

## DIAGNOSTIC AND PROGNOSTIC UTILITY OF COMPLETE BLOOD COUNT-DERIVED INFLAMMATORY MARKERS AND C-REACTIVE PROTEIN IN PENILE CANCER

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DIAGNOSTIC AND PROGNOSTIC UTILITY OF COMPLETE BLOOD COUNT-DERIVED INFLAMMATORY MARKERS AND C-REACTIVE PROTEIN IN PENILE CANCER (Abstract): Systemic inflammatory indicators obtained from standard blood tests have garnered heightened interest as prospective diagnostic and prognostic instruments in oncological urology. **Materials and methods:** This study assessed the diagnostic efficacy of complete blood count-derived inflammatory indices and C-reactive protein (CRP) in individuals with penile cancer. A total of 38 individuals with penile cancer were compared to 38 control participants receiving surgery for benign scrotal conditions. **Results:** Notable disparities were identified between the two groups for baseline characteristics. Patients with penile cancer were much older and had reduced blood hemoglobin levels and elevated serum creatinine values in comparison to controls. All assessed inflammatory markers were markedly enhanced in the cancer cohort, suggesting an increased systemic inflammatory load. Mean CRP levels were significantly elevated in patients with malignancy, accompanied by markedly higher neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI). An examination of the ROC curves for inflammatory markers revealed statistically significant differences between groups. The NLR exhibited strong discriminating capacity for penile cancer, with an area under the curve (AUC) of 0.829. CRP had significant diagnostic efficacy (AUC 0.700). Conversely, composite indices such as SIRI and AISI showed relatively little discriminatory ability, with AUC values of 0.694 and 0.697, respectively. **Conclusions:** Individuals with penile cancer exhibit markedly increased systemic inflammatory markers in comparison to controls. Among the assessed indices, NLR and CRP demonstrated the greatest diagnostic efficacy, whereas more complex composite indices provided minimal additional differentiation. **Keywords:** PENILE CANCER, INFLAMMATORY MARKERS, NEUTROPHIL-TO-LYMPHOCYTE RATIO, C-REACTIVE PROTEIN, SII, AISI, SIRI.

### INTRODUCTION

The early identification of reliable diagnostic and prognostic biomarkers remains a priority for improving cancer patient stratification, optimizing treatment decisions, and

enhancing long-term survival outcomes. Recent studies have shifted attention to blood-based biomarkers derived from routine laboratory tests. These markers possess the advantage of being readily accessible,

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minimally invasive, and cost-efficient compared to tissue-based molecular assays. According to Czajkowski *et al.*, the neutrophil-to-lymphocyte ratio (NLR) has attracted substantial attention for its potential to reflect systemic inflammation and the interplay between tumor biology and immune response (1). In penile squamous cell carcinoma (PSCC), elevated NLR has been repeatedly associated with poorer overall survival (OS), recurrence-free survival (RFS), and cancer-specific survival (CSS) (2). Systemic inflammation markers extend beyond NLR. C-reactive protein (CRP), for example, is synthesized by hepatocytes in response to interleukin-mediated pathways such as IL-6 and IL-1 $\beta$ , which trigger transcriptional activation mechanisms involving C/EBP proteins (1). While CRP is classically associated with infection or trauma, elevated levels have been observed across multiple malignancies. In penile cancer, Qin *et al.* propose that high CRP values might be linked to worse prognosis in advanced disease stages (3). Altogether, this framing underscores why a systematic synthesis examining complete blood count-derived inflammatory markers alongside CRP can provide tangible benefits: clarifying contradictory findings in the literature; quantifying predictive value across diverse patient groups; and exploring how these readily available metrics interface with disease management algorithms currently applied to penile cancer patients (4). We aimed to compare complete blood count (CBC)-derived inflammatory markers and CRP levels between patients with penile cancer and a control group.

### MATERIALS AND METHODS

Data of patients who were diagnosed with PSCC who underwent penile amputa-

tion at “Dr. C.I. Parhon” Clinical Hospital, Iasi, and Neamt County Hospital between January 2021 and December 2025 were collected retrospectively.

