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Original Research Article

A 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 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, xanthogranuloma, 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.[8] 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.[9] 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.[10]

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 histo-pathology 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.

Sensitivity, specificity, positive predictive value, negative predictive value, ROC curve analysis will be carried out establishing the optimum cut off value in predicting severity of cholecystitis. NLR will be grouped using the cut off value and pre and post-operative comparisions of variable will be carried out using student's t test/ Mann Whitney test for quantitative variable and Chi square test for categorical variables.

RESULTS

The present is a prospective observational study which was conducted in the Dept. of General Surgery, Konaseema Institute of Medical Sciences & Research Foundation and General Hospital, Amalapuram between December 2016 and October 2018. A total of 65 patients who underwent cholecystectomy owing to symptomatic cholecystitis during the period were included in the study. The patients comprised of 38 (58.46%) woman and 27 men (41.53%). Patients mostly presented with pain abdomen in the right hypochondrium or flatulent dyspepsia, 32.30% of patients had associated type 2 diabetes mellitus. 53 patients had elective admissions. Calculous cholecystitis in 63 (96.92%) patients and Acalculous Cholecystitis in 2 (3.07%). 40 % of the patients had leucocytosis in TLC. 52 (80%) had Laparoscopic cholecystectomy and 13 (20%) had Open cholecystectomy.

Table 1: Complications of surgery.

Complications	No. of patients	%
Bile leak	1	1.53
Secondary haemorrhage	2	3.07
Wound infection	5	7.69
Others (pneumonia, urinary retention)	2	3.07
No complications	55	84.61
Total	65	100.0

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

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	ROC results to predict severe cholecystitis				Cut- off	AUROC	P value
	Sensitivity	Specificity	LR+	LR-			
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 cholecystits grouped by NLR.

Variables	NL Ratio		Total(n=65)	P value
	<4.35 (n=50)	>4.35 (n=15)		
Age in years				
20-30	11 (22%)	2 (13.33%)	13(20%)	0.2402
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 cholecystits grouped by NLR.

Variables	NL Ratio		Total (n=65)	P value
	<4.35 (n=50)	>4.35 (n=15)		
Open conversion				
Yes	3 (6 %)	10 (66.66%)	13 (20 %)	0.00000368
No	47 (94 %)	5 (33.33%)	52 (80 %)	
Duration of surgery				
<2hours	32 (64%)	9 (60 %)	41 (63.07%)	0.7702
>2hours	18 (36%)	6 (40%)	24(36.92%)	

Continued.

Variables	NL Ratio		Total (n=65)	P value
	<4.35 (n=50)	>4.35 (n=15)		
Hospital Stay				
<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%)	

