Can the Neutrophil/Lymphocyte*Platelet Ratio Predict Acute Appendicitis? An Analytical Study

Nötrofil/Lenfosit*Trombosit Oranı Akut Apandisiti Öngörebilir mi? Bir Analitik Çalışma

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ABSTRACT

Aim: Our primary aim is to determine whether the neutrophil/lymphocyte*platelet ratio (NLPR) has the ability to predict acute appendicitis. Our secondary aim is to show whether the NLPR is effective in differentiating complicated and non-complicated acute appendicitis.

Materials and Methods: Our study was planned retrospectively, and patients over 18 years of age who were diagnosed with acute appendicitis and admitted to the Health Sciences University Turkey, Ümraniye Training and Research Hospital between 01.04.2022 and 01.04.2023, were included in the study.

Results: A total of 492 patients were included in our study, and 242 (49.18%) of them were diagnosed with acute appendicitis. Neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and NLPR were statistically significantly higher in patients with acute appendicitis compared to the control group (p<0.001, p<0.001, p<0.001, respectively) (the area under the curve was 0.96, 0.70, 0.94, respectively).

Conclusion: NLR, PLR and NLPR can be used as predictors for the diagnosis of acute appendicitis, but according to our study, NLR, PLR and NLPR should not be used as prognostic indicators of acute appendicitis.

Keywords: Acute appendicitis, NLR, PLR, NLPR

ÖZ

Amaç: Birincil amacımız nötrofil/lenfosit*trombosit oranının (NLPR) akut apandisiti öngörebilme yeteneğinin olup olmadığının belirlenmesidir. İkincil amacımız ise NLPR'nin komplike ve non-komplike akut apandisit ayrımında etkin olup olamadığını göstermektir.

Gereç ve Yöntem: Çalışmamız retrospektif olarak planlandı ve 01.04.2022-01.04.2023 tarihleri arasında Sağlık Bilimleri Üniversitesi, Ümraniye Eğitim ve Araştırma Hastanesi'ne başvuran 18 yaş üstü akut apandisit tanısı alan hastalar dahil edildi.

Bulgular: Çalışmamıza 492 hasta dahil edildi. Hastalarımızın 242'si (49,18%) akut apandisit tanısı alan hastalardı. Akut apandisit tanısı konulan hastaların yaş ortancası 33 (25-46) yıldı ve kontrol ve hasta grubu arasında anlamlı bir fark yoktu (p=0,078). Nötrofil lenfosit oranı (NLR), platelet lenfosit oranı (PLR) ve NLPR akut apandisit tanılı hastalarda, kontrol grubuna göre anlamlı derecede yüksekti (sırası ile p<0,001, p<0,001, p<0,001) (eğrinin altındaki alan sırasıyla 0,96, 0,70, 0,94 idi).

Sonuç: NLR, PLR ve NLPR akut apandisit tanısını koymada prediktör olarak kullanılabilir, fakat çalışmamıza göre akut apandisit prognoz göstergesi olarak NLR, PLR ve NLPR kullanılmamalıdır.

Anahtar Kelimeler: Akut apandisit, NLR, PLR, NLPR

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INTRODUCTION

Acute appendicitis is the most common cause of acute abdomen. While the rate of incidence with perforation is 20%, its prevalence is approximately 7%[1]. Diagnosis is made with clinical and radiological imaging. Laboratory tests are also helpful in diagnosing[2]. About half of adults have obvious symptoms. Periumbilical abdominal pain, anorexia, vomiting, and fever are the common symptoms[3]. C-reactive protein (CRP) and white blood cell (WBC) are often preferred for diagnosis, but there is no specific laboratory test for the diagnosis of appendicitis[4]. Although it is mostly considered as an inflammatory disease, it is known that immune dysfunctions will increase the susceptibility to infection[5].

