The Value of Inflammatory Cell Count and Its Ratio in the Diagnosis of Prostate Cancer

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Abstract

Background: Inflammatory cells play an important role in the occurrence and development of cancer. In recent years, the value of inflammatory cell count and its ratio in the diagnosis of prostate cancer has been controversial.

Methods: A retrospective analysis of 475 patients with transrectal prostate puncture with TPSA>4 ng/ml in the Third Affiliated Hospital of Xi'an Jiaotong University. Univariate analysis, multivariate analysis and Receiver Operating Characteristics curve analysis were performed to analysis the factor of age, TPSA, FPSA, PV, NC, LC, PC, NLR, PLR in the diagnosis value of prostate cancer, and further analysis the value of inflammatory cell count and its ratio in different TPSA groups of prostate cancer (4 ng/ml <TPSA ≤ 10 ng/ml, 10 ng/ml ≤TPSA ≤ 20 ng/ml, TPSA ≥ 20 ng/ml).

Results: The results of Univariate analysis in the overall data showed that Age, TPSA, PV, NC, PLC were influencing factors in the diagnosis of prostate cancer. The Area Under the Curve (AUC) of NC was 56.2% with a sensitivity of 72.2% and specificity of 41.5% in the cut -off point of 4.52 (p = 0.021). The PLC cut-off point of 205.5 gives 55.6% AUC with 67.2% sensitivity and 4.2% specificity. Multivariate binary logistic regression analysis results showed that Age, TPSA, PV, NC were independent influencing factors for the diagnosis of prostate cancer; In different TPSA group studies, it was found that NC, NLR, and PLR were valuable for the diagnosis of prostate cancer when TPSA>20 ng/ml—at the NC cut-off point of 4.52 with 67.3% AUC, 71.2% sensitivity and 62.5% specificity(p<0.001), at the NLR cut-off point of 3.14 with 65.4% AUC, 67.2% sensitivity and 61.1% specificity (p<0.001), and at the PLR cut-off point of 135.8 with 62.8% AUC , 57.6% sensitivity and 66.7% specificity (p<0.001). Multivariate binary logistic regression analysis results showed that when TPSA>20 ng/ml, the higher Age, TPSA , Low PV and NC are independent risk factors affecting the diagnosis of prostate cancer.

Conclusion: NC has promising value in predicting prostate cancer, especially when TPSA>20 ng/ml. A further prospective study in validating its diagnostic value was needed.

Background

In recent years, the incidence and mortality of prostate cancer(PCa) have been increasing year by year in the world, especially in China [1]. The patients of prostate cancer had been usually in the advanced stage when they were diagnosed. Because the early symptoms of prostate cancer are not obvious and not easy to be taken seriously. [2] Early detection and timely treatment have become an important factor affecting the prognosis of prostate cancer patients. [3]

Benign prostatic hyperplasia (BPH) and PCa are both epidemiologically and histopathologically hormone dependent diseases and prostatic inflammation associated chronic disease. Prostate-specific antigen (PSA) is an indicator used commonly for screening prostate cancer currently [4], but it is a specific antigen of prostate epithelial cells, not specific antigen of prostate cancer. PSA is related to age, prostate volume, urinary tract infection and other factors, so it has poor specificity in the diagnosis of prostate [5].

Accurate screening for prostate cancer can avoid overdiagnosis on the one hand, and on the other hand, it can actively detect or treat prostate cancer patients in a timely manner. Therefore, finding other indicators to improve the diagnosis rate of prostate cancer has always been a hotspot in this field.

Inflammatory cells play an important role in the occurrence and development of cancer. In recent years, the value of inflammatory cell count and its ratio in the diagnosis and prognosis of prostate cancer has been controversial. [6]. According to our knowledge, there is still no data on the use of inflammatory cell count or its ratio as predictors of PCa in Northwest China. Therefore, this study is conducted to evaluate its pre-biopsy value in predicting Pca based on their PSA levels, retrospectively.

Method

Subsequent to local ethics committee approval, collected the clinical and pathological data of 475 patients filtered by exclusion criteria with TPSA ≥ 4 ng/ml and complete data after undergoing transrectal prostate biopsy in the Third Affiliated Hospital of Xi'an Jiaotong University from January 2015 to December 2018. Exclusion criteria: ① Patients with indwelling catheterization and digital rectal examination within 1 week before serum PSA examination, cystoscopy within 48 hours, and ejaculation within 24 hours; ② Combined infection or acute inflammatory reaction; ③ Combined with malignant tumors in other parts of the body; ④ Already performed surgical treatment or endocrine treatment; ⑤ There is coagulation dysfunction, serious cardiovascular and cerebrovascular diseases. The Factors included Age, total PSA(TPSA), prostate volume (PV), neutrophil count (NC), lymphocyte count (LC), Platelet count (PLC), Neutrophil count/lymphocyte count ratio (NLR), Platelet count/lymphocyte count ratio (PLR). Collected fasting venous blood from all patients before puncture, used EDTA-Na₂ for anticoagulation, used SYSMEX XN550 automatic blood analyzer and supporting reagents to determine blood routine and collected Patient NC, LC, PC data, and calculated NLR, PLR. The volume of the prostate was obtained by ultrasound, and estimated with the modified ellipsoid formulation in cm³ ($0.52 \times [\text{length} \times \text{width} \times \text{height}]$). Fasting venous blood before puncture was collected from all patients, and serum was collected after centrifugation to determine TPSA and FPSA indicators by radioimmunoassay.

