

Neutrophil to Lymphocyte Ratio: A New Marker For Early Insight Into Severity of Cholecystitis: An Observational Study

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Abstract

Introduction: Acute cholecystitis is one of the common conditions leading to cholecystectomies. Distinguishing simple cholecystitis from severe cholecystitis is difficult. The role of neutrophil to lymphocyte ratio in predicting severity of cholecystitis has been recently studied.

Aim: To observe the patterns of preoperative Neutrophil-to lymphocyte Ratio in simple and severe cholecystitis.

Materials And Methods: In this hospital based observational study, data were collected from patients undergoing cholecystectomies at a single institution from June 2016 to August 2016.

Each patient's Neutrophil to Lymphocyte Ratio (NLR) was calculated as the absolute neutrophil count divided by the absolute lymphocyte count.

A cut off value of NLR was determined using Receiver Operating Curve analysis to distinguish simple cholecystitis from severe cholecystitis. Based on the cut off value the data were allocated to two groups and were compared.

Results: 47 patients were included. Based on ROC analysis, an NLR value of 3.00 was taken as cut off and data allocated to two groups, NLR >3.00 and an NLR <3.00 at admission. An NLR value of more than 3.00 was found significantly associated with an increased operating time ($p=0.0001$) and an increased length of post-operative hospital stay ($p=0.0152$). The mean operating time was 69.61 minutes while the mean length of hospital stay was 6.19 days. 3 cases were converted to open procedure.

Conclusion: NLR can be used as an adjunct in assessment and management of patients with acute cholecystitis.

Keywords: neutrophil to lymphocyte ratio, cholecystitis

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I. Bodytext

1.1 Introduction And Aim

Acute cholecystitis is one of the common conditions leading to cholecystectomies [1]. Cholecystitis or inflammation of the gall bladder presents with upper abdominal pain, anorexia, nausea, vomiting or fever [2]. Peritonitis may be present if perforation occurs [3]. Obstruction of the cystic duct by gall stones leads to the inflammation of the gall bladder most of the time. The definitive management comprises cholecystectomy [2]. If cholecystitis is severe, complicated by gangrene of gall bladder or presence of pus within the gall bladder or even perforation of the gall bladder then, it can lead to increased morbidity or even to mortality [4].

Usually it is difficult to clinically identify the presence of severe cholecystitis. Imaging modalities too, often give equivocal diagnoses [5]. The severity of cholecystitis is related to the presence of inflammation [6]. Several inflammation based scores have been suggested to predict the prognosis of inflammatory diseases. These include The Modified Glasgow Prognostic Score, Prognostic Nutritional Index, the Neutrophil to- lymphocyte Ratio (NLR) and many others [7,8]. One such score is Neutrophil to lymphocyte ratio. It is easy to calculate and no additional costs are involved in its calculation. It is derived from the standard complete blood count tests routinely performed. Inflammation leads to neutrophilia due to the release of arachidonic acid metabolites and platelet activating factors whereas cortisol induced stress leads to a relative lymphopenia. Thus, neutrophil to lymphocyte ratio reflects the inflammatory process underlying many diseases [9]. Role of NLR in simple and severe cholecystitis has been recently studied [10]. This study observes the patterns of preoperative Neutrophil-to lymphocyte Ratio in simple and severe cholecystitis.

II. Materials And Methods

2.1 Study design and data collection

The study was conducted at the general surgery department of SMS Medical College Hospital, Jaipur. The study is a hospital based observational study for which data were collected from patients undergoing cholecystectomies from June 2016 to August 2016. Patients were operated by laparoscopic approach, conversion to open been done when needed. Only those patient's data were included who gave consent for the

study and whose histopathology reports indicated presence of cholecystitis. Patients with malignant diseases, pregnant patients and immune compromised patients were not included in the study. A total of 47 patients were included in the study. NLR was calculated for each patient at the time of admission as the ratio of the absolute neutrophil count to the absolute lymphocyte count. Both these values were taken from the patient's complete blood count and differential leucocyte count tests. A Receiver Operating Curve analysis was done to study the pattern of NLR in relation to severity of cholecystitis. A cut off value was determined to distinguish simple cholecystitis from severe cholecystitis. Based on the cut off value the data were allocated to two groups and various preoperative, intra operative and post-operative data were compared.

