



Clinical value of leukocyte counts in evaluation of patients with suspected appendicitis in emergency department

Acil serviste apandisit hastalarının kuşulanılan hastaların değerlendirilmesinde lökosit sayımlarının klinik değeri

Mohammad Zikrullah TAMANNA,¹ Uzma ERAM,² Turki Mohsen AL HARBI,¹
Saleh Awad ALRASHDI,¹ Shafkat Ullah KHATEEB,¹
Saleem Ahmed ALADHRAI,¹ Abdul Muthalib HUSSAIN³

BACKGROUND

The objective of this study was to assess the value of total leukocyte count in patients presenting to the emergency department with sign and symptoms suggestive of acute appendicitis.

METHODS

Patient demographics, presenting sign, and symptoms, initials total leukocyte count and discharge diagnosis was documented retrospectively. Admitted patients were followed for surgical and clinical outcomes, and discharged patients followed up by telephonic interview.

RESULTS

Out of 116 eligible patients 48 patients was found to have acute appendicitis. Total leukocyte count $\geq 10,000$ cell/mm³ yielded a sensitivity of 89.58% and a specificity of 64.71%. The positive predictive value (PPV) was 64.18%, and the negative predictive value (NPV) was 89.80%. The positive likelihood ratio (+LR) was 2.54, and the negative likelihood ratio (-LR) was 0.16. The area under the curve for the receiver operating characteristic (ROC) curve was 0.822, which was moderately accurate.

CONCLUSION

The total leukocyte counts are helpful in the diagnosis and exclusion of acute appendicitis. The elevated leukocyte count $\geq 10,000$ cells/mm³ was statistically associated with the presence of acute appendicitis. The ROC curve suggests there is value of total leukocyte counts and has sufficient sensitivity and specificity to be clinical value in the diagnosis of acute appendicitis.

Key Words: Abdominal pain; appendicitis; leukocyte counts.

AMAÇ

Bu çalışmanın amacı acil servise akut apandisit düşündürülen belirti ve bulgularla gelen hastalarda toplam lökosit sayımının değerini belirlemektir.

GEREÇ VE YÖNTEM

Hastanın demografik özellikleri, görülen belirtiler ve bulguları, toplam lökosit sayıları ve hastaneden çıkıştaki tanıları geriye dönük olarak belgelendi. Kabul edilen hastalar cerrahi ve klinik sonuçlar açısından izlendi, çıkışı yapılan hastalar telefon görüşmeleriyle takip edildi.

BULGULAR

Yüz on altı hastanın 48'inde akut apandisit saptandı. Toplam $\geq 10,000$ /mm³ şeklindeki lökosit sayısı %89,58 duyarlılık ve %64,71 özgüllüğe sahipti. Pozitif (PPV) ve negatif (NPV) öngörü değerleri sırasıyla %64,18 ve %89,80 idi. Pozitif (+LR) ve negatif (-LR) olasılık oranları ise sırasıyla 2,54 ve 0,16 şeklindeydi. Algılayıcı işletim eğrisinin (ROC-receiver operating characteristics) altında kalan alanı 0,822 olup orta derecede doğruluk derecesini sergilemekteydi.

SONUÇ

Akut apandisit tanısı koyma veya bu tanının dışlanması da toplam lökosit sayıları yardımcı olur. Yüksek lökosit sayısı ($\geq 10,000$ /mm³) istatistiksel açıdan akut apandisit varlığıyla ilişkiliydi. ROC eğrisi akut apandisit tanısında toplam lökosit sayılarının klinik değer taşıyacak şekilde yeterli duyarlılık ve özgüllüğe sahip olduğunu düşündürmektedir.

Anahtar Sözcükler: Karın ağrısı; apandisit; lökosit sayıları.

¹Department of Emergency Medicine, King Fahad Medical City, Riyadh, Saudia Arabia; ²Department of Community Medicine, J.N Medical Collage, AMU Aligarh, India; ³Department of Pulmonary and Critical Care Medicine, King Fahad Medical City, Riyadh, Saudia Arabia.

¹Kral Fahd Tıp Kenti, Acil Tıp Bölümü, Riyad, Suudi Arabistan; ²JN Tıp Koleji, Toplum Hekimliği Bölümü, AMU Aligarh, Hindistan; ³Kral Fahd Tıp Kenti, Göğüs Hastalıkları ve Yoğun Bakım Kliniği, Riyad, Suudi Arabistan.

