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Research Article

JOURNAL OF SURGERY AND RESEARCH

ISSN: 2640-1002

Prospective Study to Assess the Use of Preoperative Neutrophil to Lymphocyte Ratio as a Predictor of Severe Cholecystitis

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Abstract

Background: Cholecystitis, commonly caused by gallstone obstruction of the cystic duct, leads to gallbladder inflammation. Severe cholecystitis carries a higher risk of complications, including perforation and systemic infection. Early and accurate diagnosis is crucial for timely management.

Aim of the study: This study evaluates the role of the preoperative neutrophil-to-lymphocyte ratio (NLR) as a predictive marker for severe cholecystitis.

Methods: This prospective analytical study was conducted at the department of surgery, Khulna Medical College and hospital, Khulna, Bangladesh from January 2021 to December 2023. A total of 65 patients diagnosed with severe cholecystitis aged 15–65 years were included. Baseline Demographic, clinical, and laboratory data, including NLR were performed. Data analysis was conducted using SPSS, with ≤0.05 considered statistically significant.

Result: Group A (severe cholecystitis) had significantly higher NLR (8.56 ± 2.77), CRP (94.8 ± 63.9 mg/L), and WCC (14.1 ± 9.77 ×10⁹/L) compared to Group B. ROC analysis showed that NLR >4.66 had a sensitivity of 69% and specificity of 85%, with an area under the curve (AUROC) of 0.59 ($p < 0.05$). Elevated NLR was associated with increased postoperative complications and prolonged hospital stays.

Conclusion: Preoperative NLR serves as a reliable biomarker for predicting severe cholecystitis. Its ability to differentiate between simple and severe cases can guide surgical decisions, optimize patient outcomes, and reduce postoperative complications.

Keywords: Neutrophil-to-Lymphocyte Ratio; Severe Cholecystitis; Gallbladder Inflammation

Introduction

Cholecystitis is a prevalent condition in hepatobiliary and pancreatic surgery, with gallstones obstructing the cystic duct in nearly 90% of patients, leading to inflammation of the gallbladder [1]. The severity of this inflammation determines the classification of cholecystitis, which can be categorized into simple and severe forms. Simple cholecystitis, when untreated, typically resolves within 7-10 days without progressing to more severe forms [2]. However, severe cholecystitis can lead to secondary complications, including hemorrhage, gangrene, emphysema, xanthogranuloma, and perforation, with delayed treatment potentially resulting in life-threatening conditions such as abscess formation and sepsis [3]. Severe cholecystitis, characterized by acute

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Citation: Anirudha Sardar, Abu Bakar Siddique, Gazi Shafiqur Rahman, Md. Masud Sattar. Prospective Study to Assess the Use of Preoperative Neutrophil to Lymphocyte Ratio as a Predictor of Severe Cholecystitis. Journal of Surgery and Research. 8 (2025): 313-318.

Received: April 07, 2025
Accepted: April 15, 2025
Published: July 07, 2025

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DOI:10.26502/jsr.10020454

inflammation, is associated with a higher risk of complications, including gallbladder perforation and systemic infection. Studies indicate that severe cholecystitis has a prevalence ranging from 22% to 30%, yet diagnosing its severity remains challenging due to variable clinical presentations and imaging findings [4]. It is crucial to distinguish between simple and severe cholecystitis early, as this has significant implications for management, morbidity, and mortality. Early and precise identification of severe cholecystitis is essential to guide appropriate therapeutic interventions and improve patient outcomes. While early laparoscopic cholecystectomy (LC) remains the gold standard with generally favorable results, it carries a 0.1–1% mortality risk and a 6–9% risk of major complications, particularly in emergency cases with severe inflammation [5]. Accurate preoperative identification of patients at risk of severe cholecystitis is crucial for optimizing surgical strategies and reducing the risk of postoperative complications [6]. Various biomarkers have been explored for their predictive value in assessing the severity of acute cholecystitis. The TG13/18 guidelines recommend grading scales that incorporate clinical evaluation, laboratory parameters such as leukocytes and C-reactive protein (CRP), and the presence of septic symptoms [7]. These scales, however, may not fully capture the inflammatory response and may require additional markers to enhance diagnostic precision [8]. The neutrophil-to-lymphocyte ratio (NLR) has gained recognition as a reliable systemic inflammatory marker [9]. The Neutrophil-to-Lymphocyte Ratio (NLR) is calculated based on the counts of circulating neutrophils and lymphocytes, which are key subtypes of leukocytes. Changes in these counts, driven by inflammatory mediators, are indicative of systemic inflammation [10]. Inflammation leads to the release of arachidonic acid metabolites and platelet-activating factors, causing neutrophilia, while stress-induced cortisol release results in relative lymphopenia. This makes the NLR an accurate representation of the inflammatory process [10,11]. Notably, the NLR is easily calculated using standard complete blood count (CBC) results, making it a cost-effective biomarker [11]. Recent studies have demonstrated strong correlations between the NLR, platelet-to-lymphocyte ratio (PLR), and the severity of acute calculous cholecystitis, as well as postoperative outcomes [12]. Elevated NLR levels are associated with more severe inflammation and longer recovery periods. Despite its proven utility in various inflammatory and malignant conditions, the application of NLR in inflammatory gallbladder diseases, such as acute cholecystitis, has been underexplored. This study aims to investigate the role of preoperative NLR in predicting the severity of acute cholecystitis, focusing on its potential to differentiate between simple and severe cases.

