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Platelet-to-lymphocyte ratio and systemic immune-inflammation index versus circulating prostate cells to predict significant prostate cancer at first biopsy

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ABSTRACT

Objective: It has been reported that the systemic immune-inflammation index (SII) and platelet-to-lymphocyte ratio (PLR) are higher in men with prostate cancer. We compare their use with the percentage of free prostate-specific antigen (PSA), PSA density, and primary circulating prostate cells (CPCs) to predict clinically significant prostate cancer at first biopsy in men with a PSA of 4–10 ng/mL.

Material and methods: Consecutive men with suspicion of prostate cancer underwent a 12-core transrectal ultrasound-guided prostate biopsy; total serum PSA, the percentage of free PSA, prostate ultrasound to calculate PSA density, and absolute neutrophil, lymphocyte, and platelet counts were used for risk assessment. CPCs were detected using differential gel centrifugation and immunocytochemistry with anti-PSA and anti-P504S. A malignant CPC was defined as a cell-expressing PSA and P504S and defined as positive or negative. Biopsies were classified as indicating cancer or no cancer. Areas under the curve for each parameter were calculated and compared, and diagnostic yields were calculated.

Results: A total of 1223 men participated, and 467 (38%) had a biopsy positive for cancer, whereas 353/467 (76%) had clinically significant prostate cancer. The PLR was significantly higher in men with prostate cancer; there was no significant difference for the SII. The areas under the curves were CPC 0.84, the percentage of free PSA was 0.79, PLR 0.65, PSA density 0.62, and SII 0.46. Neither the PLR nor the SII discriminated between patients with clinically significant prostate cancer, indolent cancer, and benign prostatic disease.

Conclusion: Based on the results of this study, neither the SII nor PLR could differentiate between clinically significant prostate cancer and indolent cancer/benign disease at initial biopsy.

Keywords: Circulating prostate cells; platelet-to-lymphocyte ratio; prostate cancer; systemic immune-inflammation index.

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Introduction

The aim of any cancer-screening program is to detect clinically significant cancer, which if left untreated, would cause morbidity or mortality. With a population that is increasingly growing older and the use of serum prostate-specific antigen (PSA), the number of men with a PSA of 4.0 ng/mL, which is used as a cut-off point as indicated by a prostate biopsy, has greatly increased as well. PSA is not an ideal biomarker for prostate cancer in that it is increased even in benign prostate disease.[1] As such, it does not differentiate benign from malignant disease. When using the cut-off value of 4.0 ng/mL, approximately only 25% of prostate biopsies will be positive for prostate cancer,[2] and of these men, the results will be clinically significant only in approximately 50%.[2]

Free percentage of PSA and PSA density have been used to try to decrease the number of prostate biopsies in men with benign disease,[3] but the need to identify biomarkers that predict the presence of clinically significant prostate cancer remains.

It has been reported that inflammation plays a role in the development of prostate cancer.[4,5] An increased neutrophil-to-lymphocyte ratio has been associated with prostate cancer, but this parameter failed to distinguish patients

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with prostatitis from those with prostate cancer, and it has not been confirmed in all studies.[6,7] Low lymphocyte counts are reported to be an adverse prognostic marker for many diseases, including prostate cancer,[5,8] while increased platelet counts have been associated with poor prognosis and tumor load in patients with cancer.[9,10] These parameters have been combined to form the systemic immune-inflammation index (SII) and determined by multiplying the absolute neutrophil and platelet counts and then divided by the absolute lymphocyte count; the platelet-to-lymphocyte ratio (PLR) was obtained using the absolute platelet count divided by the absolute lymphocyte count.

Early in prostate cancer, there is dissemination of tumor cells first to the neurovascular bundle and then into the circulation where they can be detected.[11] However, only a few of these cells will survive, and as such, they have a limited prognostic value,[12] but they could be used to detect prostate cancer. The detection of circulating tumor cells is method dependent; those using anti-EpCAM (epithelial cell adhesion molecule) such as CellSearch detected circulating prostate cells (CPCs) in only 25% of men with localized cancer and failed to distinguish between healthy controls and men with prostate cancer.[12] In contrast, when using an anti-Ber-4 and telomerase based method, CPCs were detected in 80% of men with localized prostate cancer.[13] Similarly, using a size-based filtration method, CPCs were detected in 50% of patients with clinically localized prostate cancer.[14] We used a density gradient-based enrichment system and standard immunocytochemistry. Although we have internally validated this method, it has not been externally validated. The clinical method used in this study was found to be superior to three online nomograms for the detection of prostate cancer at first biopsy.[15] More importantly the use of the combined PSA-P504S immunocytochemistry detects malignant prostate cells and as such is more specific than the other detection methods, which do not differentiate between benign and malignant cells. P504S negative circulating prostate cells, considered to be benign, have been described in patients with benign hyperplasia and more frequently in chronic prostatitis,[16] similarly circulating epithelial cells detected using the EpCAM-based CellSearch system were found in benign inflammatory colon disease.[17] This suggests that inflammation is associated with the passive release of epithelial cells (benign or malignant) into the circulation.

