DOI: http://10.5281/zenodo.6857498

JOURNAL OF CLINICAL TRIALS AND EXPERIMENTAL INVESTIGATIONS

JCTEI

ORIGINAL ARTICLE

Diagnostic Value of The Ischemia Modified Albumin and Pentraxin 3 In Pediatric Appendicitis: A Meta Analysis

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Specialty section:
This article was submitted to Pediatric Surgery section

Received: 18 June 2022
Revised: 5 July 2022
Accepted: 10 July 2022
Published: 20 July 2022

Abstract

Objective: In this meta-analysis, we aimed to review the diagnostic value of pentraxin 3 (PTX3) and ischemia-modified albumin (IMA) biomarkers in pediatric appendicitis.

Method: Studies focusing on the value of PTX3 and IMA in the diagnosis of appendicitis were searched related to the PubMed database. Only randomized prospective clinical trials were included in this study.

Results: After the screening, 6 articles based on the diagnostic value of IMA in appendicitis and 5 articles on the diagnostic value of PTX3 were reviewed. A total of 5 studies were included. The data of the 385 patients were reviewed. Sensitivity of PTX3 was 73-92% and specificity 88-100%, while IMA sensitivity was 89-96.7% and specificity was 26-99.7% in acute appendicitis.

Conclusion: Although the results of the present study indicate that PTX3 and IMA can be shown as biomarkers in the differential diagnosis of acute abdomen, further study is needed to determine the cut-off value.

Keywords: Ischemia Modified Albumin, Pentraxin 3, Pediatric, Appendicitis

Introduction

Acute appendicitis is a common disease requiring emergency surgery in both children and adults [1]. Its incidence is approximately 1 in 1000 in the United States and is slightly more common in men than in women [2]. Today, there are still some difficulties in many aspects, from the diagnosis of AA to the treatment [2]. Although there has been a significant decrease in the rate of negative appendectomy with the widespread use of imaging techniques, this rate is estimated to be around 5-15% [3]. The lack of a definitive biomarker for the diagnosis of AA has led surgeons to resort to indirect methods and improve some scores.

Most surgeons routinely use ultrasound and almost all laboratory-studied biochemical parameters such as WBC, CRP, neutrophil count [3]. Although the sensitivity and specificity of Computed tomography (CT) and Magnetic Resonance (MR) imaging are 90-95%, the radiation effects of CT, the lack of MR in every center, the long duration of the procedure, the difficulty of accessing MR and expensive remained in the background for reasons such as recently, Neutrophil lymphocyte ratio [4], platelet lymphocyte ratio [5], MPV [6], bilirubin levels [7], parameters have been used in the diagnosis of AA. However, almost none of these parameters were able to reduce the negative appendectomy rate to zero and led to the search for new biomarkers. Pentraxin 3 and IMA are two important acute inflammatory phase reactants that have been investigated recently.

Pentraxins: Pentraxin (PTX) is a family of glycoproteins derived from the Greek words “penta = five” and “ragos = fruit”, produced in response to inflammatory mediators, particularly interleukin 6 (IL-6) and Tumor Necrosis Factor alpha (TNF-α) [8]. They are acute phase reactants consisting of five subunits and are produced from hepatocytes. C-reactive protein (CRP) is a short pentraxin that is studied in almost every laboratory and is known and frequently used by all physicians. The most important member of the long pentraxins is PTX3, which was discovered in 1990 [9]. CRP rises within 48 hours, especially with the onset of inflammation [10]. Could the blood level of PTX3 rise within hours, shortly after the onset of inflammation [10], be used as a potential biomarker in the diagnosis of acute appendicitis? brought the question to mind.

Molecular and Biochemical structure of Pentraxin 3: Although PTX3 is functionally similar to CRP, it differs from CRP in many aspects [10]. PTX3 is a glycoprotein consisting of 381 amino acids encoded by the TNF14 gene [11]. The PTX3 gene is located in band 25 on the q arm of the third chromosome and contains 3 exons [11]. PTX3 activates all three pathways of the complement system [10].

Pentraxin 3 and Appendicitis: A search of the PubMed database using the keyword "Pentraxin 3" resulted in 1480 publications. Seven studies focusing on the diagnostic value of PTX3 in the diagnosis of acute appendicitis were reviewed. Only studies involving the pediatric age group were included in this article.

Duman et al. evaluated the data of 70 pediatric patients in a prospective study conducted between June 2018 and April 2019. The patients were divided into three groups; group1: histologically confirmed acute appendicitis group (n= 37 patients), group2: group followed by suspected AA and discharged without treatment (n= 25 patients), group3: group consisting of healthy individuals

(n=8 patients) [12]. PTX3, at the cut-off level of 9.31 ng /ml, had a Positive Predictive Value (PPD) higher than CRP by 90%. PTX3, CRP and WBC their predictive power and characteristics are summarized in table 1 [12].

Predictive Value (NPD), sensitivity and specificity values of 1.30 ng /ml of PTX at the time of admission of appendicitis patients were found to be 100%, 60%, 75%, and 100%, respectively (table.2) [13].

