Original Research Article

A prospective study to assess the use of preoperative neutrophil to lymphocyte ratio as a predictor of severe cholecystitis

N. Siva Durgesh*, V. Viswa Teja

Department of General surgery, KIMS and RF, Amalapuram, Andhra Pradesh, India

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*Correspondence:
Dr. N. Siva Durgesh,
E-mail: shivadurgesh.nandigrama@gmail.com

ABSTRACT

Background: Cholecystitis can be divided into simple and severe cholecystitis. Untreated simple cholecystitis resolves within 7–10 days if it does not progress to more severe cholecystitis. Aims and objectives were to evaluate whether neutrophil-to-lymphocyte ratio can differentiate between simple cholecystitis and severe cholecystitis. To evaluate role of NLR as a prognostic indicator.

Methods: The source of data for our study will be patients admitted in the department of general surgery diagnosed with acute cholecystitis in Konaseema Institute of medical sciences and research foundation, Amalapuram. All patients between 15 to 70 years of age with a clinical diagnosis of acute cholecystitis confirmed with histopathology study.

Results: With an NLR value of 4.35, the sensitivity and specificity were 67% and 87%, respectively. Therefore, we considered 4.35 as the cutoff value, and divided the patient population into two groups: those with preoperative NLR values below 4.35 (n=50) and those with values equal to or greater than 4.35 (n=15). 53.33% of higher NLR group patients had severe cholecystitis compared to only 8% of patients in lower NLR group (p<0.05).

Conclusions: It was seen that the patients with cholecystitis can be divided into low risk (NLR<4.35) and high risk (NLR≥4.35) groups for severe cholecystitis as per the NLR value at admission.

Keywords: Preoperative, Neutrophil to lymphocyte ratio, Cholecystitis

INTRODUCTION

The prevalence of severe cholecystitis has been found to be 22–30% in surgical series.¹ According to the degree of inflammation, cholecystitis can be divided into simple and severe cholecystitis. Untreated simple cholecystitis resolves within 7–10 days if it does not progress to more severe cholecystitis.² The severe forms of cholecystitis include secondary changes such as hemorrhage, gangrene, emphysema, xanithogranuloma, and perforation.³ Patients with severe cholecystitis usually require a higher number of intensive care unit admissions, prolonged postoperative hospital stays, and have increased morbidity and mortality.⁴ Delayed management can lead to increased morbidity due to progression to severe disease such as gangrenous change, abscess formation and gall bladder perforation.⁵

Prompt detection and proper management of patients at risk of severe cholecystitis are essential in preventing associated complications. Gangrenous cholecystitis (GC) is generally considered a more severe form of acute cholecystitis.⁶

A number of older studies have looked at risk factors that may distinguish GC from non-gangrenous acute cholecystitis (NGAC) with the aim of improving outcomes by providing more aggressive and timely treatment.⁷
To predict the prognosis of inflammatory diseases and some malignancies, several inflammatory scores have been suggested such as modified Glasgow prognostic score, neutrophil lymphocyte ratio (NLR), platelet to lymphocyte ratio etc. Not many studies are done on NLR and its use as a prognostic indicator on cholecystitis and hence this study.

NLR is a simple, non-invasive and cost-effective marker of inflammation in various diseases and is calculated using data obtained from the complete blood count. NLR has been tested to date regarding its ability to accurately diagnose acute appendicitis preoperatively in unselected patients. Almost 20 years ago before NLR became so popular, Goodman et al declared that 88% of patients with histologically proven appendicitis had a NLR>3.5. The authors also concluded that NLR was more sensitive to detect acute appendicitis compared with total WBC count.

Recent clinical evidence proved the association of neutrophil to lymphocyte ratio (NLR) with a number of inflammatory markers. In addition, NLR was shown to be associated with adverse clinical outcomes in various clinical settings.

**METHODS**

This prospective observational study was conducted from December 2016 to October 2018 on patients admitted in the department of general surgery diagnosed with acute cholecystitis in Konaseema Institute of Medical Sciences and Research Foundation, Amalapuram.

All patients between 15 to 70 years of age with a clinical diagnosis of acute cholecystitis confirmed with histopathology study were included in the study, while the patients presenting 72 hours after the onset of abdominal pain were excluded from the study.

The NLR will be derived from serum neutrophil and lymphocyte counts which is a part of routine complete blood count (which includes Haemoglobin%. Total leucocyte count, differential leucocyte count, platelet count, and other parameters) done in all patients before surgery. Receiver operating characteristic (ROC) curve analysis will be conducted to determine the cut-off value for pre-operative NLR that could discriminate between simple and severe cholecystitis. The most prominent point on the ROC curve will be chosen as the cut off value for the NLR. This will be compared with post-operative histopathology findings of the gall bladder specimen.

