Mevlana Tıp Bilimleri Dergisi
Mevlana Medical Sciences
eISSN:2757-976X

ARAŞTIRMA MAKALESİ/RESEARCH ARTICLE DOI:http:/dx.doi.org/10.56752/Mevmedsci.2024.71
Mev Med Sci, 2024; 4(3): 113-118

The Predictive Value of Inflammatory Biomarkers in Distinguishing Testicular Torsion and Epididymo-Orchitis in the Emergency Department

Acil Serviste Testis Torsiyonu ve Epididimo-Orşit Ayrımında İnflamatuar Biyobelirteçlerin Öngörü Değeri

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Makale Tarihleri/Article Dates:
Geliş Tarihi/Received: 11 May 2024
Kabul Tarihi/Accepted: 03 October 2024
Yayın Tarihi/Published Online: 22 December 2024

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Açıklama/Disclosure: Yazarların hiçbiri, bu makalede bahsedilen herhangi bir ürün, aygıt veya ilaç ile ilgili maddi çıkar ilişkisine sahip değildir. Araştırma, herhangi bir dış organizasyon tarafından desteklenmedi. Yazarlar çalışmanın birincil verilerine tam erişim izni vermek ve derginin talep ettiği takdirde verileri incelemesine izin vermeyi kabul etmektedirler.

ÖZET

Amaç: Bu çalışmada akut skrotumlu hastalarda testis torsiyonu ve epididimo-orşit ayrımında pan immün inflamasyon değeri, sistemik immün inflamatuar indeks ve sistemik inflamasyon yanıt indeksinin tanısal değerini belirlemeyi amaçladık.
Yöntemler: Bu retrospektif gözlemsel çalışma, acil servise testis ağrısı şikayetiyle başvuran 18 yaş ve üzeri erkek hastalar arasında gerçekleştirildi. Hastalar iki gruba ayrıldı: Ameliyat edilen testis torsiyonu grubu (n= 93); epididimo-orşit tedavisi gören epididimo-orşit grubu (n=125).
Bulgular: Çalışmaya toplam 218 hasta (testis torsiyonu: 93, epididimo-orşit: 125) dahil edildi. Testis torsiyonu tespitinde Nötrofil/lenfosit oranı, sistemik immün-inflamatuar indeks ve sistemik inflamasyon yanıt indeksinin kabul edilebilir tanısal güce sahip olduğu bulundu (Eğri altındaki alan: sırasıyla 0,75, 0,77 ve 0,78). Pan immün inflamasyon değeri, belirlenen > 980,93 kesme noktasıyla (Eğri altındaki alan: 0,81, %95 Güven aralığı: 0,76-0,86, <0,001) TT'yi tespit etmede mükemmel bir tanısal güce sahipti.
Sonuç: Acil serviste testis torsiyonu ve epididimo-orşit ayrımında ucuz, kolay ulaşılabilir ve hızlı sonuç üreten Pan immün inflamasyon değeri, sistemik immün inflamatuar indeks ve sistemik inflamasyon yanıt indeksinin kullanılması önerilebilir. Pan immün-inflamasyon değeri, testis torsiyonunu öngörmede diğer indekslere göre üstün bir indekstir.

Anahtar Kelimeler: Testis torsiyonu, epididimo-orşit, pan immün-inflamasyon değeri, inflamatuar indeks, acil hekimi

