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Systemic Immune-Inflammation Index Can Predict Clinically Significant Prostate Cancer in Patients with Atypical Small Acinar Proliferation: Descriptive Study

Sistemik İmmün-İnflamasyon İndeksi, Atipik Küçük Asiner Proliferasyonu Olan Hastalarda Klinik Olarak Anlamlı Prostat Kanserini Öngörebilir: Tanımlayıcı Çalışma

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ABSTRACT Objective: Atypical small acinar proliferations (ASAP) is defined as lesion without adequate histological atypia to be diagnosed as prostate cancer (PCa) upon prostate biopsy. The main purpose of this study was to investigate the markers that can predict clinically significant (cs)-PCa before a re-biopsy in patients with ASAP. **Material and Methods:** 2,845 cases were performed prostate biopsy due to elevated prostate-specific antigen (PSA) level and/or significant digital rectal examination findings in our clinic between January 2008 and May 2019 were evaluated. In 238 of 2,295 prostate biopsy patients ASAP was revealed and 130 cases whose data were reached taken into the study. **Results:** 78 (60%) patients were reported as benign and 52 (40%) had PCa after re-biopsy. The f/t PSA ratio was 0.21 and 0.17 in benign and malign groups (p=0.001). There was a significant difference in the systemic immune-inflammation (SII) values between patients with an International Society of Urology Pathology (ISUP) grade 1 and those with an ISUP grade ≥2 (p=0.03) Additionally, there was a statistically significant difference in SII values between Group 1 and patients with an ISUP grade ≥2 (p=0.027). However, there were no significant differences between the groups in the total-PSA, PSA density, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio values. **Conclusion:** ASAP is a well-defined risk factor for PCa. An examination of SII marker before second biopsy may prove to be an active factor in predicting the cs-PCa diagnosis. Early diagnosis and treatment of cs-PCa will make a positive contribution to management protocols of the disease.

Keywords: Biopsy; prostate; prostatic neoplasms

ÖZET Amaç: Atipik küçük asiner proliferasyonlar (ASAP); prostat biyopsisi sonrası prostat adenokarsinom tanısını koyabilmek için yeterli miktarda histolojik atipisi olmayan lezyon olarak tanımlanmaktadır. Çalışmanın ana amacı; ilk biyopsisi ASAP gelen hastaların re-biyopsi öncesinde klinik anlamlı prostat kanserini (PKa) öngörebilecek belirteç varlığının araştırılması ve klinik kullanıma koyulmasıdır. **Gereç ve Yöntemler:** Ocak 2008-Mayıs 2019 tarihleri arasında kliniğimizde prostat spesifik antijen (PSA) yüksekliği ve/veya anlamlı parmakla rektal muayene bulguları nedeniyle prostat biyopsisi yapılan 2.845 olgu değerlendirildi. 2.295 hastanın patoloji sonucuna ulaşılabildi ve ASAP olan 238 hastanın 130'unun verilerine ulaşılabildi ve çalışmaya alındı. **Bulgular:** ASAP sonuçlanan ilk biyopsi ardından hastalara yapılan ikinci biyopsinin 78'i (%60) benign ve 52'si (%40) PKa olarak raporlandı. f/t PSA değeri 1. grupta ortalama 0,21 iken 2. grupta 0,17 olarak daha düşük hesaplandı ve gruplar arasındaki bu fark istatistiksel olarak anlamlı bulundu (p=0,001). Uluslararası Ürolojik Patoloji Derneği (ISUP) derecesi 1 olan hastalar ile ISUP derecesi ≥2 olan hastalar arasında sistemik immün inflamasyon (SII) değerlerinde anlamlı fark vardı (p=0,03). Ayrıca benign patolojisi olan hastaların yer aldığı Grup 1 ile ISUP derecesi ≥2 olan hastaların SII değerleri arasında istatistiksel olarak anlamlı fark vardı (p=0,027). Gruplar arasında total-PSA, PSA dansitesi, nötrofil-lenfosit ve trombosit-lenfosit oranı değerleri arasında anlamlı fark bulunmadı. **Sonuç:** ASAP, PKa için iyi tanımlanmış bir risk faktörüdür. İkinci biyopsiden önce SII belirtecinin incelenmesi, klinik anlamlı PKa teşhisini öngörmede aktif bir faktör olabilir. Klinik anlamlı PKa'nın erken teşhis ve tedavisi şüphesiz ki hastalığın yönetimine olumlu katkı sağlayacaktır.

