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From dyspepsia to complicated peptic ulcer: new markers in diagnosis and prognosis

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Abstract. – OBJECTIVE: Peptic ulcer disease (PUD) may present with different clinical findings, ranging from mild dyspeptic complaints to mortal complications, such as gastrointestinal system perforation. The aim of this study was to investigate the potential blood parameters that can be used in the diagnosis of PUD and prediction of complications.

PATIENTS AND METHODS: A total of 80 patients with dyspeptic complaints, 83 patients with PUD, and 108 patients with peptic ulcer perforation (PUP) who were treated in our hospital between January 2017 and December 2020 were included in the study. Clinical findings, laboratory data, and imaging methods were reviewed retrospectively.

RESULTS: The mean age of 271 (154 men, 117 women) patients included in the study was 56.04 ± 17.98 (mean ± standard deviation) years. The neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet volume, white blood cell, C-reactive protein, and neutrophil values were higher in patients with PUP compared to other groups ($p < 0.001$ for all). In the PUD group, only red blood cell distribution width was significantly higher compared to the patient group with dyspeptic complaints. In the postoperative period, NLR and PLR were significantly higher in patients who developed severe complications according to the Clavien-Dindo classification compared to patients who developed mild complications.

CONCLUSIONS: This study showed that simple blood parameters can be used as diagnostic markers at different stages of PUD. NLR and PLR can be helpful in the diagnosis of PUP and red blood cell distribution width can be used to differentiate patients with peptic ulcer from dyspeptic patients. Additionally, NLR and PLR can be used to predict serious postoperative complications after PUP surgery.

Key Words:

Peptic ulcer, Dyspepsia, Perforation, Biomarker, Prediction, Diagnosis.

Introduction

Peptic ulcer is one of the most common lesions of the gastrointestinal tract. It occurs as a result of damage extending from the mucosa to the muscularis mucosa and is usually seen in the duodenum and stomach[1]. Previously, gastric acid hypersecretion, stress, and dietary factors were thought to cause peptic ulcer disease (PUD). However, recent studies[2] have demonstrated the role of Helicobacter pylori infection and nonsteroidal anti-inflammatory drugs (NSAIDs).

The lifetime prevalence of PUD is between 5%-10%[1]. The prevalence of the disease is decreasing in the last 20-30 years due to H2 receptor blockers, proton pump inhibitors, and *H. pylori* eradication[3]. Unless there are complications, nonspecific dyspeptic symptoms, such as epigastric pain and nausea, are observed[2]. Considering that dyspepsia occurs in approximately 20% of the general population, it is difficult for a clinician to diagnose PUD[4]. Endoscopy is important in the diagnosis of PUD; in addition to excluding malignancies, histological diagnosis and detection of *H. pylori* infection can also be performed[1]. Today, acid-suppressing drugs and antibiotics targeting the *H. pylori* infection are used in the treatment of peptic ulcers[2]. However, the use of acetylsalicylic acid (ASA) and NSAIDs has also become widespread. For this reason, the expected decrease in peptic ulcer complications, such as bleeding and perforation, has not been observed[3].

Peptic ulcer perforation (PUP) is the most serious complication of peptic ulcer and constitutes approximately 5% of all abdominal surgical emergencies[5]. Mortality in delayed cases can rise up to 50%. Furthermore, diagnosis may be delayed in the elderly and immunosuppressed patients. However, morbidity and mortality decrease with early surgical intervention[6].

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In recent years, simple laboratory markers have been used to diagnose or predict the prognosis of malignancy and high-risk inflammatory diseases. There are studies[6-10] showing that different parameters, such as neutrophil-lymphocyte ratio (NLR) or platelet-lymphocyte ratio (PLR), can accurately predict conditions and provide prognoses for various conditions that require emergency intervention, such as the novel coronavirus disease, sepsis, and acute appendicitis. These parameters are suitable for practical use, as they can be found in routine laboratory examinations, do not have additional costs, and can be easily calculated.

In the present study, we investigated the diagnostic values of parameters such as NLR, mean platelet volume (MPV), and PLR at different stages of PUD, from dyspeptic symptoms to perforation. We also investigated the predictive role of blood parameters for complications in patients with PUP that underwent surgery.

The aim of this study was to reveal new parameters that may be useful in the diagnosis and prognosis of patients who do not show clinical findings, especially in cases where clinical imaging and examinations are insufficient.

