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Direct bilirubin to lymphocyte ratio can discriminate acute appendicitis and ovarian torsion: a comparative study

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Abstract. – OBJECTIVE: In this study, we aimed to determine whether a patient presenting to the emergency room with abdominal pain and for whom ultrasound access is challenging until an ultrasound is performed, is suffering from ovarian torsion or acute appendicitis. We sought to make this determination based on hematological indices and to investigate the diagnostic value of the direct bilirubin-to-lymphocyte ratio (DLR) in this context.

PATIENTS AND METHODS: This study encompasses female patients who presented with abdominal pain to Çam and Sakura Training and Research Hospital between the years 2015 and 2023 and were diagnosed with either acute appendicitis or ovarian torsion. Patients' files were screened retrospectively. Key information, including patients' ages, the onset time of symptoms (duration of symptoms), and laboratory values, was meticulously recorded. The patients were divided into two groups: those with ovarian torsion (Group 1) and those with acute appendicitis (Group 2).

RESULTS: The study comprised two distinct patient groups with a total of 159 patients: Group 1 (n=57), representing ovarian torsion, and Group 2 (n=102) representing acute appendicitis. No differences were found in terms of age, symptom duration, White Blood Cell (WBC) Count, Platelet (PLT), CRP (C-reactive protein), and Platelet-to-lymphocyte ratio (PLR) ($p>0.05$ for each comparison). Direct bilirubin (DB), indirect bilirubin (IB), and total bilirubin (TB) were higher in Group 2 than in Group 1 ($p=0.011$, $p<0.001$, $p=0.044$, respectively). Neutrophil-to-Lymphocyte Ratio (NLR) and Direct Bilirubin-to-Lymphocyte Ratio (DLR) were higher in Group 2 than in Group 1 ($p=0.013$, $p=0.002$, respectively). The NLR was analyzed with a cut-off value of 4.1 (AUC: 0.642; sensitivity 82%, specificity 52%). The PLR was analyzed with a cut-off value of 116 (AUC: 0.670; sensitivity 92%, specificity 42%). The DLR was analyzed with a cut-off value of 0.14 (AUC: 0.741; sensitivity 93%, specificity 55%).

CONCLUSIONS: This research highlighted the potential of the DLR index in differentiating between ovarian torsion and acute appendicitis, revealing that DLR levels were notably higher in appendicitis patients.

Key Words:
Appendicitis, Ovarian torsion, Direct bilirubin to lymphocyte ratio.

Introduction

Ovarian torsion is a serious and urgent gynecological condition that occurs when the ovary twists around the ligaments that hold it in place, potentially cutting off blood flow[1]. It often presents with sudden and severe pain on the right side of the lower abdomen. Appendicitis, on the other hand, is an inflammation of the appendix, a small organ attached to the large intestine, and typically manifests with pain in the lower right abdomen as well[2,3]. Both conditions require prompt medical attention, but the underlying causes and treatments are quite different. Distinguishing between these two conditions can be challenging since they may present with similar symptoms, but accurate diagnosis is essential to guide appropriate medical management. Diagnostic tools such as ultrasound and examination of hematological indices can be valuable in differentiating these two conditions[2-4].

Appendicitis, a frequently occurring infection within the abdominal cavity, is often linked to bacteria such as *Escherichia coli* and *Bacteroides fragilis*[5,6]. When these bacteria cause bacteremia, it can result in endotoxemia and hindered excretion of bilirubin, thereby raising the levels of direct bilirubin in those with appendicitis. Additionally, individuals who suffer from appendicitis experience interrupted bile enterohepatic cycles and bacteremia because of bacterial translocation. These situations lead to inflammation, marked by an increase in the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the levels of direct bilirubin (DB), and direct bilirubin-to-lymphocyte ratio (DLR)[7,8].

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In the case of ovarian torsion, inflammation is not as pronounced as it is in acute appendicitis. Moreover, since there is no infectious process in ovarian torsion (or more accurately, it begins at a later stage), an increase in direct bilirubin and, consequently, in the DLR to the extent seen in appendicitis could not be observed. Therefore, in this study, we aimed to determine whether a patient presenting to the emergency room with abdominal pain and for whom ultrasound access is challenging until an ultrasound is performed, is suffering from ovarian torsion or acute appendicitis. We sought to make this determination based on hematological indices and to investigate the diagnostic value of the DLR in this context.

