Original Article

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Can the Preoperative Systemic Immune-inflammation Index be Used to Predict Biochemical Recurrence in Patients with Localized Prostate Cancer After Radical Prostatectomy: A Retrospective Cohort Study

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Abstract

Objective: The purpose of study was to identify the clinical utility of preoperative systemic immune-inflammation index (SII) in predicting biochemical recurrence (BCR) after robot-assisted radical prostatectomy (RARP).

Materials and Methods: A retrospective analysis was performed using data from our robotic surgery database, which included 531 patients with localized prostate cancer (PCa) who received RARP from March 2015 through June 2021. Patients' characteristics and outcomes were recorded. The preoperative SII of each patient was calculated. Patients with and without BCR were confronted. The predictive ability of the SII was determined by receiver operating characteristic (ROC) curve analysis.

Results: After applying the exclusion criteria, the study included 400 patients. Among them, 90 patients (22.5%) experienced BCR. Analysis of the relationship between BCR and preoperative variables demonstrated that prostate-specific antigen, biopsy International Society of Urological Pathology (ISUP) grade, clinical stage, and D'Amico classification statistically significant. Although the SII was higher in patients with BCR, the difference was not statistically significant (p=0.198). Previously reported pathological factors, such as ISUP grade at prostatectomy, pathological stage, lymphovascular invasion, perineural invasion, extraprostatic extension, seminal vesicle invasion, and positive surgical margin, were associated with BCR. The ROC curve for the SII demonstrated poor predictive ability for BCR (95% confidence interval: 0.412-0.545; p=0.532).

Conclusion: SII did not appear to be a prognostic indicator for BCR after RARP in localized PCa patients.

Keywords: Systemic immune-inflammation index, prostate cancer, biochemical recurrence, pathology

Introduction

Prostate cancer (PCa) represents the leading cancer diagnosis in the male population (1). Currently, radical prostatectomy (RP) remains the primary surgical treatment approach for managing localized PCa. The main purpose of RP is to provide tumor removal, achieve final staging, and eradicate sources of prostate-specific antigen (PSA), while preserving continence and erectile function. Biochemical recurrence (BCR) was observed in 35% of the patients after RP (2). Patients with BCR may require additional treatment and are reported to have worse oncological outcomes. The pathological results have a significant impact on prognosis in patients with localized PCa who undergo RP. The identification of biomarkers that can accurately predict pathological and oncological outcomes is needed to inform the decision-making process.

Inflammation plays a key role in the advancement and progression of multiple cancers (3). Furthermore, the host inflammatory response to malignancy has been shown to be associated with tumorigenesis and progression (4). Recently, the relationship between inflammation and cancer has received increasing attention, and the prognostic value of inflammatory

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markers has been studied extensively. Multiple inflammatory markers were evaluated to estimate prognosis in patients with various cancers. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) were the most examined biomarkers (5-7). Recently, the systemic immune-inflammation index (SII) has been suggested as a biomarker that integrates neutrophils, platelets, and lymphocytes. It was proposed that the SII was superior to known biomarkers because the SII showed better the equality between host inflammatory and immune response (8-10).

So far, the prognostic ability of SII has been evaluated in metastatic PCa patients (11-14). However, the role of SII in patients with localized PCa has rarely been reported (15-17). Therefore, we aimed to explore the prognostic ability of SII in patients with localized PCa who undergone robot-assisted RP (RARP), which may contribute to the literature.

Materials and Methods

Study Cohort

After Institutional Ethics Committee for University of Health Sciences Türkiye, Antalya Training and Research Hospital (decision no: 15/14, date: 30/09/2021) was obtained for this retrospective study, we retrospectively determined the robotic surgery data of 531 patients who undergone RARP between March 2015 and July 2021. Patients with the subsequent circumstances were excluded from the study: (1) initially received neoadjuvant androgen deprivation therapy (n=4); (2) evidence of chronic and/or acute infection (n=13); (3) history of the autoimmune or inflammatory disease (n=11); (4) a follow-up time shorter than one year (n=94); (5) lack of detailed clinical information (n=3); and (6) persistent PSA after surgery (n=6). Thus, the final study population included 400 patients. Patient selection flowchart is demonstrated in Figure 1.