Here, we present a prospective study of men, who as part of a prostate cancer-screening population, were determined to require a prostate biopsy based on an abnormal PSA level in the 4–0 ng/mL range. We compared the SII, PLR with the percentage-free PSA, PSA density and primary circulating prostate cells to determine the predictive value of each parameter with regard to the presence of clinically significant prostate cancer at initial prostate biopsy.

Main Points:

- The ideal prostate cancer screening test should only detect clinicallty significant prostate cancer which could affect the patient if not treated, in terms of mortality and morbidity.
- Inflammation has been linked with the development of prostate cancer; however neither the neutrophil:lymphocyte ratio or the systemic inflammation index differentiated between men with benign prostate disease from those with clinically significant prostate cancer. Using the established cut-off values both parameters failed to identify 40% of men with clinically significant prostate cancer, and 64% of men with a value considered to be possible had benign disease detected at biopsy. The diagnostic yield was significantly inferior to both the free percentage PSA and PSA density.
- The detection of circulating prostate cells had a significantly superior diagnostic yield, especiaaly in the high negative predictive value, 98%, few clinically significant prostate cancers were missed if men negative for circulating prostate cells did not undergo prostate biopsy. Neither the neutrophil: lymphocyte ratio or the systemic inflammation index differed between men with circulating prostate cells present or absent.

Material and methods

A single-center prospective study of all men with indications for a prostate biopsy, defined as an elevated total PSA of 4.0–10.0 ng/mL or an abnormal digital rectal examination (defined as areas of indurations, asymmetry, or nodules), attended at the Hospital de Carabineros de Chile between January 2009 and May 2015. Patients with a previous prostate biopsy were excluded from the study.

After written informed consent was obtained and immediately before the biopsy, blood samples were taken to determine the serum PSA (ng/mL) and the percentage of free PSA (Siemens Advia CentaurXR assay); a full blood count (Beckton–Coulter H250 autoanalyzer) to determine the absolute neutrophil, lymphocyte, and platelet counts; and an 8 mL sample collected in EDTA (Vacutainer, BD USA) for the detection of circulating prostate cells (CPCs). From the full blood count results the SII (neutrophil count x platelet count/lymphocyte count) and PLR were calculated.

All men underwent a trans-rectal ultrasound guided 12-core prostate biopsy using an 18-gauge Tru-cut needle. The prostate volume was calculated using the formula 0.52 x transverse x anteroposterior x longitudinal diameters, and the PSA density using total PSA/prostate volume. The PSA density was calculated using PSA ng/mL divided by prostate volume (mL). A single dedicated uropathologist analyzed the biopsies, registering the Gleason score, the number of cores positive for cancer, and maximum percentage infiltration with cancer. Biopsies positive for prostate cancer were divided into two groups: those considered as low risk using the

Epstein criteria and the rest considered as clinically significant; as both Gleason 3+4 and 4+3 are classified as clinically significant, the group was combined and cited as Gleason 7. The study was carried out in accordance with the Declaration of Helsinki and approved by the local hospital ethics committee.

Detection of primary circulating prostate cells

Independent evaluation of the prostate biopsy and CPC detection was carried out, with the evaluators being blinded to the clinical details.

Blood samples were maintained at room temperature and processed within 24 hours. Mononuclear cells were obtained by differential centrifugation using Histopaque 1,077 (Sigma-Aldrich), and they were washed and re-suspended in an 100 μL aliquot of autologous plasma. 25 μL aliquots were used to make four slides (silanized, DAKO, USA). The slides were air dried for 24 hours, fixed and washed.