Anahtar Kelimeler: Biyopsi; prostat; prostatik neoplazm

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Prostate cancer (PCa) is the second most prevalent cause of cancer-related mortality in men.[1] Digital rectal examination (DRE) along with serum prostate-specific antigen (PSA) marker are the most commonly used methods in the diagnosis and treatment step of PCa. However, since the elevated PSA and/or abnormal DRE findings are not cancer specific, PCa can be more definitively diagnosed by a prostate biopsy.[2]

Approximately 5%-10% of prostate biopsies find lesions in the gray zone, which does not allow a clear distinction between a benign or malignant condition.[3,4] The most prevalent of the aforementioned lesions are high-grade prostatic intraepithelial neoplasias and atypical small acinar proliferations (ASAP), which suggest malignancy potential.[5]

ASAP is defined as a lesion without adequate histological atypia to be diagnosed as PCa upon prostate biopsy.[6] Approximately 17%-60% of PCa diagnoses are reported in re-biopsies following ASAP diagnoses.[6,7] Therefore, the National Comprehensive Cancer Network and the European Association of Urology (EAU) guidelines recommend a re-biopsy 3-6 months after ASAP diagnosis regardless of PSA values.[8,9]

While an option to follow-up and observe is available for clinically insignificant PCa (non-cs-PCa) cases , the fact that there are different treatment options such as curative, radio-, and hormone therapy in clinically significant cases has increased the importance of accurate differentiation and prevention of unnecessary biopsies in PCa management.[2] Although, urine; serum and tissue markers, including PSA 3, alpha-methylacyl-CoA racemase, and erythroblastosis virus E26 oncogene homolog; diagnostic tests, including, PSA density and velocity; and indices, including neutrophil-lymphocyte ratio (NLR), and prostate health and prostate volume (PV) indices have been investigated, none of the above have been recommended by guidelines or are particularly prevalent in clinical use.

A systemic immune response plays a defensive role in benign processes, including infection and inflammation, and it is also associated with certain high-grade cancers.[10-12] The systemic immune-inflammation (SII) index, which was developed on the basis of the above results, has been shown to have a prognostic value in colorectal, renal cell, hepatocellular, and PCas (SII=Platelet×NLR).[13-16] SII has also been assessed in many stages of PCa and its contribution has been demonstrated, especially in the cases of castration-resistant PCa. Nevertheless, to the best of our knowledge, there is no study in the relevant literature that has investigated the reliability of evaluating SII levels to estimate the outcome of a second biopsy in patients with ASAP.

The main purpose of this study was to investigate the markers that can predict clinically significant PCa (cs-PCa) before a re-biopsy in patients with ASAP based on the findings of their first biopsy.

MATERIAL AND METHODS

STUDY DESIGN

This retrospective descriptive study was approved by the University of Health Sciences Hamidiye Scientific Research Ethics Committee (date: March 3, 2022; no: E-46418926-050.99-108901) and was conducted according to the principles of the World Medical Association Declaration of Helsinki's Ethical Principles for Medical Research Involving Human Subjects (HBAEK:22/7-9).

PATIENT POPULATION

2,845 cases were performed transrectal ultrasonography (TRUS) guided prostate biopsy due to elevated PSA level and/or significant DRE findings in our clinic between January 2008 and May 2019 were evaluated. In 238 of 2,295 prostate biopsy patients ASAP was revealed and 130 cases whose data were reached taken into the study.

