Clin. Lab. 2019;65:XXX-XXX

ORIGINAL ARTICLE

Role of Neutrophil to Lymphocyte Ratio or Platelet to Lymphocyte Ratio in Prediction of Bone Metastasis of Prostate Cancer

Jing-Ya Zhang, Peng Ge, Peng-Yu Zhang, Meng Zhao, Li Ren

Department of Clinical Laboratory, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, P.R. China

SUMMARY

Background: **Accumulating evidence has revealed that inflammation might play an important role in the genesis and development of cancer. High levels of neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ration (PLR) are parameters of systemic inflammation which have been identified to be associated with poor prognosis in PCa. Bone is one of the most common sites of metastasis from prostate cancer; however, there are few studies concerning the correlation of NLR, PLR, and bone metastases in PCa. The aim of this study was to evaluate the performance of neutrophil to lymphocyte ratio (NLR) or platelet to lymphocyte (PLR) in diagnosis of bone metastasis of prostate cancer (PCa).**

Methods: **Data of 74 PCa patients without metastases, 51 PCa patients with bone metastases, and 43 patients with benign prostatic hypertrophy (BPH) were retrospectively reviewed. The difference of patients' clinical and laboratory characteristics of the three groups was comparatively studied. ROC analysis was used to evaluate the benefit of adding NLR or PLR to prostate specific antigen (PSA) in prediction of bone metastases. Depending on this cutoff value, patients were divided into high-NLR or low-NLR group, high-PLR or low-PLR group.**

Results: **There were significant differences in NLR and PLR between groups with bone metastases and without bone metastases ($p = 0.044$; $p = 0.030$), while there was no significant difference between NLR and PLR of the patients with localized prostate cancer and BPH ($p = 0.462$; $p = 0.102$). NLR and PLR were correlated with PSA level in the patients with prostate cancer ($p = 0.006$, $r = 0.247$; $p = 0.025$, $r = 0.200$). The distribution of PSA showed significant differences between the high-NLR and low-NLR group, as well as between the high-PLR and low-PLR group. By applying the ROC curve method, the AUC values of PSA with NLR or PLR were 0.725 and 0.838 (0.763 - 0.913), respectively. Although PSA + PLR had the largest area, there was no statistical significance between PSA + PLR and PSA ($p = 0.6992$).**

Conclusions: **NLR and PLR significantly increase in PCa patients with bone metastases and are valuable in the diagnosis of bone metastases in PCa patients.**

(Clin. Lab. 2019;65:xx-xx. DOI: 10.7754/Clin.Lab.2018.181040)

Correspondence:
Dr. Li Ren
Department of Clinical Laboratory
Tianjin Medical University Cancer Institute and Hospital
National Clinical Research Center for Cancer
Tianjin's Clinical Research Center for Cancer
Key Laboratory of Cancer Prevention and Therapy
Huanhu Road, Hexi District
Tianjin 300060
P.R. China
Phone: +86 15022411875
Fax: +86 22 23340123
Email: alicia_zhangjy@hotmail.com

KEY WORDS

neutrophil to lymphocyte ratio, platelet to lymphocyte ration, prostate cancer, bone metastases

Manuscript accepted November 7, 2018

INTRODUCTION

Prostate cancer (PCa) is the most common cancer among men and is the second leading cause of cancer death among men in the western world [1]. Bone is the most common target of distant metastasis, which is an important factor of cancer progression, and the main cause of death in prostate cancer. Prostate specific antigen (PSA) is a widely used diagnostic biomarker for prostate cancer, which can predict bone metastasis of prostate cancer. Many studies revealed that inflammation might play an important role in the genesis and development of cancer [2-4]. The neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ration (PLR) are parameters of systemic inflammation which have been identified to be associated with the prognosis in several types of malignancies including PCa [5-8]. The baseline NLR and PLR have been reported to be an independent prognostic factor of prostate cancer and elevated levels of NLR and PLR were associated with poor survival in PCa. There are few studies concerning on the correlation of NLR, PLR, and bone metastases in PCa. In the current study, we aim to find the potential association between pretreatment NLR and PLR levels and bone metastases of PCa in order to access the ability of NLR and PLR to identify bone metastases of PCa.

