Journal of
Babol University of Medical Sciences
JBUMS
e-ISSN: 2251-7170 p-ISSN: 1561-4107

Diagnostic Value of C-Reactive Protein and Interleukin-6 in Prevention of Negative Appendectomy

H. Layegh (MD)[1], T. Teimour Nezhad (MD)[1], M. S. SeyedSadeghi (MD)[*1]

1.Department of Surgery, School of Medicine, Ardabil University of Medical Sciences, Ardabil, I.R.Iran.

***Corresponding Author: M. S. SeyedSadeghi (MD)**
Address: Fatemi Hospital, Ardabil University of Medical Sciences, Ardabil, I.R.Iran.
Tel: +98 (45) 33232520. **E-mail:** dr.mirsalimseyedsadeghi@gmail.com

Article Type
Research Paper

Received:
Mar 17th 2023
Revised:
May 7th 2023
Accepted:
May 31st 2023

ABSTRACT

Background and Objective: Acute appendicitis is one of the common reasons for abdominal surgery in any age group, and most cases are rarely diagnosed, which causes unnecessary surgery (negative appendectomy). The aim of this study is to determine the diagnostic value of C-reactive protein (CRP) and interleukin-6 (IL-6) in the prevention of negative appendectomy.

Methods: This cross-sectional study was conducted on 208 patients with acute abdominal surgery and primary diagnosis of acute appendicitis at Fatemi Hospital in Ardabil in a period of 6 months. C-reactive protein (CRP) and interleukin-6 (IL-6) levels were measured before surgery in all patients. Patients were divided into positive and negative groups based on pathology results. Then the laboratory results were compared with histopathological findings after surgery.

Findings: The level of IL-6 in the positive group was 107.25±3.54 and in the negative group was 75.50±2.41, and the difference was statistically significant (p=0.032). The mean CRP was 35.5±12.1 in the positive group and 11.1±5.3 in the negative group (p<0.001). There was a statistically significant relationship between IL-6 in normal patients and IL-6 in positive patients with purulent (p=0.006) and gangrene (p<0.001) pathology. There was a significant relationship between IL-6 positive patients with follicular hyperplasia pathology and IL-6 positive patients with purulent and gangrene pathology (p<0.001). Moreover, there was a statistically significant relationship between IL-6 positive patients with inflammatory pathology response and IL-6 positive gangrene patients (p<0.001). Sensitivity, specificity, positive predictive value, negative predictive value for IL-6 were 83, 88, 86, 79 and for CRP were 83, 85, 89, 81, respectively.

Conclusion: The results of the study showed that the simultaneous measurement of CRP and IL-6 are useful biomarkers in the diagnosis and prevention of negative appendectomy.

Keywords: *Appendicitis, Interleukin 6, C-Reactive Protein, Appendectomy.*

Cite this article: Layegh H, Teimour Nezhad T, SeyedSadeghi MS. Diagnostic Value of C-Reactive Protein and Interleukin-6 in Prevention of Negative Appendectomy. *Journal of Babol University of Medical Sciences*. 2024; 26: e3.

[DOI: 10.22088/jbums.26.1.3]

Introduction

Acute appendicitis is one of the common causes of acute abdominal surgery in all age groups, especially adults (1). Symptoms begin with diffuse abdominal pain, nausea, vomiting, and after several hours, local pain in the right lower quadrant (2). If not diagnosed in time, it may lead to complications such as gangrene and abscess (3). Due to the diversity of clinical manifestations in acute appendicitis and the common symptoms with many abdominal diseases, the diagnosis of appendicitis is difficult and the delay in confirming the diagnosis can increase the rate of complications and mortality of patients (3). Therefore, correct diagnosis of appendicitis is important for clinical decision making. Achieving tests with high diagnostic power leads to accurate and immediate identification of acute appendicitis and prevention of complications by performing timely surgery (4). Most cases of misdiagnosis that lead to negative appendectomy (cases where the patient does not have appendicitis and his/her appendix is removed) occur in relation to this disease (4). Despite the progress in diagnostic and laboratory methods, the rate of negative appendectomy is between 15 and 30% (5).

C-reactive protein (CRP) is an inflammatory marker used in the diagnosis of infection (6). The sensitivity of CRP in the diagnosis of acute appendicitis is estimated between 60 and 86% (7, 8). CRP is an acute phase agent that is produced by the liver in response to inflammation and infection and as a result of the release of interleukin 6 (IL-6) and begins to increase within 6 to 12 hours after the onset of tissue inflammation (9). CRP measurement can prove the presence of acute appendicitis with high accuracy, and along with other inflammatory factors such as IL-6 and clinical findings, it can increase the diagnostic accuracy to a very high extent (10). CRP increases in infections, inflammatory arthritis, autoimmune disorders, neoplasia and pregnancy (11).

