ORIGINAL ARTICLE

Total leukocyte and neutrophil count as preventive tools in reducing negative appendectomies

Muhammad Salman Rafiq, M.D., Mah Muneer Khan, M.D., Ataullah Khan, M.D., Bilal Ahmad, M.D.

Department of Surgical, Khyber Teaching Hospital, Peshawar, Pakistan

ABSTRACT

BACKGROUND: Negative appendectomies result in unnecessary admissions, health care burden, and cost. This study was conducted to assess total leukocyte and neutrophil counts as preventive tools in reducing negative appendectomies.

METHODS: Data of admitted patients who underwent appendectomies was analyzed. Receiver operator characteristic (ROC) curve analysis of total leukocyte and neutrophil counts was calculated for various cut-off points. Optimum sensitivity, specificity, overall accuracy, and area under the curve was determined.

RESULTS: Of the four hundred and eightpatients, true and negative appendicitis by operative assessment was 294 (72.1%) and 114 (27.9%) compared to 311 (76.2%) and 97 (23.8%) by histopathology, respectively. Optimal cut-off for total leukocyte count was >11.9x10^9/Liter with 87.14% sensitivity and 91.75% specificity. Optimal cut-off point for neutrophil count was >7.735x10^9/Liter with 98.71% sensitivity and 91.75% specificity. Area under the curve for total leukocyte and neutrophil counts was 0.9603 and 0.9872, respectively with overall accuracy of 91.2% and 97.1%, respectively.

CONCLUSION: Normal total leukocyte and neutrophil counts are strongly associated with negative appendectomies. Non-operative measures and careful observation of total leukocyte and neutrophil counts are of paramount importance.

Key words: Acute; appendicitis; leukocyte count; negative appendectomy; neutrophils; ROC curve.

INTRODUCTION

Acute appendicitis (AA) remains the commonest surgical abdominal emergency.[1] Its incidence is 1.5-1.9 per 100.000 and is 1.4 times more common in men.[2] Life time risk of suffering from acute appendicitis is 7%[3] with peaks in the second and third decades of life.[4] In Pakistan, over 400.000 appendectomies are performed annually.[5] It is one of the most common surgical emergencies treated by resident surgeons.

Acute appendicitis is a clinical diagnosis supported by various scoring methods, radiographic and laboratory (lab) tests.[6] Base line investigations like total leukocyte and neutrophil count are routinely carried out in every center due to the ease of availability and interpretation.[7] These are of special benefit in developing countries where modern health facilities may be out of reach. Use of such base line investigations for the diagnosis of common emergent conditions has a rewarding cost-benefit ratio. Total leukocyte count (TLC) and neutrophil count (NC) are among the commonly performed base-line investigations.

The rate of negative appendectomy (NA); however, remains high varying between 15-30%.[8] A NA rate of 5-15% is acceptable, keeping in mind the adverse effects of non-operability in a true appendix (TA) and advantages of safety in a negative exploration.[9] Radiographic tools like computed tomography (CT) can reduce the rate of NA from 24% to 7.6%.[10] However, such valuable tools are not ubiquitously available. The use of simple diagnostic tools is, therefore, of great importance, especially if they are cheap, and easy to perform and interpret. Consequently, this study was carried out to analyze the role of TLCand NC in preventing and/or reducing acute appendicitis (AA).

MATERIALS AND METHODS

This retrospective study was conducted in the Surgical Department of Khyber Teaching Hospital Peshawar after collecting the data of four hundred and eight patients from Au-

Address for correspondence: Muhammad Salman Rafiq, M.D.
House No. 5, Street H, Danish Abad. 25000 Peshawar, Pakistan
Tel: 0092-0346-9035574 E-mail: drsalmanrafiq@hotmail.com

Qucik Response Code

Ulus Travma Acil Cerrahi Derg
2015;21(2):102-106
doi: 10.5505/tjtes.2015.29626

gust 2012 to May 2014. Approval of the research and ethical committees was taken. In all cases, written informed consent and uniform guidelines of management were followed with the standard operating technique of a right lower quadrant incision, saline wash and primary closure.