MATERIALS AND METHODS

Study population

A total of 125 patients who were newly diagnosed with prostate cancer and 43 patients who were newly diagnosed with benign prostatic hypertrophy (BPH) by ultrasound-guided prostate biopsy in Tianjin Medical University Cancer Institute and Hospital from April 2014 to November 2017 were enrolled in this study. The medical data of patients regarding their clinical characteristics including blood cell counts indexes such as white blood cell, neutrophil, lymphocyte, and platelet count and prebiopsy prostate specific cancer (PSA) level at diagnosis, clinical tumor stage, and prostate volume were collected. Biopsy Gleason score of patients who were diagnosed with PCa was also reviewed.

Patients who had evidence of acute prostatitis, systemic inflammatory diseases, or had a history of hematological diseases, autoimmune diseases, and cerebrovascular diseases, high-grade prostatic intraepithelial neoplasia, liver disorders, who had received anticancer therapy or used anti-inflammatory drugs within 2 weeks before the biopsy were excluded. We also excluded the patients whose relevant data were missing or who had other types of cancer.

Laboratory Data

White blood cell, neutrophil, lymphocyte, and platelet counts were obtained using an automatic blood cell analyzer (Sysmex XN20[A]) and PSA was obtained using an electrochemiluminescence immunoassay analyzer (Roche MODULAR E170). NLR was calculated using the neutrophil counts and the lymphocyte counts, while PLR was computed using the platelet counts and lymphocyte counts. All blood samples were collected and tested before biopsy.

Statistical methods

Continuous variables were presented as the mean and standard deviation or median (IQR) depending on the distribution. The correlation of variables was assessed using Spearman's correlation. Categorical variables were presented in percentage form. Chi-square tests were used to evaluate correlations between categorical variables and *t*-tests or Mann-Whitney *U* was used for comparison of continuous variables. The NLR and PLR cutoff values were calculated by the ROC curve based on Youden's index. Their diagnostic value was evaluated using the area under the curve (AUC) analyses. Statistical analyses were conducted using SPSS Statistics version 19.0 (IBM Corp, Armonk, NY, USA). A p-value of less than 0.05 was considered statistically significant. The differences of AUC were accessed using MedCalc 18.2.1.

RESULTS

Patient characteristics

The median age of the 125 prostate cancer patients included was 66.68 ± 7.40 years and the median PSA value was 67.99 (13.14 - 473.65) µg/L. In the present study, bone metastases were found in 51 patients by CT or MR. PCa patients were categorized into groups according to bone metastasis. Clinical characteristics and blood parameters of the patients of the study groups included in the present study were summarized in Table 1. We found significant differences in NLR, PLR between groups with bone metastasis and without bone metastasis ($p = 0.044$; $p = 0.030$) (Figure 1A and 1B). We did not find any significant differences of other parameters between the two groups. There was no significant difference between NLR and PLR of the patients with localized prostate cancer and BPH ($p = 0.462$; $p = 0.102$) (Figure 1A and 1B). NLR and PLR were correlated with PSA level in the patients with prostate cancer ($p = 0.006$, $r = 0.247$; $p = 0.025$, $r = 0.200$).

ROC analysis was used to measure the sensitivity and specificity in PCa prediction of NLR, PLR, and PSA (Figure 2). The AUC analysis of different methods was listed in Table 2. The cutoff value of NLR was set at 2.35 based on the maximal Youden's index on the ROC curve. The cutoff value of PLR was set at 114.52 based on the maximal Youden's index on the ROC curve. Depending on this cutoff value, patients were divided into high-NLR or low-NLR group, high-PLR or low-PLR group (detailed in Table 3). The distribution of PSA was significantly different between the two groups. Depending on the cutoff values, we classified patients and assessed clinical usefulness of PSA, NLR,

Table 1. Clinical characteristics and blood parameters of the patients with participants.

