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Diagnostic Accuracy of Neutrophil to Lymphocyte Ratio to Differentiate Gangrenous from Non-Gangrenous Appendicitis Keeping Histopathology as Gold Standard

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Abstract

Objective: To determine diagnostic accuracy of neutrophil to lymphocyte ratio to differentiate gangrenous from non-gangrenous appendicitis keeping histopathology as gold standard.

Study Design: Cross Sectional Validation Study.

Study Setting: Department of General Surgery, MTI-KTH, Peshawar.

Study Duration: 28-01-2021 – 28-07-2021.

Subject and Methods:
This study was conducted on 148 patients with normal or inflamed appendix and gangrenous appendix. Patients having age between 18-60 Years of either gender were enrolled in the study.

Patients with malignant diseases, current course of chemotherapy or radiotherapy, pregnancy, intraoperative diagnosis of intraabdominal pathology other than appendicitis, and presence of known liver diseases were excluded. Diagnostic accuracy of Gangrenous appendicitis on NLR was determined.

Results:
This study was conducted on 148 patients. The mean age of the patients was 40.03±12.60 years. According to the diagnostic accuracy of Gangrenous appendicitis on NLR, sensitivity was 82.3%, specificity was 57.1%, Positive predictive value was 66.13%, negative predictive value was 77.03% and diagnostic accuracy was 70.20%

Conclusion:
The diagnostic accuracy of neutrophil to lymphocyte ratio to differentiate gangrenous from non-gangrenous appendicitis keeping histopathology as gold standard was 70.20%.

Introduction

Neutrophil count is one of the important parameters used for the differential diagnosis between simple appendicitis and complicated appendicitis [1].

The laboratory predictors are not constant and their accuracy is questionable, especially the leukocyte count and C-reactive protein (CRP), which are sensitive tests but are not specific for acute appendicitis. However, a combination of both tests in the presence of symptoms and signs seems to increase their specificity significantly, but the diagnosis of acute appendicitis is unlikely when both investigations are normal. It has, however, been reported that the neutrophil-to-lymphocyte ratio (NLR) is a good predictor in the preoperative diagnosis of acute appendicitis [2].

In many studies, neutrophil-to-lymphocyte ratio (NLR) is suggestive of complicated Acute Appendicitis. For this also cutoff limit is not universal. This is probably genetic factors; environmental factors also play a role in body response towards infection. Ishizuka et al. showed a cut-off value of 8.0 for neutrophil-to-lymphocyte ratio (NLR) to differentiate gangrenous appendicitis from catarrhal appendicitis [3].

Neutrophil-to-lymphocyte ratio (NLR) was effective in the differential diagnosis of appendicitis (sensitivity: 78%; specificity: 62%; AUC: 0760) [4].

In one another study, neutrophil-to-lymphocyte ratio (NLR) for diagnosis of acute appendicitis were 83.5%, 57.7%, 81.4%, 61.2%, 0.764, and 2.87, respectively; whereas the sensitivity, specificity, PPV, NPV, area under the ROC curve, and cutoff point of neutrophil-to-lymphocyte ratio (NLR) for differentiating complicated and simple appendicitis were 84.6%, 56.5%, 35.5%, 92.9%, 0.790, and 6.59, respectively [5].

In one another study, the sensitivity and specificity were 65.3% and 54.7%, respectively. A neutrophil-to-lymphocyte ratio (NLR) of 5.74 was associated with complicated appendicitis [6].

Due to scarcity of literature at the national level and with no local evidence, this study will help us obtain a more certain diagnosis in differentiating gangrenous appendicitis from non-gangrenous appendicitis and will further recommend the clinical evaluations in order keep continue taking precedence in such scenarios in our local population.

Operational definitions:

Gangrenous Appendicitis in Histopathology: The clinical diagnosis of GA will be established preoperatively by means of clinical history, physical examination, traditional laboratory tests with reference interval for leukocyte counts as 4500-10300/μL.

