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RESEARCH ARTICLE

Prognostic Value of Large Unstained Cells (LUC) in Assessing the Severity of Acute Cholecystitis

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ABSTRACT

Objective: The Tokyo Guidelines 2018 (TG18) are widely used to evaluate the severity of acute cholecystitis. However, there remains a need for simpler and faster laboratory markers. This study aimed to assess whether the large unstained cell (LUC) percentage could serve as a useful biomarker for determining disease severity.

Materials and Methods: This retrospective study included 300 patients diagnosed with acute cholecystitis between January 2019 and December 2023. Demographic characteristics, laboratory parameters, and radiological findings were reviewed. Based on TG18 criteria, patients were categorized into mild (Group 1), moderate (Group 2), and severe (Group 3) groups. The relationship between LUC% and disease severity was analyzed.

Results: According to TG18 classification, 50.3% of patients (n=151) had mild, 32.3% (n=97) moderate, and 17.3% (n=52) severe acute cholecystitis. The median LUC% was 1.4% (range: 0.02–4.0). LUC values significantly differed across groups (p=0.006), being lower in Groups 2 and 3 compared to Group 1 (p=0.049 and p=0.017, respectively). A weak but significant negative correlation was found between LUC% and TG18-defined disease severity (r=-0.184, p<0.001). A cut-off value of 0.75% for LUC% identified mild cases with 28.85% sensitivity and 88.07% specificity (AUC: 0.604, 95% CI: 0.540–0.667, p=0.002).

Conclusion: LUC% is negatively associated with the severity of acute cholecystitis and may serve as a rapid, cost-effective, and accessible marker to support early clinical assessment.

Keywords: Acute cholecystitis, large unstained cells (LUC), Tokyo Guidelines 2018

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INTRODUCTION

Acute cholecystitis is a common surgical emergency associated with significant morbidity and mortality.[1] The lifetime incidence of gallstone formation in adults is approximately 20%, and about 20% of these individuals go on to develop acute cholecystitis.[2] The condition is reported to be three times more prevalent in women than in men under the age of 50, and 1.5 times more prevalent in women at older ages.[3]

The Tokyo Guidelines 2018 (TG18) are widely utilized to classify the severity of acute cholecystitis, predict treatment needs, and estimate prognosis. According to TG18, patients are stratified into mild, moderate, and severe groups. As disease severity increases, so does the need for intensive care and the risk of mortality. Therefore, early and accurate assessment of disease severity is of critical importance. Currently, however, there is no specific biomarker that reliably indicates the severity of acute cholecystitis.

Large unstained cells (LUC%) are peroxidase-negative cells detected automatically by certain hematology analyzers and expressed as both absolute counts and percentages in complete blood counts (CBC). Previous studies have suggested that LUCs may reflect systemic inflammatory responses, comprising activated lymphocytes, plasma cells, and other atypical leukocytes not classified within standard leukocyte subtypes.[4]

Since LUC% represent activated lymphocytes, its increased amount in whole blood analysis was found to be correlat-

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ed with immunological and inflammatory activation. Those cells are beyond clear classification but have been postulated to be clinically relevant during inflammatory states, viral infections, and hematological malignancies.[4,5]

Hyperinflammation induces apoptosis of lymphocytes; therefore, it can be said that increased tissue and cell damage in acute cholecystitis causes a decrease in lymphocyte values and, therefore, as the severity of the disease increases, there will be a significant decrease in LUC%.[6]

LUC% values have been explored as potential indicators in various inflammatory and neoplastic conditions, such as invasive aspergillosis, orchitis, testicular torsion, appendicitis, hematological malignancies, and gastric and metastatic breast cancers, due to their correlation with immune and inflammatory biomarkers.[5–9] Although several biomarkers have been proposed to assess the severity of acute cholecystitis,[10–14] the LUC% value has not been previously investigated in this context.

In this study, we aimed to evaluate the prognostic value of large unstained cells (LUC) in assessing the severity of acute cholecystitis.

MATERIALS and METHODS

This retrospective study was conducted by reviewing hospital records and electronic medical data of patients aged over 18 who were diagnosed with acute cholecystitis based on TG18 criteria at a single center between January 2019 and December 2023. Patients were excluded if they were under 18 years of age, had a history of malignancy, immunosuppressive conditions, hematologic diseases, chronic cholecystitis, were pregnant, or had incomplete medical data.

