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Diagnostic Value of Platelet–To-Lymphocyte Ratio in Prostate Cancer

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Abstract

BACKGROUND: Previous studies demonstrated the promising value of platelet-to-lymphocyte (PLR) in prostate cancer.

AIM: This study was conducted to evaluate its pre-biopsy values in predicting prostate cancer.

METHODS: We included all benign prostatic hyperplasia (BPH) and prostate cancer (PCa) patients who underwent a prostate biopsy in Adam Malik Hospital between August 11th 2011 and August 31st 2015. The relationship between pre-biopsy variables which could be affecting the percentage of prostate cancer risk was evaluated, including age, prostate-specific antigen (PSA) level, and prostate volume (EPV). The PLR was calculated from the ratio of related platelets with their absolute lymphocyte counts. The values then analysed to evaluate their associations with the diagnosis of BPH and PCa.

RESULTS: As many as 298 patients consisted of 126 (42.3%) BPH and 172 PCa (57.7%) patients are included in this study. Mean age for both groups are 66.36 ± 7.53 and 67.99 ± 7.48 years old ($p = 0.64$), respectively. There are statistically significant differences noted from PSA (19.28 ± 27.11 vs 40.19 ± 49.39), EPV (49.39 ± 23.51 vs 58.10 ± 30.54), PLR (160.27 ± 98.96 vs 169.55 ± 78.07), and NLR (3.57 ± 3.23 vs 4.22 ± 2.59) features of both groups ($p < 0.05$). The AUC of PLR is 57.9% with a sensitivity of 56.4% and specificity of 55.6% in the cut-off point of 143 ($p = 0.02$). Besides, the NLR cut-off point of 3.08 gives 62.8% AUC with 64.5% sensitivity and 63.5% specificity. We asked for permission from the preceding authors of Indonesian Prostate Cancer Risk Calculator (IPCRC) and calculated its value from 98 randomised patients consist of 45 (45.92%) BPH and 53 (54.08%) PCa. We found a comparable value between PLR/NLR with IPCRC in predicting prostate cancer (AUC of 67.6%, 75.3%, and 68.4%, respectively) with a statistically significant difference of all value in both groups ($p < 0.05$).

CONCLUSIONS: PLR gives promising value in predicting prostate cancer in suspected patients. We suggest a further prospective study to validate its diagnostic values so it can be used as applicable routine calculation.

Introduction

Prostate cancer (PCa) is the second most common cancer worldwide. It accounts for more than 15% of cancer in men, its clinical relevance keeps rising, and 70% of them occurs in developed countries [1], [2]. Prostate biopsy is required for the histopathological diagnosis of prostate cancer, and Trans Rectal Ultrasound Guided procedure remains the gold standard in most countries. Since the biopsy is mostly office procedure and associated with significant complications, various non-invasive strategies have been invented to prevent unnecessary biopsy.

Serum Prostate Specific Antigen (PSA) has been used as the screening standard for patients in suspicion of prostate cancer. In most countries, PSA value of more than 4 ng/ml has been the standard threshold to perform prostate biopsy [1], [2], [3], [4], [5], [6], [7]. But, recent meta-analyses showed that in patients with PSA levels over 4 ng/ml, the positive predictive value of PSA is only 25% [5]. Also, the invasive prostate biopsy may still miss some percentage of cancer, given that up to 20% of men will have prostate cancer in a repeated biopsy [8]. Various imaging and biomolecular marker have been suggested to increase diagnostic accuracy, but none of these methods is available for widespread use, either due to availability issues or the high cost [2], [8].

Over the past decades, our study of the microenvironment of cancer has supported Virchow's hypothesis of the connection between inflammation and cancer. Inflammatory markers have been associated with more aggressive disease [6], [9]. Though small in numbers, previous studies demonstrated a promising value of platelet-to-lymphocyte (PLR) in prostate cancer. Kaynar et al. found an increased level of PLR in PCa compared with that in benign prostatic hyperplasia (BPH) with PSA value greater than 10 ng/ml [10]. A statistically significant higher value of PLR in PCa compared to BPH patients was also demonstrated by Yuksel et al., in 2015 [5]. According to our knowledge, there is still no data on the use of PLR value as a predictor of PCa in Indonesia.

Therefore, this study is conducted to evaluate its pre-biopsy value in predicting PCa.

Material and Methods

Population of Study

This is a diagnostic study with a retrospective design. All patients who underwent a prostate biopsy in Adam Malik General Hospital between August 2011 and August 2015 were included. Data related to prostate cancer prediction factors were collected, and their relationship with malignant pathology was analysed. The factors included were: age, serum PSA value, and estimated prostate volume (EPV). The PLR values were calculated using the routine blood count results, collected right before the biopsy procedures were performed. Histopathology of the biopsy specimen was applied as the gold standard of PCa diagnosis. Patients with irrelevant and incomplete data were excluded from the study.

