

## C -Reactive Protein, Leukocyte Count and Neutrophils: A Diagnostic Aid in Acute Appendicitis

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### ABSTRACT

**Background:** Many clinical methods, scoring systems, radiological and laboratory investigations are used to diagnose and differentiate simple from complicated appendicitis. Proactive approach results in high rate of negative appendectomies and conservative approach results in increased rate of post-operative complications. The objective of this study was to evaluate the role of CRP, TLC and Neutrophil percentage in the diagnosis and differentiation of simple and complicated appendicitis.

**Methodology:** This cross sectional study was conducted at department of Surgery, Nishtar medical university/hospital, Multan from 1<sup>st</sup> November, 2019 to 30<sup>th</sup> April, 2021. Blood samples from patients were collected after admission, for CRP, TLC and Neutrophil percentage. Data were collected and analyzed through SPSS version 23.

**Results:** A total of 320 patients more than 12 years of age, 168 (52.5%) male and 152 (47.5%) female with 1.10:1, were included in the study. Sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) of CRP were 90.6%, 80%, 96% and 61.5% for acute appendicitis and 96.7%, 80%, 98.3%, and 66.7% for perforated appendicitis respectively with p-value of <0.000. Sensitivity, specificity, PPV and NPV of TLC were 87.5%, 80%, 95.9% and 54.5% for acute and 93.3%, 90%, 99.1% and 52.9% for perforated appendicitis with p= <0.000. Sensitivity, specificity, PPV and NPV of Neutrophils, in acute and perforated appendicitis were 83.8%, 76.7%, 95%, and 46.9% versus 87.5%, 70%, 97.2%, 31.8% respectively with P-value < 0.000.

**Conclusion:** Sensitivity, specificity and PPV of CRP, TLC and Neutrophils increased with the severity of appendicitis. Combining the results of the above three markers increased the diagnostic accuracy.

**Keywords:** Acute appendicitis, CRP (C-reactive protein), TLC (Leukocyte count) and Neutrophils.

#### Authors' Contribution:

<sup>1,2</sup>Conception; Literature research; manuscript design and drafting; <sup>3,4</sup>Critical analysis and manuscript review; <sup>5,6</sup> Data analysis; Manuscript Editing.

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### Introduction

Abdominal pain and vomiting are the commonest presentations in surgical emergency.<sup>1</sup> Appendicitis is commonest condition, which requires surgical intervention. There is 7-8 % life time risk to develop acute appendicitis. Even in the presence of modern technology, proper diagnosis of acute appendicitis is

still a challenge. Proactive approach results in high rate of negative appendectomy and conservative approach results in increased rate of post-operative complications like pelvic abscess, fecal fistula, intestinal obstruction and wound infection. Rate of negative appendectomy mentioned in the literature is about 20%. This rate increased to 30-50% in

females of child bearing age. About 0.05% of geriatric population (>65 years) develops acute appendicitis each year, which is quite significant.<sup>2</sup> Diagnosis is difficult and complication rate is very high in this age group. Rate of complicated appendicitis reported in literature is 30 to 35%.<sup>3</sup> Literature showed that mortality rate increases to 6% in cases of perforated appendicitis as compared to only 0.3% in simple appendicitis. Hospital stay also increases in cases of perforated appendicitis as compared to acute appendicitis (5 versus 3 days).<sup>4</sup> In the past many clinical methods and scoring systems were devised for early diagnosis and differentiation of simple from complicated appendicitis. Alvarado/ Modified Alvarado scores were the most frequently used scores. These were useful in the West but their sensitivity and specificity were found to be very low in Middle East and Asia. There was a need of an objective test for proper diagnosis of acute appendicitis. Ultrasound was helpful in the diagnosis of acute appendicitis with reported sensitivity and specificity of 82% and 97% respectively.<sup>5</sup> CT scan has high sensitivity (99%) and specificity (95%)<sup>6</sup> but its use is limited because of high cost, limited availability and risk of radiations, especially in children and females of child bearing age. Efforts were made to use different inflammatory markers to make an early diagnosis. Among these are TLC, Neutrophil percentage, CRP, Serum Bilirubin, Serum Amyloid A, Procalcitonin and ESR are important markers.<sup>7</sup> CRP is an acute phase protein produced in the liver. Interleukin-6 plays an important role in its production and is increased to 10 to 1000 times in a few minutes. CRP is nonspecific and increased in pregnancy, infection, autoimmune disorders, inflammatory arthritis, neoplasia and aging.<sup>8</sup> Literature search showed variable sensitivity and specificity of CRP for the diagnosis of acute appendicitis. Sensitivity varies with duration of symptoms and presence of other inflammatory conditions.

