ORIGINAL ARTICLE

EVALUATING THE ACCURACY OF THE NEUTROPHIL-TO-LYMPHOCYTE RATIO IN DIAGNOSING ACUTE APPENDICITIS

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Background: Acute Appendicitis, a surgical emergency, is one of the most common causes of acute abdomen. Its' immediate diagnosis and surgery are of immense significance for the disease itself and its surgery carries a potential risk of morbidity and mortality. The goal of this study was to find out the role of Neutrophils to Lymphocyte Ratio (NLR) in making a confident diagnosis of acute appendicitis in a facility limited setup. **Methods:** It is a cross-sectional validation study on 100 patients admitted to the surgical wards of Ayub Teaching Hospital Abbottabad, with suspicion of Acute Appendicitis (AA), who subsequently underwent open appendectomy. Data were collected regarding the demography (name, age, gender) of the patient, physical examination, clinical presentations, and investigations including the complete blood count, from which the NLR value was calculated. Data was also collected regarding the histopathology examination of the appendix. **Results:** The sensitivity was 70.65% while the specificity was 87.5% and accuracy was 72%. Positive Predictive Value (PPV) was 98.4% and NPV was 20.6%. **Conclusion:** There is a strong correlation between NLR value and Acute Appendicitis. According to the results of our study, NLR ≥ 2.5 seems to be a reliable parameter to obtain a more certain diagnosis of Acute Appendicitis.

Keywords: Neutrophils to lymphocytes ratio; Acute Appendicitis; Alvarado score; Validity parameters

INTRODUCTION

Acute appendicitis is the most common cause of acute abdomen and a surgical emergency. The diagnosis of Acute Appendicitis poses a significant challenge for surgeons due to the overlapping signs and symptoms with other causes of acute abdomen[1]. Delay in diagnosing and treating AA can result in complications, occurring in 28–29% of cases, such as abscess formation, appendiceal perforation, systemic septic complications, wound infections, adhesions, bowel obstruction, and pulmonary issues from general anaesthesia.[2] Appendectomy accounts for approximately 10% of all abdominal surgeries worldwide, with a mortality rate ranging from 0.1–5.1%.[1,3] Therefore, prompt diagnosis and surgery for AA are of critical importance.

Obstruction of the appendicular lumen, regardless of its cause, leads to polymorphous leukocyte infiltration of the muscularis mucosae, accompanied by oedema and separation of the muscle fibres in the muscularis externa. This is the widely accepted pathogenesis of acute appendicitis.[4] Inflammation of the surrounding peritoneum results in pain in the right lower quadrant of the abdomen.[5] The systemic inflammatory response triggers neutrophilia and lymphocytopenia, which in turn increases the neutrophil-to-lymphocyte ratio (NLR) — a known marker of inflammation in various acute inflammatory conditions.[5,6]

The diagnosis of acute appendicitis (AA) is primarily based on patient's history and clinical examination, supplemented by investigations such as complete blood count (CBC), abdominal ultrasound (USG), and computed tomography (CT) scans.[6–8] A study in the UK found that the diagnostic certainty using the Alvarado scoring system ranged from 70–80%, though the diagnosis of AA remained uncertain in approximately 30–40% of cases.[9] Conditions that are commonly misdiagnosed as acute appendicitis due to the overlap of signs and symptoms with other gastrointestinal and genitourinary disorders include mesenteric lymphadenitis, constipation, gastroenteritis, obstructive hernia, orchitis, urinary tract infections, and gynaecological conditions such as ovarian cysts and pelvic inflammatory disease.[10] Prospective studies suggest that the Alvarado scoring system alone is insufficient for an accurate diagnosis of acute appendicitis, as it may lead to both false positive and false negative results.[11]

A systematic review and meta-analysis examining the diagnostic accuracy of procalcitonin, C-reactive protein (CRP), and white blood cell (WBC) count for suspected acute appendicitis found that the

diagnostic value of these variables is limited.[12] Diagnostic tools such as CT scans and ultrasounds are both expensive and often unavailable in peripheral healthcare settings, where the diagnosis of acute appendicitis is primarily based on clinical evaluation in conjunction with baseline investigations.[6] Therefore, there is a strong need for the development of new biological markers to improve clinical decision-making. In a review of randomized trials, Maximos Frountzas *et al*. recommended the use of the Alvarado and RIPASA scoring systems, with supplementary tools necessary for confident diagnosis, particularly in hospitals in developing countries and rural areas.[13] This study aims to assess the diagnostic accuracy of the neutrophil-to-lymphocyte ratio (NLR) as a biological marker for acute appendicitis.