ABSTRACT

Aim: This study aimed to determine the diagnostic value of pan immune-inflammation value, systemic immune-inflammatory index, and systemic inflammation response index in differentiating testicular torsion and epididymo-orchitis in patients with acute scrotum.
Methods: This retrospective observational study was conducted among male patients aged 18 and older who presented to the emergency department with testicular pain. The patients were divided into two groups: the operated testicular torsion group (n=93); epididymo-orchitis group treated for epididymo-orchitis (n=125).
Results: A total of 218 patients (testicular torsion:93, epididymo-orchitis:125) were included in the study. Neutrophil/lymphocyte ratio, systemic immune-inflammatory index and systemic inflammation response index were found to have acceptable diagnostic power in testicular torsion detection (The Area Under the Curve:0.75, 0.77, and 0.78, respectively). Pan immune-inflammation value had an excellent diagnostic power in detecting testicular torsion, with >980.93 cut-off determined (The Area Under the Curve:0.81, %95Confidence interval:0.76-0.86,<0.001).
Conclusion: In the emergency department, it can be recommended to utilize pan immune-inflammation value, systemic immune-inflammatory index, and systemic inflammation response index, which are inexpensive, easily accessible, and produce quick results in the differentiation of testicular torsion and epididymo-orchitis. Pan immune-inflammation value is a superior index in predicting testicular torsion compared to other indexes.

Key words: Testicular torsion, epididymo-orchitis, pan immune-inflammation value, inflammatory index, emergency physician

Atıf yapmak için/ Cite this article as: Vural N, Duyan M, Saridas A, Ertas E, Guven HC. The Predictive Value of Inflammatory Biomarkers in Distinguishing Testicular Torsion and Epididymo-Orchitis in the Emergency Department. Mev Med Sci. 2024; 4(3): 113-118

INTRODUCTION

Testicular torsion (TT) is a urological emergency in which a testis rotates about its longitudinal axis and twists the spermatic cord, resulting in loss of perfusion to the homolateral testicles. The annual incidence of TT is approximately 1 in 4,000 males younger than 25 (1). TT typically presents with abrupt onset of unilateral scrotal pain. Clinical findings that best predict TT include nausea and vomiting, past trauma, tender testicle, abnormal testicular location (i.e., elevated or transverse), and absence of cremasteric reflex (2). Early detection and treatment are critical to saving the testis and preserving future fertility (3). The optimal time to maintain testicular vitality after TT is 4-6 hours (4). After this time and before 12 hours, there is still a 50% chance of testicular viability, but this chance drops to 10% after 24 hours, followed by a large risk of atrophy and loss of testicles after 24 hours (5).

Epididymo-orchitis (EO) is a male urological disease characterized by epididymis and ipsilateral testis inflammation (6). TT is most common in the post-adolescent period between 12 and 18 years, while EO is the most common cause of acute scrotum in adults (7). It is difficult to distinguish the causes of acute scrotum only on clinical findings and examination, especially TT and EO. Therefore color Doppler ultrasonography (USG) is often used to differentiate a serious condition like TT (8). However, USG is a costly and laborious procedure that requires trained specialists and is not available in every center. Consequently, more useful, easily available, and affordable diagnostic methods are required to distinguish between TT and EO. In addition, a diagnostic tool is required to detect possible TT in centers without USG and to refer the patient to a higher center.

It has been observed that hematological parameters such as leukocyte count, platelet count, mean platelet volume (MPV), platelet/lymphocyte ratio (PLR), and neutrophil/lymphocyte ratio (NLR) are useful in the differentiation of TT and EO (9). A prognostic and diagnostic indicator based on neutrophil, lymphocyte, and platelet counts called systemic immune-inflammatory index (SII) has recently been developed. Pan immune inflammation value (PIV), SII, and systemic inflammation response index (SIRI) are indexes that have recently been used in the diagnostic processes of prostate and testicular cancer types (10–12). However, to the best of our knowledge, there has been no study on detecting PIV, SII, and SIRI in the TT diagnostic process. This study aimed to determine the diagnostic value of PIV, SII and SIRI in differentiating TT and EO in patients with acute scrotum.

MATERIALS AND METHODS

Study design and settings

Patients were enrolled between March 20, 2019, and March 20, 2023 in this retrospective observational study amongst adult males admitted to the emergency department (ED) with a complaint of testicular pain. The local ethics committee approved the study, which waived the obligation to obtain informed consent (ethics committee decision number: 2023/86, date: March 20, 2023). The current study was carried out in accordance with the Helsinki Declaration.

