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Original article

The Relationship between Neutrophil-Lymphocyte Ratio and Clinal Laboratory Data in Acute Pancreatitis

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SUMMARY

Introduction: Neutrophil-lymphocyte ratio (NLR) is one of the laboratory biomarkers used in clinical practice to predict severity and mortality of acute pancreatitis (AP), however, there is currently insufficient information about the changes of NLR in the dynamics in relationship with other clinical and laboratory data.
Aims: To assess the relationship between NLR values and other demographics, clinical and simple laboratory data in patients with acute pancreatitis.
Methods: The data of two hundred twenty-nine patients with AP were analyzed. All patients were divided into two groups: the group with a positive outcome and the group with a fatal outcome. NLR was counted on the 1st, 3rd and 5th day after admission in each group. The dynamics of NLR index by groups and days, as well as its correlation with other 18 simple laboratory parameters were evaluated.
Results: The level of NLR rate itself was significantly higher on the 1st, 3rd and 5th day in the group with the fatal result compared with the group with the positive result ($p < 0.05$). In patients with AP with the positive result of treatment, there was a gradual decrease in the rate between the 1st and the 3rd day (-21.8%) ($p < 0.05$). The overall dynamics of the indicator between the 1st and the 5th day was -21.5%. In contrast to the group of patients with the fatal outcome, despite the infusion therapy, there was an increase in NLR rate between the 1st and 3rd day of +15.7%. The overall dynamics between the 1st and 5th day was -34.0%. A significant negative relationship of the Spearman's rank correlation coefficient between NLR on the 1st and 3rd day with the fatal outcome was revealed. The highest reliability of this indicator was found on the 3rd day after admission ($p < 0.0001$). In the group of patients with a positive result, a correlation between NLR on the 1st day and stabs on the 1st day, segmental forms on the 1st day, serum amylase on the 1st day was found. A very high correlation was found with the level of lymphocytes on the 1st day ($rs = -0.98$, $p < 0001$). In the group of patients with the fatal outcome, a statistically significant correlation ($p < 0.05$) of moderate strength was found between the value of NLR and the following indicators: glucose level on the 1st day, total protein on the 5th day, prothrombin index on the 5th day. A high correlation was found with the level of segmental forms on the 1st day ($rs = 0.7$) and a very high correlation with the level of lymphocytes on the 1st day ($rs = -0.99$).
Conclusions: There was a significant increase in NLR on the 1st, 3rd, and 5th day in the group of patients with AP with the fatal outcome compared with the group of patients with AP with the positive result. Elevated NLR levels on the 1st and 3rd day seem to be associated with hospital mortality in patients with AP. No correlation was found between NLR rate and clinical data in the group with fatal outcome. The main indicators among simple laboratory parameters for determining the predictors of lethal outcome in AP in different periods after hospitalization were: the level of blood glucose, lymphocytes, total protein, serum amylase, prothrombin index.

Keywords: **acute pancreatitis, markers, neutrophil-lymphocyte ratio, laboratory parameters**

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INTRODUCTION

The question of finding a universal marker of acute pancreatitis, which is affordable, easy to use and has a high prognostic weight, is relevant in modern surgery (1).

Neutrophil-lymphocyte ratio (NLR) is one of the laboratory biomarkers used in clinical practice to determine severity, extent of inflammation and prognostic prediction of acute pancreatitis (2 - 4). In the treatment of acute abdominal pathology and, in particular, acute pancreatitis, NLR is an affordable and valuable marker that is easy to calculate and has considerable informativeness. A meta-analysis showed that NLR has a moderately high diagnostic value in predicting the severity of acute pancreatitis (5). NLR has also been described as a simple marker that may easily assess the inflammatory condition of a patient and helps to control and prevent complications with late onset in patients with AP (6). The normal NLR values are between 0.78 and 3.53 (7).

NLR is thought to be more sensitive than counting of total white blood cell counts in predicting complications of acute pancreatitis. Thus, in the group of patients with higher NLR, the average number of hospital days was higher, there were much more cases of transfer to ICU (8). In addition, there was a direct correlation between NLR, severity of acute pancreatitis, the risk of multiorgan insufficiency and systemic inflammatory response.

There is evidence of a high correlation between the Ranson scales, APACHE II level of C-reactive protein and NLR. Instead, other authors indicate that NLR, platelets-lymphocytes ratio (PLR), Atlanta, Ranson and C-reactive protein scales are independent predictors of complications (development of necrosis, acute renal failure, sepsis, cholangitis, etc.) and markers of mortality risk (9, 10).

