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Predictive value of the monocyte-to-lymphocyte ratio in the diagnosis of prostate cancer

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Abstract

It has been reported that inflammation and immune system are related to prostate cancer. The neutrophil-to-lymphocyte ratio (NLR), as well as the platelet-to-lymphocyte ratio (PLR), have already been proposed as new indices to help diagnose prostate cancer (PCa). However, the monocyte-to-lymphocyte ratio (MLR) with regard to PCa has rarely been mentioned.

To investigate the capability of the MLR to predict PCa.

Patients who were pathologically diagnosed with PCa in our hospital and healthy control subjects who conformed to the inclusion criteria were enrolled. Patient data were recorded, including age, complete blood counts, blood biochemistry, and serum prostate-specific antigen (PSA) levels. The differences in these data between the groups were analyzed and the diagnostic value of the MLR was compared with PSA.

Our study included a total of 100 patients with PCa and 103 healthy control subjects. Patients with PCa presented with a significantly higher NLR, MLR, and PLR compared to control subjects. However, the hemoglobin and lymphocyte levels were lower ($P < .05$) in PCa patients. The area under the curve (AUC) of PSA and ratio of free/total serum prostate-specific antigen were 0.899 (95% confidence interval [CI]: 0.857–0.942) and 0.872 (95% CI: 0.818–0.926), respectively, while the AUC of the MLR was 0.852 (95% CI: 0.798–0.906), which was higher than that of the NLR, PLR, and any other blood parameters. Additionally, the optimal cut-off value of the MLR for PCa was 0.264, with a specificity of 87.4% and a sensitivity of 72.0%. An evaluation of the diagnostic value of MLR + PSA gave an AUC of 0.936 (95% CI: 0.902–0.970). However, the AUC of MLR + PSA + f/tPSA was 0.996 (95% CI: 0.991–1.000). The diagnostic value of MLR + NLR + PSA gave an AUC of 0.945 (95% CI: 0.913–0.977), and the specificity is 0.971.

PSA remains the most important diagnostic indicator. MLR combined with PSA and f/tPSA has the higher predictive value than PSA. It suggests that MLR may be another good predictive indicator of PCa. It can help reduce the clinical false positive rate.

Abbreviations: AUC = area under the curve, CI = confidence interval, GS = Gleason scores, MLR = monocyte-to-lymphocyte ratio, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, PSA = prostate-specific antigen, R(f/tPSA) = ratio of free/total serum prostate-specific antigen, TAMs = tumor-associated macrophages.

Keywords: monocyte-to-lymphocyte ratio, predictive value, prostate cancer

1. Introduction

Prostate cancer (PCa) is the most frequent malignancy affecting American men, and it is also one of the most common causes of death.[1] In the meantime, the morbidity due to PCa has been rapidly increasing in Chinese men over the past decade.[2] Although many studies have presented different insights about PCa, the exact underlying mechanism of its development still remains to be explained.[3–5] Tumor cells can develop a variety of immunosuppressive mechanisms, and tumor immune escape or immune suppression are important parts of tumorigenesis and development.[6] Tumor-associated inflammation and the microenvironment are known to be key factors for neoplasia, proliferation, and metastasis.[7,8] Systemic inflammatory responses have been reported to be involved in PCa progression.[9] Some clues can be found from these past reports, and among them, inflammation is an important trigger factor. It has been recognized that inflammation increases the risk of PCa, similar to some other cancers.[10,11] A lot of oxidative materials are released by inflammatory cells that may cause cellular and gene damage, ultimately leading to gene mutations and PCa. These findings have been confirmed by epidemiologic and molecular biology studies.[12–15]

Prostate-specific antigen (PSA) is currently the dominant diagnostic biomarker for this cancer today.[16] If a significant increase in serum PSA is detected, a prostate biopsy should be

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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performed. A biopsy is the only available method for establishing a diagnosis of PCa, and they are usually performed if an elevated PSA or abnormalities on a digital rectal examination are found.[10] However, owing to its inherent limitations, PSA is not PCa specific, yet it is prostate-specific.[17] Besides PCa, acute prostatitis and benign prostate hyperplasia can also lead to an elevated PSA level. Researchers have found that PSA has only a 25% positive predictive value for PCa.[18] Due to this low specificity, numerous unnecessary biopsies are currently being performed.

