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ORIGINAL PAPER

Preoperative platelet-to-lymphocyte ratio as a predictor of inguinal lymph node metastasis in penile cancer

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Summary

***Background:** Penile cancer (PC) is a rare malignancy with poor prognosis. To date, reliable preoperative biomarkers for lymph node status and prognosis are still lacking. This study aims to explore the potential role of preoperative platelet-to-lymphocyte ratio (PLR) as a predictor of inguinal lymph node invasion in PC patients.*
***Methods:** Retrospective analysis was conducted on anamnestic, clinical, and laboratory data of PC patients who underwent surgical treatment between January 2016 and October 2023. Inguinal lymphadenectomy was performed as per EAU guidelines. PLR, calculated as the ratio between platelet-to-lymphocyte values obtained from preoperative blood analyses, was assessed within 30 days before surgery. Patients were categorized into pN- (no lymph node metastasis) and pN+ (lymph node metastasis confirmed pathologically). Statistical analyses included Kruskal-Wallis and Mann-Whitney U tests, univariate logistic regression, and ROC curve analysis with Youden index, assuming $p < 0.05$ as statistically significant.*
***Results:** Overall, 60 PC patients were retrospectively involved in the study. A total of 36 (60%) patients reported ILN metastases, confirmed by inguinal lymphadenectomy (pN+), while no ILN metastases (pN-) were reported in 24 (40%) patients. The AUC for predicting ILN metastasis by preoperative PLR was 0.71 ($p = 0.014$). According to the ROC curve analysis and the Youden Index, a cut-off for PLR was set at 122.4.*
On Univariable logistic regression analysis, the presence of T stage ≥ 2 (OR = 3.21; 95% CI: 1.43-7.47, $p = 0.011$), lymphovascular invasion (OR = 3.78; 95% CI: 1.56-5.90, $p = 0.003$), clinical node-positive disease (OR = 19.86; 95% CI: 5.91-41.03, $p < 0.001$) and PLR ratio > 122.4 (OR = 7.22; 95% CI: 1.41-22.71, $p = 0.0148$) were independent predictors of pN+ disease.
***Conclusions:** The current study confirms the relationship between cancer and inflammation. When elevated preoperatively, PLR may be associated with inguinal lymph node invasion in PC patients.*

KEY WORDS: *Penile cancer; Penile neoplasm; Platelet-to-lymphocyte; Ratio; Lymph node; Inguinal lymph node; Metastasis; Biomarkers.*

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INTRODUCTION

Penile cancer (PC) is a rare cancer with a prevalence of 0.1-1 per 100,000 men in high-income countries (1).
Several risk factors have been reported, including the absence of childhood circumcision, phimosis, chronic inflammation, inadequate penile hygiene, smoking, immunosuppression and human papillomavirus (HPV) infection (2). Lymph node status represents an important prognostic factor, in association with primary tumor grade, pathologic T stage, histologic subtype, and lymphovascular invasion (3). Several treatments for localized early-stage disease are available, ranging from topical 5-Flurouracil therapy and laser therapy to glans resur-facing and glansectomy with reconstruction (4, 5). As the disease progresses to more advanced stages, recommendations include partial or total penectomy with or without reconstruction, or radiotherapy (6, 7). However, radical surgical treatment represents the gold standard for high-grade and high-stage disease (8).
PC displays aggressive behavior and tends to metastasize primarily to locoregional *lymph nodes* (LN). Metastatic progression typically affects *inguinal LNs* (ILN) and then extends to *pelvic LN* (PLN), following the anatomical drainage route (9). Consequently, after local treatment for the primary lesion, *inguinal lymph node dissection* (ILND) is recommended if there is evidence of lymph node invasion or in high-risk patients (10). Despite significant advancements in imaging and surgical techniques, the absence of reliable biomarkers for diagnosis, prognosis, and follow-up remains a challenge (11). In this scenario, recent studies have underscored the pivotal role of inflammation in various tumorigenic processes, including proliferation, invasion, metastasis, and angiogenesis (12, 13). Hence, several inflammatory indexes such as *neutrophil to lymphocyte ratio* (NLR), *platelet to lymphocyte ratio* (PLR), *Albumin-to-Alkaline Phosphatase Ratio* (AAPR), have emerged and proposed as potential prognostic biomarkers in different cancers including genitourinary tumors (14-16). These biomarkers, char-

acterized by different sensitivity and specificity, represent a low-cost yet powerful tool in stratifying cancer patients.

