

• 临床研究 •

术前炎症指标对未触及腹股沟淋巴结的pT1a期阴茎鳞癌患者淋巴结转移的预测价值

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[摘要] 目的: 探讨3种术前炎症指标对未触及腹股沟淋巴结的pT1a期阴茎鳞癌患者发生淋巴结转移的预测价值。方法: 收集苏州大学附属第一医院和泰兴市人民医院2012年1月—2023年6月收治的103例pT1a期阴茎鳞癌患者的临床资料, 根据术后病理有无发生腹股沟淋巴结转移分为淋巴结转移组及非淋巴结转移组。比较两组间年龄、体重指数、高血压、糖尿病、肿瘤直径、中性粒细胞/淋巴细胞比值(neutrophil-to-lymphocyte ratio, NLR)、血小板/淋巴细胞比值(platelet-to-lymphocyte ratio, PLR)、淋巴细胞/单核细胞比值(lymphocyte-to-monocyte ratio, LMR)及术后病理分级的差异。采用单因素和多因素Logistic回归分析筛选出淋巴结转移的独立危险因素。采用受试者工作特征(receiver operating characteristic, ROC)曲线比较炎症指标对pT1a期阴茎鳞癌患者发生淋巴结转移的预测价值以及在调整灵敏度为100%后各炎症指标对淋巴结转移的预测效能。结果: ①腹股沟淋巴结转移组24例(23.3%), 非淋巴结转移组79例(76.7%), 两组在NLR($P < 0.001$)、PLR($P = 0.035$)和LMR($P < 0.001$)方面差异有统计学意义; ②多因素分析结果显示, NLR($P = 0.045$)和LMR($P = 0.021$)是pT1a期阴茎鳞癌发生腹股沟淋巴结转移的独立危险因素; ③ROC曲线分析结果显示, NLR、LMR和NLR+LMR的曲线下面积分别为0.833、0.816、0.835。NLR的最佳截断值为2.33, 灵敏度为95.8%, 特异度为68.4%; LMR的最佳截断值为3.80, 灵敏度为79.2%, 特异度为78.5%; NLR+LMR联合检测的灵敏度为83.3%, 特异度为74.7%; ④当调整灵敏度为100%时, NLR和LMR对pT1a期阴茎鳞癌腹股沟淋巴结转移的预测特异度为50.6%和2.5%, 截断值为1.79和11.01。结论: NLR和LMR为pT1a期阴茎鳞癌发生腹股沟淋巴结转移的独立预测因素。NLR > 2.33和LMR < 3.80时提示患者淋巴结转移风险极大, 推荐行淋巴结清扫手术, 提高患者的生存率。

[关键词] 阴茎癌; 鳞状细胞癌; 炎症指标; 淋巴结转移; 预测

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Predictive value of preoperative inflammatory markers for lymph node metastasis in patients with pT1a stage penilesquamous carcinoma without palpable inguinal lymph nodes

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[Abstract] **Objective:** To investigate the predictive value of three preoperative inflammatory markers for lymph node metastasis in patients with pT1a stage penile squamous carcinoma without palpable inguinal lymph nodes. **Methods:** Clinical data of 103 patients with pT1a stage penile squamous carcinoma admitted to the First Affiliated Hospital of Soochow University and Taixing People's Hospital from January 2012 to June 2023 were collected. Patients were divided into lymph node metastasis group and non-lymph node metastasis group based on postoperative pathological findings of inguinal lymph node involvement. Differences in age, body mass index (BMI), hypertension, diabetes mellitus, tumor diameter, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and postoperative pathological grading were compared between the two groups. Independent risk

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factors for lymph node metastasis were screened using univariate and multivariate logistic regression analyses. Receiver operating characteristic (ROC) curves were performed to compare the predictive value of inflammatory markers for lymph node metastasis in patients with pT1a stage penile squamous carcinoma, and the predictive efficacy of each inflammatory markers for lymph node metastasis was evaluated after adjusting sensitivity to 100%. **Results:** There were 24 cases (23.3%) in the inguinal lymph node metastasis group and 79 cases (76.7%) in the non-lymph node metastasis group. The differences between the two groups were statistically significant in terms of NLR ($P < 0.001$), PLR ($P = 0.035$), and LMR ($P < 0.001$). Multivariate analysis showed that NLR ($P = 0.045$) and LMR ($P = 0.021$) were independent risk factors for inguinal lymph node metastasis in pT1a stage penile cancer. ROC curve analysis results showed that the area under the curve for NLR, LMR, and NLR+LMR were 0.833, 0.816, and 0.835 respectively. The optimal cut-off value for NLR was 2.33, with a sensitivity of 95.8% and a specificity of 68.4%; the optimal cut-off value for LMR was 3.80, with a sensitivity of 79.2% and a specificity of 78.5%; the sensitivity and specificity of combined detection of NLR+LMR were 83.3% and 74.7%, respectively. When adjusting sensitivity to 100%, the specificity of NLR and LMR for predicting inguinal lymph node metastasis in pT1a stage penile squamous carcinoma was 50.6% and 2.5%, with cut-off values of 1.79 and 11.01. **Conclusion:** NLR and LMR are independent predictive factors for inguinal lymph node metastasis in pT1a stage penile squamous carcinoma. $NLR > 2.33$ and $LMR < 3.80$ suggest that patients are at great risk of lymph node metastasis, and lymph node dissection surgery is recommended to improve patient survival.