The results will help in adopting a proper and easy test in the diagnosis of the condition. It will be useful for future researchers as a catalyst. Further research in different setup may consolidate the validity of the test.

MATERIAL AND METHODS

This cross-sectional validation study was conducted on patients suspected of having Acute Appendicitis in surgical wards of Ayub Teaching Hospital Abbottabad from January to 15th April 2019. All consecutive patients during the period of data collection as per sample selection criteria were included. After informed consent, 100 patients were included while 9 patients were excluded (two pregnant ladies, 7 conservatively managed patients). Data were collected regarding the socio-demography of the patients and detailed history by interviewing them, and thorough clinical examination. Relevant investigations were performed as per ward protocols, including preoperative complete blood counts (CBC), Urine R/E, and Ultra sonography of abdomen and pelvis. Percentage Neutrophils count and percentage lymphocyte count were recorded from the CBC report and NLR value was then calculated from it. Postoperatively appendectomy specimens were taken for histopathology examination (the gold standard for diagnosis of AA). Clinical histopathologist of histopathology department of Ayub Medical College would examine the specimen after processing as per their protocols to make definitive diagnoses. Data was analyzed on SPSS version 25. A *p*-value of <0.05 was considered statistically significant.

RESULTS

A total of 100 patients were included in this study, with a mean age of 23.84±10.2992 years (ranging from 6–60 years). Of these, 92 out of 100 patients (92%) were confirmed positive for acute appendicitis (AA) based on histopathology, with a male-to-female ratio of 1.49:1. Among the confirmed cases, 55 (59.78%) were male and 37 (40.22%) were female. Regarding the geographical distribution, 51 (55.43%) patients were from urban areas, while 41 (44.56%) were from rural areas, yielding an urban-to-rural ratio of 1.24:1. The majority of patients were young, with 74% falling within the 2nd and 3rd decades of life, while only 4% of patients were over the age of 50. (Table 1)

The parameters of the Alvarado score were cross-tabulated with the gender and residence of patients. All patients reported abdominal pain in the right iliac quadrant (RIQ), and the other Alvarado scale parameters were present in varying percentages. Tenderness in the RIQ, the second most commonly observed parameter, was found in 55 out of 59 (93.2%) male patients and 53 out of 55 (96.36%) rural patients. In females, 37 out of 41 (90.2%) exhibited tenderness in the RIQ, while 39 out of 45 (86.66%) urban residents presented with this symptom, making it the second most commonly observed clinical feature. The least frequent Alvarado scale parameter was a shift in neutrophils, which was observed in only 27 out of 59 (45.7%) male patients and 29 out of 55 (52.72%) rural patients. In females, both the shift in neutrophils and temperature were the least observed Alvarado score parameters, each appearing in 22 out of 41 (53.6%) patients. Among urban residents, the shift in neutrophils was the least observed, present in only 20 out of 45 (44.44%) patients. (Table 2)

Preoperative complete blood count (CBC) reports were obtained, and data regarding the percentage of neutrophils and lymphocytes were recorded. These values were then used to calculate the Neutrophil-to-Lymphocyte Ratio (NLR). The NLR values ranged from 0.65–29.50, with a mean value of 5.76±5.23. (Table 3)

The Neutrophil-to-Lymphocyte Ratio (NLR) was correlated with the histopathological examination of the appendix. Out of the 100 patients, 92 (92%) had histopathological evidence of inflammation (positive appendectomy), while 8 (8%) had a normal appendix, resulting in a negative appendectomy rate of 8%. (Table 4)

At cut-off values of NLR ≥2.5 and NLR ≥3, the validity parameters were calculated and found to be significant with a *p*-value of 0.001 on the Chi-square test. The Pearson's correlation between an NLR value ≥2.5 and histopathologically confirmed cases of Acute Appendicitis was found to be significant at a *p*-value level of 0.01. (Table 5)

Table-1: Socio-demographic parameters of the participants.

