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ORIGINAL ARTICLE

Utility of hematological parameters in predicting the severity and course of acute gallstone pancreatitis

Hematolojik parametrelerin akut safra taşı pankreatiti şiddeti ve seyrini öngörmede kullanılabilirliği

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ABSTRACT • **Background and Aims:** Acute pancreatitis is a serious disorder which can lead to severe organ failure and mortality. Early predictors of severe disease course is crucial in the decision making process of the healthcare team. Complete blood count, or hemogram, is a commonly used laboratory test in daily clinical practice. The aim of this study is to define a potential predictive biomarker for acute gallstone pancreatitis amongst the parameters evaluated in complete blood count, hence identifying patients with risk of unfavorable outcomes through an easy-to-use serum marker. **Materials and Methods:** 233 acute pancreatitis patients secondary to gallstones were evaluated retrospectively. Patient data was gathered from hospital registry system and patient records recorded prospectively at the time of admission. Hematological parameters were compared with severity scoring systems for acute pancreatitis and disease outcomes. **Results:** White blood cell counts and neutrophil-lymphocyte ratio were correlated with severity scoring systems. Neutrophil-lymphocyte ratio was correlated with a longer hospitalization time and a cut-off point of 5 was found to be useful in predicting disease course. **Conclusion:** Hematological parameters, particularly neutrophil-lymphocyte ratio, are promising predictive biomarkers for acute gallstone pancreatitis severity.

Key words: Acute pancreatitis, hemogram, severity, neutrophil, lymphocyte.

ÖZET • **Giriş ve Amaç:** Akut pankreatit organ yetmezliği ve ölümle sonuçlanabilen ciddi bir hastalıktır. Sağlık ekibinin karar verme sürecinde, hastalığın şiddetli seyredebileceğini öngören parametreler önemlidir. Tam kan sayımı veya hemogram, günlük klinik pratikte sıklıkla kullanılan bir laboratuvar testidir. Bu çalışmanın amacı tam kan sayımı içerisindeki parametrelerin akut safra taşı pankreatiti için tahmin edici bir belirteç olarak kullanılabilirliğini araştırmaktır. Bu sayede hastalık seyrinin kötü olabileceği hastaları öngörebilecek, kolay kullanılabilir bir serum belirtecinin tanımlanması amaçlanmıştır. **Gereç ve Yöntem:** Retrospektif inceleme ile safra taşına ikincil akut pankreatit geçiren hastalar saptanmıştır. Hasta verileri hastaların yatışları esnasında prospektif olarak toplanan hastane ve hasta kayıt verilerinden elde edilmiştir. Hematolojik parametreler akut pankreatit için hastalık şiddeti skorlama sistemleri ve hastalık sonlanım noktaları ile karşılaştırılmıştır. **Bulgular:** Lökosit sayısı ve nötrofil-lenfosit oranı hastalık şiddeti skorlama sistemleri ile korele bulunmuştur. Nötrofil-lenfosit oranı ek olarak uzamış hastane yatışı ile ilişkili bulunmuştur ve eşik değer olarak 5 değerinin hastalık seyrini tahmin ettirmede kullanılabileceği saptanmıştır. **Sonuç:** Hematolojik parametreler ve özellikle nötrofil-lenfosit oran, akut safra taşı pankreatitinin şiddetini öngörmede kullanılabilecek umut vadeden belirteçlerdir.

Anahtar kelimeler: Akut pankreatit, hemogram, şiddet, nötrofil, lenfosit

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INTRODUCTION

Acute pancreatitis (AP) is a complex disorder with a varying clinical picture from mild disease to organ failure and death (1). Leading causes of AP are gallstones and alcohol (2). Early and prompt interventions are crucial in the management of AP since a delay in the treatment process can lead to unfavorable outcomes. Several biomarkers and scoring systems are investigated and used in daily clinical practice to predict patients with a probable severe disease course (3-5).

Complete blood count (CBC), or hemogram, is a commonly utilized laboratory test which consists of patients' hemoglobin, white blood cell and thrombocyte levels and additional information on the morphology and distribution of these cells. Since CBC is a widely-used, easy and quick laboratory test, its utility -with neutrophil-lymphocyte ratio particularly- in predicting disease course and severity has been investigated in a wide array of diseases such as cardiovascular disorders, cancer and also acute pancreatitis (6-8).