2.2 Definitions

Presence of gangrene, pus, perforation or organ dysfunction (organ dysfunction as defined by Tokyo Guidelines 2013) [11] was considered characteristic of severe cholecystitis. Cholecystitis with absence of any of these findings was considered Simple cholecystitis. Use of open technique for completing the procedure was considered conversion. Port site extension just for delivering the specimen was not considered open technique. The time interval between initial skin incision to completion of wound closure was taken as the operation time. An intraoperative loss of more than 150 mL blood was regarded as intraoperative bleeding. Non-iatrogenic full thickness breach of gall bladder wall with or without oozing of gall bladder contents, as seen on laparoscopy was considered perforation. Post-operative intraabdominal hemorrhage was defined as bleeding that required radiological or surgical intervention to control or bleeding that required transfusion. Bile leak was defined according to ISGLS group definition as a bilirubin concentration in the drain fluid at least three times the serum bilirubin concentration on or after postoperative day 3 or if a radiologic or operative intervention for a bile collection or bile peritonitis was required [12]. Requirement of a Foley's urinary catheter or urological intervention for voiding in patients who did not require these preoperatively was considered post-operative voiding difficulty.

2.3 Statistical analysis

Data were described as means +/- standard deviations or as medians and ranges. Continuous variables were compared using independent t tests while categorical variables were compared using chi square tests. Statistical analysis was done using MedCalc software version 17.8. P values less than 0.05 were considered statistically significant.

III. Results

Data from total of 47 patients were studied (Table 1) with median age of 36 years (range 19 - 75 years). Out of these 4 were men while 43 were women. All were admitted from the out-patient's department. All patients underwent laparoscopic cholecystectomies. Based on intra operative and histopathological findings, severe cholecystitis was found in 7 patients whereas 40 patients had simple cholecystitis. Presence of gall bladder stones was found in all patients. A Receiver Operating Curve analysis was done (Figure I) to study the NLR values and the presence of severe cholecystitis. Area under the ROC curve was 0.934 with an NLR of >3.08 associated with a sensitivity of 85.71% and a specificity of 87.50%. An NLR value of 3.00 was taken as cut off and data allocated to two groups, that is those with an NLR >3.00 at admission and those with an NLR <3.00. The continuous variables were compared using independent t tests while the categorical variables compared using the chi square test. An NLR value of more than 3.00 was found significantly associated with an increased operating time ($p < 0.0001$) and an increased length of post-operative hospital stay ($p = 0.0152$). The mean operating time was 69.61 minutes while the mean length of post-operative hospital stay was 2.3191 days. (Table 2) Out of other variables, an NLR of more than 3.00 was associated with an increased mean age at presentation and an increased mean total leukocyte count but these associations were not found statistically significant. (Table 1) In a total of 3 patients (1 from NLR less than 3.00 while 2 from NLR more than 3.00 group), the procedure had to be converted to open procedure. A drain was placed in all patients as per the unit and hospital protocols. There was no postoperative complication as defined for the study purpose.

IV. Discussion

Severe cholecystitis is associated with more morbidity and adverse features as compared to simple cholecystitis [6]. Furthermore, surgery in the setting of increasing severity of inflammation is challenging and associated with more complications [6]. So, it is important to get an early insight into the severity of the inflammatory process associated with acute cholecystitis. Traditionally, clinical acumen supported by imaging modalities like ultrasonography and CT scans has been used to assess, prioritize and treat patients presenting with acute cholecystitis [6]. Since acute cholecystitis is caused due to an inflammatory response secondary to obstruction of bile drainage by gall stones, markers of inflammatory response can be used as an adjunct in the assessment of patients with acute cholecystitis [6,10,13]. In earlier studies, the plasma levels of pro-