The objective of our study was to evaluate the role of CRP, TLC, and Neutrophils in diagnosis and

differentiation of simple from complicated appendicitis.

## Methodology

This cross-sectional study was conducted at General Surgery department, Nishtar Medical University/Hospital, Multan from 1<sup>st</sup> November, 2019 to 30<sup>th</sup> April, 2021, after approval from Institutional Review Board (IRB). A total of 320 patients more than 12 years of age and who underwent appendectomy in the emergency were selected by consecutive and nonrandomized technique. Patients with other inflammatory and autoimmune disease were excluded from the study. Blood samples were taken for CBC, Neutrophils and CRP in the first hour of admission. Predesigned proforma was used and was filled in by senior surgical resident on duty in Emergency department. Patient's information regarding age, gender, duration of signs and symptoms, CBC, Neutrophil percentage, CRP, operative findings and histopathology reports were noted. Decision for appendectomy was taken by resident consultant surgeons (Senior Registrar). The main outcome was to assess the role of CRP, TLC and Neutrophils in the diagnosis of acute appendicitis (which was later confirmed by histopathology). The efficacy of these tests was measured in terms of sensitivity, specificity, PPV and NPV. Data entry and analysis was done through SPSS version 23. Validity (sensitivity and specificity) and yield (Positive and negative predictive values) of CRP, TLC and Neutrophils were calculated. Pearson Chi-square test was applied and p-value less 0.05 was considered significant.

## Results

A total 320 patients >12 years of age who underwent emergency appendectomy in ER department, were included in the study. CRP value above 10 mg/L was taken as raised. Sensitivity, specificity, Positive predictive value (PPV) and Negative predictive value (NPV) of CRP were 87.5%, 80%, 95.9%, and 54.5%

respectively in acute appendicitis with p-value of < 0.000. Sensitivity, specificity, PPV and NPV in perforated appendicitis were 96.7%, 80%, 98.3%, and 66.7% respectively with p-value of < 0.000. Sensitivity, specificity, PPV and NPV of TLC in histologically proven acute appendicitis was 90.6%, 80%, 96% and 61.5% respectively with significant p-value, <0.000. Sensitivity, specificity and PPV of TLC increased in cases of perforated appendicitis to 93.3%, 90%, 99.1% and NPV decreased to 52.9% respectively. P-value = < 0.000. Sensitivity, Specificity, PPV and NPV of Neutrophil percentage in

acute and perforated appendicitis were 83.8%, 76.7%, 95%, and 46.9% versus 87.5%, 70%, 97.2%, 31.8% respectively with P-value= < 0.000.

Table: Demographic Data (n=320)		
Age in Years	Gender	
	Male no (percentage)	Female no (percentage)
12-20 Year	66 (20.62)	58 (18.12)
21-30 Year	76 (23.75)	60 (18.75)
>30 Year	26 (8.1)	34 (10.62)
Total	168 (52.5)	152 (47.5)

Table II: Inflammatory Markers in Acute appendicitis (n= 320)			
Histopathological Findings	Raised Leucocyte Count	Raised Neutrophils	Raised CRP
Normal Appendix n=40 (12.5%)	18/40 (45%)	21/40 (52.5%)	18/40 (45%)
Acute appendicitis n=160 (50%)	145/160 (76.25%)	134/160 (68.75%)	140/160 (74.3%)
Perforated Appendicitis N=120 (37.5%)	112/120 (91.6%)	105/120 (81.6%)	116/120 (90%)