Patients and Methods

This study encompasses female patients who presented with abdominal pain to Çam and Sakura Training and Research Hospital between the years 2015 and 2023 and were diagnosed with either acute appendicitis or ovarian torsion. Following the acquisition of the Ethical Committee Approval, the research commenced. Patients' files were screened retrospectively. Key information, including patients' ages, the onset time of symptoms (duration of symptoms), and laboratory values, was meticulously recorded.

The patients were divided into two groups: those with ovarian torsion (Group 1) and those with acute appendicitis (Group 2). The diagnoses of the patients were confirmed through surgical intervention and histopathological examination.

Clinical Monitoring

All female patients presenting to the emergency department with abdominal pain underwent a physical examination. If the examination suggested an acute abdomen, the patient was tested for hemogram and biochemical laboratory parameters. Subsequently, an x-ray was taken for all patients. Ultrasound was performed for differential diagnosis of acute abdomen to determine whether it was ovarian torsion or acute appendicitis. However, ultrasound is not always available, or access to ultrasound may not be easy. In this context, the patient's diagnosis was estimated based on hemogram parameters. Nevertheless, the presence of an acute abdomen in the patient is a sufficient reason to consult pediatric surgery. If the pediatric surgery specialist believed that the patient may have had ovarian torsion, the patient was taken to emergency surgery. However, if acute appendicitis was more strongly suspected rather than ovarian torsion, we tended to perform surgery with less urgency. In some cases, we even apply non-operative management.

Inclusion Criteria

For this study, only female patients aged between 5 and 18 were included. Those with properly documented data in retrospective file reviews were enrolled in the study.

Exclusion Criteria

Any individuals who did not meet the inclusion criteria were excluded from the study. This would mean that male patients or those outside the specified age range of 5 to 18, or those with improperly documented data, were not considered for participation in the research.

Statistical Analysis

The analysis of the patient data was carried out using descriptive statistics, including the frequency and other specific attributes for every item. For continuous data, the mean and standard deviation were calculated to present the information. Normality in continuous data was evaluated using Shapiro-Wilk and Kolmogorov-Smirnov tests. If the data deviated from a normal distribution, non-parametric methods were employed as a substitute for the Student's *t*-test, which is typically used for continuous and normally distributed variables. In the case of categorical variables, Chi-square tests were employed, and where required, Fisher's exact tests were utilized. The diagnostic efficacy of the NLR, PNLR, and DLR was examined through Receiver Operating Characteristic (ROC) analysis. All data were processed using SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). A value of $p<0.05$ was considered statistically significant.

Results

The study comprised two distinct patient groups with a total of 159 patients: Group 1 (n=57), representing ovarian torsion, and Group 2 (n=102) representing acute appendicitis. No differences were found in terms of age, symptom duration, White Blood Cell (WBC) Count, Platelet (PLT), CRP, and Platelet-to-lymphocyte ratio (PLR) ($p>0.05$ for each comparison). The mean Neutrophils (NEU) values significantly

differed between Group 1 and Group 2, being 10.26 (SD=3.32) and 11.98 (SD=2.93), respectively (p=0.002). A significant difference was found between the groups for Lymphocytes (LYM), with Group 1 having a mean of 2.26 (SD=1.08) and Group 2 having a mean of 1.55 (SD=0.55) (p=0.001). Direct bilirubin (DB), indirect bilirubin (IB), and total bilirubin (TB) were higher in Group 2 than Group 1 (p=0.011, p<0.001, p=0.044, respectively). Neutrophil-to-Lymphocyte Ratio (NLR) and Direct Bilirubin-to-Lymphocyte Ratio (DLR) were higher in Group 2 (p=0.013, p=0.002, respectively) (Table I).

The NLR was analyzed with a cut-off value of 4.1. The area under the curve (AUC) was found to be 0.642, demonstrating a moderate ability to discriminate between ovarian torsion and appendicitis. The sensitivity and specificity were 82% and 52%, respectively. The positive predictive value (PPV) was 75%, and the negative predictive value (NPV) was 60%. For PLR, a cut-off value of 116 was used. The AUC for this index was 0.67, reflecting a reasonable discriminative ability. Sensitivity was found to be high at 92%, while specificity was 47%. The PPV and NPV were 75% and 76%, respectively. Direct DLR had a cut-off value of 0.14, with an AUC of 0.741, indicating the best classification performance. Sensitivity was very high at 93%, and specificity was 55%. The PPV and NPV for this ratio were 79% and 81%, respectively (Table II and Figure 1).