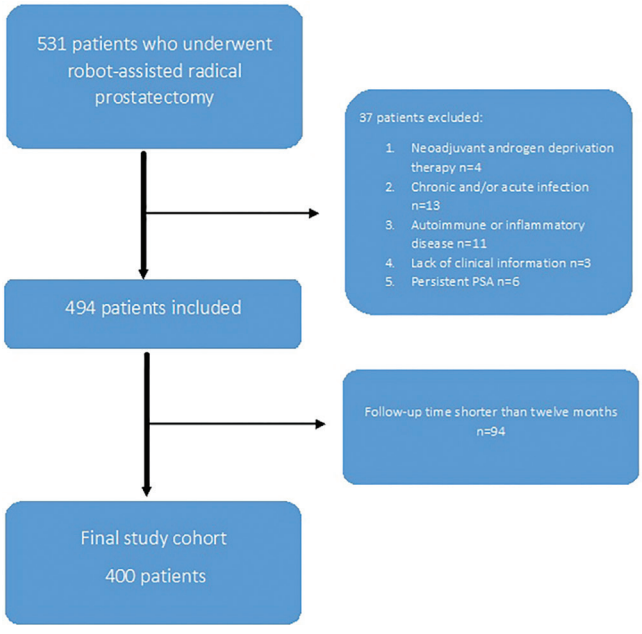

Figure 1. Patient selection flowchart

Study Parameters

Preoperative demographic data (age, body mass index), clinical information [PSA, biopsy International Society of Urological Pathology (ISUP) grade, clinical stage, D'Amico risk group, SII level], pathological outcomes [prostatectomy ISUP grade, pathological stage, surgical margin status, presence, of perineural invasion (PNI), lymphovascular invasion (LVI), extraprostatic extension (EPE), seminal vesicle invasion (SVI), positive lymph node metastasis], and follow-up data were recorded.

Blood tests were routinely obtained 3-10 days before the surgery. The SII was calculated as (platelet × neutrophil)/lymphocyte.

Surgical Technique and Follow-up

Surgeries were performed via transperitoneal and retzius-sparing approach with the da Vinci XI robotic system. Previously, we described our surgical technique of RARP (18). Extended lymph node dissection was performed in patients whose Briganti nomogram-calculated risk of lymph node metastasis was greater than 5%. PSA value of the patients was measured every 3 months during postoperative follow-up. BCR was determined when two successive PSA measurements reached or exceeded 0.2 ng/mL.

Statistical Analysis

Continuous variables were reported as mean ± standard deviation or median (interquartile range), and categorical variables as counts (percentages). The assumption of normality was tested using the Shapiro-Wilk test. Categorical variables were analyzed with the chi-square test or Fisher's exact test. Based on data distribution characteristics, we utilized either Student's t-test or Mann-Whitney U test for continuous variable comparisons. ROC curve analysis was employed to evaluate the predictive capacity of SII for BCR. Stepwise multivariate logistic regression was utilized to determine which variables independently predicted BCR following RP. The initial model included the following clinicopathological variables: prostatectomy ISUP grade, LVI, PNI, EPE, surgical margin status, lymph node involvement, D'Amico risk classification, clinical stage, SII, and preoperative PSA level. All statistical analyses were performed with IBM SPSS Statistics version 27.0, with statistical significance set at $p<0.05$.

Results

The relationship between BCR and preoperative clinical characteristics and SII was summarized in Table 1. BCR was determined in 90 patients (22.5%). PSA, biopsy ISUP grade, clinical stage, and D'Amico risk were statistically significant ($p=0.006$, $p=0.006$, $p=0.010$, and $p=0.005$, respectively). Although the SII was higher in patients with BCR, there was no statistically significant difference observed ($p=0.198$).

Table 2 shows the association between BCR and postoperative outcomes. ISUP grade at prostatectomy and pathological stage were correlated with BCR. Furthermore, the presence of LVI, PNI, EPE, SVI, and surgical margin positivity were correlated with BCR ($p<0.05$, for all).

As shown in Figure 2, the ROC curve of the SII for BCR estimation was was 0.478 [95% confidence interval (CI): 0.412-0.545; $p=0.532$].

Following the stepwise selection process, three variables remained statistically significant in the final model (Table 3). EPE presence correlated with an approximately two-fold elevation in BCR risk [odds ratio (OR)=1.923; 95% CI: 1.107-3.342; p=0.020]. Similarly, SVI independently predicted recurrence, with an odds ratio of 2.551 (95% CI: 1.331-4.889; p=0.005). Moreover, the preoperative PSA level was a continuous predictor of BCR, with each 1 ng/mL increase in PSA corresponding to a 2.4% increase in recurrence risk (OR=1.024; 95% CI: 1.0031.045; p=0.027). These results highlight EPE, SVI, and preoperative PSA as the most robust independent predictors of BCR following RP in this cohort.