Interestingly, *platelet-to-lymphocyte ratio* (PLR) has recently gained widespread recognition as a valuable prognostic factor in various types of tumors, including lung, colorectal, and esophageal cancer (17). However, the prognostic impact of PLR on PC remains poorly explored. Interestingly, *Wu et al.* developed a reliable nomogram based on clinicopathologic and laboratory data incorporating PLR, squamous cell carcinoma antigen SCC-Ag, *lymphovascular invasion* (LVI), and pT-stage for the prediction of lymph node extranodal extension in patients with PC (18). Moreover, *Hu et al.* in their single center experience found that PLR was a significant independent predictor for OS and PFS in patients treated with ILND (12). Based on these findings we aimed at investigating the utility of preoperative PLR as a prognostic indicator of *inguinal lymh node* (ILN) invasion in PC patients.

Materials and methods

We retrospectively analyzed anamnestic, clinical and laboratory data retrieved from patients who underwent surgical treatment for penile cancer at *IRCCS Hospital "Pascale" of Naples* between January 2016 and October 2023. According to EAU guidelines, sentinel lymph node biopsy and/or inguinal lymphadenectomy (modified/standard) was performed in patients with high-risk tumors (≥ T1G3) and/or patients with cN+. In case of pT1G1/G2 status a ILND following a modified template was reserved for those patients with either lymphovascular or peri-neural invasion. Due to the retrospective nature of the study and the use of procedures included in the common clinical practice, no ethical committee was required. The inclusion criteria were: (1) primary tumor treated surgically, (2) tumor pathology confirmed by an expert uro-oncology pathologist and (3) available data to calculate PLR. Exclusion criteria from the study were (1) presence of pelvic lymph node involvement or the presence of distant metastasis at diagnosis, (2) patients with conditions affecting the number of platelets such as liver diseases, hemolytic anemia, chronic infectious and inflammatory diseases, splenectomy, and alcoholism (Figure 1). Routine venous blood samples were obtained within 30 days before scheduled primary surgery. PLR was calculated as the ratio between platelet-to-lymphocyte values. Demographic, clinical and pathological data were collected in a single, customized dataset. Evaluated preoperative demographic and clinical characteristics included age, smoking status, hypertension status, *body mass index* (BMI), Charlson Comorbidity Index, *American Society of Anesthesiologists* (ASA) score and PLR calculated using the platelet and lymphocyte counts, obtained via routine complete blood counts in peripheral blood samples before primary surgery. Oncological outcomes variables included surgical margin status, final histology, staging (according to TNM classification system), grading tumor, lymph vascular and perineural invasion. Patients were further divided into two categories: pN- (i.e. those without ILN metastasis identified at the histopathological analysis after inguinal lymphadenectomy) and pN+ (i.e. those with ILN metastasis at the histopathological analysis after inguinal lymphadenectomy). Means and standard deviations were reported for continuous variables while frequencies and percentages were reported for categorical variables. The Kolmogorov-Smirnov test was used to assess the normality of data before proceeding to further analysis. A Mann-Whitney U Test was used to evaluate continuous variables, while Chi-square test was used for categorical variables analysis. Univariable logistic regression analysis was used for calculating *odds ratio* (OR), 95% *confidence interval* (CI) calculations, and to estimate pathologic node-positivity. Statistical analysis was conducted using IBM SPSS software (*version 25, IBM Corp, Armonk, NY, USA*). A p value < 0.05 was considered to be statistically significant.