Immunocytochemistry

Anti-PSA clone 284A (Novocastro Laboratory, UK) and an alkaline phosphatase–anti-alkaline phosphatase-based system (LSAB2, DAKO, USA), with new fuchsin as the chromogen, was used to detect CPCs. Samples positive for PSA-expressing cells were incubated with anti-P504S clone 13H4 (DAKO, USA) and with a peroxidase-based system (LSAB2, DAKO, USA) with DAB (3,3 diaminobenzidine tetrahydrochloride) as the chromogen. The 1999 ISHAGE (International Society of Hemotherapy and Genetic Engineering)[18] criteria were used to define a CPC and the Consensus of the American Association of Pathologists[19] for the expression of P504S. A cell that expressed both PSA and P504S was defined as a malignant CPC. One trainer observed performed manual analysis of slides using digital microphotography, and to be considered positive, at least 1 CPC/8 mL of venous blood had to be detected.

Analysis of the results

Diagnostic yield was determined using sensitivity, specificity, true positive, false positive, false negative, and true negative. The negative and positive predictive values (NPV and PPV, respectively), and the areas under the curve were calculated and compared. The patients were classified as having no cancer, insignificant cancer as defined by Epstein (1994),[20] and significant cancer. Cut-off values for each parameter were based on previously published work, i.e., percentage of free PSA ≤10%,[3] PSA density ≥0.15,[3] CPC ≥1 cell/8 mL blood[15], and PLR ≥110.[5] Cut-off values for the PLR and the SII were calculated from the area under the curve of the study population using the Youden´s index.

Using these cut-off values as a positive test, the number of biopsies that potentially could be avoided and the number of clinically significant prostate cancer cases that would be missed was calculated.

Table 1. Patient characteristics according to the prostate biopsy results

	No cancer n=756	Cancer n=467	p
Mean age±SD (years)	64.2±9.1	65.5±9.5	<0.001
PSA (ng/mL) median (IQR)	5.51 (4.40–7.51)	5.90 (4.80–9.12)	<0.001
4.0–5.0 ng/mL	301 (39.8%)	136 (29.1%)	
5.01–7.0 ng/mL	234 (31.0%)	149 (31.9%)	
7.01–9.0 ng/mL	143 (18.9%)	91 (19.5%)	
9.01–10.0 ng/mL	78 (10.3%)	92 (19.5%)	<0.001
% free PSA median (IQR)	18 (14–24)	11 (9–14)	<0.001
Abnormal DRE	53/756 (7.0%)	123/467 (26.3%)	<0.001, RR 3.76
Prostate volume (mL) mean±SD	51.8±21.2	49.7±17.9	p=0.08
Trans-rectal ultrasound Abnormal (hypoechogenic)	121/756 (16.0%)	166/467 (35.6%)	<0.001, RR 2.22
PSA density median (IQR)	0.13 (0.01–0.17)	0.16 (0.11–0.25)	<0.001
Platelet-to-lymphocyte ratio median (IQR)	112 (89–136)	121 (97–157)	0.048
Platelet x neutrophil/ lymphocyte median (IQR)	424 (300–614)	491 (301–727)	0.72
Circulating prostate cell positive (%)	143 (18.9%)	407 (87.2%)	<0.001, RR 4.60

SD: standard deviation; IQR: interquartile range; RR: relative risk

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Statistical analysis

Demographic variables were compared using descriptive statistics; Student's *t*-test was used to compare continuous variables with a normal distribution, the Mann-Whitney U test was used for ordinate and continuous variables with a non-normal distribution, and the chi-squared test for the differences in frequency. Statistical significance was defined as a p-value <0.05, and all tests were two-sided. AUC analysis was performed using the online program Vassarcalc.

Results

Out of 1223 men, 467 (38.2%) had a biopsy positive for prostate cancer of whom 114/467 (24.4%) complied with the Epstein criteria for active observation: 296/467 (63.2%) were Gleason 6 tumors, 145/467 (31.0%) were Gleason 7 (3+4 and 4+3 combined) and 27/467 (5.8%) were Gleason 8 or higher. Table 1 shows the clinical-pathological findings according to the biopsy results.