All cases presented to us in the emergency with a diagnosis of acute appendicitis during the study period were included. Patients with interval, elective or incidental appendectomies were excluded. All cases with comorbidities such as Crohn's disease, pelvic inflammatory disease, gastroenteritis, systemic infection, and pregnancy were also excluded. Pre-operative (pre-op) clinical and laboratory data was collected for all casesincluding demographic data (age, gender), TLC (x×10^9/Liter), neutrophil count (x×10^9/Liter and %), neutrophil to lymphocyte ratio NLR, ALVARADO score,[11] and pre-operative (pre-op) assessment of signs of acute appendiceal inflammation. Cases were considered NA by post-op histopathological assessment. All investigations were obtained at the Pathology Department of Khyber Teaching Hospital, Peshawar. Elevated TLC was taken as count >11.5×10^9/Litre[6] and elevated Neutrophil count was taken as >75%11.

Data analysis was carried out using SPSS 20 and MedCalc 12.5. Mean, percentage and standard deviation of the variables was calculated. Comparison of nominal data was done using Chi-Square and of interval data using t-test. Receiver-operating characteristic (ROC) curves were calculated for TLC and NC. Area under the curve (AUC) was obtained and appropriate cut-off points were identified for optimum sensitivity and specificity. In all cases, a p-value of <0.05 was considered statistically significant.

RESULTS

Pre-operative assessment showed that two hundred and ninety-four (72.1%) of the total of 408 patients had signs consistent with acute appendicitis. This was further increased by 4.1% to 311 (76.2%) patients with acute appendicitis by histo-pathological findings of the specimens. Statistical analysis is shown in Table 1. Gender distribution (p=0.654) and mean age (p=0.240) were not statistically significant between the groups. Statistically significant differences between the groups were found with higher values each in the true appendicitis group for symptom duration (hours); 28.63±5.914 (p=0.023), admission temperature (°F); 99.906±0.8534 (p<0.001), TLC (x10^9/Liter); 13.090±1.2079 (p<0.001), neutrophil count (%); 69.41±2.994 (p<0.001), neutrophil count (x10^9/Liter); 9.106±1.1521 (p<0.001), neutrophil to lymphocyte ratio; 2.8851±0.5273 (p<0.001), and ALVARADO score; 7.43±0.771 (p<0.001), respectively.

Two ROC-curves were obtained for TLC and NC after applying Logistic Regression to achieve greater probability and accurate distribution. Figure 1a represents ROC-curve for TLC (x10^9/Liter) and Figure 1b for neutrophil count (x10^9/Liter). In both figures, the Youden associated criterion is represented by the white circle. AUC represents area under the curve. Table 2 shows the salient cut-off points for both ROC-curves with estimated specificity at fixed sensitivity and vice versa. Table 3 shows the diagnostic measures obtained for both curves. In Table 3, the salient measures for TLC include associated criterion; >11.9x10^9/L at 95% confidence interval, sensitivity; 87.14%, specificity; 91.75%, area under the curve; 0.960337, overall accuracy; 91.2%, and precision; 0.972719

Table 1. True and negative appendectomy comparison

	True appendectomy			Negative appendectomy			p
	n	%	Mean±SD	n	%	Mean±SD	
Status by per operative findings	294	72.1		114	27.9		
Status by histopathology	311	76.2		97	23.8		
Gender							
Males	149	47.9		49	50.5	0.654	
Females	162	52.1		48	49.5		
Mean age (Years)			22.45±8.122			23.93±11.505	0.240
Symptom duration (Hours)			28.63±5.914			26.79±7.186	0.023
Admission temperature (°F)			99.906±0.8534			99.598±0.6561	<0.001
Total leukocyte count (x10^9/Liter)			13.090±1.2079			10.742±0.9259	<0.001
Neutrophil count (%)			69.41±2.994			62.70±1.916	<0.001
Neutrophil count (x10^9/Liter)			9.106±1.1521			6.748±0.7547	<0.001
Neutrophil to lymphocyte ratio			2.8851±0.5273			2.0147±0.1899	<0.001
ALVARADO score			7.43±0.771			6.01±0.653	<0.001

All findings in this table (after the per-op values) and the article are based on histo-pathological findings as the determinant of true or negative appendicitis status.

