

Neutrophil-to-Lymphocyte Ratio as a Predictor of Complicated Acute Appendicitis: A Multicenter Retrospective Study in Tunisia

Valeur prédictive du rapport neutrophiles/lymphocytes dans l'appendicite aiguë compliquée: Etude multicentrique tunisienne

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ABSTRACT

Background: Distinguishing complicated from uncomplicated acute appendicitis (AA) at admission remains a clinical challenge with major therapeutic implications. The Neutrophil-to-Lymphocyte Ratio (NLR) has emerged as a promising composite biomarker of systemic inflammatory stress.

Objectives: To evaluate the diagnostic performance of NLR in predicting complicated acute appendicitis (CAA) and determine its optimal cut-off value in a Tunisian surgical population.

Methods: A multicenter retrospective observational study was conducted at the General Surgery departments of CHU Fattouma Bourguiba (Monastir) and CHU Habib Bourguiba (Sfax) over 18 months (June 2024 – December 2025). A total of 380 patients aged ≥ 16 years who underwent surgery for confirmed AA were included. NLR, PLR, CRP, and WBC were measured at admission. ROC curve analysis was used to assess discriminating performance and determine the optimal cut-off using the Youden index.

Results: Of 380 patients (male-to-female ratio: 1.17; median age: 30 years), 178 (46%) had CAA. NLR was significantly higher in the CAA group (6.2 ± 3.3 vs. 3.7 ± 1.5 ; $p < 0.001$). ROC analysis revealed an AUROC of 0.75 (95% CI: 0.70–0.80; $p < 0.001$). At the optimal cut-off of 3.7, NLR achieved a sensitivity of 75.3% and specificity of 61.4%.

Multivariate binary logistic regression analysis revealed that age ≥ 40 years (AOR=3.345; $p=0.001$), CRP ≥ 100 (AOR=10.896; $p < 0.001$), intraperitoneal fluid collection in the RIF and/or Douglas pouch (AOR=3.977; $p < 0.001$), and NLR (AOR=1.993; $p < 0.001$) were independent predictive factors of complicated acute appendicitis (CAA).

Conclusion: NLR is a simple, cost-free, and useful biomarker for early stratification of acute appendicitis severity. A cut-off of 3.7 may guide clinical decision-making in emergency settings, particularly where advanced imaging is limited, as a complementary tool reinforcing clinical judgment rather than as a standalone diagnostic criterion.

Keywords: Acute appendicitis; Complicated appendicitis; Neutrophil-to-lymphocyte ratio; NLR; Biomarkers; ROC analysis; Surgical emergency; Tunisia

RÉSUMÉ

Introduction : La distinction entre appendicite aiguë compliquée et appendicite aiguë non compliquée à l'admission demeure un défi clinique, avec des implications thérapeutiques majeures. Le rapport neutrophiles/lymphocytes (NLR) est apparu comme un biomarqueur composite prometteur du stress inflammatoire systémique.

Objectifs : Évaluer les performances diagnostiques du NLR dans la prédiction de l'appendicite aiguë compliquée (AAC) et déterminer sa valeur seuil optimale dans une population chirurgicale tunisienne.

Méthodes : Une étude observationnelle rétrospective multicentrique a été menée dans les services de Chirurgie Générale du CHU Fattouma Bourguiba (Monastir) et du CHU Habib Bourguiba (Sfax), sur une période de 18 mois (juin 2024 – décembre 2025). Au total, 380 patients âgés de ≥ 16 ans, opérés pour une appendicite aiguë confirmée, ont été inclus. Le NLR, le rapport plaquettes/lymphocytes (PLR), la protéine C-réactive (CRP) et les leucocytes (WBC) ont été mesurés à l'admission. Une analyse de la courbe ROC a été réalisée afin d'évaluer les performances discriminantes et de déterminer la valeur seuil optimale selon l'indice de Youden.

Résultats : Parmi les 380 patients (sex-ratio : 1,17 ; âge médian : 30 ans), 178 (46 %) présentaient une AAC. Le NLR était significativement plus élevé dans le groupe AAC ($6,2 \pm 3,3$ contre $3,7 \pm 1,5$; $p < 0,001$). L'analyse ROC a montré une aire sous la courbe (AUROC) de 0,75 (IC 95 % : 0,70–0,80 ; $p < 0,001$). Pour une valeur seuil optimale de 3,7, le NLR présentait une sensibilité de 75,3 % et une spécificité de 61,4 %.