With this study, we aimed to investigate the relationship of hematological parameters with disease course and severity in acute gallstone pancreatitis patients to define a possible easy-to-use prognostic marker in this specific subgroup, whom comprise the majority of AP patients.

MATERIALS and METHODS

Study Design and Patient Selection

This study was conducted at Antalya Training and Research Hospital, University of Health Sciences, Antalya, Turkey. Patients hospitalized between 1 January 2021 and 31 December 2023 with a diagnosis of AP secondary to gallstones were involved in the study. AP patients with other underlying etiologies were excluded. Patient data recorded in both the hospital registry system and patient records prospectively at the time of hospitalization were evaluated retrospectively. Patients with the clinical, radiological and laboratory data needed for analysis in the study were included and patients with any missing data for analysis were excluded from the study. Overall, 233 patients were deemed eligible and enrolled in the study.

Data Collection

Study data was gathered retrospectively from hospital registry system and patient records which were recorded at the time of patient's hospitalization prospectively. Age, sex, body-mass index (BMI), smoking status, alcohol consumption, accompanying hypertension and/or diabetes mellitus were recorded. Severity indexes used and included in the study were revised Atlanta classification (RAC), Ranson score, bedside index of severity in acute pancreatitis (BISAP) and CT severity index in acute pancreatitis (CTSI). Out of 233 patients enrolled in the study, 171 patients had been evaluated by computed tomography (CT) scan hence CTSI could be evaluated only in this portion of patients. Study outcomes were designated as hospitalization time, intensive care unit (ICU) admission and mortality. Laboratory parameters included in the study were from the results of the blood sample workout at the time of admission to the hospital. Hematological parameters evaluated in the study were hemoglobin level, white blood cell (WBC) count, neutrophil count, lymphocyte count, neutrophil-lymphocyte ratio (NLR), thrombocyte level, mean platelet volume (MPV), red cell distribution width (RDW). C-reactive protein (CRP) level was also included in the study parameters since it is a widely used laboratory test to evaluate disease severity in acute pancreatitis patients. For statistical analysis purposes, patients were classified into two groups for Ranson score, BISAP, CTSI and hospitalization times.

Statistical Analysis

Categorical variables were presented as the frequency and percentage and continuous variables were presented as the mean (±SD) or median with range. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test normal distribution. Normal distributed variables between two groups were compared with Mann-Whitney U test. Rank correlation between two non-normal distributed variables were analyzed with Pearson correlation coefficient. Non-normal distributed variables between three or more groups were compared with Kruskal Wallis test. Chi-square test, Yates's correction and Fisher's exact test were used to analyze categorical variables. A cut-off value for NLR was determined by reciever operator characteristic (ROC) curve. Level of significance was $p < 0.05$. All statistical analysis was performed using SPSS version 20.0 for Windows (SPSS Inc, Chicago, IL, USA).

Ethics Approval

This study was approved by the Ethics Committee of Antalya Training and Research Hospital, University of Health Sciences (Date: 07/03/2024, No: 2/29). Since this study was a retrospective study, no informed consent was required. The study was conducted in concordance with the Declaration of Helsinki.

RESULTS

The study population consisted of 233 patients. Mean age of the study population was 60.04 (± 17.51) years. One hundred thirty-two patients (56.7%) were female and 101 patients (43.3%) were male. Mean BMI of the study population was 23.2 (± 2.5) kg/m^2. Twenty patients (8.6%) were active smokers and none of the patients declared that they consumed alcohol regularly or recently to their hospital admission. Ninety-five patients (40.8%) had accompanying hypertension whereas 60 patients (25.8%) had accompanying diabetes mellitus.

In terms of scoring systems for AP, more than half (58.4%, n = 136) of the patients were in the mild group for RAC. One hundred forty-eight patients (63.5%) had a Ranson score of 3 or higher, 51 patients (21.9%) had a BISAP score of 2 or higher and 37 patients (21.6% of patients with CTSI evaluation) had a CTSI score of 3 or higher. Median hospitalization time was 12 days (range 3-128). One hundred sixty-one patients (69.1%) were hospitalized for less than 10 days, whereas 72 patients (30.9%) were hospitalized for 10 days or more. Twelve patients (5.2%) were admitted to ICU and 4 patients (1.7%) in the study group died.