Results

Overall, 60 PC patients met the inclusion criteria. Descriptive characteristics and preoperative laboratory data of the overall cohort are reported in Table 1.

Table 1.
Baseline and pathological characteristics.

	Overall n = 60	pN+ n = 24	pN- n = 36	p value
Age, mean (SD)	66.9 (14.4)	62.6 (13.4)	68.2 (14.5)	0.17
Current Smoker, n (%)	23 (38.3)	4 (16.7)	19 (52.8)	0.34
Hypertension, n (%)	34 (56.7)	9 (37.5)	25 (69.4)	0.76
Diabetes, n (%)	10 (16.7)	3 (12.5)	7 (19.4)	0.69
Charlson Comorbidity Index, n (%)				
1	13 (21.7)	5 (20.8)	8 (22.2)	0.86
2	10 (16.7)	3 (12.5)	7 (19.4)	
3	7 (11.7)	1 (4.7)	6 (16.7)	
4	9 (15)	2 (8.3)	7 (19.4)	
5	3 (5.0)	1 (4.7)	2 (5.5)	
6	2 (3.3)	0 (0)	2 (5.5)	
7	2 (3.3)	0 (0)	2 (5.5)	
Unknown	14 (23.3)	12 (50.0)	2 (5.5)	
ASA score, n (%)				
2	30 (50)	14 (58.3)	16 (44.4)	0.57
3	26 (43.3)	8 (33.3)	18 (50.0)	
4	2 (3.3)	0 (0)	2 (5.5)	
Unknown	2 (3.3)	2 (8.3)	0 (0)	
Platelets, mean (SD)	215 (58.9)	232.3 (78.6)	210.3 (52.5)	0.51
Lymphocytes, mean (SD)	1.9 (0.8)	1.4 (0.4)	1.9 (0.8)	**0.04**
PLR, mean (SD)	147.1 (87.2)	193.8 (129.5)	122.5 (54.2)	**0.02**
Pathologic T stage, n (%)				
pTa/T1	13 (21.7)	4 (16.7)	9 (25.0)	0.25
pT2	22 (36.7)	7 (29.2)	15 (41.7)	
pT3	25 (41.7)	13 (54.2)	12 (33.3)	
pT4	0 (0)	0 (0)	0 (0)	
Grading, n (%)				
G1/G2	41 (68.3)	16 (66.7)	24 (66.7)	0.42
G3/G4	19 (31.7)	8 (33.3)	12 (33.3)	
Lymphovascular invasion, n (%)				
No	28 (46.7)	11 (45.8)	17 (47.2)	0.62
Yes	32 (53.3)	13 (54.2)	19 (52.8)	
Perineural invasion, n (%)				
No	19 (31.7)	6 (25.0)	13 (36.1)	0.34
Yes	21 (35.0)	7 (29.2)	14 (38.9)	
Unknown	20 (33.3)	11 (45.8)	9 (25.0)	
Positive Margins, n (%)	0 (0)	0 (0)	0 (0)	