Neutrophils, lymphocytes, and platelets that play a role in the coagulation cascade play an important role in immune system dysfunction and systemic inflammation[6]. Neutrophil lymphocyte ratio (NLR) was accepted as an easy-to-calculate, low-cost indicator of systemic inflammation[7,8]. Neutrophils are the most abundant cell of leukocytes, and they regulate other cell functions such as neutrophils, mast cells and macrophages and are effective in inflammation. Like NLR, platelet lymphocyte ratio (PLR) has been used as an early marker of infections in various diseases[9]. Since appendicitis is an inflammatory disease associated with immune system dysfunction, it was the subject of NLR and PLR studies[2,10-13]. Another parameter used as an early marker of inflammatory diseases was the neutrophil/lymphocyte*platelet ratio (NLPR). Whether NLPR is a prognostic marker for sepsis[14], Coronavirus disease-2019 (COVID-19)[15] and post-surgery[16] were discussed in the literature.

To the best of our knowledge, there is no study evaluating the effect of NLPR on diagnosis and prognosis in adult patients with acute appendicitis.

Our primary aim is to determine whether the NLPR has the ability to predict acute appendicitis. Our secondary aim is to show whether the NLPR is effective in differentiating complicated and non-complicated acute appendicitis.

MATERIALS AND METHODS

Ethics

The instant study was carried out with the permission of the Ümraniye Training and Research Hospital Local Ethics Committee (date: 24/04/2023, decision no: B.10.1.TKH.4.34.H.GP.0.01/131).

Study Design

Our study was retrospectively planned and more than three hundred thousand patients admitted to the emergency department of Ümraniye Training and Research Hospital between 01.04.2022 and 01.04.2023, who were diagnosed with acute appendicitis through computer tomography or ultrasound and examination findings and who were surgically over the age of 18 years were included.

Study Population

Patients whose hemogram parameters were measured and registered in the emergency department were included in the study, but patients with a history of trauma, younger than 18 years of age, and with incomplete data were excluded from the study. The control group was selected from patients without suspected acute appendicitis. Gangrenous appendicitis, intra-abdominal abscess, perforation, plastron formation, and generalized peritonitis were considered in the differentiation of complicated and non-complicated. Patients who could not differentiate between complicated and non-complicated were also excluded from the study.

Data Collection

Demographic characteristics, symptoms and examination findings of the patients were recorded using the hospital data system. Age (year), gender, localized pain, nausea, vomiting, anorexia, right lower quadrant tenderness, right lower quadrant rebound, high fever, leukocytosis, left shift in WBC and complicated appendicitis status were recorded by the investigators from the patient electronic file. The values of WBC, neutrophil count, lymphocyte count, hemoglobin, and hematocrit values, mean corpuscular volume (MCV), red cell distribution width, platelet count, mean platelet volume, and NLPR obtained from hematology laboratory were recorded. Alanine aminotransferase, aspartate aminotransferase, albumin, glucose, calcium, blood urea nitrogen, creatinine, sodium, potassium, and CRP levels were also recorded. The examinations and data of patients who attended the emergency department were used. The patients were classified both as acute appendicitis and control group, and also as complicated and uncomplicated acute appendicitis. Hematological values were compared between the patient group with acute appendicitis and the control group. Then, a comparison was made between patients with a diagnosis of complicated and uncomplicated acute appendicitis.

NLPR=Neutrophil count (10^9/L) * 100: Lymphocyte count (10^9/L) * Platelet count (10^9/L).

Statistical Analysis

Quantitative variables were presented as median and interquartile range (IQR) (IQR, 25th-75th percentile) values, and the Mann-Whitney U test was used in analyzing the paired groups. The categorical data were done using the Fisher's Exact test and chi-square test. Statistical Package for Social

Sciences (SPSS) (SPSS Inc., version 20.0; Chicago, IL) was used for statistical analyses. The Spearman's correlation analysis test was employed for correlation analysis. Statistical significance was accepted as p<0.05.

RESULTS

A total of 492 patients were included in our study, and 242 (49.18%) of our patients were diagnosed with acute appendicitis. Twenty hundred and fifty (50.82%) patients constituted the control group. The most common symptom in patients diagnosed with acute appendicitis was right lower quadrant pain (96%). The most common finding was leukocytosis with a rate of 48%. The frequency of symptoms and signs of patients diagnosed with acute appendicitis, and the median (IQR) values of laboratory tests are shown in Table 1.

