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ORIGINAL ARTICLE

Prostate Cancer

A novel robust nomogram based on peripheral monocyte counts for predicting lymph node metastasis of prostate cancer

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Accurate methods for identifying pelvic lymph node metastasis (LNM) of prostate cancer (PCa) prior to surgery are still lacking. We aimed to investigate the predictive value of peripheral monocyte count (PMC) for LNM of PCa in this study. Two hundred and ninety-eight patients from three centers were divided into a training set ($n = 125$) and a validation set ($n = 173$). In the training set, the independent predictors of LNM were analyzed using univariate and multivariate logistic regression analyses, and the optimal cutoff value was calculated by the receiver operating characteristic (ROC) curve. The sensitivity and specificity of the optimal cutoff were authenticated in the validation cohort. Finally, a nomogram based on the PMC was constructed for predicting LNM. Multivariate analyses of the training cohort demonstrated that clinical T stage, preoperative Gleason score, and PMC were independent risk factors for LNM. The subsequent ROC analysis showed that the optimal cutoff value of PMC for diagnosing LNM was $0.405 \times 10^9 \text{ l}^{-1}$ with a sensitivity of 60.0% and a specificity of 67.8%. In the validation set, the optimal cutoff value showed significantly higher sensitivity than that of conventional magnetic resonance imaging (MRI) (0.619 vs 0.238, $P < 0.001$). The nomogram involving PMC, free prostate-specific antigen (fPSA), clinical T stage, preoperative Gleason score, and monocyte-to-lymphocyte ratio (MLR) was generated, which showed a robust predictive capacity for predicting LNM before the operation. Our results indicated that PMC as a single agent, or combined with other clinical parameters, showed a robust predictive capacity for LNM in PCa. It can be employed as a complementary factor for the decision of whether to conduct pelvic lymph node dissection.

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INTRODUCTION

Prostate cancer (PCa) is one of the most common malignancies, and one of the leading causes of cancer-related death among men in the world.¹ Lymph node metastasis (LNM) is a crucial predictor of poor outcome in patients with PCa. Therefore, pelvic lymphadenectomy is one of the main treatment options for patients diagnosed with LNM. However, the benefits of lymphadenectomy are still controversial because of the limited survival benefits, and, as an invasive procedure, it may lead to a higher complication rate due to the longer operation time required.² Thus, accurate detection of pelvic LNM before the operation is of great urgent need. Although clinical imaging techniques such as magnetic resonance imaging (MRI) or computed tomography (CT) are quite useful in detecting LNM, these techniques exhibit a rather low sensitivity, with less than two-thirds of LNM being detected.³ Therefore, it is necessary to explore the minimally invasive

or noninvasive approaches with high sensitivity and specificity in order to detect LNM preoperatively.

Previous studies showed that inflammatory and immune cell infiltration play an important role in tumorigenesis and progression.^{4–6} Moreover, many research groups have reported that hematologic parameters including monocyte counts of cancer patients predict poor clinical outcomes and survival time. Wang *et al.*⁷ reported that peripheral monocyte count was an independent predictor for PCa by multivariate regression analysis, and Shigeta *et al.*⁸ showed that high absolute monocyte counts predicted poor clinical outcome and aggressive tumor features in patients with castration-resistant prostate cancer (CRPC). Besides, the immune cell ratio, such as neutrophil-to-lymphocyte ratio (NLR), has been reported beneficial in predicting poor outcome in CRPC⁹ and gastric cancer.¹⁰ Multiple studies indicated that peripheral immune cells had a corresponding relationship with

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LNM in gastric cancer,¹¹ breast cancer,¹² and endometrial cancer.¹³ Although previous individual studies showed that the higher NLR group exhibited inferior recurrence-free and overall survival in CRPC than the lower NLR group,^{14,15} only a few studies currently support the correlation between NLR and CRPC.³ Whether peripheral immune cells are associated with LNM of PCa has not been fully clarified till now. Therefore, we intend to investigate the role of peripheral immune cells in the prediction for LNM of PCa.