NLR can predict the severity and mortality of AP on admission to the emergency department (11). It has been shown to be a more sensitive marker than platelets-lymphocytes ratio (PLR) and red cell distribution width (RDW) in hypertriglyceride-induced acute pancreatitis (12). Significantly higher sensitivity of NLR in the assessment of mortality risk compared with prognostic nutritional index, lymphocyte – monocyte ratio (LMR) in patients with acute pancreatitis has also been shown (13).

In our study, we aimed to assess whether there was a relationship between NLR values and other demographics, clinical and simple laboratory data in patients with acute pancreatitis, determined on day 1, 3 and 5 after admission.

MATERIALS AND METHODS

Our study is a single-center retrospective study, which was based on the analysis of medical records of patients of the Vinnytsia city clinical emergency hospital. All patients with acute pancreatitis admitted to the department of surgery and intensive care unit from 2018 to 2020 were analyzed. Inclusion criteria were: all cases of abdominal pain combined with increased serum amylase/urine diastase levels (in 3 times and above the upper limit of normal) and appropriate findings on computed tomography or abdominal sonogram according to the criteria recommended in the Atlanta 2012 classification (14). Exclusion criteria were: age up to 18 years, the absence of the above criteria for acute pancreatitis, chronic inflammation of the pancreas.

For all patients, during hospitalization, demographic data (age, sex), clinical and anamnestic data were collected, a comprehensive clinical and laboratory examination was performed, which included laboratory tests, ECG, fibroesophagogastroduodenoscopy, abdominal ultrasound (in some cases CT of abdomen on admission was needed), X-ray of lungs, abdominal X-ray, tests for covid-19, examinations by other specialists, if necessary. Among the clinical and anamnestic data, the time from the onset of the first symptoms to the moment of hospitalization, the form and severity of acute pancreatitis, the genesis of the disease, comorbidities, complications, and type of treatment were analyzed. On the day of admission, 3 and 5 days after admission, 18 routine laboratory parameters were determined in patients: hemoglobin in blood, blood sugar, leucocytes and differential blood count, erythrocytes level, lymphocytes, monocytes, hematocrit, ESR, total protein level, total bilirubin level, serum amylase, urinary diastase, AST, ALT, urea, creatinine, prothrombin index, the neutrophil-leukocyte ratio.

All patients with acute pancreatitis were divided into two groups: the group with a positive treatment outcome and the group with a fatal outcome. NLR was counted on the 1st, 3rd and 5th day after admission in each group. The dynamics of NLR index by groups and by days, as well as its correlation with other laboratory parameters, were evaluated.

For statistical processing, quantitative values were presented as mean ± SD. The reliability of the dynamics of the indicator was calculated by T-test for independent samples. The Spearman's correlation coefficient between NLR on the 1st, 3rd and 5th day after admission and its reliability were determined. Spearman's rank correlation between NLR value, clinical and other laboratory parameters in groups of patients was determined.

RESULTS

For three years, 229 patients with an average age of 48.9 ± 14.9 years were treated at the Vinnytsia city clinical emergency hospital with a diagnosis of acute pancreatitis (AP). Gender distribution of examined patients was: 156 (68.1%) men and 73 (31.9%) women. Among all examined patients, 130 (56.7%) developed a mild form of AP, 99 (43.2%) had moderate and severe forms, with transient or persistent organ failure. The edematous form of AP occurred in 174 (76.0%) patients and necrotizing form in 55 (24%) patients. Alimentary genesis dominated in the structure of acute pancreatitis in 151 (65.9%) patients. Alcohol factor became the cause of AP in 43 (18.8%) cases, biliary genesis in 17 (7.4%), drug-induced genesis in 4 (1.7%), postoperative genesis in 2 (0.9%), post-traumatic in 1 (0.4%), and unclear etiology in 31 (13.5%) cases. Clinically significant concomitant pathology was present in the majority of patients – 194 (84.7%), the structure of which was dominated by pathology of the cardiovascular system. Complications developed in 63 (27.5%) patients. Of these, 13 (5.7%) patients developed early complications, and 20 (8.7%) developed late complications. All patients with AP received infusion therapy. Six (2.6%) patients underwent minimally invasive drainage of fluid collections. Twenty-two (9.6%) patients underwent open surgery. Two hundred and eight (90.8%) patients with AP were discharged from the hospital with a positive treatment result. Twenty-one (9.2%) patients with AP died.

