Journal of Advances in Medicine and Medical Research

27(8): 1-7, 2018; Article no.JAMMR.44421
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Neutrophil Lymphocyte Ratio in Predicting Perforated Appendices in Emergency Settings

Ahmed Makki[1], Mahdi Mohammed Abulkalam[2*], Mohammed Abdullah Aldini[2], Nawaf Turki Ashgan[2], Abdulrahman Khaled Dafterdar[3] and Saleh Aldaqal[1]

[1]Department of Surgery, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.
[2]Department of Emergency Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.
[3]Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2018/44421
Editor(s):
(1) Dr. Thomas I. Nathaniel, University of South Carolina, School of Medicine-Greenville, Greenville, USA.
Reviewers:
(1) Tolga Dinç, Ankara Numune Training Hostital, Turkey.
(2) Einar Arnbjörnsson, Lund University, Sweden.
(3) Covanțev Serghei, State University of Medicine and Pharmacy "Nicolae Testemițanu", Moldova.
Complete Peer review History: http://www.sciencedomain.org/review-history/26527

Original Research Article

Received 09 July 2018
Accepted 28 September 2018
Published 05 October 2018

ABSTRACT

Objective: Present study aims to review the Neutrophil Lymphocyte Ratio (NLR) level in patients with acute appendicitis (non-perforated appendix) and those with a complicated perforated appendix, to evaluate the effectiveness of using the NLR level to predict if patients have a complicated perforated appendix.
Introduction: Appendicitis is a common cause of abdominal emergency globally. Many laboratory tests have been utilised to diagnose appendicitis, but no single laboratory test predicts the diagnosis accurately. Several studies proposed that the NLR associated with appendiceal perforation.
Methods: We performed a retrospective study of 308 patients who had undergone an appendectomy during June 2008 to September 2016 in King Abdul Aziz University Hospital. These cases were categorised histologically as an acute non-perforated appendix and complicated

**Corresponding author: E-mail: mahdimohammed25@gmail.com;*

perforated or gangrenous appendix. The study also compared the NLR levels of the two groups regarding the mean, sensitivity, and specificity.
Results: Results showed that NLR could be helpful in differentiating perforated appendix from acute appendicitis if cut-off point is 5.7 µmol/l with a sensitivity of 85.70% and specificity of 61.60%.
Conclusion: Mostly in clinical practice, acute appendicitis is diagnosed clinically, confirmed by laboratory investigations and radiological imaging. In addition to that, adding the serum, NLR level is useful in predicting the complicated perforated appendix.

Keywords: Non-perforated appendix; complicated perforated appendix; Neutrophil Lymphocyte Ratio.

1. INTRODUCTION

Acute appendicitis is a common reason to perform abdominal surgery globally, and most commonly occurs in the second decade of life [1]. The possibility of appendicitis occurring in an individual is around 7%, with perforation rates of 17-20% in a lifetime [2]. Mortality of the general population is 1% but can increase dramatically up to 50% in elderly patients [2,3]. The appendix rests in the lower right quadrant site of the abdomen [4].

Anorexia is considered one of the significant symptoms of appendicitis, and the earliest manifestation to appear in 95% of the cases preceded by abdominal pain, nausea, and vomiting [5]. Even with the advances in medical research in the field of laboratory and radiological diagnosis, still appendicitis is diagnosed solely based on clinical findings. Thus it remains a challenge for surgeons and even more challenging to diagnose in complicated appendicitis such as gangrenous [5,6].

Laboratory tests such as white blood count and C-reactive protein could support the clinical diagnosis, but cannot be relied solely due to its low sensitivity [7,8]. Several studies recommended that a high Neutrophil Lymphocyte Ratio (NLR) level is a useful parameter associated with a complicated perforated or gangrenous appendix. Study also endorsed that the NLR level could be helpful in determining whether the appendix has progressed from inflammation to a complicated state such as gangrenous or perforation [5,9]. The study aims to review the NLR level in patients with an acute non-perforated appendicitis and those with a complicated perforated appendix, to assess the effectiveness of using the NLR level to predict the possibility of them having a perforated appendix.

2. MATERIALS AND METHODS

2.1 Ethical Consideration

Institutional ethical approval was acquired from the Ethical Committee of King Abdul Aziz Hospital, affiliated to King Abdulaziz University, Jeddah, Saudi Arabia.

