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PROGNOSTIC VALUE OF PREOPERATIVE NEUTROPHIL-TO-LYMPHOCYTE RATIO FOR PREDICTION OF SEVERE CHOLECYSTITIS

PROGNOSTIČKA VREDNOST PREOPERATIVNOG ODNOSA NEUTROFILA I LIMFOCITA ZA PREDVIĐANJE TEŠKOG HOLECISTITISA

Dušan Micić[1,2], Sanja Stanković[3], Nebojša Lalić[1,4], Vladimir Đukić[1,2], Snežana Polovina[4]

[1]Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[2]Clinic for Emergency Surgery, Emergency Center, Clinical Center of Serbia, Belgrade, Serbia
[3]Center for Medical Biochemistry, Clinical Center of Serbia, Belgrade, Serbia
[4]Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Clinical Center of Serbia, Belgrade, Serbia

Summary

Background: The predictive value of preoperative neutrophil-to-lymphocyte ratio (NLR) in patients with cholecystitis has not been established. The aim of this study was to investigate preoperative NLR in patients with cholecystitis and to identify a relevant NLR value that discriminates between simple and severe cholecystitis.
Methods: This study included 136 patients who underwent laparoscopic cholecystectomy due to cholecystitis. The Receiver Operating Characteristic (ROC) analysis was performed to identify the most useful NLR cut-off value in relation to the severity of cholecystitis. The patients were divided into two groups according to the cut-off NLR value: high NLR group (≥4.18, n=23) and low NLR group (<4.18, n=113). Severe cholecystitis was defined as a state which includes inflammation, empyema, gangrene, perforation of gallbladder, adhesions or difficulty in dissecting Calot's triangle.
Results: In the high NLR group, severe cholecystitis ($p<0.0001$) and higher C-reactive protein level (CRP) and white blood cells count (WBC) ($p<0.0001$) were significantly more frequent. There was no difference in homeostatic model assessment-insulin resistance index (HOMA-IR) between both groups before the operation ($p<0.634$). The incidence of severe cholecystitis was 16.9%. The NLR of 4.18 could predict severe cholecystitis with 78.3% sensitivity and 74.3% specificity. Spearman's correlation revealed significant association between the preoperative NLR and HOMA-IR on day 1, ($r=0.254$, $p=0.030$) and between preoperative NLR and CRP on day 1 ($\rho=0.355$; $p<0.0001$).

Kratak sadržaj

Uvod: Prediktivna vrednost preoperativnog odnosa neutrofila i limfocita (NLR) kod pacijenata sa holecistitisom nije utvrđena. Cilj ove studije je bio da se ispita preoperativni NLR kod pacijenata sa holecistitisom i da se identifikuje relevantna vrednost NLR koja vrši diskriminaciju između jednostavnog i teškog holecistitisa.
Metode: U ovoj studiji je učestvovalo 136 pacijenata kod kojih je učinjena laparoskopska holecistektomija zbog holecistitisa. ROC analiza je izvršena da bi se identifikovala najkorisnija NLR vrednost koja definiše težinu holecistitisa. Pacijenti su podeljeni u dve grupe u skladu sa graničnim vrednostima NLR: grupa sa visokim NLR (≥4,18, n=23) i grupa sa niskim NLR (<4,18, n=113). Težak holecistitis je definisan kao stanje koje uključuje upalu, empijem, gangrenu, perforaciju žučne kese, adhezije ili poteškoće pri preparisanju elemenata Kalotovog trougla.
Rezultati: Grupa sa visokim NLR imala je znatno češće težak holecistitis ($p<0,0001$) i veći nivo C-reaktivnog proteina (CRP) i broj belih krvnih zrnaca ($p<0,0001$). Nije bilo statistički značajne razlike u HOMA-IR između obe grupe pre operacije ($p=0,634$). Incidenca teškog holecistitisa iznosila je 16,9%. NLR od 4,18 može predvideti težak holecistitis sa 78,3% osetljivosti i 74,3% specifičnosti. Spearmanova korelacija je otkrila značajnu povezanost preoperativnog NLR i HOMA-IR prvog postoperativnog dana ($\rho=0,254$; $p=0,030$) i između preoperativnog NLR i CRP-a u prvom postoperativnom danu ($\rho=0,355$; $p<0,0001$).

Address for correspondence:

Dusan Micić, MD
Clinic for Emergency Surgery, Emergency Center
Clinical Center of Serbia, 11000 Belgrade, Pasterova 2
Phone number: 381 11 366 22253
Fax number: 381 11 366 22 57
e-mail: ducamicic@yahoo.com

List of abbreviations: AC, acute cholecystitis; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment, Insulin Resistance; ROC, receiver operating characteristics; WBC, white blood cells.