Patients and Methods

This retrospective study included patients treated for functional dyspeptic complaints, PUD, and PUP in a tertiary university hospital between January 2017 and December 2020. Patient files, imaging results, surgery notes, and pathology records were reviewed retrospectively. The patients were divided into three groups according to their clinical status. Omental patch and primary repair were performed with the open technique as the standard in all patients who underwent surgery. Patients who developed morbidity in the postoperative period were divided into two subgroups as those with severe and mild complications according to the Clavien-Dindo classification.

The study was carried out in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained from each patient for all procedures and publication. Ethics committee approval was received for this study from the University Clinical Trials Ethics Committee (2022/ GOKAE / 0256).

Patient Groups

This was a retrospective, cross-sectional study. Patients were divided into three groups: PUP, non-complicated peptic ulcer, and controls.

Group 1 comprised of 80 patients who presented with dyspeptic complaints and upper abdominal pain and were diagnosed with functional dyspepsia according to the Rome IV criteria[11].

Group 2 comprised of 83 patients with no other gastrointestinal (GIS) disease and complications other than peptic ulcer. These patients presented with dyspeptic complaints and abdominal pain. Abdominal ultrasonography (USG) and upper GIS endoscopy were performed in all patients. A diagnosis of non-complicated PUD was made by endoscopic and histopathologic evaluation.

Group 3 comprised of 108 patients who were operated for PUP. These patients presented with nonspecific abdominal pain and had acute abdominal findings on physical examination. As a result of suspected perforation based on the physical examination and abdominal computed tomography (CT), the patients underwent surgery for a definitive diagnosis. Surgical repair was performed for PUP and a biopsy was taken from the perforation site. Patients who did not have PUP were excluded from the study.

Exclusion Criteria

Exclusion criteria included patients: aged <18 and cases where the perforation was not caused by peptic ulcer (trauma, iatrogenic causes, and tumor); with gastrointestinal pathology other than PUD; and with gallbladder, biliary tract, and liver disease detected on USG. Additionally, patients who refused endoscopic intervention, whose laboratory data were missing, and whose data could not be accessed were not included in the study.

Blood Samples Analyses

Venous blood samples were obtained from all the patients included in the study. In the functional dyspepsia and PUD groups blood samples were collected within three days before the endoscopy, and in the PUP group, they were collected during the preoperative period. Hemoglobin, neutrophil, lymphocyte, MPV, red blood cell distribution width (RDW), and platelet values were recorded. Additionally, NLR and PLR values were calculated. We also compared the inflammatory markers such as white blood count (WBC), MPV, NLR, TLR, and C-reactive protein (CRP) in the preoperative blood parameters.

Reference values in the measuring device were Hemoglobin (11-15 g/dL), platelet (150.000–400.000 × 10 9/L), MPV (6.5-12 fL), WBC (4–10×10 9 /L), neutrophil (2-7×10 9/L) and lymphocyte (0.8-4×10 9/L), RDW (11%-16%), and CRP (0-5 mg/L). The reference values for NLR (0.78-3.53) and PLR (46.7-218) were based on previous similar studies[12,13].

Statistical Analysis

Demographic and laboratory data were presented as mean±standard deviation or median (minimum-maximum range), as appropriate. Study variables were analyzed and compared between the groups (group 1 = dyspepsia, group 2 = PUD, group 3 = PUP). The data distribution was evaluated using Kolmogorov-Smirnov test. Chi-square test was used to compare categorical variables. Mann-Whitney U test was used for binary comparisons of the groups ($p < 0.05$). Post-hoc Tukey test was performed to compare parameters between the groups after one-way analysis of variance. The receiver operating characteristic (ROC) curve test was performed to determine the predictive properties of the parameters of the disease and the sensitivity-specificity ratios were determined by setting cut-off values. A p-value of <0.05 was considered statistically significant in all analyses.

Results

The study consisted of 271 patients, out of which 117 (43.1%) were women and 154 (56.9%) were men. While the rate of female patients in group 1 was 73.7% (59), 39.7% (33) in group 2, and 23.1% (25) in group 3 ($p < 0.001$). The mean age of the patients was 56.04 ± 17.98 years and there was no difference between the groups in terms of age. In the PUP group, 100 (92.6) patients were diagnosed with imaging methods. In 8 (7.4%) patients, imaging methods were negative, and the diagnosis was made with clinical findings. Mortality rate was calculated as 16.6% in this group (Table I).