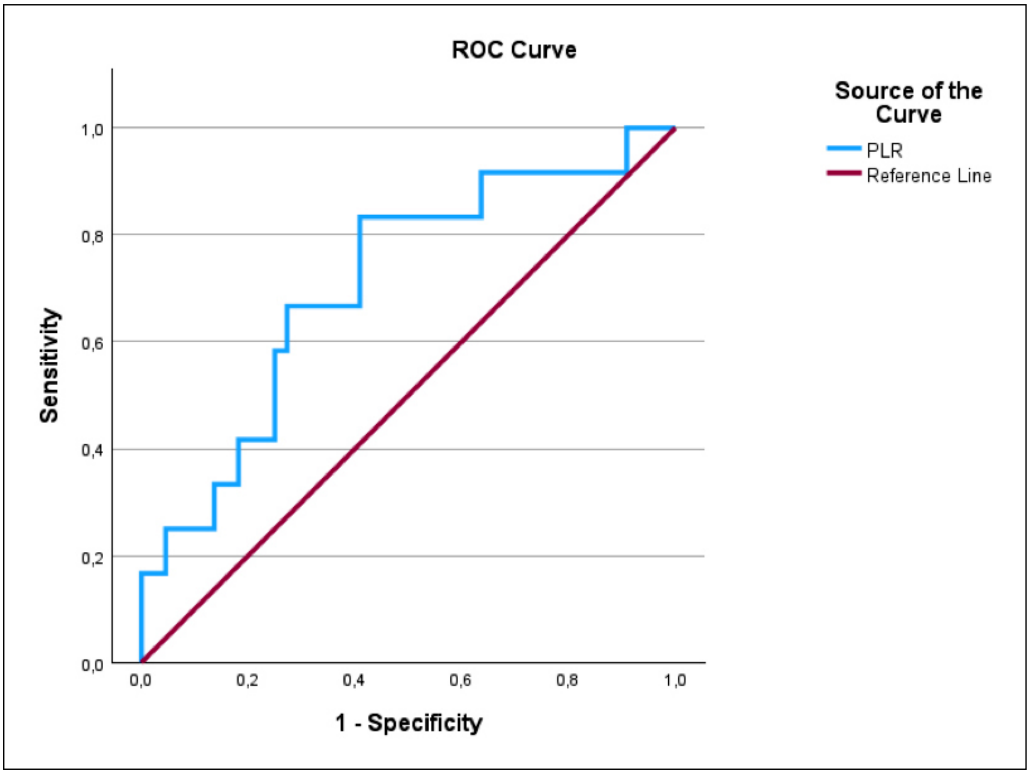

Figure 1.
Receiver operating characteristic (ROC) curve and area under the curve (AUC) to define the optimal PLR cutoff.
AUC: 0.71 (p = 0.014).

Overall n = 26 patients had cN- status. Of those, sentinel lymph node biopsy and modified inguinal lymphadenectomy was performed in n = 6 and n = 20 patients, respectively. A total of n = 34 patients with a cN+ status underwent ILND following a standard template. The mean age at the time of surgery was 66.9 ± 14.4 years. A total of 36 (60%) patients reported ILN metastases (pN+), confirmed by ILND following a standard or modified template. Conversely, no ILN metastases (pN-) were reported in 24 (40%) patients. No statistically significant differences were reported for baseline characteristics, except for preoperative lymphocytes (pN- *vs* pN+: 1.9 ± 0.8 *vs* 1.4 ± 0.4; p = 0.04) and PLR (pN+ 193.8 ± 79.5 *vs* pN- 122.5 ± 54.2; p = 0.02).

The AUC for predicting ILN metastasis by preoperative PLR was 0.71 (p = 0.014). According to the ROC curve analysis and the Youden Index, a cut-off for PLR was set at 122.4 (Figure 1).

On Univariable logistic regression analysis, the presence of T stage ≥ 2 (OR = 3.21; 95% CI: 1.43-7.47, p = 0.011), lymph vascular invasion (OR = 3.78; 95% CI: 1.56-5.90, p = 0.003), clinical node-positive disease (OR = 19.86; 95% CI: 5.91-41.03, p < 0.001) and PLR ratio > 122.4 (OR = 7.22; 95% CI: 1.41-22.71, p = 0.0148) were independent predictors of pN+ disease (Table 2).

Table 2.
Logistic regression model predicting pathologic inguinal node-positive disease (pN+).