The mean age of the patients diagnosed with acute appendicitis was 33 years (25-46 years) (p=0.078); Likewise, 58.7% of the patients diagnosed with acute appendicitis were male (p<0.001). WBC, neutrophil, and hemoglobin values were higher in patients with acute appendicitis than in the control group (p<0.001, p<0.001, p=0.001 respectively). Lymphocyte and MCV values were lower in patients with acute appendicitis than in the control group (p<0.001, p=0.001 respectively). NLR, PLR and NLPR values were statistically significantly higher in patients with acute appendicitis (p<0.001, p<0.001, p<0.001 respectively). The comparison of hemogram parameters of the control group and patients diagnosed with acute appendicitis is shown in Table 2.

Table 1. Symptoms of patients diagnosed with acute appendicitis and laboratory findings other than hematological parameters

Characteristic (n, %) (median IQR)	N=242
Localized pain (n, %)	26 (11%)
Anorexia (n, %)	21 (8.7%)
Vomiting (n, %)	74 (31%)
Sensitivity in right lower quadrant (n, %)	232 (96%)
Rebound (n, %)	114 (47%)
High fever (n, %)	3 (1.2%)
Leukocytosis (n, %)	200 (83%)
WBC left shift (n, %)	117 (48%)
Complicated (n, %)	70 (29%)
ALT (IU/L)	20 (13-31)
Albumin (g/dL)	44.6 (41.0-47.2)
AST (IU/L)	21 (17-25)
Glucose (mmol/L)	105 (93-122)
Calcium (mg/dL)	9.13 (8.85-9.40)
BUN (mg/dL)	24 (20-30)
Creatinine (mg/dL)	0.79 (0.66-0.89)
Potassium (mEq/L)	4.30 (4.07-4.63)
Sodium (mEq/L)	136.70 (135.00-137.20)
CRP (mg/mL)	40 (9-110)

WBC: White blood cell count, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen, CRP: C-reactive protein, IQR: Interquartile range

Table 2. Evaluation of hematological parameters of acute appendicitis patients and control group

(n, %), (median IQR)	Control group	Acute appendicitis group	Total	p value
Gender (n, %)				
Male	67 (26.8%)	142 (58.7%)	209 (42.5%)	<0.001
Female	183 (73.2%)	100 (41.3%)	283 (57.5%)	
Age, median (IQR)	34.0 (30.0-42.0)	33.0 (25.0-46.0)	34.0 (28.0-43.0)	0.078
WBC (10^3 µ/L)	7.0 (6.1-8.1)	14.8 (11.9-16.9)	9.4 (6.9-14.7)	<0.001
Neutrophil (10^3 µ/L)	4.0 (3.4-4.9)	12.1 (9.5-14.1)	6.2 (3.9-11.9)	<0.001
Lymphocyte (10^3 µ/L)	2.2 (1.9-2.8)	1.8 (1.2-2.3)	2.0 (1.6-2.6)	<0.001
Hemoglobin (g/dL)	13.3 (12.2-14.5)	14.0 (12.4-15.1)	13.6 (12.3-14.9)	0.001
Hematocrit (%)	40.5 (37.8-43.6)	41.7 (37.8-45.1)	40.8 (37.8-44.2)	0.059
MCV (fl)	88.3 (84.8-92.1)	86.7 (83.9-90.0)	87.5 (84.4-90.9)	0.001
RDW (fl)	13.1 (12.7-13.8)	13.2 (12.8-13.8)	13.1 (12.7-13.8)	0.472
Platelet (10^3 µ/L)	257.0 (223.0-297.0)	254.5 (215.2-311.5)	256.0 (218.0-302.0)	0.634
MPV (fl)	9.6 (9.0-10.3)	9.8 (8.9-10.5)	9.7 (8.9-10.5)	0.563
NLR	1.8 (1.4-2.2)	6.5 (4.5-10.2)	2.8 (1.8-6.4)	<0.001
PLR	112.6 (93.5-139.3)	150.9 (112.3-217.9)	125.7 (100.9-166.9)	<0.001
NLPR	0.7 (0.5-0.9)	2.7 (1.6-4.0)	1.1 (0.7-2.6)	<0.001

WBC: White blood cell count, IQR: Interquartile range, MCV: Mean corpuscular volume, RDW: Red cell distribution width, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, NLPR: Neutrophil-to-lymphocyte*platelet ratio

