

Neutrophil-To-Lymphocyte Ratio (NLR) as a Predictor of Acute Appendicitis

Sadia Tasleem¹, Nadia Gulnaz², Aamir Afzal³, Don Courtney⁴

Author's Affiliation

¹Department of Surgery and Western Vascular institute, UCHG, Ireland

²Department of General and Upper GI Surgery, UCHG, Ireland

³Bio-Statistician
Foundation University Islamabad

⁴Department of Surgery and Western Vascular institute, UCHG, Ireland

Author's Contribution

¹Manuscript writing and data collection

²Literature review, bibliography

³Data Analysis

⁴Supervising the whole research work as a supervisor

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Address of Correspondence

Dr Sadia Tasleem

Email: dr.sadia84@gmail.com

Introduction

The most common reason for an acute surgical assessment of the abdomen¹ is acute appendicitis with a rate as high as 30%. It is estimated that the annual incidence of acute appendicitis is 100 per 100,000 of the population. There is a lifetime risk of 8.6% and 6.7% in men and women respectively.² The common age for presentation is between that of 5 and 40,⁴ while 28 is the median age. For unknown reasons, it tends to affect more males especially, those in the lower socioeconomic groups and, also people living in rural areas.⁵ It caused 72,000 deaths in 2013 worldwide down from 88,000 in 1990.⁶ In the United States, the number of people presenting with appendicitis requiring hospitalizations in 2010 was nearly 293,000.³

Though it's a common presentation, diagnosing acute appendicitis can become very challenging at times, especially in patients with severe or complicated appendicitis (phlegmonous or gangrenous) and those with atypical presentation. Hence there is a delay in diagnosis and appropriate management which

ABSTRACT

Objective: To determine the diagnostic accuracy of (NLR) neutrophil-to-lymphocyte ratio to prognosticate severe/ complicated appendicitis by taking histopathology of the appendix as a gold standard.

Methodology: This cross-sectional validation study was conducted at the department of surgery and western vascular institute, University College Hospital Galway, Ireland retrospectively for a period of 6 months i.e. from 05/06/2016 to 05/01/2016. For sampling in this study, non-probability purposive convenience technique was used. An informed consent was taken from each patient. All data were analyzed on SPSS version 21.

Results: The mean age of patients in this study was 29.15±9.54 years, the ratio of male to female was 1:1.7. The sensitivity, Specificity was 97.1% and 25.2% respectively and diagnostic accuracy of NLR was 38.7% taking histopathology as the gold standard.

Conclusion: According to our study results the (NLR) neutrophil-to-lymphocyte ratio is a highly sensitive tool to predict severe/ complicated appendicitis by taking histopathology as the gold standard, but with low value of diagnostic accuracy in terms of specificity.

Keywords: Acute, Neutrophil, Lymphocyte, Appendix, Histopathology, Accuracy.

in turn may lead to perforation and peritonitis (20% of acute presentations approx.). Both complications have high rates of morbidity and mortality.⁷

Diagnosing patients with acute appendicitis still remains multifactorial i.e. a surgeon has to use clinical assessment along with the scoring systems and various inflammatory markers as a guide to help in the decision making process. However, it has been known from various studies that none of these parameters has absolute diagnostic value neither are they specific for acute appendicitis.⁸

Many randomized controlled trials have questioned the traditional operative approach in acute appendicitis and have shown that antibiotics can be equally effective as surgery, with an overall significantly lower complication rates.^{9,10} Conservative management with antibiotics has been advocated by many surgeons for selected patients with simple/ uncomplicated appendicitis. However, there is a need to differentiate

complicated from un-complicated appendicitis preoperatively to predict patients suitable for a conservative management.^{2,9}

Emergency surgery is crucial for patients diagnosed as having acute appendicitis,^{13,14} since severe phlegmonous or gangrenous appendicitis can verily lead to peritonitis if, the inflamed appendix perforates. Therefore, establishing a correct diagnosis of acute appendicitis and evaluating the severity thereof provides useful information to the surgeons, which allows them to downgrade the risk of life-threatening peritonitis leading to sepsis. Although recent advances and studies advocating the use of antibiotic therapy in acute appendicitis have broadened the range of treatment options other than surgery,^{15,16} operative approach still remains the surgeon's first choice in patients with severe appendicitis, especially gangrenous appendicitis.^{13,14}

Complications of severe appendicitis may include wound infection and dehiscence, abdominal or pelvic abscess, incisional hernia, bowel obstruction, and rarely, death. Appendicitis of the stump can also occur rarely; So far at least 36 such cases have been reported to have occurred.¹²

Although a number of useful diagnostic modalities including, clinical evaluation symptoms, scoring systems,^{16,18} and imaging methods,^{19,20} for acute appendicitis are currently in practice, very few methods exist for evaluating of the severity of appendicitis itself before surgery.

