# Systemic Inflammatory Index: A Novel Biomarker for Predicting the Progression in Active Surveillance in Patients with Prostate Cancer

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## ABSTRACT

**Objective:** To investigate active surveillance (AS) for patients with prostate cancer to show the systemic inflammatory index (SII) progression and to evaluate whether SII will be an AS criterion in PCa patients.
**Study Design:** Descriptive study.
**Place and Duration of the Study:** Department of Urology, University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital, from February 2015 to December 2021.
**Methodology:** For active surveillance follow-up criteria, patients with prostate cancer who underwent AS with PSA <10 ng/ml, GS ≤6, clinical stage t1c-t2b, ≤2 core positive, and for each positive core had ≤50% tumour cells, were inducted and SII was determined.
**Results:** As a result of the univariate analysis, high SII values, number of cores involved, and length of the tumour in one core significantly affected progression (in order of p = 0.009, B = 1.830, Exp(B) = 6.233, CI [1.58–24.497]; p = 0.018, B = 0.682, Exp(B) = 1.978, CI [1.123–3.482]; p=0.006, B = 1.835, Exp(B) = 6.263 CI [1.692-23.181]). High SII values (>443.42) had better explanations for progression than the number of core involvement but were similar to the length of the tumour in one core. As a result of the multivariate analysis, high SII values (>443.42) and the tumour 's length in one core had similar effects on progression (in order of p = 0.011, B = 1.978, Exp(B) = 7.227, CI [1.570–33.269]; p = 0.009, B = 1.958, Exp(B) = 7.084, CI [1.642–30.555]).
**Conclusion:** Th use of SII early in the course of treatment can help to identify which prostate cancer patients can be selected for active treatment instead of active surveillance, and to assess the probability of progression.

**Key Words:** Prostate cancer, Active surveillance, Systemic inflammatory index, Biomarker.

## INTRODUCTION

Prostate cancer (PCa) incidence has increased because of screening tests and improved biopsy techniques in the world.[1] However, many non-metastatic PCa progress slowly, and their symptoms or death rates are low and called low-risk.[2] For this reason, the standard treatments like radical prostatectomy (RP) or radiotherapy are unnecessary, and these treatments cause side effects that have a poor quality of life.[3] Therefore, active surveillance (AS) has become a promising treatment option for low-risk patients since 2002.[3] AS aims at postponing curative treatment until there is progression of the disease.[2,3]

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Accurately identifying patients with low-risk PCa who will benefit most from AS is crucial because approximately 36% of patients with low-grade PCa have a high-grade disease after RP.[4] Therefore, choosing the patient for AS is still complex for clinicians.[3] Due to the need to continually improve the selection of patients for AS, research for finding new biomarkers has a significant interest.[3]

Because of local recurrence and distant metastasis of urological cancers, prognosis and clinical results are not convincing.[5] Therefore, finding better indicators for urological cancers is essential.[6] Lately, evidence has shown inflammatory responses have a critical role in tumour progression, invasion, and metastasis.[7] Inflammation increases the risk of cancers. It can affect the cancer stages by affecting the first genetic mutation, or it can trigger the epigenetic mechanism that can lead to cancer growth, progression, or metastasis.[8] For this reason, inflammatory parameters can be a potential candidate for predicting cancer outcomes. The systemic inflammatory index (SII) is a new and promising biomarker associated with bad results in urologic cancers.[9,10] SII shows inflammation is more balanced, and its predictive value is higher than PLR and NLR.[11]

Although many types of biomarkers have been studied in PCa for potential application in correctly detecting patients for AS, the role of each available test remains to be determined.[3] To date, several studies have been performed to determine the association between SII and oncologic outcomes of PCa. However, these studies included patients with metastatic PCa. There is no available data to investigate the relationship with the progression of AS. Therefore, the aim of this study was to evaluate the effect of SII on progression compared with current AS criteria and whether SII will be an AS criteria in PCa patients under AS.

## METHODOLOGY

In this study, the records of 62 patients who underwent AS for prostate cancer at the Department of Urology, University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital, between 2015 and 2021 were retrospectively analysed. The sample size was determined as 62 patients with 0.86 power, 0.05 error, and 0.75 effect size. Prostate-specific antigen (PSA) value at initial biopsy (PSA1) and second biopsy (PSA2), rectal examination findings, maximum tumour length in one core, number of positive core, neutrophil counts, lymphocyte counts, and platelet counts were retrieved from patients' record. SII rate was calculated with Thrombocyte x (Neutrophile/Lymphocyte) formula.