Age			
Mean = 23.84 ± 10.2992 years Minimum 6 - Maximum 60 years		6 to 10 years	10/ 100 (10%)
		11 to 20 years	30/ 100 (30%)
		21 to 30 years	44/ 100 (44%)
		31 to 40 years	12/ 100 (12%)
		41 to 50 years	1/ 100 (1%)
		51 to 60 years	3/ 100 (3%)
Gender		Male	55 (59.78%)
Ratio M:F = 1.49:1		Female	37 (40.22%)
Residence		Urban	51 (55.43%)
Ratio U:R = 1.24:1		Rural	41 (44.56%)

Table-2: Cross-tabulation of Alvarado score parameters with gender and residence.

Alvarado Parameters	Scale	Pain RIQ	Anorexia	Nausea	Temp	Tenderness	Rebound Tenderness	Leucocytosis	Shift
Gender	Male	59/59 (100%)	41/59 (69.5%)	40/59 (67.8%)	31/59 (52.5%)	55/59 (93.2%)	47/59 (79.6%)	41/59 (69.5%)	27/59 (45.7%)
	Female	41/41 (100%)	32/41 (78%)	32/41 (78%)	22/41 (53.6%)	37/41 (90.2%)	34/41 (82.9%)	27/41 (65.8%)	22/41 (53.6%)
Residence	Rural	55/55 (100%)	41/55 (74.5%)	43/55 (78.18%)	31/55 (56.4%)	53/55 (96.36%)	46/55 (83.63%)	35/55 (63.63%)	29/55 (52.72%)
	Urban	45/45 (100%)	32/45 (71.11%)	29/45 (64.44%)	22/45 (48.9%)	39/45 (86.66%)	35/45 (77.77%)	33/45 (73.33%)	20/45 (44.44%)
Total		100	73%	72%	53%	92%	81%	68%	49%

Table-3: Descriptive statistics of Neutrophils count, Lymphocytes count, and NLR.

	Minimum	Maximum	Mean	Std. Deviation
%age Neutrophils count on CBC	36.30	94.00	72.8360	12.91844
%age Lymphocytes count on CBC	3.10	55.40	20.8660	11.52422
Neutrophils to Lymphocytes Ratio	0.65	29.50	5.7566	5.22573

Table-4: Comparison of NLR with histopathology of the appendix.

	Histopathology confirmed cases.		Total
	Yes	No	
NLR ≥2.5 (indication of AA) Yes	(TP) 65	(FP) 1	66
No	(FN) 27	(TN) 7	34
Total	92	8	100

TP= True Positive, FP= False Positive, FN= False Negative, TN=True Negative

Table-5: Outcome value for NLR

Parameters	NLR ≥ 2.5	NLR ≥ 3
Sensitivity	70.65%	63.04%
Specificity	87.5%	100%
Positive predictive value (PPV)	98.49%	100%
Negative predictive value (NPV)	20.6%	19.04%
Accuracy	72%	64%.
Chi-Square Test	$p = 0.001$	P = 0.001

DISCUSSION

Appendectomy is more common in men than in women, with a male-to-female ratio of 1.5:1.[14,15] The lifetime risk of developing acute appendicitis is higher in males (about 8.6%) compared to females (6.7%).[16] Acute appendicitis (AA) has a peak incidence during the second and third decades of life, making it a disease predominantly affecting young adults.[17] In our study group, the majority of patients were young, with 74% in their second and third decades of life. The mean age of patients was 23.84±10.2992 years, which aligns well with the mean age reported in the literature.[18] Of the 92 confirmed cases on histopathology, 55 (59.78%) were male and 37 (40.22%) were female, yielding a male-to-female ratio of 1.49:1. Kukuk E studied changes in the neutrophil-to-lymphocyte ratio (NLR) in 241 patients with AA and observed a male-to-female ratio of 1.5:1 for Acute Appendicitis.[14]

The mean negative appendectomy rate reported in various studies varies, ranging from as low as 8.2% to 15–30%.[4,6] The rate of negative appendectomy in our study was 8%. The lower rate in our study can be attributed to the heightened awareness among surgical residents when data collection began. They became more concerned about negative appendectomies and took extra precautions

by ordering all necessary investigations and seeking senior consultations before proceeding with surgery. This can be considered a classic example of Hawthorne Bias.[19] However, since the objectives of our study are not related to the quality of diagnosis in a tertiary care setting and we did not include any subjective parameters that could have been influenced by clinicians, this observation is not significant to our study.

