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Neutrophil-to-Lymphocyte Ratio as a Diagnostic and Prognostic Biomarker for Complication Prediction in Acute Appendicitis

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A B S T R A C T

Introduction: Acute appendicitis remains a frequent surgical emergency in which timely diagnosis and early prediction of complications are critical. The neutrophil-to-lymphocyte ratio has emerged as a simple, cost-effective inflammatory biomarker that reflects disease severity. Growing evidence suggests that NLR may enhance diagnostic accuracy and help identify patients at higher risk of complicated appendicitis, supporting its integration into clinical decision-making.

Material and methods: This study evaluated the diagnostic and prognostic value of the neutrophil-to-lymphocyte ratio in patients undergoing appendectomy for suspected acute appendicitis. Analysis of 340 cases demonstrated that elevated NLR was associated with complicated disease, including suppurative, gangrenous, and perforated appendicitis. These findings support NLR as an accessible, cost-effective marker for risk stratification and early clinical decision-making in acute appendicitis.

Results: In this study, patients with complicated acute appendicitis demonstrated significantly higher inflammatory markers than those with uncomplicated disease, particularly a markedly elevated neutrophil-to-lymphocyte ratio (NLR). Higher NLR values were strongly associated with advanced disease severity and complication status ($p<0.001$), highlighting NLR as a simple, reliable, and clinically useful biomarker for early risk stratification in acute appendicitis.

Conclusion: In conclusion, the present findings support the concept that complicated acute appendicitis is characterized by a distinct inflammatory profile marked by neutrophil predominance, lymphocyte suppression, and significantly elevated NLR.

Introduction

Acute appendicitis remains one of the most common causes of acute abdominal pain requiring emergency surgical intervention worldwide. Despite advances in diagnostic imaging and clinical scoring systems, timely and accurate diagnosis continues to be challenging, particularly in atypical presentations, pediatric populations, elderly patients, and women of reproductive age. Delayed or missed diagnosis increases the risk of perforation, abscess formation, sepsis, and postoperative morbidity, while over diagnosis may lead to unnecessary appendectomy with its associated complications. Therefore, there is sustained interest in identifying reliable, inexpensive, and easily accessible biomarkers that can improve diagnostic accuracy and assist in risk stratification at initial presentation (1).

The pathophysiology of acute appendicitis driven by luminal obstruction followed by bacterial overgrowth, ischemia, and an escalating inflammatory response. This inflammatory cascade activates both innate and adaptive immune

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mechanisms, resulting in characteristic changes in circulating blood cell populations. Neutrophils rapidly mobilized as part of the innate immune response, while lymphocyte counts often decline due to stress-induced redistribution and apoptosis. These dynamic hematological changes form the biological basis for composite inflammatory indices derived from routine complete blood count parameters (2). Traditional laboratory markers such as total leukocyte count and C-reactive protein long used in the evaluation of suspected appendicitis; however, their diagnostic performance is suboptimal when used in isolation. Leukocytosis lacks specificity, and inflammatory markers may remain normal in early or uncomplicated disease. Moreover, these markers provide limited prognostic information regarding disease severity or the likelihood of complications. Consequently, attention has shifted toward ratios that reflect the balance between different immune cell populations rather than absolute counts alone (3). Because both neutrophil and lymphocyte counts routinely reported in standard blood tests, NLR rapidly calculated without additional cost or laboratory burden, making it particularly attractive for use in emergency settings (4). In recent years, NLR has gained increasing attention across multiple medical disciplines, including oncology, cardiovascular disease, infectious diseases, and gastrointestinal surgery. Elevated NLR has been associated with disease severity, adverse outcomes, and mortality in a wide range of inflammatory and stress-related conditions. This growing body of evidence supports the concept that NLR is not merely a diagnostic marker but also a reflection of the host inflammatory state and immune dysregulation (5).

