

# A new, simple marker for predicting complicated appendicitis in patients with normal white blood cell count indicator; LUC %

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## ABSTRACT

**BACKGROUND:** The aim of this study was to investigate the ability of a new marker that could be easily obtained to differentiate between complicated and uncomplicated appendicitis in a patients with a white blood cell (WBC) count within the normal range.

**METHODS:** The patients who underwent surgery with histopathologically proven acute appendicitis (AA) between January 2021 and October 2022 were evaluated retrospectively. Patients were classified into two groups as uncomplicated and complicated appendicitis, based on the surgical and histopathological findings. Groups were compared in terms of laboratory parameters at the time of hospital admission.

**RESULTS:** During the study period, 2589 patients underwent an appendectomy, among these 612 patients who had a WBC count within the normal range at the time of admission were analyzed. Uncomplicated appendicitis was detected in 79.6% of the patients and complicated appendicitis in 20.4%. Neutrophil%, neutrophil-to-lymphocyte ratio, C-reactive protein, and total bilirubin levels were significantly higher, whereas lymphocyte%, lymphocyte count, lymphocyte-to-monocyte ratio, sodium levels, and large unstained cells (LUC)% were significantly lower in patients with complicated appendicitis. Multiple logistic regression analysis revealed that lower LUC% (Odds Ratio [OR]: 0.45; 95% Confidence Intervals [CI]: 1.08–2.09; P=0.01) and higher total bilirubin levels (OR: 1.50; 95% CI: 1.08–2.09; P=0.01) were independent risk factors for complicated appendicitis.

**CONCLUSION:** In patients with a diagnosis of AA with a normal WBC value, LUC% obtained from the complete blood count can be used as a new parameter predicting the diagnosis of complicated appendicitis.

**Keywords:** Acute appendicitis; complicated appendicitis; large unstained cells; predictive biomarkers.

## INTRODUCTION

Acute appendicitis (AA) is an inflammatory process beginning from the appendiceal wall and followed by localized ischemia, if not treated properly, perforation, abscess formation, and finally generalized peritonitis may occur.<sup>[1]</sup> Perforation may develop in 16–39% of the patients,<sup>[2]</sup> and it is associated with an increased risk of morbidity and postsurgical complications.<sup>[3–6]</sup> Therefore, it is important to differentiate between uncomplicated and complicated (perforation, gangrenous appendicitis,

intra-abdominal abscess, and localized or generalized peritonitis) appendicitis, as the two types have different pathophysiology and treatment recommendations.<sup>[7]</sup> Due to the serious morbidity and mortality associated with complicated appendicitis, early diagnosis and prompt evaluation are crucial.

Several diagnostic markers have been investigated in the diagnosis of complicated AA. White blood cell (WBC) and C-reactive protein (CRP) are the most commonly used parameters and recently neutrophil-to-lymphocyte (NLR) and

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platelet-to-lymphocyte ratio<sup>[8]</sup> and delta neutrophil index<sup>[9]</sup> have been evaluated to differentiate uncomplicated from complicated appendicitis. Several studies state that WBC counts are sensitive but not specific for AA and have low sensitivity in distinguishing between complicated and uncomplicated cases.<sup>[10-12]</sup> Since accurate and early preoperative diagnosis of perforated appendicitis is very important to prevent complications, it would be useful to define new, easily accessible diagnostic methods.

In this study, we aimed to describe patients with normal preoperative WBC among patients with histopathologically proven appendicitis and investigate the ability of a new marker that could be easily obtained to differentiate between complicated and uncomplicated appendicitis.

## MATERIALS AND METHODS

This was a single-center, retrospective cohort study that included a total of 2589 adult patients with a diagnosis of AA who underwent surgery between January 2021 and October 2022 at Ankara City Hospital. For the current analysis, only patients with histopathologically proven AA were evaluated. Among these, 612 patients with a WBC count within the normal range at the time of admission were enrolled in the study. Patients were classified into two groups: uncomplicated (simple AA) and complicated (perforation, gangrenous appendicitis, intra-abdominal abscess, and localized or generalized peritonitis) based on the surgical and histopathological findings.<sup>[7]</sup> Demographic and clinical characteristics, laboratory findings, surgical procedures, and histopathological results of the appendix examination were obtained from the medical records of patients.