Statistical Analysis

Used SPSS22.0 software to analyze the data. In univariate analysis, continuous variables were first tested for normality. If they obeyed a normal distribution, an independent sample T test would be selected. The results were displayed as mean $\pm$ standard deviation. If they did not obey a normal distribution, then selected the Mann-Whitney U test, and the results were displayed as the median (upper quartile to lower quartile). Receiver Operating Characteristics (ROC) curve combined with Youden index was performed to determine the diagnostic value of inflammatory cell count and its ratio. Statistically significant risk factors from univariate analysis were included in the multivariate logistic regression analysis. All data analysis takes $P < 0.05$ as the difference was statistically significant.

Result

Factors affecting the diagnosis of prostate cancer in the overall data

As many as 475 patients consisting of 277 (58.32%) BPH and 198 PCa (41.68%) patients were included in this study. Patients characteristics and laboratory values are shown in Table 1.

Comparing the laboratory results of both groups, there were statistically significant differences noted from [69.00~64.00~74.00 vs 73.50~67.00~79.00], TPSA[12.90~8.53~20.85 vs 27.95~13.73~74.25], PV[67.17~46.07~92.35 vs 41.970~31.24~66.74], NC[4.07~3.18~5.34 vs 3.84~3.01~4.71] and PLC[197.00~154.00~245.00 vs 179.00~146.00~229.50].

We then performed a ROC analysis to define the Area Under Curve (AUC) of NC and PLC in predicting prostate cancer (Figure 1A).

The NC cut-off point of 4.52 gives 56.2% AUC with 72.2% sensitivity and 41.5% specificity ($p=0.021$). The AUC of PLC was 55.6% with a sensitivity of 67.2% and specificity of 46.2% in the cut-off point of 205.5 ($p=0.038$).

Included the above-mentioned risk factors affecting the diagnosis of prostate cancer into the multivariate binary logistic regression analysis, the results showed that higher age, TPSA, lower PV, and NC were independent risk factors that affect the diagnosis of prostate cancer (Figure 1B).

The value of inflammatory cell count and ratio in different TPSA groups in the diagnosis of prostate cancer

According to TPSA, patients were divided into 3 groups, namely 4 ng/ml < TPSA ≤ 10 ng/ml group, 10 ng/ml < TPSA ≤ 20 ng/ml group and TPSA > 20 ng/ml group.

Factors affecting the diagnosis of prostate cancer when 4ng/ml < TPSA ≤ 10ng/ml

A total of 120 people, aged 52-86 years old, with an average age of 68.87 ± 6.10 years old. The pathological results of puncture confirmed 30 cases of prostate cancer (25.00%) and 90 cases (75.00%) of benign prostatic hyperplasia. The results of univariate analysis found that the inflammatory cell count and its ratio are not factors that affect the diagnosis of prostate cancer. Only PV was a factor that could affect the diagnosis of prostate cancer ($p < 0.001$) (Table 2).

Factors affecting the diagnosis of prostate cancer when 10 ng/ml < TPSA ≤ 20 ng/ml

A total of 158 patients, aged 43-88 years, average age 70.09 ± 8.07 years, of which 43 cases (27.22%) were pathologically confirmed prostate cancer, 115 cases (72.78%) were prostate hyperplasia. It was found that the inflammatory cell count and its ratio were not factors that affect the diagnosis of prostate cancer. Only Age and PV were factors that could affect the diagnosis of prostate cancer ($p < 0.01$) (Table 3).

Factors affecting the diagnosis of prostate cancer when TPSA > 20 ng/ml

A total of 197 patients, aged 50-91 years, average age 71.73 ± 7.54 years, of which 125 cases (63.45%) were pathologically confirmed prostate cancer, 62 cases (36.55%) were benign prostatic hyperplasia. Univariate analysis found that NC, NLR, PLR, age, TPSA, and PV were factors that may affect the diagnosis of prostate cancer ($p < 0.01$) (Table 4).

We then performed a ROC analysis to define the AUC of NC, NLR and PLR in predicting prostate cancer (Figure 2A).