Table 1. Preoperative characteristics compared between patients experiencing and not experiencing biochemical recurrence

Variables	BCR		p-value
	Yes (n=90)	No (n=310)	
Age, years (mean ± SD)	65.73±6.13	64.50±6.08	0.093
BMI, kg/m^2 (mean ± SD)	27.09±2.72	27.53±3.63	0.463
PSA, ng/mL (median, IQR)	9.87 (10.48)	8.00 (6.34)	**0.006**
Biopsy ISUP, n (%)			**0.006**
1	41 (45.5%)	196 (63.2%)	
2	28 (31.1%)	67 (21.6%)	
3	7 (7.8%)	23 (7.4%)	
4	11 (12.2%)	23 (7.4%)	
5	3 (3.3%)	1 (0.03%)	
Clinical stage, n (%)			**0.010**
T1	53 (58.9%)	216 (69.7%)	
T2	35 (38.9%)	92 (29.7%)	
T3	2 (2.2%)	2 (0.6%)	
D'Amico risk classification, n (%)			**0.005**
Low	25 (27.8%)	142 (45.8%)	
Intermediate	40 (44.4%)	116 (37.4%)	
High	25 (27.8%)	52 (16.8%)	
SII (mean ± SD)	608.87±780.07	537.79±311.62	0.198

BMI: Body mass index, SD: Standard deviation, BCR: Biochemical recurrence, PSA: Prostate-spesific antigen, ISUP: International Society of Urological Pathology, SII: Systemic immune-inflammation index, IQR: Interquartile range

Table 2. Postoperative characteristics compared between patients experiencing and not experiencing biochemical recurrence

Variables	BCR		p-value
	Yes (n=90)	No (n=310)	
Prostatectomy ISUP, n (%)			**0.001**
1	25 (27.8%)	134 (43.2%)	
2	27 (30.0%)	103 (33.2%)	
3	22 (24.4%)	39 (12.6%)	
4	4 (4.4%)	20 (6.5%)	
5	12 (13.3%)	14 (4.5%)	
Pathological stage, n (%)			**<0.001**
T2	39 (43.3%)	222 (71.6%)	
T3	51 (56.7%)	88 (28.4%)	
Lymphovascular invason, n (%)			**<0.001**
Absent	59 (65.6%)	261 (84.2%)	
Present	31 (34.4%)	49 (15.8%)	
Perineural invasion, n (%)			**0.024**
Absent	13 (14.4%)	77 (24.8%)	
Present	77 (85.6%)	233 (75.2%)	

Table 2. Continued			
Variables	**BCR**		**p-value**
	Yes (n=90)	**No (n=310)**	
Extraprostatic extension, n (%)			**<0.001**
Absent	44 (48.9%)	230 (74.2%)	
Present	46 (51.1%)	80 (25.8%)	
Seminal vesicle invasion, n (%)			**<0.001**
Absent	63 (70.0%)	280 (90.3%)	
Present	27 (30.0%)	30 (9.7%)	
Surgical margin, n (%)			**0.015**
Positive	31 (34.4%)	69 (22.3%)	
Negative	59 (65.6%)	241 (77.7%)	
Lymph node involment, n (%)			0.279
Positive	5 (5.5%)	11 (3.5%)	
Negative	85 (94.5%)	299 (96.5%)	
Mortality, n (%)			0.333
Yes	8 (8.9%)	35 (11.3%)	
No	82 (91.1%)	275 (88.7%)	
ISUP: International Society of Urological Pathology, BCR: Biochemical recurrence			

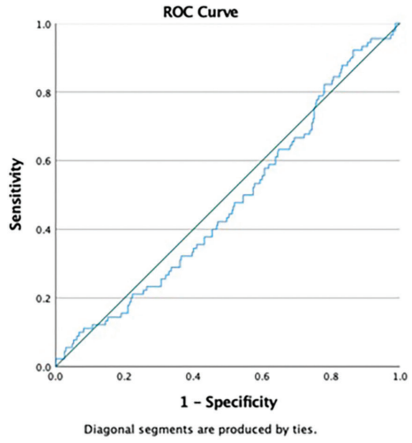

Figure 2. The ROC curve of the SII

ROC: Receiver operating characteristic, SII: Systemic immune-inflammation index

Discussion

In recent years, markers based on blood tests have shown great potential for predicting oncological outcomes in patients with malignancies. The NLR is one of the most extensively studied biomarkers, and it has been shown to have prognostic value in many malignancies. Subsequently, it was suggested that the SII better reflects immune status and its prognostic significance in cancers has frequently been studied. In the present study, we assessed the ability of preoperative SII to predict BCR in localized PCa patients treated with RP. We observed that the SII was not identified as a predictor of BCR.