PATIENTS AND METHODS

Patients and study design

We retrospectively collected data of 669 PCa patients from January 2010 to October 2018 who underwent laparoscopic radical prostatectomy (LRP) and pelvic lymph node dissection from three centers in southern China (The Third Affiliated Hospital of Southern Medical University, Guangzhou; The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou; and Cancer Center of Sun Yat-sen University, Guangzhou). The exclusion criteria were as follows: (1) total prostate-specific antigen (tPSA) >1000 ng ml⁻¹, or (2) missing of the tPSA, or free prostate-specific antigen (fPSA), or preoperative Gleason score, or clinical and pathological tumor node metastasis (TNM) stage. This study was approved by the ethics committees of The Third Affiliated Hospital of Southern Medical University (2020-ky13-110), The Third Affiliated Hospital of Sun Yat-sen University ([2020]02-108-01), and Cancer Center of Sun Yat-sen University (17ykpy80). Due to the retrospective nature of the study, informed consent was waived, and anonymous clinical data were used for the analysis.

The study was divided into two phases: a training set (patients admitted from January 2010 to December 2014) and a validation set (patients admitted from January 2016 to October 2018) as shown in **Supplementary Figure 1**. According to the postoperative pathological results, the patients were divided into two groups of negative LNM (N-LNM) and positive LNM (P-LNM). Considering that the number of N-LNM cases was significantly higher than that of P-LNM cases, we randomly selected only 50%–60% of the negative cases for the final statistical analysis to avoid statistical bias. Finally, 125 patients were selected, which comprised the training set with 35 P-LNM patients and 90 N-LNM patients, and the validation set of 173 patients with 63 P-LNM and 110 N-LNM patients.

Clinical data assessment

Baseline information of patients, such as age, tPSA, fPSA, Gleason score, and peripheral blood cells counts, was derived from medical records. Patients' clinical and pathological stages were identified according to the 8th American Joint Committee on Cancer (AJCC) staging system. The preoperative lymph node (LN) status was identified by MRI, specifically, a lymph node diameter which was larger than 8 mm was considered metastatic LN, according to the previous report.¹⁶ The numbers and areas of LN dissection during the LRP were obtained from the operation record and postoperative pathological report.

Construction of the nomogram

To estimate the predictive efficiency of monocyte combined with other clinical parameters, a nomogram of risk factors was established by the regression modeling strategies (rms) package in R version 3.5.1 (<http://www.r-project.org/>) for predicting LNM in all the 298 PCa patients. Several clinical factors involving fPSA, clinical T stage, preoperative Gleason score, monocyte-to-lymphocyte ratio (MLR), and monocyte were selected based on univariate analysis to calculate the risk points by nomogram, where the length of the line segment in the nomogram represents the differently predictive contribution

of each factor. Furthermore, by adding each risk point of different factors, the total points were then obtained and converted into the predicted value of P-LNM based on a functional nomogram method, which reflected the overall predictive ability of LNM under the total points. The nomogram performance of each factor was evaluated by the concordance index (C-index); a high score of C-index indicates a high predictive efficiency of the model. Furthermore, a calibration curve was generated to explore nomogram performance, by comparing the predicted probability for LNM and the actual observed rate with 1000 repeated samplings in internal validation cohorts.¹⁷

Statistical analyses

Characteristics of the patients were presented as percentages for categorical variables and medians (ranges) for continuous variables. The differences of hematological values were analyzed using Mann–Whitney *U* test in two groups. In the training set, univariate analyses were used to identify the clinical risk factor for predicting LN metastasis, and forward step-wise multivariate analysis was performed with the variables that were significantly associated with LN metastasis in the univariate analysis. We calculated the sensitivity and specificity of monocyte for predicting LNM by receiver operating characteristic (ROC) analysis, and the best cutoff value was further obtained by the Youden Index.^{18,19} The difference of the sensitivity between monocyte threshold and MRI for predicting LNM was calculated by McNemar's test. All statistical analyses were performed by SPSS 22.0 (IBM SPSS Inc., Chicago, IL, USA), and the results were considered statistically significant if $P < 0.05$.