[Key words] penile cancer; squamous cell carcinoma; inflammatory marker; lymph node metastasis; prediction

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阴茎癌是一种罕见的恶性肿瘤,它对患者的生理和心理造成显著的影响。在欧洲和北美所有恶性肿瘤中其发病率 $<1/10$ 万,但在一些非洲、亚洲和南美地区,它占男性恶性肿瘤的10%^[1]。这通常被归因于包茎、慢性炎症、阴茎卫生不良、吸烟、免疫抑制和人乳头瘤病毒感染^[2]。在我国的发病率约为0.6/10万^[3]。大多数(95%)阴茎癌是鳞状细胞癌,起源于包皮内侧或龟头。阴茎癌的外科治疗取决于疾病分期。目前2022版《中华泌尿外科和男科疾病诊断治疗指南》指出,pT1a期阴茎癌患者,若腹股沟淋巴结未触及肿大淋巴结(cN0期),则推荐主动监测,但此期患者依旧承担着约11%的淋巴结微转移的风险^[4],而指南上也明确指出,阴茎癌患者的预后与是否发生腹股沟淋巴结转移密切相关^[5]。因此,这部分患者是否需要采取淋巴结清扫值得讨论。明确可知的是,早期发现和预测未触及淋巴结肿大的pT1a期阴茎癌患者发生腹股沟淋巴结转移的风险对个体化治疗方案的选择和改善患者预后尤为重要。

越来越多的研究表明,肿瘤的发生、发展不仅受肿瘤本身特征的影响,宿主炎症水平在肿瘤的出现、恶化中也起着至关重要的作用^[6-8]。尤其是中性粒细胞/淋巴细胞比值(neutrophil-to-lymphocyte ratio, NLR)、血小板/淋巴细胞比值(platelet-to-lymphocyte ratio, PLR)以及淋巴细胞/单核细胞比值(lymphocyte-to-monocyte ratio, LMR),都可以作为全身炎症水平的指标,用来评价机体炎症反应的程度,对肿瘤的

发生、发展以及临床的诊疗、预后判断具有一定的指导作用^[9-12]。目前,国内外尚无关于NLR、PLR和LMR用于评价未触及腹股沟淋巴结的pT1a期阴茎癌淋巴转移情况的相关研究。本研究旨在分析3种术前炎症指标与未触及肿大淋巴结的pT1a期阴茎癌患者发生腹股沟淋巴结转移的关系,探讨术前炎症指标对pT1a期阴茎鳞癌发生淋巴结转移的预测价值。

1 对象和方法

1.1 对象

回顾性分析2012年1月—2023年6月在苏州大学附属第一医院和泰兴市人民医院接受治疗的103例pT1a期阴茎癌患者的临床资料,包括年龄、体重指数(body mass index, BMI)、高血压、糖尿病、肿瘤直径、NLR、PLR、LMR、术后病理分级及腹股沟淋巴结是否转移等信息。根据患者术后病理有无腹股沟淋巴结转移划分为淋巴结转移组和非淋巴结转移组。术前1~7 d采血查血常规。阴茎癌患者的分期参照2017年美国癌症联合委员会(American Joint Committee on Cancer, AJCC)阴茎癌TNM分期,组织学分级参照2016年世界卫生组织/国际泌尿系统病理学会(World Health Organization/International Society of Urological Pathology, WHO/ISUP)的三级分级系统。本研究经苏州大学附属第一医院伦理委员会批准[批准号:219(2022)],所有患者均知情同意。