Acute appendicitis is a common consideration in the differential diagnosis of patients with right lower abdominal pain presenting to the emergency department (ED). Both routine history and physical examination remain the most effective and practical diagnostic modalities. To increase diagnostic accuracy, inflammatory variables such as leukocyte count, C-reactive protein (CRP), and body temperature have been studied.^[1,2] None of these is specific for acute appendicitis, and their ability to improve on the pre-operative diagnosis is doubtful. The prevailing perception is that the patients with appendicitis will have a high leukocyte count. Most of the ED physicians, while evaluating acute appendicitis, obtain a complete blood cell count (CBC), with the expectation that a high leukocyte count will support the diagnosis. Considering the overlap with other inflammatory processes mimicking acute appendicitis, the diagnostic value of the leukocyte count remains controversial. Several literatures recommend total leukocyte count as part of the evaluation with suspected appendicitis.^[3] However, some studies do not recommend total leukocyte count because of the limitation of this test.^[4] Most of the studies have calculated the sensitivity and specificity at arbitrarily chosen threshold values for acute leukocyte count. Only a few have used receiver operating characteristic (ROC) curve analysis in patients with suspected acute appendicitis, but either without calculating the area under the ROC curve (AUC) or without defining the cut-off values with highest sensitivity and specificity.^[5,6] However, in this continuous variable, ROC curve analysis is a statistically more appropriate approach.

In this study, we tried to evaluate retrospectively the diagnostic value of total leukocyte count by performing ROC curve analysis in consecutive patients presenting to an ED with signs and symptoms suggestive of acute appendicitis.

MATERIALS AND METHODS

This retrospective study was conducted in a 1500-bed tertiary care teaching hospital in Saudi Arabia. The institutional review board approval was obtained. The present investigation included patients who presented to the ED between June 2011 and January 2012 with right lower quadrant pain who were suspected as having acute appendicitis. A total of 159 patient charts that met the inclusion criteria were reviewed. The study was designed to assess the impact of Alvarado score and computed tomography (CT) scan in the diagnosis of acute appendicitis. This investigation represents a planned subanalysis of the total leukocyte count obtained as part of routine data collected from the enrolled patients.

Patient demographics and presenting signs and

symptoms were documented from the pro forma. All laboratory tests were obtained at the discretion of the managing physicians. If appendectomy or surgical intervention was performed, all appendices and other specimens were submitted to the pathology department. Official radiology reports, the surgical pathology report, and medical records were reviewed retrospectively. Patients were excluded if lost to follow-up or transferred to another hospital. Other alternative diagnoses were recorded. If acute appendicitis was considered unlikely and no other acute etiology was found, patients were discharged with discharge instruction to return if symptoms worsened, with appropriate follow-up. All patients discharged from the ED were followed up by telephone interview after the index visit.

Recorded data included age, gender, total leukocyte counts from the CBC count obtained during the initial ED presentation, presence of appendicitis (operative and pathologic report), and final diagnosis. Total leukocyte counts or white blood cell count (WBC) $>10,000$ cells/mm³ were a priori classified as abnormal. Total leukocyte counts of up to 10,000 cells/mm³ were chosen empirically to maximize sensitivity.

Data analysis

Analysis of the data on total leukocyte counts included determination of sensitivities, specificities, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (-LR). All results were reported with 95% confidence intervals (95% CIs). ROC curves were plotted for these variables along with calculation of the AUC with 95% CI. We calculated the AUC for leukocyte counts using the Hanley-McNeil method for paired data.^[7] The AUC is a summary statistic of diagnostic accuracy (based on all possible cut-off values). The AUC can have values between 0 and 1. The practical lower limit for the AUC of a diagnostic test is 0.5. The test results are classified as uninformative (AUC=0.5), less accurate ($0.5 < \text{AUC} \leq 0.7$), moderately accurate ($0.7 < \text{AUC} \leq 0.9$), highly accurate ($0.9 < \text{AUC} < 1$), and perfect (AUC=1).^[8] To calculate sensitivity and specificity, we used cut-off values for the leukocyte counts. The selected cut-off value provided an ideal balance between sensitivity and specificity for the diagnosis of acute appendicitis. Clinical and analytical variables of the acute appendicitis and normal appendix group were compared using chi-square test (Table 1). Statistical analyses were performed using MedCalc for Windows version 8.2.1.0.

RESULTS

The study began with retrieval of 159 patients who presented to the ED with right lower quadrant pain. Forty-three were excluded because they were transferred to another hospital after being diagnosed as ap-

Table 1. Chi-square tests

| | Value | Df | Asymp. Sig. (2-sided) | Exact Sig. (2-sided) | Exact Sig. (2-sided) |
|------------------------------------|---------------------|----|-----------------------|----------------------|----------------------|
| Pearson chi-square | 33.991 ^a | 1 | .000 | | |
| Continuity correction ^b | 31.802 | 1 | .000 | | |
| Likelihood ratio | 37.630 | 1 | .000 | | |
| Fisher's exact test | | | | .000 | .000 |
| N of valid cases | 116 | | | | |

^a0 cells (.0%) have expected count less than 5. The minimum expected count is 20.28.
^bComputed only for a 2x2 table.