Uncomplicated and complicated groups were compared in terms of laboratory parameters at the time of admission, including WBC, neutrophil, lymphocyte, monocyte, platelet count, NLR, lymphocyte-to-monocyte ratio (LMR), LUC%, CRP, total bilirubin, and sodium levels.

Patients receiving any immunosuppressive agent, patients with any hematologic and solid cancers, acute viral infections, particularly coronavirus disease 2019, pregnant women, and those with leukocytosis and leukopenia were excluded from the study.

The study was approved by the local Ethics Committee of Ankara City Hospital (Number: E1-23-3254).

## Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) for Windows version 24.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was checked with the Kolmogorov–Smirnov test. The Student's t-test or the Mann–Whitney U test was used for continuous variables and Pearson's chi-square or Fisher's exact test for categorical variables. Parameters associated with complicated appendicitis at the P<0.1 level were included in the univariate logistic regression analysis. Parameters found to be associated with complicated appendicitis at the P<0.1 level in the univariate analysis were included in the forward stepwise multivariate logistic regression analysis to determine independent risk factors for complicated appendicitis. The odds ratios for the parameters were calculated with 95% confidence intervals.

**Table 1.** Univariate and multivariate regression analysis of laboratory parameters

	Univariate analysis			Multivariate regression analysis		
	Uncomplicated (n=487)	Complicated (n=125)	P-value	Odds ratio	95% Confidence interval	P-value
Neutrophil (%)*	67 (±11.3)	73.3 (±10.9)	<0.001			
Lymphocyte (%)*	23.5 (±9.5)	17.7 (±9.0)	<0.001			
Lymphocyte (×10 <sup>9</sup> /L)*	2.01 (±3.07)	1.50 (±0.78)	<0.001			
Monocyte (×10 <sup>9</sup> /L)*	0.50 (±1.35)	0.55 (±0.51)	0.053			
NLR*	3.79 (±3.25)	5.99 (±5.12)	<0.001			
LMR*	4.78 (±5.80)	3.29 (±1.76)	<0.001			
LUC (%)*	1.81 (±0.88)	1.68 (±0.99)	0.016	0.45	0.07-0.96	0.01
Platelet (×10 <sup>9</sup> /L) *	255 (±63)	248 (±73)	0.075			
CRP (mg/dL) *	1.65 (±0.44)	7.69 (±2.96)	<0.001			
Total bilirubin (mg/dL)*	0.8 (±0.5)	1.1 (±0.9)	0.002	1.50	1.08-2.09	0.01
Sodium (mEq/L)*	139.4 (±2.2)	138.2 (±3.2)	<0.001			

WBC: White blood cell; NLR: Neutrophil to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio; LUC: Large unstained cell; CRP: C-reactive protein, \*Mean±standart deviation.

## RESULTS

Among 612 patients with a WBC count within the normal range at the time of admission, three hundred and thirty-three (54.4%) of the patients were male, whereas 279 (45.6%) were female. Based on the surgical and histopathological findings, 487 (79.6%) patients had uncomplicated (simple) appendicitis and 125 (20.4%) patients had complicated (perforation, abscess, and localized or generalized peritonitis) appendicitis. Groups were compared in terms of laboratory parameters at the time of admission. The mean ( $\pm$ SD) age was 36 ( $\pm$ 14) and 43 ( $\pm$ 17) years in uncomplicated and complicated groups, respectively ( $p$ , NS). Laparoscopic appendectomy was performed in 121 (19.7%) cases.

WBC count, neutrophil%, lymphocyte%, lymphocyte count, monocyte count, NLR, LMR, LUC%, platelet count, CRP, and total bilirubin and sodium levels were evaluated using univariate analysis and variables with a statistically significant difference between the groups were included for multivariate logistic regression analysis (Table 1).

