

Role of Leucocytosis and Neutrophilia in Diagnosis of Appendicitis and Differentiating Complicated from Uncomplicated Appendicitis

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ABSTRACT

INTRODUCTION: Despite advances in diagnosis of acute abdomen, diagnosis of acute appendicitis still proves difficult at times. While negative appendicectomy subjects the patients to unnecessary morbidity, the risk associated with misdiagnosis of appendicitis and delayed surgery cannot be ignored either. This risk is further increased in patients with complicated appendicitis characterized by appendicular perforation, gangrene or abscess formation. Although, appendicitis is usually associated with leucocytosis and neutrophilia, there have been studies which conclude that normal leucocyte counts and absence of neutrophilia cannot rule out appendicitis. In this regard, we have sought to assess the role of total leucocyte counts and neutrophilia in diagnosis of acute appendicitis and differentiation of complicated from uncomplicated appendicitis.

METHOD: A retrospective review of charts was performed to identify all patients who underwent appendicectomy between July 2018 and December 2018 in the Department of General Surgery at Bir Hospital. Based on intra-operative findings and histopathology, patients were divided into three groups: uncomplicated appendicitis, complicated appendicitis and non-appendicular pathology. Complicated appendicitis was defined as perforated or gangrenous appendicitis or appendicular abscess formation. Total leucocyte counts (TLC) and neutrophil percentages were compared among the three groups. Receiver operating characteristic (ROC) curve analyses were done to find out cut-off levels and accuracy of total leucocyte counts and neutrophil percentages to discriminate appendicular pathology from non-appendicular and also to differentiate complicated appendicitis from uncomplicated appendicitis.

RESULT: Out of 150 cases, appendicitis was histopathologically confirmed in 136 (90.67%) cases. Negative appendicectomy rate was 9.33%. Among appendicitis cases, mean age was 24 ± 2.2 years and male to female ratio was 2.49:1. Complicated appendicitis was found in 36 (26.47%) patients. There was no significant differences in mean of TLC among patients with uncomplicated appendicitis (12592/mm³), complicated appendicitis (12524/mm³) or non appendicular pathology (10757/mm³) ($p=0.278$). On ROC curve analysis, area under the curves (AUC) of TLC and neutrophil percentages were 0.676 and 0.707 respectively for discriminating appendicular from non-appendicular pathology. For differentiating uncomplicated appendicitis from complicated, AUCs were 0.527 and 0.516 for TLC and neutrophils respectively.

CONCLUSION: Neither TLC nor neutrophil percentages have sufficient discriminatory power to diagnose acute appendicitis or to differentiate between uncomplicated and complicated appendicitis.

KEY WORDS: Acute appendicitis, Complicated appendicitis, Leucocytosis, Neutrophilia.

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INTRODUCTION

The first documented appendectomy was performed by Amyand in 1736.¹ In 1886, Reginald Fitz of Harvard Medical School first described the natural history of the inflamed appendix and coined the term "appendicitis."² Since then there have been numerous advances in the diagnosis and treatment of appendicitis. However surgeons face a dilemma in diagnosis of appendicitis even today with more diagnostic tools and scores available. Because of the difficulty in diagnosing appendicitis, negative appendectomies occur more than 15% of the time, with considerably higher percentages in infants, the elderly and young women.³ If untreated, acute appendicitis will progress from inflammation to perforation with abscess formation or diffuse peritonitis, making timely operative intervention imperative. Generally, the morbidity and mortality of missing a case of acute appendicitis with subsequent peritonitis or abscess formation far outweigh the complications associated with a negative appendectomy.⁴

The total leucocyte count (TLC) is the test probably most often used to diagnose acute appendicitis. Several reports suggest that an elevated TLC is usually the earliest laboratory test to indicate appendiceal inflammation, and most of the patients with acute appendicitis present with leucocytosis.⁵ Mild leukocytosis, ranging from 10,000 to 18,000 cells/mm³, usually is present in patients with acute, uncomplicated appendicitis and often is accompanied by a moderate polymorphonuclear predominance. TLCs are variable, however. It is unusual for TLC to be >18,000 cells/mm³ in uncomplicated appendicitis. TLC above this level raise the possibility of a complicated appendicitis characterized by a perforated or gangrenous appendix with or without abscess formation.⁶ In this study we have sought to evaluate the role of increased leucocyte counts and neutrophilia in the diagnosis of acute appendicitis and assess whether it can help in differentiating uncomplicated appendicitis (without perforation, gangrene or abscess) from complicated appendicitis (with perforation, gangrene or abscess).