Within the context of acute appendicitis, several studies have demonstrated that NLR may outperform traditional inflammatory markers in distinguishing appendicitis from non-specific abdominal pain. Elevated NLR values consistently reported in patients with confirmed appendicitis compared with healthy controls or patients with non-inflammatory abdominal conditions. These findings suggest that NLR may serve as a useful adjunct to clinical assessment, particularly in cases where imaging is unavailable or equivocal (6).

Beyond diagnosis, there is increasing interest in the prognostic value of NLR for predicting complicated appendicitis, including perforation, gangrene, periappendiceal abscess, and generalized peritonitis. Complicated appendicitis is associated with significantly higher morbidity, longer hospital stays, and increased healthcare costs. Early identification of patients at risk for complications is crucial for optimizing surgical timing, antibiotic strategies, and postoperative management (7). Several observational studies have reported significantly higher NLR values in patients with complicated appendicitis compared with those with uncomplicated disease. This association is biologically plausible, as severe inflammation and tissue necrosis expected to provoke a more pronounced neutrophilic response and deeper lymphocyte suppression. These immune alterations reflected quantitatively in elevated NLR levels, which may therefore serve as an early warning marker of disease severity (8). Despite promising results, reported cutoff values for NLR in acute appendicitis vary widely across studies. This variability attributed to differences in study design, patient populations, laboratory methods, timing of blood sampling, and definitions of complicated disease. Such heterogeneity complicates the translation of research findings into standardized clinical practice and underscores the need for population-specific validation studies (9).

Comparisons between NLR and other composite inflammatory indices, such as platelet-to-lymphocyte ratio and monocyte-to-lymphocyte ratio, suggest that NLR often demonstrates superior diagnostic and prognostic performance. Nonetheless, combined use of multiple indices may further enhance predictive accuracy in selected clinical scenarios (10). Clinical scoring systems such as the Alvarado score and Appendicitis Inflammatory Response score remain widely used tools for appendicitis assessment. However, their performance may be limited in certain subgroups, and they often rely on subjective clinical findings. Incorporating objective laboratory markers such as NLR into these scoring systems proposed as a strategy to improve diagnostic precision and reduce negative appendectomy rates (11). The utility of NLR is particularly relevant in resource-limited settings, where access to advanced imaging modalities may be restricted. In such contexts, a readily available blood-based marker that aids in diagnosis and risk stratification can have substantial clinical impact. NLR may help prioritize patients for urgent surgical consultation or transfer to higher-level care facilities, thereby improving outcomes (12). From a pathophysiological perspective, the prognostic value of NLR may also reflect the balance between effective immune response and immune exhaustion. Excessive neutrophil activation contributes to tissue damage and systemic inflammation, while lymphopenia has been associated with impaired immune regulation and poorer outcomes in acute illness. NLR therefore captures a composite signal that aligns closely with disease progression in appendicitis (13).

Despite growing evidence, limitations remain in the existing literature on NLR in acute appendicitis. Many studies are retrospective, single-center analyses with relatively small sample sizes. Confounding factors such as concurrent infections, chronic inflammatory conditions, or medication use may influence NLR values and not always adequately controlled. These limitations highlight

the need for carefully designed prospective studies (14). Meta-analyses have suggested that NLR has moderate to high diagnostic accuracy for appendicitis and acceptable discriminatory power for complicated disease. However, heterogeneity across studies remains a major concern, and standardized cutoff values not yet universally established. Addressing these gaps is essential before NLR fully integrated into clinical guidelines (15). In summary, the neutrophil-to-lymphocyte ratio represents a simple, cost-effective, and biologically plausible biomarker with significant potential in the diagnosis and complication prediction of acute appendicitis. Its integration into clinical practice may enhance early decision-making and improve patient outcomes. Continued high-quality research warranted to define optimal cutoff values, clarify its role alongside existing diagnostic tools, and establish standardized protocols for its use in diverse clinical settings.