Diagnosis of acute cholecystitis was made based on clinical signs of local and systemic inflammation, along with radiological findings from computed tomography or ultrasonography, in accordance with TG18 criteria. Demographic variables, including age, gender, body mass index (BMI), and comorbidities (none, <2, >2), were recorded. Comorbidities, except the exclusion criteria, were recorded numerically, independent of their type. Laboratory parameters such as white blood cell (WBC) count (*10^9/L), C-reactive protein (CRP, mg/L), and LUC (%) values were obtained.

LUC levels were analyzed using an automated hematology analyzer (Siemens Medical Solutions Diagnostics, ADVIA 2120i, Tarrytown, NY, USA). The analyzer employs advanced optical and staining technologies to detect and categorize blood cell populations.

Patients were categorized into three groups based on disease severity: mild (Group 1), moderate (Group 2), and severe (Group 3), as defined by TG18. LUC values were compared across the three groups. The study was approved by the institutional ethics committee under protocol number E1/23/4053. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation if normally distributed, or as median (minimum–maximum) with interquartile range (IQR) if not. The Shapiro–Wilk test was used to assess normality. Categorical variables were presented as frequencies and percentages. The chi-square test was applied for categorical variable comparisons. For non-normally distributed continuous variables, the Kruskal–Wallis test was used; the ANOVA test was applied for normally distributed variables across groups. Post hoc analysis was conducted using the Dunn test with Bonferroni correction. Correlations between variables were analyzed using the Spearman correlation test. The optimum cut-off value was calculated using ROC analysis to differentiate mild cholecystitis from moderate and severe cholecystitis. After calculating the optimum cut-off value for LUC% by ROC analysis, the chi-square test was used to calculate positive and negative predictive values. All statistical analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

RESULTS

A total of 300 patients diagnosed with acute cholecystitis were included in the study. Median age was 54 years, IQR: 23 years. 47.3% (142) of patients were male, and 52.7% (158) of patients were female. Demographic characteristics of the patients are shown in Table 1.

Table 1. Demographic characteristics

	n	%
Age (years) (median)/(IQR)	54/23	
Gender		
Female	158	52.7
Male	142	47.3
BMI (kg/m^2) (median)/ (IQR)	30/5	
Comorbidity		
None	164	54.7
≤2	105	35
>2	31	10.3

IQR: Interquartile range; BMI: Body mass index

Table 2. Comparison of demographic data between the groups

	Group 1 151 (50.3)		Group 2 97 (32.3)		Group 3 52 (17.3)		p
	n	%	n	%	n	%	
Age (years) (medain)/ IQR)	51/21		55/26		67/20.25		**<0.001**
BMI (kg/m^2) (median)/(IQR)	29/6		31/5		32/4.75		**<0.001**
Gender							0.443
Female	85	56.3	48	49.5	25	48.1	
Male	66	43.7	49	50.5	27	51.9	
Comorbidity							0.051
None	93	61.6	51	52.6	20	38.5	
≤2	47	31.1	34	35.1	24	46.2	
>2	11	7.3	12	12.4	8	15.4	

According to the TG18 acute cholecystitis severity score, 151 (50.3%) patients were in Group 1, 97 (32.3%) patients were in Group 2, and 52 (17.3%) patients were in Group 3. Patients in Group 3 were older (p<0.001), and similarly, BMI was higher in Group 3 (p<0.001). There was no significant difference between the groups in terms of additional diseases (p=0.051). Comparison of demographic data between the groups is shown in Table 2.

Laboratory findings revealed a median WBC count of 12.5x10^9/L (range: 3.5–28.1; IQR: 5.4) and a median CRP value of 41.5 mg/L (range: 1.1–326; IQR: 75). Median LUC% was 1.4% (range: 0.02–4.0; IQR: 1.1). A statistically significant difference in LUC values was observed among the groups (p = 0.006). Post hoc analysis indicated significantly lower LUC values in Group 3 vs. Group 1 (p=0.017), and in Group 2 vs. Group 1 (p=0.049). No significant difference was found between Groups 2 and 3 (Table 3).

Spearman correlation analysis revealed a negative correlation between LUC% and TG18-defined disease severity (r=–0.184, p<0.001) (Fig. 1).

A 0.75 LUC% value was found to be the cut-off value to differentiate mild cholecystitis from moderate and severe cholecystitis, with a sensitivity of 28.85%, specificity of 88.07%, positive predictive value of 44.5%, and negative predictive value of 31.3% (AUC: 0.604, CI95%: 0.540–0.667, p=0.002) (Fig. 2).