Post hoc power analysis

The main outcome variable, the NLR value, was used to determine the reliability assessment (post-study power) of the number of patients included in the groups. While NLR was 7.52±3.84 in TT patients, it was 5.72±4.21 in patients with EO. According to the difference in NLR levels between the independent group averages, the post-study power was 99 %. According to the difference in the secondary outcome variables SII, SIRI and PIV the post-study power was above 80%.

Study protocol

Data were scanned retrospectively from our hospital information system. Patients aged 18 years and older who presented to the ED with acute scrotal pain were included in the study.

Exclusion criteria were testicular trauma, testicular surgery history, previous hematologic and chronic liver disease, anticoagulant and steroid use, previous testicular exploration with normal results, other acute and chronic infections, and missing data. After 15 out of a total of 233 patients were excluded, 218 patients were included in the study.

The diagnostic process of the patients was supported by physical examination, imaging, and laboratory tests. All patients underwent scrotal USG by a radiologist in the ED. The patients were examined by a urologist, and those diagnosed with TT were operated on. The patients were divided into two groups: the operated TT group (n =93) and EO group treated for EO (n =125).

Laboratory analyses

An automated hematology analyzer (Coulter Gen-S Hematology Analyzer; Beckman Coulter Corp, Hialeah, FL, USA) was used to determine the full blood count (FBC). Haematological parameters total leucocyte count and differential, haemoglobin, haematocrit, platelet levels, NLR, PIV, SII and SIRI values were recorded. The NLR, PIV, SII and SIRI were defined as "neutrophil count/lymphocyte count", "neutrophil count × platelet count × monocyte count/lymphocyte count", "neutrophil count × platelet count/lymphocyte count", and "neutrophil × monocyte/lymphocyte count", respectively.

Data analysis

Parametric tests were used without the normality test due to the compatibility of the central limit theorem (13). In the analysis of the data, the mean and standard deviation and minimum and maximum values of the features were used

while performing the statistics of continuous data. Categorical variables were defined using frequency and percentage values. Student's t test statistics were used to compare TT and EO. The cutoff in diagnostic value measurements was determined using the receiver operating characteristic (ROC) analysis. Statistical significance was determined by the statistics of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The area under the curve (AUC) of 0.5 to 0.6 was interpreted as poor, 0.6 to 0.7 as fair, 0.7 to 0.8 as acceptable, 0.8 to 0.9 as excellent, and >0.9 as outstanding. Comparison of ROC curves for NLR, SII, SIRI, and PIV were evaluated with a pairwise comparison of ROC curves and a 95% confidence interval. The level of statistical significance of the data is considered P < 0.05. New York software (e-picos, New York, NY, USA, www.e-picos.com) and the MedCalc statistical package program (MedCalc Software Ltd., Ostend, Belgium) were used for data evaluation and post-study power analysis.

RESULTS

A total of 218 patients (TT: 93, EO: 125) were included in the study. The mean age of patients with TT was 28.8±6.9 years, and the mean age of patients with EO was 35.5±5.8 years. Patients with TT were significantly younger than patients with EO (p= 0.001). Table 1 shows the ages of the patients and the mean and standard deviation values of the studied indexes. Mean white blood cells (WBC), platelet count, neutrophil count, monocyte count, NLR, SII, SIRI, and PIV were higher in the TT group (p= 0.001). The mean of lymphocyte count was found to be significantly higher in the EO group (p= 0.001) (Table 1).

In Table 2, the diagnostic accuracy of the important indexes in the differential diagnosis of TT and EO in ROC analysis is given in detail (Table 2, Figure 1). NLR, SII and SIRI were found to have acceptable diagnostic power in TT detection (AUC: 0.75, 0.77, and 0.78, respectively). PIV had an excellent diagnostic power in detecting TT, with >980.93 cut-off determined (AUC: 0.81, 95% Cl: 0.76-0.86, <0.001). In addition, the sensitivity of the test was 91.4%, specificity was 60.8%, positive predictive value was 63.4% and negative predictive value was 90.5%, respectively (Table 2, Figure 1).