	Group1 (n=37)	Group2 (n=25)	Group3 (n=8)	P
WBC (cells/µL)	16108±3684	12004±6387	7125±1044	<0.001
CRP (mg/L)	31.64±38.50	7.65±15.98	0.57±0.59	<0.001
PTX3 (ng /ml)	14.35±7.32	6.88±2.93	4.33±0.34	<0.001

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
WBC	12750	83.78	76	83.78	76
CRP	5,65	72.97	84	87.1	67.74
PTX3	9,31	72.97	88	90	68.75

Table 1: *The Results of Duman et al, (Characteristics and Results)*

**PPV: Positive Predictive Value, NPV: Negative Predictive Value*

Ateş et al, evaluated the data of 55 pediatric patients, 15 of whom were in the control group, in a prospective study conducted between June 2018 and April 2019. The patients were divided into 3 groups: Group 1: group without signs of inflammation (control, n= 15 patients), Group 2: non-perforated simple appendicitis group (n= 25 patients), Group 3: Perforated appendicitis group (n= 15 patients) patients. It was stated that the PTX3 level was significantly higher in groups 2 and 3 compared to group 1 ($p<0.01$), but there was no difference between group 2 and group 3 ($p=0.114$). PPD, Negative

Oztan et al. reviewed the results of 88 pediatric patients in a prospective study conducted between February 2018 and July 2018. The patients were divided into 3 groups. Group1: The control consisting of 28 patients consisted of healthy individuals. Group2: It consisted of 26 patients who were admitted with non-specific abdominal pain and discharged after 24-48 hours, and who were called 2 weeks later to confirm that they did not have AA. Group3: 34 patients who underwent appendectomy. When the PTX3 levels were compared with the first and second groups, it was found to be significantly higher

in the third group (p<0.05). 5.6 ng /ml PTX3 level was found to have the maximum specificity and sensitivity in the diagnosis of AA: 90.7% and 91.8%, respectively (table 3) [14].

	Group1 (n=15)	Group2 (n=25)	Group3 (n=15)	G2 and G3 vs G1 (P)	G2-G3 (P)
WBC (cells/µL) (mean)	6950±1340	16710±5100	15760±5540	<0.001	0.796
CRP (mg/L) (median)	0,9	6,30	128,6	<0.001	<0.001
PTX3 (ng /ml) (median)	1,01	20,68	1,46	<0.001	0.114

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
WBC	8465	92.5	93.3	97	82
CRP	3,80	80	93	96	63
PTX3	1,30	75	100	100	60

Table 2: *The Results of Ateş et al, (Characteristics and Results)*

**PPV: Positive Predictive Value, NPV: Negative Predictive Value*

Ischemia Modified Albumin (IMA): Albumin is synthesized from the liver and is a protein consisting of 585 amino acids (aa) [15]. Half-life of IMA is 20 days [16]. Albumin binds molecules such as bilirubin, drugs, some hormones, and fats and is a molecule responsible for its transport in the blood. The N-terminal end of albumin binds heavy metals such as nickel, copper and cobalt [17]. Exposure of albumin to hypoxia, free oxygen radical damage, and heavy metals results in a modified N-terminal end and a reduced capacity to bind these metals [17]. Ischemia to this modified version of the album It is called Modified Albumin (IMA) [18] IMAs were identified in the late 1990s. In the early stages of ischemia, serum levels rise in as little as 10 minutes [19]. In this respect, it has started to be used frequently, especially in acute coronary syndromes and ischemic events [20].

IMA and Appendicitis: A search of the Pubmed database using the keyword "ischemia modified albumin" yielded 622 publications. Seven studies focusing on the diagnostic value of IMA in the diagnosis of acute appendicitis were reviewed. Only studies involving the pediatric age group were included in this article.

Nazik et al. evaluated the data of 63 pediatric patients in a prospective study conducted between May 2015 and November 2015. The patients were divided into three groups; group1: acute appendicitis (n=30 patients), group2: control group (n=33

patients). IMA, 0.445 AbsU At the cut-off level, it was found to have maximum specificity and sensitivity in the diagnosis of AA: 99.7% and 96.7%, respectively [21]. Patients with inflammatory biomarker levels are summarized in table 4 [21].