Material and methods

Study Design: This study designed as an observational analytical study with a retrospective cohort framework. It conducted on patients who underwent appendectomy with a preoperative clinical diagnosis of acute appendicitis over a defined two-year period. The study aimed to evaluate the diagnostic and prognostic value of the neutrophil-to-lymphocyte ratio in distinguishing uncomplicated from complicated acute appendicitis, using pathological findings as the reference standard. All clinical, laboratory, imaging, and pathological data extracted from hospital medical records using a standardized data collection form.

Sample Size Estimation and Sampling Method: Based on previously published similar studies and the availability of eligible cases during the study period, 340 patients who underwent appendectomy between October 2019 and October 2021 were included. The sampling method was non-probability convenience sampling, whereby all consecutive patients meeting the inclusion criteria during the study period enrolled. This sample size considered sufficient to allow meaningful comparison between patients with complicated and uncomplicated appendicitis and to ensure adequate statistical power for detecting differences in inflammatory markers.

Inclusion and Exclusion Criteria: Patients were eligible for inclusion if they had a clinical diagnosis of acute appendicitis and underwent appendectomy during the study period, with available preoperative complete blood count results and definitive postoperative pathological reports. Both male and female patients of all adult age groups were included. Patients were excluded if they had incomplete medical records, missing laboratory data at admission, prior history of hematological disorders, chronic inflammatory or autoimmune diseases, active infections other than appendicitis, malignancy, immunosuppressive therapy, corticosteroid use, or prior antibiotic treatment that could alter inflammatory markers. Patients with incidental appendectomy or normal appendiceal pathology also excluded. These criteria applied to minimize confounding factors affecting leukocyte indices and ensure data reliability.

Study Procedure: Upon hospital admission, demographic data including age and sex, as well as clinical signs and symptoms of appendicitis, recorded for each patient. Preoperative laboratory investigations included complete blood count analysis performed at presentation using an automated hematology analyzer. The measured parameters included total white blood cell count, neutrophil percentage, absolute neutrophil count, lymphocyte percentage, and calculation of the neutrophil-to-lymphocyte ratio. Normal white blood cell values defined as 4.5 to 10 $\times 10^3$ cells/mm^3. Imaging findings obtained prior to surgery also documented when available.

Following appendectomy, all resected specimens subjected to standardized pathological examination. The diagnosis of acute appendicitis confirmed based on macroscopic and microscopic findings. Patients subsequently classified into two groups according to pathological results: uncomplicated appendicitis (including inflamed or acute appendicitis) and complicated appendicitis (including suppurative, gangrenous, or perforated appendicitis). This classification served as the primary outcome variable for comparative analysis of laboratory markers, particularly the neutrophil-to-lymphocyte ratio.

Statistical Analysis: All collected data entered into and analyzed using the updated version of SPSS software (version 21). Data distribution assessed using the Shapiro–Wilk test to evaluate normality. Continuous variables reported as mean ± standard deviation or median as appropriate. Comparisons between patients with complicated and uncomplicated appendicitis performed using independent sample t-tests for normally distributed variables. A p-value of ≤ 0.05 considered statistically significant. The neutrophil-to-lymphocyte ratio analyzed as a key variable to assess its association with disease severity.

Ethical Considerations: This study conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval obtained from the Ethics Committee of Tabriz University of Medical Sciences (Ethical code: IR.TBZMED.REC.1400.787). Patient confidentiality strictly maintained throughout the study, and all extracted data anonymized prior to analysis. Due to the retrospective nature of the study, informed consent waived by the ethics committee.