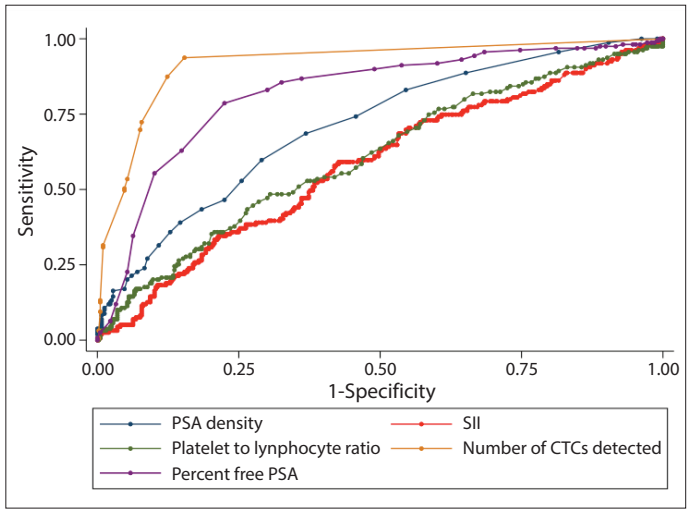

Figure 1. Area under the curve for differing parameters: CPC 0.84, percentage of free PSA 0.79, PSA density 0.71, PLR 0.62, and SII 0.52.
CPC: circulating prostate cell; PSA: prostate-specific antigen; PLR: platelet-to-lymphocyte ratio; SII: systemic inflammation index

Men with a biopsy positive for cancer were significantly older, had a higher median PSA, a lower percentage of free PSA, a higher PSA density, a higher PLR, and they were positive for circulating prostate cells. There was no significant difference in the SII value between men with and without prostate cancer.

The median SII ratio was not significantly different between CPC positive and negative patients, i.e., 501 (interquartile range [IQR] 361–727) versus 396 (IQR 290–616); p=0.5. However, men who were CPC positive had a significantly higher median PLR when compared to men who were CPC negative, i.e., 125 (IQR 101–159) versus 111 (IQR 86–134); p<0.02.

The area under curve (AUC) for total PSA in the range 4.0–10.0 for the study population was 0.57. For the study parameters, the AUC in descending order were CPC 0.84, percentage of free PSA 0.79, PSA density 0.71, PLR 0.65, and SII 0.52 (Figure 1). The predictive accuracy showed that the CPC detection was significantly better than all the other variables; percentage-free PSA was significantly better than the PSA density, PLR, and SII; there was no significant difference between the PSA density and PLR, and both were significantly better than the SII (all p<0.05). The SII was significantly worse than the total PSA. The Youden´s index for the SII was ≥450, and for the PLR, it was ≥120.

Detection of clinically significant prostate cancer

Using the pre-determined cut-off values, the number of biopsies that potentially could be avoided and the number of missed clinically significant cancers was calculated (Table 2). Using a percentage of free PSA of ≤10% to indicate biopsy, 80% of biopsies could potentially be avoided, but at a cost of missing 58% of all clinically significant prostate cancers. In comparison, the results for PSA density, SII, and PLR were similar, potentially avoiding 52%–56% of all biopsies, while missing 40%–46% of all clini-

Table 2. Detection of clinically significant prostate cancer according to test

Test negative	n	Cancer needing treatment	% Significant cancer not detected	Test positive	n	Cancer needing treatment	% Benign biopsies
CPC (-)	696 (57%)	12	12/353 (3%)	CPC (+)	527 (43%)	341/353 (97%)	186/527 (35%)
% free PSA >10%	985 (80%)	205	205/353 (58%)	% free PSA ≤10%	238 20%)	148/353 (42%)	90/238 (38%)
PSA density <0.15	685 (56%)	142	142/353 (40%)	PSA density ≥0.15	538 (44%)	211/353 (60%)	327/538 (61%)
SII <450	637 (52%)	143	143/353 (40%)	SII ≥450	586 (48%)	210/353 (60%)	376/586 (64%)
PLR <110	535 (44%)	121	121/353 (34%)	PLR ≥110	688 (56%)	232/353 (66%)	456/688 (66%)
PLR <120	683 (56%)	161	161/353 (46%)	PLR ≥120	540 (44%)	192/353 (54%)	348/540 (64%)

SII: systemic inflammation index; PLR: platelet-to-lymphocyte ratio; CPC: circulating prostate cell

Table 3. Sensitivity, specificity, and positive and negative predictive values for the detection of clinically significant prostate cancer