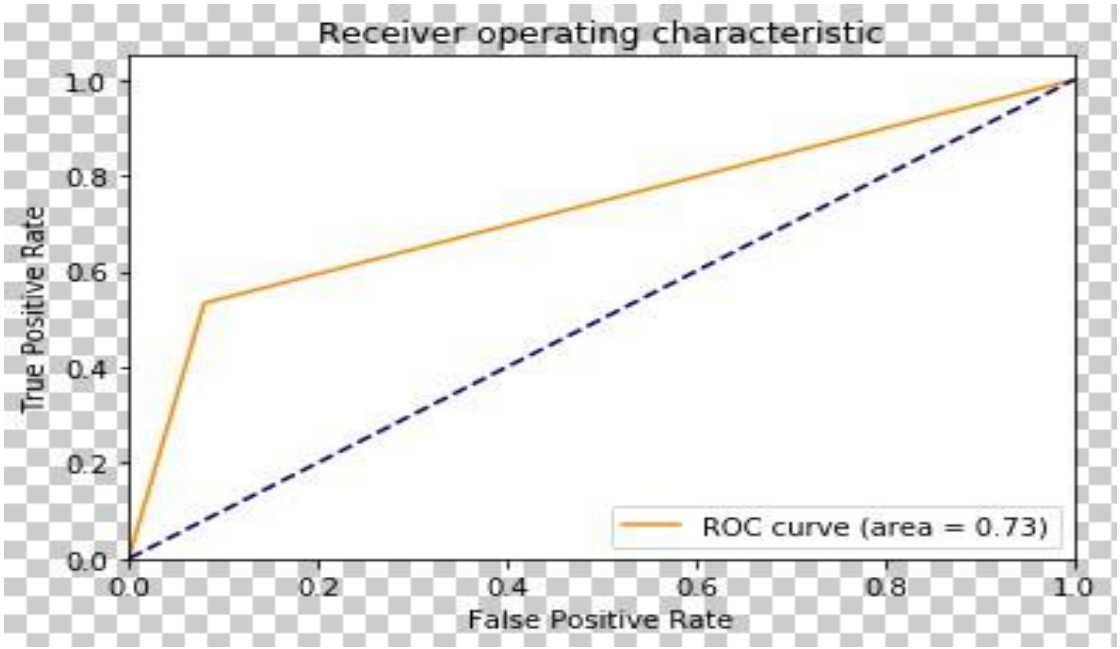

Figure 1: ROC curve analysis.

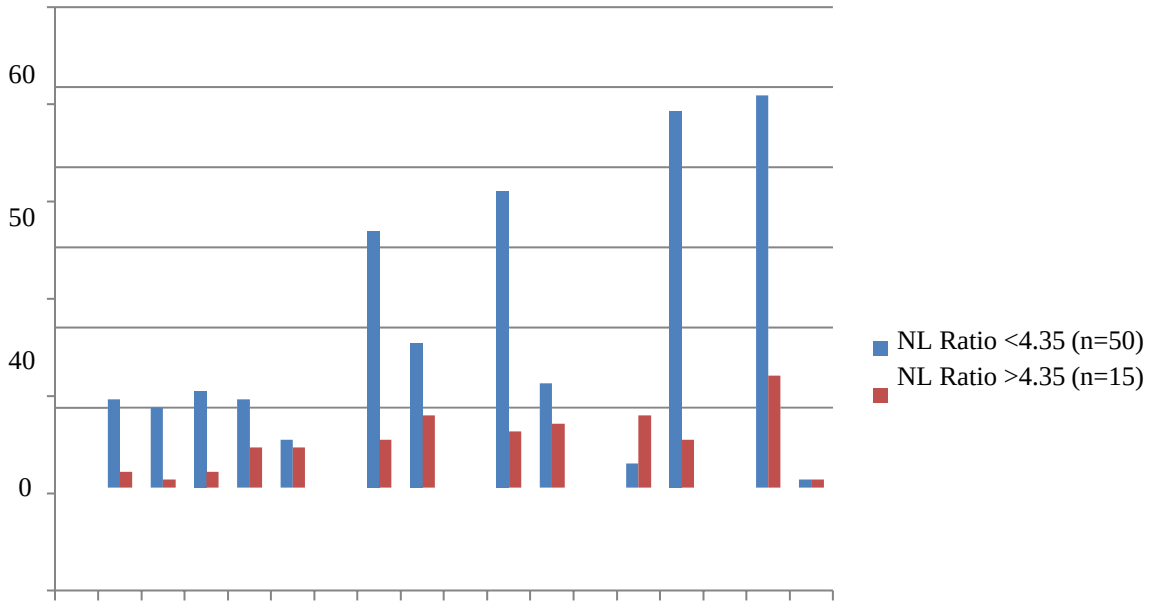

Figure 2: Demographic and preoperative characteristics of patients who underwent cholecystectomy due to cholecystitis grouped by NLR.