The indications for prostate biopsy included suspicious findings at digital rectal examination (DRE) and a serum PSA level above 2.5 ng/mL. All biopsies were performed under transrectal ultrasonography by targeting peripheral zones, and at least 12 core were taken. A targeted magnetic resonance/ultrasound fusion prostate biopsy could not be performed due to a lack of equipment. Different pathologists evaluated the first biopsy specimens; the same pathologist evaluated the second specimens. Both of them scored the Gleason score (GS) according to the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason grading of prostatic carcinoma.[12] Although there are many different inclusion criteria for AS published in the literature, the authors used Prostate Cancer Research International: Active Surveillance (PRIAS) study criteria for selecting patients for AS.[13] Accordingly, the inclusion criteria were as follows: GS ≤3+3, clinical stage based on DRE of the prostate ≤T2c, PSA ≤ 10 ng/mL, ≤2 positive cores, and PSA density (PSAD) ≤0.2 ng/mL. Patients with an active infection or history of last three weeks of previous infections, or autoimmune diseases and chronic use of drugs for these diseases were excluded from the study.

Periodic clinical evaluations, DRE and PSA testing every three months for one year, and second biopsies at the end of one year were performed as follow-up criteria. Progression was defined on rebiopsy as a change in histological pattern, e.g. Gleason ISUP 1 to 2 or 3.[3]

The analyses were made *via* IBM SPSS statistics 21.0. The Kolmogorov-Smirnov test was used to examine the normality of numerical variables. The difference of discrete variables was analysed with a Chi-square test. Prediction for progression cut-off value of SII determined with ROC analyses. A logistic regression analysis was used to evaluate the parameters affecting the progression. A paired-sample t-test was used to test the significance of the difference between the arithmetic means of the two related groups. The Greenhouse-Geisser test was applied to evaluate the change in PSA values measured at different times. Categorical variables were expressed as frequency and percentage, and continuous measurements were expressed as mean (±) standard deviation. The p-values <0.05 were considered statistically significant.

The study was compatible with the Helsinki Declaration for laws and regulations, good clinical practice, and ethical principles. It was approved by the ethics committee of the hospital.

## RESULTS

Thirty-two percent (n = 20) of the patients had progression and sixty-eight percent (n = 42) had no progression. The mean age was 60.52 ± 3.79 years for patients with no progression, and 58.90 ± 2.90 years for patients with progression (p=0.096, Table I). The average PSAD was 0.12 ± 0.02, for the patients without progression and 0.12 ± 0.02 for those with progression. Showing the progression, there were no statistically significant differences with PSAD (p=0.379). The mean tumour length in one core was 1.59 ± 0.47 for the patients without progression and 1.99 ± 0.46 for those with progression. There were statistically significant differences in the tumour length between groups (p=0.003). When the T stage and the number of cores involved with cancer were examined in terms of progression, T Stage did not affect progression (p=0.132), but the number of cores involved with cancer had a statistically significant effect on progression (p=0.015, Table I).

Patients without progression had a mean value of PSA1 5.68 ± 1.63 and PSA2 5.57 ± 1.49. Compared to this, the patients with progression had a mean value of PSA1 5.51 ± 1.58 and PSA2 5.98 ± 1.50. There was no significant statistical difference between the two groups. However, the time and group togetherness showed a statistically significant difference (p=0.002). This difference was in the group with patients with progression PSA value before the second biopsy compared to the first biopsy was high (p=0.001). Of twenty patients with progression, 16 had higher PSA2 than PSA1 (p=0.010).