According to the multivariate logistic regression analysis, increase in total bilirubin levels and decrease in the LUC% independently predicted complicated appendicitis.

## DISCUSSION

In this study, we demonstrated that an increase in total bilirubin levels and decrease in the LUC% independently predicted complicated appendicitis. LUC% is one of the routine parameters of a complete blood count, and to the best of our knowledge, there is no study, in which the predictive ability of LUC% in diagnosing complicated appendicitis was investigated in patients with a WBC count within the normal range at the time of admission.

Early and accurate diagnosis of perforated appendicitis is crucial because it is associated with an increased risk of morbidity and postsurgical complications. Perforated, gangrenous, or appendicitis with an intra-abdominal abscess is considered complicated AA. These cases require immediate surgical intervention. Postoperative morbidities such as an increased rate of wound infection, intra-abdominal abscess, and postoperative ileus increase in complicated appendicitis.<sup>[1,7]</sup> In addition, more detailed information could be provided to patients with complicated appendicitis about the risks of surgical procedures taking into account medical legal issues. Therefore, in patients presenting with the symptoms of appendicitis, careful clinical assessment and diagnosis should be aimed at differentiating complicated appendicitis.

Treatment modalities change between uncomplicated and complicated appendicitis, so differentiation of these conditions is important. Furthermore, in terms of increased risk of morbidity and mortality, longer duration of hospitalization,

and the occurrence of complications, it is imperative to distinguish complicated appendicitis from uncomplicated cases. Although appendectomy has been the standard treatment for AA, especially with the advancement of diagnostic imaging studies in the recent years, non-operative medical treatment for uncomplicated AA has gained popularity.<sup>[1]</sup> In the literature, there have been studies comparing conservative management with antibiotics to appendectomy as a primary treatment modality for uncomplicated appendicitis.<sup>[13,14]</sup> The main benefits of antibiotic treatments are faster return to work, no exposure to anesthesia and surgery risks, and lower medical costs. Because of the advantages of antibiotic treatment in eligible patients with uncomplicated AA, this option may be recommended as an alternative to surgery. Hence, differentiating complicated from uncomplicated appendicitis with accurate, easy, feasible, and reliable diagnostic methods seems important to take advantage of this benefit.<sup>[15,16]</sup>

As is well known, computed tomography is the most useful tool for the diagnosis of AA, but the use of this method is expensive and exposes patients to ionizing radiation. Therefore, identifying a reliable and easily measurable marker for the preoperative diagnosis of complicated appendicitis is of paramount importance. Several studies have focused on markers including laboratory tests, scoring methods for the precise diagnosis of complicated appendicitis.<sup>[7,17]</sup> The laboratory indicators currently used, such as WBC and CRP are not consistently reliable and their accuracy is questionable. In literature, there have been many studies on various parameters such as serum sodium and bilirubin levels, delta neutrophil index, and NLR that was used for distinguishing complicated appendicitis from uncomplicated cases.<sup>[8,9,17-24]</sup>

In our study, neutrophil%, lymphocyte%, lymphocyte count, NLR, LMR, and sodium levels were significantly different between the uncomplicated and complicated appendicitis. However, those parameters except for LUC% and total bilirubin levels were not reliable enough to predict patients with complicated appendicitis. Hyperbilirubinemia has shown to be associated with the severity of the appendicitis due to increased inflammation.<sup>[17,25]</sup> As a result of the edema of the intestine and increased intraluminal pressure, ischemia and necrosis of the appendix occur. These mechanisms induce the occurrence of cholestasis in patients with complicated appendicitis.<sup>[17,26]</sup> However, in the literature it was shown that hyperbilirubinemia alone could not be a reliable predictor of complicated appendicitis because of the low sensitivity of this parameter.<sup>[17]</sup>