L'analyse de régression logistique binaire multivariée a révélé que l'âge ≥ 40 ans (ORa=3,345 ; $p=0,001$), la CRP ≥ 100 (ORa=10,896 ; $p < 0,001$), la présence d'une collection liquidienne intrapéritonéale dans la fosse iliaque droite et/ou le cul-de-sac de Douglas (ORa=3,977 ; $p < 0,001$), ainsi que le NLR (ORa=1,993 ; $p < 0,001$), étaient des facteurs prédictifs indépendants d'AAC.

Conclusion : Le NLR est un biomarqueur simple, accessible et utile pour la stratification précoce de la gravité de l'appendicite aiguë. Une valeur seuil de 3,7 pourrait contribuer à orienter la prise en charge clinique en situation d'urgence, notamment lorsque l'imagerie avancée est limitée, en complément du jugement clinique et non comme critère diagnostique isolé.

Mots-clés : Appendicite aiguë; Appendicite compliquée; Rapport neutrophiles/lymphocytes; NLR; Biomarqueurs; Analyse ROC; Urgence chirurgicale; Tunisie.

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INTRODUCTION

Acute appendicitis (AA) is the most common abdominal surgical emergency worldwide, accounting for approximately 42% of non-traumatic emergency abdominal operations (1). While the overall management has been historically dominated by early appendectomy, growing evidence now supports non-operative antibiotic-based treatment for uncomplicated forms, with success rates reaching up to 90% (2).

This paradigm shift makes the preoperative distinction between uncomplicated AA (UAA) and complicated AA (CAA) (defined by the presence of perforation, gangrene, appendicular abscess, or plastron) a cornerstone of contemporary surgical decision-making. Misclassifying a CAA as UAA risks delaying urgent surgical intervention with potentially life-threatening consequences.

Classical diagnostic approaches combining clinical scores (Alvarado, AIR), biological markers, and imaging studies are constrained by operator-dependency, limited resource availability, and lack of standardized thresholds (3). These limitations have prompted the search for robust composite biomarkers capable of integrating multiple dimensions of the immune response.

The Neutrophil-to-Lymphocyte Ratio (NLR) has gained increasing recognition as a reliable indicator of systemic inflammatory stress, faithfully reflecting the dynamic balance between innate immunity (neutrophils) and adaptive immunity (lymphocytes)(4,5). Its simplicity (derived from a routine complete blood count (CBC)) and negligible cost make it particularly suited to resource-constrained settings.

Despite a growing body of literature, significant methodological heterogeneity persists in reported optimal thresholds, limiting clinical transferability. The present multicenter study was therefore designed with the following objectives:

To describe the epidemiological, clinical, biological, radiological, and therapeutic characteristics of CAA patients.

To identify factors independently associated with CAA.

To evaluate the diagnostic performance of NLR in discriminating CAA from UAA.

To determine the optimal NLR cut-off (Youden index) in our population.

METHODS

Study design and settings

This was a multicenter, retrospective, observational, descriptive and analytical study conducted in the General Surgery departments of two Tunisian university hospitals: CHU Fattouma Bourguiba (Monastir) and CHU Habib Bourguiba (Sfax). Both centers are regional referral institutions for abdominal surgical emergencies. The inclusion period spanned 18 months, from June 1, 2024 to December 31, 2025. The retrospective design, while pragmatic, carries an inherent risk of information and misclassification bias linked to the completeness

and accuracy of archived medical records, as well as a selection bias, since only patients who ultimately underwent surgery were eligible for inclusion (see Section 2.2). These limitations were anticipated at the design stage and are further discussed in Section 4.5.

Study Population and Sample Size

The minimum required sample size was calculated based on an expected prevalence of complicated appendicitis of 30%(6), a precision margin of 5%, and a 95% confidence level ($\alpha=5\%$; $\alpha/2=1.96$), yielding a minimum of 323 patients. Accounting for a 15% attrition rate for incomplete records, the target was at least 372 patients. All patients aged ≥ 16 years admitted for suspected AA and operated on in either center were eligible.

Inclusion required: confirmed AA diagnosis by intraoperative findings and/or histopathology; a preoperative CBC performed at admission prior to any antibiotics; and a complete medical record with all required clinical, biological, radiological, and operative variables.