The SII average value for patients with no progression was 533.88 ± 194.92, and for patients with progression was 736.07 ± 486.80 with statistically significant differences (Table I). Determining progression for the SII cut-off value, AUC 0.663 (95% CI 0.532-0.778) was statistically significant. SII optimal cut-off of 443.42 was determined according to the ROC analysis. While no progression was observed in 20 (47.62%) patients with high SII (>443.42), progression was observed in 17 (85.00%) patients (p=0.006, Table I). According to the 443.42 cut-off point, the sensitivity and specificity of SII in predicting progression were found to be 85% and 52.38%, respectively (Figure 1).
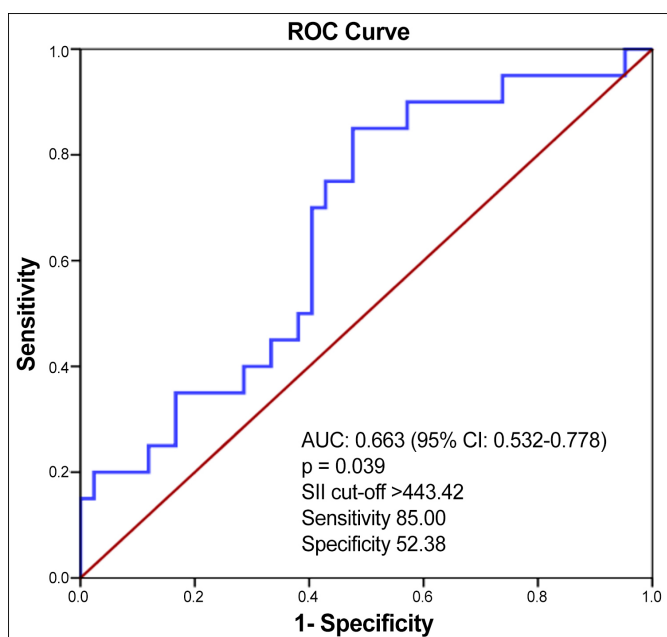
**Table I: The characteristics of the patients.**

| | | No | Yes | p | Total |
|---|---|---|---|---|---|
| Age (year) | | 60.52±3.79 | 58.9±2.90 | 0.096[a] | 60.0±3.59 |
| PSAD (ng/mL) | | 0.12±0.02 | 0.12±0.02 | 0.379[a] | 0.12±0.02 |
| Lenght (mm) | | 1.59±0.47 | 1.99±0.46 | 0.003[a]* | 1.72±0.5 |
| SII | | 533.88±194.92 | 736.07±486.8 | 0.023[a]* | 599.1±329.28 |
| SII | ≤443.42 | 22 (%52.38) | 3 (%15.00) | 0.006[b]* | 25 (%59.52) |
| | >443.42 | 20 (%47.62) | 17 (%85.00) | | 37 (%88.1) |
| T stage | T1c | 35 (%83.33) | 12 (%60.00) | 0.132[b] | 47 (%111.9) |
| | T2a | 5 (%11.9) | 6 (%30.00) | | 11 (%26.19) |
| | T2b | 2 (%4.76) | 2 (%10.00) | | 4 (%9.52) |
| Number of core | 1 | 32 (%76.19) | 9 (%45.00) | 0.015[b]* | 41 (%97.62) |
| | 2 | 10 (%23.81) | 11 (%55.00) | | 21 (%50) |

a: t-test (Independent); b: Chi-square test; *statistically significant (p <0.05).

**Table II: Logistic regression analysis has shown the parameters affecting the progression.**

| | Progression – Univariate | | | 95% CI for Exp(B) | | Progression – Multivariate | | | 95% CI for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | B | p | Exp(B) | Lower | Upper | B | p | Exp(B) | Lower | Upper |
| SII (>443.42) [a] | 1.830 | 0.009* | 6.233 | 1.586 | 24.497 | 1.978 | 0.011* | 7.227 | 1.570 | 33.269 |
| Core (1) [b] | 0.682 | 0.018* | 1.978 | 1.123 | 3.482 | 0.592 | 0.077 | 1.808 | 0.939 | 3.481 |
| Length | 1.835 | 0.006* | 6.263 | 1.692 | 23.181 | 1.958 | 0.009* | 7.084 | 1.642 | 30.555 |

* Statistically significant (p<0.05); a: reference <=443,42; b: reference "none."



**Figure 1: Cut-off value for SII with ROC curves for progression.**

ROC Curve
AUC: 0.663 (95% CI: 0.532-0.778)
p = 0.039
SII cut-off >443.42
Sensitivity 85.00
Specificity 52.38

The variables of the length of the tumour in one core were evaluated, the number of cores involved, and SII groups shown to be statistically significant with logistic regression. As a result of the univariate analysis, high SII values, number of core involved, and length of the tumour in one core significantly affected progression (in order of p = 0.009, B = 1.830, Exp(B) = 6.233, CI [1.58–24.497]; p = 0.018, B = 0.682, Exp(B) = 1.978, CI [1.123–3.482]; p=0.006, B = 1.835, Exp(B) = 6.263 CI [1.692-23.181]). High SII values (>443.42) had better explanations for progression than the number of core involvement but were similar to the length of the tumour in one core. As a result of the multivariate analysis, high SII values (>443.42) and the tumour's length in one core had similar effects on showing the progression (in order of p = 0.011, B = 1.978, Exp(B) = 7.227, CI [1.570–33.269]; p = 0.009, B = 1.958, Exp(B) = 7.084, CI [1.642–30.555], Table II).