For all patients on the 1st, 3rd and 5th day after admission, standard laboratory parameters were determined and the NLR index was calculated. In the general sample of patients, there was an increased level of the indicator on the 1st day of observation, with its gradual decrease on the 3rd and 5th day. There was a gradual decrease in NLR with unreliable dynamics, which between the 1st and 3rd day was -16.7%, between the 3rd and 5th day -7.6%. At the same time, between the 1st and 5th day there was a significant dynamics of the indicator, which equaled - 22.9% (Figure 1).

In patients with AP with a positive result of treatment on the 3rd day after the admission on the background of infusion therapy, there was a significant decrease in the rate with a dynamics between the 1st and 3rd day (-21.8%). Later, between days 3 and 5, the indicator stabilized at the same level without significant dynamics (+0.34%). The overall dynamics of the indicator between the 1st and 5th day was -21.5% (Figure 2).

In contrast, in the group of patients with fatal outcome, despite the infusion therapy, there was an increase in NLR. The dynamics of the indicator between the 1st and 3rd day of hospital stay was +15.7%, followed by a sharp decrease from the 3rd to the 5th day by -44.4%. The dynamics between the 1st and 5th day was -34.0% (Figure 3).

There was a significant negative relationship of Spearman's rank correlation coefficient between NLR on the 1st and 3rd day with fatal outcomes. On the 1st day after admission, this figure was -0.2, on the 3rd day -0.3. The highest reliability of this indicator was found on the 3rd day of hospital stay ($p < 0.0001$). On the 5th day, the Spearman's rank correlation coefficient between NLR and fatal outcomes was -0.15 with a reliability $p = 0.08$ (Figure 4).

Mild correlation between the value of NLR on the 1st day and the following indicators was found in the group of patients with AP with a positive treatment result during Spearman's rank correlation: stabs neutrophils on the 1st day, segmented neutrophils on the 1st day, serum amylase on the 1st day. A very high correlation was found with the level of lymphocytes on the 1st day ($rs = -0.98$).

In the group of patients with fatal outcome during Spearman's rank correlation for the value of NLR on day 1, a statistically significant correlation ($p < 0.05$) of moderate strength was found between the

Table 1. *Spearman's rank correlation between the value of NLR and other indicators in different groups of patients with AP*

Indicators that were statistically significantly (p < 0.05) correlated	Spearman
Mild course of AP (yes - 1, no - 0)	-0.35
Hospital length of stay	0.35
Edematous type of AP (yes - 1, no - 0)	-0.34
Aseptic necrotic type of AP (yes - 1, no - 0)	0.37
The presence of early complications of AP (yes - 1, no - 0)	0.29
The presence of fluid collections (yes - 1, no - 0)	0.27
The presence of peritonitis (yes - 1, no - 0)	0.14
The presence of pleurisy (yes - 1, no - 0)	0.14
Treatment is open surgery (yes - 1, no - 0)	0.18
Hemoglobin on 1st day, g/L	0.19
Blood sugar level on 1st day, mmol/L	0.24
Leukocytes level on 1st day, $\times 10^9$/L	0.44
Stabs neutrophils level on 1st day, %	0.50
Segmented neutrophils level on 1st day, %	0.50
Lymphocytes level on 1st day, %	-0.98
Total blood bilirubin level on 1st day, micromol/L	0.23
Serum amylase level on 1st day, units/L	0.55
Urinary diastase level on 1st day,units	0.22
Serum urea level on 1st day, mmol/L	0.31
Leukocytes level on 3rd day, $\times 10^9$/L	0.36
Stabs neutrophils level on 3rd day, %	0.39
Lymphocytes level on 3rd day, %	-0.39
Monocytes level on 3rd day, %	-0.20
NLR for 3rd day	0.40
ESR on 3rd day, mm/hour	0.18
Total protein level on 3rd day, g/L	-0.37
Serum urea level on 3rd day, mmol/L	0.18
Prothrombin index on 3rd day, %	-0.29
Leukocytes level on 5th day, $\times 10^9$/L	0.42
Stabs neutrophils level on 5th day, %	0.44
Segmented neutrophils level on 5th day, %	0.21
Lymphocytes level on 5th day, %	-0.40
NLR for 5th day	0.41
ESR on 5th day, mm/hour	0.20
Total protein level on 5thd day, g/L	-0.37
Serum urea level on 5th day, mmol/L	0.24
Prothrombin index on 5th day, %	-0.29
Blood sugar level on 1st day, mmol/L	0.69
Segmented neutrophils level on 1st day, %	0.70
Lymphocytes level on 1st day, %	-0.99
Leukocytes level on 3rd day, $\times 10^9$/L	0.49
Total protein level on 5 th day, g/L	-0.57
Prothrombin index on 5th day, %	-0.59

value of NLR and the following indicators: glucose level on the 1st day, total protein on the 5th day, prothrombin index on the 5th day. High correlation was found with the level of segmented neutrophils on the 1st day (rs = 0.7) and very high with the level of lymphocytes on the 1st day (rs = - 0.99) (Table 1).