METHOD

A retrospective review of charts was performed to identify all patients admitted with clinical diagnosis of acute appendicitis in the Department of General Surgery, Bir Hospital from July 2018 to December 2018.

All operated cases were included. Those managed conservatively and those with incomplete data were excluded. Patients on steroids and immunosuppressive drugs were also excluded. Histopathology was taken as standard for final diagnosis.

Based on intra-operative finding and histopathology, patients were divided into three groups: 'uncomplicated appendicitis' (without appendicular perforation, gangrene or abscess), 'complicated appendicitis' (with appendicular perforation, gangrene or abscess) and 'nonappendicular pathology' (diagnosis other than appendicitis). TLC and neutrophil counts were compared among the three groups. A TLC of $\geq 11,000/\text{mm}^3$ was taken as raised whereas neutrophil counts >70 % was taken as elevated. Receiver operating characteristic (ROC) curve analysis was done to find out cut-off levels and accuracy of TLC and neutrophil counts to discriminate appendicular pathology from non-appendicular pathology. ROC analysis was also performed to assess whether TLC and neutrophil counts can be used to differentiate between uncomplicated and complicated appendicitis. A p value of < 0.05 was taken as significant and a confidence interval of 95 % was accepted.

RESULT

A total of 150 cases were included in this study. Acute appendicitis was confirmed histopathologically in 136 (90.67%) patients. Overall negative appendectomy rate was 9.33%. The negative appendectomy rate was higher among females (7 out of 46, 15.22 %). Among acute appendicitis cases (n=136), 97 (71.3%) were male. Male to female ratio (M:F) was 2.49:1. Mean age was 24 ± 2.23 years. As shown in table 1, complicated appendicitis was diagnosed in 36 (26.47%) patients. Perforated appendicitis was noted in 18 patients.

Table 1: Distribution of acute appendicitis cases

Types of acute appendicitis (No.136)	Frequency (%)
Uncomplicated acute appendicitis	100 (73.53%)
Complicated acute appendicitis	36 (26.47%)
Perforated -18	
Gangrenous - 10	
Abscess- 8	
Total	136 (100%)

Normal TLC (<11,000/mm³) was observed in 26.5% of cases of acute appendicitis while 35.7% without appendicitis had elevated TLC. Sixty (44.1%) patients

with appendicitis had TLC $>14,000/\text{mm}^3$ as compared to none without appendicitis. At a cutoff value of $\geq 11,000/\text{mm}^3$, TLC had a sensitivity of 75.53%, specificity of 64.29%, and an accuracy of 79.62% for diagnosing acute appendicitis. (Table 2 and Table 3)

Table 2: Relationship between TLC and diagnosis of acute appendicitis

TLC /mm ³	Final diagnosis (HPE)		Total
	AA *	Not AA *	
< 11,000	36 (26.5%)	9 (64.3%)	45 (30%)
$\geq 11,000$ -14000	40 (29.4%)	5 (35.7%)	45 (30%)
>14000-17000	34 (25%)	0 (0%)	34 (22.7%)
> 17000-20000	26 (19.1%)	0 (0%)	26 (17.3%)
	136	14	
Total	(100%)	(100%)	150 (100%)

*AA = Acute appendicitis

Table 3. Accuracy of total leucocyte count for AA at cutoff $\geq 11,000/\text{mm}^3$

TLC /mm ³	Final diagnosis (HPE)		Total
	AA*	Not AA	
≥ 11000	100 (73.5%)	5 (35.7%)	105 (70%)
<11000	36 (26.5%)	9 (64.3%)	45 (30%)
Total	136 (100%)	14 (100%)	150 (100%)

p value=0.008 (Chi square test)

*AA = Acute appendicitis

Twenty patients (14.7%) of acute appendicitis cases had normal neutrophil counts. On the other hand, 57.2% without appendicitis had neutrophilia. At a cutoff value of $>70\%$, presence of neutrophilia had sensitivity of 85.29%, specificity of 42.86% and accuracy of 81.33% for diagnosing acute appendicitis (Tables 4 and 5).