The patient's medical records were reviewed. Patients age, PV which was calculated with the ellipse method (length X depth X width X π X 1/6) by TRUS, total PSA (tPSA) and free PSA (fPSA) level, rate of percentage of free to total PSA (f/tPSA), PSA-Density (PSA-D) which was analysed as tPSA (ng/mL) divided by PV (mL) and complete blood count (neutrophil, lymphocyte, platelet counts), SII, NLR, platelet-lymphocyte ratio (PLR) were recorded.

TRUS GUIDED PROSTATE BIOPSY PROCEDURE

One day before the procodure, oral administraten of 500-mg levofloxacin and 400-mg etodolac was started and it was continued after the biopsy. The biopsy was performed while the patient was in lateral decubitus position with guidance of ultrasound device with a 7.5 mHz biplanar probe.

Local anesthesia and periprostatic nerve blockade were performed by using lidocain gel and 5 cc of 2% lidocain. The biopsies were performed by experienced urologists. In initial biopsy, standard 12 (both lateral and medial biopsies from the base, medial and apex on the right and left side of the prostatic peripheral zone) or 10 core prostate biopsy was performed. Second prostate biopsy was performed in patients within a period of 3-6 months after the initial biopsy. The core number of taken at the second biopsy was 16 or 18. Pathology specimens of all patients were evaluated by expert pathologists.

STATISTICAL ANALYSIS

PSPP (GNU PSPP version 2.0.0-pre2, software for statistical analysis, USA) (PSPP is free software; you can redistribute it and/or modify it under the terms of the GNU General Public License as published by the Free Software Foundation) and Microsoft Excel (Microsoft Corporation, USA) were used to analyze the data.

As a statistical method in the analysis of data in the research; descriptive analyzes were given with frequency distributions, percentage, mean, standard deviation or median values. Kolmogorov-Smirnov test was used to evaluate the normal distribution of the data. Mann-Whitney U test and Kruskal-Wallis test were used to measure the difference between groups, since the data were found to be not suitable for normal distribution. Receiver operating characteristic (ROC) analysis was used to find the cutoff point, followed by Sensitivity-Specificity analysis. The results were evaluated at the 95% confidence interval, at the $p<0.05$ significance level.

RESULTS

The mean age, PV, tPSA, fPSA, f/tPSA, and PSA-D values of 130 patients with ASAP diagnosis upon pathological examination are summarized in Table 1.

A second biopsy was carried out on these patients diagnosed with positive ASAP, where 78 (60%) patients were reported as benign and 52 (40%) had PCa with varying Gleason scores: Gleason 3+3: 37 patients, Gleason 3+4: 10 patients, Gleason 3+5: 3 patients, and Gleason 4+4: 2 patients. The patients diagnosed as benign and with PCa were classified as Group 1 and Group 2, respectively.

The f/t PSA ratio was 0.21 and 0.17 in Group 1 and 2, respectively, which was a statistically significant difference between the groups (p=0.001). However, there were no significant differences between the groups in the tPSA, PSA, NLR, and PLR values. SII was higher in Group 1 compared to Group 2 (598.45 and 556.75, respectively), but there was no statistically significant difference between the groups (p=0.921). The relevant data are summarized in Table 2.

TABLE 1: Demographic data of patients whose pathology result was atypical small acinar proliferations.

	Mean	Minimum	Maximum	SD
Age (year)	63.01	40	78	7.8
Prostate volume (cc)	54.23	10	160	28.9
Total PSA	8.55	0.9	32.5	6.3
Free PSA	1.57	0	8.9	1.35
f/t PSA	0.19	0	0.6	0.08
PSA-Density	0.19	0.01	1.41	0.17
Neutrophil-lymphocyte ratio	2.4	0.33	16.22	2.14
Platelet-lymphocyte ratio	115.74	32.17	400.99	55.89
Systemic immune-inflammation	581.76	97.6	3941.68	539.27

SD: Standard deviation; PSA: Prostate-specific antigen.

TABLE 2: Comparison of the data of patients with benign and malignant results of the second biopsy.

	Group 1	Group 2	p value
Total PSA	8.57	8.52	0.633
f/t PSA	0.21	0.17	0.001
PSA-Density	0.18	0.21	0.094
Neutrophil-lymphocyte ratio	2.52	2.46	0.750
Platelet-lymphocyte ratio	116.05	115.29	0.844
Systemic immune-inflammation	598.45	556.75	0.921

PSA: Prostate-specific antigen.