Since the severity of acute appendicitis is based on inflammation, it can be correlated better with data from inflammatory markers, such as leucocyte count,^{21,22} neutrophil count, and platelet count as well as the neutrophil to lymphocytes ratio (NLR).^{23,24} In the same way, C-reactive protein (CRP) and albumin are known to be acute phase proteins and their serum levels correlate to the activity of inflammatory cytokines. CRP, in general, is used as an inflammatory marker not only in acute appendicitis but also in other several inflammatory diseases, including cancer.²⁵

The (NLR) neutrophil-lymphocyte ratio is an inexpensive and simple marker of subclinical inflammation, and verily easy to calculate from the differential leucocyte count.⁶ In studies reported recently, some authors have accounted that the (NLR) neutrophil to lymphocytes ratio is a good predictor of inflammation since it has been found to be effective in demonstrating the activation and the severity of acute attacks of the intestinal inflammatory disease.^{10,11} It is therefore advocated to be useful in the preoperative diagnosis of both simple and complicated appendicitis too.¹¹

NLR imparts information about 2 different immune and inflammatory pathways. The Neutrophil counts indicate active and continuous inflammation, while the regulatory pathway is demonstrated by the lymphocyte counts.¹¹

In this study, we propose that determining of the NLR may provide a sensitive parameter in the prediction of the severity of acute appendicitis in preoperative cases and may help delineate cases of simple or complicated appendicitis. In addition, variable values have been cited for the sensitivity and specificity of the NLR in the literature, which is another reason to carry out this study in our configuration to know exactly what are the statistics in our population, so that it serves as a more useful modality in patients needing surgery without considerable delay

Methodology

This Cross section validation study was conducted retrospectively in the department of surgery and western vascular institute, University College Hospital Galway, Ireland. The duration of study was 06 months Sample size (n) of approximately 186 cases were enrolled in the study with following sample size calculation; sensitivity = 70.8 %³, specificity = 48.5 %³, prevalence = 30%¹, precision= 10 % and confidence level = 95 %. Non-Probability consecutive sampling technique was used to collect data.

Patient age between 18 to 60 years of both genders presented with pain abdomen, nausea, vomiting, anorexia, temperature (Generalized pain abdomen, pain right iliac fossa or peri-umbilical pain) were included in the study. Patients who did not agree to participate in this study; Appendicitis in pregnancy (Serum Beta-Human chorionic gonadotropin values suggestive of pregnancy) those with significant co-morbidities and diagnosed cases of the colorectal tumor were excluded from the study.

A retrospective data collection was performed. All patients had both clinical diagnoses preoperatively by means of clinical history (abdominal pain, nausea, vomiting, anorexia, temperature), physical examination, laboratory test, and ultrasonography. An informed consent was taken from all patients. Gangrenous or perforated appendicitis was termed as complicated appendicitis. Histopathological findings; Acute inflammation within appendiceal mucosa, purulent serositis with necrotic /gangrenous appendiceal tissue or perforation at tip, body or base of the appendix. Automated hematology analyzer (Coulter LH 780 Hematology Analyzer, Beckman Coulter Inc., Brea, CA USA) was used to determine Neutrophil-to-lymphocyte ratio (NLR). The minimum value of NLR was taken 6 for complicated appendicitis. Diagnostic Accuracy of NLR in complicated appendicitis was measured in terms of sensitivity,

specificity, positive predictive value and negative predictive value. The ability of NLR to correctly identify those who have complicated appendicitis out of the total diseased population was defined as Sensitivity. The ability of the NLR to correctly identify those who do not have complicated appendicitis out of the total non-diseased population was defined as Specificity. Positive predictive value; the probability of having complicated appendicitis if NLR is positive. Negative predictive value; the probability that a patient with negative NLR results really does not have complicated appendicitis. True positive included the cases that are positive on both NRL and histopathology. True negative included the cases that are negative both on NLR and histopathology. Similarly, false positive included cases that are positive on NLR but negative on histopathology whereas false negative includes cases that are negative on NLR but positive on histopathology.

SPSS version 21.0 was used for data analysis. For quantitative variables like age and duration of symptoms Mean and standard was calculated whereas, for qualitative variables like gender and findings on NLR and histopathology, Frequency and percentage was calculated. Formulae based on 2x2 table was used for sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy, as follows; Sensitivity = $a / a + c \times 100$, Specificity = $d / b + d \times 100$, Positive predictive value = $a / a + b \times 100$, Negative predictive value = $d / c + d \times 100$, Diagnostic Accuracy = $a + d / a + b + c + d \times 100$.

Results

This study enrolled a total of 186 cases. Mean age (years) of the patients was 29.15 ± 9.54 . In our study 70 (37.63%) patients were male and 116 (62.37%) patients were females. The study results showed that the mean duration of symptoms of appendicitis was 2.25 ± 1.38 days. The study results showed that the mean neutrophil count was 11.49 ± 4.21 whereas mean lymphocytes count was 1.58 ± 0.57 . The mean NLR of the patients was 8.47 ± 4.75 whereas appendix was diagnosed positive by NLR in 147 (79%) patients and it was negative in 39(21%) patients. Out of 186 cases, the appendix was diagnosed positive by histopathology in 35(18.82%) patients and it was negative in 151(81.18%) patients, as shown in Table I