Table 4: Relationship between neutrophilia and diagnosis of acute appendicitis

Neutrophil %	Final Diagnosis (HPE)		Total
	AA*	Not AA*	
$\leq 70\%$	20 (14.7%)	6 (42.8%)	26 (17.3%)
71-80 %	27 (19.9%)	4 (28.6%)	31 (20.7%)
81-90%	65 (47.8%)	2 (14.3%)	67 (44.7%)
>90 %	24 (17.6%)	2 (14.3%)	26 (17.3%)
Total	136 (100%)	14 (100%)	150 (100%)

*AA = Acute appendicitis

Table 5: Accuracy of neutrophil count for acute appendicitis at cutoff $>70\%$

Neutrophil %	Final diagnosis (HPE)		Total
	AA*	Not AA*	
$> 70\%$	116 (85.3%)	8 (57.1%)	124 (82.7%)
$\leq 70\%$	20 (14.7%)	6 (42.9%)	26 (17.3%)
Total	136 (100%)	14 (100%)	150 (100%)

p value=0.008 (Chi square test)

*AA = Acute appendicitis

Area under the ROC curve (AUC) of TLC for discriminating between appendicular and non-appendicular pathology was 0.676. At cutoff $\geq 13950/\text{mm}^3$, sensitivity was only 45.6% and accuracy was 50.7%. Although positive predictive value (PPV) was 100%, negative predictive value (NPV) was only 15.9%. Compared to TLC, neutrophil counts had better ability to discriminate appendicular from non-appendicular pathology. However, AUC of ROC curve analysis of neutrophil counts for discriminating between appendicular and non-appendicular pathology was only moderate at 0.707. At cutoff $\geq 80.5\%$, accuracy was 68.7% (Figures 1 and 2).

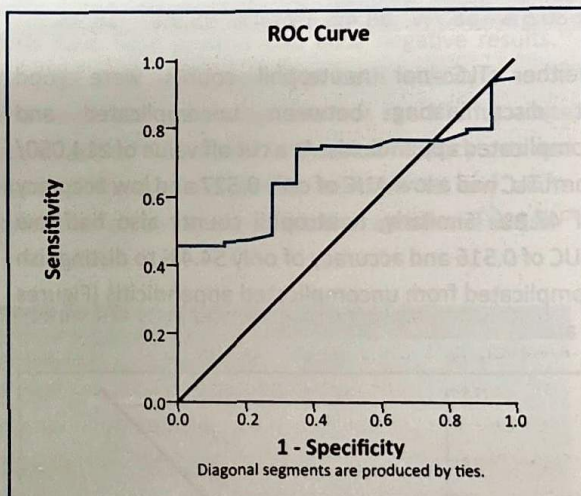


Figure 1: ROC curve for TLC to diagnose acute appendicitis

AUC	Standard error	Asymptotic significance	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.676	0.051	0.031	0.576	0.776

Cutoff value	Accuracy	Sensitivity	Specificity	PPV	NPV
$\geq 13950/\text{mm}^3$	50.7%	45.6%	100%	100%	15.9%

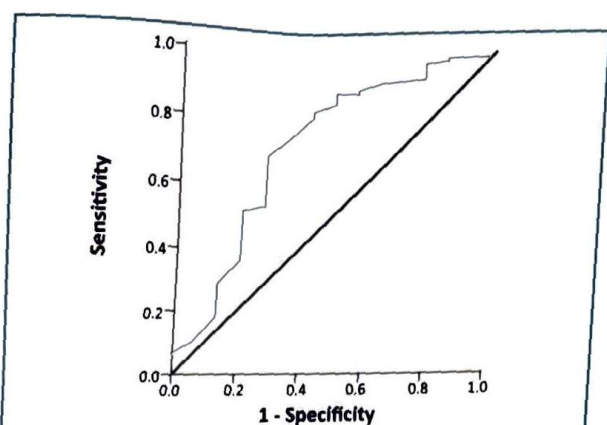


Figure 2: ROC curve for neutrophil to diagnose acute appendicitis

AUC	Standard error	Asymptotic significance	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.707	0.083	0.011	0.544	0.870

Cutoff value	Accuracy	Sensitivity	Specificity	PPV	NPV
≥ 80.5%	68.7%	68.4%	71.4%	95.9%	18.9%

Neither TLC nor neutrophil counts were good at discriminating between uncomplicated and complicated appendicitis. At a cut off value of $\geq 14,050/\text{mm}^3$ TLC had a low AUC of only 0.527 and low accuracy of 47.8%. Similarly, neutrophil counts also had low AUC of 0.516 and accuracy of only 54.4% to distinguish complicated from uncomplicated appendicitis (Figures 3 and 4).