The similarities of NLR, SII, SIRI, and PIV in diagnosing TT were evaluated by ROC curve comparison. While there was no significant difference between NLR and SII, between

Table 1. Comparison of basic and laboratory characteristics of study groups

	Total (n=218)	Testicular torsion (n=93)	Epididymo-Orchitis (n=125)	
Features	x̄±SD	x̄±SD	x̄±SD	p-value*
Age	32.6±7.2	28.8±6.9	35.5±5.8	0.001
PLT (103mcL)	282.28±60.07	304.48±61.61	265.76±53.41	0.001
NEU (103mcL)	9.69±6.02	10.05±2.21	9.09±7.69	0.001
LYM (103mcL)	1.71±0.57	1.53±0.39	1.84±0.64	0.001
MON (103mcL)	0.87±0.37	1.03±0.41	0.74±0.26	0.001
NLR	6.49±5.07	7.52±3.84	5.72±4.21	0.009
SII	1861.75±1416.21	2319.76±1351.58	1520.99±1370.94	0.001
SIRI	5.87±4.32	7.81±5.73	4.42±3.27	0.001
PIV	1692.45 ±1303.09	2373.38 ±1863.41	1185.84 ±918.17	0.001

Student's t test (p<0.05 significance)
WBC: White Blood Cells, PLT: Platelets, NEU: Neutrophil, LYM: Lymphocyte, MON: Monocyte, NLR: Neutrophil to Lymphocyte Ratio, SII: Systemic Immune Inflammation Index, SIRI: Systemic Inflammation Response Index, PIV: Pan-Immune Inflammation Value

Table 2. Diagnostic accuracy of inflammatory parameters for differentiation of testicular torsion from epididymo-orchitis

Testicular torsion:93 Epididymo-Orchitis :125	AUC	Cut-off	Sensitivity %	Specificity %	AUC 95% CI	P-value	PPV %	NPV%
NLR	0.75	>5.71	74.19	71.21	0.68-0.80	<0.001	65.7	78.8
SII	0.77	>1366.46	82.1	62.4	0.71-0.83	<0.001	63.1	85.7
SIRI	0.78	≥4.35	81.7	67.2	0.73-0.84	<0.001	65.2	83.2
PIV	0.81	>980.93	91.4	60.8	0.76-0.86	<0.001	63.4	90.5

AUC, Area Under Curve; SE, Standard Error; PPV, Positive Predictive Value; NPV, Negative Predictive Value; CI, Confidence Interval;
NLR: Neutrophil to lymphocyte Ratio, SII: Systemic Immune Inflammation Index, SIRI: Systemic Inflammation Response Index, PIV: Pan-Immune Inflammation Value

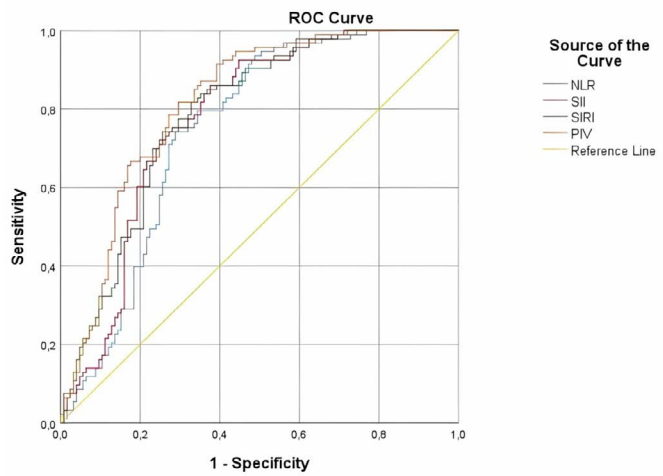

Figure 1. Receiver operating characteristic curve analysis of inflammatory parameters for differentiation of testicular torsion from epididymo-orchitis
ROC: Receiver Operating Characteristic, NLR: Neutrophil to Lymphocyte Ratio, SII: Systemic Immune Inflammation Index, SIRI: Systemic Inflammation Response Index, PIV: Pan-Immune Inflammation Value