RESULTS

Clinical characteristics of the training and validation cohorts

The detailed clinical characteristics of patients in the training set (125 patients) and the validation set (173 patients) are summarized in **Table 1**. The median (range) of tPSA in the training and validation sets was 16.24 (0.02–221.21) ng ml⁻¹ and 24.29 (0.18–407.90) ng ml⁻¹, respectively. In the training set, the median (range) number of LN by dissection was 7 (1–27) with a positive LN detection median number of 3 (1–18), whereas in the validation set, the median (range) number of dissected LN was 11 (1–66) with a positive LN detection median (range) number of 2 (1–63). Patients with P-LNM accounted for 28.0% (35/125) and 36.4% (63/173) of the total patients in the training set and the validation set, respectively. Four kinds of peripheral blood immune cell counts were further analyzed in the training set and validation set (**Figure 1**). The results showed that the peripheral monocyte counts were significantly higher for patients with P-LNM than those with N-LNM, both in the training (median: 0.40×10^9 [range: $0.18 \times 10^9 - 0.90 \times 10^9$] l⁻¹ vs median: 0.50×10^9 [range: $0.12 \times 10^9 - 0.96 \times 10^9$] l⁻¹) and validation (median: 0.40×10^9 [range: $0.20 \times 10^9 - 1.20 \times 10^9$] l⁻¹ vs median: 0.50×10^9 [range: $0.20 \times 10^9 - 1.20 \times 10^9$] l⁻¹) set of patients. There was no statistical difference of white blood cell (WBC), neutrophil (NEU), and lymphocyte (LYM) counts between patients with N-LNM and P-LNM.

Optimal cutoff value of monocyte count for predicting LNM

Univariate and multivariate logistics regression analysis was used to identify best-fit predictors for P-LNM (**Table 2**). In univariate analysis, fPSA, clinical T stage, Gleason score, monocyte counts, and MLR were significantly related to P-LNM ($P < 0.05$). The results of multivariate analysis showed that only the clinical T stage, Gleason score, and monocyte counts were the independent risk factors for predicting P-LNM regardless of fPSA and MLR. Based on the results of the multivariate analysis, the ROC curve was employed to calculate

Table 1: Characteristics of 298 patients in the training set and validation set

Variables	Training set	Validation set
Patient (<i>n</i>)	125	173
Age (year), median (range)	68 (45–80)	66 (45–84)
tPSA (ng ml ⁻¹), median (range)	16.24 (0.02–221.21)	24.29 (0.18–407.90)
fPSA (ng ml ⁻¹), median (range)	1.95 (0.01–27.48)	2.25 (0.01–87.34)
f/t PSA, median (range)	0.11 (0.03–0.86)	0.09 (0.01–0.46)
Clinical T stage, <i>n</i> (%)		
T1+T2	98 (78.4)	146 (84.4)
T3+T4	27 (21.6)	27 (15.6)
Clinical N stage, <i>n</i> (%)		
N0	111 (88.8)	155 (89.6)
N1	14 (11.2)	18 (10.4)
Clinical M stage, <i>n</i> (%)		
M0	114 (91.2)	165 (95.4)
M1	11 (8.8)	8 (4.6)
Gleason score, <i>n</i> (%)		
≤7	76 (60.8)	103 (59.5)
>7	49 (39.2)	70 (40.5)
Pathological T stage, <i>n</i> (%)		
T2	73 (58.4)	85 (49.1)
T3a	9 (7.2)	23 (13.3)
T3b + T4	43 (34.4)	65 (37.6)
Pathological N status, <i>n</i> (%)		
N0	90 (72.0)	110 (63.6)
N1	35 (28.0)	63 (36.4)
Pathological M stage, <i>n</i> (%)		
M0	121 (96.8)	172 (99.4)
M1	4 (3.2)	1 (0.6)
Number of detected LN, median (range)	7 (1–27)	11 (1–66)
Number of positive LN, median (range)	3 (1–18)	2 (1–63)
Area of LN dissection, <i>n</i> (%)		
Bilateral obturator	89 (71.2)	50 (28.9)
Bilateral obturator + iliac vessels	35 (28.0)	117 (67.6)
Iliac vessels	1 (0.8)	6 (3.5)
WBC (×10 ⁹ l ⁻¹), median (range)	6.27 (2.25–13.66)	6.10 (3.04–12.54)
NEU (×10 ⁹ l ⁻¹), median (range)	3.60 (0.52–11.87)	3.55 (1.50–10.10)
LYM (×10 ⁹ l ⁻¹), median (range)	1.80 (0.40–3.30)	1.80 (0.60–4.20)
MONO (×10 ⁹ l ⁻¹), median (range)	0.40 (0.12–0.96)	0.43 (0.20–1.20)
MNR, median (range)	0.11 (0.03–0.30)	0.13 (0.03–0.37)
MLR, median (range)	0.23 (0.09–0.71)	0.25 (0.08–1.13)
NLR, median (range)	2.10 (0.29–13.93)	1.97 (0.69–9.13)