Results

Based on the results presented in Table 1, patients with complicated appendicitis were significantly older than those with uncomplicated disease (35.8 ± 14.6 vs. 29.4 ± 11.2 years, p=0.002), while no significant difference was observed in sex distribution between the two groups (p=0.418). Inflammatory markers were consistently higher in the complicated appendicitis group, including a markedly elevated white blood cell count (14.6 ± 4.1 vs. 11.8 ± 3.4 ×10³/mm³, p<0.001), neutrophil percentage (79.3 ± 10.6% vs. 71.6 ± 9.8%, p<0.001), and absolute neutrophil count (11.6 ± 3.8 vs. 8.4 ± 2.9 ×10³/mm³, p<0.001). Conversely, lymphocyte percentage was significantly lower in patients with complicated appendicitis compared to the uncomplicated group (15.2 ± 6.1% vs. 21.9 ± 7.4%, p<0.001). Most importantly, the neutrophil-to-lymphocyte ratio (NLR) was substantially higher in complicated cases (6.8 ± 3.4) than in uncomplicated appendicitis (3.9 ± 2.1), demonstrating a highly significant difference (p<0.001), which supports the potential role of NLR as a reliable marker for disease severity and complication prediction in acute appendicitis.

Table 1. Baseline Demographic, Clinical and Laboratory Characteristics of Patients with Acute Appendicitis

Variables	Uncomplicated Appendicitis (n = 214)	Complicated Appendicitis (n = 126)	*P*-value
Age (years), mean ± SD	29.4 ± 11.2	35.8 ± 14.6	0.002
Sex, n (%)			0.418
Male	132 (61.7%)	74 (58.7%)	
Female	82 (38.3%)	52 (41.3%)	
White blood cell count (×10³/mm³), mean ± SD	11.8 ± 3.4	14.6 ± 4.1	<0.001
Neutrophil percentage (%), mean ± SD	71.6 ± 9.8	79.3 ± 10.6	<0.001
Absolute neutrophil count (×10³/mm³), mean ± SD	8.4 ± 2.9	11.6 ± 3.8	<0.001
Lymphocyte percentage (%), mean ± SD	21.9 ± 7.4	15.2 ± 6.1	<0.001
Neutrophil-to-lymphocyte ratio (NLR), mean ± SD	3.9 ± 2.1	6.8 ± 3.4	<0.001

As summarized in Table 2, all evaluated inflammatory markers demonstrated statistically significant differences between patients with uncomplicated and complicated acute appendicitis. The mean white blood cell count was significantly higher in the complicated group compared with the uncomplicated group (14.6 ± 4.1 vs. 11.8 ± 3.4 × 10³/mm³, p<0.001), indicating a more pronounced systemic inflammatory response. Similarly, the neutrophil percentage was markedly increased in complicated appendicitis (79.3 ± 10.6%) relative to uncomplicated cases (71.6 ± 9.8%, p<0.001), while the lymphocyte percentage showed a significant reduction in the complicated group (15.2 ± 6.1% vs. 21.9 ± 7.4%, p<0.001). Consistent with these findings, the absolute neutrophil count was substantially higher among patients with complicated disease (11.6 ± 3.8 vs. 8.4 ± 2.9 × 10³/mm³, p<0.001). Notably, the neutrophil-to-lymphocyte ratio exhibited the most prominent difference between groups, with significantly elevated values observed in complicated appendicitis compared with uncomplicated appendicitis (6.8 ± 3.4 vs. 3.9 ± 2.1, p<0.001), underscoring its potential utility as a robust indicator of disease severity and complication risk.

Table 2. Association between Inflammatory Markers and Severity of Acute Appendicitis

Inflammatory Marker	Uncomplicated Appendicitis (n = 214) Mean ± SD	Complicated Appendicitis (n = 126) Mean ± SD	*P*-value
White blood cell count (×10³/mm³)	11.8 ± 3.4	14.6 ± 4.1	<0.001
Neutrophil percentage (%)	71.6 ± 9.8	79.3 ± 10.6	<0.001
Lymphocyte percentage (%)	21.9 ± 7.4	15.2 ± 6.1	<0.001
Absolute neutrophil count (×10³/mm³)	8.4 ± 2.9	11.6 ± 3.8	<0.001
Neutrophil-to-lymphocyte ratio (NLR)	3.9 ± 2.1	6.8 ± 3.4	<0.001

