

## Accuracy of neutrophil-to-lymphocyte ratio in the diagnosis of acute appendicitis

Arshadullah Khan, Sumayya Tajwar

### Abstract:

**Objective:** To study the accuracy of neutrophil-to-lymphocyte ratio in the diagnosis of acute appendicitis.

**Study Design:** Cross sectional study.

**Setting and duration:** The study was conducted in the Department of Surgery, Saudi National Hospital, Makkah Saudia arabia, one of the oldest private hospital in Makkah consist of 200 beds and cover all kind of emergencies from 1st March 2013 to 28th February 2015

**Methodology:** Patients suspected of having acute appendicitis subjected to appendicectomy of either gender between the ages of 15-60 years were included. Frequencies are presented for all categorical variables gender, sign and symptoms, neutrophil-to-lymphocyte ratio and histopathological results. Mean and standard deviation are presented for age of the patient and duration of disease. Sensitivity analysis was performed to compute sensitivity, specificity, accuracy, positive and negative predictive values of neutrophil-to-lymphocyte ratio in the diagnosis of acute appendicitis on the basis of histopathology as gold standard criteria. Effect modifiers was controlled through stratification of age, gender, duration of disease to see the effect of these on outcome variable. Post-stratification chi square test applied taking p-value of  $\leq 0.05$  as statistically significant.

**Result:** Out of 100 patients mean age was  $26.06 \pm 9.14$  years. Male were 70 and 30 were female. Mean duration of disease was  $5.58 \pm 2.78$  days. Sensitivity and specificity was found to be 78.75% and 80% respectively. Positive predictive value and negative predictive value was 94% and 48.48%. Diagnostic accuracy was 79%.

**Conclusion:** Neutrophil-to-lymphocyte ratio carries better diagnostic accuracy than histopathology in the diagnosis of acute appendicitis. Precision is further improved when both are considered together. We suggest that a neutrophil-to-lymphocyte ratio of  $>3.5$  may be considered as a diagnostic cut-off value in adults with appendicitis and that negative operations for suspected appendicitis in adults can be effectively reduced; we thus recommend the neutrophil-to-lymphocyte ratio as a useful diagnostic test for appendicitis in adults.

**Keywords:** Appendicitis, acute abdomen, diagnosis, neutrophil/lymphocyte (N/L) ratio, positive predictive value, negative predictive value, sensitivity analysis

### Received:

23rd January 2017

### Accepted:

23rd September 2017

King Khalid National  
Guard Hospital, Jeddah,  
Saudia Arabia.

A Khan  
S Tajwar

### Correspondence:

Dr. Arshad Ullah Khan,  
Consultant Surgical  
Oncology, King Khalid  
National Guard Hospital,  
King Abdul Aziz Medical  
City, Department of  
Surgical Oncology, Jeddah  
Saudia Arabia.  
Cell: +966566278980  
Email: drarshadpk@  
hotmail.com

### Introduction:

Acute appendicitis is one of the most common cause of right iliac fossa pain and surgical emergency.<sup>1</sup> It can lead to complications such as perforation, peri-appendicial abscess, peritonitis, and rarely death.<sup>2-3</sup> Its diagnosis is established by surgeons clinical impression depending on the presenting history, clinical evaluation and laboratory tests. Advances have been made in

diagnostic modalities, yet the surgeon's clinical acumen is put to test in almost 30-40% of patient population.<sup>4</sup> This raises the rate of negative appendicectomies to around 20%.<sup>5</sup> In classic description of acute appendicitis, the first symptom is peri-umbilical pain, followed by nausea, right iliac fossa pain and later on vomiting and fever. This sequence of events is noted in only 50% adults. Acute appendicitis with protean

manifestation may simulate almost any other acute abdominal condition and in turn may be mimicked by a variety of conditions. It is estimated that the accuracy of clinical diagnosis of acute appendicitis lies between 76% and 92%.<sup>6</sup>