PSA: prostate-specific antigen; tPSA: total PSA; fPSA: free PSA; f/t PSA: free/total PSA; LN: lymph node; WBC: white blood cell; NEU: neutrophil; LYM: lymphocyte; MONO: monocyte; MNR: monocyte-to-neutrophil ratio; MLR: monocyte-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio

the optimum cutoff value for P-LNM detection by monocyte counts in the training set (**Figure 2**). The best cutoff value of monocyte was $0.405 \times 10^9 \text{ l}^{-1}$, and the area under the curve (AUC) was 0.624 (95% confidence interval [CI]: 0.505–0.742) with a sensitivity of 60.0% and a specificity of 67.8%.

Validation of optimal cutoff

One hundred and seventy-three PCa patients were selected for the validation set to evaluate the efficiency of the monocyte threshold in predicting LNM (**Figure 3**). The results showed that the sensitivity and the specificity of monocyte for predicting P-LNM were 61.9% and 55.4%, respectively, which showed a similar efficiency to the training set. Moreover, in both the training set and validation set, the sensitivity of monocyte in discriminating between patients with N-LNM and P-LNM was superior to that of conventional MRI (training

set: sensitivity [monocyte] = 60.0% vs sensitivity [MRI] = 31.4%, $P = 0.052$; validation set: sensitivity [monocyte] = 61.9% vs sensitivity [MRI] = 23.8%, $P < 0.001$; McNemar's test). The specificity of MRI was superior to monocyte count for predicting LNM additionally, which showed less effective for monocyte to exclude N-LNM patients.

Nomogram for predicting LNM preoperation

Furthermore, the predictive efficiency of monocyte classification combined with other clinical factors (fPSA, clinical T stage, Gleason score, and MLR) in all the 298 PCa patients preoperatively was assessed. A nomogram was established to calculate the risk points of each variable for predicting LNM (**Figure 4a**). By calculating the predicted C-index of each factor, assessment of the nomogram axes demonstrated that the predictive efficiency of the monocyte threshold accounted for a high weight among all risk factors. What's more, a calibration curve for

the nomogram also showed an accuracy prediction result (Figure 4b). Our studies showed that monocyte combined with clinical factors improved the accuracy of predicting LNM.

DISCUSSION

The relationship between inflammation and cancers has become a hot topic of research in recent years. Inflammatory responses were relatively active in the development and progression of tumors,^{4-6,20,21} which indicates that the change of inflammatory cell parameters may be utilized as a favorable predictor for disease evaluation and outcome prediction in clinical practice. In literature, many inflammatory markers, such as NLR, platelet-to-lymphocyte ratio (PLR), monocyte, or other hematologic parameters, have been studied for evaluating the clinical role of diagnosis,^{7,22} poor prognosis,^{8,9,23} and biochemical recurrence²⁴ of PCa. However, the association between hematologic parameters and LNM in PCa has rarely been studied. Recently, Lu *et al.*²⁵ have assessed the prognostic efficacy of NLR in patients with localized prostate cancer (*n* = 668) and found that NLR did not correlate with LNM events. In our study, we first systematically assessed the predictive efficiency of the peripheral blood cell counts

and ratios for LNM in PCa (Table 2). Multivariate analysis showed that monocyte count was among the best predictors for LNM of PCa (both clinical T stage and Gleason score were other two independent risk factors), while NLR was not statistically significant. This, to some extent, indicates the limited role of NLR in predicting LNM in PCa patients. Consistently, in the validation set, the significant performance of monocyte count for predicting LNM was also revealed, indicating the utility of monocyte count in the prediction of LNM (Figure 3).

