

Evaluation of Diagnostic Accuracy .of C-Reactive Protein and Leucocyte Count in Operated Cases of Suspected Acute Appendicitis

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I. Introduction

Acute appendicitis (also called as epityphlitis) is one of the most common cause of acute abdomen in young adults and appendectomy is the most commonly done emergency abdominal surgery.

Even though surgeons have been dealing with acute appendicitis for more than 100 years, its diagnosis remains complicated. Most of the senior surgeons diagnose acute appendicitis accurately in more than 80 percent of cases. But, in most cases, it is junior surgeons who are deciding whether a patient with right iliac fossa pain should be operated upon or not. Their decision have an accuracy rate which can go down up to 50%, so it can go wrong in about 50% of time.

In spite of careful clinical, laboratory and ultrasound examinations, the rates of removing non-diseased, normal appendix (negative appendectomy rate) is high. If appendectomy is performed on the basis of clinical diagnosis alone the rate of negative appendectomy will be 15-30 percent (more in females and extremes of age)(1). Accuracy rates of variable tests in diagnosis of appendicitis is different. The role of blood tests, radiological investigation and laparoscopy has been studied. The use of laparoscopy, ultrasonography and CT scanning all have helped in increasing the diagnostic accuracy and decreasing the negative appendectomy rates, but in primary health care setting these diagnostic approaches are not available.

Additional tests that would improve diagnostic accuracy and hence reduce the number of unnecessary operations have to be identified. This is very important in these days when health system is driven by cost parameters. CRP is a non-specific inflammatory marker that is used routinely in many hospitals as an aid in the diagnosis of patients with an acute abdomen. An acute phase protein is produced in the liver. Normal serum concentration is less than 10 mg/l 8–12 hours after infection or trauma; the increase of acute phase protein in liver the CRP is more important in clinical practice. CRP is increased in infections, inflammatory arthritis, autoimmune disorders, neoplasia, pregnancy, and aging (2)(3). This study aims to correlate the serum levels of C - reactive protein (CRP), WBC count and raised neutrophil count with histopathology of the appendectomy specimen.

II. Review Of Literature

- Sengupta et al. in 2009 conducted a study on 98(75 females and 23 males) patients and found out that Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for C-reactive protein (CRP) alone were 65,68,34,88 resp, for WBC alone 85,72,44,95 and if both combined 50,90,56 88 . The study entitled as “White Cell Count and C-Reactive Protein Measurement in Patients with Possible Appendicitis”(4).
- Amalesh et al. in 2004 conducted a study on 192 patients and found out that CRP was normal in 14 out of 33 negative explorations (normal appendix on histopathology). The specificity and sensitivity of serum CRP was 42% and 91% respectively. The predictive value of a positive (raised CRP) and negative (normal CRP) test is 88% and 48% respectively. They concluded that neither raised nor normal CRP value is helpful in the diagnosis of acute appendicitis . Title:”CRP in acute appendicitis –Is it a necessary investigation?”(5)
- Schellekens DH et al. in 2013 conducted a study on 233 patients and found out that CRP and WBC were significantly higher in patients with AA. They concluded that none of the test had a cutoff points that could be helpful to accurately discriminate between AA and other pathology in patients with suspected AA. A WBC < 7.5 × 10⁹ /L, and with a low level of clinical suspicion for AA, can identify a subgroup of patients who can be sent home without further evaluation.(6)
- Panagiotopoulou IG et al. in 2013 conducted a retrospective analysis of 1,169 appendectomies performed and found that in perforated appendicitis, the median CRP level was significantly higher than that of AA).