1.2 方法

纳入标准: ①初治阴茎癌患者; ②术前未接受新辅助放化疗; ③术前专科检查未触及腹股沟肿大淋巴结及影像学检查(腹股沟B超及胸腹盆CT)排除淋巴结及远处转移; ④行阴茎部分切除术和腹腔镜下或开放性双侧腹股沟淋巴结清扫术, 术后病理确诊为阴茎鳞癌, 且病理分期为pT1a期。排除标准: ①患有艾滋病或合并其他肿瘤; ②患有炎症性疾病或血液系统疾病; ③患者或家属拒绝参与临床研究。

1.3 统计学方法

采用SPSS 26.0和GraphPad Prism 9.4进行统计学分析。分类变量以例数(百分比)表示, 组间比较采用 χ^2 检验, 若频数少于5, 则采用Fisher确切概率法检验。连续变量中符合正态分布的数据用均数 \pm 标准差($\bar{x} \pm s$)表示, 非正态分布的数据用中位数(四分位数)[$M(P_{25}, P_{75})$]表示, 独立 t 检验、Mann-Whitney U 检验分析这些变量在淋巴转移组与非淋巴转移组中的分布差异。二元Logistic回归分析筛选淋巴转移的独立风险因素。受试者工作特征(receiver operating characteristic, ROC)曲线评估各炎症指标对淋巴转移的鉴别能力以及最佳截断值(optimal cut-off, OCF)。最后, 比较各炎症指标在调整灵敏度为100%后对淋巴结转移的预测效能。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 淋巴结转移组与非淋巴结转移组的临床病理资料比较

本研究共纳入103例pT1a期阴茎鳞癌患者, 其中伴腹股沟淋巴结转移24例(23.3%), 非淋巴结转移78例(76.7%)。入组患者平均年龄为(62.14 \pm 12.09)岁; BMI为24.22(21.89, 26.33)kg/m²; 肿瘤直径为28(20, 40)mm; NLR为2.26(1.23, 3.31); PLR为112.32(92.92, 144.25); LMR为4.38(3.33, 5.33)。术

后WHO/ISUP病理分级中1级70例(67.96%), 2级33例(32.04%)。另外, 高血压和糖尿病患者各37例(35.92%)和10例(9.70%)。

根据术后腹股沟淋巴结的病理结果将患者分为淋巴结转移组和非淋巴结转移组。淋巴结转移组与非淋巴结转移组间年龄($P=0.595$)、BMI($P=0.761$)、高血压($P=0.628$)、糖尿病($P=1.000$)、肿瘤直径($P=0.628$)以及WHO/ISUP病理分级($P=0.248$)等方面差异无统计学意义, 在NLR($P < 0.001$)、PLR($P=0.035$)和LMR($P < 0.001$)方面差异有统计学意义。

2.2 pT1a期阴茎癌患者发生腹股沟淋巴结转移的危险因素

单因素和多因素分析结果见表1。单因素分析结果显示, NLR($P < 0.001$)、PLR($P=0.041$)和LMR($P < 0.001$)与pT1a期阴茎癌患者发生腹股沟淋巴结转移相关; 多因素分析结果显示, NLR($P=0.045$)、LMR($P=0.021$)是pT1a期阴茎癌患者发生腹股沟淋巴结转移的独立危险因素。

2.3 NLR、LMR单独及联合检测对pT1a期阴茎癌患者发生腹股沟淋巴结转移的预测价值

NLR、LMR单独检测和NLR+LMR联合检测的ROC曲线见图1。NLR、LMR和NLR+LMR的曲线下面积(area under curve, AUC)分别为0.833、0.816、0.835。NLR的最佳截断值为2.33, 灵敏度为95.8%, 特异度为68.4%; LMR的最佳截断值为3.80, 灵敏度为79.2%, 特异度为78.5%; NLR+LMR联合检测的灵敏度为83.3%, 特异度为74.7%。另外, LMR的AUC低于NLR($Z=7.613$, 95%CI: 0.482~0.816, $P < 0.001$)和NLR+LMR($Z=-6.218$, 95%CI: -0.857~-0.446, $P < 0.001$), 而NLR和NLR+LMR的AUC比较差异无统计学意义($Z=-0.075$, 95%CI: -0.071~0.066, $P=0.940$)。

2.4 NLR和LMR调整灵敏度后预测淋巴结转移的效能比较

当调整灵敏度为100%时, NLR和LMR对pT1a

表1 pT1a期阴茎鳞癌患者发生腹股沟淋巴结转移的单因素和多因素Logistic回归分析

Table 1 Univariate and multivariate logistic regression analysis of inguinal lymph node metastasis in patients with stage pT1a penile squamous carcinoma

Variable	Univariate				Multivariate			
	B	OR	95%CI	P	B	OR	95%CI	P
NLR	0.476	1.610	1.232-2.102	<0.001	0.544	1.723	1.013-2.932	0.045
PLR	0.009	1.009	1.000-1.017	0.041	-0.017	0.983	0.966-1.000	0.051
LMR	-0.815	0.442	0.292-0.671	<0.001	-0.653	0.521	0.299-0.907	0.021

B: the unstandardized beta; OR: odds ratio; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio.