Exclusion criteria included: known hematological disorders (neutropenia, leukemia, lymphoma); immunosuppressive therapy, chemotherapy, or systemic corticosteroids (>5 mg/day prednisolone equivalent for >1 week); active chronic inflammatory diseases (Crohn's disease, ulcerative colitis, rheumatoid arthritis); concurrent systemic infection; pregnancy; and blood transfusion within the preceding month. Because histopathological and/or intraoperative confirmation of AA was an inclusion requirement, this cohort by design comprises only operated patients. Patients initially managed non-operatively (antibiotic-first strategy) or discharged after clinical surveillance without surgery were not captured in this analysis, as the absence of a surgical/histopathological reference standard precluded reliable classification as CAA or UAA in this subgroup.

Data Collection and Variables

Data were collected retrospectively from computerized medical records using a standardized, pre-validated data collection form. Variables included sociodemographic data (age, sex, comorbidities); clinical data (symptom duration, fever, abdominal examination findings); biological data (CBC, CRP); radiological findings (ultrasound, CT scan); operative findings (approach, macroscopic appearance of appendix, associated lesions); histopathological results; and postoperative outcomes.

The NLR was calculated as: $NLR = \text{Absolute Neutrophil Count (G/L)} / \text{Absolute Lymphocyte Count (G/L)}$, using values from the admission CBC obtained prior to any therapeutic intervention.

Operative classification:

CAA: Presence of at least one of the following intraoperative findings: perforation with free or loculated purulent/turbid effusion; gangrene (macroscopic

necrosis); appendicular abscess; or appendicular plastron.

UAA: Catarrhal or phlegmonous appendicitis without perforation, gangrene, or abscess.

Statistical Analysis

Data were analyzed using SPSS version 21. Categorical variables were described as frequencies and percentages, and compared using Chi-square or Fisher's exact test. Continuous variables were tested for normality (Kolmogorov-Smirnov and Shapiro-Wilk tests) and expressed as mean $\pm$ SD or median [IQR] accordingly, and compared using Student's t-test or Mann-Whitney U test. The diagnostic performance of NLR was assessed by ROC curve analysis. Area under the curve (AUC) was computed with 95% confidence intervals, and inter-marker AUC comparisons were performed using the DeLong test. The optimal NLR cut-off was determined by maximizing the Youden index (Sensitivity + Specificity – 1). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated at this threshold. In line with the STARD (Standards for Reporting of Diagnostic Accuracy Studies) recommendations, 95% confidence intervals were computed for sensitivity and specificity using the normal approximation to the binomial distribution.

A binary logistic regression (stepwise, backward method) was performed including all variables with $p < 0.20$ on univariate analysis. Results are expressed as adjusted odds ratios (aOR) with 95% CI. Model calibration was assessed by the Hosmer-Lemeshow test ($p > 0.05$ indicating good fit). A two-sided $p < 0.05$ was considered statistically significant.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was obtained from both institutions, and all data were processed anonymously and confidentially. Given the retrospective non-interventional design, individual patient informed consent was not required under Tunisian research regulations.

RESULTS

During the study period, 410 consecutive patients presenting with suspected acute appendicitis were screened for eligibility. Thirty patients (7.3%) were excluded according to the predefined exclusion criteria, including incomplete medical record and cases not meeting the study eligibility criteria. Consequently, 380 patients (92.7%) were included in the final analysis. No data imputation was performed; patients with missing key variables were excluded rather than having missing values imputed.

Sociodemographic Characteristics

A total of 380 patients met the inclusion criteria. The median age was 30 years (IQR: 20–44), with the 16–35 age group most frequently represented. The male-to-female ratio was 1.17 (205 males; 53.9%). Comorbidities were present in 138 patients (36%), with diabetes mellitus being the most frequent ($N=54$; 14%). Only 5 patients (1%) had a history of prior abdominal surgery (Table 1).

Clinical Presentation

The median symptom duration before consultation was 3 days (IQR: [2,7]). A total of 217 patients (57.1%) presented after ≥ 48 hours of symptom onset. Abdominal pain was the leading complaint in 99.5% of cases ($N=378$), localized to the right iliac fossa (RIF) in 95% ($N=361$). Nausea/vomiting were reported in 67% and fever in 65% of cases. On examination, fever $\geq 38.5^\circ\text{C}$ was present in 247 patients (65%), and localized RIF tenderness in 72.1% (Table 1).