CRP also showed the highest sensitivity (100%) and negative predictive value (100%) for PA. CRP had the highest diagnostic accuracy in PA and this was increased when it was combined with WCC. Title: "The diagnostic value of white cell count, C-reactive protein and bilirubin in acute appendicitis and its complications"(7)

- Stefanutti G et al. in 2007 performed a study on 100 children (55 males) found out that elevated WBCC alone had a sensitivity of 0.6 (confidence interval [CI], 0.506-0.694). Sensitivity of elevated CRP alone was 0.86 (CI, 0.926-0.793). Elevation of either WBCC or CRP or both had a sensitivity of 0.98 (CI, 1.0-0.953) and they concluded White blood cell count or CRP values alone do not appear to provide any useful additional information to the surgeon. However, the sensitivity of the 2 combined tests is extremely high, and normal values of both WBCC and CRP are very unlikely in pathologically confirmed appendicitis.(8)
- Yang HR et al. in 2005 conducted a study on 85 patients and found out that there was no significant difference in leukocyte counts or CRP values between patients with acute appendicitis and those with a normal appendix. The sensitivities of leukocyte count, neutrophil percentage, and CRP in the diagnosis of acute appendicitis were 71.4 per cent, 88.3 per cent, and 90 per cent, respectively, while the specificities were 37.5 per cent, 25 per cent, and 37.5 per cent, respectively. They concluded that patients with normal results in all three tests are highly unlikely to have acute appendicitis(9)
- Khan MN et al. in 2004 conducted a study on 259 patients and found out that sensitivity and specificity of WBC count was 83% and 62.1% and that for CRP was 75.6% and 83.7 %. They concluded that WBC and C-reactive protein can be helpful in the diagnosis, when measured together as this increases their positive predictive value. Title: The role c-reactive protein and white cell count in the diagnosis of acute appendicitis.(10)
- Eryilmaz R et al. in 2001 studied 126 patients(71 males) and noticed that the mean CRP level was significantly higher ($p < 0.001$) in patients with complicated acute appendicitis than in those with noncomplicated acute appendicitis and in those with negative appendectomy, the mean leukocyte count was significantly lower ($p < 0.001$) in patient with negative appendectomy than in those with noncomplicated appendicitis and in those with complicated appendicitis. They concluded that CRP measurements or leukocyte counts are not effective alone to prevent negative appendectomies. Title: The value of C-reactive protein, leukocytic count in preventing negative appendectomies.(11)
- Asfar S et al. in 2000 conducted a study on 78 patients who had undergone surgery for acute appendicitis. Their results were as follows: In patients with histopathologically proven acute appendicitis both the WBC count and serum CRP level were significantly raised ($P = 0.025$ and $P < 0.000,1$ respectively). Serum CRP level was normal in 13 out of 15 negative explorations (normal appendix on histopathology). The specificity and sensitivity of serum CRP was 86.6% and 93.6%, respectively. They concluded that, a normal pre-operative serum CRP measurement in patients with suspected acute appendicitis is most likely associated with a normal appendix. Title: "Would measurement of C-reactive protein reduce the rate of negative exploration for acute appendicitis" (12)
- Grönroos JM in 1999 conducted a study on 83 elderly patients and found out that there was no statistically significant difference in leukocyte counts or CRP values between patients with an uninfamed appendix and those with acute appendicitis. He concluded that, Although elevated leukocyte count and CRP value cannot effectively establish the diagnosis of acute appendicitis in the elderly, unelevated values excludes it.(13)
- Eriksson S et al. in 1994 studied 229 appendectomy patients and noticed that repetitive tests showed a continuing rise in CRP values but a continuing decrease in WBC. They said repeated laboratory tests for CRP and WBC should be performed in patients with suspected acute appendicitis requested to stay for further observation. If these test results are normal, the surgeon should preferably refrain from operating but consider other differential diagnoses. (14)

Aims And Objectives

To analyze the diagnostic accuracy of C-Reactive Protein, total leukocyte count and differential neutrophil count in patients operated for suspected acute appendicitis.

III. Materials And Methods

Descriptive study, Department of surgery, M.O.S.C Medical College, Kolenchery, from January 2013 – Dec 2014. Sample Size: A total number of 84 patients were involved in the study. Approval of the local ethics committee had been obtained and patients were informed about the study and written consents were taken.