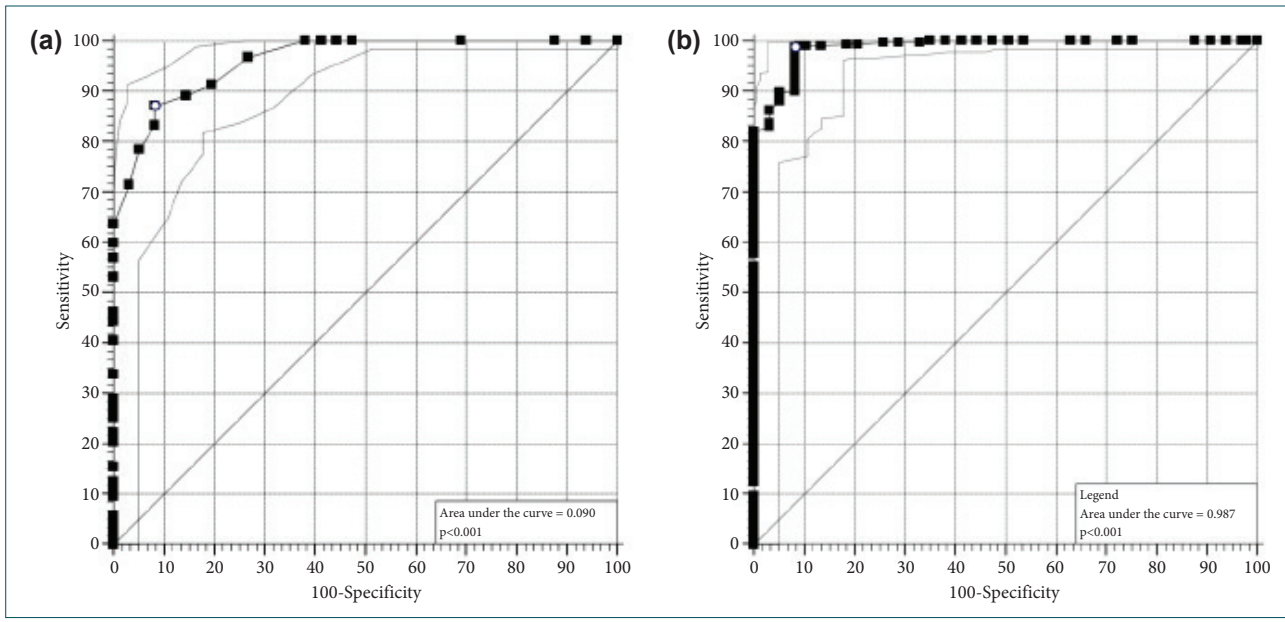

Figure 1. (a) ROC-curve analysis of total leukocyte count. **(b)** ROC-curve analysis of neutrophil count.

at p<0.0001. The salient measures for NC include associated criterion; >7.735x10⁹/L at 95% confidence interval, sensitivity; 98.71%, specificity; 91.75%, area under the curve; 0.987221, overall accuracy; 97.1%, and precision; 0.972719 at p<0.0001.

DISCUSSION

The presentation of acute appendicitis has been extensively described. Diagnosis of the classical presentation is considered clinical.[12] The risk for emergency appendectomy in men and women is 12% and 23%, respectively.[13] The overall risk has been reduced due to modern antibiotics and surgical techniques.[14] Rates of complications are still higher for extremes of age, immune-compromisation, and co-morbid cases6. Complicated cases such as those with perforation, protracted course and morbidity are associated with higher costs of resources.[15] However, it is satisfactory to mention that with modern tools and techniques, mortality associated with acute appendicitis has been brought down to <1%.[16] Acute appendicitis and appendectomy is associated with costs of time and money, risks and complications, pain and morbidity. The role of reducing negative appendectomies is, therefore, understandable. A helpful tool in this regard can be the use of the TLC and neutrophil counts.