Biological Findings

Leukocytosis was present in 342 patients (90%), with a median WBC of $13,400/\text{mm}^3$. WBC $\geq 15,000/\text{mm}^3$ was found in 120 patients (31%). The median neutrophil count was $10,000/\text{mm}^3$, with hyper-neutrophilia ($\geq 10,000/\text{mm}^3$) in 51.1%. The mean NLR was 4.8 ± 2.8 . CRP was positive ($>6 \text{ mg/L}$) in 89% of patients, with a median of 55 mg/L; CRP $\geq 100 \text{ mg/L}$ was found in 31% of cases (Table 1).

Radiological Findings

Abdominal ultrasound was performed in 234 patients (61.6%), with a dilated appendix ($>10 \text{ mm}$ diameter) in 32% and peri-appendicular fat infiltration in 49%. CT scan was obtained in 198 patients (52%), revealing appendicular enlargement in 49%, abdominal effusion in 30%, and abscess in 16% (Table 1).

Operative Findings and Pathology

The McBurney incision was used in 50% of cases, laparoscopy in 39% (conversion rate: 3%), and midline laparotomy in 6.1%. The most common macroscopic appearance was phlegmonous (51%), followed by gangrenous (31%) and perforated (18%). Histopathology confirmed phlegmonous appendicitis in 55.5% and gangrenous in 22.3%.

Postoperative Outcomes

Postoperative course was uneventful in 336 patients (88.4%). Median hospital stay was 3 days (IQR: [5,15]). Surgical complications occurred in 31 patients (8.1%), most commonly wound abscess ($N=15$; 3.9%) and intra-abdominal abscess ($N=13$; 3.4%). Medical complications were observed in 13 patients (3.4%). No deaths were recorded.

Tableau 1. Baseline Characteristics of Patients with Acute Appendicitis (N = 380)

Variable	n	%
Sociodemographic Characteristics		
• Median age, years [IQR]	30 [20–44]	—
• Male sex	205	53.9%
• Sex ratio (M:F)	1.17	—
Medical History & Comorbidities		
• Any medical comorbidity	138	36.0%
• Diabetes mellitus	54	14.0%
• Arterial hypertension	17	4.0%
Clinical Presentation		
• Median symptom duration, days [IQR]	3 [2–7]	—
• Symptom duration ≥ 48 hours	217	57.1%
• Right iliac fossa pain	361	95.0%
• Nausea/Vomiting	258	67.0%
• Fever (T° ≥ 38.5°C)	247	65.0%
• Diffuse abdominal pain	69	18.0%
• Obesity (BMI ≥ 30)	42	11.1%
• RIF tenderness on palpation	274	72.1%
• Abdominal guarding	31	8.0%
• Generalized peritoneal defense	27	7.0%
Laboratory Findings		
• WBC count, ×10 ³ /mm ³ — median [IQR]	13.4 [11.6–15.8]	—
• WBC ≥ 15,000/mm ³	120	31.0%
• PMN, ×10 ³ /mm ³ — median [IQR]	10.0 [8.1–12.3]	—
• PMN ≥ 10,000/mm ³	194	51.1%
• Lymphocytes, ×10 ³ /mm ³ — median [IQR]	2.5 [1.8–3.0]	—
• NLR — mean ± SD	4.8 ± 2.8	—
• CRP, mg/L — median [IQR]	55 [19–113]	—
• CRP ≥ 100 mg/L	120	31.0%
Imaging Findings		
• Peri-appendiceal fat infiltration	187	49.0%
• Diameter > 10 mm	124	32.0%
• Free fluid in RIF/Douglas	75	19.0%
• Appendicolith/faecolith	27	7.0%
• RIF collection	23	6.1%
• Peritonitis	35	9.0%

IQR = Interquartile Range; WBC = White Blood Cell count; PMN = Polymorphonuclear Neutrophils; NLR = Neutrophil-to-Lymphocyte Ratio; CRP = C-Reactive Protein; RIF = Right Iliac Fossa; COPD = Chronic Obstructive Pulmonary Disease; CT = Computed Tomography.

Prevalence of Complicated Acute Appendicitis

178 patients (46.8%) were classified as CAA based on intraoperative and/or histopathological findings.