Inclusion Criteria:

All patients with acute abdominal pain, with a clinical or radiological diagnosis of Acute appendicitis and posted for surgery will be included in the study.

Clinical Diagnosis of acute appendicitis: Acute abdominal pain with at least one of the following positive

1. tenderness,
2. rebound tenderness,
3. localized rigidity/guarding
4. mass in right iliac fossa,

Exclusion criteria:

- Patients who are managed conservatively
- Pregnancy
- Patients with associated diseases like
Rheumatoid arthritis, SLE, Glomerulonephritis, Gout, Inflammatory bowel disease, Malignant neoplasm, Myocardial infarction, Any other condition where CRP is raised.

IV. Results

All of the patients in our study were presented with abdominal pain. Fever was a presenting complaint for 42 patients(50%). Vomiting was present in 36 patients (42.9%). Anorexia, Nausea, Diarrhoea, constipation were present in 71(84.5%), 17(20.2%), 9(10.7%), 17(20.2%) patients respectively. The classic Migratory abdominal pain was present in only in 11 patients i.e. 13.1%. On examination Tenderness was present in all 84 patients. Classic rebound tenderness was present only in 48(57.1%) patients. Guarding was present in 20(23.8%) patients. 3 patients (3.6%) had a mass in RIF while presenting to the casualty. Bowel sounds were absent in 3 patients (3.6%) who had complicated acute appendicitis. Simple acute appendicitis was present in 47 (56.0%) of patients. A complicated appendicitis, either perforated or gangrenous was seen in 17 patients (20.2%). 20 patients(23.80%) patient had either a normal appendix or other diagnosis. 1 patient had sub-acute appendicitis. 2 patients had mucinous neoplasm, 1 patient had foreign body granuloma of appendix, 2 patients had Meckel's diverticulum.

Mean total count is 11338.10 +/- 3680.980 (table 1)

Mean Neutrophil count is 73.65 +/-12.373

Median CRP value is 34.1(IQR =11.025-55.950)

Total count >10000 is seen in 53(63.1%) of patients. Neutrophil count was positive in 50(59.5%) patients. CRP value is >10 in 65(79.8%) of patients. USG was showing acute appendicitis in 65 patients which is 77.4%. (graph 1) Of these symptoms, only constipation had a significant association with acute appendicitis (Chi-Square value-6.660 and P-value-0.010) and complicated appendicitis (Chi-Square value-8.258 and P-value-0.004). Fever had a significant association with complicated acute appendicitis (Chi-Square value-3.925 and P-value-0.048)

In our study there is a definite association between CRP and diagnosis of acute appendicitis with a Chi-Square value and P-values are 48.766 and 0.000 resp. Same as the case of WBC and Neutrophil count where Chi-square, P-values were 20.937, 0.000 and 26.722, 0.000 respectively. It is same in the case of combined tests. But it should be noted that the association between CRP, Neutrophil count, combined tests with the severe form of acute appendicitis (perforated, gangrenous) was insignificant or weak, except T.C which showed a significant association (3.976 & 0.046). But the high CRP value is often associated with a complicated appendicitis. The sensitivity, specificity and positive predictive value of CRP values in our study are 96.9%, 75%, 92.6% respectively. The sensitivity, specificity and positive predictive value of Total WBC count in our study are 76.6%, 80%, 92.5% respectively and for Neutrophil count the sensitivity, specificity and positive predictive values are 75%, 90%, 96% respectively. When the WBC count and Neutrophil counts are combined the sensitivity, specificity and PPV became 67.2%, 90%, 95.6%. When all the three tests are combined the values were 65.6%, 95%, 97.7% respectively.