The neutrophil-to-lymphocyte ratio (NLR) has been previously recommended as a biomarker not only in inflammatory diseases, but also in a number of different cancers.[19–25] One study showed that NLR may function as a biomarker to predict prostate cancer in men undergoing prostate needle biopsy.[26] Another study suggested that increased NLR could predict poor prognosis in patients with PCa.[27]

Monocyte-to-lymphocyte ratio (MLR) is the absolute monocyte count divided by the absolute lymphocyte count and has been demonstrated to be a novel hematological and inflammatory parameter. Monocytes are able to suppress lymphocyte activation and enhance tumor progression.[28] While an elevated monocyte count may promote tumorigenesis and angiogenesis through local immune suppression and stimulation of tumor neovasculogenesis.[29] On the other hand, lymphocytes have an important role in the immune responses against cancer both in the circulation and in the tumor microenvironment, for example, via T-cell mediated cellular cytotoxicity.[30] A low lymphocyte count might result in a weak, insufficient immunologic reaction to a tumor.[31] A high MLR, as a simple biomarker of host immune system, has been suggested to be related to poor prognosis in various cancers.[32] So far, no studies have been found to pay attention to the role of MLR in the prediction of prostate cancer. This study aimed to evaluate the predictive value of the MLR in PCa.

2. Patients and methods

2.1. Patient characteristics

One hundred patients diagnosed with PCa by prostate biopsy in the Department of Urology, Foshan Hospital of Traditional Chinese Medicine, from February 1, 2018, to December 31, 2019, were enrolled in our study as the PCa group. Biopsy was performed within 4 weeks after the blood tests. One hundred three healthy control subjects were recruited as the control (C) group. Those subjects with symptomatic prostatitis, an active infection, hypertension, liver failure, renal failure, diabetes mellitus, rheumatic disease, or malignancy were excluded. Our research was approved by the ethics committee office of the Foshan Hospital of Chinese Medicine (2018-136).

2.2. Laboratory and clinical assessments

The following information was recorded: age, complete blood counts, white blood cell counts, hemoglobin, neutrophils, lymphocytes, monocytes, platelets, creatinine, alanine aminotransferase, aspartate aminotransferase, PSA, and its f/t ratio (f/tPSA) from all of the subjects, and the Gleason score of the patients with PCa. Complete blood counts and biochemistry indicators were obtained simultaneously with PSA. The NLR, MLR, and platelet-to-lymphocyte ratio (PLR) were also determined.

Table 1

Basic features of the patients with PCa and controls.

Parameters	Control (n = 103)	Patients (n = 100)	*P*
Age (yrs)	73.94 ± 6.90	74.59 ± 8.10	.540
WBCs ($\times 10^9$/L)	6.49 ± 1.80	6.74 ± 2.11	.371
Neutrophils ($\times 10^9$/L)	3.66 ± 1.23	4.48 ± 1.96	<.001
Lymphocytes ($\times 10^9$/L)	2.23 ± 1.26	1.39 ± 0.52	<.001
Monocytes ($\times 10^9$/L)	0.42 ± 0.16	0.48 ± 0.20	.019
Platelets ($\times 10^9$/L)	218.74 ± 55.90	218.95 ± 64.27	.98
Hemoglobin (g/dL)	144.34 ± 13.36	119.29 ± 22.24	<.001
NLR	1.81 ± 0.68	3.76 ± 2.50	<.001
PLR	108.61 ± 34.12	182.70 ± 108.02	<.001
MLR	0.21 ± 0.08	0.39 ± 0.22	<.001
AST (U/L)	19.69 ± 6.72	21.09 ± 6.60	.136
ALT (U/L)	19.52 ± 4.85	20.59 ± 5.56	.147
CREA (μmol/L)	77.48 ± 10.81	76.65 ± 10.69	.584
PSA (ng/mL)	4.32 ± 1.87	17.71 ± 23.51	<.001
f/t PSA ratio	0.37 ± 0.09	0.20 ± 0.12	<.001
Gleason score		7.73 ± 1.07	