Variables median (range, mean ± SD)	Benign prostate hyperplasia	Non-bone metastasis	Bone metastasis	p-value
Ages (years)	66.58 ± 7.83	67.22 ± 6.82	65.90 ± 8.17	0.331
Neutrophil count (x 10^9/L)	3.45 (2.89 - 4.40)	3.52 (2.70 - 4.53)	3.95 (2.56 - 5.29)	0.125
Lymphocyte count (x 10^9/L)	1.84 (1.50 - 2.26)	1.93 (1.39 - 2.32)	1.78 (1.46 - 2.15)	0.351
Platelet count (x 10^9/L)	203.00 (171.00 - 244.00)	202.50 (180.00 - 256.75)	235.00 (181.00 - 278.00)	0.148
NLR	1.85 (1.35 - 2.61)	1.86 (1.34-2.34)	* 2.10 (1.69-3.19)	0.044
PLR	112.44 (84.54 - 133.15)	110.71 (90.00-140.68)	* 129.23 (104.92-159.46)	0.030
tPSA (ng/mL)	8.85 (5.55-12.36)	25.45 (9.61-95.14)	601.90 (116.60 - 1270.00)	< 0.001
Prostate volume (cm^3)	-	72.20 (54.02 - 119.27)	83.60 (60.48 - 133.95)	0.154

*** p < 0.05. Bone metastases compared with non-bone metastases group.**

Table 2. AUC analysis of different methods.

Marker	Sensitivity	Specificity	AUC
PSA + NLR	0.529	0.959	0.725 (0.627 - 0.823)
PSA + PLR	0.686	0.905	0.838 (0.763 - 0.913)
PSA	0.706	0.878	0.831 (0.753 - 0.910)
NLR	0.451	0.757	0.606 (0.505 - 0.707)
PLR	0.706	0.568	0.615 (0.515 - 0.714)

Table 3. Association between clinical characteristics of prostate cancer patients and NLR and PLR.

Variable	NLR		p	PLR		p
	≥ 2.35	< 2.35		≥ 114.52	< 114.52	
Age (years)	66.80 ± 9.03	66.62 ± 6.52	0.907	66.69 ± 8.13	66.67 ± 6.52	0.992
PSA µg/L	334.00 (36.08 - 976.75)	52.87 (10.34 - 199.60)	0.001	147.00 (20.46 - 783.30)	52.87 (10.32 - 195.78)	0.024
Gleason						
< 8	6	20	0.235	8	18	0.009
≥ 8	35	64		59	40	
T						
1 - 2	14	36	0.351	27	23	0.942
3 - 4	27	48		40	35	
Prostate volume (cm^3)	100.67 (67.69 - 158.80)	70.26 (54.58 - 112.21)	0.010	84.92 (59.13 - 133.95)	71.07 (54.43 - 113.31)	0.079

PLR, PSA + NLR and PSA + PLR in discriminating real PCa with bone metastasis.

By applying the ROC curve method, the AUC values of PSA with NLR or PLR were 0.725 (95% C.I. = 0.627 - 0.823) and 0.838 (0.763 - 0.913), respectively (Table 2). Although PSA + PLR had the largest area, there was no statistical significance in comparison with PSA (p = 0.6992).