	Univariable analysis 95.0% CI			
		Lower	Higher	p value
Clinical N stage				
cN0	Ref.	-	-	-
cN+	19.86	5.91	41.03	< 0.001
T stage				
Ta/T1	Ref.	-	-	-
≥ T2	3.21	1.43	7.47	0.011
Primary tumor grade				
G1/G2	Ref.	-	-	-
G3/G4	1.53	0.58	2.3	0.41
Lymphovascular Invasion				
No	Ref.	-	-	-
Yes	3.78	1.56	5.90	0.003
Platelet-to-Lymphocyte ratio				
≤ 122.4	Ref.	-	-	-
> 122.4	7.22	1.41	22.71	0.018

OR = odds ratio; C I= confidence interval.

Discussion

In PC patients, nodal metastasis emerges as the foremost predictor of a poor clinical outcome, with tumor grade and lymph vascular invasion also serving as significant prognostic indicators (10, 19). According to EAU guidelines, sentinel lymph node biopsy and/or inguinal lymphadenectomy is crucial for patients with intermediate or high-risk tumors (≥ T1G2) and/or those with clinically positive lymph nodes (cN+) (10). In spite of unequivocal endorsements advocating the adoption of these potentially life-saving interventions, several authors have underscored suboptimal adherence to clinical guidelines (20, 21). This phenomenon may be ascribed to the foreseen morbidity stemming from compromised lymphatic drainage in the lower extremities and scrotum, with reported morbidity rates reaching as high as 50% (9).

Moreover, the poor compliance may also be caused by the lack of reliable biomarkers and a small number of predictors included in the current guidelines.
It is well established that cancer-related inflammation and systemic inflammatory responses contribute to tumor initiation and progression, including neo-angiogenesis, tumor progression, and metastasis. Several studies have investigated the role of PLR in various types of cancers. *Jiang et al.* found that a high PLR was associated with poorer survival prognosis in ovarian cancer (OS: HR 1.80 (95% CI 1.37-2.37), p = 0.000; PFS: HR 1.63 (95% CI 1.38-1.91), p = 0.000) and cervical cancer (OS: HR 1.36 (95% CI 1.10-1.68), p = 0.005; PFS: HR 1.40 (95% CI 1.16-1.70), p = 0.002) (22). Moreover, when examining urological malignancies, *Wang et al.* demonstrated that an elevated PLR predicted poor overall survival (OS; HR = 1.85, 95% CI = 1.51-2.25, p < 0.001) and disease-free survival (DFS; HR = 1.4, 95% CI = 1.1-1.79, p = 0.007) in prostate cancer patients (23). Nevertheless, subgroup analyses showed that the PLR remained a significant prognostic factor for OS irrespective of ethnicity, tumor stage, or cut-off value (23).
To the best of our knowledge our study is the first to explore the predictive value of preoperative PLR in ILN invasion within a PC cohort. Several noteworthy findings emerged from the analysis.
Firstly, the cut-off of the PLR set by the ROC analysis was 122.4 in the present study.
Similar PLR cut-offs points were found for other urological tumors. Herraiz-Raya and colleagues discovered that germ cell tumor patients with a PLR > 150 were more likely to experience disease progression, advanced stage II and III, and residual disease. Additionally, they found that PLR levels were significantly higher in seminoma patients compared to non-seminoma patients (24). Moreover, Imamoglu observed a PLR > 104 to be a significant predictor of advanced disease (stage II and III) with a sensitivity of 71% and a specificity of 88%, exclusively in non-seminoma patients (25). Conversely, a higher PLR (> 212) was depicted by *Peksa et al.* in a testis cancer cohort. Authors examined the correlation between immune checkpoint proteins microenvironments and systemic inflammatory reactions. In their study elevated PLR was associated with the presence of nodal and distant metastases as well as an advanced disease stage (26).
Furthermore, patients with high PLR showed significantly better five-year event-free survival compared to those with low PLR (89% *vs.* 69%, p = 0.018) (26). Notably, a combination of high PLR and low expression of immune checkpoint regulators (V-domain Ig suppressor of T cell activation) in tumor-infiltrating and peritumoral lymphocytes and macrophages was identified as a sole predictor of relapse and disease progression in multivariate analysis. These findings support the idea that the clinical behavior of tumors is influenced by a complex interaction between the local tumor immune environment and systemic inflammation.