Table 2. Total leukocyte count and appendicitis

| Count | Diagnosis | | |
|------------------------|--------------------|-----------------|------------|
| | Acute appendicitis | No appendicitis | Total |
| Total WBC count | | | |
| WBC ≥10,000 | 43 | 24 | 67 |
| <10,000 | 5 | 44 | 49 |
| Total | 48 | 68 | 116 |

A 2x2 table for patients with and without appendicitis. For the purpose of this analysis, a WBC (leukocyte count) ≥10,000 cells/mm³ was considered abnormal.

pendicitis due to non-availability of beds in the surgical ward. Two were discharged against medical advice, and these two patients were lost to follow-up. One hundred and sixteen patients were included in the study.

Total leukocyte count was measured in 116 patients. Table 2 shows a standard 2x2 table for total leukocyte count in patients with and without appendicitis. Total leukocyte count ≥10,000 cells/mm³ yielded a sensitivity of 89.58% (95% CI: 77.34%-96.53%) and a specificity of 64.71% (95% CI: 52.17%-75.92%). The PPV was 64.18% (95%CI: 51.53%-75.3%) and the NPV was 89.80% (95% CI=77.77%-96.60%). The +LR was 2.54 (95% CI: 1.81-3.55) and the -LR was 0.16 (95% CI: 0.07-0.38) (Table 3).

Table 4 shows the diagnosis of acute appendicitis for different ranges of total leukocyte counts, which

was statistically significant (p<0.0001).

Table 5 shows an ROC curve for total leukocyte counts. The AUC for the ROC curve was 0.822 (95% CI: 0.740-0.887), which was moderately accurate. If one chose to maximize both sensitivity and specificity, an optimum cut-off for an abnormal total leukocyte count would be 10,700 cells/mm³, which yielded a sensitivity of 89.6% and a specificity of 73.5% (Fig. 1).

DISCUSSION

Inflammatory markers have long been used to improve the diagnostic performance in acute appendicitis. Measurement of total leukocyte count is usually considered a routine part of the work-up for acute appendicitis. Several studies suggest that an elevated total leukocyte count is usually the earliest laboratory finding of appendiceal inflammation.^[1,2,6,9] Neither leukocyte count nor neutrophil percentage is specific for acute appendicitis. Leukocytosis is a nonspecific reaction caused by acute or chronic inflammation, acute physical or emotional stress, and several other conditions. Most of the previous studies have tried to compare the relationship between total leukocyte count and acute appendicitis using sensitivity, specificity, PPV, and NPV using arbitrary cut-off points with the upper reference limit.^[1,2,6,7,10,11] The difficulty with this type of analysis is that PPV and NPV are directly dependent on the prevalence of the disease. As these variables are obtained from various study

Table 3. Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), positive likelihood ratios (+LR), and negative likelihood ratios (-LR) with 95% confidence intervals (95% CIs) at the cut-off value of total leukocyte count ≥10,000 cells/mm³

| | | |
|---------------------------|--------|-----------------|
| Sensitivity | 89.58% | 77.34% - 96.53% |
| Specificity | 64.71% | 52.17% - 75.92% |
| Positive likelihood ratio | 2.54 | 1.81 - 3.55 |
| Negative likelihood ratio | 0.16 | 0.07 - 0.38 |
| Disease prevalence | 41.38% | 32.31% - 50.90% |
| Positive predictive value | 64.18% | 51.53% - 75.53% |
| Negative predictive value | 89.80% | 77.77% - 96.60% |

Table 4. Acute appendicitis for different ranges of total leukocyte counts

| Diagnosis | <8 | 8 to <10 | 10 to <12 | 12 to <15 | ≥15 |
|----------------------|----|----------|-----------|-----------|-----|
| Appendicitis (48) | 1 | 4 | 8 | 14 | 21 |
| No appendicitis (68) | 23 | 21 | 9 | 9 | 6 |
| Total (116) | 24 | 25 | 17 | 23 | 27 |

Chi-square 38.914; DF 4; Significance level $p < 0.0001$; Contingency coefficient 0.501.

populations with different prevalences of the disease, the results have to be interpreted carefully. Moreover, sensitivity and specificity alone do not allow clinicians to directly apply the result of diagnostic tests to individual patients. ROC analysis allows calculation of cut-off values with the highest sensitivity and specificity. ROC analysis, however, is independent of disease prevalence.