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CREA = creatinine, MLR = monocyte-to-lymphocyte ratio, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, PSA = prostate-specific antigen, R(f/tPSA) = ratio(free/total prostate-specific antigen), WBCs = white blood cell counts.

2.3. Statistical analysis

SPSS 13.0 was used for data analysis. Normally distributed parameters data were analyzed by Student's *t* test, and for non-normally distributed data, we used the Wilcoxon rank sum test. Continuous variables are presented as the mean ± standard deviation. Categorical variables are expressed as numbers (n) and percentages (%). Qualitative variables were compared with chi-square tests. Specificity and sensitivity were summarized by receiver operating characteristic curves. Ultimately, we used Pearson's correlation to analyze the associations of different data. $P < .05$ was considered significant.

3. Results

3.1. Basic characteristics of all of the subjects

Table 1 presents the main characteristics of the patients with PCa and the healthy control subjects. There were no significant differences between the two groups in terms of age, white blood cell counts, platelets, aspartate aminotransferase, alanine aminotransferase, or creatinine between the two groups (100 PCa patients and 103 healthy subjects). Monocytes were slightly higher in patients with PCa than in the healthy subjects ($P < .05$), but the f/tPSA ratio, hemoglobin, and lymphocytes of the patients with PCa were significantly lower than those of the healthy subjects ($P < .001$). The NLR, MLR, and PLR values were 1.81 ± 0.68, 0.21 ± 0.08, and 108.61 ± 34.12 for the control subjects, which were significantly lower than those in the patients with PCa (3.76 ± 2.50, 0.39 ± 0.22, and 182.70 ± 108.02, respectively; $P < .001$). In the patients with PCa, PSA (17.71 ± 23.51) and neutrophils (4.48 ± 1.96) were significantly higher than those in the healthy subjects (4.32 ± 1.87 and 3.66 ± 1.23, respectively; $P < .001$), and the mean Gleason score of the PCa group was 7.73 ± 1.07.

3.2. MLR has high diagnostic value for PCa following PSA

We researched the diagnostic value of these mentioned parameters for PCa by receiver operating characteristic and compared them