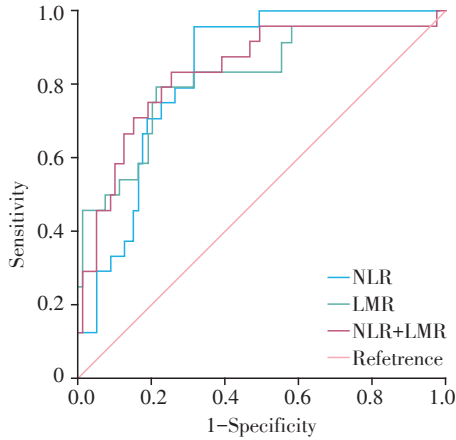


图1 炎症指标对预测腹股沟淋巴结转移的ROC曲线图
Figure 1 ROC curve of inflammatory markers in predicting inguinal lymph node metastasis

表2 NLR、LMR以及NLR+LMR预测腹股沟淋巴结转移的曲线下面积和最佳截断值

Table 2 Area under the curve and optimal cutoff value of NLR, LMR and NLR+LMR in predicting inguinal lymph node metastasis

Variable	AUC(95%CI)	OCF	Sensitivity(%)	Specificity(%)	Youden index
NLR	0.833(0.755-0.910)	2.33	95.8	68.4	0.642
LMR	0.816(0.710-0.923)	3.80	79.2	78.5	0.577
NLR+LMR	0.835(0.737-0.934)	0.21	83.3	74.7	0.580

表3 NLR和LMR调整截点后预测淋巴结转移的效能比较

Table 3 Comparative efficacy of predicting lymph node metastasis after adjusting cut-off values for NLR and LMR

Variable	OCF	Sensitivity (%)	Specificity (%)	Youden index	True positive (n)	True negative (n)	False positive (n)	False positive (n)
NLR	1.79	100	50.6	0.506	24	40	39	0
LMR	11.01	100	2.5	0.025	24	2	77	0

因素^[14]。研究表明,淋巴结微转移如果早期行淋巴结清扫无病存活率为84%,而监测中复发患者的存活率仅为35%^[15]。可见,与补救性淋巴结清扫相比,早期治疗性淋巴结清扫明显提高了患者生存率。因此,早期发现pT1a期患者淋巴结微转移对治疗方案的选择和改善患者预后具有重要的临床意义。目前,传统的CT和MRI检查仅能够诊断直径>1 cm的淋巴结,无法可靠检测微转移灶。氟脱氧葡萄糖-正电子体层扫描(FDG-PET)/CT也只能发现直径0.5 cm以上的淋巴结。Sadeghi等^[16]的一项Meta分析显示FDG-PET/CT对于cN0期阴茎癌患者淋巴转移检测的灵敏度仅为56.5%,其应用受到质疑。而前哨淋巴结活检对于淋巴结是否转移的判断也是不可靠的。对于触诊阴性的患者,由于活检过程中难以准确判断前哨淋巴结的位置,所以也不

期阴茎癌患者发生腹股沟淋巴结转移的预测效能比较见表3。NLR的特异度为50.6%,截断值为1.79;LMR的特异度为2.5%,截断值为11.01。

3 讨论

阴茎癌转移途径以淋巴结转移为主,并具有逐级转移的特点,其中腹股沟淋巴结是第一转移部位^[13]。但临床上未触及肿大的淋巴结并不能完全排除腹股沟淋巴结转移尤其是微小转移。因为无可触及淋巴结的患者发生微转移的可能性约为23%,其中pT1a期肿瘤淋巴结微转移的风险约为11%^[4]。而腹股沟淋巴结是否转移以及淋巴结清扫的手术时机是影响阴茎癌患者生存最重要的预后

推荐常规前哨淋巴结活检。因此,学者们一直寻找和探索更为简便有效的指标来评估和预测pT1a期阴茎癌淋巴结微转移风险。Zekan等^[17]基于31项研究的荟萃分析发现,通过T分期、G分级及肿瘤特征可在一定程度上预估阴茎癌淋巴转移,但仍不完善。最近一项纳入42项高质量研究的荟萃分析结果显示,血清较高NLR值(OR: 4.22; 95%CI: 1.36~13.09; P=0.010)和CRP值(OR: 4.78; 95%CI: 2.48~9.20; P<0.001)是腹股沟淋巴结转移的预测因素^[5],这也提示了炎症对阴茎癌淋巴转移的潜在影响。