Discussion

Secondary to ovarian torsion (OT), ovarian tissue necrosis sets off systemic inflammation, meaning that inflammatory markers may be valuable in detecting OT[9]. In addition to specific markers like interleukin-6, interleukin-8, tumor necrosis factor-α, and E-selectin,12 have been suggested for pinpointing OT. Complete blood cell count (CBC) parameters present benefits such as widespread availability, rapid analysis, and cost efficiency[10,11]. Elevated levels of WBC and neutrophils, along with reduced lymphocytes, have been noted in OT cases among adults in past studies[12,13]. This inflammatory reaction likely

Table I. Comparison of ovarian torsion and appendicitis cases in terms of laboratory findings and hematological indexes.

	Group 1 (n=57)		Group 2 (n=102)		
	Mean	SD	Mean	SD	*p*-value
Age	12.8	2.91	12.2	3.27	0.216
Symptom duration (h)	19.5	9.3	24.7	14.6	0.145
WBC	13.86	3.01	14.68	2.79	0.109
NEU	10.26	3.32	11.98	2.93	0.002
LYM	2.26	1.08	1.55	0.55	0.001
PLT	313	97	302	82	0.452
IB	0.49	0.41	0.69	0.46	0.011
DB	0.34	0.32	0.59	0.38	<0.001
TB	0.99	0.92	1.27	0.87	0.044
CRP	18.6	30.27	36.26	54.6	0.117
NLR	5.8	5.21	8.24	6.16	0.013
PLR	185	136	228	131	0.053
DLR	0.253	0.346	0.472	0.449	0.002

SD: standart deviation. NLR: Neutrophil-to-Lymphocyte Ratio; DLR: Direct Bilirubin-to-Lymphocyte Ratio; PLR: Platelet to lymphocyte ratio; CRP: C-reactive protein; TB: Total bilirubin, IB: Indirect bilirubin, DB: Direct bilirubin; PLT: Platelet; LYM: Lymphocyte; NEU: Neutrophil; WBC: White blood count.

Table II. ROC Analysis of the indices.

Index	Cut-off	AUC	Sensitivity	Specificity	PPV	NPV
NLR	4.10	0.642	82%	52%	75%	60%
PLR	116.00	0.67	92%	47%	75%	76%
DLR	0.14	0.741	93%	55%	79%	81%

NLR: Neutrophil-to-Lymphocyte Ratio; DLR: Direct Bilirubin-to-Lymphocyte Ratio; PLR: Platelet to lymphocyte ratio; AUC: Area under curve; PPV: Positive predictive value, NPV: Negative predictive value.