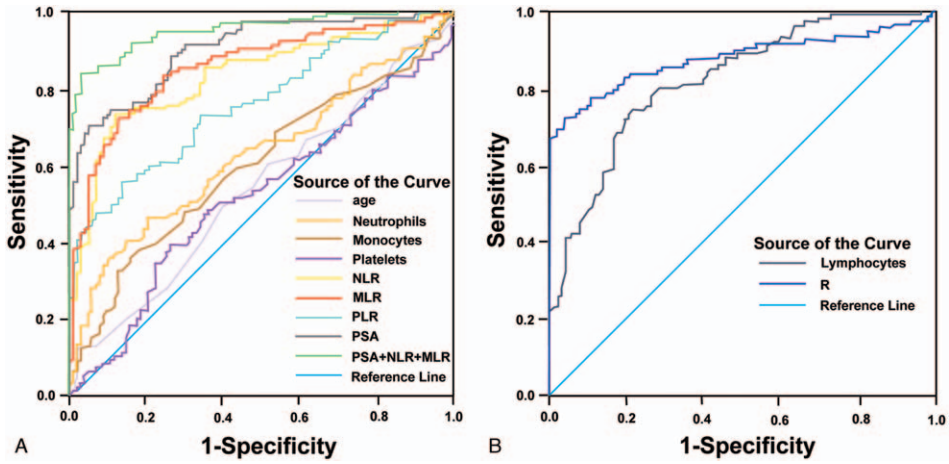

Figure 1. ROC curves were used to evaluate the diagnostic value of different blood parameters for PCa. (A) Diagnostic value of age, neutrophils, monocytes, platelets, MLR, NLR, PLR, and PSA; (B) diagnostic value of lymphocytes and R(f/tPSA). MLR = monocyte-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; PCa = prostate cancer; PLR = platelet-to-lymphocyte ratio; PSA = prostate-specific antigen; ROC = receiver operating characteristic.

with PSA. The results revealed that the area under the curves (AUCs) of these parameters were as follows: neutrophils, 0.626 (95% confidence interval [CI]: 0.548–0.704); monocytes, 0.596 (95% CI: 0.517–0.675); platelets, 0.518 (95% CI: 0.438–0.599); lymphocytes, 0.822 (95% CI: 0.765–0.878); MLR, 0.852 (95% CI: 0.798–0.906); NLR, 0.831 (95% CI: 0.773–0.888); PLR, 0.764 (95% CI:0.699–0.829); PSA, 0.899 (95% CI: 0.857–0.942); and ratio of free/total serum prostate-specific antigen (R(f/tPSA)), 0.872 (95% CI: 0.818–0.926). Except for PSA and R(f/tPSA), the MLR had the highest AUC value among the parameters. Additionally, the optimal cut-off value of the MLR for PCa was 0.264, and the specificity and sensitivity were 87.4% and 72.0%, respectively (Fig. 1 and Table 2). An evaluation of the diagnostic value of MLR combined with PSA (MLR + PSA) gave an AUC of 0.936 (95% CI: 0.902–0.970). However, when MLR combined with PSA and f/tPSA (MLR + PSA + f/tPSA), AUC ascended to 0.996 (95% CI: 0.991–1.000). An evaluation of the diagnostic value of MLR + NLR + PSA gave an AUC of 0.945 (95% CI: 0.913–0.977), and the specificity is 0.971.

3.3. Correlations among the variables

The NLR, MLR, and PLR were weakly positively correlated with PSA ($r = 0.223$, $P = .001$; $r = 0.196$, $P = .005$; $r = 0.201$, $P = .004$; respectively). Lymphocytes showed a weak negative correlation with PSA ($r = -0.169$, $P = .016$), and it was weakly positively correlated with R(f/tPSA) ($r = 0.162$, $P = .021$). Neutrophils, NLR, MLR, and PLR were all weakly negatively correlated with R(f/tPSA) ($r = -0.173$, $P = .013$; $r = -0.303$, $P < .001$; $r = -0.288$, $P < .001$; $r = -0.282$, $P < .001$, respectively). The Gleason score had a moderately positive correlation with PSA and was weakly positively correlated with f/tPSA ($r = 0.514$, $P < .001$; $r = 0.318$, $P = .001$, respectively) (Table 3).

4. Discussion

This study estimated the diagnostic value of the NLR, MLR, and PLR in patients with PCa, which in prior studies have been reported as cost-effective and non-invasive markers of many inflammatory or infectious diseases. In addition, we compared the predictive value of the NLR, MLR, and PLR with PSA and f/tPSA. In our study, PSA remains the most important diagnostic marker for PCa, with the highest diagnostic value. The Gleason score was positively correlated with PSA. Interestingly, patients with PCa had higher NLR, MLR, and PLR values. Except for PSA and f/tPSA, the diagnostic value of the MLR was higher than that of the NLR, PLR, and any other parameters. The NLR, MLR, PLR were weakly positively associated with PSA, and they

Table 2

ROC curves were used to assess the diagnostic value of different blood parameters for PCa.