The results of a study by Gürünlüoglu et al. showed that CRP, IL-6 and WBC biomarkers are useful laboratory parameters that can complement clinical examinations in diagnosing appendicitis in patients and identifying complications that may occur after surgery. The results of this study also showed that WBC, IL-6 and CRP levels decrease on the first day after surgery in nonperforated appendicitis patients, 4 to 6 days after surgery in perforated appendicitis patients, and 3 to 6 days after surgery in appendicitis patients with COVID-19 (5). In a study by Yuksel et al., it was suggested to use the C-reactive protein/albumin biomarker as a key indicator in determining perforated appendicitis. In this study, it has also been emphasized that in some patients, such as pregnant women, for whom it is not possible to perform a CT scan, the CRP/albumin biomarker can be a more appropriate indicator to confirm the disease (12). In their study, Rastgoo Haghi et al. found procalcitonin biomarkers along with IL-6 to be useful for preventing negative appendectomy (13). In the study of Dimić et al., it is emphasized that the use of biomarkers is effective in diagnosing and even predicting the severity of appendicitis. In this study, it has been confirmed that the use of several biomarkers together can facilitate the diagnosis of the disease. CRP biomarker was introduced in Dimić's study as a powerful predictive factor in the diagnosis of acute appendicitis, which can be used to diagnose the disease more quickly (14).

Although negative appendectomy occurs frequently and is a part of the record of surgeons, even great surgeons (15), but perhaps measures can be taken to reduce negative appendectomies and also to reduce the missed cases of acute appendicitis that come back with more severe complications in the following days (16). Considering that acute appendicitis is one of the most important causes of acute surgery and diagnostic biomarkers are essential components to confirm the diagnosis of appendicitis, and determining the

[DOI: 10.22088/jbums.26.1.3]

sensitivity of each biomarker in the quick and correct diagnosis of appendicitis can prevent complications and negative appendectomy, and noting that most of the studies have examined the relationship between biomarkers and appendectomy, and less have been dedicated preventively to biomarkers in the context of negative appendectomy based on pathology results, and considering surgeons' interest in diagnostic biomarkers interleukin-6 and C-reactive protein for diagnosis in recent years, this study was conducted with the aim of determining the sensitivity and specificity and examining the diagnostic value of C-reactive protein and interleukin-6 in the prevention of negative appendectomy based on the pathology results of patients. The results of this study can be used as a practical method in helping surgeons to make timely diagnosis and reduce negative appendectomy cases.

Methods

After being approved by the ethics committee of Ardabil University of Medical Sciences with the code IR.ARUMS.REC.1398.597, this cross-sectional study was conducted on all patients suspected of acute appendicitis who referred to Fatemi Hospital in Ardabil between September 2020 and March 2021. A total of 208 people were included in the study. Patients with no underlying systemic disease and consent to participate in the study were included in the study, and patients with acute abdominal complaints who were not candidates for surgery and if surgery was indicated, appendicitis was not the first and main diagnosis, were excluded from the study. CRP and IL-6 tests were performed on the patients after obtaining the history and performing the initial examinations. Pathology samples were taken from all patients after appendectomy. The pathology report was determined as the basis for the diagnosis of the disease, and in this study, the patients were divided into two groups: positive (having positive pathological criteria for acute appendicitis) and negative (lacking pathological criteria for acute appendicitis) based on the pathology results. In this study, the confidentiality of the personal information of the participants, the right to withdraw from the study and obtaining written informed consent were observed.

The collected data and the level of CRP and IL-6 as well as the histopathology results were entered into SPSS version 22 after coding. T-Test, Chi-square, Mann-Whitney, Kruskal-Wallis, and ANOVA were used for statistical analysis and ROC curve was used to determine the cut-off point and the results were compared in two groups of patients and $p<0.05$ was considered significant.

Results

The mean age of the positive group was 22.6±11.6 and the negative group was 24.2±12.3 years. 5 men (4.2%) and 13 women (14.2%) were in normal appendicitis group according to the pathology results, and 112 men (95.8%) and 78 women (85.8%) were included in the positive group according to the pathology results (acute appendicitis with complications or without complications). There was a statistically significant difference between the two positive and negative groups in terms of gender distribution ($p=0.01$). The pathology results of the patients showed that out of a total of 208 patients, 18 people (8.7%) were in the normal group (negative) and 190 people (91.34%) were reported in the appendicitis group (positive). In the positive group, the highest frequency was related to purulent pathology result with 47.1%.