There was no statistically significant difference between the groups in terms of platelet and MPV values. For NLR, PLR, WBC, CRP, and neutrophil values, a statistically significant difference was found between group 1 and group 3 and between group 2 and group 3 ($p < 0.001$). RDW was significantly different between groups 1 and 2 ($p = 0.001$) and groups 2 and 3 ($p = 0.031$). No significant difference was found between group 1 and group 3 (Table II).

ROC analysis of NLR, PLR, and other blood parameters was performed to differentiate perforation and peptic ulcer between the three groups (Figure 1). It was found that NLR > 2.2 and PLR > 133.56 could predict PUD in patients with dyspeptic complaints, with a sensitivity of 67% and 62% and a specificity of 72% and 67%, respectively [areas under the curve (AUC) = 0.718, 0.635, respectively, $p < 0.001$]. It was also found that NLR > 5.27 and PLR > 215 could predict perforation in peptic ulcer patients with a sensitivity of 77% and 67% and a specificity of 92% and 88%, respectively (AUC = 0.891, 0.782, respectively, $p < 0.001$). For predicting PUP, cut-off values for WBC, CRP, and neutrophil were calculated as 11.15, 4.7, and 7.07 with a sensitivity of 64%, 46%, and 75% and a specificity of 90%, 84%, and 86%, respectively (AUC = 0.789, 0.661, 0.845; $p < 0.001$) (Table II). Sub-groups with mild and severe complications were compared in terms

Table I. Laboratory data from all groups.

	Group 1 – Control (n=80)	Group 2 – Peptic ulcer (n=83)	Group 3 – Peptic ulcer perforation (n=108)	p
Age	51.08±14.89	56.69±18.02	59.24±19.34	0.008[a]
Sex (female)	59 (% 73.75)	33 (%39.75)	25 (%23.14)	<0.001[a]
Neutrophil	4.57±1.49	5.28±2.02	11.68±6.16	<0.001[a]
Lymphocyte	2.40±0.79	1,96±0.86	1.23±1.13	<0.001[a]
Thrombocyte	278.82±76.49	267.54±89.63	290.35±107.72	0.25[a]
WBC ($\times 10^9$/L)	7.63 ± 1.73	7.99 ± 2.36	13.63 ± 6.49	<0.001[a]
CRP (mg/dL)	1.42 ± 5.34	2.63 ± 4.62	8.75 ± 11.34	<0.001[a]
NLR	2.17 ± 1.34	3.18 ± 2.01	16.30 ± 14.48	<0.001[a]
PLR	127.21 ± 53.41	157.86 ± 81.12	421.03 ± 386.24	<0.001[a]
MPV (fL)	10.38 ± 1.12	10.08 ± 1.14	10.22 ± 1.14	0.239[a]
RDW (%)	13.98 ± 1.70	15.63 ± 3.74	14.56 ± 2.48	0.001[a]

[a]One-way ANOVA test. (NLR= neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; CRP= c-reaktif protein. RDW= red blood cell distribution width; WBC= White Blood Cell)

Table II. The results of the receiver operating characteristic curve analysis of the NLR, PLR, WBC, CRP, RDW and neutrophil.

		Sensitivity	Specificity	Cutoff	AUC	*p*
WBC ($\times 10^9$/L)	Group1/2	41	63	8.26	51.6	0.729
	Group1/3	64	98	11.02	80.7	<0.001
	Group2/3	64	90	11.15	78.9	<0.001
CRP (mg/dL)	Group1/2	74	56	0.34	68.3	<0.001
	Group1/3	73	75	0.67	77.9	<0.001
	Group2/3	46	84	4.7	66.1	<0.001
NLR	Group1/2	67	72	2.20	71.8	<0.001
	Group1/3	87	75	3.62	94.8	<0.001
	Group2/3	77	92	5.27	89.1	<0.001
PLR	Group1/2	62	67	133.56	63.5	0.003
	Group1/3	77	82	160.77	83.9	<0.001
	Group2/3	67	88	215.05	78.2	<0.001
Nötrofil	Group1/2	60	56	4.49	59.8	0.031
	Group1/3	87	92	3.62	88.3	<0.001
	Group2/3	75	86	7.07	84.5	<0.001
RDW (%)	Group1/2	65	62	13.95	65.7	0.001
	Group1/3	54	57	13.75	54	0.35
	Group2/3	41	41	14.15	38.8	0.08

Receiver operating characteristic (ROC) curve test, $p < 0.05$; The Post-Hoc Test (NLR= neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; CRP= c-reaktif protein. RDW= red blood cell distribution width; WBC= White Blood Cell).

of NLR, PLR, WBC, MPV, and RDW (Table III). NLR and PLR were significantly higher in patients with severe complications (Clavien-Dindo grade 3-4-5) ($p = 0.30$, $p = 0.48$, respectively).