Only a few studies have done ROC analysis of inflammatory variables in acute appendicitis.^[6,12] However, in some, only the appearance of the ROC curve was used or the AUC was calculated without reporting the cut-off value with the highest sensitivity and specificity.

In our study, while doing ROC analysis, the AUC for the ROC curve was 0.822 (95% CI: 0.740-0.887), which was moderately accurate. If one chose to maximize both sensitivity and specificity, an optimum cut-off for an abnormal total leukocyte count would be 10,700 cells/mm³, which yielded a sensitivity of 89.6% and a specificity of 73.5% (Fig. 1).

Other investigators have constructed ROC analysis with comparable results. Andersson et al.^[13] found an AUC of 0.80, Paajanen et al.^[6] found an AUC of 0.76, Rodriguez-Sanjuan et al.^[14] found an AUC of 0.67, and Körner et al.^[15] found an AUC of 0.69 (95% CI: 0.65-0.73).

Table 5. Receiver operating characteristic curve analysis of total leukocyte count and area under curve with 95% confidence interval

| Variable | Count |
|--------------------------------------|----------------|
| Classification variable | Diagnosis |
| Sample size | 116 |
| Positive group: diagnosis = 1 | 48 |
| Negative group: diagnosis = 0 | 68 |
| Disease prevalence (%) | Unknown |
| Area under the ROC curve (AUC) | 0.822 |
| Standard Error ^a | 0.0398 |
| 95% Confidence interval ^b | 0.740 to 0.887 |
| z statistic | 8.092 |
| Significance level P (Area=0.5) | <0.0001 |

^aHanley & McNeil, 1982; ^bBinomial exact; Criterion values and coordinates of the ROC curve; Criterion corresponding with highest Youden index.

Our present study has several limitations due to inherent flaws of a retrospective study. Our study comprised a review of patients' medical records and pathological reports. The retrospective nature of the study may limit the diagnostic performance, and was limited to one institution. Another limitation was that we did not study the diagnostic value of neutrophils. We also did not study how total leukocyte counts might perform as part of a scoring system or combination of test results.

There is a statistically significant relationship between total leukocyte count and acute appendicitis in ED patients presenting with signs and symptoms suggestive of acute appendicitis. According to our study, the relationship is modest and clinically very useful. There is need to perform more investigations to provide further information for the diagnosis of acute appendicitis, such as imaging, short-term observation for clinical evaluation, and repeated physical and labora-

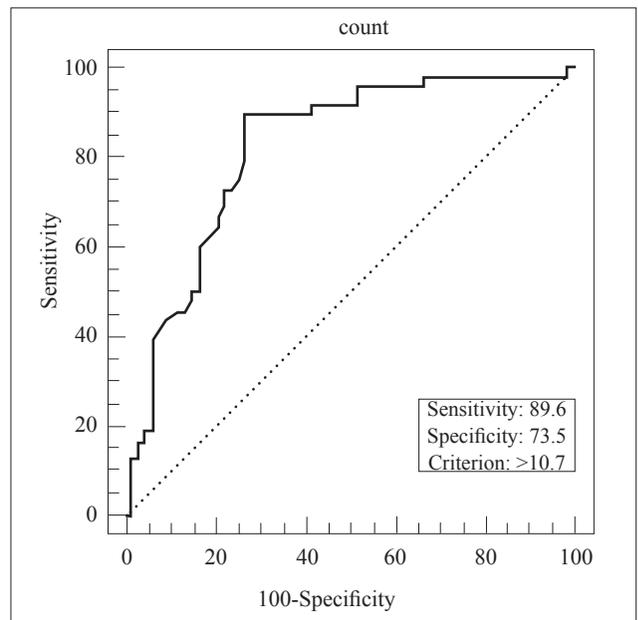


Fig. 1. ROC curve for total leukocyte counts. The AUC for the ROC curve was 0.822 (95% CI: 0.740-0.887), which was moderately accurate. If one chose to maximize both sensitivity and specificity, an optimum cut-off for an abnormal total leukocyte count would be 10,700 cells/mm³, which yielded a sensitivity of 89.6% and a specificity of 73.5%.

tory examinations. Our findings indicate that the total leukocyte count offers a rapid and helpful method to predict and discriminate appendicitis in the ED.

In conclusion, although elevated leukocyte count is a nonspecific inflammatory marker, high leukocyte count is helpful in the diagnosis and exclusion of appendicitis. It is inexpensive, objective, and readily available without the risk of radiation, and useful for the emergency physician.

Acknowledgements

The author thanks Dr. Abdul Muthalib Hussain for inspiring and giving proper guidance in writing this article.

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