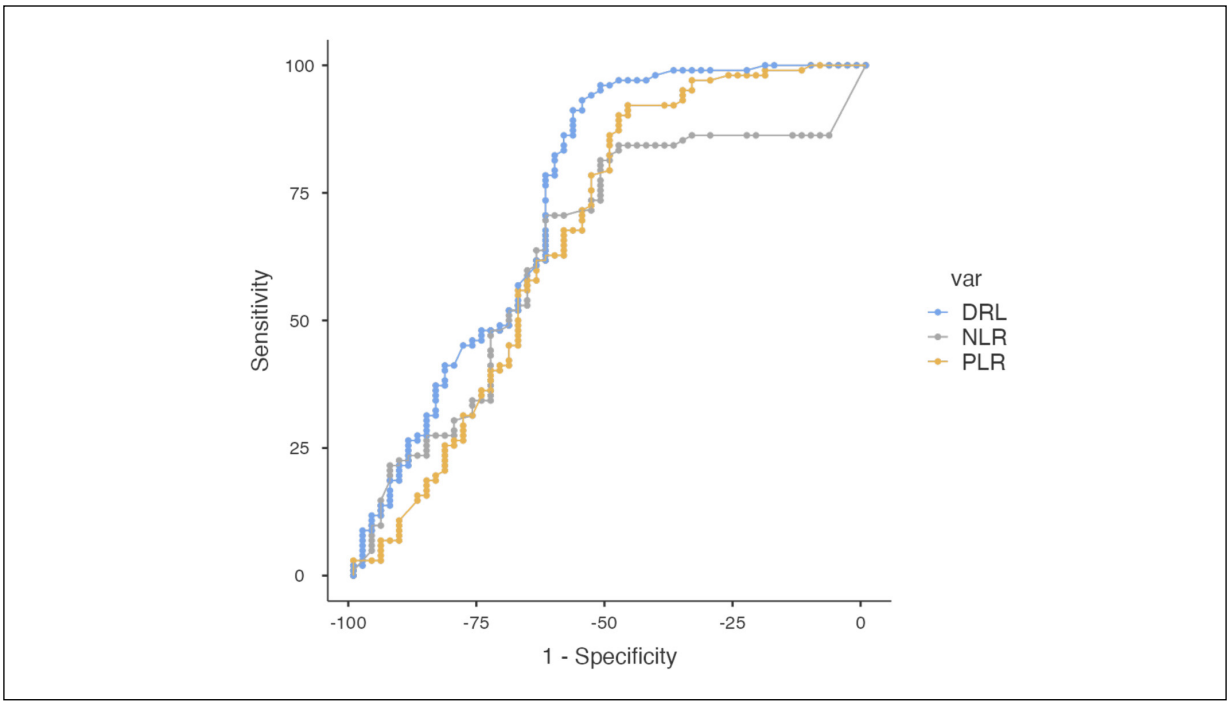

Figure 1. ROC Curves.

stems from acute ischemia caused by torsion, which is sustained by neutrophils through the release of inflammatory agents. Lymphocytes play a crucial role in long-term inflammation, facilitating the healing process by infiltrating the affected and reperfused tissue[12]. Recently a study[13] has reported that before surgery they can serve as a distinguishing marker for the diagnosis of adnexal torsion, and it has the ability to differentiate between adnexal torsion and ovarian cysts.

Many past research[14-16] efforts have looked into the impacts and outcomes of various blood tests in the lab on distinguishing between, diagnosing, treating, and understanding the complications of both simple and complicated appendicitis. Lately, particular focus has been given to specific parameters, such as the ratios of neutrophils to lymphocytes and platelets to lymphocytes[16]. In a meta-analysis conducted by Azizoğlu et al[17], it was determined that the values for total bilirubin, direct bilirubin, and indirect bilirubin were elevated in cases of complicated appendicitis compared to simple appendicitis. The study concluded that both total bilirubin and direct bilirubin could be utilized as diagnostic indicators in childhood appendicitis to distinguish between complicated and simple forms of the condition.

Appendicitis, a common abdominal infection often tied to bacteria like *Escherichia coli* and *Bacteroides fragilis*, can lead to complications such as endotoxemia and increased direct bilirubin levels6. The infection interferes with the excretion of bilirubin and disrupts bile enterohepatic cycles, contributing to inflammation marked by elevated neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and direct bilirubin levels[7,8,18]. In contrast, inflammation in ovarian torsion is less pronounced than in acute appendicitis and lacks an early infectious process, leading to no noticeable increase in direct bilirubin or DLR.

Up to the present, this research is the first study to emphasize the employment of the DLR index in distinguishing between ovarian torsion and acute appendicitis in the context of differential diagnosis.

The NLR and DLR were found to be higher in the appendicitis group compared to the ovarian torsion group. Specifically, the DLR demonstrated significant diagnostic performance with an AUC of 0.741 in the ROC analysis. We determined that in acute appendicitis patients, the DLR level was higher than in patients with ovarian torsion. From this perspective, this study presents important findings regarding the use of the preoperative DLR index in the differential diagnosis of these two conditions.

Limitations

The most significant limitations of this study include its retrospective nature, the insufficient

number of patients, and the fact that it was conducted in a single center. These factors may affect the generalizability and robustness of the findings, necessitating careful interpretation and application of the results.

Conclusions

This research highlighted the potential of the DLR index in differentiating between ovarian torsion and acute appendicitis, revealing that DLR levels were notably higher in appendicitis patients. Further prospective studies are needed for the validation of these indexes.

Conflict of Interest
The authors declare no conflict of interest.

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Ethics Approval
The ethics approval of this study was obtained from the Local Ethical Committee of Başakşehir Çam and Sakura Training Hospital (number: KAEK/26.07.2023.442).

Informed Consent
Informed consent was obtained from all patients and their guardians.

Data Availability
Data are available upon request from the author.

Authors' Contributions
Research concept and design: BK, MÖK.
Data analysis and interpretation: BK, MÖK.
Collection and/or assembly of data: BK.
Writing the article: BK.
Critical revision of the article: MÖK.
Final approval of the article: BK, MÖK.

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