Although the mechanisms remain unclear, there are several explanations. Tumor cells usually secrete inflammatory chemokines to recruit inflammation-related cells to regulate microenvironment, which was considered an important mechanism to promote cancer development and progression. Furthermore, monocytes can be recruited to differentiate tumor-associated macrophage (TAMs) infiltration,²⁶⁻²⁹ suggesting that increased monocyte counts are adaptive to tumor-mediated immune responses. It was reported that peripheral blood monocyte count can reflect tumor-infiltrating macrophages in PCa,²⁹ and TAM infiltration can promote tumor immunosuppression and metastasis.^{28,30,31} Therefore, the change of monocyte count might

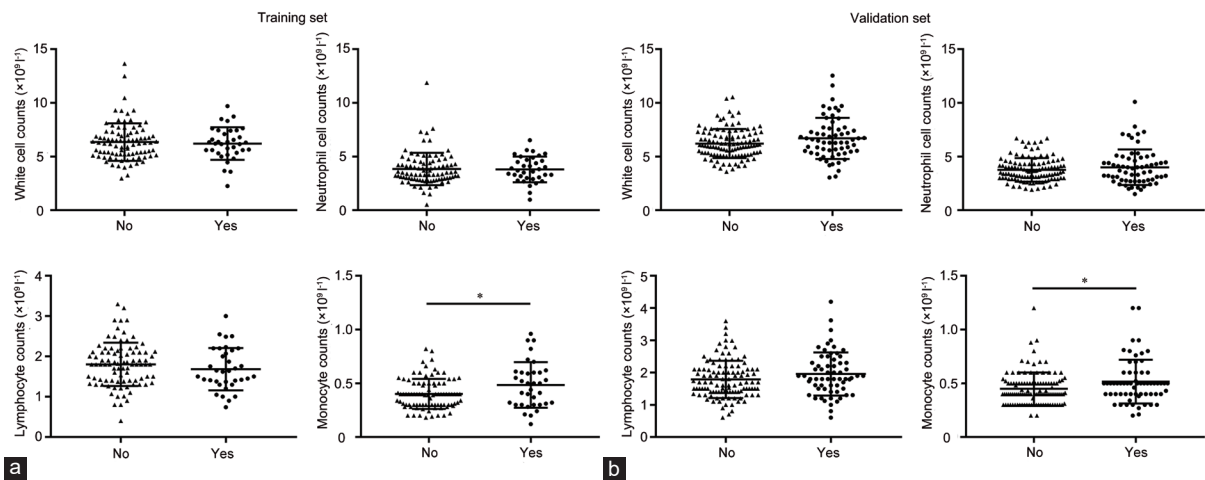


Figure 1: Peripheral blood inflammatory cell counts of PCa patients with or without LNM in two cohorts. (a) Training set; (b) validation set. Mean ± standard deviation. **P* < 0.05. PCa: prostate cancer; LNM: lymph node metastasis.