2.2 Study Design

The retrospective study of the patients, who had undergone an appendectomy, was conducted at King Abdulaziz University Hospital during June 2008 to September 2016. Patients' data were obtained by using an existing database (Phoenix by Al Anaiah). The study included all appendectomy cases with pre-operative lab test mostly complete blood count that provides neutrophil and lymphocyte counts. The study acknowledged the histopathology of the removed appendix and the type of surgical approach. The study also highlighted the NeutrophilLymphocyte Ratio as an NLR level of greater than 8 µmol/l. The patient records included their demographics, hospital progress, laboratory results, and operations. They were de-identified before analysis.

Overall, 906 patients underwent an appendectomy during the study, but only 308 patients (both pediatric and adults) were included. The study excluded the patients with acute abdomen other than appendicitis and didn't have a complete blood count (CBC) test during admission or had a missing histopathological data.

Patients were divided according to the histopathological result of the surgically removed appendix into two groups. Group 1 included patients with complicated perforated or gangrenous appendix and group 2 included patients with acute, non-perforated appendix.

2.3 Statistical Analyses

The statistical analysis was conducted by using SPSS version 22 (IBM SPSS Statistics; Armonk, NY, USA). Data were analysed using the mean and range by independent sample test distribution of age with a histogram. The chi-square test was performed to estimate the presence of a statistically significant relationship between the categorical variables. the study also measured the sensitivity, specificity, and optimal cutoff point for NLR, Area Under the Curve (AUC), CI levels of AUC of NLR in each group by Receiver Operating Characteristics (ROC) analysis and Youden's index. A p-value of ≤0.05 was deemed statistically significant.

3. RESULTS

The medical records of 308 patients were analysed and revealed that the peak occurrence of acute appendicitis was between 15 to 30 years with the mean age of 24 years as shown in Fig. 1.

Among 308 patients, nearly 2/3 (200 patients) were male (65%), and 1/3 (108 patients) were female (35%) (Table 1).

According to the histopathological findings, the patients were divided into two groups; group 1 (complicated perforated appendix) consisting of 49 patients (16%) and group 2 (acute non-perforated appendix) consisting of 259 patients (84%) (Table 2).

Among 49 patients with a complicated perforated appendix, 42 patients (86%) had high NLR level, with a range of 5.7-64 µmol/l. Among 259 patients with acute, non-perforated appendix, 160 patients (62%) had a high NLR level, with a range of 5.7-203 µmol/l (Table 3).

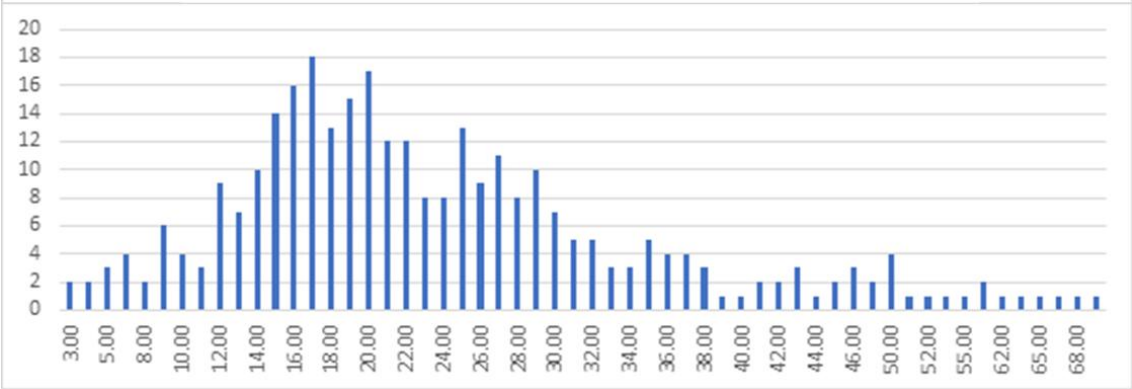

Fig. 1. Age distribution of both patients with a perforated appendix and acute non-perforated appendecitis

Table 1. Gender distribution of patients with a complicated perforated Appendix and those with an acute, non-perforated appendix

	Perforated appendix	Acute appendix	Total	p value
Male	38	162	200 (65%)	0.04
Female	11	97	108 (35%)	
Total	49 (16%)	259 (84%)	308 (100%)	

Table 2. Appendiceal histopathology of the patients

	Number of patients	Percentage (%)
Perforated appendix	49	16
Acute, non-perforated appendix	259	84
Total	308	100

Table 3. The Neutrophil Lymphocyte Ratio level in patients with a complicated perforated appendix and acute, non-perforated appendix

	Acute, perforated appendix		Acute, non-perforated appendix		p value
	Number of patients	Percentage (%)	Number of patients	Percentage (%)	
Normal NLR	7	14%	99	38%	0.078
High NLR	42	86%	160	62%	
Total	49	100%	259	100%	

As for other tests in Complete Blood Count (CBC), only White Blood Count (WBC) showed a difference with a p value (p = 0.040) while there was no notable difference among the complicated perforated appendix and acute, non-perforated (Table 4).