Gangrenous Appendicitis on Neutrophil to lymphocyte ratio (NLR): The recommended cutoff value of the NLR for positive and negative appendectomies will be decided using ROC curve analyses. The recommended cutoff value of the NLR will be based on the most prominent point on the ROC curve for sensitivity (0.653) and specificity (0.547). Because these two parameters indicated a cutoff value of 4.68, the recommended NLR cutoff value will be defined as 4.68.

Diagnostic accuracy: will be measured in term of sensitivity, specificity, positive and negative predictive values.

Materials and methods
Study Design: Cross Sectional Validation Study.
Setting: Department of General Surgery, MTI-KTH, Peshawar.
Duration Of Study: 28-01-2021 – 28-07-2021.
Sample Size: Total sample 148 size will be keeping 35.5%[5] proportion of appendicitis with sensitivity (84.6%)[5], specificity (56.5%%[5] with confidence interval 95%, margin of error 10%.
Sampling Technique: Consecutive Non probability sampling technique.

Sample Selection:
Inclusion Criteria:
Patients with normal or inflamed appendix and gangrenous appendix.
Patients with reliable results regarding the diagnosis of acute appendicitis and the prediction of perforation, respectively.
Patients of either gender.
Patients having age between 18-60 Years.

Exclusion Criteria:
Presence of malignant diseases, current course of chemotherapy or radiotherapy, pregnancy, intraoperative diagnosis of intraabdominal pathology other than appendicitis, and presence of known liver diseases.

Data Collection Procedure:
Approval was taken from Hospital's Ethical and REU Deptt at CPSP Karachi. This study was carried out in the Department of General Surgery. Written informed consent were obtained from all patients prior to the conduct of study. All patients were subjected to histopathology and Neutrophil to lymphocyte ratio (NLR) and diagnosis of gangrenous appendix in both procedures were recorded as per operational definition. All the information regarding

including age, gender, height, weight, findings on Neutrophil to lymphocyte ratio (NLR) and findings on histopathology were recorded in a pre-designed proforma attached to this synopsis.

Data Analysis:
Data were entered and analyzed using SPSS version 23.0. Mean and SD were calculated for numerical variables such as age, duration of disease, height, weight, BMI, Neutrophil to lymphocyte ratio (NLR). Frequencies and percentages were calculated for Gangrenous Appendicitis on Neutrophil to lymphocyte ratio (NLR), Gangrenous Appendicitis on Histopathology, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV). Diagnostic Accuracy was stratified with age, height, weight, BMI in order to see effect modifiers. Post stratification diagnostic accuracy was calculated keeping $\leq$ 0.05 as significant by taking Histopathology as gold standard from 2x2 table mentioned below:-

Results
This study was conducted on 148 patients. The mean age of the patients was 40.03±12.60 years. The mean height of the patients was 1.57±0.08 meters, the mean weight of the patients was 75.7±6.9 kg. The mean BMI recorded was 30.28±3.46 kg/m². The mean NLR was 6.12±0.80. The mean duration of disease was 17.52±3.5 hours. (Table 1). According to age distribution there were 43 (29.1%) patients in the age group of 18 to 30. There were 46 (31.1%) patients in the age group of 31 to 45 years and 59 (39.9%) patients in the age group of 46 to 60 years (Table 2). According to gender distribution there were 76 (51.4%) males and 72 (48.6%) females in our study (Table 3). According to the diagnostic accuracy of Gangrenous appendicitis on NLR, sensitivity was 82.3%, specificity was 57.1%, Positive predictive value was 66.13%, negative predictive value was 77.03% and diagnostic accuracy was 70.20% (Table 4). Stratification of diagnostic accuracy of Gangrenous appendicitis on NLR with age, height, weight and BMI can be seen from Table 5 to Table 8.