There were no statistically significant differences in the NLR, PLR, and SII values between the subgroups based on the Gleason scores in Group 2 (Table 3). However, there was a significant difference in the SII values between patients with an International Society of Urology Pathology (ISUP) grade of 1 and those with an ISUP grade of ≥2 (p=0.03), where a ISUP grade of ≥2 was considered a cs-PCa as per the EAU guidelines (Table 4). Additionally, there was a statistically significant difference in SII values between Group 1, including patients with benign pathology, and patients with an ISUP grade of ≥2 (p=0.027) (Table 5).

The ROC curve was drawn for f/tPSA in the diagnosis of PCa in second biopsy. The area under the curve was 0.679 and the standard error was 0.049. The area under the ROC curve was significantly higher than 0.5 (p: 0.015). The detected cut-off point of the f/tPSA in the diagnosis of PCa was >0.185. The sensitivity of this value was found to be 67.3% and its specificity as 32.7% (Figure 1).

TABLE 3: Comparison of inflammation markers of patients whose second biopsy results were reported as malignant according to ISUP classification.

	Benign (n=78)	ISUP 1 (n=37)	ISUP 2 (n=10)	ISUP 3 (n=3)	ISUP 5 (n=2)	p value
Neutrophil-lymphocyte ratio	1.94 (0.89)	2.23 (1.49)	1.30 (1.3)	1.58 (-)	3.58 (-)	0.056
Platelet-lymphocyte ratio	103.29 (38.87)	114.97 (58.35)	90.87 (31.41)	73.33 (-)	155 (-)	0.153
Systemic immune-inflammation	428.05 (258.72)	493.12 (461.18)	301.86 (372.85)	243.47 (-)	733.97 (-)	0.153

ISUP: International Society of Urology Pathology.

TABLE 4: Comparison of inflammation markers in non-clinically significant-PCa and clinically significant-PCa patients whose second biopsy results were reported as malignant.

	ISUP 1 (n=37)	ISUP 2 or higher (n=15)	p value
Neutrophil-lymphocyte ratio	2.23 (1.49)	1.39 (1.57)	0.193
Platelet-lymphocyte ratio	114.97 (58.35)	93.26 (38.87)	0.113
Systemic immune-inflammation	493.12 (461.18)	301.33 (375.83)	0.03

PCa: Prostate cancer; ISUP: International Society of Urology Pathology.

TABLE 5: Comparison of the inflammation markers of patients with a diagnosis of clinically significant-prostate cancer reported as malignant with patients whose second biopsy results were reported as benign.

	Benign (n=78)	ISUP 2 or higher (n=15)	p value
Neutrophil-lymphocyte ratio	1.94 (0.89)	1.39 (1.57)	0.195
Platelet-lymphocyte ratio	103.29 (38.87)	93.26 (38.87)	0.12
Systemic immune-inflammation	428.05 (258.72)	301.33 (375.83)	0.027

ISUP: International Society of Urology Pathology.

The ROC curve in group 2 patients was drawn for NLR, PLR and SII to distiguish of ISUP 2 or higher patients in second biopsy. The area under the curve was 0.694 and the standard error was 0.087. The area under the ROC curve was significantly higher than 0.5 (p: 0.03). The detected cut-off point of the SII in the distiguish of cs-PCa was <324.72. The sensitivity of this value was found to be 75.7% and its specificity as 66.7% (Figure 2).