Regarding the strength of the test, it was revealed that the sensitivity of NLR in those with complicated perforated appendix was 85.70%, and the specificity was 61.60%, and the findings are shown in Table 5.

Open and laparoscopic appendectomy techniques were nearly equally performed where the percentage being slightly higher (161 patients i.e. 52%) for open appendectomy than the later (147 patients i.e. 48%).

4. DISCUSSION

Appendicitis is defined in the literature as inflammation of the worm-like structure known as vermiform appendix. Anatomically it arises from the post-eromedial aspect of the caecal wall (2 cm or less) below the end of the ileum [4].

Acute appendicitis affects around 233/100,000 people globally, and the highest point is in between 10 to 19 years old patient, that occurs more commonly in the second decades of life than others. The study reveals that the peak age of appendicitis was between 15 to 30 years. It was also higher among male than in female (ratio of 2:1), that corroborates with the previous findings (male to female ratio: 1.4:1) [10].

The key symptom of acute appendicitis is abdominal pain. Classically, it starts as dull, moderate periumbilical pain migrating to the right iliac fossa, within 4 to 6 hours. This localising pain is the most substantial diagnostic sign of appendicitis [11,12] other than the rebound test which is enough on its own for a diagnosis, especially in male patients. In addition to the mentioned symptoms, the complicated perforated appendix might also present with high fever and rectal fullness [13]. In addition to the previous signs and symptoms of peritonitis, as decreased appetite, fever, nausea, thirst, vomiting, and chills [14]. However, this could show a typical signs and symptoms.

Table 4. The mean of the other tests of CBC excluding NLR

	Acute, perforated appendix	Acute, non-perforated appendix	Overall	p value
WBC	17.12	14.35	14.79	0.040
Neutrophil	12.44	11.74	11.85	0.533
Eosinophil	0.05	0.07	0.07	0.173
Basophil	0.04	0.03	0.03	0.464

NLR: Neutrophil Lymphocyte Ratio
WBC: White Blood Count

Table 5. The sensitivity and specificity of neutrophil lymphocyte ratio in patients with a perforated appendix

Sensitivity	85.70%		
Specificity	61.60%		p value
Optimal cut-off point	5.7		0.03
Area Under the Curve (AUC)	0.598		
Area Under the Curve CI	LB	UB	
	0.521	0.675	

It is challenging to distinguish clinically between acute, non-perforated appendix from a complicated perforated appendix, especially in older adults and children. It is crucial for a timely and accurate diagnosis of patients presenting to emergency departments with acute appendicitis because a delayed diagnosis and surgical intervention of patients with appendicitis results in increased risk of complications such as perforation. In contrast, early surgical decisions may lead to negative laparotomies [15,16]. The choice of surgery cannot depend only on the clinical picture but should be supported by laboratory and imaging studies.

Multiple diagnostic imaging techniques are helpful in diagnosing acute appendicitis. Ultrasound is less expensive than other methods and saves time with an accuracy rate of 71-97% [5,17]. Multi-detector computed tomography is regarded as a gold standard imaging method to diagnose suspected appendicitis due to its high sensitivity, specificity and accuracy rate of 95% [5,18,19]. Magnetic resonance imaging has precise diagnostic accuracy in the assessment of acute appendicitis in paediatrics and pregnant patients [18,19]. However, the radiological facilities might not be available in every ER centre especially in rural areas or small centres.

For this reason, various scales have been developed, and several biomarkers are being investigated to help in diagnosing acute appendicitis. Some of these tests are the white blood cell count and C-reactive protein levels; Wilson et al. [20] demonstrated that white cell count over 20000/mm^3 suggests gangrenous, perforated appendix. Individually, these tests are weak and non-specific discriminators but have a high discriminatory potential when they are combined with each other [9,10]. However, their specificity varies among studies and may be only sufficiently elevated once appendiceal perforation occurs [15,16,21].