In this study the sensitivity of NLR was 97.1% with a specificity of 25.2%, PPV value was 23.1%, NPV value was 97.4% and the diagnostic accuracy of NLR was 38.7% taking histopathology as the gold standard, as shown in Table II

		Mean \pm SD
Age (years)		29.15 \pm 9.54
Duration of symptoms (months)		2.25 \pm 1.38
Lymphocytes		1.58 \pm 0.57
Neutrophil count		11.49 \pm 4.21
NLR		8.47 \pm 4.75
		n (%)
Gender	Male	70 (37.63)
	Female	116 (62.37)
Neutrophil-to-Leukocyte Ratio (NLR)	Positive	147 (79.0)
	Negative	39 (21.0)
Appendix Histopathology	Positive	35 (18.82)
	Negative	151 (81.18)

		HISTOPATHOLOGY		Total
		positive	negative	
NLR	Positive	34	113	147
	Negative	1	38	39
Total		35	151	186
Sensitivity = 97.1%		Positive Predictive Value = 23.1%		
Specificity = 25.2%		Negative Predictive Value = 97.4%		
Diagnostic Accuracy = 38.7%				

We observed that the sensitivity, specificity and diagnostic accuracy of NLR changes with duration of symptoms in days, the sensitivity, specificity and diagnostic accuracy of NLR was 100%, 17.0%, and 28.7% respectively for <3days and 92.3%, 93.75% and 93.1% respectively for >3 days.

In patients of age ≤ 40 years, the sensitivity, specificity and diagnostic accuracy of NLR was 100%, 24.2%, and 38.7% respectively while In patients of age > 40 years, the sensitivity, specificity and diagnostic accuracy of NLR was 75%, 31.6% and 39.1% respectively taking histopathology as the gold standard.

Discussion

This retrospective cross-sectional validation study was conducted to determine the diagnostic accuracy of (NLR) neutrophil-to-lymphocyte ratio to prognosticate severe/complicated appendicitis by taking histopathology as the gold standard.

Appendicitis is the most common cause of acute right lower abdominal pain in patients presenting to the emergency department. A serious dilemma for surgeons is the decision to

observe the patient until the diagnosis either becomes evident or to work early to avoid undesirable complications, such as perforation and peritonitis.⁷ The likely hood of this disease in life is around 7%, with rates of perforation from 17 to 20%. The risk of mortality is less than 1% in the general population, but this figure can reach 50% in the elderly.^{26,27}

In studies reported recently, some authors suggested that the neutrophil-to-lymphocyte ratio (NLR) is a good predictor of inflammation and hence useful in the preoperative diagnosis of Acute appendicitis.^{23,28,29}

In our study, the mean NLR of the patients was 8.47 ± 4.75 which correlates to other studies performed on NLR.

A study conducted by Kahramanca S et al⁷ suggested that the likely hood of acute appendicitis with the NLR of 4.68 was high (G1 vs G2, $p < 0.001$) Whereas the sensitivity was 65.3% and specificity and 54.7%. They advocated that the NLR is a useful preoperative parameter in the diagnosis of acute appendicitis and also in differentiating between complicated and simple appendicitis. Our study showed higher values of sensitivity, and lower value of Specificity i.e. 97.1% and 25.2% respectively.

In a study by Kelly M.E et al³⁰ NLR has been reported to be a useful adjunct in predicting the severity of appendicitis. In patients with postoperative complications the Mean NLR has been found to be statistically higher (13.69 for severe vs. 7.29 for simple appendicitis group, p -value = 0.016). This idea is supported by our study because we observed that in the patients with symptoms of the appendix of duration > 3 days, the diagnostic accuracy of NLR increases to 93.1% as compared to 28.7% in patients with symptoms of lesser duration.

Yazici et al advocated that the sensitivity is maximum when NLR is > 3.5 ,²⁹ it was also reported that specificity and PPV increase only steadily when NLR increases, whereas the most prominent values are reached when NLR is > 5.0 . It is interesting to note that at our cutoff point of 6 the PPV, NPV and diagnostic accuracy of NLR was, 23.1%, 97.4%, and 38.7% respectively

NLR on admission to the hospital can serve as an independent predictor of positive appendicitis on histology was suggested Markar et al.²⁸ and another study by Si Kyung Jung et al³¹ concluded that the initial NLR is a most powerful predictive factor in the elderly patient for the diagnosis of acute appendix leading to a perforation in the ED. However our study results did not show any significant difference in the diagnostic accuracy at ages below and above 40 years i.e. 38.7% and 39.1% respectively in each group, whereas NLR has been found

to be more sensitive in the earlier age group i.e. 100% as compared to 75% in the later. In our study specificity is lower in both groups i.e. 24.2% and 31.6% respectively. Mitsuru Ishizuka et al in their study showed that NLR value of (> 8) shows a significant correlation with gangrenous appendicitis in patients undergoing an appendectomy.²⁵ Our study was based on these reports and we found interesting similarities on our own observations.

Conclusion

Our study results suggest that the neutrophil to lymphocyte ratio (NLR) is a highly sensitive tool to predict severe/complicated appendicitis by taking histopathology of as gold standard, but with lower value of diagnostic accuracy in terms of specificity.

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