Appendectomy for suspected acute appendicitis is a common procedure. The rate of normal appendix, unnecessary removed remains high 15-30% despite several technique.<sup>7</sup> On one hand a normal appendix at appendectomy represents a misdiagnosis on the other hand delayed diagnosis of appendicitis may lead to perforation, peri-appendicial abscess, peritonitis, and rarely death. Equally distressing is the fact that perforation may occur in upto 35% of cases. So traditionally surgeons have accepted a higher incidence of unnecessary appendectomies in order to decrease the incidence of perforation this approach is being questioned in today's era of evidence based medicine. The high rate of negative exploration for appendicitis is a burden faced not only by the general surgeon but also the patient and the society as a whole since appendectomy like any other operation result in socio-economic impacts in the form of hospital expenses lost working days and declined productivity.<sup>8</sup> The goal of surgical treatment is removal of an inflamed appendix before perforation with a minimal number of negative appendectomies.

The major part in diagnosis of acute appendicitis is made by the patient's history, physical examination along with few supportive investigations like the white blood cell (WBC) count,<sup>9,10</sup> neutrophil count,<sup>11</sup> and platelet count<sup>12</sup> along with the neutrophil-to-lymphocyte ratio (NLR).<sup>13,14</sup> Different scoring systems like Alvarado and Ohmann score have been devised to achieve more accuracy in diagnosis. Radiological investigations like Ultrasonography (USG) and Computerized Tomographic Scan (CT scan) of the abdomen are also used to diagnose the disease; which all carry some inherent limitations.<sup>15</sup> Total Leukocyte count (TLC) is one of the helpful investigations in diagnosis of acute appendicitis. Mild leukocytosis, ranging from 10,000 to 18,000 is usually present in patients

with acute, uncomplicated appendicitis and is often accompanied by a moderate polymorphonuclear predominance.<sup>16</sup> TLC is easily available test and not very expensive. It can be done in almost all laboratories round the clock. The diagnostic accuracy of TLC is increased further if combined with CRP, neutrophil count, shift to the left, sequential leukocyte count and neutrophil : lymphocyte ratio. Recently Goodman et al. advocated the use of neutrophil-to-lymphocyte (N/L) ratio as a diagnostic tool in adults, and a ratio above 3.5 was stated as optimally diagnostic for appendicitis.<sup>17,18</sup> We aimed to investigate whether the neutrophil-to-lymphocyte ratio might provide a more sensitive parameter and to find the optimal neutrophil-to-lymphocyte ratio for the diagnosis of appendicitis. The aim and objective of this study is to improve the diagnostic accuracy and with the decline in negative appendectomy rate and morbidity.

#### **Operational definition:**

Neutrophil/lymphocyte ratio: Neutrophil lymphocyte ratio can be calculated from the total leucocyte count and is an important measure of systemic inflammation. Acute appendicitis mean inflammation of the appendix.

#### **Methods and materials:**

Study design: Hospital based cross-sectional study.

Study setting: Study was conducted at surgical ward of Saudi National Hospital.

Duration of study: Two year after approval from ethical committee

Sample Size: 100 cases of acute appendicitis admitted to Surgical ward in Saudi National hospital Makkah Saudi Arabia

Sampling technique: Non-probability consecutive

Sample selection:

Inclusion criteria:

- All patients between the age of 15-60 yrs of either gender diagnosed clinically to have acute appendicitis and subjected to appendectomy.
- Exclusion Criteria: the patient with appendicular mass, Mackle's diverticulum,

Ovarian torsion and concomitant conditions where neutrophil, lymphocyte count is elevated like Rheumatoid arthritis, SLE, Gout etc. Patients having right iliac fossa pain with other pathology also excluded from the study.