Estimated values for false positive and false negative cases for TLC were 8.722 and 45.896, respectively. Estimated values for false positive and false negative cases for NC were 8.722 and 4.06, respectively. Estimated false positive for both TLC and NC was the same, 8.722. As mentioned previously, the true and negative appendectomy status by pre-op assessment was 294 (72.1%) and 114 (27.9%), respectively. However, with histo-pathological reporting, the number of true appen-

Table 2. Summary table for various criterions of TLC and NC

	Estimated specificity at fixed sensitivity			Estimated sensitivity at fixed specificity		
Variable	**Criterion**	**Sensitivity (%)**	**Specificity (%)**	**Criterion**	**Specificity (%)**	**Sensitivity (%)**
TLC count (x10⁹/L)	>12.068	80.00	93.86	>11.694	80.00	91.63
	>11.758	90.00	83.43	>11.871	90.00	87.68
	>11.632	95.00	75.55	>12.107	95.00	77.93
	>11.511	97.50	70.67	>12.219	97.50	66.90
Neutrophil Count (x10⁹/L)	>8.1799	80.00	100	>7.5679	80.00	99.36
	>7.9743	90.00	92.06	>7.6758	90.00	99.04
	>7.8099	95.00	91.75	>8.0409	95.00	87.96
	>7.7741	97.50	91.75	>8.1091	97.50	82.77

Table 3. TLC and neutrophil count diagnostic measures

	TLC	NC
Associated criterion	>11.9 (x10^9/L)	>7.735 (x10^9/L)
Sensitivity	87.14%	98.71%
Specificity	91.75%	91.75%
Estimated false negative	45.896947	4.06432
Estimated false positive	8.72207	8.72207
Positive likelihood ratio	10.57	11.97
Negative likelihood ratio	0.14	0.014
Confidence interval	95.0%	95.0%
Area under the curve	0.960337	0.987221
Significance level - p	<0.0001	<0.0001
Overall accuracy	91.2%	97.1%
Precision	0.972719	0.972719
F1 score	0.9192765	0.9217731

TLC: Total leukocyte count; NC: Neutrophil count. F1 score; harmonic mean of precision and sensitivity.

dicitis cases increased to 311 (76.2%) i.e. an increase in the true appendectomy cases by 4.1%.

Of the ninety-seven cases of negative appendectomy by histo-pathological assessment, 36 (37.1%) had faecolith obstruction of the lumen, 26 (26.8%) had parasitic infestation and obstruction, 17 (17.5%) had fibrotic strictures, 2 (2.1%) had growth in their wall, and in the remaining 16 (16.5%) cases, both pre-op and histo-pathological assessment failed to identify acute appendicitis as the cause. The statistical data obtained from these patients included TLC; 10.742±0.92 x10^9/L, NC; 6.748±0.75 x10^9/L, ALVARADO; 6.01±0.65 and NLR 2.014±0.18, respectively.

In the current study, mean TLC and NC were found to be normal in patients with negative appendectomy which are both components of the ALVARADO score.[17] It was, therefore. not surprising to find statistically significant differences between the two groups regarding these three variables with p-values for all three; TLC, NC and ALVARADO <0.001. NLR or neutrophil to lymphocyte ratio for the TA group was 2.885±0.527 compared to 2.014±0.189 for the NA group, which was statistically significant with a p-value of <0.001. The calculated sensitivity and specificity for NLR was 82.64% and 100%, respectively.

The sensitivity and specificity of TLC has been variably reported in the literature including Saaiq M. et al. 81.77% and 43.55%,[17] Anwar M. et al. 86.9% and 81.25%,[18] Kamran H. et al., 76.5% and 73.7%,[19] respectively. The sample sizes for these studies were: Saaiq M. et al. 233, Anwar M. et al. 100 and Kamran H. et al. 100. The sensitivity and specificity of TLC for this study was 87.14% and 91.75%, respectively with a sample size of 408 patients at the Youden associated criterion of >11.9x10^9/L. As shown in Table 2, the ROC-curve analysis revealed that the highest sensitivity of 91.63% at the fixed specificity of 80% was obtained at the cut-off value of >11.694x10^9/L. The highest specificity of 93.86% at the fixed sensitivity of 80% was obtained at the cut-off value of >12.068x10^9/L.

The sensitivity and specificity for NC was also analyzed. In the literature, the sensitivity and specificity for NC has been reported as; Anwar M. et al. 82% and 68.75%,[18] Bates M. F. et al., 91% and 95%,[6] respectively. Their sample sizes were 100 and 847, respectively. The sensitivity and specificity of NC for this study was 98.71% and 91.75%, respectively with a sample size of 408 patients at the Youden associated criterion of >7.735x10^9/L. As shown in Table 2, the ROC-curve analysis revealed that the highest sensitivity of 99.36% at the fixed specificity of 80% was obtained at the cut-off value of >7.5679x10^9/L. The highest specificity of 100% at the fixed sensitivity of 80% was obtained at the cut-off value of >8.1799x10^9/L.