Of the 242 patients diagnosed with acute appendicitis, 70 (28.92%) were those diagnosed with complicated acute appendicitis. 58.6% of patients with complicated acute appendicitis were male (p=1.00). While WBC was high in patients with complicated acute appendicitis, neutrophils and hemoglobin levels were lower than in patients with uncomplicated acute appendicitis. However, WBC, neutrophil and hemoglobin values were not statistically significant in the diagnosis of complicated and uncomplicated acute appendicitis (p=0.902, p=0.952, p=0.836 respectively). While lymphocyte is higher in patients with complicated acute appendicitis, MCV was lower. Lymphocyte and MCV values were not statistically significant in the diagnosis of complicated and uncomplicated acute appendicitis (p=0.427, p=0.337, respectively). NLR, PLR and NLPR values were not statistically significant in the differentiation of complicated and non-complicated acute appendicitis (p=0.561, p=0.973, p=0.280, respectively). Hemogram and NLPR values of patients with complicated and uncomplicated acute appendicitis are shown in Table 3.

Table 4 presents the cut-off, sensitivity, specificity, 95% confidence interval and area under the curve (AUC) values.
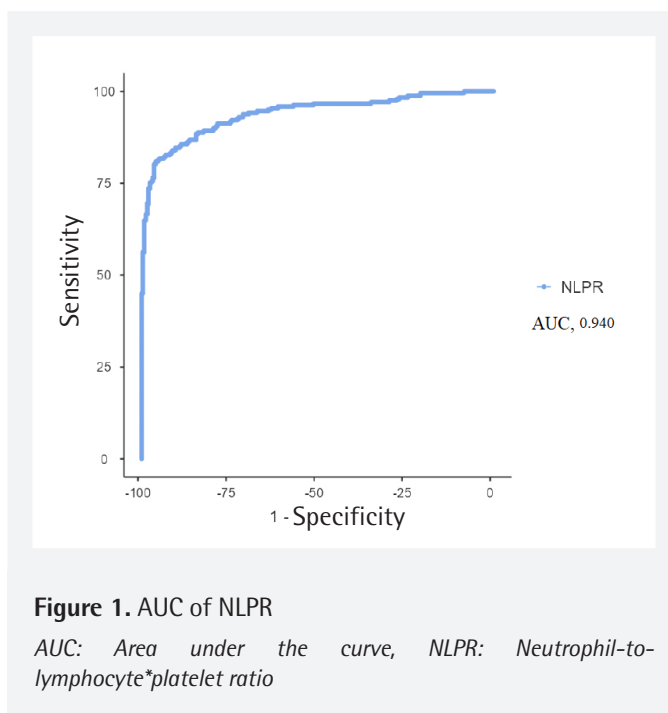

Figure 1. AUC of NLPR

AUC: Area under the curve, NLPR: Neutrophil-to-lymphocyte*platelet ratio

Table 3. Evaluation of hematological parameters of patients with non-complicated and complicated acute appendicitis				
	Non-complicated	**Complicated**	**Total**	**p value**
Gender n (%)				0.999
Male	101 (58.7)	41 (58.6)	142 (58.7)	
Female	71 (41.3)	29 (41.4)	100 (41.3)	
Age, median (IQR)	31 (24-41)	43 (29-56)	33 (25-46)	<0.001
WBC (10^3 μ/L)	14.7 (11.9-16.9)	14.9 (11.8-16.7)	14.8 (11.9-16.9)	0.902
Neutrophil (10^3 μ/L)	12.1 (9.3-14.2)	12.0 (9.6-14.0)	12.1 (9.5-14.1)	0.952
Lymphocyte (10^3 μ/L)	1.7 (1.2-2.3)	1.9 (1.2-2.5)	1.8 (1.2-2.3)	0.427
Hemoglobin (g/dL)	14.0 (12.4-15.1)	13.9 (12.5-15.1)	14.0 (12.4-15.1)	0.836
Hematocrit (%)	41.8 (37.9-45.0)	41.0 (37.7-45.1)	41.7 (37.8-45.1)	0.821
MCV (fl)	86.8 (84.1-90.0)	86.2 (83.5-89.7)	86.7 (83.9-90.0)	0.337
RDW (fl)	13.1 (12.7-13.8)	13.2 (12.8-14.0)	13.2 (12.8-13.8)	0.324
Platelet (10^3 μ/L)	253.5 (214.8-304.2)	258.0 (221.8-331.5)	254.5 (215.2-311.5)	0.278
MPV (fl)	9.8 (8.9-10.5)	9.7 (8.8-10.5)	9.8 (8.9-10.5)	0.538
NLR	6.5 (4.6-10.5)	6.4 (4.1-9.8)	6.5 (4.5-10.2)	0.561
PLR	151.7 (113.7-213.9)	150.9 (107.5-236.7)	150.9 (112.3-217.9)	0.973
NLPR	2.7 (1.7-4.3)	2.4 (1.4-3.8)	2.7 (1.6-4.0)	0.280
WBC: White blood cell count, IQR: Interquartile range, MCV: Mean corpuscular volume, RDW: Red cell distribution width, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, NLPR: Neutrophil-to-lymphocyte*platelet ratio				