Univariate Analysis: Predictors of CAA

Sociodemographic factors significantly associated with CAA were age ≥40 years (67.6% vs. 38.3%; p<0.001) and diabetes mellitus (64.8% vs. 43.9%; p=0.004). Gender was not significantly associated with CAA (p=0.832). Clinically, fever ≥38.5°C (57.5% vs. 27.1%; p<0.001), symptom duration ≥48h (60.4% vs. 28.8%; p<0.001), and generalized abdominal guarding (92.6% vs. 43.3%; p<0.001) were significantly associated with CAA.

Biologically, WBC ≥15,000/mm³ (80.8% vs. 31.2%; p<0.001), CRP ≥100 mg/L (83.3% vs. 30%; p<0.001), and neutrophils ≥10,000/mm³ (70.1% vs. 22.6%; p<0.001) were all strongly associated with CAA (Table 2).

Table 2. Univariate analysis

Variable	Complicated AA (n = 178)	Uncomplicated AA (n = 202)	p-value
Sociodemographic Characteristics and Comorbidities			
• Male sex	95 (46.3%)	110 (53.7%)	0.832
• Age ≥ 40 years	75 (67.6%)	36 (32.4%)	< 0.001
• Diabetes mellitus	35 (64.8%)	19 (35.2%)	0.004
Clinical Factors			
• Fever (T° ≥ 38.5°C)	142 (57.5%)	105 (42.5%)	< 0.001
• Symptom duration ≥ 48 hours	131 (60.4%)	86 (39.6%)	< 0.001
• Nausea/Vomiting	124 (48.1%)	134 (51.9%)	0.488
• Diarrhea	12 (60.0%)	8 (40.0%)	0.226
• RIF tenderness	164 (50.6%)	160 (49.4%)	< 0.001
• Generalized peritoneal defense	25 (92.6%)	2 (7.4%)	< 0.001
Laboratory Findings			
• WBC ≥ 15,000/mm ³	97 (80.8%)	23 (19.2%)	< 0.001
• CRP ≥ 100 mg/L	100 (83.3%)	20 (16.7%)	< 0.001
• PMN ≥ 10,000/mm ³	136 (70.1%)	58 (29.9%)	< 0.001
• NLR — mean ± SD	6.2 ± 3.3	3.7 ± 1.5	< 0.001
• Hemoglobin < 11 g/dL	16 (50.0%)	16 (50.0%)	0.708
Imaging Findings (Ultrasound + CT Scan)			
• Peri-appendiceal fat infiltration	115 (63.5%)	66 (36.5%)	< 0.001
• Appendiceal diameter ≥ 10 mm	95 (60.9%)	61 (39.1%)	< 0.001
• Free fluid in RIF or Douglas	89 (76.1%)	28 (23.9%)	< 0.001
• RIF collection/abscess	56 (90.3%)	6 (9.7%)	< 0.001
• Diffuse intraperitoneal fluid	30 (88.2%)	4 (11.8%)	< 0.001
• Appendicolith/Faecolith	9 (33.3%)	18 (66.7%)	0.144

Data presented as n (%) unless otherwise stated. Bold red p-values indicate statistical significance (p < 0.05). AA = Acute Appendicitis; WBC = White Blood Cell count; PMN = Polymorphonuclear Neutrophils; NLR = Neutrophil-to-Lymphocyte Ratio; CRP = C-Reactive Protein; RIF = Right Iliac Fossa; CT = Computed Tomography.

NLR Performance for Predicting CAA

The mean NLR was significantly higher in the CAA group compared to UAA (6.2 ± 3.3 vs. 3.7 ± 1.5; p<0.001). ROC curve analysis demonstrated good discriminating ability with an AUROC of 0.75 (95% CI: 0.70–0.80; p<0.001). At the optimal cut-off of 3.7 (maximized Youden index), NLR yielded a sensitivity of 75% and a specificity of 70% for predicting CAA (Figure 1).

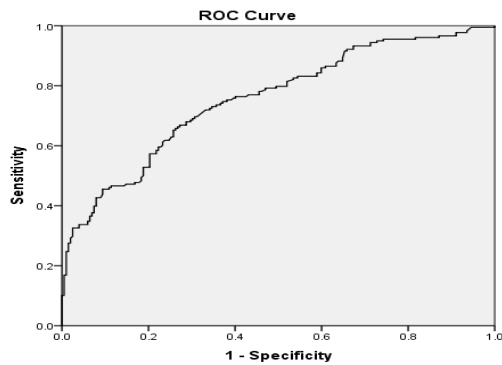


Figure 1. NLR ROC curve for predicting complicated acute appendicitis.