Penile amputation was performed after confirmation of neoplasia by a previous biopsy in accordance with the recommended guidelines. The blood sample was taken before surgery. Patients with disorders that could influence inflammatory markers, including additional malignancies, active or chronic infections, immunosuppressive diseases, systemic inflammatory conditions, the use of immunosuppressive medications, and renal or hepatic dysfunction, were excluded from the study. The control group was formed by patients who presented for benign scrotal pathology, namely hydrocele, in a number equal to that of the study group, in the order in which they presented for surgical treatment in the last period of the study. From both groups, we collected data including age at the time of surgery, complete blood count, C-reactive protein, and serum creatinine. The CBC-derived inflammatory markers have been calculated as follows: NLR = neutrophil count / lymphocyte count, MLR = monocyte count / lymphocyte count, Systemic Immune-Inflammation Index (SII) = platelet /  $\times$  neutrophil-to-lymphocyte ratio, Systemic Inflammation Response Index (SIRI) = (neutrophil count  $\times$  monocyte count) / lymphocyte count; Aggregate Index of Systemic Inflammation (AISII) = (Neutrophil count  $\times$  Monocyte count  $\times$  Platelet count) / Lymphocyte count (5-7).

The Mann-Whitney U test was employed to compare each parameter between groups. Data were presented as mean  $\pm$  standard deviation and median;  $p < 0.05$  was accepted as statistically significant. The area under the receiver operating char-

acteristic (ROC) curves was assessed for the markers that were significantly different between the two groups.

Approval was obtained from the hospital Ethics Committee (Approval No.1372/09-FEB-2026). Statistical analysis was performed using the *Statistical Package for the Social Sciences version 26.0* (SPSS Inc., Chicago, IL, USA).

## RESULTS

We included a total of 38 patients diagnosed with penile cancer and 38 subjects in the control group. Comparative analysis demonstrated statistically significant differences between the two groups for sever-

al baseline clinical and laboratory parameters, including mean age, serum hemoglobin levels, and serum creatinine levels. Patients in the cancer group were significantly older and exhibited lower hemoglobin concentrations and higher serum creatinine levels compared with controls.

Regarding systemic inflammatory status, marked differences were observed between the two groups. All evaluated inflammatory markers showed statistically significant elevations in the cancer group compared with the control group (tab. I). These findings suggest a substantially higher inflammatory burden among patients with malignancy.

TABLE I.  
Comparison of characteristics between the two groups

Parameter	Penile cancer (n=42)	Control (n=98)	p
Mean age (years), SD	65.71 ( $\pm$ 10.79)	42.65( $\pm$ 13.92)	<b>0.001</b>
Serum Hemoglobin (g/dl)	13.12 ( $\pm$ 2.61)	14.77 ( $\pm$ 1.02)	<b>0.0013</b>
Serum creatinine mg/dl	1.58 ( $\pm$ 0.13)	0.92 ( $\pm$ 0.16)	<b>0.05</b>
CRP (mg/L)	13.64 ( $\pm$ 12.80)	2.98 ( $\pm$ 2.84)	<b>0.0069</b>
NLR	3.64 ( $\pm$ 2.18)	1.84 ( $\pm$ 0.62)	<b>0.001</b>
MLR	0.41 ( $\pm$ 0.23)	0.29 ( $\pm$ 0.12)	<b>0.007</b>
SII	1001.88 ( $\pm$ 766.08)	468.10 ( $\pm$ 184.64)	<b>0.001</b>
SIRI	2.42 ( $\pm$ 1.94)	1.39 ( $\pm$ 0.6)	<b>0.003</b>
AISI	718.39 ( $\pm$ 736.23)	313.15 ( $\pm$ 188.85)	<b>0.003</b>

To further evaluate the discriminatory performance of the inflammatory markers that differed significantly between the two groups, we performed receiver operating characteristic (ROC) curve analyses, focusing particularly on CRP and NLR. The ROC analysis revealed that NLR demonstrated good discriminatory ability, with an area under the curve (AUC) of 0.829. CRP showed a moderate discriminatory capaci-

ty, with an AUC of 0.700.

In contrast, the composite indices SIRI and AISI exhibited relatively poor discriminative performance, with AUC values of 0.694 and 0.697, respectively. These results are illustrated in Figure 1. During the study, we did not record any patient deaths. Pathological examination revealed that 60.52% (n=23) have been classified as T1, 31.57% (n=12) as T2, and 7.89% (n=3) as T3.

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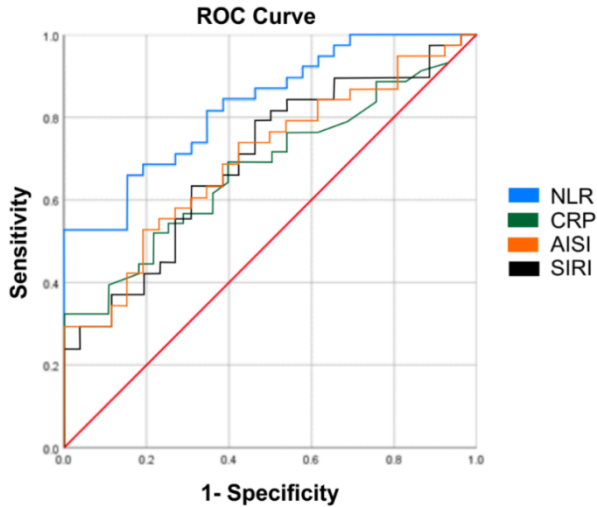