V. Discussion

Different clinical classification have been used for the acute appendicitis, but, since we are studying correlation of CRP values with the histopathology findings, the classification which combines the gross appearance of the appendix and pathologic stage is used in this study with some modification (15)

On HPE acute appendicitis was diagnosed in 64 patients. Simple acute appendicitis was present in 47 patients and complicated appendicitis, either perforated or gangrenous was seen in 17 patients (perforated-13, gangrenous-4). 20 patients had either a normal appendix or other diagnosis. 1 patient had sub-acute appendicitis. 2 patients had mucinous neoplasm, 1 patient had foreign body granuloma of appendix, 2 patients had Meckel's diverticulum

Many people have investigated the value of CRP and WBC counts in improving the diagnostic accuracy of acute appendicitis with conflicting results. The values of CRP, WBC count and neutrophil count in our study is compared with other studies. The positive CRP is more accurate than the WBC and neutrophil counts and combined together it further improves diagnostic accuracy. A multivariate analysis conducted by

Oosterhuis et al.(1993) showed that serial CRP measurement can improve the accuracy of diagnosing acute appendicitis. They concluded that acute appendicitis is very unlikely when both the leucocyte count and CRP value are normal(16).

A double blind study done by Asfar et al. (2000) showed the sensitivity and specificity of CRP were 86.6% and 93.6%, respectively. They concluded a normal CRP value probably indicates a normal non-inflamed appendix. CRP is a more sensitive test than the WBC and neutrophil counts and if all are investigations are combined that will increase sensitivity and specificity(12).

Erkassap (2000) in a positive study on 102 patients reported that sensitivity and specificity of the CRP were 96% and 78%, respectively; the positive predictive value was 100% (89). In a retrospective study, Wu and coworkers (2005) concluded that the combined usage of the WBC, neutrophil count, and the CRP monitoring increased the positive predictive value(17). Grönroos (1999) emphasized based on his study that if both the WBC and CRP are normal, acute appendicitis is very unlikely(13). Schellekens DH et al. (2013) concluded that none of the test (CRP,WBC) had a cutoff value, but a WBC < 7.5 × 10⁹ /L, and with a low level of clinical suspicion for AA, can identify a subgroup of patients who can be sent home without further evaluation(71). Khan MN et al. in 2004 concluded that WBC and C-reactive protein can be helpful in the diagnosis of acute appendicitis, when measured together as this increases their positive predictive value(10).

But there were conflicting studies. Sengupta et al. (2009), noticed that, no patients with WCC and CRP both in the normal range had acute appendicitis. They concluded that raised WCC and CRP were poor positive predictors of appendicitis, both alone and in combination, and correlated poorly with the development of complications(4). Amalesh et al. (2004) In their study they found out specificity and sensitivity of serum CRP was 42% and 91% respectively. The predictive value of a positive (raised CRP) and negative (normal CRP) test was 88% and 48% respectively. They concluded that neither raised nor normal CRP value is helpful in the diagnosis of acute appendicitis(5).

The sensitivity, specificity and positive predictive value of CRP values in our study are 96.9%,75.0%,92.6% respectively. The WBC and neutrophil percentage are also increased with acute appendicitis. The sensitivity, specificity and positive predictive value of Total WBC count in our study are 76.6%, 80%, 92.5% respectively and for neutrophil count the sensitivity, specificity and positive predictive values are 75%,90%, 96% respectively.

In our study there is a definite association between CRP and diagnosis of uncomplicated acute appendicitis with a Chi-Square value and P-values are 48.766 and 0.000 resp. Same as the case of WBC and Neutrophil count where Chi-square, P-values were 20.937, 0.000 and 26.722,0.000 respectively. But surprisingly as a different observation from other studies the association between CRP, Neutrophil count, combined tests with the severe form of acute appendicitis (perforated, gangrenous) was insignificant or weak except TC where the chi-square value was 3.976 and P-value was 0.046. But the high CRP value is often associated with a complicated appendicitis.