Methodology and Materials

This prospective observational study was conducted at the department of surgery, Khulna Medical College and hospital, Khulna, Bangladesh from January 2021 to December 2023. Patients included in the study were clinically diagnosed with severe cholecystitis. According to the ninth edition of the Surgery of People's Health Publishing House [13], the diagnostic criteria for acute cholecystitis include clinical symptoms, hematological findings, and imaging results. Clinical indicators may involve fever, a positive Murphy's sign, or the presence of pain, tenderness, or a mass in the right upper abdomen. Hematological assessments often reveal elevated C-reactive protein (CRP), increased white blood cell count, and elevated serum bilirubin levels, which are present in approximately half of the cases. Imaging studies, such as ultrasound, typically show gallbladder enlargement, marked edema, and bilateral signs of inflammation. For chronic or severe cholecystitis, diagnostic features included recurrent upper abdominal pain radiating to the right subscapular region (often following high-fat meals), occasional nausea and vomiting, and ultrasonographic evidence consistent with chronic gallbladder inflammation [14]. The study included 60 patients. All of the patients were divided into two groups.

Group A (n=43): Patients with severe cholecystitis

Group B (n=22): Patients without cholecystitis

Inclusion Criteria for Group A:

- Patients aged 15 to 65 years old.
- Diagnosed with severe cholecystitis.
- Underwent surgery.
- Evaluated using imaging techniques such as ultrasound (US), abdominal CT, or magnetic resonance hydrography (MRI).

Exclusion Criteria for Group B:

- Presence of neoplastic diseases.
- Diagnosis of gallbladder polyps or adenomyosis.
- Coexisting cholelithiasis with cholangitis.

Group B Selection:

- Comprised 15 to 65 years old people randomly chosen from hospital records.
- Included based on normal gallbladder histology and absence of significant comorbid conditions.

Data Collection

The study received approval from the hospital's Ethics Committee. Verbal consent was given by study patients before collecting data. Data for the study population were retrieved from medical records. General demographic information, laboratory findings, comorbidities, operative information were extracted from hospital records. Venous blood samples were collected from fasting patients 12 hours prior to surgery

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DOI:10.26502/jsr.10020454

to measure biochemical parameters. An automatic blood analyzer was used for routine blood tests, and the neutrophil-to-lymphocyte ratio (NLR) was calculated. All of the data compared between groups.

Data Analysis

For statistical analysis, data were processed using SPSS (Statistical Package for the Social Sciences) version 26. Quantitative variables were analyzed using descriptive statistics, including the mean and standard deviation. Qualitative variables, such as gender, were expressed in terms of frequency and percentage. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated to establish the optimal NLR cut-off for predicting cholecystitis severity. NLR values were categorized based on this cut-off, and comparisons of pre- and postoperative variables were performed using Student's t-test for continuous data, and chi-square tests for categorical data. A p-value of <0.05 was considered statistically significant.

Results

The mean age was slightly higher in Group A (51.22 ± 8.12 years) compared to Group B (45.27 ± 10.87 years), though the difference was not statistically significant. Gender distribution was similar, with males comprising 41.86% in Group A and 45.45% in Group B, and females accounting for 58.14% and 54.55%, respectively. The mean BMI was comparable between the groups, with Group A at 22.54 ± 2.72 kg/m² and Group B at 21.55 ± 3.33 kg/m², showing no significant differences in any parameter (Table 1). Hemoglobin levels and liver enzymes (GGT, ALP, AST, and ALT) showed no significant differences between the groups. However, Group A had significantly higher CRP (94.8 ± 63.9 mg/L vs. 6.2 ± 1.8 mg/L), WCC (14.1 ± 9.77 ×10⁹/L vs. 9.4 ± 1.45 ×10⁹/L), neutrophil count (5.88 ± 3.32 ×10⁹/L vs. 2.76 ± 0.88 ×10⁹/L), and NLR (8.56 ± 2.77 vs. 1.88 ± 0.56). Lymphocyte counts were slightly lower in Group A, while total bilirubin (16.87 ± 6.34 mmol/L vs. 11.1 ± 5.39 mmol/L) and amylase (40.6 ± 13.12 U/L vs. 68.6 ± 35.44 U/L) also showed significant differences ($p < 0.001$) (Table 2). Hypertension and diabetes were significantly more prevalent in Group A, affecting 34.88% and 44.19% of patients, respectively, compared to 13.64% and 9.09% in Group B ($p < 0.001$). Other comorbidities, including TIA/stroke, angina, arrhythmia, and heart failure, showed no significant differences between the groups, with low prevalence in both (Table 3). Open conversion was required in 63.64% of Group B than only 6.98% in Group A ($p < 0.001$). While the duration of surgery was similar between the groups, hospital stays were longer in Group B, with 54.55% hospitalized for 7-14 days and 4.55% for more than 14 days, compared to 20.93% and 0%, respectively, in Group A ($p < 0.001$). Postoperative complications were more common in Group B, including bile leak (4.55%), wound infection (22.73%), and other complications (13.64%), whereas 93.02% of Group A had no complications ($p < 0.001$) (Table 4). Table 5 shows that with a cutoff value of >4.66, the sensitivity and specificity were 69% and 85%, respectively. The positive likelihood ratio (LR+) was 5.732, and the negative likelihood ratio (LR-) was 0.432, with an area under the ROC curve (AUROC) of 0.59, indicating statistical significance ($p < 0.05$).

