Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio Alone or Combined with Prostate-Specific Antigen for the Diagnosis of Clinically Significant Prostate Cancer

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Abstract

Background: Many patients undergo unwanted prostate biopsy due to unreliability of prostate-specific antigen (PSA). PSA density (PSAD), free PSA, free-to-total PSA ratio, prebiopsy MRI are used to diagnose prostate cancer (PCa). Since 1863, correlations between inflammation and cancer have been identified and explored; thus, the role of various blood parameters in detecting cancer has been studied, especially neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Here, we evaluated whether these parameters before prostate biopsy can diagnose prostate cancer in our hospital.

Methods: We conducted a retrospective study from January 2014 to January 2018. Prostate cancer patients were divided into significant cancer (Gleason Score ≥ 7) and insignificant cancer (Gleason Score < 7). NLR, PLR, and other clinical parameters were taken before the prostate biopsy. We then analyzed the associations of NLR and PLR alone or with PSA, with significant prostate cancer.

Results: We included 463 patients, of whom 60.3% (279) had prostate cancer and 75.6 % (211) had a Gleason score (GS) of ≥ 7 . PSA and PSAD in the clinically significant prostate cancer patient group were around two times more than those in the insignificant prostate cancer group. PV, NLR, PLR, and combined markers were more in the GS ≥ 7 population group. PSA combined with PLR (PPLR) and PSA with NLR (PNLR) had better area under a curve (AUC) (0.732 and 0.730, resp.), with statistical significance, than PSA, NLR, and PLR alone (0.723, 0.585, and 0.590). In the multivariate analysis using separate models with PSA and NLR or PLR compared to age, DRE-positive lesions, PV, PSAD; PNLNLR, and PPLR were statistically significant in finding aggressive prostate cancer. When combined markers were used together, despite the high correlations, PSA and NLR were nearly significant ($p = 0.062$) in detecting the GS ≥ 7 population.

Conclusion: The combined use of PSA with PLR and PSA with NLR helps detect the differences between clinically significant and insignificant prostate cancer.

Background

Prostate-specific antigen (PSA) for screening prostate cancer (PCa) lacks adequate sensitivity, specificity and positive predictive value (PPV) [1, 2]. Many patients undergo unnecessary prostate biopsy which has several disadvantages: financial burden and stress due to hospital admission, biopsy needle insertion, and risk of infection. Moreover, in 20% of patients with normal first biopsy results, PCa was found at the second biopsy [3]. Thus, various measures have been taken to improve the diagnostic results and reduce unnecessary biopsy, such as using PSA density (PSAD), free PSA, free/total PSA (f/t PSA), prebiopsy MRI, and prostate biopsy nomograms [2, 4, 5].

In 1863, Virchow discovered leukocytes in cancerous lesions [6]; since then, the role of inflammation in cancer has been explored and generated interest. In 2018, approximately 13% of global cancer is due to infections [7]; chronic inflammation plays a major role in these infections [6].

The use of blood parameters in PCa diagnosis and outcomes has generated interest due to their easy availability and cost-effectiveness. The utilization of prebiopsy blood parameters to identify PCa and its outcomes remains controversial. Several previous approved the use of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) [8, 9, 10, 11, 12, 13], whereas other studies disagreed as upon comparison, other clinical parameters such as age, PSA, PSAD, free PSA, and f/t PSA were better markers [14, 15, 16].

In this study, we investigated whether these blood parameters can detect clinically significant PCa before conducting a prostate biopsy. We included NLR and PLR combined with other examinations in screening for PCa (such as PSA; DRE, digital rectal exam; PV, prostate volume; PSAD). The samples were collected before the prostate biopsy procedure.

This study aims to find out whether NLR and PLR could improve detecting clinically significant PCa ($GS \geq 7$) if used alone or in combination with PSA (PNLR, PSA combined with NLR; PPLR, PSA combined with PLR; PNPLR, PSA with NLR and PLR) in our hospital. As per our knowledge, this is the first study to use combined PSA with PLR or NLR in detecting $GS \geq 7$ PCa.

Methods

In this study, 463 patients were included from 2014 to February 2018 who underwent all examinations required. Exclusion criteria were patients with lacking data and those with prostatitis, inflammation, other organ tumors, and chemotherapy and radiotherapy history.

Blood counts were taken prior to the prostate biopsy. PLR and NLR were calculated by dividing platelet and absolute neutrophil counts by absolute lymphocyte counts.