[DOI: 10.22088/jbums.26.1.3]

Data analysis using the Mann-Whitney test showed that the level of IL-6 in the positive group was 107.25±3.54 and in the negative group was 75.50±2.41 (p=0.032). The Kruskal-Wallis test showed that there was a statistically significant relationship between the two groups in terms of interleukin 6 level and the pathology result (p<0.001) (Table 1). The mean CRP was 35.5±12.1 in the positive group and 11.1±5.3 in the negative group (p<0.001). ANOVA test showed that there is a statistically significant difference between positive and negative groups in terms of CRP level and pathology results (p=0.001) (Table 2).

Table 1. IL-6 level in positive and negative groups and its relationship with pathological results

	Number	Mean±SD	p-value
Group			
Negative	18	75.50±2.41	0.032
Positive	190	107.25±3.54	
Pathology results			
Normal	18	75.50±2.41	
Follicular hyperplasia	28	67.48±1.12	
Inflammatory	38	105.33±3.10	<0.001
Purulent	98	113.32±2.04	
Gangrene	26	129.98±1.41	

Table 2. CRP level in positive and negative groups and its relationship with pathology results

	Mean±SD	p-value
Group		
Negative	11.1±5.3	0.001
Positive	35.5±12.1	
Pathology results		
Normal	11.1±5.22	
Follicular hyperplasia	18.4±4.13	
Inflammatory	23.7±1.32	0.001
Purulent	36.2±2.42	
Gangrene	79.0±8.6	

The results of the follow-up test showed that there was a statistically significant relationship between IL-6 in normal patients (negative) and IL-6 in positive patients with purulent pathology (p=0.006) and gangrene (p<0.001). There was a significant correlation between IL-6 of positive patients with follicular hyperplasia pathology and IL-6 of positive patients with purulent pathology (p<0.001) and gangrene (p<0.001). Also, there was a statistically significant relationship between IL-6 of positive patients with inflammatory pathology and IL-6 of positive gangrene patients (p<0.001) and there was a significant relationship between IL-6 of positive patients with purulent pathology and IL-6 of positive gangrene patients (p<0.001) (Table 3). The ROC curve was drawn for CRP and IL-6, and the AUC (area under the curve) was 0.695 for CRP and 0.585 for IL-6. In the case of CRP, the borderline range was between 2.9 and 14.9, and for IL-6, it was 1.4 to 1.7. The cut-off point for IL-6 was 3.45 and the sensitivity, specificity, positive predictive value, and negative predictive value for IL-6 were 83 (95% CI=0.85-0.78), 88 (95% CI=0.90-

[DOI: 10.22088/jbums.26.1.3]

0.79), 86 (95% CI=0.88-0.80), 79 (95% CI=0.89-0.85), respectively and for CRP with a cut-off point of 0.95, they were 83 (95% CI=0.85-0.80), 85 (95% CI=0.89-0.80), 89 (95% CI=0.95-0.88), 81 (95% CI=0.85-0.80) (Figure 1).

Table 3. Follow-up examination based on the pathology results of the patients

Pathology	Mean difference	Standard error	p-value
Normal			
Follicular Hyperplasia	2.66	5.86	1.000
İnflammatory	-12.66	7.45	0.635
Purulent	-25.24	6.82	0.006
Gangrene	-67.90	10.82	<0.001
Follicular hyperplasia			
Normal	-2.66	5.89	1.000
Inflammatory	-15.33	5.80	0.104
Purulent	-27.91	4.97	<0.001
Gangrene	-70.57	9.76	<0.001
Inflammatory			
Normal	12.66	7.45	0.635
Follicular hyperplasia	15.33	5.80	0.104
Purulent	-12.58	6.74	0.492
Gangrene	-55.24	10.77	<0.001
Purulent			
Normal	25.24	6.82	0.006
Follicular hyperplasia	27.91	4.97	<0.001
Inflammatory	12.58	6.74	0.492
Gangrene	-42.66	10.35	<0.001
Gangrene			
Normal	67.90	10.82	<0.001
Follicular hyperplasia	70.57	9.76	<0.001
Inflammatory	55.24	10.77	<0.001
Purulent	42.66	10.35	0.002