Table 1: Demographic characteristics of the study patients.

Characteristics	Group A (n=43)		Group B (n=22)		P-Value
	n	%	n	%	
Age, year (mean±SD)	51.22 ± 8.12		45.27 ± 10.87		NS
Gender					
Male	18	41.86	10	45.45	NS
Female	25	58.14	12	54.55	
BMI, kg/m2 (mean±SD)	22.54 ± 2.72		21.55 ± 3.33		NS

Table 2: Laboratory findings of the study population.

Laboratory results	Group A (mean±SD)	Group B (mean±SD)	P-Value
Hemoglobin, g/L	134.4 ± 17.34	132.5 ± 11.3	NS
CRP, mg/L	94.8 ± 63.9	6.2 ± 1.8	< 0.001
WCC, ×109/L	14.1 ± 9.77	9.4 ± 1.45	< 0.001
Neutrophils, ×109/L	5.88 ± 3.32	2.76 ± 0.88	< 0.001
Lymphocyte, ×109/L	1.34 ± 0.48	1.44 ± 0.23	< 0.001
NLR	8.56 ± 2.77	1.88 ± 0.56	< 0.001
Total bilirubin, mmol/L	16.87 ± 6.34	11.1 ± 5.39	< 0.001
GGT, U/L	55.12 ± 10.82	63 ± 6.43	NS
ALP, U/L	91.1 ± 22.65	77 ± 46.65	NS
AST, U/L	27.9 ± 11.6	28.7 ± 8.22	NS
Amylase, U/L	40.6 ± 13.12	68.6 ± 35.44	< 0.001
ALT, U/L	28.5 ± 8.55	39.6 ± 5.49	NS

Table 3: Comorbidities among study patients.

Comorbidities	Group A (n=43)		Group B (n=22)		P-Value
	n	%	n	%	
Hypertension	15	34.88	3	13.64	< 0.001
Diabetes	19	44.19	2	9.09	< 0.001
TIA/stroke	1	2.33	1	4.55	NS
Angina	2	4.65	0	0.00	NS
Arrhythmia	2	4.65	1	4.55	NS
Heart failure	3	6.98	0	0.00	NS

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DOI:10.26502/jsr.10020454

Table 4: Intra-operative and postoperative characteristics of patients.

Variables	Group A (n=43)		Group B (n=22)		P-Value
	n	%	n	%	
Open conversion					
Yes	3	6.98	14	63.64	< 0.001
No	40	93.02	8	36.36	
Duration of surgery					
<2hours	28	65.12	13	59.09	NS
>2hours	15	34.88	9	40.91	
Hospital Stay					
<7 days	34	79.07	9	40.91	< 0.001
7-14 days	9	20.93	12	54.55	
>14 days	0	0.00	1	4.55	
Complications					
Bile leak	0	0.00	1	4.55	< 0.001
Bleeding	1	2.33	1	4.55	
Wound infection	2	4.65	5	22.73	
Others	0	0.00	3	13.64	
Nocomplication	40	93.02	12	54.55	

Table 5: ROC curve analysis.