Recently, several studies stressed that NLR might be a better marker for acute appendicitis than C-reactive protein, leukocyte or neutrophil count alone [22,23].

NLR is an easily acquired parameter to assess the inflammatory status of a subject. Many studies have proven its value in multiple medical fields such as in determining the mortality in major cardiac events [24,25], as a strong prognostic factor in various types of malignancies [26-33], or as a marker of inflammatory or infectious pathologies and post-operative complications [9,34]. Recently, it was proposed that it could provide diagnostic value in differentiation between the perforated appendix from the acute appendix.

Multiple studies consisting of authors (Kahramanca et al. [9] and Ishizuka et al. [34]) proved that it is a good indicator, However, they suggested numerous cutoff points for NLR level 5.7 and 8 µmol/l with different sensitivities ranging from 63% and 73% and specificities ranging from (39% to 49%) (9, 34) respectively to differentiate between the two groups of complicated perforated appendix and acute, non-perforated. The study also recorded the optimal cut-off point of 5.7 µmol/l with a sensitivity of 85.70% and specificity of 61.60% (Table 5).

The standard approved treatment method of acute appendicitis is appendectomy either by conventionally or laparoscopically [19,22,23]. Both techniques were used equally in the present study.

5. STRENGTHS AND LIMITATIONS

The research limitation includes its retrospective design and single-centered study, even so, it can be recommended to use NLR cut-off point of 5.7 to differentiate between acute appendicitis and complicated perforated appendicitis. It is also recommended in determining the optimal NLR and its effects on further prospective multi-centered studies.

6. CONCLUSION

Acute appendicitis is a common reason of acute abdomen irrespective of their age. NLR is a low-cost and easily accessible test that has been determined in this study. It has been proved to be a useful indicator in the diagnosis of complicated perforated appendix combined with clinical sign and symptoms.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Institutional ethical approval was acquired from the Ethical Committee of King Abdul Aziz Hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Stewart B, Khanduri P, McCord C, Ohene-Yeboah M, Uranues S, Vega Rivera F, et al. Global disease burden of conditions requiring emergency surgery. Br J Surg. 2014;101(1):e9-22.
2. 2.Franz MG, Norman J, Fabri PJ. Increased morbidity of appendicitis with advancing age. Am Surg. 1995;61(1):40-4.
3. 3.Freund HR, Rubinstein E. Appendicitis in the aged. Is it really different? Am Surg. 1984;50(10):573-6.
4. Standring S. Gray's anatomy: The anatomical basis of clinical practice. London: Churchill Livingstone Elsevier; 2008.
5. Akgül N, Gündeþ E. Neutrophil/ lymphocyte ratio in acute appendicitis: A state hospital experience. Turk J Colorectal Dis. 2016;26(4):121-4.
6. 6.Prystowsky JB, Pugh CM, Nagle AP. Current problems in surgery. Appendicitis. Curr Probl Surg. 2005;42(10):688-742.
7. 7.Yang HR, Wang YC, Chung PK, Chen WK, Jeng LB, Chen RJ. Laboratory tests in patients with acute appendicitis. ANZ J Surg. 2006;76(1-2):71-4.
8. 8.Hallan S, Asberg A, Edna TH. Additional value of biochemical tests in suspected acute appendicitis. Eur J Surg. 1997; 163(7):533-8.
9. Kahramanca S, Özgehan G, Þeker D, Gökce EÝ, Þeker G, Tunç G, et al. Neutrophil-to-lymphocyte ratio as a predictor of acute appendicitis. Ulus Travma Acil Cerrahi Derg. 2014;20(1):19-22.
10. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol. 1990;132(5):910-25.
11. Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, et al. Schwartz's principles of surgery; 2015.
12. Varatorn R, Suchato C. Sabiston textbook of surgery the biological basis of modern surgical practice 19th Edition 2012. bkkmedj The Bangkok Medical Journal. 2012;04(01):122.
13. Lee SL, Walsh AJ, Ho HS. Computed tomography and ultrasonography do not improve and may delay the diagnosis and treatment of acute appendicitis. Arch Surg. 2001;136(5):556-62.
14. Brennan GD. Pediatric appendicitis: Pathophysiology and appropriate use of diagnostic imaging. CJEM. 2006;8(6):425-32.
15. Escriba A, Gamell AM, Fernandez Y, Quintilla JM, Cubells CL. Prospective validation of two systems of classification for the diagnosis of acute appendicitis. Pediatr Emerg Care. 2011;27(3):165-9.
16. Konan A, Hayran M, Kilic YA, Karakoc D, Kaynaroglu V. Scoring systems in the diagnosis of acute appendicitis in the elderly. Ulus Travma Acil Cerrahi Derg. 2011;17(5):396-400.
17. Mostbeck G, Adam EJ, Nielsen MB, Claudon M, Clevert D, Nicolau C, et al. How to diagnose acute appendicitis: ultrasound first. Insights Imaging. 2016; 7(2):255-63.
18. Humes DJ, Simpson J. Acute appendicitis. BMJ. 2006;333(7567):530-4.
19. Shogilev DJ, Duus N, Odom SR, Shapiro NI. Diagnosing appendicitis: Evidence-based review of the diagnostic approach in 2014. West J Emerg Med. 2014;15(7): 859-71.
20. Wilson EB, Cole J, Nipper ML, Cooney DR, Smith RW. Computed tomography and ultrasonography in the diagnosis of appendicitis: When are they indicated? Archives of Surgery. 2001;136(6):670-5.
21. Temple CL, Huchcroft SA, Temple WJ. The natural history of appendicitis in adults. A prospective study. Ann Surg. 1995;221(3):278-81.
22. Markar SR, Karthikesalingam A, Falzon A, Kan Y. The diagnostic value of neutrophil: lymphocyte ratio in adults with suspected acute appendicitis. Acta Chir Belg. 2010; 110(5):543-7.
23. Goodman DA, Goodman CB, Monk JS. Use of the neutrophil:lymphocyte ratio in the diagnosis of appendicitis. Am Surg. 1995;61(3):257-9.
24. Azab B, Chainani V, Shah N, McGinn JT. Neutrophil-lymphocyte ratio as a predictor of major adverse cardiac events among diabetic population: A 4-year follow-up study. Angiology. 2013;64(6): 456-65.
25. Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G, et al. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass