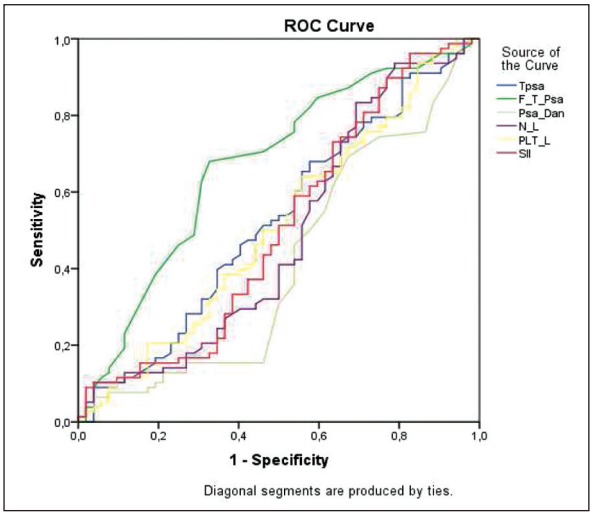

FIGURE 1: ROC curves for all variables in the diagnosis of prostate cancer in second biopsy.
ROC: Receiver operating characteristic.

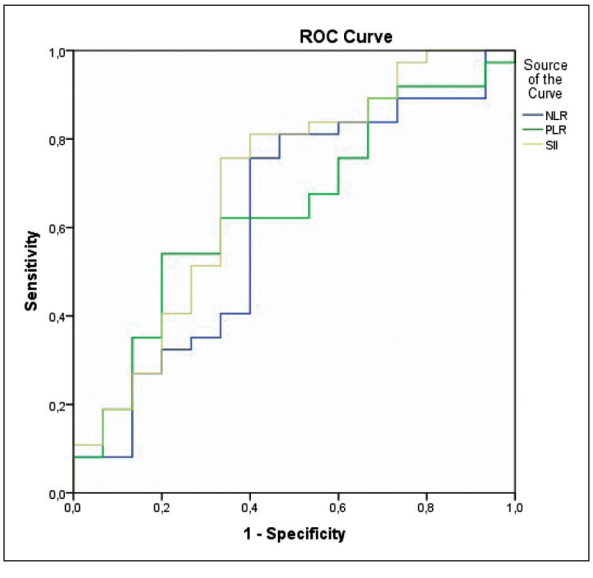

FIGURE 2: ROC curves for NLR, PLR and SII in the distiguish of clinically significant-prostate cancer in second biopsy.
ROC: Receiver operating characteristic; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation.

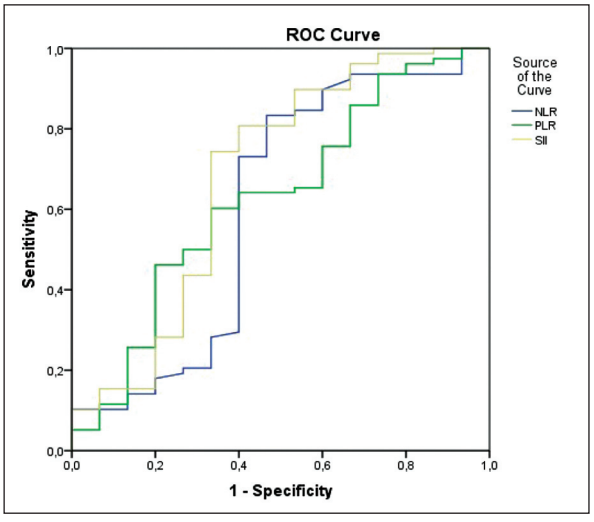

FIGURE 3: ROC curves for NLR, PLR and SII in the distinguish of International Society of Urology Pathology 2 or higher patients from patients with benign pathology in second biopsy.
ROC: Receiver operating characteristic; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation.

The ROC curve in all patients was drawn for NLR, PLR and SII to distiguish of ISUP 2 or higher patients from patients with benign pathology in second biopsy. The area under the curve was 0.681 and the standard error was 0.09. The area under the ROC curve was significantly higher than 0.5 (p: 0.027). The detected cut-off point of the SII in the distiguish of ISUP 2 or higher patients from patients with benign pathology was <323.37. The sensitivity of this value was found to be 74.4% and its specificity as 66.7% (Figure 3).

