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Neutrophil-to-lymphocyte ratio in diagnosing acute cholecystitis: A retrospective cohort study

Balakrishna TV[1*], Abhilash TSV[2]
[1] Professor, GSL medical college, Rajahmundry, Andhra Pradesh, India
[2] Senior Resident, Kusuma hospital, Kakinada, Andhra Pradesh, India

Abstract
Introduction: Acute cholecystitis accounts for most of the hospital admissions related to gastrointestinal diseases. In approximately 90% of patients, inflammation develops due to obstruction of the cystic duct by one or more gall-tones. Delayed management can lead to increased morbidity, due to progression to severe cholecystitis, such as gangrenous change, abscess formation, and gallbladder perforation. The Neutrophil-to-Lymphocyte ratio is derived from the counts of circulating neutrophils and lymphocytes, both of which are major leukocyte subpopulations. The inflammation-triggered release of arachidonic acid metabolites and platelet-activating factors results in neutrophilia, and cortisol-induced stress results in relative lymphopenia, and thus, the Neutrophil-to-Lymphocyte ratio accurately represents the underlying inflammatory process.
Objectives: 1. To evaluate the utility of the Neutrophil-to-Lymphocyte ratio (NLR) as a prognostic indicator in patients with cholecystitis
2. To identify a relevant NLR value that discriminates between simple and severe cholecystitis.
Materials and methods: A retrospective analysis of patient data compiled by assessment of operative findings documented and patient follow up recorded over the period encompassing ten years (2019-2010) at Kusuma Hospital, Kakinada.
Results: Our study population comprised of 359 patients with simple cholecystitis (69.63%) and 109 patients with severe cholecystitis (30.36%). The NLR of 3.0 could predict severe cholecystitis with 70.5% sensitivity and 70.0% specificity. A higher NLR (≥3.0) was significantly associated with older age (p =0.001), male gender (p =0.001), admission via the emergency department (p <0.001), longer operation time (p <0.001), higher incidence of postoperative complications (p =0.056), and prolonged length of hospital stay (LOS) (p <0.001).
Conclusion: NLR ≥3.0 was significantly associated with severe cholecystitis and prolonged LOS in patients undergoing cholecystectomy. Therefore, preoperative NLR in patients undergoing cholecystitis due to cholecystitis seemed to be a useful surrogate marker for severe cholecystitis.

Keywords: NLR; Cholecystitis.

1. Introduction

Acute cholecystitis is one of the most common conditions requiring an emergency care [1]. In majority of patients, inflammation develops due to obstruction of the cystic duct by gallstones [2]. Delayed management can worsen the condition leading to increased morbidity, due to progression to severe cholecystitis, such as gangrenous changes, abscess formation, gallbladder perforation, etc [3,4]. Diagnosis in patients with severe cholecystitis is often tough to establish both clinically and radiologically, since the clinical manifestations can vary, and imaging studies are often equivocal [5]. However, marked contrasts in the morbidity and mortality rates have been observed between patients with simple cholecystitis and severe cholecystitis [3,6]. Therefore, accurate detection and proper management of patients who are at risk of developing severe cholecystitis is very much essential in preventing associated complications.

To predict the prognosis of inflammatory conditions, several scores have been suggested, including the neutrophil-to-lymphocyte ratio (NLR), Modified Glasgow Prognostic Score, platelet-to-lymphocyte ratio, etc [7,8]. Of these, the NLR received greater importance, since it is simple to calculate, and involves no additional cost, as it uses results from a standard complete blood counts. The NLR is derived from the ratios of counts of circulating neutrophils and lymphocytes, both of which are major leukocyte subpopulations. Inflammation usually triggers the release of arachidonic acid metabolites and platelet-activating factors which results in Neutrophilia. Simultaneously cortisol-induced stress results in relative Lymphopenia, and thus, the NLR accurately represents the ongoing inflammatory process [9]. The aim of the present study is to evaluate the utility of the NLR as a prognostic indicator in patients with cholecystitis, and to identify a relevant ratio value that discriminates between simple and severe cholecystitis.