The NC cut-off point of 4.52 gives 67.3% AUC with 71.2% sensitivity and 62.5% specificity ($p = 0.001$). The AUC of NLR was 65.4% with a sensitivity of 67.2% and specificity of 61.1% in the cut-off point of 3.14 ($p = 0.001$). The AUC of PLR was 62.8% with a sensitivity of 57.6% and specificity of 66.7% in the cut-off point of 135.8 ($p = 0.001$).

Included the above-mentioned risk factors that could affect the diagnosis of prostate cancer into the multivariate binary logistic regression analysis. The results showed that when $TPSA > 20$ ng/ml, higher age, TPSA, lower PV and NC were independent risks factors that affect the diagnosis of prostate cancer. (Figure 2B).

Discussion

Many studies have shown that inflammation is related to the occurrence, development and metastasis of malignant tumors [7–11]. Because the leukocyte count and various types of white blood cells are indicators of systemic inflammation and immune response, these values may be good candidate biomarkers for predicting aggressive tumors.

The value of inflammatory cell count and its ratio in the diagnosis of prostate cancer is still controversial. Neutrophils are an important part of the tumor microenvironment and the largest number of white blood cells in the circulatory system. Inflammation and cancer have an important connection through neutrophils which play an active role in tumor progression and metastasis. Neutrophils are thought to be one of the new targets for many cancer types [12]. The study by FUJITA K et al. showed that low serum neutrophil count in Japanese men can predict positive prostate biopsy, and leukocyte count is negatively correlated with prostate cancer [13], which is consistent with our study. Decreased neutrophil count is at risk of poorly differentiated prostate cancer among African Americans [14]. A retrospective study by Naito H et al. found that PSA and Gleason score had a significant association with NLR [15]. ADHYATMA K P et al confirmed NLR has a promising performance in predicting PCa in patients with PSA above 4 ng/dL [16]. However, Kamali K et al. found that neutrophil count and neutrophil-to-lymphocyte ratio cannot be predictive factors for positive prostate cancer biopsy [17]. A retrospective analysis study by Oh JJ et al. found that NLR may be a potentially useful clinical marker in the detection of prostate cancer among men with a PSA level in the 4–10 ng ml⁻¹ range. A higher NLR was significantly associated with prostate cancer detection [18]. In this study, it was found that the NLR value of the prostate cancer group was greater than that of the benign prostatic hyperplasia group, but there was not statistically significant, which may be related to the smaller sample size. But a prospective study found that the

neutrophil/lymphocyte ratio did not discriminate between benign and malignant prostatic disease in patients with a PSA between 4–10 ng/ml [19]. A retrospective study by Adhyatma KP et al. found that PLR gives promising value in predicting prostate cancer in suspected patients [20]. A retrospective study by Kaynar M et al. found that statistically significant differences were observed in the mean PLR values only if the PSA level was 10 ng/ml and above in the BPH and PCa groups [21]. Therefore, the value of inflammatory cell count and its ratio in the diagnosis of prostate cancer needs further research to confirm.

Our study found that when $PSA \leq 20$ ng/ml, no significant difference in inflammatory cell count and its ratio was found between the benign prostatic hyperplasia group and the prostate group, which may be related to factors such as small sample size and ethnic differences. When $TPSA > 20$ ng/ml, NC, NLR and PLR had statistically significant differences between the benign prostatic hyperplasia group and the prostate group. REDUCE clinical trial made with a series of 8,824 patients revealed a high incidence of chronic prostatic inflammation in BPH. Inflammation is one of the reasons leading to elevated PSA, which may be the reason why NC, NLR, and PLR are valuable for the diagnosis of prostate cancer when $TPSA > 20$ ng/ml.

In BPH patients with PSA levels of 20 ng/ml and above, NC, NLR and PLR levels were significantly higher than that in the PCa group. Prostate cancer secretes interleukin-8 and other pro-inflammatory chemokines which can recruit neutrophils [22]. These chemokines may affect the neutrophil count in prostate cancer patients. Another study reported that prostate hyperplasia is an immune inflammatory disease [23], neutrophils are related to the volume of the prostat [24]. Therefore a possible explanation may be that asymptomatic prostate inflammation may increase the number of neutrophils. Thrombocytosis is seen in clinical situations including chronic inflammation and malignancy [25, 26]. It is considered to be related to the excessive production of some hematopoietic growth factors that act on megakaryocytes [26]. Thrombocytosis is related with the majority of all common cancer types. These may be the reason for the higher levels of NC, NLR, and PLR in the BPH group when the PSA is higher.