Role of combining all the Tests:

Grönroos and Grönroos (1999) concluded that acute appendicitis is very unlikely when all the tests are normal, and acute appendicitis can be excluded with a 100% predictive value(13).

Ng and Lai (2002) found that if the combination of elevated CRP, leucocytosis and elevated neutrophil count was used, satisfactory specificity and positive predictive value were achieved in diagnosing acute appendicitis(18).

Khan et al.(2004) in their study stated that, both the inflammatory markers i.e., WBC and CRP can be helpful in the diagnosis, when measured together it increases their positive predictive value(10).

Yang et al.(2005) in their study concluded that patients with normal results in all these tests were highly unlikely to have acute appendicitis and should be evaluated with extra caution before surgery(9).

In our study also we found out that combining the results of all the tests significantly improves the specificity and positive predictive value, in other words we can rule out acute appendicitis if the patient has all the three tests in normal range. In our study when the WBC count and Neutrophil counts are combined the sensitivity, specificity and PPV became 67.2%, 90%, 95.6%. When all the three tests are combined the values were 65.6%, 95%, 97.7% resp.

In the assessment of patients with acute abdominal pain and suspected appendicitis in particular, the decision is multifactorial, and still it relies on clinical judgment to a large extent. When the history and clinical findings are typical of acute appendicitis, clinical decision should outweigh the use of investigations. But where the diagnosis of appendicitis is considered unlikely, and no other obvious diagnosis which could be a concern is being considered, a normal WBC and CRP in them can re-assure the clinician and the patient may be allowed to go home. Our results and other studies as well suggested that CRP can predict the diagnosis of acute appendicitis. We think that CRP, WBC count and neutrophil counts are not absolutely specific tests for appendicitis, therefore, before diagnostic decision and indication for treatment, clinicians must depend on

structural interpretation of their experience, clinical information and modalities such as laboratory tests, USG and CT which is available. Laboratory tests combined with imaging modalities can be used as tools in establishing the diagnosis of acute appendicitis and to exclude other causes of acute abdominal pain.

In our study 20 patients (23.8%) had negative appendicectomy which is slightly higher than other studies. In a study conducted by Xharra et al.(2012) the rate of negative appendicectomy was 14.45% (19).Study by Eryilmaz et al.(2001) showed 15.8% negative appendicectomy rate. Study by Khan et al.(2004) had 14.28% negative appendicectomy rate(10). Of the 20 patients of negative appendicectomy the CRP was normal in 15 patients. That means the rate of appendicectomy could have been much low if the CRP value also was taken in to consideration.

VI. Conclusion

The first and most important tool for effective diagnosis of acute appendicitis is Surgeon’s clinical diagnosis using time tested clinical signs. Imaging modalities can also help in the diagnosis. But **elevated serum CRP** levels and total counts support the surgeon’s diagnosis and hence avoid chances of **error in diagnosis**, due to atypical presentations. Also a normal preoperative serum CRP level and total count in patients with suspected acute appendicitis is most likely to be associated with a normal appendix on histopathological examination.

VII. Recommendations

Therefore based on this study, for all patients who is presented to a surgeon with atypical symptoms and signs and suspecting acute appendicitis we recommend to do CRP estimation along with the other routine blood investigations A normal serum CRP level and total count should be used to take a decision to defer surgery and to observe the patient to reduce the rate of negative appendicectomies, and also to reduce burden on patient as well as on health system ,especially in places where there is limitations of availability of imaging modalities.