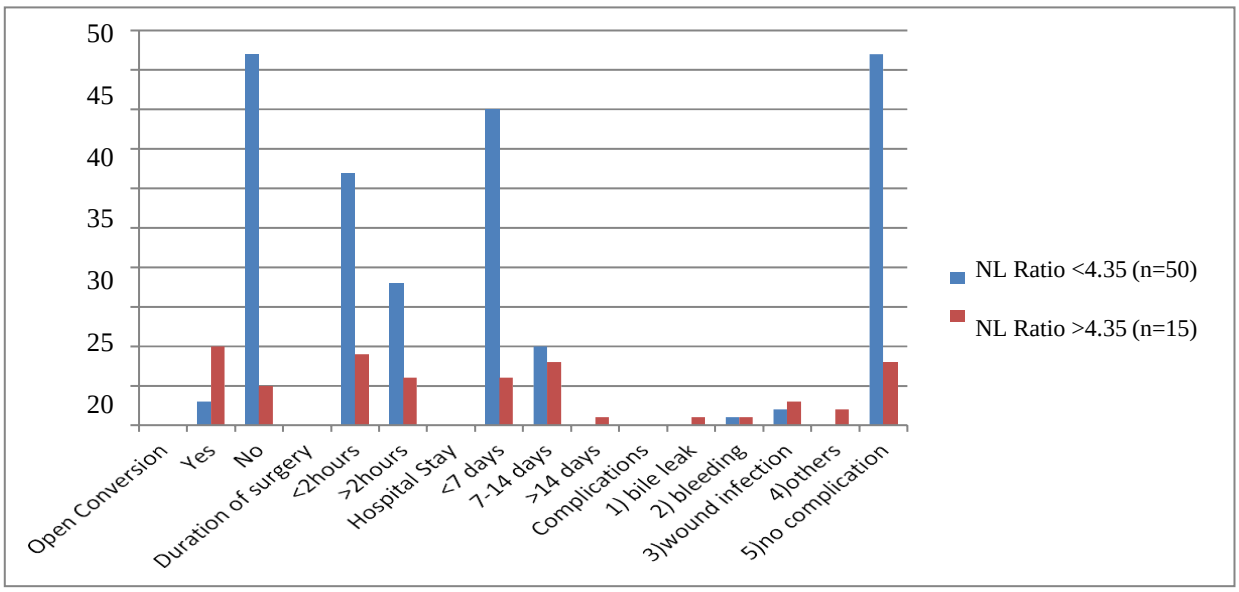

Figure 3: Intra-operative and post-operative characteristics of patients who underwent cholecystectomy due to cholecystitis grouped by NLR.

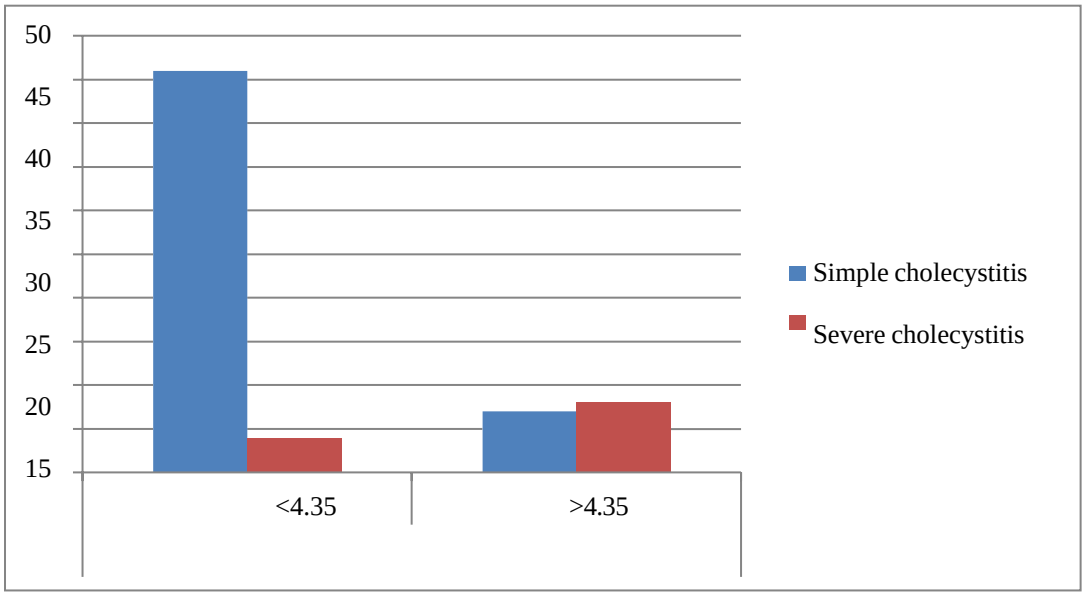

Figure 4: Biopsy findings in relation to NL ratio

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.[11] The mortality rate was reported to be upto 22%, and is directly related to other severe complications, like gallbladder perforation, abscess formation, and peritonitis.[12] 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.[13] 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.[14] 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. 66. 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 ($NLR\geq4.35$) 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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Ethical approval: The study was approved by the Institutional Ethics Committee

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