Table 4. Receiver operating characteristic analysis of NLPR, NLR, and PLR for the prediction of diagnosis								
	Cut point	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Youden's index**	**AUC**	**Metric Score**
NLPR	1,42	80.58%	96%	95.12%	83.62%	0.77	0.94	1.77
NLR	3,27	89.26%	95.60%	95.15%	90.19%	0.85	0.96	1.85
PLR	148	52.48%	81.20%	72.99%	63.84%	0.34	0.7	1.34
PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, NLPR: Neutrophil-to-lymphocyte*platelet ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio								

The cut-off values of NLR, PLR and NLPR were statistically significant in the diagnosis of acute appendicitis, and the AUC values were at a good level. According to the diagnostic test performance analysis report, the NLR, PLR, and NLPR were statistically significant predictors of the diagnosis of acute appendicitis with AUC values being calculated as 0.96 (0.919-0.95) for NLR at a cut-off value of 3.27, 0.70 (0.63-0.72) for PLR at a cut-off value of 148, and 0.94 (0.83-0.95) for NLPR at a cut-off value of 1.42. AUC of NLPR is presented in Figure 1.

DISCUSSION

In our study, it was determined that NLR, PLR and NLPR were effective in diagnosing acute appendicitis, and NLR, PLR and NLPR were not effective in distinguishing complicated and non-complicated acute appendicitis. In the ROC analysis of NLR, PLR and NLPR for the diagnosis of acute appendicitis, it was determined that NLR had the highest AUC value. NLPR, on the other hand, was found to be a strong predictor in diagnosing acute appendicitis with a value of 0.94 AUC. In addition, we have concluded that it cannot be an indicator of prognosis. As far as we could detect, there was no study showing the relationship between acute appendicitis and NLPR in terms of diagnosis and prognosis in adult patients over the age of 18 years. However, studies evaluating the relationship of acute appendicitis with hematological parameters were available in the literature[10-13].

In a study conducted in pregnant patients diagnosed with appendicitis, the lymphocyte value was statistically significantly lower in patients compared to the control group, similar to our study, and no statistically significant difference was observed in platelet values. NLR and PLR were found to be significantly higher than those in the control group[10]. In a meta-analysis, it was reported that NLR was effective in both the clinical course and diagnosis of acute appendicitis[11]. In a study conducted in pediatric acute appendicitis patients, NLR and NLPR were found to be statistically high in patients, and it was stated that these rates could be used in diagnosis[12]. In the literature, different results were obtained from our study in differentiating complicated and non-complicated acute appendicitis[2,13]. In a study comparing NLR and PLR in complicated and uncomplicated acute appendicitis cases, unlike our study, NLR and PLR were found to be statistically significantly higher in complicated acute appendicitis cases[2]. In a study by Ribeiro et al.[13] in which 841 patients with acute appendicitis were included, leukocyte value and NLR were statistically significantly higher in cases of complicated acute appendicitis than in cases of uncomplicated acute appendicitis. In a study by Uludağ et al.[17], including 702 acute appendicitis patients, it was found that perforation developed in 10% of the patients, and NLR and PLR were statistically significantly

higher in the perforated patient group compared to the non-perforated acute appendicitis patients.