#### **Data collection procedure:**

This study was conducted after approval from ethical committee of Saudi National Hospital. Permission from the institutional ethical review committee was taken prior to carry out the study. A total of 100 patients admitted to surgical unit of Saudi National Hospital; fulfilling the inclusion criteria, were included in the study. Informed consent was taken from each patient and/or their attendants to participate in this study. Clinical diagnosis of acute appendicitis was based on symptoms of pain, migration, nausea and vomiting, anorexia, fever and signs of peritoneal inflammation like right iliac fossa tenderness, rebound tenderness and guarding. Once acute appendicitis is suspected patient was undergo routine investigation. Peripheral blood samples were taken and CBC, total leucocytes count and differential count was done in all cases. Neutrophil-to-lymphocyte ratio was calculated by dividing the percentage values of neutrophils and lymphocytes obtained. Leukocytosis was accepted for TLC levels higher than 10,000 per cubic millimeter, and 3.5 was accepted as the cut-off value. Ultrasonography of abdomen and CT scan of abdomen was done to rule out acute appendicitis and other causes of acute abdomen. Patients with strong suspicion of acute appendicitis were advised emergency appendectomy. After obtaining informed consent, patient was operated and the appendectomy specimen sent for histopathological examination. The histopathological report was considered as the final diagnosis. The findings of variables as mentioned above were entered in proforma attached as annexure.

#### **Data analysis procedure:**

Data was analyzed on SPSS Version 16. Frequencies are presented for all categorical variables gender sign and symptoms, Neutrophil-to-

lymphocyte ratio and histo-pathological results. Mean and standard deviation are presented for age of the patient and duration of disease. Sensitivity analysis was performed to compute sensitivity, specificity, accuracy, positive and negative predictive values of neutrophil-to-lymphocyte ratio in the diagnosis of acute appendicitis on the basis of histo-pathology as gold standard criteria. Effect modifiers was controlled through stratification of age, gender, duration of disease to see the effect of these on outcome variable. Post-stratification chi square test applied taking p-value of  $\leq 0.05$  as statistically significant.

#### **Result:**

A total of 100 patients were admitted in Surgical Unit-Saudi National Hospital who met the inclusion and exclusion criteria were included in this study. Out of 100 patients minimum age of the patient was 15 while maximum age of the patients was 52 years. Mean age in our study was 26.06 years with the standard deviation of  $\pm 9.14$ . Mean duration of disease in our study was 5.58 days with the standard deviation of  $\pm 2.78$ . Out of 100 patients, 70 were male and 30 were female.

Sensitivity and specificity was found to be 78.75% and 80% respectively. Positive predictive value and negative predictive value was 94% and 48.48%. Diagnostic accuracy was 79% and p value was  $< 0.001$ .

Frequency distribution of age showed that out of 100 patients, 34, 41, 16, 5 and 4 patients were in age group  $< 20$  years, 20-29 years, 30-39 years, 40-49 years and 50-59 years respectively.

Frequency distribution of duration of disease showed that out of 100 patients duration of disease of 25 (2 patients was between 1-3 days, 43 patients was between 4-6 days, 20 patients was between 7-9 days and 12 patients was between 10-12 days as presented in Figure 1.

Out of 100 patients, 80 had positive histo-pathology and 20 had negative histo-pathology. Out of the 80 positive histo-pathology reports 49 had inflamed appendix, 3 had perforated

Table 1: Positive histopathology report

Histo-pathology positive report	Percentage
Normal appendix	20 (20%)
Inflamed appendix	49 (49%)
Perforated appendix	03 (03%)
Gangrenous appendix	28 (28%)

Table 2: Neutrophil-to-lymphocyte ratio according to duration of disease (days)

Duration of disease (days)	Neutrophil-to-lymphocyte ratio		Total
	>3.5	<3.5	
1-3	0(0%)	25(100%)	25
4-6	35 (81.40%)	08 (18.60%)	43
7-9	20 (100%)	0 (0%)	20
10-12	12 (100%)	0 (0%)	12
P-Value	<0.001		