inflammatory cytokines (e.g., IL-1ra, IL-6, IL-7, IL-8, IL-12) have been found elevated in patients who also had elevated NLR [14,15,16]. This is reflective of an overall enhanced inflammatory response in the body. In the background of knowledge that acute inflammation tends to elevate the neutrophil counts and more inflammation leads to a relative fall in the lymphocyte counts, an elevated neutrophil to lymphocyte ratio may be said to be associated with an overall more severe inflammatory process as compared to a condition with low NLR values. This study assesses the patterns of NLR values in the setting of cholecystitis. The ROC analysis gave an area under the RO curve similar to that found in earlier studies with an NLR of 3.08 associated with sensitivity of 85.71% and a specificity of 87.50% which is similar to the values of around 70% each as found by researchers in earlier studies with more number of subjects [10]. The raised NLR values were found significantly associated with presence of severe cholecystitis, increased operating time and a lengthier post-operative hospital stay. This is similar to what has been described earlier [10]. Increased age, male gender and raised total leukocyte counts were not found associated with raised NLR values in a statistically significant manner. However, two of these variables did show differences among the two groups with raised NLR value group showing an increased mean age and an increased mean total leukocyte count as has been described by researchers earlier [10]. The reason for this lack of statistical significance may be the smaller number of subjects studied. The findings that elevated NLR values were associated significantly with severe cholecystitis explains the association of increased operating time with elevated NLR as more severe cholecystitis presents a more difficult surgical scenario to deal with. Gangrenous gall bladder, abscess formation, presence of pus and frank perforation are all associated with increased difficulty in surgery requiring more skill and patience from the surgeon. Similarly, more severe the cholecystitis, severe and intense is the overall inflammatory response mounted by the body. This may be the reason for a relatively delayed convalescence and a longer hospital stay. The study had several limitations, most important of which was a smaller number of cases studied. A larger study group tends to be more representative of the population at large. Another limitation was that this study was an observational study and prospective trials are required to further validate its results.

V. Conclusion

Preoperative NLR calculation is an easy way to get an early insight about the severity of cholecystitis. As per the patterns found in this study, the patients with cholecystitis can be considered to be at low risk for severe cholecystitis if NLR at admission is < 3.0 and at a higher risk for severe cholecystitis if NLR at admission is > 3.0 . The results substantiate the view that NLR can be used as an adjunct in assessing, managing and prioritizing patients as far as acute cholecystitis is concerned. However more research is needed to find out more details and develop patterns of management based on NLR values at the time of admission.

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5.1 Figure And Table Legends

Figure I: Receiver Operating Curve

Table I: Pre-operative data

Table II: Post-operative data

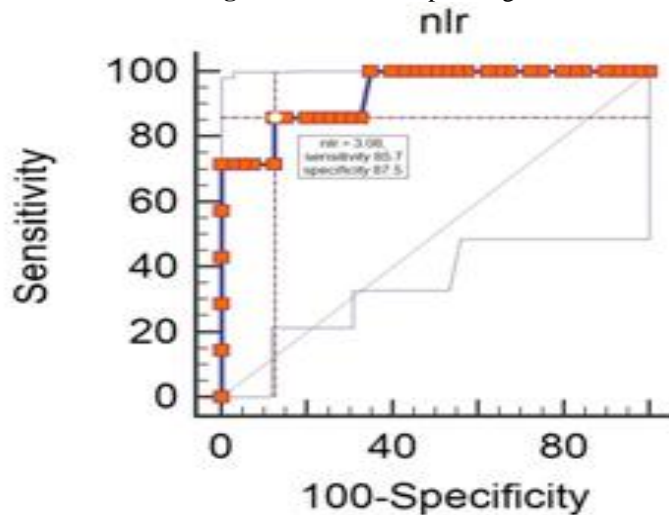
Table I Pre-Operative data

	total n= 47	less than 3 n=36	more than 3 n=11	P value
Age (years)	38.85	37.4	43.08	0.262
Sex				0.2457
men		2	2	
women		33	10	
Procedure	lap 47	lap 35	lap 12	
Total Leucocyte Count (x 10 ⁹ per L)	7.69	7.33	8.73	0.0762
History of Previous surgery	14	10	4	0.7929
Contents of Gall Bladder	stones	stones	stones	
Presenting symptoms				
pain	45	34	11	0.4224
indigestion	23	17	6	0.9326
nausea	2	2	0	0.4025
vomitting	7	7	0	0.0966
fever	1	0	1	0.0877
Follow up case of pancreatitis	2	1	1	0.4224

Table II Post-operative data

	total n= 47	less than 3 n=36	more than 3 n=11	P value
Severity		1	6	0.0001
conversion	3	1	2	0.0948
operating time	69.617	63.657	87	<0.0001
drain placement	47	35	12	
post-operative complications	nil	nil	nil	
length of stay	6.1915	5.25	6.5143	0.1728
post-operative length of stay (days)	2.3191	2.1143	3	0.0152

Figure I: Receiver Operating Curve



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