Secondly, the predictive role of PLR in the prediction of ILN invasion was confirmed on univariable analysis (OR = 7.22). However, given the absence of comparative data, we must view our study as an introductory investigation into the potential of PLR as a prognostic biomarker for ILN invasion, as this outcome has not been previously addressed in the literature.
Third, our analysis confirmed the role of lymphovascular invasion as a crucial prognostic indicator (OR = 3.78, p = 0.018 univariable analysis). These ORs are similar to the study by *Winters et al.* (OR = 3.10), where lymphovascular invasion emerged as the primary independent predictor of occult lymph node metastasis (27). Similar findings have been reported by other studies, corroborating the significance of lymphovascular invasion as a substantial risk factor for occult micro metastases (28, 29). Taken together, these findings imply a potential enhancement in current risk stratification schemes. Specifically, the presence of LVI, irrespective of tumor stage or grade, warrants consideration as high-risk disease.
The precise role of PLR in oncological patients remains largely unexplored. Nevertheless, several theories have been proposed. Platelets serve as a crucial source of cytokines, binding to FGF, PDGF, VEGF, and TGF-β family proteins, and thereby acting as a reservoir for secreted growth factors that promote tumorigenesis and metastasis development. Tumor cells can activate and aggregate platelets through both direct and indirect mechanisms, which play a crucial role in metastatic spread. Platelets function as key transporters of both proangiogenic and antiangiogenic factors (30, 31). Moreover, they influence the process of angiogenesis, including platelet-derived microparticles, microRNA, lipids, and surface receptors. They are active in both the early and late stages of angiogenesis (32). This understanding raises the potential for targeting platelet functions as a promising strategy for cancer treatment. On the other hand, inflammatory response is linked to conditions such as lymphocytopenia, neutrophilia, and thrombocytosis. Lymphocytes are essential for immune function and play a significant role in suppressing cancer progression. Hence, a lower lymphocyte count, reflected by a high PLR, may translate in a reduced immune surveillance, thus allowing tumor progression (33-35). We acknowledge several limitations of our study. These include its retrospective, single-center design, and the relatively small sample size, which may introduce selection and treatment biases. Additionally, the restricted cohort size and limited number of events precluded multivariable analysis, preventing identification of more reliable predictors for ILN involvement.
Furthermore, the absence of follow-up data limits our ability to assess patient prognosis, and certain critical variables, such as tumor multifocality, tumor cell koilocytosis, and keratinization, were not included. Our results should be validated by external cohorts with multi-center studies prior to considering PLR for clinical use as an adjunctive biomarker in the diagnostic setting of inguinal lymph node metastasis.

Conclusions

The current study must be considered as an initial experience regarding the role of PLR as a potential biomarker in this setting of population. We identified potential predictors of ILN invasion in PC patients. However, further investigations and larger cohorts are required to confirm the clinical utility of PLR in patients' outcomes.

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Declarations

Ethical approval: Retrospective study exempt from ethics committee approval.

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Competing interests: The authors declare no conflicts of interest.

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Authors' contributions: Conception and design, B.B., P.A., A.A. , F.A.S., R.L., F.D.B., G.S., A.I. and A.T.; Analysis and interpretation of data, G.P., L.R., C.B., S.D.P., F.P., S.C., S.P., A.C. and L.N.; drafting the article B.B., P.A., A.A., F.A.S., F.P., S.C., S.P., A.C. and L.N.; revising the article critically R.L., F.D.B., G.S., A.I., A.T., G.P., L.R., C.B. and S.D.P.; final approval of the version to be published B.B., P.A., A.A., F.A.S., R.L., F.D.B., G.S., A.I. and A.T.; agreement to be accountable for all aspects of the work G.P., L.R., C.B., S.D.P., F.P., S.C., S.P., A.C. and L.N. All authors have read and agreed to the published version of the manuscript.

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