Table 2: Univariate and multivariate logistic regression analyses of clinical risk factors

Parameter	Univariate		Multivariate	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Age (year)	0.972 (0.924–1.024)	0.287	NA	NA
tPSA (ng ml ⁻¹)	1.006 (0.996–1.015)	0.247	NA	NA
fPSA (ng ml ⁻¹)	1.122 (1.019–1.236)	0.019	NA	NA
f/t PSA	33.157 (0.814–1351.190)	0.064	NA	NA
Clinical T stage, T3+T4 versus T1+T2	2.609 (1.070–6.361)	0.035	3.049 (1.030–9.022)	0.044
Gleason score, >7 versus ≤7	4.197 (1.834–9.606)	0.001	4.537 (1.757–11.721)	0.002
WBC (×10 ⁹ l ⁻¹)	0.952 (0.750–1.208)	0.683	NA	NA
NEU (×10 ⁹ l ⁻¹)	0.981 (0.743–1.295)	0.893	NA	NA
LYM (×10 ⁹ l ⁻¹)	0.648 (0.306–1.376)	0.259	NA	NA
MONO (×10 ⁹ l ⁻¹)	19.146 (1.800–203.616)	0.014	42.170 (2.408–738.459)	0.010
MNR	9.628 (0.078–1183.729)	0.356	NA	NA
MLR	54.017 (1.806–1615.841)	0.021	NA	NA
NLR	1.009 (0.802–1.269)	0.942	NA	NA

PSA: prostate-specific antigen; tPSA: total PSA; fPSA: free PSA; f/t PSA: free/total PSA; WBC: white blood cell; NEU: neutrophil; LYM: lymphocyte; MONO: monocyte; MNR: monocyte-to-neutrophil ratio; MLR: monocyte-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; OR: odds ratio; CI: confidence interval; NA: not analyzed



reflect altered anti-tumor cellular response. However, to date, the mechanisms of the interaction between monocyte and TAMs are still

unclear. Another possible explanation is that a high monocyte count is the manifestation of hematologic activation by tumor metastatic lesions.

For patients with PCa, the presence of pelvic LNM is a strong predictor of poor outcome.³²⁻³⁴ However, the approaches with promising sensitivity and specificity to detect LNM are still lacking. Clinical N staging of preoperative prostate cancer patients is still based on imaging reports, such as CT or MRI. However, they have very limited ability to predict lymph node involvement, as they can only detect lymph node enlargement and cannot accurately tell if it is a positive cancer lymph node or not. Recently, a new study had assessed the predictive value of preoperative prostate-specific membrane antigen (68Ga-PSMA) positron emission tomography/CT to predict LNM in PCa, which also showed low positive predictive value.³⁵ We have compared the predictive efficiency of high monocyte count and MRI for LNM in the training set and validation set (Figure 3). The results demonstrated that monocyte count as a predictor of LNM with a higher sensitivity may compensate for that of the MRI's in the preoperative diagnosis of P-LNM. At the same time, MRI for excluding N-LNM patients showed a higher specificity compared with using the monocyte, which indicated that MRI is still an important tool to exclude N-LNM patients in the clinical practice.

Another way, the nomogram showed that high fPSA value indicated a high risk of predicting LNM in our study (Figure 4a). This may reflect that patients with LNM had a high-grade tumor invasion compared to those with N-LNM. Indeed, high-grade PCa (Gleason score ≥ 7) patients have shown a high fPSA in some data.^{36,37} In our study, there were only two P-LNM patients with a Gleason score < 7 on biopsy. This demonstrated that high fPSA value could be a risk factor for predicting LNM in PCa.

We acknowledge several limitations of this study, as this is a retrospective analysis, and the number of patients is relatively small. Although we conducted a validation model for testing the predictive efficacy of monocytes, a large prospective study is necessary to further verify it. Furthermore, this study does not provide evidence of a direct correlation between peripheral blood monocyte and TAMs in PCa. Further study and verification are necessary to clarify the cross-talk of the monocyte and TAMs of PCa.

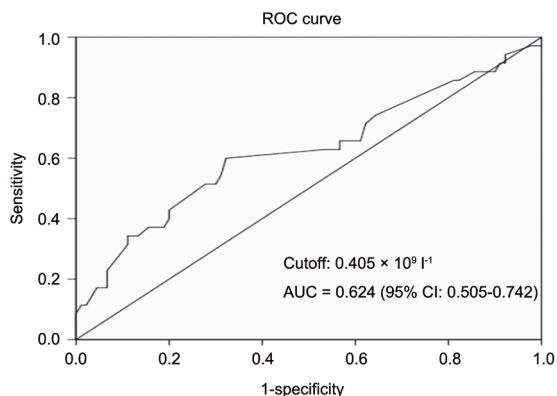


Figure 2: ROC curve for monocyte count. The AUC was 0.624 (95% CI: 0.505–0.742), with a sensitivity of 60.0% and a specificity of 67.8% by the Youden index. The cutoff value was $0.405 \times 10^9 \text{ l}^{-1}$. CI: confidence interval; AUC: area under the curve; ROC: receiver operating characteristic.