For the prostate biopsy, patients were admitted the morning of the procedure and were given fluoroquinolone antibiotics. All patients underwent ten- to 12-core standard prostate biopsies. PV was calculated using the following formula: $0.52 \times \text{length} \times \text{width} \times \text{height}$. Urology residents with considerable experience and senior urologists performed the prostate biopsies.

PSAD was calculated by dividing total PSA by PV.

Statistical Analysis

We used Statistical Package for the Social Sciences (SPSS), version 16.0 (SPSS Inc., Chicago, IL, USA), for analyzing the data. As the variables in our data are not normally distributed, we used the Mann–Whitney *U* test to compare cancer and noncancerous population groups. Moreover, Chi-square test was employed. Then, we performed receiver operating characteristic (ROC) curve analysis to find AUC values with $p < 0.05$ being considered statistically significant. Then, sensitivity, specificity, PPVs, and negative predictive values (NPV) for our data in interest and significant PCa were calculated ($GS \geq 7$). Furthermore, we performed a logistic regression analysis using 3 models; all the models were comprised of age, DRE-

positive lesions, PV, and PSAD. We included PNLN in the first model, PPLN in the second, and both PNLN and PPLN in the third. *p* values less than 0.05 were considered significant in the multivariate analysis.

Results

In the $GS \geq 7$ group, PSA and PSAD were approximately twice the values in the $GS < 7$ population; PV, NLR, PLR, and combined parameters were higher in the clinically significant cancer group with statistical significance, whereas lymphocytes were lower than those in the $GS < 7$ population. No differences were observed in age, DRE-positive lesions, PV, neutrophils, and platelets between the two groups (Table 1).

Table 1
Mann–Whitney test and Chi-square test of variables of interest and Gleason score ≥ 7 .

Variables	Significant cancer	Insignificant cancer	<i>p</i> value
Sample	211	68	
Age	73 (9)	73.5 (10)	0.825
PSA	14 (58)	7.25 (4.7)	< 0.001
DRE positive*	87 (80.6%)	21 (19.4%)	0.128
PV	36 (20)	32 (18.75)	0.076
PSAD	0.40 (1.660)	0.23 (0.185)	< 0.001
ANC	6.2 (1.38)	5.94 (1.37)	0.065
Platelets	21.4 (7.5)	20.5 (6.8)	0.155
ALC	2.7 (1.11)	2.96 (1.45)	0.024
NLR	2.3 (4.76)	2.05 (1.47)	0.035
PLR	77.39 (46.916)	66.94 (40.934)	0.026
PNLR	34.1 (152.90)	15.40 (11.39)	< 0.001
PPLR	1160 (5073.83)	494.80 (496.27)	< 0.001
PNPLR	3005.41 (15534.28)	1061.62 (1303.82)	< 0.001
*Chi-square; IQR: interquartile range. PSA: prostate-specific antigen; DRE: digital rectal examination; PV: prostate volume; PSAD: prostate-specific antigen density; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNLN: PSA and neutrophil-to-lymphocyte ratio; PPLR: PSA and platelet-to-lymphocyte ratio; PNPLR: PSA with neutrophil- and platelet-to-lymphocyte ratio.			
For PSA, we utilized our cutoff value and standard ≥ 4 ng/dl value used in clinical practice. The sensitivity of PSA ≥ 4 ng/dl was 98.1 with very low specificity of 2.9 and PPV of 75.80, whereas our cutoff values of PSA ≥ 9.35 ng/dl showed sensitivity, specificity, and PPV of 62.6, 70.6, and 86.80, respectively.			
We found PSA with PLR and PSA with NLR to be better in diagnosing GS ≥ 7 PCa. AUC for the variables were as follows: PPLR, 0.732; PNLN, 0.730; PSA, 0.723; NLR, 0.585; PLR, 0.590; PNPLR, 0.721. AUC values of age did not show any statistical significance. Figure 1. Table 2.			

Table 2
ROC values in the detection of clinically significant PCa.