DISCUSSION

Early diagnosis and accurate assessment of the severity of acute cholecystitis are crucial for determining appropriate treatment modalities. Furthermore, early risk stratification is essential to reduce postoperative morbidity and mortality.

Table 3. Relationship between WBC, CRP and LUC% values and groups

	Group 1 151 (50.3) (M/IQR)	Group 2 97 (32.3) (M/IQR)	Group 3 52 (17.3) (M/IQR)	p
WBC (*10^9/L)	9.31/5.8	15.37/10.03	13.68/21.1	**<0.001**
CRP (mg/L)	13.8/10.15	17.5/20.05	16/13	**0.042**
LUC (%)	1.5/1.2^{a,b}	1.3/1.1^{a,c}	1.2/1.98^{b,c}	**0.006**

^{a}: Group 1 vs Group 2, p=0.049; ^{b}: Group 1 vs Group 3, p=0.017; ^{c}: Group 2 vs Group 3, p=1.000. WBC: White blood cell; CRP: C-reactive protein; LUC: Large unstained cells; M: Median

In this study, we demonstrated that the LUC value, routinely available through standard hemogram tests, serves as a fast and cost-effective parameter for determining the severity of acute cholecystitis.

Although acute cholecystitis can occur at any age, its incidence increases with age, plateauing after the age of 50 in women and 60 in men.[15] Nikfarjam et al.[16] found no significant difference in the incidence of acute cholecystitis between sexes. In our study, the median age was 54 years, and females constituted a slightly higher proportion (52.7% vs. 47.3%), aligning with existing literature.

Yacoub et al.[17] identified male gender as a risk factor for gangrenous cholecystitis in patients with acute cholecystitis (p<0.001). Conversely, Sakalar et al.[12] and Mahmood et al.[13] reported no significant association between gender and disease severity. Similarly, our study did not reveal any statistically significant difference in gender distribution across severity groups (p=0.443).