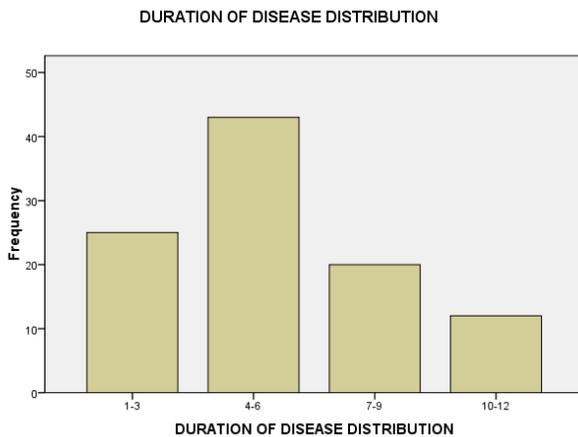


Figure-1: Duration of disease distribution in days

appendix and 28 had gangrenous appendix. As shown in Table 1. Out of 100 patients, 33 had neutrophil-to-lymphocyte ratio <3.5 and 67 had neutrophil-to-lymphocyte ratio >3.5.

Frequency distribution of sign and symptoms in our study showed that out of 100 patients abdominal pain was found in all patients, pain in RIF (58%), anorexia (80%), vomiting (50%) and fever (40%) were the common symptoms and rebound tenderness (70%), tachycardia (48%), Rovsing sign and Psoas sign (20%) were the common signs.

Stratification for age with respect to neutrophil-to-lymphocyte ratio showed that 01, 41, 16, 05 and 04 patients in age group <20, 20-29, 30-39, 40-49, 50-59 had Neutrophil-to-lympho-

cyte ratio >3.5 respectively. Whereas 33 in age group <20, and no any one in age group 20-29, 30-39, 40-49, 50-59 had Neutrophil-to-lymphocyte ratio <3.5 respectively. P-value was <0.001.

Stratification for gender with respect to Neutrophil-to-lymphocyte ratio showed that 45 (64.3%) and 25 (35.7%) had Neutrophil-to-lymphocyte ratio >3.5 and <3.5 in the male gender respectively. Whereas 22 (73.3%) and 08 (26.6%) had Neutrophil-to-lymphocyte ratio >3.5 and <3.5 in the female gender respectively. P-value was 0.37.

Stratification for duration of disease with respect to Neutrophil-to-lymphocyte ratio showed that 0 (0%), 35 (81.4%), 20 (100%) and 12 (100%) in duration of disease group <1-3, 4-6, 7-9 and 10-12 days had Neutrophil-to-lymphocyte ratio >3.5 respectively. Moreover, 25 (100%), 08 (18.6%), 0 (0%) and 0 (0%) in duration of disease group <1-3, 4-6, 7-9 and 10-12 days had Neutrophil-to-lymphocyte ratio <3.5 respectively. P-value was <0.001 as presented in Table-2.

**Discussion:**

Diagnosis of appendicitis in adults is a challenging task. Several diagnostic methods are used for appendicitis. Delay in diagnosis can be fatal. Thus, the surgeons aim to not only diagnose and operate early to avoid its adverse outcome and negative appendectomies. Unfortunately, there is no laboratory value for true and certain diagnosis of appendicitis. CBC is one of the initial labs done to confirm the diagnosis and various markers of acute inflammation have been used to diagnose appendicitis but their specificity and sensitivity values are low. Thus, emphasizing on the need for a new and strong parameter on which the diagnosis of appendicitis can be established.

Acute appendicitis is mainly an acute inflammatory state characterized by changes in blood flow, increase in permeability of blood vessels and migration of cells from the blood stream into the tissue. The inflammatory response is marked by a rise in neutrophils, lymphocytes

and other acute phase reactants. Both of these variables are mainly affected by inflammation and non-specific increases in TLC and neutrophils are observed in appendicitis. Thus Neutrophil-to-lymphocyte ratio can be used to evaluate the presence of appendicitis.