	Sensitivity	Specificity	PPV	NPV	PLR	NLR
% free PSA	0.42 (95% CI 0.34–0.44)	0.90 (95% CI 0.87–0.92)	0.62 (95% CI 0.56–0.68)	0.79 (95% CI 0.77–0.82)	4.05 (95% CI 3.22–5.11)	0.26 (95% CI 0.23–0.30)
PSA density	0.60 (95% CI 0.54–0.65)	0.62 (95% CI 0.59–0.66)	0.39 (95% CI 0.35–0.44)	0.79 (95% CI 0.76–0.82)	1.59 (95% CI 1.41–1.80)	0.26 (95% CI 0.23–0.30)
SII	0.60 (95% CI 0.54–0.65)	0.57 (95% CI 0.53–0.60)	0.36 (95% CI 0.32–0.40)	0.78 (95% CI 0.74–0.81)	1.38 (95% CI 1.23–1.54)	0.71 (95% CI 0.63–0.81)
PLR						
≥110	0.66 (95% CI 0.61–0.71)	0.48 (95% CI 0.44–0.51)	0.34 (95% CI 0.30–0.37)	0.77 (95% CI 0.74–0.81)	1.25 (95% CI 1.14–1.38)	0.72 (95% CI 0.62–0.83)
≥120	0.54 (95% CI 0.49–0.60)	0.60 (95% CI 0.57–0.63)	0.36 (95% CI 0.32–0.40)	0.76 (95% CI 0.73–0.80)	1.36 (95% CI 1.20–1.54)	0.76 (95% CI 0.68–0.85)
CPC	0.97 (95% CI 0.94–0.98)	0.79 (95% CI 0.76–0.81)	0.65 (95% CI 0.60–0.69)	0.98 (95% CI 0.97–0.99)	4.52 (95% CI 3.97–5.14)	0.02 (95% CI 0.01–0.03)

PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NR: negative likelihood ratio; SII: systemic inflammation index; PLR: platelet-to-lymphocyte ratio; CPC: circulating prostate cell; CI: confidence interval

cally significant prostate cancers. The CPC detection potentially could only reduce the number of biopsies by 40%, however only 3% of significant cancers were missed.

Table 3 shows the sensitivity, specificity, and PPV and NPV for each parameter in the detection of clinically significant prostate cancer using the defined cut-off values. The results for PSA density, SII, and PLR were similar, while the percentage of free PSA had a higher PPV and was more specific than these three parameters. The CPC detection was the better of the five parameters studied, due to its high NPV.

Discussion

This study evaluated the diagnostic yield of the SII and the PLR in a general screening population and their potential in selecting patients for prostate biopsy. Of the total study population, 24.2% had a clinically significant prostate cancer detected at biopsy. We classified non-significant prostate cancer as part of the no-cancer group, as these patients normally undergo active observation with yearly biopsies. Screening leads to overdiagnosing and overdetection of prostate cancer, and as indicated by the European Randomised Study of Screening for Prostate Cancer, over half of the detected cancers did not lead to symptomatic disease during the patients' lifetime.[2] Some authors have suggested that anxiety and depression reported in 10% of patients with active surveillance should be classified as an adverse effect.[21]

The study compared the diagnostic yield of the SII and the PLR with the percentage of free PSA and PSA density, two parameters used to try to compensate for the low specificity of total PSA and with the detection of primary CPCs. We used two cut-off values for the PLR: the first was 110, as suggested by previous authors with a sensitivity of 61%, specificity of 52%, and positive and NPV of 35% and 75%, respectively[5]; and the second was 120, calculated from the AUC from our patient population. The cut-off value for the SII was similarly calculated from the AUC of our patient population.

There was no significant difference in the SII between patients with benign pathologies of the prostate and those with prostate cancer. In the clinical situation using a SII with a cut-off value of 450 failed to detect 40% of clinically significant prostate cancers, and 64% of patients classified as having a positive test had benign pathologies detected in the prostate biopsy. However, this was similar to the use of PSA density with a cut-off value of 0.15. Although the PLR was statistically significantly higher in men with prostate cancer, as reported by others,[4,5,22] in the clinical situation, neither the suggested cut-off value of 110 or the cut-off value of 120 based on our study population improved the diagnostic yield. Similar to the SII and PSA density, approximately 40% of clinically significant prostate cancers would not

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have been detected, and of those men with a positive test, 60% had benign pathologies detected on prostate biopsy.

Using the AUC analysis, the SII was statistically and clinically significantly inferior to the other tests used in terms of diagnostic yield, while the PLR was similar to PSA density. Both the SII and PLR were significantly inferior to the widely used percentage of free PSA and CPC detection. However, using the cut-off value of 10% for percentage of free PSA, 58% of clinically significant prostate cancers would not be detected. The best fit to the clinical reality in this study was the use of CPC detection, which missed only 3% of significant cancers, but at a "cost" of 35% of biopsies taken for a positive test were benign.