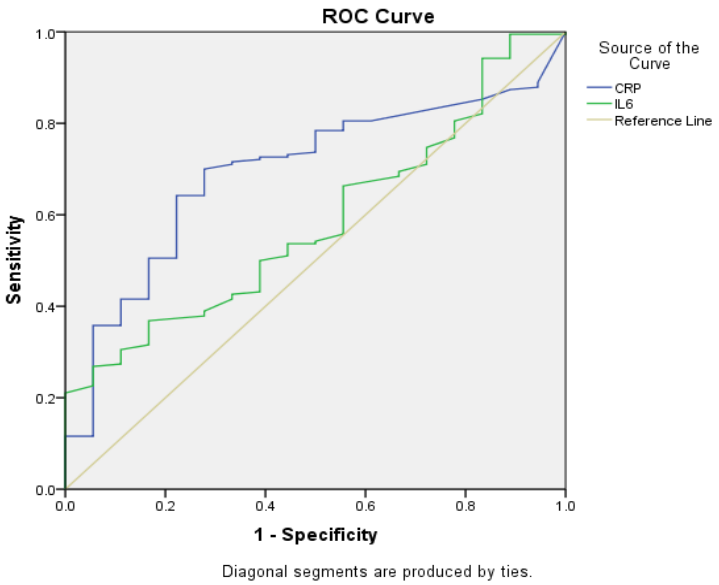

Figure 1. ROC curve

[DOI: 10.22088/jbums.26.1.3]

Discussion

The results of this study showed that the level of CRP and IL-6 with high sensitivity can be effective in confirming the clinical diagnosis of appendicitis and reduce unnecessary negative appendectomies. In a study on 187 cases with suspected acute appendicitis, Yang et al. showed that the mean serum level of CRP in patients with appendicitis was 29.6 mg/dL, while this level was 24.1 mg/dL in healthy people, and there was no statistically significant relationship between people with appendicitis and people without appendicitis. In Yang's study, the sensitivity of CRP was 76.5 and its specificity was 26.1 (17). In the present study, there was a significant difference between people with appendicitis and people without appendicitis in terms of CRP level, which was contrary to the results of Yang's study. The reason for the difference in the results of their study and the present study could be that in Yang's study, the comparison was made in two healthy and sick groups, but we made the comparison in two groups with positive and negative appendicitis. However, the mean level of quantitative CRP in positive patients in the current study was 35.5, which showed a higher figure than the study of Yang et al. Also, the sensitivity and specificity of CRP in the present study were 83 and 85, respectively, which was different from the results of Yang's study. Although the numbers obtained in different studies are diverse and show a significant difference with the present study, all the results obtained indicate that the CRP diagnostic test can be used as an auxiliary diagnostic method along with other tests in the diagnosis of acute appendicitis.

In the retrospective study by Yang et al. on 3-18-year-old children with acute appendicitis from 2007 to 2017, 613 patients had perforated appendicitis. Patients with perforation had significantly longer symptoms, higher white blood cell count, higher CRP and neutrophil percentage, and lower serum sodium level. A high white blood cell count and a high percentage of neutrophils were associated with a slightly higher CRP level and an increased risk of perforation (18). Comparing the results of the present study with Yang's study is important from the point of view that in our study, increased level of CRP and interleukin significantly resulted in more severe inflammatory results in the pathology of patients, which shows that the level of CRP and interleukin both in terms of the probability of perforation and the severity of appendicitis is significantly important.

Salam et al. showed that measurement of procalcitonin and IL-6 reduces unnecessary negative appendectomy (8). In the present study, procalcitonin was not measured, but interleukin 6 and CRP could show a significant difference in both positive and negative groups. Therefore, it can be said that in Salam's study, interleukin 6 had a greater role in predicting negative appendectomy, and in a way, our results are complementary to the results of the mentioned study.

One of the limitations of the present study was the reduction of the number of patients due to the lack of requests for required tests in some cases for the intended patients, which was resolved by allocating more time to complete the expected number of patients. Another existing limitation was the time limit; if more time is allocated, more accurate results can be obtained.

The results of the study showed that the simultaneous measurement of CRP and IL-6 are useful as important biomarkers in the diagnosis and prevention of negative appendectomy.

Conflict of interest: The authors declare that there is no conflict of interest.

[DOI: 10.22088/jbums.26.1.3]

Acknowledgment

Hereby, we would like to thank the Deputy of Research and Technology of Ardabil University of Medical Sciences, all the patients participating in the study, the staff of Fatemi Hospital in Ardabil for their support and cooperation in the implementation of the project, and Mr. Hossein Asadi for his cooperation in writing the article.

[DOI: 10.22088/jbums.26.1.3]

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