All the quantitative variables like neutrophil to lymphocyte values will be summarized employing descriptive statistical methods such as mean and standard deviation or median and inter quartile range. All the qualitative variables like gender will be presented using frequency and percentages.

Duration of surgery was less than 2 hours in 41(63.07%) patients and more than 2 hours in 24(36.92%). Majority of patients 46 (70.76%) had<7 days hospital stay. 55 (84.61%) had no complication, while in rest 5(7.69%) had wound infection (Table 1). According to final histopathology 53 (81.53%) had simple cholecystitis and 12 (18.46%) had severe cholecystitis (which includes Gangrenous cholecystitis, Emphysematous Cholecystitis, Xanthogranulomatous cholecystitis) (Table 2).

An ROC curve was established to determine the cut-off value for preoperative NLR that could discriminate between simple cholecystitis and severe cholecystitis. The ROC area under the curve was 0.73 (Figure 1) (Table 3).

With an NLR value of 4.35, the sensitivity and specificity were 67% and 87%, respectively. Therefore, we can conclude that NLR is a simple, non-invasive and cost-effective marker of inflammation in various diseases and can be used as a diagnostic tool to predict the severity of cholecystitis.
considered 4.35 as the cutoff value, and divided the patient population into two groups: those with preoperative NLR values below 4.35 (n=50) and those with values equal to or greater than 4.35 (n=15).

Table 2: Final histopathology report of patients.

| Biopsy                | No. of patients | %   |
|-----------------------|-----------------|-----|
| Simple cholecystitis  | 53              | 81.53 |
| Severe cholecystitis  | 12              | 18.46 |
| Total                 | 65              | 100.0 |

When comparing preoperative variables, the two groups showed no differences in age, sex, association with T2DM, and gall bladder contents. The higher NLR (NLR≥4.53) group included more patients who were admitted via the emergency (p value<0.005) (Table 4) (Figure 2).

Next, surgical outcomes were compared between the groups. Cholecystectomies were performed mainly laparoscopically. The higher NLR group (>4.35) had: More conversion rate 66.66% compared to 3%, (p<0.05). longer length of stay at hospital (more than 7 days)-60% compared to 20% (p<0.05). Higher incidence of postoperative complications, it was strongly significant (p<0.05). A longer operation time (>2 hours) - 40% patients compared to 36% patients (p=0.7702) not significant (Table 5) (Figure 3).

Table 3: ROC curve analysis.

| Variables                              | Sensitivity | Specificity | LR+ | LR- | Cut-off | AUROC | P value |
|----------------------------------------|-------------|-------------|-----|-----|---------|-------|---------|
| NLR                                    | 67          | 87          | 5.153 | 0.379 | >4.35   | 0.73  | <0.05** |

Table 4: Demographic and preoperative characteristics of patients who underwent cholecystectomy due to cholecystitis grouped by NLR.

| Variables            | NL Ratio          | Total (n=65) | P value |
|----------------------|-------------------|--------------|---------|
| Age in years         | <4.35 (n=50)      | >4.35 (n=15) | 0.2402  |
| 20-30                | 11 (22%)          | 2 (13.33%)   | 13(20%) |
| 31-40                | 10 (20%)          | 1 (6.66%)    | 11(16.92%) |
| 41-50                | 12 (24%)          | 2 (13.33%)   | 14(21.53%) |
| 51-60                | 11 (22%)          | 5 (33.33%)   | 16(24.61%) |
| 61-70                | 6 (12%)           | 5 (33.33%)   | 11(16.92%) |
| Gender               | Female            | 32 (64 %)    | 6 (40 %) | 38(58.46%) | 0.1946 |
|                      | Male              | 18 (36 %)    | 9 (60 %) | 27(41.53%) |
| Associated T2DM      | No                | 37(74%)      | 7(46.66%) | 44(67.69%) | 0.6246 |
|                      | Yes               | 13(26%)      | 8(53.33%) | 21(32.30%) |
| Route of admission   | Emergency         | 3 (6 %)      | 9 (60%)   | 12 (18.46%) | 0.00002529 |
|                      | Elective          | 47 (94%)     | 6 (40%)   | 53 (81.53%) |
| Scan                 | Calculous cholecystitis | 49 (98 %) | 14 (93.33%) | 63 (96.92%) | 0.4111 |
|                      | Acalculous cholecystitis | 1 (2 %) | 1 (6.66%) | 2 (3.07%) |

Table 5: Intra-operative and postoperative characteristics of patients who underwent cholecystectomy due to cholecystitis grouped by NLR.