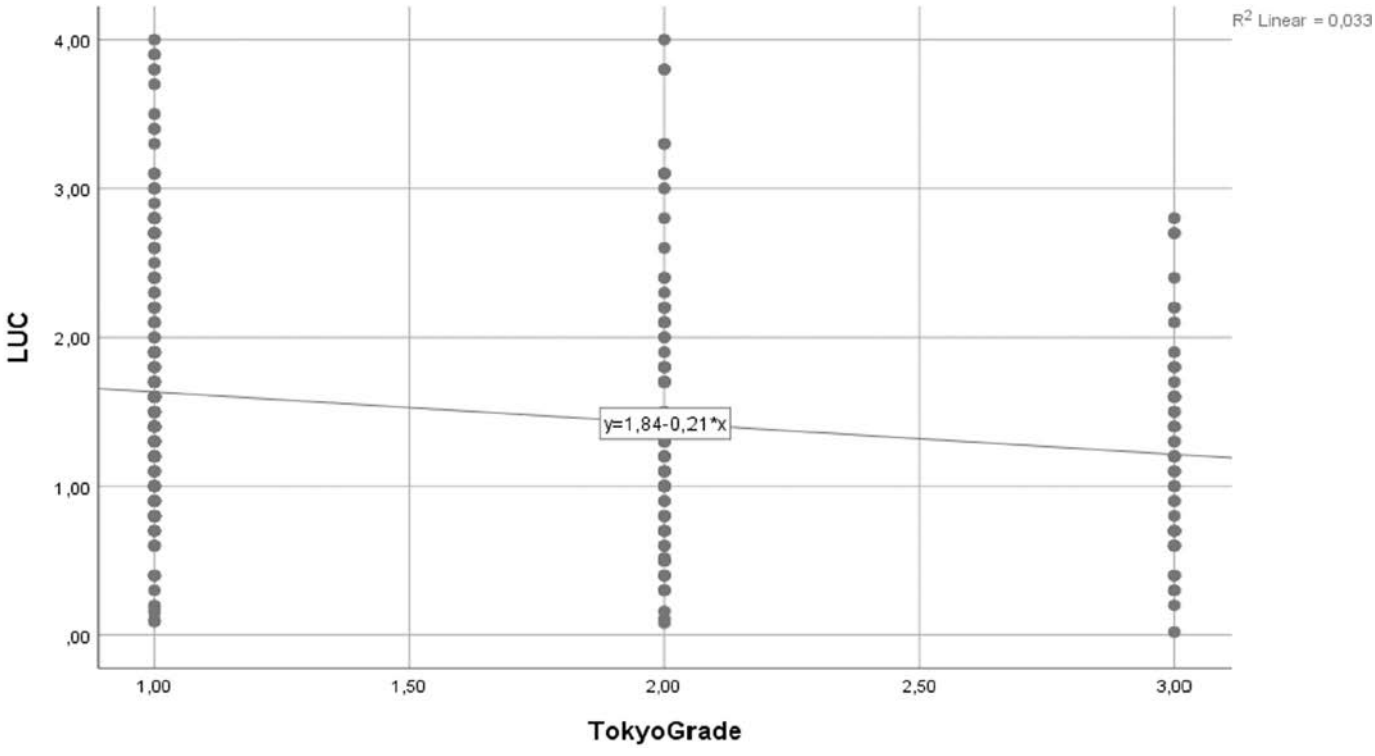

Figure 1. Correlation analysis

LUC: Large unstained cells

Wang et al.[18] reported that elderly individuals are more prone to severe acute cholecystitis due to atypical presentations, diminished physiological inflammatory responses, and increased comorbidities. Another study noted that patients aged 60 years and older are at a higher risk for complicated acute cholecystitis.[19] However, Xia et al.[11] found no significant association between age and the various forms of cholecystitis. In line with some previous findings, our results indicated that patients in Group 3 were older ($p<0.001$).

While Borzellino et al.[20] found no correlation between comorbidities such as diabetes and cardiovascular diseases and gangrenous cholecystitis, Nikfarjam et al.[21] demonstrated a significant association between advanced age, diabetes, and gangrenous cholecystitis. In our study, we observed no significant association between comorbidities and disease severity. Although TG18 emphasizes the role of comorbidities in disease prognosis, we believe the lack of correlation in our findings may be attributed to the limited number of patients with two or more comorbid conditions among those with severe acute cholecystitis.

Lee et al.[19] investigated the relationship between BMI and disease severity, reporting that non-obese males had higher rates

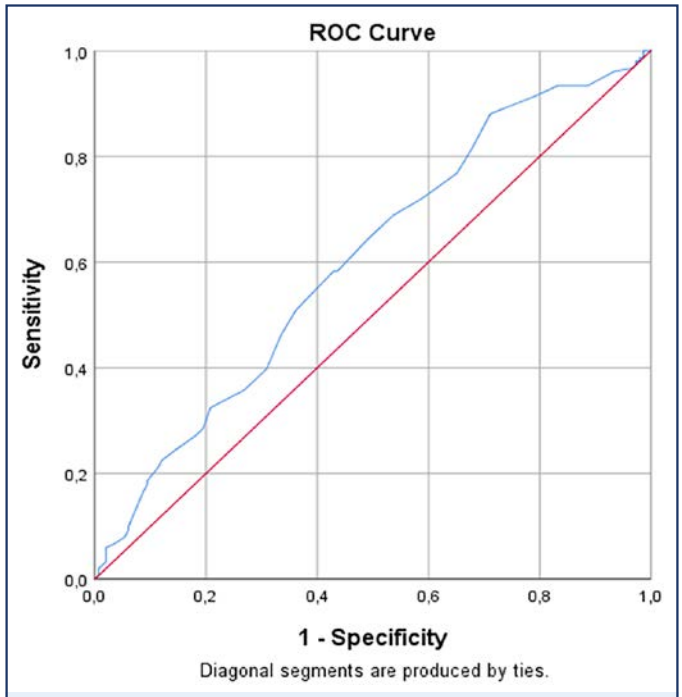

Figure 2. ROC curve

ROC: Receiver operating characteristic

of complicated acute cholecystitis than obese counterparts (21.5% vs. 8.1%). Another study comparing gangrenous and non-gangrenous cases found no association between BMI and disease severity.[21] In contrast, our study showed significantly higher BMI values among patients with severe acute cholecystitis ($p<0.001$), which we believe may be related to elevated inflammatory cytokine levels in overweight and obese individuals.

WBC and CRP are widely used laboratory markers in diagnosing and evaluating the severity of acute cholecystitis. Notably, WBC is included in TG18 as a criterion for severity assessment.[1] Yacoub et al.[17] reported that WBC values above $13x10^9$/L are indicative of severe disease, and Nikfarjam et al.[21] observed higher WBC levels in patients with gangrenous versus non-gangrenous cholecystitis. Conversely, Sakalar et al.[12] argued that WBC is not a reliable indicator across varying disease severities. Our study showed that WBC levels were significantly higher in Group 3 compared to Group 1, and in Group 2 compared to Group 1 ($p<0.001$), though no difference was noted between moderate and severe groups. This may be due to a transition from leukocytosis to leukopenia as inflammation progresses, potentially explaining the lack of difference between Groups 2 and 3.