Our study revealed, out of 100 patients mean age was  $26.06 \pm 9.14$  years. Male were 70 and female were 30. Mean duration of disease was  $5.58 \pm 2.78$  days. Sensitivity and specificity was found to be 78.75% and 80% respectively. Positive predictive value and negative predictive value was 94% and 48.48%. Diagnostic accuracy was 79%.

Bialas M et al showed in the study that out of 469 patients enrolled in the study 280 (59.7%) patients were female and 189 (40.3%) were male. Mean age was 34 + 18 years. Optimal values of neutrophil-to-lymphocyte ratio and leukocytosis, according to sensitivity and specificity, were  $> \text{ or } = 3.5$  for neutrophil-to-lymphocyte and  $> \text{ or } = 12000/\text{mm}^3$  for leukocytosis. Neutrophil-to-lymphocyte ratio  $> \text{ or } = 3.5$  occurred to have much higher sensitivity (77.5% vs. 55%) but lower specificity (73.3% vs. 81.6%) than leukocytosis. Both leukocytosis and neutrophil-to-lymphocyte had satisfactory values of prediction and likelihood ratio for positive and negative results.<sup>19</sup>

Markar et al. showed that out of 1117 patients who underwent an appendectomy were included in the study. The median age was 34 years. NLR appears was found to have greater diagnostic accuracy than either WCC or CRP alone. The area under the ROC curve for NLR was 0.836, compared to 0.779 for WCC, 0.732 for CRP and 0.815 for  $\text{NLR} \times \text{CRP}$ .<sup>20</sup>

Yazici et al showed that out of 240 patients 183 were treated operatively and were histopathologically proven appendicitis. The remaining 57 patients were found to have non-specific abdominal pain. 90.2% of the appendicitis group and 12.3% of the NAP group had neutrophil-to-lymphocyte ratio higher than 3.5. The neutrophil-to-lymphocyte ratio was found to be more

sensitive parameter than TLC when evaluated retrospectively. Neutrophil-to-lymphocyte ratio of 3.5 can be used in the prediction of appendicitis.<sup>21</sup>

Neutrophil-to-lymphocyte ratio has higher sensitivity and specificity in diagnosing acute appendicitis. Neutrophil-to-lymphocyte ratio has greater diagnostic accuracy and is comparable with histo-pathology proven appendicitis which is a gold standard. Thus due to easiness of calculation, cost effectiveness, accuracy and simplicity neutrophil-to-lymphocyte ratio is worth using in establishing the diagnosis of appendicitis along with other diagnostic tools.

#### **Conclusion:**

Neutrophil-to-lymphocyte ratio carries better diagnostic accuracy than histopathology in the diagnosis of acute appendicitis. Precision is further improved when both are considered together. We suggest that a neutrophil-to-lymphocyte ratio of  $> 3.5$  may be considered as a diagnostic cut-off value in adults with appendicitis and that negative operations for suspected appendicitis in adults can be effectively reduced; we thus recommend the Neutrophil-to-lymphocyte ratio as a useful diagnostic test for appendicitis in adults.

**Conflict of interest:** None

**Funding source:** None

#### **Role and contribution of authors:**

Dr Arshadullah Khan, collected the data, references and wrote the initial write up including introduction, discussion, result and conclusion

Dr Sumayya Tajwar, helped in collecting the data and references also helped in discussion and results writing.