Table 1: Descriptive statistics (n = 148)

Variables	Mean	Std. Deviation
Age (Years)	40.03	12.605
Height in meters	1.5783	.08047
Weight in kg	75.0782	6.98046
BMI (kg/m²)	30.2860	3.46158
Neutrophil to lymphocyte ratio (NLR)	6.1209	.80885
Duration of disease (Hours)	17.52	3.590

Table 2: Age distribution

Age distribution	Frequency	Percent
18 to 30	43	29.1
31 to 45	46	31.1
46 to 60	59	39.9
Total	148	100.0

Table 3: Gender distribution

Gender distribution	Frequency	Percent
Male	76	51.4
Female	72	48.6
Total	148	100.0

Table 4: Diagnostic accuracy of Gangrenous appendicitis on NLR

		Gangrenous appendicitis on Histopathology		Total
		Positive	Negative	
Gangrenous appendicitis on NLR	Positive	93 (TP) 82.3%	15 (FP) 42.9%	108 73%
	Negative	20 (FN) 17.7%	20 (TP) 57.1%	40 56.4%
Total		113 100.0%	35 100.0%	148 100.0%

Abbreviation

TP = True Positive   FP = False Positive
FN = False Negative   TN = True Negative
Sensitivity = 82.3%   Specificity = 57.1%

Positive Predictive Value = 86.11%
Negative Predictive Value = 50%
Diagnostic accuracy = 76.35%

Table 5: Stratification of diagnostic accuracy of Gangrenous appendicitis on NLR with age

Age distribution			Gangrenous appendicitis on Histopathology		Total	P value
			Positive	Negative		
18 to 30 years	Gangrenous appendicitis on NLR	Positive	24 80.0%	6 46.2%	30 69.8%	0.02
		Negative	6 20.0%	7 53.8%	13 30.2%	
	Total		30 100.0%	13 100.0%	43 100.0%	
31 to 45 years	Gangrenous appendicitis on NLR	Positive	29 85.3%	8 66.7%	37 80.4%	0.16
		Negative	5 14.7%	4 33.3%	9 19.6%	
	Total		34 100.0%	12 100.0%	46 100.0%	
46 to 60 years	Gangrenous appendicitis on NLR	Positive	40 81.6%	1 10.0%	41 69.5%	0.0001
		Negative	9 18.4%	9 90.0%	18 30.5%	
	Total		49 100.0%	10 100.0%	59 100.0%	

Age groups (Years)	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
18 to 30	80%	53.54%	63.49%	72.60%	66.83%
31 to 45	85.29%	33.33%	78.38%	44.44%	71.74%
46 to 60	81.63%	90.00%	97.56%	50.00%	83.05%

Table 6: Stratification of diagnostic accuracy of Gangrenous appendicitis on NLR with height

Height distribution			Gangrenous appendicitis on Histopathology		Total	P value
			Positive	Negative		
1.40 to 1.50 meter	Gangrenous appendicitis on NLR	Positive	7 70.0%	1 16.7%	8 50.0%	0.03
		Negative	3 30.0%	5 83.3%	8 50.0%	
	Total		10 100.0%	6 100.0%	16 100.0%	
1.51 to 1.84 meter	Gangrenous appendicitis on NLR	Positive	86 83.5%	14 48.3%	100 75.8%	0.0001
		Negative	17 16.5%	15 51.7%	32 24.2%	
	Total		103 100.0%	29 100.0%	132 100.0%	

Height	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
1.40 to 1.50 meter	70.00%	83.33%	87.50%	62.50%	75.00%
1.51 to 1.84 meter	83.50%	51.72%	86.00%	46.88%	76.52%

Table 7: Stratification of diagnostic accuracy of Gangrenous appendicitis on NLR with weight

Weight distribution			Gangrenous appendicitis on Histopathology		Total	P value
			Positive	Negative		
61 to 75 kg	Gangrenous appendicitis on NLR	Positive	44	7	51	0.0001
			84.6%	41.2%	73.9%	
		Negative	8	10	18	
			15.4%	58.8%	26.1%	
	Total		52	17	69	
			100.0%	100.0%	100.0%	
76 to 89 kg	Gangrenous appendicitis on NLR	Positive	49	8	57	0.003
			80.3%	44.4%	72.2%	
		Negative	12	10	22	
			19.7%	55.6%	27.8%	
	Total		61	18	79	
			100.0%	100.0%	100.0%	

Weight	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
61 to 75 kg	84.62%	58.82%	86.27%	55.56%	78.26%
76 to 89 kg	80.33%	55.56%	85.96%	45.45%	74.68%