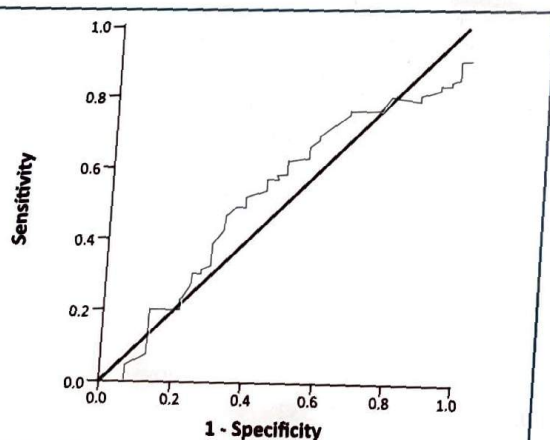


Figure 3: ROC curve for TLC to diagnose complicated appendicitis

AUC	Standard error	Asymptotic significance	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.527	0.056	0.636	0.417	0.636

Cutoff value	Accuracy	Sensitivity	Specificity	PPV	NPV
≥ 14050/ mm ³	47.8%	33.3%	53%	20.3%	68.8%

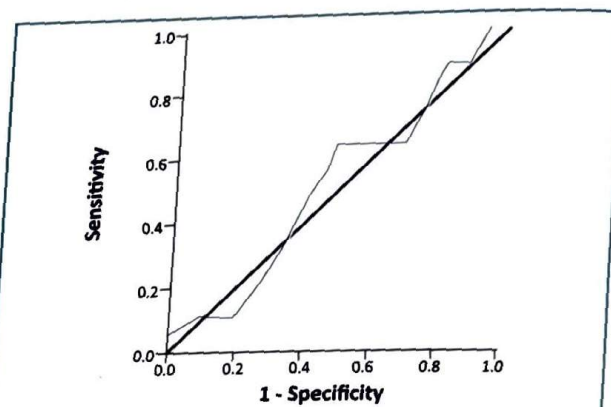


Figure 4: ROC curve for neutrophil to diagnose complicated appendicitis

AUC	Standard error	Asymptotic significance	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.516	0.055	0.771	0.408	0.625

Cutoff value	Accuracy	Sensitivity	Specificity	PPV	NPV
≥ 83.5%	54.4%	63.9%	51%	31.9%	79.7%

DISCUSSION

In this study, we sought to analyse the association between elevated TLC and neutrophil counts with appendicitis. Moreover, we also examined whether TLC and neutrophil counts can help to discriminate cases of complicated appendicitis from uncomplicated ones.

Our study included 150 patients, of whom 136 (90.67%) had appendicitis. The mean age was 24.23 years and male to female ratio was 2.32:1. This is similar to most studies which report predominance of young males. In

a study by Sigdel GS et al, mean age was 27.5 years and male to female ratio was 2.6:1⁷. In another study by Agrawal CS et al, most of patients (59.2%) were from age group 11-30 years⁸.

Thirty six (26.47%) patients had complicated appendicitis (perforation, gangrene or abscess) in our study. This is slightly higher than reported in most literature. A study by Flum DR et al has reported a perforation rate of 25.8 %.³ Korner H et al reported a perforation rate of 19%.⁹ Higher rates in our study could be the result of delayed presentation. Compared to those studies, mean time from onset of symptoms to presentation at hospital was longer (41.2 hours) in our patients. According to one study, the average rate of perforation was between 16% and 36% after the first 36 hours from the onset of symptoms, and the risk of perforation increased by 5% for every subsequent 12 hour period.¹⁰

Our study showed that TLC had a sensitivity of 75.53%, specificity of 64.29% and PPV of 95.24% to diagnose appendicitis. Sensitivity of TLC in our study is similar to that reported by Agrawal CS et al and Birchley D et al.^{8,11} However, TLC had a low NPV of 20% at cut off of 20% at cut off of $\geq 11,000/\text{mm}^3$ in our study and 26.47% of our patients with acute appendicitis had normal counts ($<11,000/\text{mm}^3$). Thus from our study, it is seen that normal TLC cannot rule out appendicitis.

Shaw PGV et al and Anderson M et al also agreed that normal inflammatory markers did not rule out appendicitis.^{12,13}

Sensitivity of neutrophilia ($>70\%$) to diagnose appendicitis in our study was 85.29% and specificity was 42.86%. Our sensitivity is comparable to Yang HR et al but lower than reported by Shafi SM et al.^{14,15} Specificity in our study is higher compared to both Yang HR et al and Shafi SM et al.^{14,15} Higher sensitivity and lower specificity in study by Shafi SM et al could be because of the different cutoff point for defining neutrophilia in their study. In our study, 20 patients (14.7%) with acute appendicitis had normal neutrophil counts. On the other hand, 57% of even those without appendicitis had elevated neutrophil counts. Thus it can be inferred from our study that while higher neutrophils make the diagnosis of appendicitis more likely, it does not confirm it and at the same time normal neutrophil count does not rule out appendicitis. Lau WY et al have also noted that the total counts and neutrophil counts should only be interpreted in the light of physical findings in patients with suspected appendicitis because these blood tests have false positive and false negative results.¹⁶ Yang HR et al also report that both leukocyte count and neutrophil percentage are not specific for acute appendicitis.¹⁴ This could be because leucocytosis and neutrophilia are nonspecific reaction to any acute inflammation and acute physical or emotional stress.¹⁷