Conclusions: NLR ≥4.18 was significantly associated with severe cholecystitis. The preoperative NLR in patients undergoing cholecystectomy due to cholecystitis could be a useful surrogate marker of severe cholecystitis.

Keywords: cholecystitis, inflammatory biomarkers, neutrophil-to-lymphocyte ratio, prognosis

Zaključak: NLR≥4,18 je značajno povezan sa teškim holecistitisom. Preoperativni NLR kod pacijenata koji će biti holecistektomisani zbog holecistitisa može biti surogatni marker teškog holecistitisa.

Ključne reči: holecistitis, biomarkeri zapaljenja, odnos neutrofila i limfocita, prognoza

Introduction

Acute cholecystitis (AC) is one of the most common gastrointestinal diseases which require hospitalization and surgical treatment. According to Tokyo guidelines from 2007, updated in 2013, acute cholecystitis is defined by right upper quadrant pain, presence of resistance and Murphy's sign, fever, elevated white blood cell count (WBC) and C-reactive protein (CRP) (1).

Inflammation in the biliary system develops due to obstruction of the bile duct by gallstones. Delay in surgical treatment can lead to progression to severe or gangrenous cholecystitis and gallbladder perforation. Neutrophil-to-lymphocyte ratio (NLR) calculated by dividing the count of neutrophils by the count of lymphocytes was proposed as a biomarker for systemic inflammation and stress (2). Different acute inflammatory diseases like appendicitis, abscesses, septic shock are followed by increased NLR, also seen in critically ill trauma patients. Recently, it was suggested that NLR can be considered as a potential inflammatory biomarker for AC (1).

Inflammatory response during the operation leads to impaired insulin sensitivity. Insulin sensitivity can be measured by the hyperinsulinemic euglycemic clamp. This method is highly specific and sensitive for insulin sensitivity, but at the same time, it is an expensive diagnostic procedure. On the other hand, measurement of insulin resistance using homeostatic model assessment-insulin resistance (HOMA-IR) has the same diagnostic value, and it is much simpler and cheaper. Positive correlation between HOMA-IR and CRP concentration and the severity of inflammatory response was reported in several studies (3–7). It was also demonstrated that postoperative insulin resistance is a temporary phenomenon for at least five days after uncomplicated cholecystectomy, particularly after an open approach (8).

CRP as an independent, nonspecific systemic marker for inflammation correlates with severity of surgical trauma, infection and inflammation. In the postoperative period, CRP becomes a sensitive marker for postoperative complications, especially in elderly (9).

Therapeutic management depends on the severity of AC and physiological state of patients (10). Severe cholecystitis was defined as a state which includes inflammation, empyema, gangrene, perforation of gallbladder, adhesions or difficulty in dissecting Calot's triangle (11). Previously proposed white blood cell count (WBC) and CRP as indicators of severity of acute cholecystitis are insufficient because in some patients those parameters can be within a normal reference range. In some studies, it was suggested that raised NLR can be associated with severity of cholecystitis and prolonged hospitalization after surgery (1, 2, 12–14).

Laparoscopic cholecystectomy is the first line treatment for gallbladder stone disease with many advantages in comparison with the open approach. The main advantage regarding laparoscopic cholecystectomy is reduced trauma with lower physical stress. (15).

The aim of this study was to determine preoperative NLR in patients with cholecystitis and to identify a relevant NLR value that discriminates between simple and severe cholecystitis. At the same time, the association of severity of acute cholecystitis with changes in NLR, CRP and HOMA-IR during postoperative follow-up was investigated in patients after laparoscopic cholecystectomy.

Materials and Methods

The non-randomized, prospective study on 136 patients with laparoscopic cholecystectomy was con-

Table I Baseline characteristics of the studied population.

Variable	LC Group (n=136)
Age*, yrs	53.41±14.14
Male sex, n (%)	79 (58.1)
BMI*, kg/m2	25.1±1.31
Glucose*, mmol/L	5.0±1.82
Insulin**, mU/mL	6.95 (3.91–11.10)
HOMA-IR**	1.4 (0.80–2.40)
CRP**, mg/L	8.0 (2.17–13.77)
WBC *,109/L	8.75±3.39
Neu*,109/L	6.33±3.36
Ly*,109/L	1.72±0.73
Simple cholecystitis, n (%)	113 (83.1)
Severe cholecystitis, n (%)	23 (16.9)