Hematological parameters and CRP levels were evaluated. Mean hemoglobin level of the patients was 13.1 ± 1.8 g/dl, mean WBC count was 12.4 ± 8.9 (x103/ml), mean neutrophil count was 9.65 ± 4.72 (x103/ml), mean lymphocyte count was 1.46 ± 0.84 (x103/ml), mean thrombocyte count was 270 ± 9 (x103/ml), mean MPV was 10.7 ± 1.1, mean RDW was 14.1 ± 1.8 (%) and mean NLR was 9.21 ± 8.42. Median CRP level was 43 mg/l (range 0.4 - 550). Baseline characteristics of the study population are given in Table 1.

Relationship of study parameters with scoring systems used in AP was evaluated. WBC count and neutrophil count were correlated to both RAC and Ranson score statistically significantly (p values of 0.012 and 0.002, 0.016 and 0.000 respectively). Increase in the level of both cell counts were correlated to higher scores in RAC and Ranson score. Lymphocyte count was negatively correlated to Ranson score ($p = 0.000$). NLR and CRP level were positively correlated with RAC, Ranson score and BISAP score statistically significantly. None of the study parameters were related with CTSI score. Relationship of study parameters with scoring systems are given in Table 2.

Table 1 Baseline characteristics of patient population

		Number of Patients (n = 233)	Percentage (%)
Age (years, mean, ± SD)	60.04 ± 17.51		
Sex			
Male		101	43.3
Female		132	56.7
BMI (kg/m², mean, ± SD)	23.2 ± 2.5		
Smoking			
No		211	91.4
Yes		20	8.6
Hypertension			
No		238	59.2
Yes		95	40.8
Diabetes mellitus			
No		173	74.2
Yes		60	25.8
RAC			
Mild		136	58.4
Moderately severe		77	33.0
Severe		20	8.6
Ranson score			
< 3		85	36.5
≥ 3		148	63.5
BISAP			
< 2		182	78.1
≥ 2		51	21.9
CTSI			
< 3		134	78.4
≥ 3		37	21.6
Hospitalization time (days, median, range)	12 (3-128)		
ICU admission			
No		221	94.8
Yes		12	5.2
Mortality			
No		229	98.3
Yes		4	1.7

Laboratory workout of the study population (mean, ± SD)			
Hemoglobin (g/dl)	13.1 ± 1.8	Thrombocyte count (x10³/ml)	270 ± 9
WBC count (x10³/ml)	12.4 ± 8.9	MPV (fL)	10.7 ± 1.1
Neutrophil count (x10³/ml)	9.65 ± 4.72	RDW (%)	14.1 ± 1.8
Lymphocyte count (x10³/ml)	1.46 ± 0.84	NLR	9.21 ± 8.42
CRP (mg/l, median, range)	43 (0.4 - 550).		

SD: Standard deviation, BMI: Body mass index, RAC: Revised Atlanta classification, BISAP: Bedside index of severity in acute pancreatitis, CTSI: CT severity index, ICU: Intensive care unit, WBC: White blood cells, CRP: C-Reactive protein, MPV: Mean platelet volume, fL: FemtoLiters, RDW: Red cell distribution width, NLR: Neutrophil-to-lymphocyte ratio.

Table 2 Relationship of study parameters with scoring systems for acute pancreatitis.

	RAC	Ranson score	BISAP	CTSI
Hemoglobin (g/dl)	0.493	0.420	0.107	0.272
WBC count (x10³/ml)	**0.012**	**0.002**	0.050	0.771
Neutrophil count (x10³/ml)	**0.016**	**0.000**	0.025	0.661
Lymphocyte count (x10³/ml)	0.075	**0.000**	0.115	0.098
Thrombocyte count (x10³/ml)	0.405	0.570	0.297	0.376
MPV (fL)	0.339	0.552	0.665	0.147
RDW (%)	0.108	0.324	0.343	0.453
NLR	**0.004**	**0.000**	**0.030**	0.126
CRP (mg/l)	**0.000**	**0.000**	**0.000**	0.079

RAC: Revised Atlanta classification, BISAP: Bedside index of severity in acute pancreatitis, CTSI: CT severity index, WBC: White blood cells, CRP: C-Reactive protein, MPV: Mean platelet volume, fL: FemtoLiters, RDW: Red cell distribution width, NLR: Neutrophil-to-lymphocyte ratio.