Variables	AUC	<i>p</i> value	Cutoff	Sensitivity	Specificity	PPV	NPV
Age	0.509 (0.428–0.590)	0.826					
PSA	0.723 (0.661–0.784)	< 0.001	9.35	62.6	70.6	86.80	37.80
		< 0.001	4.00	98.1	2.9	75.80	33.30
NLR	0.585 (0.505–0.664)	0.035	2.45	44.1	70.6	82.30	28.90
PLR	0.590 (0.514–0.665)	0.026	92.59	38.4	75.0	82.70	28.20
PNLR	0.730 (0.668–0.792)	< 0.001	21.03	64.9	75.0	89.00	40.80
PPLR	0.732 (0.671–0.793)	< 0.001	802.87	63.5	73.5	88.20	39.40
PNPLR	0.721 (0.658–0.784)	< 0.001	1772.70	63.0	72.1	87.50	38.60
PSA: prostate-specific antigen; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNLR: PSA and neutrophil-to-lymphocyte ratio; PPLR: PSA and platelet-to-lymphocyte ratio; PNPLR: PSA with neutrophil- and platelet-to-lymphocyte ratio.							
As the ROC curve values for PSA combined with NLR or PLR were better these parameters' values when used alone, we investigated whether the use of combined markers was better in predicting aggressive PCa using different models.							
In the multivariate analysis, PNLR > 21.03 (Model 1) or PPLR > 802.87 (Model 2) was compared with age, DRE-positive lesion, PSAD, and PV; <i>p</i> < 0.05 was statistically significant. We did not use PSA in the models due to its high correlation with PNLR and PPLR (Spearman's correlation > 0.8; <i>p</i> < 0.001). Table 3.							

Table 3
Models 1 and 2.

Model 1				Model 2			
Categories	OR	CI	<i>p</i> value	Categories	OR	CI	<i>p</i> value
Age	0.983	0.940–1.028	0.460	Age	0.990	0.948–1.035	0.662
DRE positive	0.683	0.683–2.426	0.435	DRE positive	1.288	0.686–2.418	0.431
PSAD	2.415	0.954–6.112	0.063	PSAD	2.693	0.979–7.124	0.055
PV	1.002	0.981–1.023	0.861	PV	1.004	0.982–1.024	0.765
PNLR (> 21.03)	2.780	1.344–5.752	0.006	PPLR (> 802.87)	2.172	1.042–4.525	0.038
DRE: Digital Rectal Exam; PSAD: Prostate Specific Antigen Density; PV: Prostate Volume; PNLr: PSA with neutrophil and platelet to lymphocyte ratio; PPLR: PSA and platelet to lymphocyte ratio							

Although PNLr and PPLR are highly correlated (Spearman's correlation for PNLr and PPLR categorical data: 0.797, $p < 0.001$; PNLr and PPLR continuous data: 0.931, $p < 0.001$), when these combined markers were used together with age, DRE-positive lesions, PSAD, and PV, PSA with NLR was found to be nearly significant ($p = 0.062$).

Discussion

It is hypothesized that inflammatory cells and cytokines in the tumor microenvironment have a role in the development of cancer. Virchow discovered leukocytes in tumor tissues, suggesting that there is a relationship between inflammation and cancer; inflammatory cytokines are correlated with DNA disruption, tumor suppressor genes inactivation, angiogenesis, tumor growth promotion, and metastasis [6, 16]. The inflammatory cells release substances that cause tumor vessel proliferation and sustenance and tissue remodeling, leading to more vessel formation [6, 16]. In a tumor microenvironment, neutrophils release Reactive Oxygen Species (ROS) and Reactive Nitrogen Species having mutagenic effects; furthermore, inducible Nitric Oxide Synthase (iNOS) release leads to DNA and tissue injury [17].

The interaction between platelets and cancer can promote the tumor's ability to evade immune cells' action, which does not result in the eradication of neoplastic cells and the arrest of the blood vessels, hence enhancing the survival and persistence of cancer cells [18, 19]. Platelets are comprised of P-selectin, Platelet Endothelial Cell Adhesion Molecule-1 (PECAM-1), glycoprotein IIb/IIIa (GPIIb/IIIa), GPIb/IX, and GPVI which cause platelet and cancer cell adhesion, escaping immune function, and metastasis and the release of VEGF and PDGF causes tumor cell proliferation, vascular permeability, and

the formation of new blood vessels. Furthermore, the release of Transforming Growth Factor Beta (TGF- β) results in cancer cell invasion and proliferation [19].

The link between PCa and inflammation is explored and studied in the literature. Atrophic epithelium with stromal changes was found in older patients' prostate biopsy. In this area, it is observed that inflammatory cells have high proliferative capacity compared to the surrounding normal prostate tissue, known as Proliferative inflammatory Atrophy (PIA) which may progress to High-Grade Prostatic Intraepithelial Neoplasia (HGPIN) and early prostate adenocarcinoma [20, 21]. During inflammation, PIA is exposed to ROS; loss of protective agents against ROS might change PIA to HGPIN or prostate carcinoma [22]. According to a previous meta-analysis, a history of prostatitis increases the risk of PCa with an odds ratio of 1.6 [23]. Moreover, in another meta-analysis, there were associations between syphilis and gonorrhea and PCa [24].