Discussion

PUD often manifests as dyspeptic complaints[14]. Alarming symptoms, such as bleeding, weight loss, or dysphagia, are factors suggestive of serious pathologies, such as underlying ulcer, malignancy, and stenosis[15]. However, the predictive value of alarm symptoms in upper GI pathologies is not satisfactory[6,15,16]. Endoscopy, on the other hand, is not routinely recommended for all patients[14].

In the present study, patient groups who presented with dyspeptic complaints and abdominal pain were investigated. After invasive and noninvasive examinations, it was observed that functional dyspepsia patients constituted the largest group among all patients. In many patients, no underlying pathology was found.

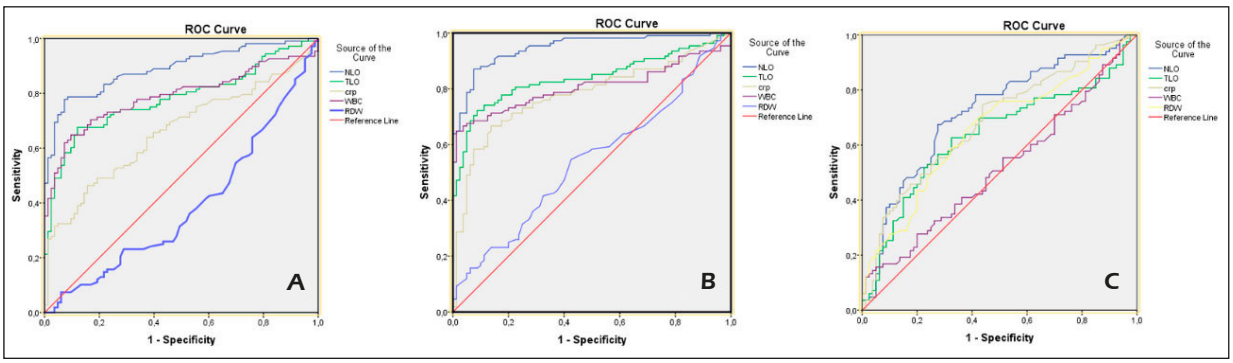

Figure 1. The receiver operating characteristic (ROC) curve analysis results of the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), CRP= c-reaktif protein, neutrophil, RDW= red blood cell distribution width and WBC= White Blood Cell. **A**, Roc curve for group-1 and group-2. **B**, Roc curve for group-1 and group-3. **C**, Roc curve for group-2 and group-3.

Table III. Comparison of inflammatory markers in Clavien-Dindo classification.

	Clavien-Dindo Grade 1-2	Clavien-Dindo Grade 3-4-5	*p*-value
WBC[#] (10^9/L)	16.63±6.86	16.59±5.96	0.742[b]
MPV[#] (fL)	10.51±0.54	10.48±1.43	0.974[b]
NLR[#]	21.88±10.01	39.21±18.78	0.030[b]
TLR[#]	486.5±278.23	930.34±576.65	0.048[b]
RDW[#] (mg/L)	14.49±2.11	14.71±1.51	0.539[b]

[#]; mean±standard deviation. WBC; white blood cells, MPV; mean platelet volume, RDW= red blood cell distribution width, NLR; neutrophil-lymphocyte ratio, TLR; platelet-lymphocyte ratio. [b]; Mann-Whitney U-test.

The prevalence of patients presenting with dyspepsia complaints is higher among women[17,18]. In the present study, 73.7% of the patients in the group with dyspeptic complaints were women and the mean age was 51, which is consistent with the literature. The frequency of duodenal and gastric ulcers in dyspepsia patients is 7.47% and 7.07%, respectively. It has been reported in the literature that the prevalence of peptic ulcer in dyspepsia patients increases with age and is higher in male patients[19-21]. Consistent with previous studies[22,23], in the present study, 60% of the patients in the PUD group were men and the mean age was 56.6. Also, PUP is mostly seen in the fourth decade of life and the male/female (M/F) ratio is in the range of 6-10/1. Again, in the present study, the mean age of the PUP group was 59 years, and the M/F ratio was 3.3/1, which is consistent with previous studies.