Materials and Methods

A retrospective analysis of patient data compiled by assessment of operative findings documented and patient follow up recorded over the period encompassing ten years (2019-2010) at Kusuma Hospital, Kakinada. During the study period, 399 cholecystectomies were performed, majority of which were done through laparoscopic approach. To identify gallbladder inflammation, we only selected 371 patients in whom the pathology reports indicated the presence of cholecystitis. Finally, a total of 359 patients were selected for inclusion in this study. Each patient's NLR was calculated at admission time.

Terminology and Definitions

Cholecystitis is usually defined by a histological finding of inflammatory infiltrate of the gallbladder wall. Severe

cholecystitis is defined as cholecystitis complicated by secondary changes, which include haemorrhage, gangrenous changes, emphysema, or perforation, etc and/or when the pathological examination indicated Xantho-granulomatous cholecystitis.

Statistical analysis

Data were described as means ± standard deviations, or as medians and ranges. Continuous variables were compared using the independent t-test, while categorical variables were compared using the chi-squared test. Multiple regression analyses were performed using a proportional hazards model to identify factors independently associated with the LOS greater than the 80th percentile after cholecystectomy, and to estimate corresponding odds ratio (OR) in 95% confidence intervals (CI). Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL). Statistical significance was accepted for P-values less than 0.05.

Results

A total of 359 patients who underwent cholecystectomy owing to symptoms of cholecystitis during the study period were included. The median age was 55.2 (13 – 91) years, and the patients comprised 165 women (45.96%) and 194 men (54.03%).

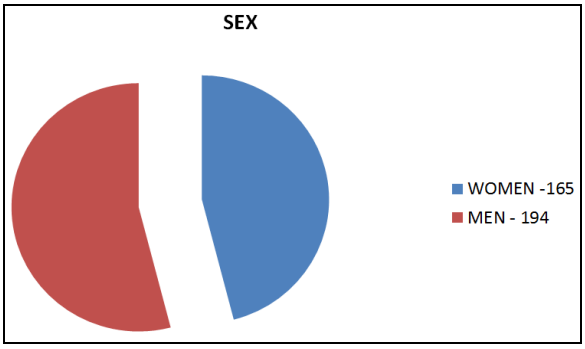

Fig 1: Sex Ratio

Of these, 294 patients (81.89%) exhibited calculous cholecystitis and 65 patients(18.1%) exhibited acalculous cholecystitis.

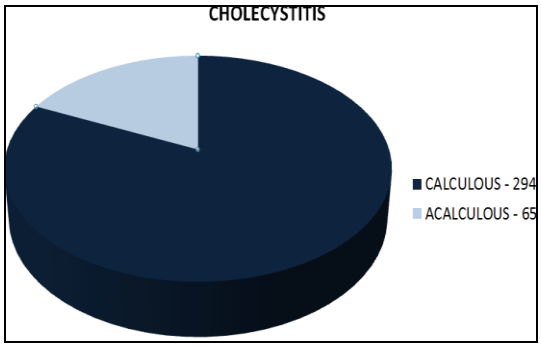

Fig 2: Presence of Calculus

Pathologic examination confirmed the presence of simple cholecystitis in 298 patients (83%) and severe cholecystitis in 61 patients (16.99%). Regarding the admission, 283 patients (78.83%) were admitted via the emergency department (ED) and 76 (21.16%) via the outpatient clinic.

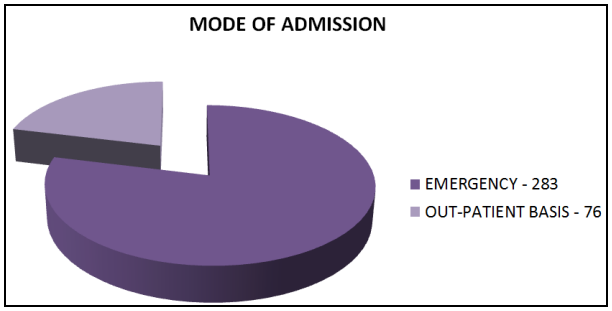

Fig 3: Mode of Admission

An ROC curve was established to determine the cut-off value for preoperative NLR, which could discriminate between simple and severe cholecystitis.