Table 8: Stratification of diagnostic accuracy of Gangrenous appendicitis on NLR with BMI

BMI distribution			Gangrenous appendicitis on Histopathology		Total	P value
			Positive	Negative		
> 27 kg/m2	Gangrenous appendicitis on NLR	Positive	68	11	79	0.0001
			81.9%	37.9%	70.5%	
		Negative	15	18	33	
			18.1%	62.1%	29.5%	
	Total		83	29	112	
			100.0%	100.0%	100.0%	
24 to 27 kg/m	Gangrenous appendicitis on NLR	Positive	25	4	29	0.34
			83.3%	66.7%	80.6%	
		Negative	5	2	7	
			16.7%	33.3%	19.4%	
	Total		30	6	36	
			100.0%	100.0%	100.0%	

BMI	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
> 27 kg/m2	81.93%	62.07%	86.08%	54.55%	76.79%
24 to 27 kg/m	83.33%	33.33%	86.21%	28.57%	75.00%

Discussion

One of the most typical causes of acute abdomen is acute appendicitis (AA). This illness affects roughly 7% of people in their lifetime, and perforation rates range from 17 to 20%. In the general population, the mortality risk is less than 1%, but in the senior population, this risk might reach 50%. Numerous well-known symptoms and indicators of this entity include right lower quadrant pain and an elevated leukocyte count [8]. These predictors are not continuous, and it is unclear how accurate they are. Raised leukocyte counts are a sensitive test for AA but are not diagnostic due to their low sensitivity, according to many authors. Atypical presentations are very common, particularly in the elderly. A negative appendectomy is fairly accepted historically to combat the morbidity and mortality of perforation prior to surgery. Since the procedure itself is a cause of morbidity and mortality, many have recently deemed this unacceptable and have researched ways to improve the preoperative diagnosis [9].

It's not always simple to diagnose AA early. Because perforation occurs in one-third of patients before treatment, acute appendicitis, which is initially a very benign condition, frequently develops into a serious condition that is life-threatening. The magnitude of the issue is also indicated by the high frequency of surgical complications. A substantial number of kids are unnecessarily exposed to the risk of surgery as a result of the significant number of misdiagnoses. In addition, a lot of kids undergo surgery very late, following perforation, which raises the risk of postoperative problems [10]. It is crucial to make the diagnosis early in order to lower the rate of complications and unsuccessful appendectomy in individuals with AA. Miserably, there is no laboratory indicator for a precise and conclusive diagnosis of AA [11].

There have been numerous attempts to figure out how to lower the negative laparotomy rate following a clinical suspicion of AA. It would be crucial to distinguish between nonspecific stomach discomfort and moderate early appendicitis for this reason. A definite answer in the detection of early AA is, however, missing despite a detailed clinical history, a thorough physical examination, and the customary laboratory investigations [12]. The usage of ultrasonography has grown over the last few years, with excellent outcomes and high sensitivity and specificity rates. Ultrasonography has shown to be a reliable diagnostic tool in experienced hands. In AA diagnosis, a prospective study found that ultrasonography was more reliable than the surgeon's initial clinical assessment [13].

What current laboratory tests are beneficial in the early detection of AA in children is one of the important topics. The leucocyte count has been the primary laboratory test for a very long time. Laboratory inflammatory markers'

diagnostic use has been investigated in the past with varying and conflicting outcomes [14].

The neutrophil-to-lymphocyte ratio (NLR), according to some authors, is a valuable diagnostic in the preoperative diagnosis of AA and a predictor of inflammation in recent years. Based on its predictive value, a study revealed that NLR calculation might offer a sensitive measure in the preoperative prediction of AA and avert negative appendectomy. Using an NLR greater than 3.5 has been reported to have higher specificity and sensitivity. Additionally, according to some experts, the NLR may be useful in differentiating between difficult and uncomplicated appendicitis. There are studies where this observation was not supported, though [15].