近年来,炎症与癌症的关系已成为研究的热点。炎症增加癌症风险并影响癌症分期,触发最初的基因突变或表观遗传机制,促进癌症的启动、进展和转移扩散^[18]。而持续的全身炎症和肿瘤自身的炎症反应会引起机体中性粒细胞、淋巴细胞等血

液炎症指标的异常^[19]。研究发现中性粒细胞可被肿瘤微环境的外部刺激触发,并在抗肿瘤和促肿瘤表型之间切换。抗肿瘤中性粒细胞通过直接细胞毒性作用以及激活适应性免疫反应的间接作用杀死肿瘤细胞。相反,中性粒细胞的促肿瘤表型可能与肿瘤微环境中的细胞增殖、血管生成和免疫抑制有关^[20]。淋巴细胞通过促进细胞毒性细胞死亡和抑制肿瘤细胞的增殖和迁移,从而决定宿主对恶性肿瘤的免疫反应,在肿瘤防御中发挥关键作用^[21]。单核细胞是单核吞噬细胞系统的先天性免疫细胞,不同的单核细胞亚群发挥着促进肿瘤和抗肿瘤免疫的功能,包括吞噬、分泌杀瘤介质、促进血管生成、重塑细胞外基质、招募淋巴细胞以及分化为肿瘤相关巨噬细胞和树突状细胞^[22]。血小板与癌细胞之间的旁分泌作用被认为可促进癌细胞在血液循环中的扩散、存活以及在远处转移部位的外渗。血小板发出的信号还被认为会导致表观遗传学改变,包括上调循环肿瘤细胞中的癌细胞蛋白,而分泌的强效生长因子可能会在促进有丝分裂、血管生成和转移生长方面发挥作用^[23]。因此,基于这4种免疫炎症性细胞的NLR、PLR和LMR可以很好地反映pT1a期阴茎癌患者促肿瘤及抗肿瘤免疫状态之间的平衡。

更为重要的是,术前NLR、PLR和LMR已在多种泌尿系肿瘤的研究中显示了较好的预测价值。Hu等^[10]对84例cN0期阴茎癌患者进行了回顾性分析,发现NLR是发生淋巴结转移的独立预测因子,并且在阴茎癌中呈线性正相关。Ferro等^[24]观察发现,在接受前列腺癌根治的患者中,术前PLR增加可能与Gleason评分升级有关。Bi等^[9]发现,在膀胱癌根治性术后患者中,较高的术前LMR与显著改善的总生存期和无瘤生存期之间存在独立关联。据我们所知,目前还没有研究探讨术前炎症指标与未触及腹股沟淋巴结的pT1a期阴茎癌发生淋巴结转移的关系。

本研究中,3种炎症指标都与淋巴细胞相关,但淋巴结转移组和非淋巴结转移组淋巴细胞计数差异无统计学意义,而NLR、PLR和LMR之间有显著的差异($P < 0.05$),这与之前的研究结果有相似之处^[10-11]。另外,两组WHO/ISUP病理学分级无明显差异($P=0.248$),这可能与本研究对象仅为pT1a期阴茎癌患者有关。Logistic回归结果显示,NLR和LMR是发生腹股沟淋巴结转移的独立危险因素($P < 0.05$),而不包括PLR。本研究的ROC曲线也证实NLR和LMR均有较强的预测淋巴结转移的能

力,AUC分别为0.833和0.816,但NLR+LMR联合检测的预测价值并没有显著提升($P > 0.05$)。此外,临床中不能简单取约登指数最大值为截断值,这会造成一部分淋巴转移患者的漏诊,延误治疗。因此,本研究进行了修改,使得所选取的截断值能避免所有阳性患者的漏诊,即灵敏度为100%,相应的截断值分别为1.79和11.01。本研究各炎症指标的截断值还需要外部验证以及后续研究进一步完善。

综上所述,NLR和LMR为pT1a期阴茎鳞癌发生腹股沟淋巴结转移的独立预测因素。当NLR > 2.33和LMR < 3.80时提示患者淋巴结转移风险极大,推荐行淋巴结清扫手术,提高患者的生存率。但本研究样本数量有限,仍需要大规模、前瞻性的临床对照试验来证实NLR和LMR对pT1a期阴茎癌发生腹股沟淋巴结转移的预测价值及最佳截断值。

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