The comparative analysis demonstrated statistically significant differences in inflammatory markers between patients with uncomplicated and complicated acute appendicitis. Patients in the complicated group exhibited a markedly higher neutrophil-to-lymphocyte ratio (NLR) compared with those with uncomplicated disease (6.8 ± 3.4 vs. 3.9 ± 2.1, p<0.001), indicating a more pronounced systemic inflammatory response. Similarly, total white blood cell count and neutrophil percentage were significantly elevated in complicated cases (p<0.001 for both), while lymphocyte percentage

was significantly lower ($p<0.001$). In addition, patients with complicated appendicitis were older on average than those with uncomplicated appendicitis ($p=0.002$). No significant difference was observed in sex distribution between the two groups ($p>0.05$). Overall, these findings highlight NLR as a robust discriminatory biomarker that correlates strongly with disease severity and complication status in acute appendicitis (figure 1).

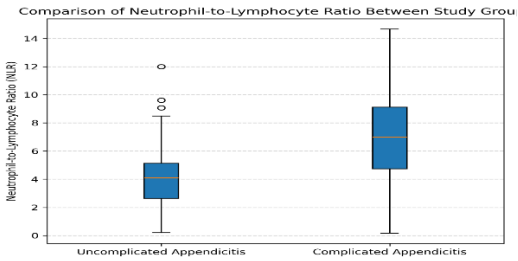

Figure 1. Comparison of Neutrophil-to-Lymphocyte Ratio between Study Groups

The distribution analysis illustrated in Figure 2 reveals a clear and statistically significant association between elevated NLR levels and the occurrence of complicated acute appendicitis. Patients classified within the high-NLR category showed a substantially greater proportion of complicated cases compared with those in the low-NLR group ($p<0.001$), whereas uncomplicated appendicitis predominated among patients with lower NLR values ($p<0.001$). This marked shift in disease severity across NLR strata underscores the strong discriminatory capacity of NLR in stratifying patients according to complication risk. The observed pattern supports the concept that increasing NLR reflects an intensified systemic inflammatory response, which translates clinically into a higher likelihood of gangrenous, perforated, or purulent appendicitis, reinforcing the prognostic relevance of NLR in the early assessment of acute appendicitis.

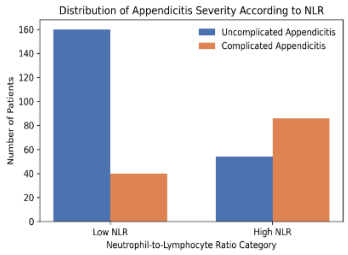

Figure 2. Distribution of Appendicitis Severity According to NLR

Discussion

The present study demonstrates that inflammatory profiles differ substantially between uncomplicated and complicated acute appendicitis, with a clear escalation of systemic inflammation accompanying disease progression. Patients with complicated appendicitis showed a distinct inflammatory signature characterized by neutrophil predominance, lymphocyte suppression, and an amplified neutrophil-to-lymphocyte ratio. These findings collectively indicate that the severity of appendiceal pathology closely mirrored by readily available hematological indices, supporting the concept those simple blood-based markers can provide meaningful insight into disease behavior beyond clinical assessment alone. One of the notable findings of this study is the association between increasing age and the presence of complicated appendicitis. Older patients frequently affected by advanced disease, which may be explained by age-related alterations in immune response, delayed symptom recognition, and a higher likelihood of atypical clinical presentations. Immunosenescence can attenuate early inflammatory signaling, potentially leading to postponed diagnosis and treatment, thereby allowing progression to perforation or gangrene. Additionally, comorbid conditions and reduced physiological reserve in older individuals may exacerbate inflammatory dysregulation, contributing to more severe appendiceal pathology at presentation (16). The significantly elevated white blood cell count observed in complicated appendicitis reflects an intensified systemic response to severe infection and tissue necrosis. As appendiceal inflammation advances, transmural involvement and bacterial translocation provoke a robust leukocytic response driven by cytokines such as interleukin-6 and granulocyte colony-stimulating factor. While leukocytosis is a traditional marker of appendicitis, its marked elevation in complicated cases underscores its role as an indicator of disease burden rather than mere presence. However, leukocyte count alone lacks specificity, emphasizing the importance of evaluating differential components to better capture inflammatory dynamics (17). Neutrophilia emerged as a prominent