Table 3 Relationship of study parameters with hospitalization time.

	Hospitalization Time < 10 Days (n = 161, mean ± SD)	Hospitalization Time ≥ 10 days (n = 72, mean ± SD)	p value
Hemoglobin (g/dl)	13.1 ± 1.7	13.1 ± 2.0	0.944
WBC (x10³/ml)	12.2 ± 10.1	12.9 ± 5.4	0.634
Neutrophil count (x10³/ml)	9.17 ± 4.39	10.72 ± 5.26	**0.020**
Lymphocyte count (x10³/ml)	1.56 ± 0.88	1.25 ± 0.70	**0.009**
Thrombocyte count (x10³/ml)	270 ± 94	270 ± 110	0.989
MPV (fL)	10.7 ± 1.2	10.6 ± 1.0	0.708
RDW (%)	14.0 ± 1.9	14.4 ± 1.7	0.175
NLR	8.21 ± 8.39	11.45 ± 8.10	**0.007**
CRP (mg/l)	68.6 ± 86.8	102.0 ± 88.0	**0.007**

SD: Standart deviation, WBC: White blood cells, MPV: Mean platelet volume, fL: FemtoLiters, RDW: Red cell distribution width, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-Reactive protein.

Correlation of hematological parameters with CRP was evaluated. WBC count, neutrophil count and NLR values were all found to be positively correlated with CRP levels and these correlations were statistically significant (p values of 0.013, 0.000 and 0.000 respectively).

Study outcomes were designated as hospitalization time, ICU admission and mortality. Relationship of study parameters with these three end-points were evaluated. Higher neutrophil count and low lymphocye count were correlated with longer hospitalization times (p = 0.020 and p = 0.009 respectively). NLR and CRP level were also positively correlated with longer hospitalization times (p = 0.007 and p = 0.007 respectively). None of the study parameters were found to be related to ICU admission. CRP levels were found to be positively correlated to mortality. Patients without mortality had a mean CRP level of 76.8 ± 87.2 compared to mean CRP level of 200.8 ± 75.5 in patients with mortality (p = 0.005). Relationship of study parameters with hospitalization time, ICU admission and morality are given in Tables 3, 4 and 5.

Table 4 Relationship of study parameters with intensive care unit admission.

	ICU Admission (-) (n = 221, mean ± SD)	ICU Admission (+) (n = 12, mean ± SD)	p value
Hemoglobin (g/dl)	13.1 ± 1.8	13.6 ± 2.1	0.367
WBC (x10³/ml)	12.4 ± 9.0	12.9 ± 6.7	0.842
Neutrophil count (x10³/ml)	9.60 ± 4.64	10.57 ± 6.25	0.489
Lymphocyte count (x10³/ml)	1.47 ± 0.83	1.35 ± 0.94	0.647
Thrombocyte count (x10³/ml)	272 ± 99	230 ± 94	0.150
MPV (fL)	10.7 ± 1.1	10.4 ± 0.8	0.443
RDW (%)	14.2 ± 1.8	13.7 ± 1.2	0.384
NLR	9.14 ± 8.41	10.47 ± 8.90	0.596
CRP (mg/l)	13.1 ± 1.8	13.6 ± 2.1	0.367

SD: Standart deviation, WBC: White blood cells, MPV: Mean platelet volume, fL: FemtoLiters, RDW: Red cell distribution width, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-Reactive protein.

Table 5 Relationship of study parameters with mortality.

	Mortality (-) (n = 229, mean ± SD)	Mortality (+) (n = 4, mean ±SD)	p value
Hemoglobin (g/dl)	13.1 ± 1.8	13.8 ± 3.4	0.429
WBC (x10³/ml)	12.4 ± 9.0	16.7 ± 4.8	0.344
Neutrophil count (x10³/ml)	9.58 ± 4.70	13.36 ± 5.12	0.114
Lymphocyte count (x10³/ml)	1.45 ± 0.83	2.10 ± 1.03	0.129
Thrombocyte count (x10³/ml)	270 ± 98	281 ± 142	0.820
MPV (fL)	10.7 ± 1.1	10.3 ± 0.7	0.480
RDW (%)	14.2 ± 1.8	13.5 ± 0.7	0.456
NLR	9.24 ± 8.48	7.47 ± 4.04	0.677
CRP (mg/l)	76.8 ± 87.2	200.8 ± 75.5	**0.005**

SD: Standart deviation, WBC: White blood cells, MPV: Mean platelet volume, fL: FemtoLiters, RDW: Red cell distribution width, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-Reactive protein.

