with its high negative predictive value, moderate negative LR, and moderate to high sensitivity, SCUBE1 alone does not perform sufficiently to exclude acute appendicitis. Likewise, it cannot be used for diagnosing acute appendicitis due to its moderate positive predictive value, specificity, and positive LR rates. Hence, a combination of SBUBE1 and other laboratory and clinical findings may perform better for the diagnosis of AA. To the best of our knowledge, the present study is the first of its kind on the diagnostic value of SCUBE1 in AA in the pediatric age group.

Our study's most important limitation is that it is single centered, and the sample size is small. However, we believe that this did not have a negative effect on the diagnostic value of biomarkers in AA diagnosis, which is the primary aim of our study. The most important result of this limitation is the fact that we could not examine the significance of biomarkers in understanding the severity of acute appendicitis since the number of cases was insufficient in pathological stage sub-groups.

Conclusions

In pediatric patients with abdominal pain, WBC, ANC, and IMA levels might be used in the diagnosis of acute appendicitis. Additionally, SCUBE1 might be useful in ruling out acute appendicitis. However, the role of these biomarkers is not superior to the clinical assessment of patients. Therefore, emergency physicians and surgeons should use them in combination with other clinical findings in the decision-making of acute appendicitis.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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