## DISCUSSION

The current study was the first to investigate the predictive and prognostic utility of SII for predicting progression in patients with clinically localised PCa who received AS. According to the results, SII of 443 was established to be an independent predictor of progression at AS before the initial biopsy.

It is known that immune cells, which are components of SII, such as neutrophils, lymphocytes, and platelets play a role in cancer-related inflammation.[10,14] The current evidence showed that neutrophils facilitate tumour cell growth and promote angiogenesis.[15] Platelets contribute to angiogenesis and metastasis by releasing various matrix metalloproteinases.[16] In contrast, a reduced number of lymphocytes may have a relationship with a corrupted response to carcinogenesis.[17] In light of this information, SII may be used as a biomarker of inflammatory status in PCa.

Recently, SII as a prognostic biomarker had been investigated for PCa patients by several researchers. The fact that these investigations included individuals with advanced and metastatic PCa was notable. According to the findings of one of these investigations, a high SII value (>535) was related to poor treatment response.[9] Another study found that salvage RRP given to patients who relapsed after radiation was linked to negative pathological characteristics at high SII (≥730).[18]

The effects of age, tumour involvement per core, the number of positive cores and PSAD had been evaluated on GS upgrading (GSU) in patients with AS. Most of this research for

AS compared the pathologies after RP. PRIAS reported that the number of positive biopsy cores, and PSA density were the strongest predictors of switching from surveillance to treatment.[13] Gershman *et al.* suggested small prostate size and aging have a relationship between GSU, and Zhang *et al.* came up with a higher T stage in cohort GS = 6 which increases the risk of GSU.[19,20] PSAD is related to both PSA level and PV. Evaluation of PSAD has been proposed in many AS protocols, as it appears accurate enough to correctly assign the patient to AS.[13] Sebastianelli *et al.* showed that low-risk PCa patients with higher PSAD have ten times more risk for GSU.[21] Similarly, Gandaglia *et al.* reported having PSAD≤0.2 ng/mL during radical prostatectomy, patients with AS criteria had a 46% ratio to upgrading.[22] Merder *et al.* showed a 1mm increase in tumour length in a core increases GSU 3.866 fold higher. These researchers suggested that the maximum tumour length in a core can be used in PCa patients for AS selection.[23] In another study, Hamidi *et al.* evaluated effect of PSA fluctuation on GSU, disease upstaging, and oncological outcomes. This study emphasised that the low PSA fluctuation rate predicts GSU and suggested to use it for AS criteria.[24]

The current study showed that high SII values, the number of positive cores, and tumour length in one core affected progression. More importantly, the result of this study indicated that high SII values (>443.42) and the tumour length in one core had similar effects on slowing the progression. The lower cut-off value compared to the previous studies can be explained by the low number of patients and the early stage of patients. For this reason, instead of a single value, different cut-offs can be determined according to the cancer's stages.

Being a single-centre study, including a small number of patients, and having a retrospective nature were the limitations of this study. Moreover, the fact that different pathologists evaluated the first prostate biopsy specimens that may lead to a low GS. Owing to the retrospective nature of this study, there may be selection bias; therefore, conclusions should be carefully drawn when evaluating the results. Despite these limitations, the results do not contradict the existing literature describing the relationship between inflammation and cancer. SII should be part of the AS criteria in addition to tumour length in one core and number of cores. Pre-treatment SII is a widely available, inexpensive, objectively measurable, and safely reproducible biomarker if confirmed by other large-scale prospective studies. In this way, it may be possible to define AS patient groups more precisely.

## CONCLUSION

The study showed that higher SII values had important predictive factors for progression in low-risk PCa patients. High SII can partly reflect the status of immune inflammation and can be an independent prognostic factor for selecting patients for AS. Therefore, in addition to other criteria, SII values should be included in the AS criteria.

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