ROC curve analysis was performed to find a threshold for NLR value in predicting longer hospitalization times. A cut-off value of 5 was determined with a sensitivity of 75% and a specificity of 41.6% (area under the curve 64.9%).

DISCUSSION

Relationship of hematological parameters with severity and course of acute gallstone pancreatitis was investigated in this study. The study results revealed that several hematological parameters were correlated to severity scoring systems used in AP, and NLR value was a predictor of hospitalization time in acute gallstone pancreatitis patients.

AP is a complex and serious disorder of pancreas. Despite recent advances in therapeutic modalities across various disciplines of medicine, mortality rates are still high, especially in severe AP patient (9). Several scoring systems are utilized in daily practice to predict patients with probable severe

disease course, in order to implement necessary therapeutic interventions promptly to prevent unwanted outcomes (5).

CBC consists of hematological parameters including levels, percentages and morphological properties of hemoglobins, WBCs and thrombocytes. It is a commonly utilized, easy-to use laboratory workout. Given the accessible nature of CBC workout, hematological parameters have been investigated thoroughly in various disorders as potential prognostic indicators. In a large population-based study consisting of 48 305 participants, CBC related biomarkers including NLR were found to be associated with mortality in adult asthma patients (10). A study by Shimoni et al. revealed that CBC parameters can be used to predict mortality in hospitalized patients (11). Hematologic parameters were also shown to be useful in predicting disease severity in COVID-19 patients (12). Hematological parameters, particularly NLR, are also related to disease severity in AP (8,13). A study by Wang et al. revealed that RDW-to-albumin ratio is a predictor of severe acute pancreatitis (14). In addition to CBC, several novel biomarkers such as serum vitamin D and serum cystatin C levels are shown to predict disease severity and organ injury (4,15).

Our study data revealed that total WBC count, neutrophil count, lymphocyte count and NLR were correlated to scoring systems used in AP. NLR was also found to be correlated to longer hospitalization times, with the level of 5 being a reasonable cut-off in predicting disease course in terms of length of hospital stay. CRP levels were also correlated with scoring systems, as well as mortality.

The relationship of white blood cell counts and their ratios with AP course and severity should not be seen as a mere correlation of laboratory results. Inflammation is the basis of AP pathophysiology. White blood cells, being the prominent actors of immune system, also partake in AP development. While leukopenia is considered to be related to AP severity, neutrophils are on the spotlight of investigation in AP (16). Neutrophils are traditionally regarded as promoters of cytokine and chemokine cascades thus contributors in AP pathology (17). Recently, studies on the molecular level revealed more on the role of neutrophils in AP. Certain peripheral neutrophil subtypes (S100A6, S100A9, S100A12) are shown to be predictors of severe pancreatitis (18). Neutrophil extracellular traps (NETs) are structures made of extracellular DNA strings, histones and granular and cytosolic proteins which partake in inflammation (19). NETs are shown to be related to inflammation and thus severity in AP in various studies (20, 21, 22). Considering the active role of neutrophils in AP, NLR is a promising predictive biomarker with backing pathophysiological mechanisms.

The are several limitations to our study. First one is the retrospective nature of the study, although this limitation is amended partially since the data used were recorded prospectively at the time of hospital admission of patients. Secondly, cases with ICU admission and mortality are low on numbers, hence preventing a strong analysis between these two outcomes and study parameters. Lastly, since our institution is a tertiary referral center of the region, patients enrolled in the study might be overall more severe than general population. The major strengths of our study are the large number of acute gallstone pancreatitis patients enrolled in the study and incorporation of several scoring systems together in the analysis.

In conclusion, hematological parameters and NLR in particular are promising predictive biomarkers for disease severity in AP patients. Prospective, multi-center studies will reveal more on the utility of this easy-to-use laboratory workout in AP, as well as other inflammatory-driven disorders.

Ethics Committee: *This study was approved by the Ethics Committee of Antalya Training and Research Hospital, University of Health Sciences (Date: 07/03/2024, No: 2/29). Since this study was a retrospective study, no informed consent was required. The study was conducted in concordance with the Declaration of Helsinki.*

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