(Reference Values: TLC= 4000-10,000 mm<sup>3</sup>, Neutrophils=50-75%, CRP= <10 mg/dl)

Table III: Inflammatory Markers in Acute appendicitis (n = 320)			
Histopathological Finding	TLC Mean ± SD	Neutrophils Mean ±SD	CRP Mean ± SD
Normal Appendix n=40 (12.5%)	6.8 ± 5.1	64.6 ± 13.4	8.6 ± 11
Acute appendicitis n=160 (50%)	11.4 ± 4.2	76 ± 14.2	18.6 ± 22.4
Perforated Appendicitis N=120 (37.5%)	12.3 ± 6.4	81.6 ± 7.3	61.4 ± 52

TableIV: Predictive Value of Inflammatory Markers (n=320)			
Diagnostic Test	Validity & Yield	Acute appendicitis	Gangrenous/Perforated Appendicitis
CRP	Sensitivity	87.5%	96.7%
	Specificity	80%	80%
	PPV	95.9%	98.3%
	NPV	54.5%	66.7%
	<b>p-value</b>	<b>&lt; 0.000</b>	<b>&lt; 0.000</b>
TLC	Sensitivity	90.6%	93.3%

	Specificity	80%	90%
	PPV	96%	99.1%
	NPV	61.5%	52.9%
	<b>p-value</b>	<b>&lt; 0.000</b>	<b>&lt; 0.000</b>
<b>Neutrophils</b>	Sensitivity	83.8%	87.5%
	Specificity	76.7%	70%
	PPV	95%	97.2%
	NPV	54.5%	31.8%
	<b>p-value</b>	<b>&lt; 0.000</b>	<b>&lt; 0.000</b>

(CRP= C-reactive protein, TLC= Total leukocyte count, PPV= Positive predictive value and NPV= Negative predictive value)

## Discussion

Appendicitis always poses a diagnostic challenge for general surgeons. Clinical findings can confirm the diagnosis in only 50 % cases. Delay in diagnosis leads to gangrene and perforation of the appendix (in upto 50% cases).<sup>9</sup> In the past many scoring systems, inflammatory markers, ultrasonography and CT scan were used to reduce the rate of negative and complicated appendicitis. Ultrasound is cost effective, noninvasive and repeatable investigation but it is operator dependent thus, has wide range of sensitivity (67-100%) and specificity (95-100%). Visualization of the appendix can increase sensitivity and specificity of USG.<sup>5</sup> External diameter of the appendix can be used to differentiate between acute and perforated appendicitis, 6.9mm versus 7.63 mm respectively.<sup>10</sup>

Among total of 320 patients in current study, sixty (18.75%) were above the age of 30 years and 260 (81.25%) were below 30 years, among these, the most prevalent age group was 21-30 years (38.8%). Rimsha et al mentioned age range of 13-60 years with the most prevalent group 21-30 years (38.8%) in their study.<sup>11</sup> Shefki et al reported age range of 5-59 years with median age of 19.7 years.<sup>8</sup> Faith Mehmet et al mentioned mean age of 39.23±18.02 and 35.27±14.8 years in histologically positive and negative appendicitis respectively.<sup>12</sup> The M:F ratio mentioned in different studies was 2.2: 1<sup>11</sup>, 1:1.21<sup>9</sup> and 1: 1.18.<sup>13</sup> Results of two studies were comparable with our study but the study done by

Rimsha showed male patients double of the female patients.<sup>11</sup>

Among 320 patients included in our study, 40 (12.5%) were found to have a normal appendix on histopathology, the findings somewhat comparable to 20% mentioned by Satendra Kumar.<sup>1</sup> High rate was mentioned by David Keohane<sup>14</sup> (27.4%) and Rimsha et al<sup>11</sup> (19.78%) respectively and a low rate was mentioned by Nauman Ahmed (7.1%).<sup>13</sup> In the present study, 160 (50%) patients had acute and 120 (37.5%) gangrenous/ perforated appendicitis. Rate of gangrenous/ perforated appendicitis in our study was comparable to that reported by Cristina et al and Savas Bayrak (31.7 % and 17.14% respectively).<sup>3,2</sup> Khurram et al and Shefki et al reported high rate in 15.7%<sup>9</sup> and 52.6%<sup>8</sup> respectively.