As mentioned previously, the sensitivity and specificity of NLR in our study was 82.64% and 100%, respectively compared to the sensitivity and specificity of NC which was 98.71% and 91.75%, respectively. NLR, therefore, seems to be a more specific indicator of acute appendicitis than NC; whereas, NC had greater sensitivity at 98.71%.

The overall accuracy for TLC and NC as reported by Anwar M. et al. was 86% and 80%,[18] respectively. For this study, the overall accuracy for TLC and NC was 91.2% and 97.1%, respectively. The area under the Curve (AUC) calculated by Bates M. F. et al. was 0.86 and 0.87, respectively.[6] For this study, the AUC for TLC and NC was 0.96 and 0.987, respectively.

Conclusion

With modern tools and techniques, the accuracy of diagnosis of acute appendicitis has greatly improved with resultant reduction in morbidity and mortality. In order to improve upon this, we need to further improve our diagnostic accuracy and reduce negative appendectomies. TLC and NC serve qualitatively on the ALVARADO score which notes their presence or absence. Qualitative use of the TLC and NC using appropriate cut-off points can not only improve the diagnostic accuracy but also reduce the rate of negative appendectomies, health care burden, and cost. The criterion values for our study were from a single institution, and further research must be carried out in this regard before these cut-off values can be recommended.

All authors read and approved the final manuscript.

Ethical consideration

In each case, written informed consent was taken and infor-

mation about the importance of this study was elaborated. The study was approved by the Research and ethical committee of Khyber Teaching Hospital, Peshawar.

Conflict of interest: We wish to confirm that there are no known conflicts of interest associated with this publication & there has been no financial support for this work that could have influenced its outcome.

REFERENCES

1. Wei PL, Liu SP, Keller JJ, Lin HC. Volume-outcome relation for acute appendicitis: evidence from a nationwide population-based study. PLoS One 2012;7:e52539. CrossRef
2. Chong CF, Adi MI, Thien A, Suyoi A, Mackie AJ, Tin AS, et al. Development of the RIPASA score: a new appendicitis scoring system for the diagnosis of acute appendicitis. Singapore Med J 2010;51:220-5.
3. Ohle R, O'Reilly F, O'Brien KK, Fahey T, Dimitrov BD. The Alvarado score for predicting acute appendicitis: a systematic review. BMC Med 2011;9:139. CrossRef
4. O'Connel PR. The vermiform appendix. In: Williams NS, Bulstrode CJK, O'Connel PR, editors. Bailey and Love's Short Practice of Surgery. 25th ed. London: Arnold; 2008. p. 1204-16.
5. Khan KI, Mahmood S, Akmal M, Waqas A. Comparison of rate of surgical wound infection, length of hospital stay and patient convenience in complicated appendicitis between primary closure and delayed primary closure. J Pak Med Assoc 2012;62:596-8.
6. Bates MF, Khander A, Steigman SA, Tracy TF Jr, Luks FI. Use of white blood cell count and negative appendectomy rate. Pediatrics 2014;133:e39-44. CrossRef
7. Mehraj A, Naqvi MA, Din HU, Waqas. Importance of clinical assessment in diagnosis of acute appendicitis and its role in decreasing negative appendicectomy rate. J Ayub Med Coll Abbottabad 2012;24:7-9.
8. Kamran H, Naveed D, Asad S, Hameed M, Khan U. Evaluation of modified Alvarado score for frequency of negative appendicectomies. J Ayub Med Coll Abbottabad 2010;22:46-9.
9. Buchman TG, Zuidema GD. Reasons for delay of the diagnosis of acute appendicitis. Surg Gynecol Obstet 1984;158:260-6.
10. Ceydeli A, Lavotshkin S, Yu J, Wise L. When should we order a CT scan and when should we rely on the results to diagnose an acute appendicitis? Curr Surg 2006;63:464-8. CrossRef
11. Alvarado A. A practical score for the early diagnosis of acute appendicitis. Ann Emerg Med 1986;15:557-64. CrossRef
12. Cuschieri A. The small intestine and vermiform appendix. In: Cuschieri A, Grace P, Darzi A, editors. Clinical Surgery. 2nd ed. Blackwell Publishing Company; 2003. p. 386-406.
13. Paajanen H, Grönroos JM, Rautio T, Nordström P, Aarnio M, Rantanen T, et al. A prospective randomized controlled multicenter trial comparing antibiotic therapy with appendectomy in the treatment of uncomplicated acute appendicitis (APPAC trial). BMC Surg 2013;13:3. CrossRef
14. Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. BMJ 2012;344:e2156. CrossRef
15. Kırkıl C, Karabulut K, Aygen E, Ilhan YS, Yur M, Binnetoğlu K, et al. Appendicitis scores may be useful in reducing the costs of treatment for right lower quadrant pain. Ulus Travma Acil Cerrahi Derg 2013;19:13-9.
16. Humes DJ, Simpson J. Clinical Presentation of Acute Appendicitis: Clinical Signs-Laboratory Findings-Clinical Scores, Alvarado Score and Derivate Scores. In: Keyzer C, Gevenois PA, eds. Imaging of acute appendicitis in adults and children. Springer Publishing Company 2012:13-21.
17. Saaiq M, Niaz-Ud-Din, Jalil A, Zubair M, Shah SA. Diagnostic accuracy of leukocytosis in prediction of acute appendicitis. J Coll Physicians Surg Pak 2014;24:67-9.
18. Anwar MW, Abid I. Validity of total leucocytes count and neutrophil count in diagnosing suspected acute appendicitis. Pak Armed Forces Med J Sept 2012;3:38-42.
19. Kamran H, Naveed D, Nazir A, Hameed M, Ahmed M, Khan U. Role of total leukocyte count in diagnosis of acute appendicitis. J Ayub Med Coll Abbottabad 2008;20:70-1.