Apart from acute appendicitis, sepsis[14], COVID-19[15], kidney damage after major surgery[16], pneumonia[18], inflammatory diseases such as spondylarthritis[19], decompensated heart failure[20], contrast nephropathy[21], minor surgery and even psychiatric diseases[22] were evaluated together with hematological parameters. In a study conducted in 173 patients diagnosed with sepsis, in which mortality was found to be close to 38%, a statistically significant correlation was found between the 5th day neutrophil and platelet values and mortality. In the same study, NLR and NLPR calculated on the 5th day were also found to have a statistically significant relationship with mortality[14]. In a study in which hematological parameters were examined in patients with a diagnosis of COVID-19 and 500 patients were included, there was no statistically significant relationship between neutrophil and platelet values and disease severity, although lymphocyte was statistically significantly lower in the severe COVID-19 patient group compared to mild COVID-19 patients. NLR and NLPR were statistically significantly higher in severe COVID-19 patients[15]. In a study examining the development of acute kidney injury after major abdominal surgery, no statistically significant correlation was found between postoperative neutrophil and platelet values and the development of acute kidney injury. However, there was a statistically significant correlation between low lymphocyte count and high NLPR and the development of acute kidney injury[16]. In an examination of pneumonia patients in inpatient and outpatient group and control group, it was determined that CRP, NLR and PLR were statistically significantly higher in inpatients and outpatients compared to the control group. In the same study, there was no statistically significant difference between inpatients and outpatients in terms of CRP, NLR, and PLR[18]. In a study examining spondylarthritis, it was reported that NLR and PLR could be considered as independent predictors in patients with severe sacroiliitis[19]. In a study evaluating cardiac deaths in patients with decompensated heart failure, NLR and PLR were found to be statistically significantly higher in cardiac deaths[20]. In a study examining the relationship between contrast nephropathy and hematological parameters and including patients with acute coronary syndrome, it was found that neutrophil lymphocyte and platelet values were not associated with contrast development. NLR and NLPR were also not associated with the development of contrast nephropathy[23]. In a prospective study examining patients who underwent septorhinoplasty, with a high postoperative periorbital ecchymosis score, while lymphocytes were statistically significantly lower, neutrophil and platelet values were not statistically significant. No statistically significant correlation was found between NLR and high periorbital ecchymosis score. PLR, on the other hand,

was statistically significantly higher[22]. In a study in which patients with a diagnosis of schizophrenia were compared with a healthy control group, neutrophils and lymphocytes were statistically significantly higher in patients with schizophrenia. No statistically significant correlation was found between platelet and NLR and schizophrenic patients. PLR was found to be statistically significantly lower in male patients compared to the control group[22]. In a study conducted in Turkey that evaluated the ability of hematological parameters to predict short-term mortality in patients with acute cholecystitis, there was a significant difference between survivors and non-survivors in terms of NLR, but not in terms of PLR. Additionally, among the combined hematological parameters evaluated, the parameter with the highest AUC value was NLR, which was 0.708[24]. In our study, while high levels of NLR, PLR and NLPR, as well as high neutrophil and low lymphocyte levels, were statistically significant in diagnosing acute appendicitis, it was determined that the platelet level was not statistically significant in diagnosing. It was determined that neutrophil, lymphocyte, and platelet levels were not statistically significant in the differentiation of complicated and non-complicated acute appendicitis.

Study Limitations

Since our study was planned retrospectively, the clinical progress of the patients was obtained from the records. Although the included patients were over the age of 18 years, they consisted of young patients and the number of patients diagnosed with complicated acute appendicitis was small.

CONCLUSION

NLR, PLR and NLPR can be used as predictors for the diagnosis of acute appendicitis, but according to our study, NLR, PLR and NLPR should not be used as prognostic indicators of acute appendicitis.

Ethics

Ethics Committee Approval: The instant study was carried out with the permission of the Ümraniye Training and Research Hospital Local Ethics Committee (date: 24/04/2023, decision no: B.10.1.TKH.4.34.H.GP.0.01/131).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: A.Ö., S.Ö., H.Ş.A., M.T.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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