DISCUSSION

Acute pancreatitis is a common disease with high mortality up to 17% (15, 16). Many scoring systems, clinical and laboratory markers (17) have been proposed to assess the severity of AP and predict its consequences, most of which allow to assess the severity of the patient after 48 - 72 hours and later after admission (18); they are expensive or difficult to use at the patient's bedside in the admission department (19). That is why the search for simple and rapid prognostic markers of acute pancreatitis continues to this day.

Neutrophil/lymphocyte ratio (NLR) is useful as an indicator of prognosis and survival rate prediction in patients with AP (2). It was found that elevation of the NLR during the first 48 h of admission is significantly associated with severe acute pancreatitis and is an independent negative prognostic indicator in AP (20, 21). In our study, we did not determine a correlation between the value of NLR and the severity of acute pancreatitis, but the analysis of data showed a significantly greater increase in NLR on the 1st day after admission in the group of patients with fatal outcome, among whom all patients had moderate or severe acute pancreatitis, compared with the same indicator in the group of patients with a positive result, most of whom had a mild form of acute pancreatitis: 11.69 ± 5.79 and 7.48 ± 3.42, respectively ($p < 0.05$). There was a large deviation from the mean of the indicators, which can be explained by its large variability in groups.

A significant increase in NLR in the first two days after hospitalization is described in studies by a number of authors. The data we obtained resonates with the data of the authors in which the NLR index determined in the first days after hospitalization gives a reliable relationship with mortality (22). In our study, we determined the relationship of NLR on the 1st, 3rd, 5th days with hospital mortality. We found a significant relationship of Spearman's rank correlation coefficient between NLR on days 1 and 3 in patients with fatal outcomes ($p = 0.003$, $p < 0.0001$). On the 5th day after admission, this indicator lost its reliability ($p = 0.08$).

The NLR rate for the 1st day in the group of patients with positive result of treatment was high, and very high correlation coefficients for indicators of the level of stabs on the 1st day (rs = 0.5), segmental leukocytes (rs = 0.5) on the 1st day, serum amylase level on the 1st day (rs = 0.55) and lymphocyte level on the 1st day (rs = - 0.98) were found. For the NLR rate for the 1st day in the group of patients with fatal outcomes, there was a moderate and high strength of correlation coefficients for the indicator of glucose level on the 1st day (rs = 0.69), segmental leukocytes on the 1st day (rs = 0.70), lymphocytes on the 1st day (rs = - 0.99), total protein on the 5th day (rs = - 0.57), and prothrombin index on the 5th day (rs = - 0.59).

According to our observations, the rate of NLR was significantly correlated with a considerably higher number of clinical and laboratory parameters in the group of patients with a positive treatment result than in the group of patients with a lethal outcome. We can explain this by the fact that the group of patients with fatal outcome was represented by a small sample (n = 21), as a result of which correlations were not found with clinical and most of laboratory parameters. Instead, moderate and high-strength correlations were found in this group with the level of blood glucose on the 1st day, total protein on the 5th day and prothrombin index on the 5th day.

The high strength of correlations in both groups of the NLR rate with the level of lymphocytes and neutrophils, is obligate, because these indicators are "linked" and are used in the mathematical formula to calculate the value of the NLR index. However, analyzing the data obtained, we can assume that the level of lymphocytes in both groups is more informative for predicting mortality in AP than the level of neutrophils.

As a result of our analysis, we can determine the indicators that are informative and will allow to predict changes in the level of NLR in AP in different groups and at different times; in the future, it can be useful for prediction of fatalities in AP.