The LUC% is a parameter that is routinely assessed as a part of complete blood cell (CBC) tests, reflecting activated lymphocytes and peroxidase-negative cells. The LUC% value has been evaluated in the literature in a few studies as a marker in differential diagnosis or prognosis of infections.<sup>[27-30]</sup> Hyperinflammation induces apoptosis of lymphocytes,<sup>[31,32]</sup> so we can conclude that increased tissue and cell damage during the oc-

currence of complicated appendicitis, results in the decrease of lymphocyte values. As LUC refers to activated lymphocytes and other atypical cells we hypothesized that LUC% could not increase during the course of complicated appendicitis where lymphocyte values are relatively low. Although lymphocyte count and LUC% were significantly lower in patients with complicated appendicitis, in multivariate analysis we observed that LUC% value was an independent predictor that is negatively correlated with severe complicated cases. Since LUC% can easily be obtained along with a routine CBC test, it could help clinicians predict complicated appendicitis earlier.

## CONCLUSION

There is currently no accurate laboratory test or imaging approach for diagnosing and identifying the severity of AA in routine surgical practice. LUC% is a simple parameter that is routinely obtained from a CBC test and found to be independent parameter predicting complicated appendicitis in patients with a WBC count within the normal range. If confirmed by well-designed prospective randomized studies, we believe LUC% has the potential to be a significant predictive marker.

**Ethics Committee Approval:** This study was approved by the Ankara City Hospital Clinical Research Ethics Committee (Date: 25.01.2023, Decision No: EI-23-3254).

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**Conflict of Interest:** None declared.

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## ORJİNAL ÇALIŞMA - ÖZ

### Beyaz küre sayısı normal olan hastalarda komplike apandisit tanısı için yeni, basit bir belirteç: LUC %

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**AMAÇ:** Bu çalışmanın amacı, beyaz küre sayısı normal aralıkta olan akut apandisit tanılı hastalarda, komplike ve komplike olmayan apandisit ayırıcı tanısı için kolayca elde edilebilecek yeni bir belirteci araştırmaktır.

**GEREÇ VE YÖNTEM:** Ocak 2021-Ekim 2022 tarihleri arasında histopatolojik olarak kanıtlanmış akut apandisit nedeniyle ameliyat edilen hastalar geriye dönük olarak değerlendirildi. Hastalar cerrahi ve histopatolojik bulgulara göre komplike olmayan ve komplike apandisit olarak iki gruba ayrıldı. Gruplar hastaneye yatış anındaki laboratuvar parametreleri açısından karşılaştırıldı.

**BULGULAR:** Çalışma süresi boyunca 2589 hastaya apendektomi yapılmıştır. Bu hastalardan başvuru anında beyaz küre sayısı normal sınırlar içerisinde olan 612 hasta analiz edildi. Hastaların %79.6'sında komplike olmayan apandisit, %20.4'ünde komplike apandisit saptandı. Komplike apandisit grubundaki hastalarda nötrofil yüzdesi, nötrofil/lenfosit oranı (NLR), C-reaktif protein ve total bilirubin düzeyleri anlamlı olarak daha yüksek, lenfosit yüzdesi, lenfosit sayısı, lenfosit/monosit oranı (LMR), serum sodyum düzeyi ve LUC yüzdesi anlamlı olarak daha düşük bulundu. Lojistik regresyon analizinde, düşük LUC yüzdesi (OR: 0.45; %95 CI: 1.08-2.09; p=0.01) ve yüksek total bilirubin düzeylerinin (OR: 1.50; %95 CI: 1.08-2.09; p=0.01) komplike apandisit için bağımsız risk faktörleri olduğu gösterildi.

**SONUÇ:** Beyaz küre sayısının normal olduğu akut apandisit tanılı hastalarda, tam kan sayımından elde edilen LUC yüzdesi, komplike apandisit tanısını öngören yeni bir parametre olarak kullanılabilir.

**Anahtar sözcükler:** Akut apandisit; komplike apandisit; biobelirteçler; LUC

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