LC – laparoscopic cholecystectomy, BMI – body mass index; HOMA-IR – homeostatic model assessment-insulin resistance; CRP – C-reactive protein level; WBC – white blood cells; Neu – neutrophils, Ly – lymphocytes.
* Data are presented as mean ± standard deviation.
**Data are presented as median with interquartile range.

ducted in the Clinic for Emergency Surgery of the Clinical Center of Serbia in Belgrade, after getting approval of the Ethical Committee of the Faculty of Medicine, University of Belgrade. Study was conducted according to the Helsinki Declaration and each patient gave written informed consent to participate in the study. Inclusion criteria were: patients undergoing laparoscopic cholecystectomy. Exclusion criteria were: known diabetes Type I or II, liver, renal (serum creatinine over 150 μmol/L) or heart failure, malignancy, severe infection and mental disease. All the participants were operated in the period between 2012 and 2016, and divided in groups according to the severity of acute cholecystitis. Baseline characteristics of all participants are presented in *Table I*.

Fasting glucose, insulin, CRP, white cells count (neutrophil-to-lymphocyte ratio) were determined before operation (baseline, day 0) and on days 1 and 3 after the operation. Glucose was measured using a commercial assay on a Roche Cobas 6000 automated analyzer (Roche Diagnostics, Manheim, Germany). Reference range for glucose was 3.9–6.1 mmol/L. The serum C-reactive protein (CRP) concentration was measured using commercial assays on a Roche Cobas 6000 automated analyzer. Reference range for CRP was 0–10 mg/L. The serum insulin measurement was done by an electrochemiluminescence immunoassay on a Roche Cobas 6000 automated analyzer. Insulin assay has a measurement range of 0.20–1000 μU/mL with a limit of detection of 0.20 μU/mL. The validation of the Roche Insulin assay in our laboratory revealed intra- and inter-assay coefficients of variation between 1.0% and 4.5%. Reference value for fasting insulin was < 25 μU/L. Homeostatic model assessment-insulin resistance (HOMA-IR) is based on fasting glucose and insulin levels and the index is calculated as follows: HOMA-IR = Go × Io /22.5, where Go = fasting glucose concentration (mmol/L), Io = fasting plasma insulin concentration (μU/mL) (16). EDTA-anti-coagulated whole blood samples were used to measure cell blood count by employing a newer generation automated hematology analyzer, XN-1000 (Sysmex).

With the XN-1000 analyzer (Sysmex, Kobe, Japan), a new technology has been introduced for the determination of the white blood cell (WBC) differential. This analyzer uses three new channels, white cell differential (WDF), white cell nucleated (WNR), and white cell precursor (WPC) channels, with optimized separation of the cell populations, and a systematic nucleated red blood cell (NRBC) count. The blood cells are analyzed by flow cytometry-based optical measurement, after red cell and platelet lysis, membrane permeabilization of the leukocytes, and introduction of a fluorochrome which binds to leukocyte and NRBC nucleic acids. Scattergrams are generated after tridimensional analysis of each cell signal according to cell volume, cell structure, and cell fluorescence. The WNR channel evaluates the leukocyte and basophil counts and provides a systematic NRBC count. The WDF channel provides a count of the neutrophils, lymphocytes, eosinophils, monocytes, immature granulocytes, and a high-fluorescence lymphocyte count.

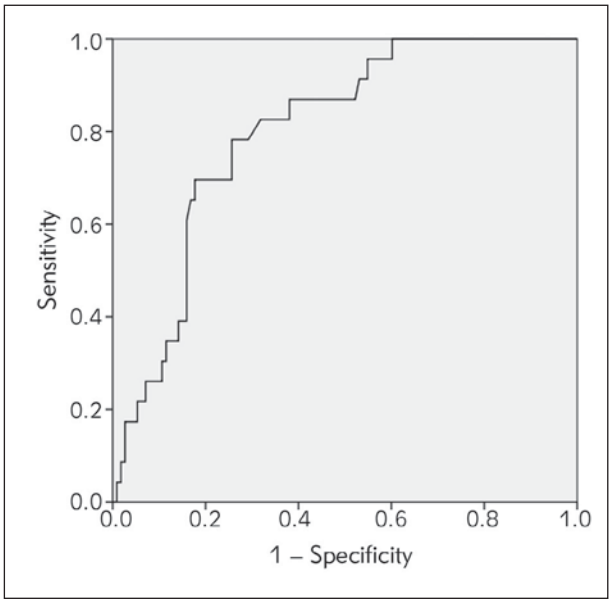

Figure 1 Receiver operating characteristic (ROC) curve for predicting severe cholecystitis.