Multivariate Analysis

Multivariate binary logistic regression analysis identified several independent predictors of complicated acute appendicitis (CAA). Age ≥ 40 years (OR = 3.345; $p = 0.001$), history of diabetes mellitus (aOR = 2.821; $p = 0.015$), fever $\geq 38.5^\circ\text{C}$ (aOR = 2.791; $p = 0.004$), right iliac fossa (RIF) guarding (aOR = 3.736; $p = 0.017$), CRP ≥ 100 mg/L (aOR = 10.896; $p < 0.001$), presence of intraperitoneal fluid in the RIF and/or Douglas pouch (OR = 3.977; $p < 0.001$), and neutrophil-to-lymphocyte ratio (NLR) (aOR = 1.993; $p < 0.001$) were independently associated with CAA (table3) .

Table 3. Multivariate Logistic Regression: Independent Predictors of Complicated Acute Appendicitis

Variable	Adjusted OR	95% CI	p-value
Age ≥ 40 years	3.345	1.65 – 6.74	0.001
Diabetes mellitus	2.821	1.22 – 6.52	0.015
Fever ($T^\circ \geq 38.5^\circ\text{C}$)	2.791	1.39 – 5.59	0.004
RIF tenderness	3.736	1.27 – 11.00	0.017
CRP ≥ 100 mg/L	10.896	5.26 – 22.59	< 0.001
Intraperitoneal fluid (RIF/ Douglas)	3.977	2.00 – 7.89	< 0.001
NLR (continuous)	1.993	1.68 – 2.37	< 0.001

OR = Odds Ratio; CI = Confidence Interval; CRP = C-Reactive Protein; NLR = Neutrophil-to-Lymphocyte Ratio; RIF = Right Iliac Fossa

Final Model Validation

Assessment of the model calibration demonstrated good agreement between predicted and observed outcomes, with a non-significant Hosmer–Lemeshow goodness-of-fit test ($\chi^2 = 7.7$; $p = 0.46$).

The model also showed excellent discriminative performance, with an area under the receiver operating characteristic curve (AUROC) of 0.92 (95% CI: 0.89–0.94; $p < 0.001$), corresponding to a sensitivity of 87% and a specificity of 80%.

DISCUSSION

Epidemiological and Clinical Profile

Our multicenter cohort of 380 patients closely mirrors the established epidemiological profile of AA. The median age of 30 years, with a predominance in the 16–35 age group, aligns with reports from Europe and North Africa, confirming the universal predilection for young adults(7). The mild male predominance (sex-ratio 1.17) is consistent with most published series(8,9) , although some studies report a female majority attributable to the frequency of gynecological differential diagnoses(10).

The prevalence of CAA in our cohort (46%) is higher than the 25–35% reported in European series, but is consistent with North African and Middle Eastern reports. This relatively high rate likely reflects the significant proportion of patients (57.1%) presenting after 48 hours of symptom onset, a delay associated with socioeconomic and geographic barriers to healthcare access. This observation corroborates findings by Lee et al. (11), who established a strong correlation between delayed presentation and complication rates.

Diabetes mellitus emerged as a significant predictor of CAA ($p=0.004$), a finding in agreement with Malkiely Gal et al.(12), who attributed this to the characteristically insidious and more severe infectious presentations in diabetic patients. The pathophysiological basis likely involves impaired neutrophil function, attenuated pain perception due to neuropathy, and a blunted febrile response.

NLR as a Diagnostic Tool for CAA

The mean NLR in the CAA group (6.2 ± 3.3) was significantly higher than in the UAA group (3.7 ± 1.5 ; $p < 0.001$), with an AUROC of 0.75, confirming its good discriminating ability. At a cut-off of 3.7, sensitivity reached 75.3% and specificity 61.4%, parameters that are clinically relevant for emergency triage.

Our cut-off of 3.7 is notably lower than those reported by Kahramanca et al. (5.74) (13), Jung et al. (5.6) (14), Shaikh et al. (8.0) (15) , and Zarog et al. (N/A)(16). This discrepancy is likely multifactorial and reflects: (1) the younger median age of our population (30 years vs. ≥ 65 years in the Korean study), which is associated with a more reactive immune response and higher lymphocyte counts at baseline; (2) differences in the timing of blood sampling relative to symptom onset, as early sampling captures a lower NLR before lymphopenia peaks; and (3) the relatively high proportion of early-presenting forms (42.9% within 48h), which may compress the NLR distribution in the CAA group.