Table 1:

Investigation	No: of patients	Percentage
T.C>10000	53	63.1
Neutrophil>75	50	59.5
CRP>10	67	79.8
USG +	65	77.4

Graph 1:

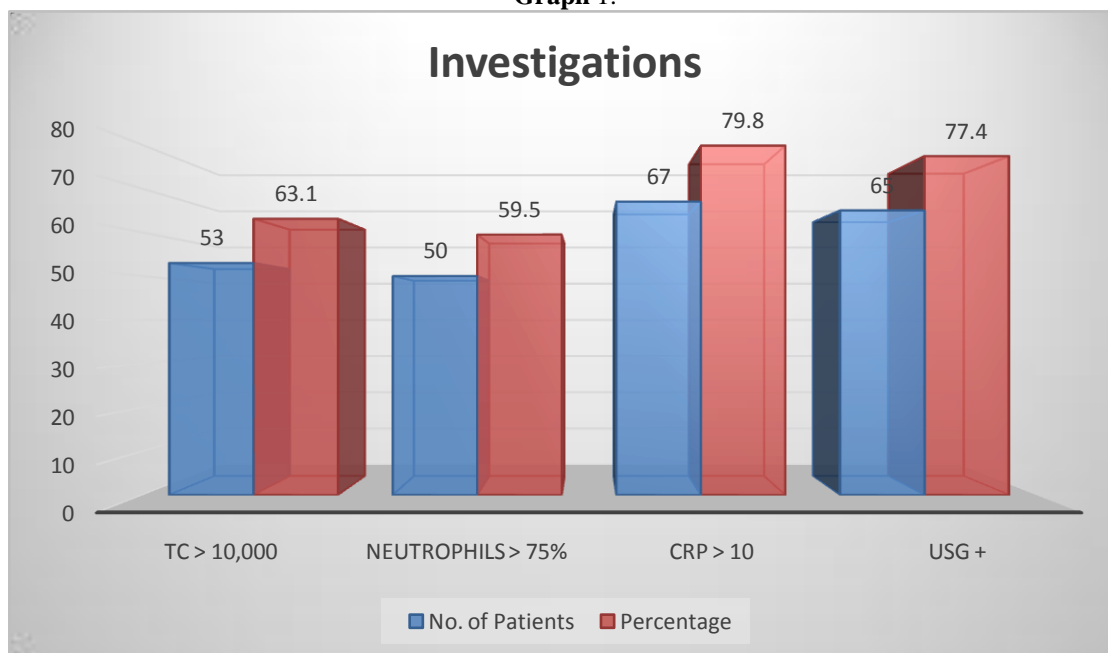


Table 3: Investigations significantly associated with Acute appendicitis and Complicated Acute appendicitis

Investigation	Chi-Square		P-value	
	AA	CA	AA	CA
USG	4.531	0.003	0.033	0.953
T.C	20.937	3.976	0.000	0.046
Neutrophil count	26.722	0.668	0.000	0.414
CRP	48.766	0.747	0.000	0.388

Table 4: Correlation between HPE CRP , Total Count and Neutrophil count

T.C, N.C CRP	HPE			Sensitivity	Specificity	PPV
	Pos	Neg				
Pos	39	4	45	0.65625	0.95	0.976744
Neg	21	20	39			
	60	24				