Although CRP is not yet an accepted prognostic marker in TG18,[1] several studies have reported its utility in severity assessment. Mahmood et al.[13] identified CRP values above 55 mg/L as indicative of complicated cholecystitis, and a large cohort study found CRP to be superior to WBC in evaluating disease severity.[14] In our study, similar to WBC, CRP values significantly differed between Groups 1 and 2 but not between Groups 2 and 3.

LUC% has been scarcely investigated in the literature. Urbanowicz et al.[5] found that a LUC value below 0.16 could predict carotid artery occlusion, an acute inflammatory condition. In a study on appendicitis, significantly lower LUC% values were found in complicated cases, and LUC% was identified as an independent risk factor for complications.[6] Çakır et al.[7] found high LUC% values useful in diagnosing and monitoring invasive aspergillosis, while low LUC% values were predictive of prognosis in critically ill COVID-19 patients.[8] Elevated LUC% values have also been linked to viral conditions such as Kaposi varicelliform eruption, Herpes zoster, and varicella.[9]

The LUC value, representing active lymphocytes, tends to rise in viral infections but declines through apoptosis during intense inflammation, showing a negative correlation.[22] Lymphocytes in peripheral blood play a cytotoxic and tumor-suppressive role, and their reduction in advanced inflammation or sepsis has been associated with increased mortality.[23]

In our study, as the severity of acute cholecystitis—a condition characterized by acute inflammation—increased, LUC% values significantly decreased. LUC% was lower in Group 1 compared to Groups 2 and 3 (1.2 vs. 1.5 and 1.3 vs. 1.5, respectively), with a negative correlation observed between disease severity and LUC% ($r=-0.184$, $p<0.001$). The correlation coefficient is relatively low and does not appear to provide a clinically robust predictive value. This suggests that LUC% may have limited prognostic capacity in determining disease severity when used in isolation. Additionally, the retrospective nature of our study, the variability in patient characteristics, the presence of comorbidities, and potential pre-analytical variations in LUC measurements may have further limited the robustness of the observed association.

In our study, sensitivity was calculated as 28.85%, specificity as 88.07%, positive predictive value (PPV) as 44.5%, and negative predictive value (NPV) as 31.3%. Similarly, in the study conducted by Merter et al.,[24] which evaluated the prognostic role of LUC parameters prior to autologous stem cell transplantation, the area under the ROC curve (AUC) for LUC percentage was reported as 0.669, with a cut-off value of 2.15%, sensitivity of 64%, and specificity of 63%. Based on these findings, we believe that LUC% should not be used alone in clinical decision-making but rather in combination with established biomarkers to achieve better diagnostic and prognostic accuracy. Luca et al.[25] suggested that the percentage of large unstained cells (LUC) may serve as an early and supportive hematological parameter in the evaluation of systemic inflammatory response; however, due to its limited sensitivity and specificity, they recommended that it should be interpreted in combination with other inflammatory biomarkers for diagnostic and prognostic purposes.

In terms of practical clinical applicability, LUC% may be particularly useful in emergency settings where there is a need for rapid and cost-effective biomarkers. In our study, the identified cut-off value of 0.75% demonstrated relatively high specificity despite its low sensitivity. This finding suggests that in patients with elevated acute-phase reactants but LUC% values significantly below this threshold, close clinical monitoring may be warranted due to the potential risk of progression to more severe stages of inflammation.

Our study has several limitations. The relatively small sample size, retrospective design, and reliance on hospital information systems led to missing data for some patients.

CONCLUSION

The quest for an effective biomarker to determine the severity of acute cholecystitis remains ongoing. Particularly in

emergency department settings, where rapid and cost-effective biomarkers are needed, the availability of LUC% as part of the routine complete blood count and its correlation with inflammatory response present a noteworthy potential for clinical application. However, our study has certain limitations, as it represents the first clinical investigation evaluating the association between LUC% and the severity of acute cholecystitis. The lack of comparative data in the existing literature limits the generalizability of our findings and necessitates cautious interpretation. Therefore, prospective, multicenter studies with larger patient cohorts are needed to clarify the role of LUC% in clinical practice.

Disclosures

Ethics Committee Approval: The study was approved by the Ankara Bilkent City Hospital No 1 Clinical Research Ethics Committee (No: E1/23/4053, Date: 20/09/2023).

Informed Consent: Informed consent was obtained from all participants.

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