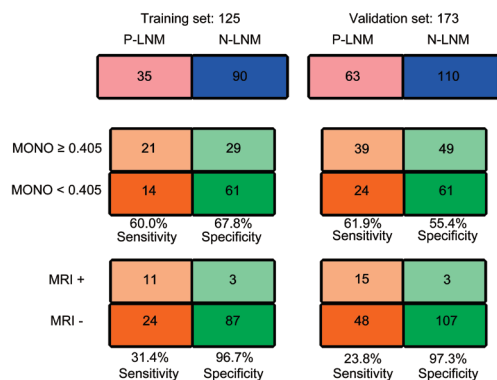


Figure 3: Diagnostic utility of monocyte count and conventional MRI examination. McNemar test: MONO versus MRI in training set, $P = 0.052$; MONO versus MRI in validation set, $P < 0.001$. P-LNM: positive lymph node metastasis; N-LNM: negative lymph node metastasis; MONO: monocyte; MRI: magnetic resonance imaging.

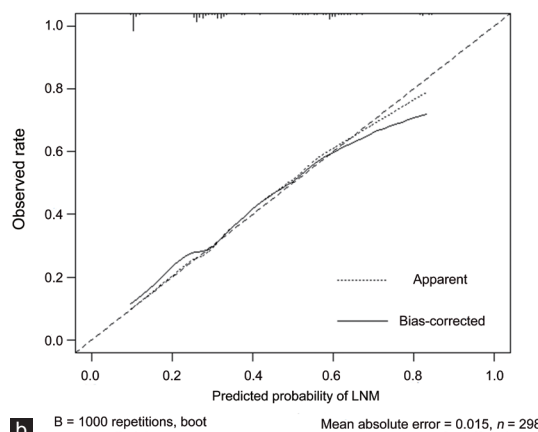
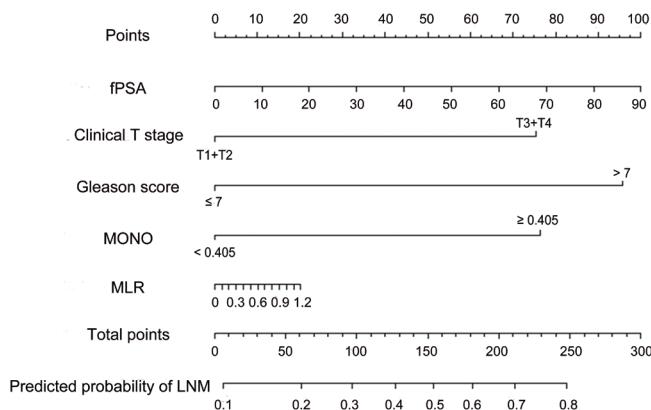


Figure 4: Nomogram of monocyte classification combined with other clinical parameters for predicting LNM. (a) Nomogram plot of calculating the contribution value of risk factors for LNM. (b) Calibration plot of the nomogram for the predicted versus the observed risk of LNM. X-axis: nomogram-predicted probability of LNM; Y-axis: actually observed probability of LNM; dashed line: the reference line in which the predicted and actual probabilities are identical; solid line: bias-corrected estimates of accuracy. Repeated sampling 1000 times. PSA: prostate-specific antigen; fPSA: free PSA; MONO: monocyte; MLR: monocyte-to-lymphocyte ratio; LNM: lymph node metastasis.