Reference

- [1]. KEYZER C, Gevenois PA. Imaging of Acute Appendicitis in Adults and Children. Springer Science & Business Media; 2011. 244 p.
- [2]. Gurleyik E, Gurleyik G, Unalmişer S. Accuracy of serum C-reactive protein measurements in diagnosis of acute appendicitis compared with surgeon’s clinical impression. Dis Colon Rectum. 1995 Dec;38(12):1270–4.
- [3]. Grönroos JM, Grönroos P. A fertile-aged woman with right lower abdominal pain but unelevated leukocyte count and C-reactive protein. Acute appendicitis is very unlikely. Langenbecks Arch Surg Dtsch Ges Für Chir. 1999 Oct;384(5):437–40.
- [4]. Sengupta A, Bax G, Paterson-Brown S. White Cell Count and C-Reactive Protein Measurement in Patients with Possible Appendicitis. Ann R Coll Surg Engl. 2009 Mar;91(2):113–5.
- [5]. Amalesh T, Shankar M, Shankar R. CRP in Acute Appendicitis — Is It a Necessary Investigation? Int J Surg. 2004 May;2(2):88–9.
- [6]. Schellekens DHSM, Hulsewé KWE, van Acker BAC, van Bijnen AA, de Jaegere TMH, Sastrowijoto SH, et al. Evaluation of the Diagnostic Accuracy of Plasma Markers for Early Diagnosis in Patients Suspected for Acute Appendicitis. Lewis L, editor. Acad Emerg Med. 2013 Jul;20(7):703–10.
- [7]. Panagiotopoulou IG, Parashar D, Lin R, Antonowicz S, Wells A, Bajwa F, et al. The diagnostic value of white cell count, C-reactive protein and bilirubin in acute appendicitis and its complications. Ann R Coll Surg Engl. 2013 Apr 1;95(3):215–21.
- [8]. Inflammatory markers for acute appendicitis in children: are they h... - PubMed - NCBI [Internet]. [cited 2014 Nov 5]. Available from: <http://hinariologin.research4life.org/uniqueisigwww.ncbi.nlm.nih.gov/uniqueisig0/pubmed/17502181>
- [9]. Role of leukocyte count, neutrophil percentage, and C-reactive prot... - PubMed - NCBI [Internet]. [cited 2014 Nov 5]. Available from: <http://hinariologin.research4life.org/uniqueisigwww.ncbi.nlm.nih.gov/uniqueisig0/pubmed/15943411>
- [10]. The role of white cell count and C-reactive protein in the diagnosi... - PubMed - NCBI [Internet]. [cited 2014 Nov 5]. Available from: <http://hinariologin.research4life.org/uniqueisigwww.ncbi.nlm.nih.gov/uniqueisig0/pubmed/15631364>
- [11]. Eryilmaz R, Sahin M, Alimoğlu O, Baş G, Ozkan OV. [The value of C-reactive protein and leucocyte count in preventing negative appendectomies]. Ulus Travma Derg Turk J Trauma Emerg Surg TJTES. 2001 Jul;7(3):142–5.
- [12]. Would measurement of C-reactive protein reduce the rate of negative... - PubMed - NCBI [Internet]. [cited 2014 Nov 5]. Available from: <http://hinariologin.research4life.org/uniqueisigwww.ncbi.nlm.nih.gov/uniqueisig0/pubmed/10815376>
- [13]. Grönroos JM. Is there a role for leukocyte and CRP measurements in the diagnosis of acute appendicitis in the elderly? Maturitas. 1999 Mar 15;31(3):255–8.
- [14]. The diagnostic value of repetitive preoperative analyses of C-react... - PubMed - NCBI [Internet]. [cited 2014 Nov 5]. Available from: <http://hinariologin.research4life.org/uniqueisigwww.ncbi.nlm.nih.gov/uniqueisig0/pubmed/7886405>
- [15]. Carson.D, David W Mcfadden. Acute abdomen and appendix. Essentials of Surgery:Scientific principles and practice. Lippincott Williams & Wilkins;
- [16]. Oosterhuis WP, Zwinderman AH, Teeuwen M, van Anel G, Oldenziel H, Kerkhoff JF, et al. C reactive protein in the diagnosis of acute appendicitis. Eur J Surg Acta Chir. 1993 Feb;159(2):115–9.
- [17]. Wu H-P, Lin C-Y, Chang C-F, Chang Y-J, Huang C-Y. Predictive value of C-reactive protein at different cutoff levels in acute appendicitis. Am J Emerg Med. 2005 Jul;23(4):449–53
- [18]. Ng K-C, Lai S-W. Clinical analysis of the related factors in acute appendicitis. Yale J Biol Med. 2002 Feb;75(1):41
- [19]. Xharra S, Gashi-Luci L, Xharra K, Veselaj F, Bicaj B, Sada F, et al. Correlation of serum C-reactive protein, white blood count and neutrophil percentage with histopathology findings in acute appendicitis. World J Emerg Surg. 2012;7(1):27.