The literature includes studies on various laboratory markers such as CRP, MPV, TLC, red blood cell distribution width, interleukin-6, and procalcitonin for diagnosing acute appendicitis (AA). However, the neutrophil-to-lymphocyte ratio (NLR) has demonstrated greater diagnostic accuracy than any other laboratory marker when used alone.[1,20] Rabindra K.C. and colleagues investigated the relationship between NLR and the severity of Acute Appendicitis. They found that a preoperative NLR value greater than 5.60 is a valuable predictor of gangrenous appendicitis.[17]

Faraj F.H. et al. concluded that the neutrophil-to-lymphocyte ratio (NLR) has high diagnostic accuracy in diagnosing acute appendicitis, especially when used in conjunction with clinical examination.[5] Prasetya D. et al. also demonstrated that NLR is highly accurate in diagnosing acute appendicitis and distinguishing between uncomplicated and complicated cases.[21] The NLR increases, and the lymphocyte percentage decreases in acute appendicitis, making it a useful diagnostic marker[22]. However, the literature suggests that individual differences in inflammation response among patients may cause NLR to vary from person to person in response to inflammatory stimuli.[14]

Kostakis ID et al. reported that an NLR ≥3 showed [sensitivity: 90%, specificity: 88%, accuracy: 89%], while an NLR ≥3.5 demonstrated [sensitivity: 90%, specificity: 90%, accuracy: 90%] in diagnosing acute appendicitis.[23] Chirag Pereira et al. correlated NLR values with histopathology and found a significant relationship between acute appendicitis and NLR at a cutoff value of >2.4 ($p=0.0001$), with sensitivity of 70.1% and specificity of 43.2%. An NLR >4.3 was associated with complicated appendicitis cases, showing a sensitivity of 72.25% and specificity of 54.09%.[18]

In our study, the cutoff value for NLR was set at ≥2.5. Of the 92 confirmed cases on histopathology, 65 cases were true positives based on NLR, resulting in a sensitivity of 70.65% for NLR, while 27 cases were false negatives. Of the 8 confirmed negative cases on histopathology, 7 were true negatives based on NLR, yielding a specificity of 87.5% for NLR. Among the 66 positive cases on NLR, 65 were true positives, providing a positive predictive value (PPV)

of 98.49% for NLR in diagnosing acute appendicitis. Out of the 34 negative cases on NLR, 7 were true negatives, resulting in a negative predictive value (NPV) of 20.6%. The overall accuracy of NLR in diagnosing acute appendicitis was 72%. When the cutoff value for NLR was set at ≥3, we found a sensitivity of 63.04%, specificity of 100%, PPV of 100%, NPV of 19.04%, and accuracy of 64%. The Pearson's correlation between NLR value ≥2.5 and histopathology confirmed cases of Acute Appendicitis was found significant at the p-value levels of 0.01.

The strengths of the study are that procedural rigor was applied to enhance the internal validity. However, a small size sample makes the external validity difficult to employ.

CONCLUSION

In conclusion, an NLR ≥2.5 appears to be a reliable parameter for enhancing the accuracy of acute appendicitis diagnosis. However, a normal NLR value does not exclude the diagnosis.[21] To determine the optimal NLR cutoff and assess its accuracy, prospective randomized studies are required. A primary limitation of our study is that it only included patients who underwent appendectomy, and we lack data from patients with suspicious abdominal findings who did not have surgery. The diagnosis of acute appendicitis can be made with confidence through a thorough history, proper examination, and correlation with CBC, abdominal USG, and urine analysis.[24] The NLR can be particularly useful in diagnosing doubtful cases of right lower quadrant pain.[12,25] Additionally, in peripheral healthcare settings, where acute appendicitis is diagnosed clinically in conjunction with baseline investigations due to the unavailability of advanced tools, this simple, cost-effective, and easily interpretable marker can be a valuable diagnostic aid.

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