CONCLUSION

There was a significant increase in NLR on the 1st, 3rd, 5th day in the group of patients with AP with fatal outcome compared with the group of patients

with AP with a positive result. Elevated NLR levels on days 1 and 3 seem to be associated with hospital mortality in patients with AP. Increased levels of NLR on the 1st, 3rd, 5th day were found to be associated with some clinical and laboratory parameters in patients with acute pancreatitis. No correlation was found between NLR rate and clinical data in the group with fatal outcome. The main simple indicators for determining the predictors of lethal outcome in AP in different periods after hospitalization were: the level of blood glucose, lymphocytes, total protein, serum amylase, prothrombin index.

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Korelacija odnosa neutrofila i limfocita i kliničko-laboratorijskih podataka kod akutnog pankreatitisa

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SAŽETAK

Uvod: Odnos neutrofila i limfocita (NLR – eng.) jedan je od laboratorijskih biomarkera koji se koriste u kliničkoj praksi za predviđanje težine akutnog pankreatitisa (AP) i mortaliteta izazvanog ovom bolešću. Međutim, trenutno nema mnogo informacija o promenama odnosa između neutrofila i limfocita u dinamici korelacije sa ostalim kliničkim i laboratorijskim podacima.

Ciljevi. Cilj rada je procena korelacije NLR vrednosti i ostalih demografskih, kliničkih i osnovnih laboratorijskih podataka kod bolesnika sa akutnim pankreatitisom.

Metode. Analizirani su podaci 229 bolesnika sa AP. Svi bolesnici bili su podeljeni u dve grupe: grupu sa pozitivnim ishodom i grupu sa fatalnim ishodom. Vrednosti NLR beležene su prvog, trećeg i petog dana nakon prijema, u svakoj grupi. Procenjena je dinamika NLR indeksa po grupama i danima, kao i korelacija sa osamnaest osnovnih laboratorijskih parametara.

Rezultati. Nivo NLR stope bio je značajno povećan prvog, trećeg i petog dana u grupi bolesnika sa fatalnim ishodom, u poređenju sa grupom bolesnika, kod kojih je rezultat bio pozitivan ($p < 0,05$). Kod bolesnika sa AP sa pozitivnim ishodom lečenja zabeležen je postepeni porast stope u vrednostima prvog, trećeg i petog dana: - 21,8% ($p < 0,05$). Ukupna dinamika indikatora između prvog i petog dana iznosila je - 21,5%. Za razliku od grupe bolesnika sa fatalnim ishodom, uprkos infuzionoj terapiji, zabeležen je porast NLR stope između prvog i trećeg dana od + 15,7%. Ukupna dinamika između prvog i petog dana iznosila je - 34,0%. Utvrđen je značajan negativan odnos Spirmanovog koeficijenta korelacije ranga između vrednosti NLR prvog, trećeg i petog dana kod bolesnika sa fatalnim ishodom. Najveća verovatnoća ovog indikatora zabeležena je trećeg dana nakon prijema ($p < 0,0001$). Kod bolesnika sa pozitivnim ishodom zabeležena je korelacija NLR vrednosti prvog dana i nezrelih neutrofila prvog dana, segmentnih formi prvog dana, kao i vrednosti amilaze u serumu prvog dana. Veoma visoka korelacija zabeležena je za nivo limfocita prvog dana ($rs = - 0,98$, $p < 0001$). U grupi bolesnika sa fatalnim ishodom utvrđena je statistički značajna korelacija ($p < 0,05$) umerene jačine između vrednosti NLR i sledećih indikatora: vrednosti glukoze prvog dana, totalnog proteina petog dana i protrombinskog indeksa petog dana. Visoka korelacija zabeležena je sa nivoom segmentnih formi prvog dana ($rs = 0,7$), kao i visoka korelacija sa nivoom limfocita prvog dana ($rs = - 0,99$).

Zaključak: Zabeležen je značajni porast NLR vrednosti prvog, trećeg i petog dana u grupi bolesnika sa AP sa fatalnim ishodom, u poređenju sa grupom bolesnika sa AP sa pozitivnim ishodom. Povećani nivoi NLR prvog i trećeg dana dovode se u vezu sa bolničkim mortalitetom kod bolesnika sa AP. Nije utvrđena korelacija NLR stope i kliničkih podataka u grupi sa fatalnim ishodom. Glavni indikatori među osnovnim laboratorijskim parametrima za određivanje prediktora letalnog ishoda kod AP u različitim periodima hospitalizacije bili su: nivo glukoze u krvi, limfociti, ukupni proteini, amilaza u serumu i protrombinski indeks.

Ključne reči: **akutni pankreatitis, markeri, odnos između neutrofila i limfocita, laboratorijski parametri**