KLİNİK ÇALIŞMA - *ÖZET*

Total lökosit ve nötrofil sayısı negatif apandektomilerin azaltılmasını sağlayan belirteçlerdir

Dr. Muhammad Salman Rafiq, Dr. Mah Muneer Khan, Dr. Ataullah Khan, Dr. Bilal Ahmad

Khyber Eğitim Hastanesi, Cerrahi Kliniği, Peşaver, Pakistan

AMAÇ: Negatif apandektomiler gereksiz hasta kabullerine neden olarak, sağlık hizmetlerine yük ve mali külfet getirmektedir. Bu çalışma, negatif apendektomilerin azaltılmasında total lökosit ve nötrofil sayılarını değerlendirmek üzere yürütüldü.

GEREÇ VE YÖNTEM: Hastaneye kabul edilen ve apandektomi geçiren hastaların verileri incelendi. Değişik kestirim noktaları için total lökosit ve nötrofil sayılarının alıcı işletim karakteristik eğrisi (ROC) analizi hesaplandı. Optimal duyarlılık, özgüllük, genel doğruluk derecesi ve eğrisi altında kalan alan belirlendi.

BULGULAR: Toplam 408 hastada cerrahi değerlendirmeye göre gerçek ve negatif apandisit oranları %72.1 (n=294) ve %27.9 (n=114) iken histopatolojik olarak bu oranlar sırasıyla %76.2 (n=311) ve %23.8 (n=97) idi. Total lökosit sayımının optimal kestirim değeri olan >11.9x10^9/L, %87.14 duyarlılık ve %91.75 özgüllüğe sahipti. Total nötrofil sayısının optimal kestirim değeri olan >7.735x10^9/L %98.71 duyarlılık ve %91.75 özgüllüğe sahipti. Total lökosit ve nötrofil sayıları için eğri sırasıyla 0.9603 ve 0.9872 olup, genel doğruluk oranları sırasıyla %91.2 ve 97.1 idi.

TARTIŞMA: Normal total lökosit ve nötrofil sayıları negatif apandektomilerle kuvvetle ilişkilidir. Cerrahi dışı önlemler, toplam lökosit ve nötrofil sayıları dikkatli klinik takip oldukça önemlidir.

Anahtar sözcükler: Akut; apandisit; lökosit sayısı; negatif apandektomi; nötrofiller; ROC eğrisi.

Ulus Travma Acil Cerrahi Derg 2015;21(2):102-106 doi: 10.5505/tjtes.2015.29626