In our study, sensitivity, specificity, Positive predictive value (PPV) and Negative predictive value (NPV) of CRP was 87.5%, 80%, 95.9%, 54.5% in acute appendicitis and 96.7%, 80%, 98.3%, and 66.7% in perforated appendicitis respectively. Significant increase was noted in perforated appendicitis. The results were comparable with sensitivity and specificity of 57% and 87% respectively for CRP reported by C.-W. Yu et al in his meta-analysis.<sup>15</sup> Faith Mehmet et al mentioned very low sensitivity (37.5%) and 86.7% specificity for CRP.<sup>12</sup> Khurram Siddique et al reported sensitivity, specificity, PPV, NPV and diagnostic accuracy of CRP in simple acute and perforated appendicitis were 75%, 72%, 90%, 46%, 75.5% versus 93%, 40%, 23%, 97% and 50%

respectively.<sup>9</sup> Very low sensitivity (25.9%) but high specificity (100%) of CRP was reported by Nauman Ahmed et al from Quetta when they use CRP > 24 mg/L. He also mentioned that CRP> 48 mg/L as an indicator for perforated appendix.<sup>13</sup> Okus et al reported that patients having CRP=80.8 mg/L or above did not respond to conservative therapy.<sup>16</sup> Nalin H et al mentioned that 8.54% patients with confirmed acute appendicitis present with normal CRP.<sup>17</sup> Sevgi Buyukbese et al highlighted the importance of cut off value of CRP regarding its sensitivity and specificity. They reported change in sensitivity, specificity, PPV, NPV and diagnostic accuracy of CRP from 70.9%, 68.7%, 62.9%, 75.8% and 69.6% when CRP= 6mg/L to 86.1%, 81.9%, 58.6%, 95.2% and 77.7% when CRP=11.7 mg/L respectively.<sup>18</sup> This explains the difference in results among studies.

In our study, sensitivity, specificity, PPV and NPV of TLC in histologically proven acute appendicitis were 90.6%, 80%, 96%, 61.5% and 93.3%, 90%, 99.1%, 52.9% in perforated appendicitis respectively. Results showed that there is increase in sensitivity, specificity and PPV while decrease in NPV in cases of perforated appendicitis. Our results are comparable to the study done by C.-W.Yu et al in which sensitivity and specificity of TLC were 62% and 75% respectively.<sup>15</sup> Faith Mehmet et al reported sensitivity and specificity of TLC 65% and 60% respectively.<sup>12</sup> Sensitivity, specificity, PPV and diagnostic accuracy of TLC reported by Shefki Xharra were 82.6%, 85%, 68% and 94% respectively.<sup>8</sup> Sensitivity, specificity, PPV, NPV and diagnostic accuracy of TLC in acute and perforated appendicitis reported by Khurram Siddique were 80.5%, 68%, 89%, 50% and 77% versus 93%, 40%, 21%, 96% and 44% respectively.<sup>9</sup>

Sensitivity and specificity of Neutrophils were low in our study as compared to CRP and TLC. Sensitivity, Specificity, PPV and NPV in acute and perforated appendicitis were 83.8%, 76.7%, 95%, and 46.9% versus 87.5%, 70%, 97.2%, 31.8% respectively with P-value= < 0.000. Our results are close to the results

reported by Shefki Xharra et al which showed sensitivity, specificity, PPV and diagnostic accuracy of Neutrophils were 79.1%, 68%, 93.6% and 77.5% respectively.<sup>8</sup> Faith Mehmet et al mentioned sensitivity and specificity of 74.7% and 80% for Neutrophil count.<sup>12</sup> Joshua Davis et al<sup>19</sup> and David Keohane et al<sup>14</sup> reported sensitivity and specificity of Neutrophil percentage were 86.5%, 70.8% and 82%, 62.5% respectively.