CONCLUSIONS

This study firstly evaluates the efficiency of hematologic parameters in the prediction of LNM in PCa. Our findings confirm that higher monocyte counts are a robust predictor for LNM of PCa patients. Moreover, a nomogram involving the peripheral monocyte could combine with other clinicopathological parameters as a useful tool in clinically diagnosing N stages before surgery. Therefore, peripheral monocyte counts can be a complementing factor in the decision of whether to conduct pelvic lymph node dissections, especially in those patients with a negative MRI.

AUTHOR CONTRIBUTIONS

JWZ, YHM, MKC, and SCZ designed the study and analyzed the clinical data. JWZ and YHM participated in the data collection, statistical analysis, and manuscript preparation. YL and HTL participated in the review of clinical reports. CCS participated in the data collection and language editing of the manuscript. YWF, YLY, GX, and ZKQ participated in the study design and coordination. CDL participated in the data collection. JKY and QZZ participated in the statistical analysis. WBG and KYX reviewed the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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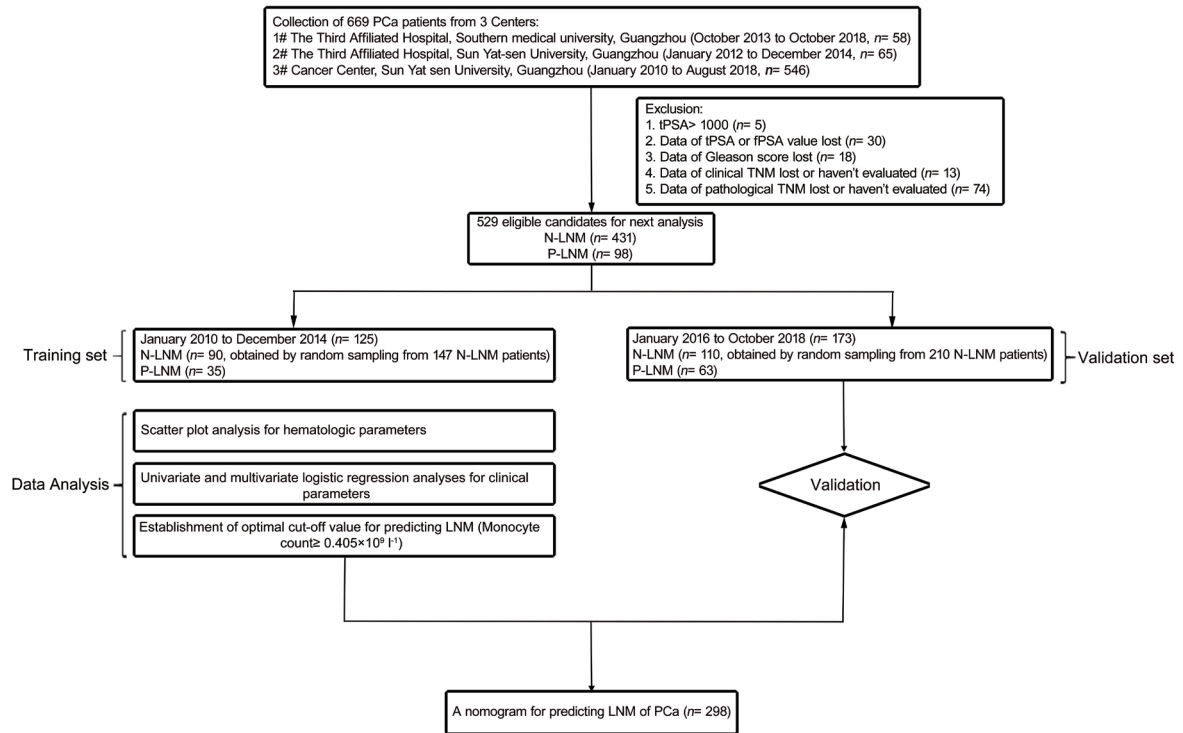
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Supplementary Figure 1: Flowchart of sample processing and data analysis. PCa: prostate cancer; PSA: prostate-specific antigen; tPSA: total PSA; fPSA: free PSA; P-LNM: positive lymph node metastasis; N-LNM: negative lymph node metastasis.