The diagnosis of PUP is made by laboratory and imaging methods together with a clinical picture of severe abdominal pain. Elevated inflammatory parameters, subdiaphragmatic air on X-ray, and detection of pneumoperitoneum on CT are diagnostic, but cannot be detected in every patient. In a retrospective study of patients with a preoperative diagnosis of PUP, no perforation was detected by imaging methods in 8.2% of the patients[24]. Furthermore, prolongation of the time from perforation to surgery is a risk factor for high morbidity and mortality[22,25]. Surapaneni and Reddi[26] showed that mortality and morbidity increased in patients with perforation and an operation time of >24 hours.

Consistent with the literature, direct-indirect perforation findings were not detected in 7.4% of our patients, and diagnostic delays were experienced. Ultimately, these patients underwent diagnostic laparoscopy due to the development of acute abdomen on examination, and perforation was detected. In all imaging-negative patients, inflammatory markers were elevated and above the cut-off values (NLR, 20.89 ± 15.26; PLR, 558.07 ± 266.92).

Diagnostic difficulties in different stages of PUD and high morbidity and mortality rates due to delay in surgical treatment have encouraged researchers to find new diagnostic indicators. In a study by Gulbagci et al[27], while there was a statistically significant difference between the peptic ulcer and gastritis group and the control group in terms of NLR, no significant difference was found in terms of PLR. In another study, no significant difference was found between the PUD and control groups in terms of NLR and WBC, while CRP was statistically higher in the PUD group[28]. Li et al[29] examined the relationship between gastric diseases and RDW and found that RDW was significantly higher in patients with gastric ulcers compared with the control group. In the present study, only RDW was found to be a significant marker for PUD (cut-off value, 13.95; $p = 0.001$).

There are many studies[7-10,27-33] examining the relationship of parameters such as NLR, PLR, and RDW with malignancies, inflammatory and autoimmune diseases and their diagnosis, prognosis, and mortality. These are used to predict diagnosis and mortality in colorectal and gastric cancers, appendicitis, GIS perforations, sepsis, and the novel coronavirus disease. As a result, NLR and PLR are also part of the routine peripheral blood parameters evaluated in many laboratories.

Additionally, different scoring systems have been introduced over the years to predict mortality in PUP. The Boey and ASA scoring systems are the most commonly used in clinical settings[25]. They have been used in practice for a long time

and have yielded accurate results for mortality but are not good at predicting diagnosis and morbidity. On the other hand, inflammatory indicators such as NLR and PLR are helpful in both diagnosis and prediction of mortality[28,32,34]. In the present study, both parameters were significantly higher in the severe morbidity group (NLR, $p < 0.30$; PLR, $p < 0.48$).

Various studies[28,31] in the literature comparing patients with PUP with healthy controls report significantly higher NLR, WBC, and CRP values and lower MPV values in the perforation group. In another study, Yahri et al[4] report that a high preoperative PLR value could predict the length of hospital stay after PUP repair. Aydin et al[32] also found that NLR and PLR were good predictors of postoperative mortality in those who underwent PUP repair.

In the present study, NLR was higher in the PUP group compared with group 1 and group 2 ($p < 0.001$). Additionally, PLR, WBC, CRP, and neutrophil values were also significantly higher in the PUP group compared with other groups. Based on our results, an NLR > 5.27 and a PLR > 215 may be an indication of perforation in patients with peptic ulcers. Since it is a simple method, it can be used in all cases. It is especially valuable in PUP cases that are not detected by imaging methods. However, these inflammatory markers should be used as ancillary diagnostic methods to CT, endoscopy, and clinical examinations. This is because the diagnostic power of CT is higher in PUP[24]. Additionally, endoscopy and CT are still the gold standard for the exclusion of malignancy.

Conclusions

Based on the results of this study, NLR and PLR values were found to be reliable diagnostic markers for detecting perforation in patients with PUD. The clinical use of these parameters will be useful in clinical examinations for early diagnosis in patients who develop PUP, especially in imaging-negative patients, where results above the cut-off value may guide the surgeon to quickly perform a laparotomy.

Furthermore, an increased RDW value in peripheral blood is an important indicator of the transition from functional dyspepsia to PUD and should encourage a clinician to perform additional imaging. Additionally, high NLR and PLR can be used during follow-up visits as a precursor of serious postoperative complications.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Informed Consent

All subjects gave their informed consent for inclusion before they participated in the study.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by Izmir Katip Celebi University.

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Authors' Contributions

AA, FK, ÖG, SG, OND: conception and planning of the study. FK, ÖG, SG: data collection. AA, OND: data analysis. AA, FK, OND: writing the manuscript. All authors reviewed and approved the final manuscript.

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