Variables	ROC results to predict severe cholecystitis				Cut- off	AUROC	P value
	Sensitivity	Specificity	LR+	LR-			
NLR	69	85	5.732	0.432	>4.66	0.59	<0.05

Discussion

Gallbladder stones are a widespread health issue, commonly encountered in clinical practice in my country. The development of gallstones is multifactorial, with obesity and high-fat diets being significant contributors. Cholecystitis, the inflammation of the gallbladder, is usually caused by cystic duct obstruction due to gallstones, and it can have a chronic course with a high risk of recurrence. Studies suggest that approximately 95% of cholecystitis cases are linked to gallstones. Delayed treatment can lead to chronic bile duct obstruction, resulting in gallbladder lumen dilation, wall thickening, and submucosal edema, which exacerbates patient burden and complicates treatment. Thus, timely intervention is essential to prevent further complications [15,16]. Diagnostic imaging, including ultrasound (US), CT, MRI, and MRCP, is used to detect severe cholecystitis; however, their sensitivity is not always adequate [17]. Recent research has highlighted the association between systemic inflammatory responses and poor prognosis in various inflammatory diseases and cancers. Inflammatory markers such as the modified Glasgow prognostic score (mGPS), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) have emerged as significant prognostic indicators. NLR, in particular, has garnered attention due to its easy calculation, low cost, and role in assessing immune responses to inflammation, infection, and tissue damage. Elevated NLR is often seen in advanced inflammatory diseases and malignancies, correlating with poor outcomes. Monitoring NLR can be a useful tool for predicting the severity of cholecystolithiasis with cholecystitis in elderly patients, offering a reliable pre-operative biomarker for assessing disease severity and guiding treatment decisions [19]. In our study, the demographic characteristics, including age, gender, and BMI, were comparable between the two groups (Group A: severe cholecystitis, Group B: non-severe cholecystitis). These results suggest that these factors did not significantly influence the severity of cholecystitis. Notably, the mean age was higher in Group A compared to Group B, although this difference was not statistically significant. This finding aligns with previous literature suggesting that older age is a risk factor for severe cholecystitis [20]. The laboratory results in our study revealed significant differences between the two groups, with Group A patients exhibiting higher levels of C-reactive protein (CRP), white blood cell count (WCC), neutrophil count, and NLR. Furthermore, the NLR was markedly higher in Group A (8.56 ± 2.77) compared to Group B (1.88 ± 0.56), which supports our hypothesis that NLR can serve as a reliable predictor of severe cholecystitis [21]. In addition to NLR, other laboratory parameters, such as total bilirubin and amylase, were also significantly higher in Group A, further supporting the association between

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DOI:10.26502/jsr.10020454

inflammation, biliary dysfunction, and disease severity. The ROC curve analysis in the present study demonstrated that NLR has moderate predictive value for severe cholecystitis, with an AUROC of 0.59 and a sensitivity of 69% and specificity of 85% at a cut-off value of >4.66. These findings suggest that NLR may be a useful biomarker for identifying patients at higher risk of severe disease. While the sensitivity is moderate, the high specificity indicates that NLR could be a reliable marker for ruling out severe cholecystitis in patients with low NLR values. Similar findings have been reported in other studies, which have demonstrated the utility of NLR in predicting the severity of inflammatory conditions, including acute cholecystitis [21,22]. In our study, significant differences were observed in comorbidities between the two groups, particularly with hypertension and diabetes being more prevalent in Group A ($p < 0.001$). This finding is consistent with literature that identifies comorbid conditions as risk factors for complications in surgical patients [23]. Additionally, intra-operative outcomes reflected a higher rate of open conversions and prolonged hospital stays in patients with severe cholecystitis, emphasizing the clinical implications of accurately predicting disease severity preoperatively.

Limitations of the study

Despite the promising results, our study has several limitations. The observational design of the study does not allow for a causal inference between NLR and severe cholecystitis. Additionally, other potential biomarkers, such as PLR, CRP-to-albumin ratio (CAR), and procalcitonin, were not evaluated in this study and could be explored in future research to improve the predictive accuracy of inflammatory markers.

Conclusion

Preoperative neutrophil-to-lymphocyte ratio (NLR) demonstrates significant potential as a predictor of severe cholecystitis, showing strong correlations with systemic inflammation, surgical complexity, extended hospital stays, and increased postoperative complications. A cut-off value of >4.66 highlights its utility as a simple, accessible, and cost-effective tool for risk stratification in clinical settings. NLR can aid in early identification of high-risk patients, enabling timely interventions and optimized perioperative management. To enhance clinical application, NLR should be integrated into preoperative evaluation protocols, particularly for patients with suspected acute cholecystitis. Combining NLR with other inflammatory markers and clinical parameters may further improve predictive accuracy and patient outcomes. Standardized thresholds for NLR should be developed through larger studies across diverse populations.

Acknowledgement

We deeply thank the study participants for providing data.

Funding

No funding sources

Conflict of interest

No conflict of interest was found.

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Citation: Anirudha Sardar, Abu Bakar Siddique, Gazi Shafiqur Rahman, Md. Masud Sattar. Prospective Study to Assess the Use of Preoperative Neutrophil to Lymphocyte Ratio as a Predictor of Severe Cholecystitis. Journal of Surgery and Research. 8 (2025): 313-318.