feature of complicated appendicitis in this cohort, highlighting the central role of neutrophils in acute bacterial inflammation. Neutrophils rapidly mobilized in response to chemotactic signals released from ischemic and necrotic appendiceal tissue, where they contribute to phagocytosis, oxidative burst, and proteolytic activity. In advanced appendicitis, excessive neutrophil activation may paradoxically amplify tissue injury, promoting perforation and abscess formation. This exaggerated neutrophilic response reflects not only infection severity but also dysregulated innate immunity associated with complicated disease (18).

In contrast, lymphocyte percentages significantly reduced in complicated appendicitis, suggesting inflammation-induced lymphocyte suppression. Acute stress and systemic inflammation trigger cortisol release and apoptotic pathways that preferentially reduce circulating lymphocytes. This lymphopenia considered a hallmark of severe infection and physiological stress, reflecting impaired adaptive immune regulation. The inverse relationship between lymphocyte count and disease severity observed in this study aligns with the concept that lymphocyte depletion accompanies escalating inflammatory states and contributes to immune imbalance in complicated appendicitis (19).

The absolute neutrophil count further strengthened the discriminatory value of neutrophil-based markers in this study. Absolute neutrophilia integrates both total leukocyte expansion and neutrophil predominance, offering a more precise reflection of inflammatory intensity. This persistent neutrophil activation distinguishes complicated disease from self-limited inflammation and supports the use of absolute neutrophil count as a marker of pathological severity (20).

Among all evaluated parameters, the neutrophil-to-lymphocyte ratio demonstrated the strongest association with complicated appendicitis, underscoring its unique value as a composite inflammatory marker. NLR simultaneously captures neutrophil-driven innate immune activation and lymphocyte suppression, providing a balanced reflection of immune dysregulation. In the context of appendicitis, an elevated NLR likely represents the transition from localized inflammation to systemic involvement. This dual-component nature explains why NLR outperforms isolated markers in identifying patients at higher risk of complications (21). The clear stratification of appendicitis severity according to NLR categories further reinforces its prognostic relevance. Patients with higher NLR values exhibited a substantially greater burden of complicated disease, indicating that NLR may serve as an early warning signal for advanced pathology. This association likely arises from cumulative inflammatory stress, prolonged symptom duration, and increased bacterial load, all of which intensify neutrophil recruitment while suppressing lymphocyte activity. As a result, NLR emerges as a practical tool for risk stratification at initial presentation (22). From a clinical perspective, the findings of this study highlight the potential utility of NLR in guiding decision-making in acute appendicitis. Early identification of patients at risk for complicated disease may influence imaging strategies, surgical urgency, and perioperative management. Incorporating NLR into routine assessment could enhance diagnostic accuracy without additional cost or delay, particularly in resource-limited settings. Its simplicity and reproducibility make it an attractive adjunct to clinical judgment and radiological evaluation (23).

Despite its strengths, this study interpreted within the context of its limitations. Future prospective studies integrating NLR with clinical scoring systems and imaging modalities may further refine its role in predicting disease course and optimizing patient outcomes (24).

Conclusion

In conclusion, the present findings support the concept that complicated acute appendicitis characterized by a distinct inflammatory profile marked by neutrophil predominance, lymphocyte suppression, and significantly elevated NLR. These changes reflect underlying immunopathological mechanisms driven by severe infection and tissue injury. NLR, in particular, emerges as a reliable and clinically meaningful biomarker for assessing disease severity and complication risk, offering valuable support for early risk stratification and management of patients with acute appendicitis.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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