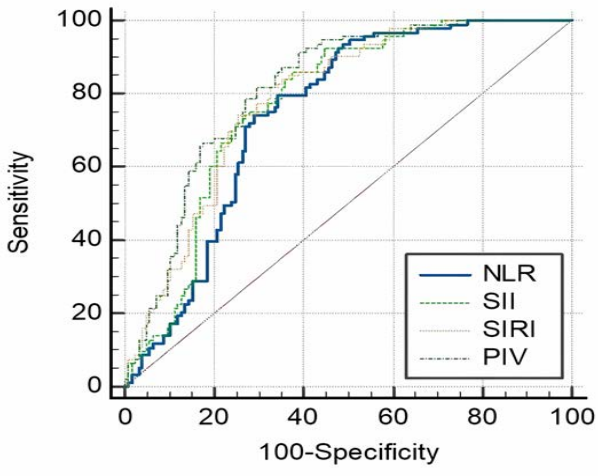

Figure 2. Pairwise comparison of ROC curves ve Difference between areas 95% Confidence Interval
ROC: Receiver Operating Characteristic, NLR: Neutrophil to lymphocyte Ratio, SII: Systemic Immune Inflammation Index, SIRI: Systemic Inflammation Response Index, PIV: Pan-Immune Inflammation Value

Table 3. Pairwise comparison of ROC curves ve Difference between areas 95% Confidence Interval

	Difference between areas	95% Confidence Interval	p value
NLR-SII	0.029	-0.003-0.061	0.08
NLR-SIRI	0.039	-0.012-0.092	0.13
NLR-PIV	0.068	0.018-0.118	0.01
SII-SIRI	0.011	-0.045-0.067	0.69
SII-PIV	0.039	-0.004-0.083	0.07
SIRI-PIV	0.028	0.005-0.052	0.02

ROC: Receiver Operating Characteristic, NLR: Neutrophil to Lymphocyte Ratio, SII: Systemic Immune Inflammation Index, SIRI: Systemic Inflammation Response Index, PIV: Pan-Immune Inflammation Value

NLR and SIRI, between SII and SIRI, and between SII and PIV (p>0.05), there was a difference between other diagnostic parameters used in the diagnosis (p>0.05). As a result, parameters with insignificant p values in Table 3 can be used interchangeably in the diagnosis of TT, but NLR and SIRI cannot be used instead of PIV (Table 3, Figure 2).

DISCUSSION

Diagnosing and managing acute scrotal pain remain challenging problems for emergency physicians. Since torsion may occur again, even in patients with torsion and orchiopexy before, also these patients should be approached with the same sensitivity (14). Early diagnosis of TT is very important for timely scrotal exploration and salvage of the affected testis. It has been reported in previous studies that some inflammatory indices such as platelet mass index (PMI), PLR, and NLR can be used in the diagnosis of TT (15–17). In this study, we found that PIV, SII and SIRI can be used in the differential diagnosis of TT and EO to consider in favor of TT. Additionally, when we compared the diagnostic power of these parameters, we found that PIV was superior to other indices.

Neutrophils, being the progenitor cells of inflammation, serve as the primary triggers of inflammatory processes. NLR has been shown to play a decisive role in the prognosis of acute and chronic inflammatory processes (18). In the study of Bitkin et al., NLR was similar in the epididymitis and torsion groups, but it was significantly higher in both groups compared to the control group (9). Similarly, in the study of Girgin et al., while NLR was similar in TT and EO groups, it was higher than in the control group (15). Güneş et al. compared only TT and the healthy group and showed that NLR could predict TT with a cut-off of 2.95 (84% sensitivity, 92% specificity) (16). In this study, NLR was relatively larger in the TT group. However, NLR had lower sensitivity and

specificity with a higher cut-off.