Recently, various blood parameters (NLR, PLR, LMR, and MPV) [8, 9, 10, 11, 12, 13] have been utilized to predict the diagnosis of PCa, clinically significant PCa, and its outcomes. However using these blood parameters is still a matter of debate and controversial as different studies argued that they are unreliable in detecting PCa [14, 15].

In this study, we assessed the ability of PSA combined with NLR or PLR in detecting significant PCa. We found that NLR, PLR, PNLR, and PPLR were high in the $GS \geq 7$ group ($p < 0.05$) and that combined markers are associated with high GS PCa using different models in the multivariate analysis.

Toriola et al. found that the elevated number of leukocytes increased the risk of death from PCa by 2.57 times [25]. In another study, an increase in NLR and PLR was associated with poor oncologic findings [8]. Kawahara et al. in a study including 810 men who underwent prostate biopsy with PSA between 4 and 10 ng/dl found NLR to be a risk factor of PCa [10]. Minardi et al. revealed that NLR is related to disease-free survival in PCa patients; however, no correlation was observed with GS [9]. In this study, we found that NLR and PLR alone or combined with PSA are associated with GS. In Korean patients with gray-zone PSA, NLR was associated with PCa detection and $GS \geq 4 + 3$ cancer [11]. Adhyatma et al. discovered that prebiopsy PLR is valuable in detecting PCa [12]. Mehmet et al. reported that aggressive PCa is associated with NLR increase; however, they suggested that prostatitis limited the use of NLR in detecting PCa [13].

On the other hand, Vidal et al. found no associations of PCa outcomes among black or white patients [14]. Murray et al. reported that the PLR and systemic immune-inflammation index (SII, NLR combined with PLR) did not differentiate between BPH, indolent cancer, and clinically significant PCa [15].

This study had several limitations as follows. Our study is a nonrandomized retrospective study from a single institution with a small population sample. Thus, various biases might affect the detection of clinically significant PCa. Although the use of blood parameters with PSA had better specificity and PPV, the NPV was low. Thus, despite improving the detection of aggressive PCa, these parameters are still not ideal.

Conclusion

NLR and PLR combined with PSA exhibited better results in detecting clinically significant PCa than NLR, PLR, and PSA alone. Thus, utilizing PSA with NLR or PLR can provide an idea about the aggressiveness of PCa before conducting the prostate biopsy.

Abbreviations

PCa – Prostate cancer; PSA – Prostate specific antigen; PSAD – Prostate specific antigen density; BPH – Benign Prostate Hypertrophy; F / t PSA - free to total PSA; MRI – Magnetic Resonance Imaging; NLR – Neutrophil to Lymphocyte ratio ; PLR - Platelet to Lymphocyte ratio; MPV – Mean Platelet Volume; GS – Gleason Score; SPSS – Statistical Package for the Social Sciences ; ROS - Reactive Oxygen Species; RNS - Reactive Nitrogen Species; iNOS - inducible Nitric Oxide Synthase; PECAM1 - Platelet Endothelial Cell Adhesion Molecule-1; VEGF – Vascular Endothelial Growth Factor; PDGF – Platelet Derived Growth Factor; TGFB - Transforming Growth Factor Beta; PIA - Proliferative inflammatory atrophy; HGPIN - High Grade prostatic Intra-epithelial Neoplasia ; PNLR - PSA combined with NLR ; PPLR - PSA combined with PLR; PNPLR - PSA with NLR and PLR; ROC – Receiver operating curve; AUC – Area Under Curve

Declarations

Ethics approval and consent to participate

This study was approved by local ethics committee, Showa University (3244 – 31/8/2020) and in complete agreement with the Declaration of Helsinki. The ethics committee waived the need for informed consent due to retrospective nature of our study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Availability of data and materials

The datasets generated and/or analysed during the current study are available in the Showa University Hospital medical records

Authors` contributions

TS, YO, TN, YN, SPN designed the study. TU, TI, RK, SA, MM and SPN gathered the data and performed the statistical analysis. JN, YM KO, TS interpreted the data and edited the manuscript. YO, TS, JN, YM, YN, TN reviewed the manuscript. SPN drafted the manuscript. All authors read and approved the final manuscript

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Figures

Figure 1

ROC of NLR and PLR alone or combined with PSA PSA: prostate-specific antigen; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNLR: PSA and neutrophil-to-lymphocyte ratio; PPLR: PSA and platelet-to-lymphocyte ratio; PNPLR: PSA with neutrophil- and platelet-to-lymphocyte ratio.