Table 6: Comparison of accuracy of TLC/ neutrophilia reported by various authors

Authors	Parameter studied & cutoff value	Sensitivity	Specificity	PPV	NPV
Agrawal CS et al ⁸	TLC $> 11,000$	78.6%	54.8 %	81 %	51.1%
Yang HR et al ¹⁴	TLC	85.8 %	31.9 %		
	Neutrophilia	87.2%	33.1%		
Shaw PGV et al ¹²	TLC $> 10,000$	70	82	88	59
	N $> 75 \%$	80	80	88	67
Birchley D et al ¹¹	TLC	78	67		
Shafi SM et al ¹⁵	TLC	97.8	55.55 %		
	Neutrophilia	98.9	38.88	89.21	
Our study	TLC $\geq 11,000$	75.53%	64.291%	95.24%	20%
	N $> 70 \%$	85.29%	42.86%	93.55%	23.08 %

In our present study, ROC curves showed that TLC and neutrophil counts had only moderate ability to discriminate between patients with and without appendicitis. AUC was 0.676 and 0.707 for TLC and

neutrophils respectively. A perfect discriminatory test has an AUC of 1 and a good discriminatory test has an AUC above 0.8. At a cut off $\geq 13950/\text{mm}^3$, TLC had specificity of 100% but sensitivity was only

45.6% and accuracy was 50.67%. Similarly neutrophil counts had an accuracy was 68.7% at cutoff $\geq 80.5\%$ for appendicitis. Both TLC and neutrophil counts had low NPVs of 15.9% and 18.9% respectively suggesting that normal TLC and neutrophil counts cannot rule out appendicitis. Al-gaithy ZK et al also found that AUCs of TLC and neutrophil for diagnosis of appendicitis to be 0.701 and 0.680 respectively which is similar to our findings.¹⁸ Rodriguez-sanjuan JC et al also had an AUC of 0.67 for TLC.¹⁹ Both authors recommend against TLC or neutrophil counts to rule out acute appendicitis.

We also did ROC curve analyses to assess the role of TLC and neutrophils in differentiating complicated appendicitis from uncomplicated appendicitis. In our study neither total count nor neutrophil percentages had sufficient sensitivity or specificity to differentiate uncomplicated appendicitis from complicated. AUCs of ROC curves were only 0.527 and 0.516 for TLC and neutrophils respectively. At a cutoff $\geq 14050/\text{mm}^3$ for complicated appendicitis, TLC had a low sensitivity of 33.3%, specificity of 53% and accuracy of 47.8%. Similarly, at cutoff $\geq 83.5\%$ for complicated appendicitis, neutrophil percentage had low specificity of 51% and accuracy of 54.4%. The cutoff values of TLC and neutrophils for diagnosis of complicated appendicitis were higher than the cutoff values for diagnosis of appendicitis. However, they cannot be relied upon to confirm or rule out the diagnosis of complicated appendicitis. Keskek M et al also reported an AUC of only 0.55 for TLC to differentiate complicated from uncomplicated appendicitis, which is similar to our study and suggest that it has no value to predict complicated appendicitis.²⁰ Furthermore, Al-gaithy ZK et al have also concluded that TLC and neutrophil counts do not indicate severity of appendicitis.¹⁸

CONCLUSION

Mean of TLC or neutrophil percentages are not significantly different among patients with uncomplicated appendicitis, complicated appendicitis and non-appendicular pathology. Neither TLC nor neutrophil percentages have sufficient discriminatory power to diagnose acute appendicitis or to differentiate between uncomplicated and complicated appendicitis as shown by low AUCs on ROC analysis. Hence normal leucocyte counts or neutrophil counts cannot rule out acute appendicitis. More prospective studies with larger sample will help to better define the association.

LIMITATION

There are some limitations to our study. Since we took histopathology as the basis for confirmation of diagnosis of appendicitis, those cases who did not undergo surgery were excluded, which meant many complicated cases including appendicular abscesses that were managed conservatively could not be included. Secondly small sample size and retrospective design limited the scope of our conclusion.

ACKNOWLEDGEMENT

We are highly grateful to our patients who formed the basis of our study.

CONFLICT OF INTEREST: None

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