The biological rationale underpinning NLR's predictive value in CAA lies in its dual mechanistic architecture. Neutrophilia in AA reflects the innate immune response to bacterial translocation and tissue necrosis, while lymphopenia results from cortisol-mediated apoptosis and lymphocyte redistribution during physiological stress. The NLR thus captures not merely inflammation but the overall homeostatic disruption — a feature absent from

single-lineage markers (4,5,17) .

4.3. NLR versus Conventional Biomarkers

While CRP ≥ 100 mg/L demonstrated a strong association with CAA ($p < 0.001$) in line with its well-established role as a sensitive inflammation marker several considerations favor NLR in specific clinical contexts. CRP is kinetically slow, rising 6–8 hours after the inflammatory insult and peaking at 48 hours (18), potentially limiting its sensitivity in early-presenting patients. NLR, conversely, is available immediately from the admission CBC, precedes CRP elevation, and adds a prognostic dimension through its stress-response component.

A prospective Irish study (Zarog et al., 2023) reported an AUROC of 0.84 for NLR versus 0.82 for CRP, with NLR showing a marginally superior discriminating ability (16). A Turkish study (Uludag et al., 2021) confirmed that both markers significantly elevated in perforated forms, proposing decision thresholds of CRP > 44 mg/L and NLR > 7.65 (19). These data collectively suggest a complementary rather than competitive relationship, supporting combined use of NLR and CRP in a multiparameter approach. This complementary role is further supported by a recent meta-analysis by Li et al., which confirmed that both NLR and the platelet-to-lymphocyte ratio (PLR) reliably differentiate appendicitis severity across pooled international cohorts (24).

NLR in the Broader Clinical Context

Beyond its application in AA, NLR has demonstrated robust prognostic utility across surgical and medical specialties. In acute pancreatitis, proposed severity thresholds of 4.76–4.88 predict organ failure risk (20). In colorectal and gastric cancer, an elevated preoperative NLR correlates with reduced overall survival and higher metastatic risk (4,21). In acute coronary syndromes, NLR predicts short-term and long-term mortality and correlates with validated scores such as GRACE and SYNTAX [38]. During the COVID-19 pandemic, NLR proved a reliable early triage marker for severe pulmonary disease (22,23). This multidomain validity underscores the biological universality of the neutrophil-lymphocyte axis as a marker of systemic host response intensity.

Strengths and Limitations

Strengths

Multicenter design involving two major Tunisian university hospitals, enhancing external validity. Large and representative cohort (N=380) exceeding the calculated minimum sample size. Histopathological confirmation as the gold standard for all included cases. Comprehensive multivariable analytical model adjusting for potential confounders. Clinically relevant endpoint directly applicable to emergency triage practice.

Limitations

Retrospective design with inherent information bias risk. Selection bias inherent to the inclusion of only operated

patients with histopathological confirmation; patients managed non-operatively or discharged after surveillance without surgery were not represented, so the reported diagnostic performance applies specifically to patients ultimately selected for surgery.

Absence of comparison with newer biomarkers (procalcitonin, IL-6) due to local resource constraints.

Single time-point NLR measurement without dynamic reassessment.

Potential inter-center heterogeneity in imaging protocols and operative decision-making.

CONCLUSION

This multicenter retrospective study suggests that the NLR is a simple, universally available, and cost-effective biomarker with clinically meaningful discriminating ability for predicting CAA. A threshold of 3.7 (sensitivity 75%, specificity 70%, AUROC 0.75) provides a practical decision-support tool for emergency surgeons, particularly in resource-limited settings where advanced imaging is not immediately accessible. Given the moderate discriminating ability reflected by an AUROC of 0.75, NLR should be regarded as a complementary biomarker that reinforces, rather than replaces, clinical judgment and should be interpreted alongside clinical, biological, and radiological findings.

Age ≥ 40 years, diabetes mellitus, fever $\geq 38.5^\circ\text{C}$, symptom duration ≥ 48 hours, generalized guarding, WBC $\geq 15,000/\text{mm}^3$, and CRP ≥ 100 mg/L collectively constitute a multiparameter profile that, combined with NLR, enables more accurate stratification of AA severity at admission. Future prospective multicenter studies should aim to validate a composite predictive score integrating NLR with clinical and biological variables, and to define context-specific optimal thresholds for Tunisian and broader North African populations.

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