Conclusion

In summary, when the patient's serum $PSA > 20$ ng/mL, the patients with low-NC, low-NLR and low-PLR value may take significant higher risk to be diagnosed with PCa. And NC is an independent risk of prostate cancer Factors. If validated, the NC will become a promising, accessible, inexpensive biomarker for PCa prediction. However, due to single-center studies and the small number of samples, the clinical value of NC, NLR, and PLR in the diagnosis of prostate cancer still needs to be prospective, Multi-center, large sample research.

Abbreviations

PCa: prostate cancer; BPH: benign prostatic hyperplasia; PSA: prostate-specific antigen; TPSA: total PSA; PV: prostate volume; NC: neutrophil count; LC: lymphocyte count; PLC: Platelet count; NLR: Neutrophil

count/lymphocyte count ratio; PLR: Platelet count/lymphocyte count ratio; ROC: Receiver Operating Characteristics; AUC: Area Under Curve.

Declarations

Ethics approval and consent to participate

This clinical study is a retrospective study. It only collects patient clinical data, does not interfere with the treatment plan of the patient, and will not bring risks to the patient's physiology. The study was implemented after approval by the ethics committee of the Third Affiliated Hospital of Xi'an Jiaotong University.

Consent to publish

Not Applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to private protection but are available from the corresponding author on reasonable request.

Competing interests

The authors declared that they have no conflicts of interest to this work.

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Authors' Contributions

Conception: Duan Wanli, Sun Yi. Data collection: Duan Wanli, Xu Boyu Dataanalysis: Duan Wanli, Deng Qian. Manuscript writing: Duan Wanli, Deng Qian, Tie Peng, Cheng Yongyi and Sun Yi. All authors read and approved the final manuscript.

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Not Applicable

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Tables

Table 1
Factors affecting the diagnosis of prostate cancer in the overall data of univariate analysis

Variable	BPH(n=277)	PC(n=198)	Z	P
Age**	69.00±64.00~74.00	73.50±67.00~79.00	-5.47	P=0.001
TPSA**	12.90±8.53~20.85	27.95±13.73~74.25	-8.47	P=0.001
PV**	67.17±46.07~92.35	41.970±31.24~66.74	-6.83	P=0.001
NC**	4.07±3.18~5.34	3.84±3.01~4.71	-2.30	0.021
LC**	1.45±1.08~1.95	1.5±1.12~1.88	-0.31	0.755
PLC**	197.00±154.00~245.00	179.00±146.00~229.50	-2.07	0.038
NLR**	2.71±1.87~4.07	2.59±1.82~3.63	-1.25	0.212
PLR**	138.42±97.43~188.36	123.92±91.62~175.78	-1.44	0.150

Note: *T-test **Mann-Whitney U Test.

Table 2
univariate analysis of factors affecting the diagnosis of prostate cancer when 4 ng/ml
TPSA≤10 ng/ml

Variable	BPH	PC	T/Z	P
Age*	68.32±7.05	70.05±6.69	-1.48	0.141
TPSA**	7.03±5.60~8.45	7.64±6.14~8.70	-1.22	0.222
PV**	60.55±42.01~77.05	40.11±31.03~47.10	-3.76	P=0.001
NC*	3.67±1.21	3.89±1.17	-0.87	0.388
LC**	1.63±1.14~2.04	1.50±1.04~1.93	-0.92	0.358
PLC**	190.00±148.75~245.00	173.50±148.75~191.75	-0.92	0.36
NLR**	2.25±1.61~3.03	2.34±1.79~3.31	-1.06	0.287
PLR**	113.75±87.76~167.23	122.82±90.74~170.34	-0.45	0.654

Note: *T-test **Mann-Whitney U Test

Table 3
univariate analysis of factors affecting the diagnosis of prostate cancer when 10
ng/ml≤TPSA≤20 ng/ml

Variable	BPH	PC	Z	P
Age*	68.37±7.66	74.72±7.34	-4.69	P=0.001
TPSA**	13.40[11.80~15.67]	14.02[11.62~16.60]	-0.37	0.713
PV**	71.55[46.33~95.67]	35.47[26.68~54.25]	-4.73	P=0.001
NC**	4.16[3.27~5.49]	3.72[3.05~4.55]	-1.66	0.097
LC**	1.44[1.09~1.89]	1.34[1.10~1.99]	-0.30	0.765
PLC**	192.00[159.00~243.00]	170.00[146.00~226.00]	-1.95	0.051
NLR**	2.72[2.03~4.38]	2.92[1.68~3.73]	-1.05	0.296
PLR**	135.88[96.80~190.11]	137.85[85.00~190.00]	-0.95	0.343

Note: *T-test **Mann-Whitney U Test.

Table 4 is not available in this version of the manuscript.

Figures

Figure 1

The ROC Curves and Multivariate binary logistic regression analysis of overall data

Figure 2

The ROC Curves and Multivariate binary logistic regression analysis when $TPSA \geq 20$ ng/ml