| Variables      | NL Ratio          | Total (n=65) | P value |
|----------------|-------------------|--------------|---------|
| Open conversion| <4.35 (n=50)      | >4.35 (n=15) | 0.00000368 |
| Yes            | 3 (6 %)           | 10 (66.66%)  | 13 (20 %) |
| No             | 47 (94 %)         | 5 (33.33%)   | 52 (80 %) |
| Duration of surgery | <2hours             | >2hours      | 0.7702 |
| <2hours        | 32 (64%)          | 9 (60 %)     | 41 (63.07%) |
| >2hours        | 18 (36%)          | 6 (40%)      | 24(36.92%) |
Variables | NL Ratio | Total (n=65) | P value
--- | --- | --- | ---
Hospital Stay | <4.35 (n=50) | >4.35 (n=15) | 
<7 days | 40 (80%) | 6 (40 %) | 46 (70.76%) | 0.0038
7-14 days | 10 (20%) | 8 (53.33%) | 18 (27.69%) | 
>14 days | 0 (0%) | 1 (6.66%) | 1 (1.53%) | 
Complications |  
Bile leak | 0 (0%) | 1 (6.66%) | 1 (1.53%) | 0.000903
Bleeding | 1 (2%) | 1 (6.66%) | 2 (3.07%) | 
Wound infection | 2 (4%) | 3 (20%) | 5 (7.69%) | 
Others | 0 (0%) | 2 (13.33%) | 2 (3.07%) | 
Nocomplication | 47 (94%) | 8 (53.33%) | 55(84.61%) | 

Figure 1: ROC curve analysis.

Figure 2: Demographic and preoperative characteristics of patients who underwent cholecystectomy due to cholecystitis grouped by NLR.
Finally, to summarize our study, 53.33% of higher NLR group patients had severe cholecystitis compared to only 8% of patients in lower NLR group (p<0.05) (Table 6) (Figure 4).

**DISCUSSION**

The representative forms of severe cholecystitis are gangrenous cholecystitis and gallbladder perforation. Around 30% of patients of cholecystitis, suffer from Gangrenous cholecystitis, in which inflammation interrupts the blood flow to the gallbladder, resulting in gangrenous change. The mortality rate was reported to be up to 22%, and is directly related to other severe complications, like gallbladder perforation, abscess formation, and peritonitis. Gallbladder perforation is the eventual result of severe cholecystitis, where inflammation can either be localized or spread throughout the whole abdominal cavity via the perforated gallbladder. In our study severe cholecystitis was seen in 18.46% of the patients (n=12 of the total 65) (p<0.05).

This study shows the usefulness of preoperative NLR in predicting prognosis and thereby, in determining operative priority in patients with cholecystitis. Patients with acute severe cholecystitis have higher incidences of postoperative complications and a prolonged LOS. In this study, high NLR was found to be a predictor of severe cholecystitis as well as an independent risk factor for prolonged LOS. In our study it is seen that 60% of...
patients with high NLR stayed for more than 7 days in the hospital (p<0.05). Early cholecystectomy was shown to decrease LOS in patients with acute severe cholecystitis. Therefore, prioritizing patients with high NLR for operation would reduce postoperative morbidity and LOS. Similarly, operation time was longer in the high NLR group than in the low NLR group, 40% of the patients in the high NLR group had >2 hours as the duration of surgery (p=0.05). According to the disease entities or their severity, a range of NLR cut-off values have been proposed, usually from 3 to 8. Of these, a threshold of >5.0 has been most frequently proposed [54], while recent reports have recommended a value of 3.0 [15, 55]. We determined the cut-off value of severe cholecystitis as 4.35 based on our ROC curve analysis; the NLR value of 4.35 had an acceptable reliability in the analysis (the sensitivity and specificity were 67% and 87%, respectively). The index study showed NLR of 3.0 and 70.5% sensitivity and a specificity of 70.0% [16]. Therefore, we believe that a NLR cut-off value of 4.35 is suitable, and consistent with previous studies. However, NLR depends on laboratory values and technical errors may influence it. So more study is needed to validate the cut-off value, and to precisely determine the best NLR with greatest prognostic power in cholecystitis.

**CONCLUSION**

Routine calculation of preoperative NLR in patients of cholecystitis serves as a simple and easy means of identifying patients with severe cholecystitis. It also acts as a surrogate marker to predict the prolonged LOS. It was seen that the patients with cholecystitis can be divided into low risk (NLR<4.35) and high risk (NLR≥4.35) groups for severe cholecystitis as per the NLR value at admission. This approach of deciding the operative priority depending on the NLR value is expected to achieve better surgical outcome by abiding to the “sickest first” principle and thus enabling expectant perioperative management.

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