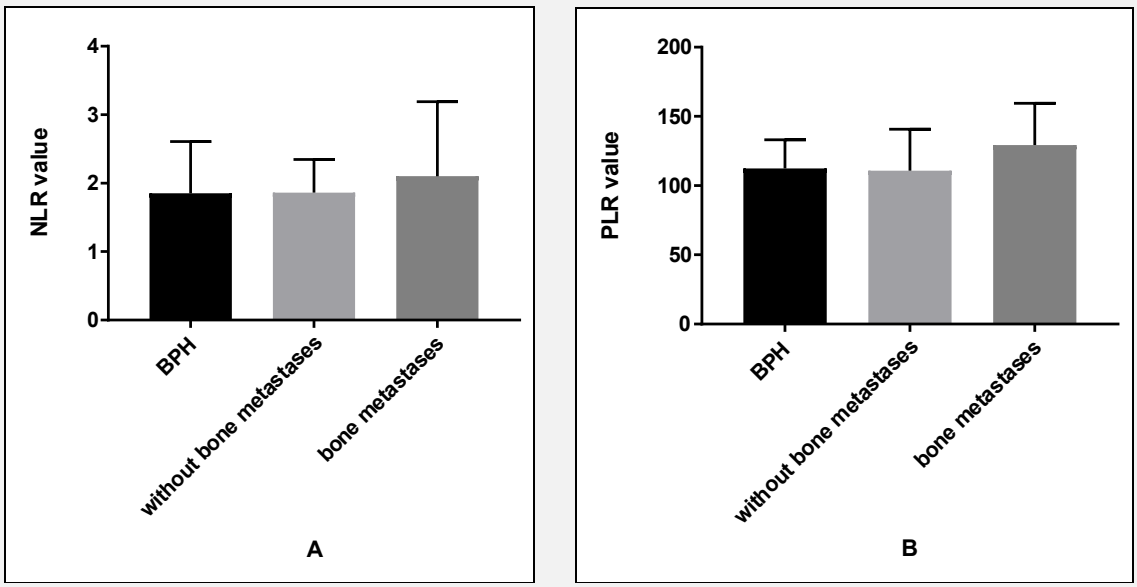

Figure 1. Comparison of NLR (A) and PLR (B) in BPH patients, PCa patients without bone metastases, PCa patients with bone metastases.

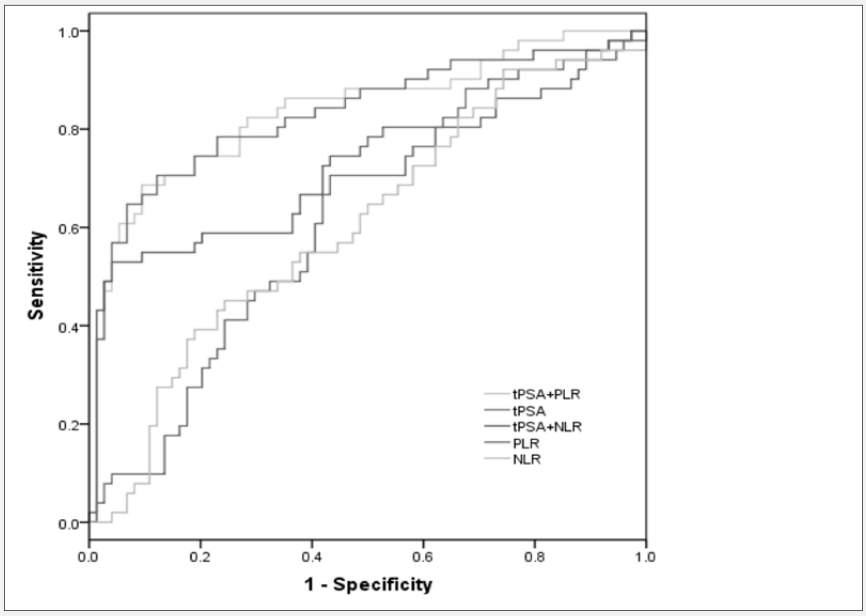

Figure 2. ROC curve of different methods.

DISCUSSION

The inflammation parameters can reflect systemic inflammation. As blood-based inflammation parameters, NLR and PLR can be easily calculated from the neutrophil, lymphocyte, and platelet counts which are from routine complete blood counts. Several studies accessed the predictive value of pretreatment measurement of NLR and PLR in diagnosis of PCa. However, the results of these studies were controversial [9-14]. The prognostic value of NLR and PLR may indicate the increasing potential for aggressive disease or tumor progression. The bone metastases commonly happen in the development of prostate cancer which usually lead to death from prostate cancer. However, there are few studies focusing on the role of NLR and PLR in the prediction of bone metastases. In the present study, we observed an interesting phenomenon that there was no significant difference between the NLR and PLR levels of patients with prostate cancer and BPH, but the difference between patients with bone metastases and without bone metastases was statistically significant.