Parameters	AUC	95% CI	*P*	Optimal cut-off value	Specificity	Sensitivity
PSA	0.899	0.857–0.942	<.001	7.505	0.951	0.70
R(f/tPSA)	0.872	0.818–0.926	<.001	0.202	0.961	0.72
MLR	0.852	0.798–0.906	<.001	0.264	0.874	0.72
NLR	0.831	0.773–0.888	<.001	2.429	0.883	0.73
Lymphocytes	0.822	0.765–0.878	<.001	1.625	0.806	0.72
PLR	0.764	0.699–0.829	<.001	142.72	0.864	0.56
Neutrophils	0.626	0.548–0.704	.002	4.285	0.796	0.46
Monocytes	0.596	0.517–0.675	.018	0.505	0.825	0.37
Age	0.536	0.457–0.616	.371	84.5	0.981	0.12
Platelets	0.518	0.483–0.599	.652	244.5	0.738	0.39

95% CI = 95%confidence interval; AUC = the area under the curve; MLR = monocyte-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; PCa = prostate cancer; PLR = platelet-to-lymphocyte ratio; PSA = prostate-specific antigen; R(f/tPSA) = ratio(free/total prostate-specific antigen); ROC = receiver operating characteristic.

Table 3

Correlations among the variables.

	Neutrophils		Lymphocytes		Monocytes		Platelets		NLR		MLR		PLR		Gleason score	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
PSA	0.071	.315	−0.169	.016	0.048	.498	0.098	.165	0.223	.001	0.196	.005	0.201	.004	0.514	<.001
R(f/tPSA)	−0.173	.013	0.162	.021	−0.084	.235	−0.080	.256	−0.303	<.001	−0.288	<.001	−0.282	<0.001	0.318	.001
Gleason score	0.042	.679	−0.192	.057	0.072	.477	0.040	.691	0.121	.234	0.136	.181	0.091	.369	1	

MLR = monocyte-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; PSA = prostate-specific antigen; R(f/tPSA) = ratio(free/total prostate-specific antigen).

were all negatively correlated with f/tPSA. Additionally, we found that lymphocytes were negatively correlated with PSA. According to these findings, we drew the conclusion that MLR maybe a good auxiliary indicator for the diagnosis of PCa.

With the development of molecular biology, immunology, biochemistry, ultrasound diagnostics, and radiography, as well as MRI diagnosis, great progress has been made in the management of PCa. Early diagnosis of PCa is of great value because it increases the probability of a complete clinical cure being achieved. In recent years, a lot of evidence has shown that inflammation plays a potential role in tumorigenesis and progression.[5] Researchers have also recognized the association between inflammation and PCa.[33] Some researchers have shown that the longer the duration of prostatitis symptoms, the higher is the risk of PCa.[4] Some prospective studies have reported that chronic inflammation and infection of the prostate, as well as sexual transmitted diseases, may lead to men being much more susceptible to PCa.

Recently, nonsteroidal anti-inflammatory medicines were recommended to reduce the risk of PCa, which further indicates that there is a very important relationship between inflammation and PCa.[34,35] Excitingly, some inflammation-related biomarkers were found to be useful during early diagnosis of PCa, for example, serum interleukin-7 (IL-7) levels and C-reactive protein, among others.[36,37] However, since they lack satisfactory specificity and sensitivity, none of the newly reported markers can completely replace PSA.

Nowadays, PSA is still the most important serum indicator for the diagnosis of PCa.[16] Our study also confirm this opinion. As is well known, PSA has its disadvantages, since it is a prostate-specific antigen but is not PCa specific. Acute prostatitis and benign prostate hyperplasia can often raise serum PSA, which increases the diagnostic complexity of PCa when using a screening method of PSA alone.[38,39] In addition, its overuse leads to numerous unnecessary biopsies and related complications. Excitingly, we found that the combination of PSA + MLR + NLR has the highest specificity (0.971) in diagnosing PCa in our study. The combination of the three indicators has not been reported in the current study. The combination of PSA + MLR + NLR may make up for the shortcomings of PSA. It may help to reduce unnecessary clinical biopsy. However, this has not been fully confirmed clinically. The confirmation of this clinical advantage requires further study. We hope that more similar research to be reported.