The ROC area under the curve was 0.775. With an NLR value of 3.090, the sensitivity and specificity values were 70.5% and 70.0%, respectively. Therefore, we considered 3.0 as the cut-off value, and divided the patient population into two groups: those with preoperative NLR values less than 3.0 (n =216) and those with NLR values equal to or greater than 3.0 (n =143). When comparing preoperative variables, the two groups showed significant differences in age, sex, severity of cholecystitis, serum leukocyte count, presenting symptoms and admission route. The higher NLR (NLR ≥3) group included more patients who had advanced age (p =0.001), more number of males(p =0.001), with severe cholecystitis (p <0.001) and with higher leukocyte count (p <0.001).

Discussion

Severe cholecystitis is associated with more adverse clinical features than simple cholecystitis. So, prompt detection of the severe cholecystitis and intervention before its further advancement is essential to avoid complications. These patients are at an increased risk of injury to the biliary ducts, injury to the right hepatic artery during surgery, etc [10].

In the current study, we elicited that a preoperative NLR of 3.0 has the usefulness to differentiate between simple and severe cholecystitis. Therefore, in patients whom the CT findings are ambiguous and are at a risk of progressing from simple to severe cholecystitis, NLR could be used to determine surgical priority. Patients with inflammatory and other associated malignant conditions usually present with elevated NLR as a manifestation of the systemic response. The underlying molecular basis of NLR has found that there is an elevation in the levels of pro-inflammatory cytokines (e.g., IL-1ra, IL-6, IL-7, IL-8, IL-12) in the plasma of these patients [11-13]. Moreover, high peritumoral infiltration of macrophages was observed in cancer patients with elevated NLR [12]. Therefore, elevated NLR appears to be a good indicator of up-regulation of the innate immune response. The representative forms of severe cholecystitis are gangrenous cholecystitis and gallbladder perforation. Gangrenous cholecystitis occurs in up to 30-35% of patients with cholecystitis [5]. This occurs because the inflammation causes interruption of blood flow to the gallbladder which results in gangrenous changes. The mortality rate was reported to be up to 22% in these patients, and it is directly related to other severe complications, such as gallbladder perforation, abscess formation, peritonitis, etc [14]. This study shows the usefulness of preoperative NLR in

predicting the prognosis and in determining the operative priority in patients with cholecystitis. Patients with severe cholecystitis have higher incidences of postoperative complications and a prolonged length of hospital stay (LOS) [16-19]. Early cholecystectomy showed decrease LOS in patients with acute severe cholecystitis [20]. Therefore, NLR helps in prioritizing the patients for surgery thus reducing the post-opearative morbidity and LOS. Similarly, operation time was prolonged in the high NLR group than in the low NLR group. Here, we determined the cut-off value of severe cholecystitis as 3.0 based on the ROC curve analysis. This NLR value of 3.0 had an acceptable reliability in the analysis (70.6% sensitivity and a specificity of 70.1%). Therefore, we believe that the NLR cut-off value of 3.0 is suitable and consistent [27-30]. However, further study is required to validate the cut-off value and to more precisely identify an optimal NLR with the perfect and suitable prognostic power in cholecystitis. There are few limitations of this study; most of those common to all database research. This study involves a retrospective review of prospectively collective data. Thus, these results should be confirmed by prospective trials. Moreover, patient distribution was not well-balanced according to the NLR cut-off value. In addition, the incidence of acalculous cholecystitis herein is more (18.1%) which did not fall within the general range of 2% to 15% as noted by other studies. Acute acalculous cholecystitis has generally shown poor prognosis than acute calculous cholecystitis.

Conclusions

Routine preoperative NLR calculation in patients with cholecystitis not only provided a simple means of identifying patients with severe cholecystitis, but also served as a surrogate marker for predicting prolonged LOS. It was found that the patients with cholecystitis could be divided into low risk group for severe cholecystitis (NLR <3.0) and high risk group for severe cholecystitis (NLR ≥3.0) according to the NLR value at the time of admission. This kind of approach of determining the operative priority based on the NLR value is expected to induce a good surgical outcome by prioritising the sickest to be treated first principle and enabling proper perioperative management.

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