Kelly Me et al used NLR (Neutrophil to Lymphocyte ratio) to differentiate simple (7.29) from perforated appendicitis (13.6%).<sup>20</sup> Muhammad H. Abbas et al used different inflammatory markers and they reported high sensitivity of SAA (Serum Amyloid A) and ProCT (Procalcitonin) 91.8% and 85% than TLC (80.3%) and CRP (75%).<sup>21</sup> When CRP, TLC and Neutrophil percentage were combined, there was a marked increase in sensitivity (96.5%), specificity (80%), PPV(98%) and NPV(56.6%). Similar trend was seen in other studies also. In combination sensitivity, specificity, PPV and NPV reported were 96%, 45.3%, 82.7% and 80.6% by David Keohane et al<sup>14</sup> and 95.3%, 72.2%, 95.3% by Shefkin Xharra<sup>8</sup> respectively. Limitations of this study are that it was done in only one center and CRP, TLC and Neutrophils were done only once after admission. In equivocal cases, if we had repeated the inflammatory markers after 12 or 24 hours, it would have been more beneficial.

## Conclusion

Inflammatory markers CRP, TLC and Neutrophils are useful and their sensitivity, specificity and PPV increase with the severity of appendicitis. Sensitivity and specificity of CRP and TLC are greater than Neutrophils. Combining the results of above three markers increased the diagnostic accuracy.

## Recommendation

We recommend to perform CRP in addition to TLC and Neutrophils as a routine test for the diagnosis of acute appendicitis.