Variables

Serum PSA was collected from recent laboratory results just before biopsy procedures were performed. We collected EPVs from their initial prostatic Trans Abdominal ultrasound (TAUS) data. Prostate was measured in 3-dimensional aspects, and its volume was estimated with the modified ellipsoid formulation in cm^3 (0.523 [(length x width x height)]. PLR value is a direct ratio of platelets and absolute lymphocyte count which was acquired from the routine blood count at initial assessment.

Analysis

Data input and analyses were performed using SPSS ver 20.0 software. Data will be divided into two groups according to their histopathology of prostate biopsy, the BPH and PCa group. Data related to PCa prediction such as routine blood count and PLR of each group will be distributed in frequency table and analysed for their value in predicting biopsy results with bivariate analysis. A p value of < 0.05 (α = 5%) was considered statistically significant.

Results

Characteristics and Bivariate Analysis

As many as 298 patients consisted of 126 (42.3%) BPH and 172 PCa (57.7%) patients are included in this study. Mean age for both groups are 66.36 ± 7.53 and 67.99 ± 7.48 years old (p = 0.64), respectively. Patient's characteristics and laboratory values are shown in Table 1.

Table 1: Patients Characteristics and Hematologic Parameters

Parameters	BPH (n = 126) Mean ± SD (Median)	PCa (n = 172) Mean ± SD (Median)	p
Age (years)	66.36 ± 7.53	67.99 ± 7.48	0.64*
PSA (ng/dL)	19.28 ± 27.11	40.19 ± 49.39	< 0.0001*
EPV (cm^3)	49.39 ± 23.51	58.10 ± 30.54	0.02*
Hb	12.99 ± 2.00 (13.20)	12.95 ± 2.01 (13.10)	0.754**
Leucocytes Count (x $10^3/mm^3$)	8.67 ± 3.45 (8.11)	9.19 ± 3.29 (8.46)	0.1**
Absolute Lymphocyte Count (x $10^3/mm^3$)	2.09 ± 0.83 (2.02)	2.00 ± 0.76 (1.87)	0.29**
Platelets Count (x $10^3/mm^3$)	286.16 ± 112.24 (266)	311.61 ± 120.81 (294)	0.049**
PLR	160.27 ± 98.96 (128.13)	169.55 ± 78.07 (151.28)	0.02**

*T-test **Mann-Whitney Test

Comparing the laboratory results of both groups, statistically, significant differences were noted from PSA (19.28 ± 27.11 vs 40.19 ± 49.39), EPV (49.39 ± 23.51 vs 58.10 ± 30.54), and PLR (160.27 ± 98.96 vs 169.55 ± 78.07) in each bivariate analysis.

PLR and PSA

We then performed a Receiver Operating Characteristics (ROC) analysis to define the Area under Curve (AUC) of PLR in predicting prostate cancer (Figure 1 and Table 2).

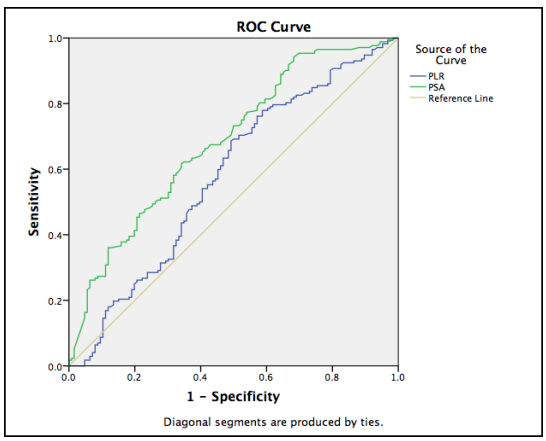

Figure 1: The ROC Curves of PLR and PSA

The AUC of PLR is 57.9% with a sensitivity of 56.4% and specificity of 55.6% in the cut-off point of 143 (p = 0.02).

Table 2: The AUC of PLR and PSA

Parameters	AUC	p
PLR	57.9%	0.02
PSA	68.5%	< 0.0001

PLR and IPCRC

We asked for permission from the preceding authors of Indonesian Prostate Cancer Risk Calculator (IPCRC) and calculated its value from 98 randomised patients which consist of 45 (45.92%) BPH and 53 (54.08%) PCa.