The SII has been shown in many studies to be associated with poor prognosis in many malignancies (19). Başbuğ et al. found that SII helps predict outcomes in the prediction of sperm presence during microdissection testicular sperm extraction (20). Wang et al. found that SII could predict testicular germ cell tumors with a cut-off of 881.24 (AUC: 0.725, Sensitivity: 45.7%, specificity: 91.4%) (11). Yang et al. demonstrated that high SII might indicate unfavorable prognoses in patients with testicular diffuse large B-cell lymphoma (21). However, we found no information on using SII in the TT diagnostic process in the literature. In this study, we determined that SII may contribute to the diagnostic period of TT and EO.

SIRI, which combines the absolute values of neutrophils, monocytes, and lymphocytes, is a new inflammatory index widely accepted in disease diagnosis and prognosis assessment in recent years (22). Zhang et al. found that SIRI predicted 90-day mortality with 0.6216 AUC in stroke patients (23). Chai et al. showed that it could be used to diagnose bacteria-negative pulmonary tuberculosis with a cut-off of 0.97 and AUC of 0.82 (24). Bumbasirevic et al. found that SIRI had AUC: 0.714 in predicting metastatic disease in patients diagnosed with testicular germ cell tumor (683.21 cut-off, specificity: 66.10%, sensitivity: 70.37%) (12). In this study, SIRI was useful in distinguishing EO, an inflammatory process, and TT, which may require urgent surgery.

PIV, a new equation that includes neutrophil count, platelet count, monocyte count, and lymphocyte count from peripheral blood, has been reported as a prognostic index in some cancer types (25). Zhu et al. revealed that PIV is a potential marker for predicting prostate cancer (10). Kazan et al. found that a PIV of 447.4 had 100% sensitivity and 70.6% specificity in predicting non-remission in patients with idiopathic low- and intermediate-risk membranous nephropathy (26). Gambichler et al. discovered that patients with Merkel cell carcinoma had a PIV greater than 372 and higher as independent predictors of disease stage and recurrence (27). However, the relationship of PIV with the acute scrotum diagnostic process was unclear. This study determined that PIV is an important predictor of TT diagnosis and superior to other indices.

Since these indexes can be used to give an idea about the necessity of USG, they may also have benefits such as a decrease in the number of referrals and consultations. However, since Doppler USG is still the reference examination, USG should be delayed. In cases where there is doubt despite Doppler USG, examinations such as scintigraphy and magnetic resonance imaging (MRI) can be used without disrupting emergency treatment, but in case of doubt, surgical exploration is required for diagnosis and treatment.

There are some limitations in this study. This study was conducted retrospectively in a single center and included relatively few patients. Only the adult age group was included in our study. This study may be suggestive for this study to be carried out in the pediatric age group as well. USG, which is necessary for physical examination, surgical treatment, and diagnosis, was performed by different physicians and radiologists. In addition, since the follow-up and post-treatment values of the indexes were not included in the study, it was impossible to compare them with the baseline values. These indices may also increase in other causes that cause acute scrotum, such as testicular appendix torsion, incarcerated inguinal hernia, hydrocele, testicular tumor, and leukemic infiltration. Not including these cases in the study is a limitation. However, since TT and EO are the most frequent admissions to the emergency department, it is thought that these indices may be useful.

CONCLUSION

The use of PIV, SII and SIRI, which are cheap, easily accessible and provide rapid results in the distinction between TT and EO in the emergency department, may be recommended to support the suspicion in favor of TT. PIV is a superior index to other indexes in supporting the suspicion of TT.

Etik Kurul: Prof. Dr. Cemil Taşçıoğlu City Hospital Ethics Committee approved the study, which waived the obligation to obtain informed consent (ethics committee decision number: 2023/86, date: March 20, 2023). The current study was carried out in accordance with the Helsinki Declaration.

Çıkar Çatışması: Çalışmada herhangi bir çıkar çatışması yoktur.

Finansal Çıkar Çatışması: Çalışmada herhangi bir finansal çıkar çatışması yoktur.

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