grafting. Am Heart J. 2007;154(5):995-1002.
26. Hung HY, Chen JS, Yeh CY, Changchien CR, Tang R, Hsieh PS, et al. Effect of preoperative neutrophil-lymphocyte ratio on the surgical outcomes of stage II colon cancer patients who do not receive adjuvant chemotherapy. Int J Colorectal Dis. 2011;26(8):1059-65.
27. Tomita M, Shimizu T, Ayabe T, Yonei A, Onitsuka T. Preoperative neutrophil to lymphocyte ratio as a prognostic predictor after curative resection for non-small cell lung cancer. Anticancer Res. 2011; 31(9):2995-8.
28. Sharaiha RZ, Halazun KJ, Mirza F, Port JL, Lee PC, Neugut AI, et al. Elevated preoperative neutrophil:lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. Ann Surg Oncol. 2011;18(12):3362-9.
29. Kim HS, Han KH, Chung HH, Kim JW, Park NH, Song YS, et al. Neutrophil to lymphocyte ratio for preoperative diagnosis of uterine sarcomas: A case-matched comparison. Eur J Surg Oncol. 2010; 36(7):691-8.
30. Garcea G, Ladwa N, Neal CP, Metcalfe MS, Dennison AR, Berry DP. Preoperative neutrophil-to-lymphocyte ratio (NLR) is associated with reduced disease-free survival following curative resection of pancreatic adenocarcinoma. World J Surg. 2011;35(4):868-72.
31. Azab B, Bhatt VR, Phookan J, Murukutla S, Kohn N, Terjanian T, et al. Usefulness of the neutrophil-to-lymphocyte ratio in predicting short- and long-term mortality in breast cancer patients. Ann Surg Oncol. 2012;19(1):217-24.
32. Keizman D, Ish-Shalom M, Huang P, Eisenberger MA, Pili R, Hammers H, et al. The association of pre-treatment neutrophil to lymphocyte ratio with response rate, progression free survival and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma. Eur J Cancer. 2012;48(2):202-8.
33. Proctor MJ, Morrison DS, Talwar D, Balmer SM, Fletcher CD, O'Reilly DS, et al. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow inflammation outcome study. Eur J Cancer. 2011;47(17):2633-41.
34. Ishizuka M, Shimizu T, Kubota K. Neutrophil-to-lymphocyte ratio has a close association with gangrenous appendicitis in patients undergoing appendectomy. Int Surg. 2012;97(4):299-304.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/26527