At present, the leukocyte subpopulation test is the most common way to detect inflammation.[40] Yet, recent reports have revealed that the MLR, NLR, and PLR could be more suitable for detecting inflammation than leukocyte subpopulations. These tests are simple, cost-effective, and useful indicators of inflammation.[41–44] Although changing physiological conditions can alter the absolute value of each test, the influence on the MLR, NLR, and PLR is slight.[45]

In our study, the results showed that for patients with PCa, the NLR, MLR, and PLR were all significantly higher than those in healthy subjects. Except for PSA and f/tPSA, the AUCs of these three parameters (MLR, NLR, and PLR) showed the highest diagnostic value for PCa, especially the MLR, with the highest AUC among them. It has been proven that the NLR in peripheral blood is a potential marker to predict PCa,[26] and some reports found that the PLR can be an important assistant predictor of PCa,[46] A few immune disease reports showed the diagnose values of MLR, revealed that it might reflect systemic inflammation and the severity of immune injury.[47,48] In this research, except for PSA with the highest diagnostic value, a valuable finding is that the MLR has a superior predictive value for PCa than the NLR and PLR.

The exact reason why the MLR increases in patients with PCa remains unclear and needs further research. Our study showed that most patients with PCa had higher serum monocytes and lower serum lymphocytes. Some studies have shown that the MLR is an important indicator of advanced disease-stages, which refers to immune regulation as well as immune escape. Monocytes and lymphocytes are two critical components of natural and acquired immunity, and thus, the MLR shows the condition of disease-related immunity progression.[47] In addition, circulating monocytes, which are often supposed to differentiate into tumor-associated macrophages (TAMs), play a key role in the tumor microenvironment. A large amount of serum monocytes may accelerate the production of TAMs within the tumor microenvironment and further promote tumor growth, angiogenesis, and metastasis. Conversely, lymphocytes can suppress tumor cell proliferation and migration.[49,50] Therefore, the observed increase in monocytes and decrease in lymphocytes may accelerate the progression of immunity damage, which reflects the severity of the disease.

In some previous research, the monocyte proportion of the peripheral blood was correlated with the Gleason score (GS),[51] and they found that the monocyte proportion was significantly increased in patients with high Gleason PCa, but the exact mechanism needs further research. None of our 100 patients with PCa had metastatic disease. These 100 pathological findings included a signet ring cell carcinoma of the prostate, the GS of the remaining 99 patients with PCa is available: 1 (1%) GS5, 10 (10%) GS6, 30 (30%) GS7, 39 (39%) GS8, 12 (12%) GS9, and 7 (7%) GS10. However, in our research, there were no significant correlations to be found between these blood inflammatory parameters and the GS.

In vitro studies showed that monocytes induce PCa cell invasion and mediate NF-κB and chemokine ligand 2 activity.[52] TAMs may interact with PCa cells to facilitate the disease progression by releasing different chemokines and cytokines.[53] Numerous studies of prostate biopsy specimens have shown that there is a lot of TAM infiltration around the PCa cells. It was

previously reported that TAM infiltration in biopsy specimens was an important sign of PCa progression.[54]

Several limitations exist in our study that should be pointed out. First, this was a retrospective single-centre study, and it enrolled a relatively small cohort of patients. Second, we have not researched the pathogenesis behind the elevated NLR, MLR, and PLR. Third, the peripheral MLR is a biomarker that indicates an inflammatory condition, which is not specific to PCa. Consequently, multi-centre investigations and molecular biology studies are urgently needed in the future.

In conclusion, the MLR, which can easily be evaluated, may be a good auxiliary indicator for PCa. Though this needs further study and proof. Men with an increased PSA and MLR should be recommended for prostate biopsy.

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