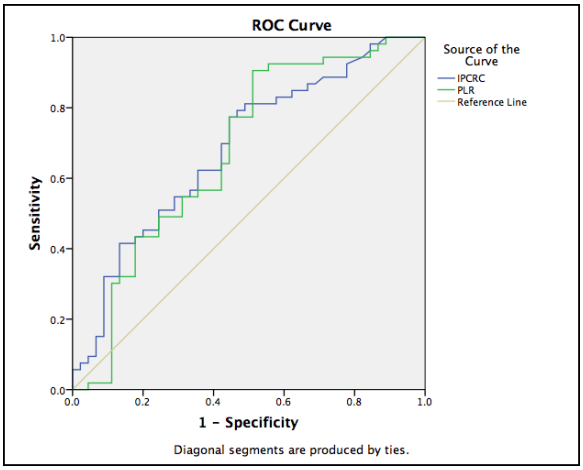

Figure 2: The ROC Curves of PLR and IPCRC Score

We found a comparable value between PLR with IPCRC in predicting prostate cancer (AUC of 67.6% and 68.4%, respectively) with a statistically significant difference was noted between each value (p < 0.05) as shown in Figure 2 and Table 2.

Table 2: The AUC of PLR and IPCRC

Parameters	AUC	p
PLR	67.6%	0.003
IPCRC	68.5%	0.002

Discussion

The body response to cancer parallels with inflammation and wound healings. In 1863, Rudolf Virchow noted leucocytes in neoplastic tissues and suggested a connection between inflammation and cancer. He suggested that the "lymphoreticular infiltration" reflected the origin of cancer at sites of chronic inflammation. Tumour-infiltrating lymphocytes may contribute to cancer growth and spread, and the immunosuppression-associated malignant diseases. In his review in 2001, Balkwill et al. still mentioned the theory of "Tumors: wounds that do not heal" previously showed by Dvorak in 1986. This theory showed how wound healing and tumour stroma formation share many important features. Wound healing is usually self-limiting, but tumours secrete a vascular permeability factor, vascular endothelial growth factor (VEGF), that can lead to persistent extravasation of fibrin and fibronectin and continuous regeneration of extracellular matrix. Platelets in wounds are critical sources of cytokines, especially for transforming growth factor β (TGF-β) and VEGF. Platelet release may also play an important role in angiogenesis. Also, malignant cells secrete proinflammatory cytokines independently [9]. This will be the basis of predicting cancer through platelets count [6], [9]. Our study found a significant difference between platelet counts of PCa and benign prostatic lesions (311.61 ± 120.81 vs 286.16 ± 112.24; p=0.049) which supported the previous theory. But, a previous larger sample study from Yuksel et al., did not show the same results (p = 0.094) [5]. From these findings, we concluded that platelet count could not stand alone as the only predictive marker.

Though inflammatory markers such as lymphocytes were mentioned in previous studies, not all markers are coherent with every cancer. Leucocytes, mainly lymphocytes, are the most prominent marker in many cancers, but not in PCa. Study of Cihan Y, et al. showed that patients with PCa had a lower level of lymphocytes, neutrophils, and a higher level of monocytes with a significant difference in lymphocyte count, compared to healthy controls [11]. McDonald et al., also found that lymphocytes count is significantly lower in patients with elevated PSA compared with patients with PSA below 4 ng/ml [3]. Though this study found that the absolute lymphocyte counts of PCa patients are lower, the difference was not statistically significant compared with a benign group (2.09 ± 0.83 vs 2.00 ± 0.76; p = 0.23).

In this study, though we found a significant difference of platelets count with no statistical difference in lymphocyte count between both groups, the ratio of PLR value gives the event more significant difference (p = 0.02). A similar result was also shown by Yuksel et al., where a significant intergroup statistical difference was found for PLR (p = 0.041) but not for lymphocyte count (p > 0.05) [5]. This also supported by the study of Li et al., who found a statistical difference between PCa and normal/BPH patient (p < 0.05). Kaynar et al., also found that statistically significant value of PLR was observed in PCa and BPH patients with PSA above 10 ng/ml [10].

Yuksel et al. found a statistically significant difference of PLR value between PCa and BPH patients, but not between PCa and prostatitis (p = 0.018 vs p = 0.067). This could be related to the

previous theory of “Tumors: wounds that do not heal” [9]. According to this theory, inflammation cascade, which always happens in the inflammation process, is also continuously happening in tumours without receding. In this study, we put aside the prostatic non-BPH benign lesions to selectively reduce this bias. So we merely compared the histopathologically proven BPH and PCa patients. However, this can only happen in the study with the retrospective design. In the case of prospective design, we cannot conclude whether the prediction of PCa through PLR value can differentiate the histopathology of PCa and prostatitis. Further prospective studies, as well as more predictive marker, are needed.

In conclusion, inflammation cascade, which always happens in the inflammation process, is also continuously happening in tumours without receding. PLR gives promising value as a systemic inflammatory marker in predicting prostate cancer in suspected patients. And in this study, we tried to investigate the applicability in Indonesia. But, if to be applied as routine testing and to selectively decide candidates for prostate biopsy in a patient with PSA value more than 4 ng/ml, this value needs a further prospective trial.

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