DISCUSSION

Inflammatory processes that occur in the prostate tissue can play an active role in the transformation of the benign character of the tissue into malignancy. In patients with ASAP, where this transformation is not complete and could be considered transitional, current guidelines suggest that there is up to a 40% likelihood that the tissue might manifest as malignant. The predictability of this process before the second biopsy was reviewed in the relevant literature based on different methods. However, the current urology guidelines do not yet recommend such methods.

Recently, there is an increased emphasis on diagnosis and treatment of patients with cs-PCa. For the purposes of this study, we planned to evaluate the possible importance of examining inflammatory markers in patients with ASAP, on the grounds that relevant studies have reported that SII occurs in different stages of PCa. An examination of SII before the second biopsy decision in patients diagnosed with ASAP may play an active role in the second biopsy decision in cs-PCa cases, as SII levels especially stand out at this point.

Approximately 30%-40% of the patients with ASAP may develop cs-PCa over a 5-year period. Nearly 90% of the patients who were diagnosed with PCa upon the second biopsy were reported as low-risk patients and an active follow-up approach was recommended for disease management.[8] In the present study, 71.15% (37/52) of all the patients diagnosed with PCa had low-risk PCa, based on the modified Epstein criteria.

Recently, the modified Epstein criteria have been more frequently used to predict cs-PCa. Relevant studies have reported 6%-12% cs-PCa in patients with ASAP.[17-21] In a study by Totaro et al., the cs-PCa ratio based on the modified Epstein criteria was reported as 12.6% in patients ASAP who underwent a second biopsy.[22] Furthermore, it was reported that cs-PCa was diagnosed in 35% of patients with a non-cs-PCa diagnoses after a second biopsy, who then underwent a radical prostatectomy (RP).[22] Kim et al. reported a cs-PCa ratio of 19.6% and pointed out a 48.6% increase in the Gleason score post-RP.[23] These results support the observation that the cs-PCa rates after the second biopsy are higher compared to those found during the procedure, due to the nature of the prostate biopsy. In this study, the cs-PCa was 11.53% (15/130) in patients with ASAP diagnosis, while the Gleason score upgrade was 29.7% (11/37), which is considered consistent with the relevant literature.

An early diagnosis is of vital importance for disease management in patients with cs-PCa diagnosis. The progression of the disease is more aggressive in patients with cs-PCa compared to those with non-cs-PCa. This distinction is reflected in the treatment strategies and options stated in the current urology guidelines. While the curative treatment methods are preferred in the patients with cs-PCa, one of the treatment options for the patients with non-cs-PCa has been active monitoring. Accordingly, the inflammatory markers are extremely valuable as they can be examined via non-invasive processes that do not add any extra costs to the evaluation of the disease. A study by Ha et al. reported that the De Ritis ratio predicted the likelihood of cs-PCa in repeated prostate biopsies.[24] Furthermore, Wang et al. reported that NLR, PLR, and SII were independent risk factors for PCa, and the SII level was a more powerful marker compared to others.[25] However, to the best of our knowledge, there is no study in the relevant literature that investigates the value of SII in predicting second biopsy results and a cs-PCa diagnosis in patients with ASAP. The results of this study demonstrate the power of SII levels in predicting cs-PCa in patients with ASAP for the first time in the relevant literature. The sole examination of tPSA may prove to be inadequate to decide upon the second biopsy. Both serum tPSA and NLR levels were significantly elevated in patients with Gleason score ≥7 PCa. Wang et al. suggested that a combination of tPSA and NLR could provide benefits in addition to a biopsy to differentiate the true Gleason score ≥7 PCa from biopsy-based Gleason score ≤6 PCa.[26] Based on the results of this study, we suggest that adding SII levels to the tPSA examination before the second biopsy could be useful in patients with ASAP diagnosis.

One of the limitations of this study is the fact that it was designed as a retrospective evaluation. The relatively small number of patients with cs-PCa in the study population also restricted the confirmation of more precise threshold values.

CONCLUSION

ASAP is a well-defined risk factor for PCa. An examination of the SII marker before the second biopsy may prove to be an active factor in predicting the cs-PCa diagnosis. Early diagnosis and treatment of cs-PCa will make a positive contribution to management protocols of the disease.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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