Several studies reported that NLR and PLR values between PCa patients and patients without PCa were statistically significant [13,15]. However, the controversial results were found other studies [10,11,16]. The sample size and the number of the excluding factors of these studies may influence the property of the patients included. Meanwhile, the inflammation in the BPH patients might cause the insignificant difference between the PCa patients without bone metastases and BPH patients. Sonpavde et al. also found that NLR was closely related to PCA metastasis [17]. PSA is an important predictor for bone metastasis [18]. We also found that PSA was significantly higher in the PCa patients with bone metastases than in those without bone metastases in this study. The association of NLR and PLR with PSA suggests that NLR and PLR might be related to bone metastasis. However, there was little change in predictive accuracy of PSA with or without NLR and PLR, which may be because the NLR and PLR levels correlated with PSA levels in patients with PCa.

High levels of NLR and PLR may be associated with cancer progression, however, the exact mechanisms remains unclear. In the tumor microenvironment, inflammation plays a critical role in carcinogenesis, development, and progression of cancer through facilitating angiogenesis, proliferation, and protecting tumors from apoptosis, survival of malignant cells, and metastasis [19]. Tumor cells also generated several kinds of proinflammatory agents to induce more infiltration of inflammatory cells into tumor tissues [20]. An elevated platelet reflects promoting tumor cancer growth and metastasis. Platelets stimulate the invasiveness of PCa cells and protect tumor cells from natural killer cell cytotoxicity [21,22]. In breast cancer, platelets were shown to be related to bone metastasis [23]. Neutrophils significantly influence the tumor microenvironment and mediate tumor progression by producing cytokines to stimulate tumor cells growth. Intra-tumoral infiltration of neutrophils promotes tumor invasion and in turn cancer cells secret chemokines to attract pro-inflammatory cells into the tumor microenvironment [24]. In contrast, lymphocytes inhibit tumor cell proliferation and metastasization mediated by cytotoxic CD8+ and CD4+ expressing T lymphocytes. So, decreased lymphocytes inhibit anti-tumor immune response. Cells and cytokines involved in inflammation participate in osteoclast formation and bone destruction [25-26].

There are some limitations in the present study. First, this study was derived from retrospective review, the data for some of the parameters were missing and we did not take the factors into consideration which might easily introduce recall bias. Secondly, we were unable to completely exclude factors that might cause influences to the white blood cell counts in PCa. Thirdly, the patient data were collected from a single institution and the sample size was relatively small. Our results need to be confirmed by large-scaled prospective data from multicenters.

CONCLUSION

Overall, NLR and PLR are significantly elevated in PCa patients with bone metastases and have clinical value in the diagnosis of bone metastases in PCa patients.

Acknowledgment:
This study was supported by the National Natural Science Foundation of China (Grant No. 81602026) and National Natural Science Foundation of Tianjin (Grant No. 18JCZDJC32600).

Declaration of Interest:
None.

References:

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30 (PMID: 26742998).
2. Neĭman IM. [Inflammation and cancer]. Nature 2002;420(6917): 860-7 (PMID: 4437978).
3. Candido J, Hagemann T. Cancer-Related Inflammation. J Clin Immunol 2013;33(1):S79-84 (PMID: 23225204).
4. Grivennikov SI, Greten FR, Karin M. Immunity, Inflammation, and Cancer. Cell, 2010;140(6):883-99 (PMID: 20303878).
5. Cho IR, Park JC, Park CH, et al. Pre-treatment neutrophil to lymphocyte ratio as a prognostic marker to predict chemotherapeutic response and survival outcomes in metastatic advanced gastric cancer. Gastric Cancer 2014;17(4):703-10 (PMID: 24442663).

6. Min GT, Wang YH, Yao N, et al. The prognostic role of pretreatment platelet-to-lymphocyte ratio as predictors in patients with colorectal cancer: a meta-analysis. Biomark Med 2017;11(1):87-97 (PMID: 27917650).

7. Kawahara T, Yokomizo Y, Ito Y, et al. Pretreatment neutrophil-to-lymphocyte ratio predicts the prognosis in patients with metastatic prostate cancer. BMC Cancer 2016;16(1):111 (PMID: 26883640).

8. Diem S, Schmid S, Krapf M, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer 2017;111:176-81 (PMID: 28838390).

9. Maeda Y, Kawahara T, Kumano Y, et al. The Neutrophil-to-Lymphocyte Ratio before Repeat Prostate Needle Biopsy for Predicting Prostate Cancer. Urol Int 2015;96(1):123-4 (PMID: 26669562).