## REFERENCES

- 1- Kumar S, Maurya J, Kumar S, Patne SK, Dwivedi A. A study of C-reactive protein and D-dimer in patients of appendicitis. *J Family Med Prim Care*, 2020; 9(7):3492-95. DOI: 10.4103/jfmprc.jfmprc\_197\_20.
- 2- Bayrak S, Tatar C, Cakar E, Colak S, Gunes ME, Tekesin K et al. Evaluation of the predictive power of laboratory markers in the diagnosis of acute appendicitis in the elderly. *North Clin Istanbul* 2019;6(3):293-301. DOI: 10.14744/nci.2019.93457.
- 3- Amador CG, Arteaga V, Plaza RD, Torralba M, Veladco AM, Ramia JM. Evaluation of preoperative clinical and serological determination in complicated acute appendicitis: A score for predicting complicated Appendicitis. *Cir Esp* 2021; 99 (4): 282-288. DOI: 10.1016/j.ciresp.2020.05.031.
- 4- Koymen S, Ismail D. The role of C-Reactive Protein to Lymphocyte ratio in the differentiation of Acute and Perforated appendicitis. *Ulus Travma Acil Cerrahi Derg* 2020; 26: 760-64. DOI: 10.147444/tjtes.2020.47973.
- 5- Lofvenberg F, Salo M. Ultrasound for Appendicitis: Performance and Integration with clinical parameters. *BioMed Research International* 2016; 5697692. Doi.org/10.1155/2016/5697692.
- 6- Kim TH, Sun Cho B, Jung JH, Lee MS, Jang JH, Kim CN. Predictive Factors to distinguish between patients with non-complicated Appendicitis and those with complicated Appendicitis. *Ann Coloproctol* 2015; 31 (5):192-197. doi: 10.3393/ac.2015.31.5.192.
- 7- Tanrikulu CS, Karamercan MA, Tanrikulu Y, Ozturk M, Yuzbasioglu Y, Coskun F et al. The predictive value of Alvarado score, inflammatory parameters and ultrasound imaging in the diagnosis of acute appendicitis. *Ulus Cerrahi Derg* 2016; 32: 115-121. DOI: 10.5152/UCD.2015.3103.
- 8- 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 Journal of Emergency Surgery* 2012; 7:27. Doi: 10.1186/1749-7922-7-27.
- 9- Siddique K, Baruah P, Bhandari S, Mirza S, Harinath G. Diagnostic accuracy of White cell count and C-reactive protein for assessing the severity of paediatric appendicitis. *J R Soc Med Sh Rep* 2011; 2:59. DOI: 10.1258/shorts.2011.011025.
- 10- Kartal K, Yazici P, Unlu TM, Uludag M, Mihmanli M. How to avoid negative appendicectomies: Can US achieve this? *Ulus Trauma Acil Cerrahi Derg* 2017; 23(2): 134-138. DOI: 10.5505/tjtes.2016.79328.
- 11- Fatima SR, Zaheer F, Moosa FA, Shah S, Arqam M, Mussab RM et al. Combine diagnostic accuracy of total leukocyte count, Neutrophil %age and ultrasonography for the diagnosis of acute appendicitis. *Cureus* 2021; 13086. DOI: 10.7759/Cureus.13086.
- 12- Yazar FM, Urfalioglu A, Bakacak M, Boran OF, Bulbuloglu E. Efficacy of the evaluation of inflammatory markers for the reduction of negative appendectomy rates. *Indian J Surg* 2018; 80(1): 61-67. DOI: 10.1007/s12262-016-1558-y.
- 13- Ahmed N. C-Reactive Protein: An aid for diagnosis of acute appendicitis. *J Ayub Med Coll Abbottabad* 2017; 29(2): 250-3.
- 14- Keohane D, Leary PO, Nagle M, Cichelli K, McCormack T. A correlation of Blood Panel results and histologically confirmed Appendicitis. *Cureus* 2020; 12 (9): e 10641. DOI: 10.7759/Cureus.10641.
- 15- Yu CW, Juan LI, Wu MH, Shen CJ, Wu JY, Lee CC. Systemic review and meta-analysis of the diagnostic accuracy of Procalcitonin, C-reactive protein and White blood cell count for suspected acute appendicitis. *British Journal of Surgery* 2013; 100: 322-29. DOI: 10.1002/bjs.9008.
- 16- Okus A, Ay S, Karahan O, Eryilmaz MA, Sevinc B, Aksoy N. Monitoring C-reactive protein levels during medical management of acute appendicitis to predict the need for surgery. *Surg Today* 2015; 45(4): 451-6. DOI:10.1007/s00595-014-10996
- 17- Nalin H, Dayawansa, Julian D, Segan S, Yao HHI, Hon I et al. Incidence of normal White cell count and C-reactive protein in adults with Acute appendicitis. *ANZ J Surg* 2016. DOI: 10.1111/ans.13760.
- 18- Sarsu SB, Sarc F. Diagnostic value of White Blood Cell and C-Reactive Protein in Pediatric Appendicitis. *Bio Med Research International*, 2016; 6508619. DOI: org/10.1155/2016/6508619.
- 19- Davis J, Kasmire K. Utility of symptom duration and C-Reactive Protein, White Blood cell count and absolute Neutrophil %age in the evaluation of pediatric Appendicitis. *J Emerg Med* 2021; 60 (4): 428-35. DOI: 10.1016/J.Jemermed.2020.10.040.
- 20- Kelly ME, Khan A, Riaz M, Bolger JC, Bennani F, Khan W et al. *Dig Surg* 2015; 32 (6): 459-63. DOI: 10.1159/000440818.
- 21- Abbas MH, Choudhry MN, Hamza N, Ali B, Amin AA, Ammori BJ. Admission levels of Serum Amyloid A and Procalcitonin are more predictive of the diagnosis of acute appendicitis compared with C-Reactive Protein. *Surg Laparosc Endosc Percutan*

Tech 2014; 24 (6): 488-494. doi:  
10.1097/SLE.0000000000000067.