Interestingly, P504S negative circulating prostate cells, considered to be benign, have been described in patients with benign hyperplasia and more frequently in chronic prostatitis,[16] similarly circulating epithelial cells detected using the EpCAM-based CellSearch system were found in benign inflammatory colon disease.[17] This suggests that inflammation is associated with the passive release of epithelial (benign or malignant) into the circulation. However, the SII as a marker of systemic inflammation was not significantly different between the patients negative or positive for CPCs. In contrast, the PLR was higher in patients who were CPC positive. It is possible that local chronic prostate inflammation is not sufficient to increase systemic inflammation markers. It must be noted that the study differed from others in that the men suffering from chronic disease or taking non-steroidal anti-inflammatory agents (NSAIDs) were not excluded from the study group. We believe that this represented a more typical real-world screening population, but the use of NSAIDs may have altered the inflammatory profile.

Newer biomarkers include the PCA3 over-expression in post-digital rectal examination urine samples. Its use appears to be most useful in men considered for a second biopsy. Using a PCA-3 cut-off score of 25, 13% of high-grade cancers would be missed, while in the repeat biopsy setting, this is reduced to 3%.[23] As such, the Food and Drug Administration (FDA) recommends its use for determining the need for a second biopsy. The Prostate Health Index is a combination of total PSA, percentage of free PSA, and pro-PSA, and it was approved by the FDA in 2012. It has been reported to have twice the sensitivity of the percentage of free PSA/total PSA ratio when the total PSA is in the range of 2–10 ng/mL and was able to discriminate high-grade from low-grade cancer, with an AUC of 0.72, and using a cut-off of 24 would miss approximately 2.5% of high-grade cancers.[24] The 4k score is a combination of total PSA, percentage of free PSA, human Kallikrein 2 and intact PSA combined with age, digital rectal examination, and results of any previous biopsy. Using a cut-off threshold of ≥15% risk to recommend a prostate biopsy, the AUC was 0.82l however, 21% of all high-grade cancers were not detected. With a cut-off threshold of ≥6%, the number of missed high-grade cancers decreased to 11%.[25] However, no consensus on the optimum cut-off threshold has been established. The MDx systems use epigenetic assays; the ConfirmMDx uses the first-biopsy tissue samples with the hypermethylation status of the *GSTP1, APC,* and *RA*SSF1 assessed; whereas the SelectMDx assays *DLX1* and *HOXC6* expression in post-digital rectal examination urine samples and compares them with the *KLK3* expression, both are considered to be investigational in nature.

Obesity, as measured by body mass index (BMI), has an important value in men with prostate cancer, being correlated with a more aggressive disease, higher risk of treatment failure, and cancer specific mortality[26,27] and is associated with upstaging and upgrading in patients with low-risk prostate cancer.[28] An increased BMI is associated with higher levels of inflammatory cytokines, increased *de novo* lipogenesis, accumulation of metabolic intermediates, and increased expression of genes in the tricarboxylic acid cycle, all considered to be significant in prostate cancer development.[26] Interestingly, in low-risk prostate cancer, the presence of CPCs is associated with upstaging and upgrading,[29] and the frequency of CPC detection increases with increasing BMI.[30] The neutrophil-to-lymphocyte, platelet-to-lymphocyte, and eosinophil-to-lymphocyte ratios have also been reported as associated with upgrading but not upstaging,[31] and they could be used to evaluate low-risk patients when considering active surveillance.

The CPC detection to indicate the need for a prostate biopsy was used as a sequential test in men with an increased PSA and not as a general screening test. Due to its high NPV, men negative for CPCs may not need to undergo prostate biopsy and be exposed to risks of complications, but they can be followed up more closely.

In conclusion, the ideal biomarker for the detection of prostate cancer in a screening population is one that detects clinically significant cancers, does not detect indolent cancer, and has a high NPV to avoid unnecessary biopsies. SII and PLR did not fulfill these requirements and did not discriminate between patients with clinically significant prostate cancer, indolent cancer, and benign prostatic disease in a Chilean screening population with a PSA 4–10 ng/mL. As such, the use of SII and PLR in predicting significant prostate cancer prior to prostate biopsy is not supported by these findings. The use of CPC as a sequential test to identify patients with an elevated total PSA who require a prostate biopsy needs to be externally validated. It is a simple low-cost test, which could be performed in the routine immunocytochemical laboratory of a general hospital.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

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