#### **References:**

1. Hospital Episode Statistics. Main procedures and interventions: summary 2008–2009. London: The NHS Information Centre for Health and Social Care, 2009. See <http://www.hesonline.nhs.uk>
2. Simpson J, Samaraweera AP, Sara RK, et al. Acute appendicitis – a benign disease? *Ann R Coll Surg Engl* 2008;90:313–16.
3. Eryilmaz R, Sahin M, Alimoglu O, Bas G, Ozkan OV. The value of C-reactive protein and leukocyte count in preventing negative appendicectomies. *Ulus Travma Derg.* 2001;7:142-45

4. Eryilmaz R, Sahin M, Alimoglu O, Bas G, Ozkan OV. The value of C-reactive protein and leukocyte count in preventing negative appendectomies. *Ulus Travma Derg.* 2001;7:142-45.
5. Shakhathresh HS. The accuracy of C-reactive protein in the diagnosis of acute appendicitis compared with that of clinical diagnosis. *Med Arh* 2000;54(2):109-10.
6. Keskek M, Tez M, Yoldas O, Acar A, Akgul O, Gocmen E et al. Receiver operating characteristic analysis of leukocyte counts in operations for suspected appendicitis. *Am J Emerg Med* 2008;26:769-772.
7. Shafi SM, Afsheen M, Reshi FA. Total leucocyte count, C-reactive protein and neutrophil count: diagnostic aid in acute appendicitis. *Saudi J Gastroenterol* 2009;15:117-120.
8. Albayrak Y, Albayrak A, Albayrak F, Yildirim R, Aylu B, Uyanik A et al. Mean platelet volume: a new predictor in confirming acute appendicitis diagnosis. *Clin Appl Thromb Hemost* 2011;17:362-366.
9. Markar SR, Karthikesalingam A, Falzon A, Kan Y. The diagnostic value of neutrophil: lymphocyte ratio in adults with suspected acute appendicitis. *Acta Chir Belg*;110:543-547.
10. Kamal D, Akhtar A, Siraj A. Accuracy of Total Leukocyte Count and C - Reactive Protein in the Diagnosis of Acute Appendicitis. *Journal of Rawalpindi Medical College (JRMC)*; 2010;14(2):75-77.
11. Ho HS. Appendectomy. In: Wilmore DW, Cheung LY, Harden AL eds. *ACS Surgery, Principle & Practice.* Web MD, 2002:815-23
12. Grays anatomy. *The Anatomical Basis of Clinical practice* Susan Stranding (Ed);39th ed;Elsevier Churchill Livingstone; 2008;1366-7.
13. Douglass. *mink/DavidL.soybel; Appendix and appendectomy; In Maingots abdominal operations; Michel J, Zinner (Ed) 11th ed; McGraw-Hill; 2007;589-608.*
14. Schumpelick V, Dreua B, Ophoff K et al. Appendix and caecum: Embryology, anatomy and surgical applications. *Surg Clin North Am* 2000;80:295-318.
15. John Maa, Kimberly S, Kirkwood. The Appendix. In: *Sabiston Text Book Of Surgery: Courtney M. Townsend (Ed); 18th ed; Saunders;2008:1333-46.*
16. Carr NJ. The pathology of acute appendicitis. *Annals of diagnostic pathology.* 2000;4(1):46-58.
17. Bhasin SK, Khan AB, Kumar V, Sharma S, Saraf R. Vermiform appendix and acute appendicitis. *JK-Sciences.* 2007;9(4):167-170.
18. Andersson R (2004). Meta-analysis of the clinical and laboratory diagnosis of appendicitis. *Br J Surg.* 91(1):28-37.
19. Białas M, Taran K, Gryszkiewicz M, Modzelewski B. Evaluation of neutrophil-lymphocyteratiousefulness in the diagnosis of appendicitis. *Wiad Lek.* 2006;59(9-10):601-6.
20. Markar SR, Karthikesalingam A, Falzon A, Kan. The diagnostic value of neutrophil: lymphocyte ratio in adults with suspected acute appendicitis. *Acta Chir Belg.* 2010 Sep-Oct;110(5):543-7.
21. Yazici M, Ozkisacik S, Oztan MO, Gürsoy H. Neutrophil/lymphocyteratio in the diagnosis of childhood appendicitis. *Turk J Pediatr.* 2010 Jul-Aug;52(4):400-3.