The area under the curve was 0.801 (95% CI 0.717–0.886, p<0.0001). When the cut-off level of NLR was 4.18, the sensitivity and specificity were 78.3% and 74.3%, respectively for predicting severe AC.

Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. Data for continuous variables were expressed as mean ± standard deviation (SD) and comparisons between groups were performed with Student's t-test. Non-normally distributed data were presented as median and interquartile range (25^{th}, 75^{th} percentile) and compared by Mann-Whitney U-test. Categorical data were shown as frequencies and percentages. Correlations between the examined variables were determined by Spearman correlation. The Receiver Operating Characteristics (ROC) curve was used to determine the best NLR cut-off value for prediction of severe AC. A value of $p < 0.05$ was considered as significant. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 21 (SPSS, Inc., Chicago, Illinois).

Results

A total of 136 patients with symptomatic cholecystitis who underwent laparoscopic cholecystectomy during the study period were included in the study. The median age was 53.41±14.14; 57 were women (41.9%) and 79 were men (58.1%). Physical examination and intraoperative findings confirmed simple

Table II Preoperative characteristics of patients who underwent cholecystectomy due to cholecystitis grouped by NLR.

Variable	NLR<4.18 (N=113)	NLR≥4.18 (N=23)	p
Age*, yrs	52.79±12.395	54.19±17.04	0.417
Male sex, n (%)	66 (58.4)	13 (57.4)	0.912
BMI*, kg/m^2	25.4±1.37	24.89±1.12	0.093
Illness severity, (%)	5.6	38.3	<0.0001
Glucose*, mmol/L	4.98±1.47	5.06±2.38	0.802
Insulin**, mU/mL	7.00 (4.55–11.20)	5.90 (3.42–10.80)	0.787
HOMA-IR**	1.40 (0.80–2.40)	1.30 (0.70–2.40)	0.634
CRP**, mg/L	7.00 (2.00–8.25)	11.30 (4.00–65.10)	<0.0001
WBC*,10^9/L	7.49±1.99	11.14±4.17	<0.0001
Neu*,10^9/L	4.78±1.57	9.28±3.87	<0.0001
Ly*,10^9/L	2.05±0.60	1.09±0.50	<0.0001

BMI – body mass index; HOMA-IR – homeostatic model assessment-insulin resistance; CRP – C-reactive protein level; WBC – white blood cells; Neu – neutrophils, Ly – lymphocytes.
* Data are presented as mean ± standard deviation; **data are presented as median with interquartile range.

cholecystitis in 113 patients (83.1%) and severe cholecystitis in 23 patients (16.9%) (*Table I*).

In order to determine the cut off value for NLR to discriminate simple from severe cholecystitis, receiver operating characteristics (ROC) curve was established. The area under the curve was 0.801 (95% CI 0.717–0.886, p<0.0001). With an NLR value of 4.18, the sensitivity was 78.3% and specificity 74.3%, respectively (*Figure 1*). Therefore, we defined 4.18 as the cut-off value and divided the patients in two groups: the group with preoperative NLR < 4.18 (n=113) and the group with preoperative NLR ≥ 4.18 (n=23). There was no significant difference in age (p=0.417), BMI (p=0.093), and sex (p=0.912). Statistically significant difference (p<0.0001) in severity of illness was found between the groups. Also, significant difference was found in the baseline CRP (p<0.0001), WBC (p<0.0001), and neutrophil levels counts (p<0.0001). Lymphocytes were significantly higher in the lower NLR group (p<0.0001) than in the higher NLR group. There were no significant differences in the baseline value of glucose (p=0.802), insulin (p=0.782) and HOMA-IR (p=0.634) between high and low NLR groups (*Table II*).

CRP on the first postoperative day was significantly higher in the higher NLR compared with the lower NLR group (22.30 (9.29–50.45) mg/L vs. 62.9 (33.8–127.4 mg/L)) (P<0.001). The same trend was noticed for HOMA-IR but the difference was borderline significant (p=0.05). HOMA-IR on the first postoperative day in the higher NLR group was 3.64 (2.20–6.92) and in the lower NLR group 2.40 (1.30–4.10).

Spearman's correlation revealed significant association between the preoperative NLR and HOMA-IR on day 1 (r=0.254, p=0.030), and between preoperative NLR and CRP on day 1 (r=0.355; p<0.0001). There was also a correlation between preoperative NLR and severity of AC on day 1 (r=0.991; p<0.0001).