Many studies have reported the association between inflammation and cancer, suggesting that immune cells play an essential role in promoting tumor development and progression by secreting various cytokines and chemokines (3,4). Neutrophils facilitate tumor development, progression, and metastasis by inducing angiogenesis (19). Lymphocytes exert an antitumor effect by inhibiting tumor cell proliferation (20). Therefore, lymphopenia indicates an insufficient host immune response. Furthermore, platelets have been shown to protect cancer cells from immune cells and promote metastasis (21). In light of this information, inflammatory biomarkers such as NLR, PLR, and LMR have been proposed as indicators of cancer prognosis. Inflammatory markers have been extensively studied as predictors of prognosis in various cancers (5-8). Inflammation markers can be readily calculated from routine blood tests without additional cost or examination. Recently, SII has been proposed based on the proportions of neutrophils, platelets, and lymphocytes. SII has been suggested as a better predictive biomarker. Because it projects better the equation between host inflammatory and immune response status when compared to NLR, PLR, and LMR (22,23). As a simple, convenient, easily obtained, inexpensive, and non-invasive marker, the capacity of the SII to estimate oncological outcomes in cancer patients is promising. SII could provide an information regarding prognosis and treatment response in cancer patients.

The prognostic importance of SII in PCa patients has mostly been studied in metastatic disease (11-14). Few studies have investigated SII to predict prognosis in localized PCa (15-17). In a multicenter study, Rajwa et al. (15) showed that high preoperative SII (≥620) was associated with BCR in the preoperative multivariable model but not in the postoperative multivariable model. In another study, high preoperative SII (>528) was associated with an increased risk of BCR in localized PCa after RP (17). Unlike these studies, there was not a significant predictive role of SII for BCR in our study. A recent meta-analysis demonstrated that SII was not correlated with biochemical recurrence free survival in patients with localized PCa, which supports our findings (24). Conflicting results may have been

Table 3. Stepwise logistic regression model for predicting BCR after radical prostatectomy						
Variables	**Beta**	**SE**	**p-value**	**OR**	**95% CI**	
Extraprostatic extension						
Absent (reference)						
Present	0.654	0.282	**0.020**	1.923	1.107	3.342
SV invasion						
Absent (reference)						
Present	0.937	0.332	**0.005**	2.551	1.331	4.889
Preoperative PSA, ng/mL	0.023	0.011	**0.027**	1.024	1.003	1.045
BCR: Biochemical recurrence, SE: Standard error, OR: Odds ratio, CI: Confidence interval, SV: Seminal vesicle, PSA: Prostate-spesific antigen						

obtained in previous studies due to differences in sample sizes, SII cut-off values, and follow-up periods. The optimal cut-off values of SII reported in prior literature were not uniform, ranging from 300 to 1600. Therefore, optimal cut-off values should be clarified in larger prospective studies. Small sample size and short follow-up duration may also affect the efficacy of SII in predicting BCR after RP.

We also evaluated the potential role of conventional parameters in BCR following RP. PSA, biopsy ISUP grade, clinical stage, D'Amico risk classification, prostatectomy ISUP grade, pathological stage, LVI, PNI, EPE, SVI, and positive surgical margin were associated with BCR. Furthermore, EPE, SVI, and PSA were independent predictors of BCR, which is consistent with a recent meta-analysis. This meta-analysis involving 21,682 patients reported that clinicopathological features, including SVI, EPE, LVI, PNI, lymph node positivity, and surgical margin positivity were related with biochemical recurrence free survival (25).

Study Limitations

This study has certain limitations that warrant consideration. The primary limitation involves the retrospective design, limited patient cohort size, and relatively brief follow-up duration. The time range for preoperative blood collection may introduce variability in SII. Furthermore, the SII can be a variable biomarker that can be affected by various situations such as smoking, medications, inflammatory diseases, and cardiovascular diseases. Larger sample-sized prospective studies can help to negate these issues.

Conclusion

We evaluated the association between SII and BCR after RP. SII did not appear to be a prognostic biomarker for BCR after RP in localized PCa patients. SII, an easily calculated and cost-effective marker, has potential utility in cancer prognosis. However, the optimal cut-off value of SII should be determined by prospective studies.

Ethics

Ethics Committee Approval: Approval was received from the Institutional Ethics Committee of University of Health Sciences Türkiye, Antalya Training and Research Hospital (decision no: 15/14, date: 30/09/2021).

Informed Consent: Retrospective study.

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Publication: The results of the study were not published in full or in part in form of abstracts.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A., Concept: K.K., M.T.Ö., M.R.İ., M.A., Design: K.K., M.T.Ö., H.A., K.Y., M.A., Data Collection or Processing: Y.D., M.R.İ., H.A., Analysis or Interpretation: Y.D., M.R.İ., H.A., Literature Search: K.K., M.T.Ö., H.A., K.Y., Writing: K.K., M.T.Ö.

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