Discussion

Although conservative treatment methods are used in acute appendicitis, the standard treatment is surgical intervention. Patients who are diagnosed in the early period and undergo appendectomy recover without any problems. Perforation of the appendix in children is more common than adults [1, 23]. Incorrect or late diagnosis may cause appendiceal perforation. In one study, 7% of patients developed appendiceal perforation within 24 hours of the onset of symptoms [24]. Appendicitis causes a systemic inflammatory response, leading to elevated blood levels of inflammatory biomarkers [25]. Biomarkers such as CRP and WBC are used by many surgeons. In the literature, sensitivity of WBC (62-97%) [14, 25-27], specificity (53-80%) [14, 25-28], and sensitivity of CRP (35-86%) [25, 26, 29-31], specificity has been reported as (57-93%) [25, 26, 29-31]. Previous studies have reported that CRP is a more valuable biomarker

	Group1 (n=28)	Group2 (n=26)	Group3 (n=34)	P
WBC (cells/µL)	7971 ± 1926	13,450 ± 6070	16,100 ± 4332	<0.05
CRP (mg/L)	0.88 ± 0.68	17.41 ± 34.77	42.09 ± 15.80	<0.05
PTX3 (ng /ml)	1.09 ± 0.97	4.07 ± 1.55	12.82 ± 4.96	<0.05

	Cut-off value	Sensitivity (%)	Specificity (%)
WBC	12700	85.3	79.6
CRP	5	82.4	81.5
PTX3	5,60	91.8	90.7

Table 3: *The Results of Oztan et al, (Characteristics and Results)*

Ulusoy et al. evaluated 109 pediatric patients with an appendicitis score (PAS) greater than 7. They noted that the level of IMA was significantly higher in the appendicitis group compared to the control group ($p<0.001$). IMA levels were found to be higher in the complicated appendicitis group than in the control group and negative appendectomy group ($p<0.001$), but there was no difference with the uncomplicated appendicitis group ($p=0.249$). The IMA was found to have maximum specificity and sensitivity in the diagnosis of appendicitis at a cut-off value of 20.60 ng /ml: 26% and 89%, respectively [22].

in complicated appendicitis than in acute

	Group1 (n=30)	Group2 (n=33)	P
WBC (103/µL)	12.12±4.8	7.73±2.1	0.000
CRP (mg/ dL)	29.63±41.3	7.45±9.2	0.007
IMA (AbsU)	0.56±0.1	0.33±0.1	0.000

	Cut-off value	Sensitivity (%)	Specificity (%)
WBC	8,87	70,00	69.7
CRP	5,20	73.3	75.8
IMA	0.445	96.7	99.7

Table 34 *The Results of Nazik et al, (Characteristics and Results)*

appendicitis [14, 29, 32, 33]. Although CRP is helpful in the diagnosis of appendicitis as an acute phase reactant, its increase in 24-48 hours is more important in the diagnosis of complicated appendicitis rather than acute appendicitis [28]. Although WBC elevation is significant for appendicitis, appendicitis cases with normal WBC levels are also encountered in children. WBC is not an excellent marker for diagnosing or excluding appendicitis from this point of view. WBC may also be elevated in conditions such as gastroenteritis, infection, mesenteric ischemia [28].

PTX3 is an acute phase reactant from the pentraxin group. It is more valuable than CRP with its ability to rise within hours. In a prospective study by Duman et al, PTX3 was found to be a more valuable marker than CRP with a positive predictive value of 90% [12]. Similar results were found in the study by Oztan et al. with a positive predictive value of 90.7% [14]. On the other hand, in the study of Ateş et al., both the specificity and positive predictive value of PTX were noted as 100% [13]. This was thought to be due to the insufficient number of patients included in the study and the diversity of the population.

IMA is a protein that rises within minutes in the presence of ischemia [19]. It is a marker whose blood levels increase in ischemic events such as acute coronary syndrome [34], acute mesenteric ischemia [35], incarcerated hernia [36], testicular torsion [37], and ovarian torsion [38]. Although there are limited studies in neonates recently, it is thought to be a potential biomarker that can be used to predict the degree of ischemia and necrosis in patients with necrotizing enterocolitis (NEC), and to stage NEC together with PTX3 [39].

There are few studies in the literature showing that IMA is elevated in acute appendicitis cases [34, 40-42]. Nazik et al. noted the specificity of IMA as 99.7% and sensitivity as 96.7% in the diagnosis of AA [21]. Ulusoy et al. reported that the sensitivity of IMA was 89% in patients with appendicitis [22].

Ulusoy et al. selected patients from the group with a pediatric appendicitis score >7 [22]. It was thought that both the population in which the patients were selected and the fact that IMA was studied as AbsU in one study and as ng / ml in the other study, caused the results of the two studies to be different.

In conclusion, in this meta-analysis, the sensitivity of PTX3 in the diagnosis of acute appendicitis was 73-92%, the specificity was 88-100%, while the sensitivity of IMA was 89-96.7%, and the specificity was 26-99.7%. Although it was conducted with a limited number of patients, the results of this study show that IMA and PTX3 can be a biomarker that can be used for the diagnosis of appendicitis in childhood period. Since existing studies are insufficient to determine the cut-off value for these two markers, studies with larger numbers of patients are needed.

Conflict of interest:

The authors report no conflict of interest.

Funding source:

No funding was required.

Ethical approval:

Manuscript: Meta Analysis

Contributions

Research concept and design: **DF, ACB, SIA**
Data analysis and interpretation: **DF, SIA**
Collection and/or assembly of data: **TR, HAT**
Writing the article: **TR, SY, HAT, SIA**
Critical revision of the article: **SY, DF, ACB**
Final approval of the article: **DF, SIA**

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