Discussion

Surgical tissue trauma induces an inflammatory and metabolic response. Reaction of the body to tissue damage depends on the magnitude of surgical trauma (17). Severe AC is followed with more complications than simple AC and early detection of severe AC is important in order to avoid perioperative inflammatory and metabolic complications and longer hospitalization. Usual visualization diagnostic procedures such as ultrasound or computed tomography are not sensitive enough in the detection of severe AC (12). There are some data that some biochemical markers could be useful as predictors of severity of AC.

It is very well known that hematological and biochemical predictors of severe inflammation are C-reactive protein, white cell count, and the platelet-to-lymphocyte ratio. The number of white blood cells is an inexpensive and good indicator of inflammation but, unfortunately, could not assess the clinical severity of disease (11). White blood cells subtypes follow various inflammatory reactions of the body. Recently, neutrophilia and relative lymphopenia were proposed as predictors of mortality in patients with heart failure, but could also be successful indicators in the determination between simple and severe acute cholecystitis

(1, 13, 14). NLR represents a combination of two markers where neutrophils are the active non-inflammatory mediator initiating the first line of defense, whereas lymphocytes represent the regulatory or protective component of inflammation (18, 19). Inflammation enhances the release of arachidonic acid metabolites and factors for platelet activation which leads to neutrophilia and relative lymphopenia due to cortisol induced stress (20). The NLR is an easy and inexpensive marker which can be calculated from routinely determined cell blood counts. Determining the NLR is more accurate at predicting poor postoperative outcomes than measuring each of white blood cells subgroups individually (21).

Power of NLR for diagnosing simple AC is higher than white blood cell count but equal as CRP, and at the same time this marker is more powerful for severe AC than WBC and CRP (1). In our study, cut-off value of NLR in predicting severe AC was > 4.18 with 78.3% sensitivity and 74.3% specificity. Similar results have been published by the authors of a study which aimed to define more powerful predictors for severe AC. They demonstrated that a cut-off for NLR of 4.17 was predictive for severe AC (1). Some authors have published data regarding the association of NLR and right iliac fossa pain, in the definition of gangrenous appendicitis as well as in patients at increased risk for sepsis (22, 23). In our group with severe AC, we detected higher CRP, WBC and neutrophils than in the group with simple AC. This finding is comparable with the results of the study performed by Beliaev et al. in which patients with AC had raised NLR due to neutrophilia per se or accompanied with lymphopenia (1).

Tissue injury during the surgery induces a stress response that is followed with insulin resistance as a part of the metabolic response to stress (24, 25). Sato et al. calculated that a decrease in insulin sensitivity of 1 mg/kg/minute increased the incidence rates of major complications (OR 2.23), minor infections (OR 1.99) and severe infections (OR 4.98) (26). Perioperative starvation as well as release of stress hormones and inflammatory markers leads to insulin resistance which is associated with postoperative complications and longer hospital stay (25, 26). The exact molecular action that is related to development of insulin resistance is not yet quite understood, but there are studies which have confirmed the relationship between systemic inflammation and insulin resistance. It was proposed that NLR may be used as a simple clinical indicator of insulin resistance, which is more sensitive than neutrophilic granulocyte count and CRP levels in the assessment of insulin resistance (28). Our results confirm this proposal, since we found a positive correlation between NLR and HOMA-IR among our patients on day 1 after the operation. From the clinical point of view, previous investigations have shown that administration of oral carbohydrate supplementation before the surgery resulted in a decrease in postoperative HOMA-IR and therefore lower risk for early postoperative complications (29).

Different results concerning postoperative levels of CRP were reported, favoring the laparoscopic approach over open surgery (30). CRP was superior to white cell count in predicting acute cholecystitis except in the case of pericholecystitis abscesses and biliary peritonitis due to gallbladder perforations when CRP and WBC performed equally well (14). Our results indicate that the level of CRP increased significantly on day 1 postoperatively both in low and high NLR groups compared with day 0, but a significantly higher increase in CRP was established in the severe AC group. This result is consistent with the findings of other investigators and supports the assumption that minimally invasive surgical procedures such as laparoscopic cholecystectomy impair inflammatory response less (31). In our investigation, we have found a positive correlation between CRP and NLR. The other authors have shown higher diagnostic power of NLR than CRP, WBC and neutrophils for predicting emergency operation in acute appendicitis (19).

The limitations of our study could be the missing data regarding preoperative anti-inflammatory therapy.

Conclusion

This study demonstrated that NLR ≥ 4.18 was significantly associated with severe cholecystitis. The preoperative NLR in patients undergoing cholecystectomy due to cholecystitis could be a useful surrogate marker of severe cholecystitis. The association between the preoperative NLR and HOMA-IR and CRP on day 1 may be helpful in the prediction of impaired insulin sensitivity with higher possibility of perioperative complications.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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