NLR is a simple way to measure a systemic inflammatory response and can be found in differential WBC counts. NLR is a significant predictive factor in individuals with coronary artery disease, different malignancies, and gastrointestinal stromal tumor, according to earlier studies. According to a study[11], NLR may be used as a reliable indicator of the presence of epicardial adipose tissue in dialysis patients. Furthermore, the findings of a different study demonstrated that the NLR value was a reliable predictor of in-hospital mortality in patients who presented with acute pulmonary embolism. Inadequate research has been done on the predictive significance of NLR in the diagnosis and prediction of AA problems in children [15].

In our study the sensitivity and specificity of gangrenous appendicitis on NLR was 82.3% and 57.1% respectively. Our findings are in agreement with a study[5] which showed sensitivity and specificity on NLR 84.6% and 56.5% respectively.

Conclusion

The diagnostic accuracy of neutrophil to lymphocyte ratio to differentiate gangrenous from non-gangrenous appendicitis keeping histopathology as gold standard was 70.20%.

References

1. Sengul S, Guler Y, Calis H, Karabulut Z. The Role of serum laboratory biomarkers for complicated and uncomplicated appendicitis in adolescents. J Coll Physicians Surg Pak. 2020; 30(4):420-424.
2. Virmani S, Prabhu PS, Sundeep P T, Kumar V. Role of laboratory markers in predicting severity of acute appendicitis. Afr J Paediatr Surg. 2018; 15:1-4.
3. Rabindra KC, Abhishek B, Rakshya J, Ashok K, Ishwar l. Comparison of the use of neutrophil: lymphocyte count ratio (NLCR) to total leukocyte count in diagnosing appendicitis in adults with right iliac fossa pain. J Society Surg Nepal. 2018; 21(2):24-27.
4. Ahmet A, Tuncer SC, Ayse BS. Can mean platelet volume, neutrophil-to-lymphocyte, lymphocyte-to-monocyte, platelet-to-lymphocyte ratios be favourable predictors for the differential diagnosis of appendicitis? J Pak Med Assoc. 2019; 69(5):647-52.
5. Prasetya D, Rochadi, Gunadi. Accuracy of neutrophil lymphocyte ratio for diagnosis of acute appendicitis in children: A diagnostic study. Ann Med Surg (Lond). 2019; 48:35-38.
6. Şahin K, Gülay Ö, Duray Ş. Neutrophil-to-lymphocyte ratio as a predictor of acute appendicitis. Ulus Travma Acil Cerr Derg. 2014; 20(1):19-22.
7. Humes DJ, Simpson J. Acute appendicitis. BMJ. 2006; 333(7567):530-534. Doi: 10.1136/bmj.38940.664363.AE. PMID: 16960208; PMCID: PMC1562475.
8. Detmer DE, Nevers LE, Sikes ED Jr. Regional results of acute appendicitis care. JAMA 1981; 246(12):1318-1320.
9. Alvarado A. Inflammatory Markers in Acute Appendicitis: Are we Still Looking for the Philosopher's Stone? J Surg. 2018; JSUR-1104.
10. Podany AB, Tsai AY, Dillon PW. Acute appendicitis in pediatric patients: an updated narrative review. J Clin Gastroenterol Treat. 2017; 3:42.
11. Carr NJ. The pathology of acute appendicitis. Ann Diagn Pathol. 2000; 4:46-58.
12. Styrud J, Eriksson S, Nilsson I, et al. Appendectomy versus antibiotic treatment in acute appendicitis. A prospective multicenter randomized controlled trial. World J Surg. 2006; 30:1033-1037.
13. Andersson RE, Hugander A, Thulin AJ. Diagnostic accuracy and perforation rate in appendicitis: association with age and sex of the patient and with appendicectomy rate. Eur J Surg. 1992; 158:37-41.
14. Dunn JCY. Appendicitis. In: Pediatric Surgery. Coran AG, Adzick NS, Krummel TM, et al. (eds.). Elsevier, Philadelphia. 2012; 1255.
15. Lessin MS, Chan M, Catallozzi M, et al. Selective use of ultrasonography for acute appendicitis in children. Am J Surg. 1999; 177:193-196.