10. Gokce MI, Hamidi N, Suer E, Tangal S, Huseynov A, Ibiş A. Evaluation of neutrophil-to-lymphocyte ratio prior to prostate biopsy to predict biopsy histology: Results of 1836 patients. Can Urol Assoc J 2015;9(11-12):E761-5 (PMID: 26600880).

11. Yuksel OH, Urkmez A, Akan S, Yldirim C, Verit A. Predictive Value of the Platelet-To-Lymphocyte Ratio in Diagnosis of Prostate Cancer. Asian Pac J Cancer Prev 2015;16(15):6407-12 (PMID: 26434851).

12. Fujita K, Imamura R, Tanigawa G, et al. Low serum neutrophil count predicts a positive prostate biopsy. Prostate Cancer Prostatic Dis 2012;15(4):386-90 (PMID: 22777394).

13. Li F, Hu H, Gu S, Chen X, Sun Q. Platelet to lymphocyte ratio plays an important role in prostate cancer's diagnosis and prognosis. Int J Clin Exp Med 2015;8(7):11746-51 (PMID: 26380014).

14. Kaynar M, Yildirim ME, Gul M, Kilic O, Ceylan K, Goktas S. Benign prostatic hyperplasia and prostate cancer differentiation via platelet to lymphocyte ratio. Cancer Biomark 2015;15(3):317-23 (PMID: 25586096).

15. Oh JJ, Kwon O, Lee JK, et al. Association of the neutrophil-to-lymphocyte ratio and prostate cancer detection rates in patients via contemporary multi-core prostate biopsy. Asian J Androl 2016;18(6):937-41 (PMID: 26470836).

16. Camtosun A, Celik H, Cakmak B S, et al. Are neutrophil-lymphocyte and platelet-lymphocyte ratios valuable in predicting prostate cancer? Arch Clin Exp Surg 2016;5(4):194-9. https://www.ejmanager.com/mnstemps/64/64-1436780683.pdf?t=1540764130

17. Sonpavde G, Pond GR, Armstrong AJ, et al. Prognostic impact of the neutrophil-to-lymphocyte ratio in men with metastatic castration-resistant prostate cancer. Clin Genitourin Cancer 2014;12(5):317-24 (PMID: 24806399).

18. Kitajima K, Murphy RC, Nathan MA, et al. Detection of recurrent prostate cancer after radical prostatectomy: comparison of 11C-choline PET/CT with pelvic multiparametric MR imaging with endorectal coil. J Nucl Med 2014;55(2):223-32 (PMID: 24434294).

19. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis 2009;30(7):1073-81 (PMID: 19468060).

20. Candido J, Hagemann T. Cancer-Related Inflammation. J Clin Immunol 2013;33(1):S79-S84 (PMID: 23225204).

21. Dashevsky O, Varon D, Brill A. Platelet-derived microparticles promote invasiveness of prostate cancer cells via upregulation of MMP-2 production. Int J Cancer 2010;124(8):1773-7 (PMID: 19101987).

22. Zheng S, Shen J, Jiao Y, et al. Platelets and fibrinogen facilitate each other in protecting tumor cells from natural killer cytotoxicity. Cancer Sci 2010;100(5):859-65 (PMID:19302289).

23. Boucharaba A, Serre C M, Grès S, et al. Platelet-derived lysophosphatidic acid supports the progression of osteolytic bone metastases in breast cancer. J Clin Invest 2004;114(12):1714-25 (PMID: 15599396).

24. Gregory AD, Houghton AM. Tumor-associated neutrophils: new targets for cancer therapy. Cancer Res 2011;71(7):2411-6 (PMID: 21427354).

25. Rodan GA. The development and function of the skeleton and bone metastases. Cancer 2010;97(S3):726-32 (PMID: 12548569).

26. Suva LJ, Nicholas RW, Gaddy D. Inflammatory Cytokines and Their Role in Bone Metastasis and Osteolysis. Bone and Cancer. Springer London 2010:141-55. https://link.springer.com/chapter/10.1007%2F978-1-84882-019-7_9