Fig. 1. ROC analysis of the inflammatory markers

### DISCUSSION

To investigate oncological diseases, markers are used that, although effective, are often too expensive for current practice (8). On the other hand, CBC-derived inflammatory markers are cheap and have proven useful in certain types of cancer (9, 10). CBC profiles, including absolute counts and subtype proportions, provide a window into the systemic immune status of patients with penile squamous cell carcinoma. Distinct white blood cell subtypes, neutrophils, lymphocytes, monocytes, and platelets, reflect different facets of inflammation and immunity, and when these parameters shift in characteristic ways, they can mark progression or prognosis in PSCC. Neutrophils, as primary components of the innate immune system, play a dual role in cancer. Tumor-associated neutrophils can be recruited via chemokine gradients established within the microenvironment and may contribute to tumor initiation and growth by activating cancer cells or suppressing cytotoxic lymphocyte function. Such suppres-

sion could manifest as elevated peripheral neutrophil counts relative to lymphocytes, leading to an elevated NLR. The elevation of NLR itself can arise from several physiological scenarios: increased neutrophil counts coupled with reduced lymphocyte numbers; increased neutrophils without lymphocytic changes; or diminished lymphocytes without altered neutrophils (11).

Elevated NLR has been linked not only to disease-specific mortality but also correlates with nodal stage severity, offering a potential bridge between routine hematology results and staging models traditionally constructed from imaging or intraoperative findings (12). Lymphocytes are central to immune surveillance against malignancy. Their depletion reduces the capacity to mount adaptive immune responses and is linked to enhanced tumor progression due to weakened control over aberrant cells. A reduction in circulating lymphocytes relative to platelets, the platelet-to-lymphocyte ratio (PLR), has been suggested as a marker for poor prognosis in diverse cancers

because it reflects both diminished immunity and increased platelet-mediated tumor support functions (13). According to Steffens *et al.*, combining NLR with CRP levels has shown potential in improving predictive ability for poor outcomes, especially in non-metastatic patients who nonetheless harbor aggressive local or regional disease patterns (14).

Elevated monocyte-to-lymphocyte ratio (MLR), a CBC-derived value, is another CBC-derived value proposed as an independent prognostic factor across cancers (13). In PSCC research cohorts, reduced LMR may indicate a skewing toward a microenvironment dominated by macrophages, which typically favors tumor facilitation over elimination. Platelets themselves transport proangiogenic and antiangiogenic factors within their granules and microparticles (15).

CRP belongs to the pentraxin family of proteins and is categorized as an acute-phase reactant, with production predominantly occurring in hepatocytes under stimulation by proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 $\beta$  (IL-1 $\beta$ ), and tumor necrosis factor- $\alpha$ . Under conditions of infection, trauma, or malignancy, circulating CRP levels can rise profoundly, sometimes exceeding baseline by over 1000-fold, in a relatively short timeframe (16, 17). In PSCC studies investigating prognostic markers, threshold values above 15 mg/L have been associated with increased nodal disease incidence and reduced cancer-specific survival (18). Lower but persistently elevated ranges, for example above 5 mg/L, have been incorporated into multi-factor prognostic scoring models alongside surgical margin status and pathological stage to stratify patient mortality risk (16).

Tumor-associated macrophages, malignant keratinocytes, and reactive stromal fibroblasts secrete IL-6 continuously, maintaining hepatic CRP synthesis without reverting to basal levels (1). Unlike infection-mediated acute peaks that resolve as pathogens are cleared, malignancy-associated CRP elevation can remain stable or fluctuate at moderately high levels depending on ongoing tumor activity and metastatic spread. This chronicity imbues CRP readings with prognostic relevance: persistent concentrations above modest thresholds have correlated with reduced disease-specific survival and advanced pathological stages in genitourinary cancers including PSCC (19). In patients with PSCC, correlations have been observed between elevated pre-treatment CRP and adverse clinical indicators such as extranodal extension or bilateral pelvic lymph node metastasis (20).

Elevated neutrophil-to-lymphocyte ratio (NLR) values have been repeatedly associated with adverse outcomes, such as reduced overall survival (OS) or cancer-specific survival (CSS), though the strength of these associations may diminish after adjustment for established pathological factors, such as tumor grade, lymph vascular invasion, and clinical nodal status (21). The platelet-to-lymphocyte ratio (PLR) shows similar trends, with higher values generally observed among individuals with extranodal extension or advanced TNM staging. In smaller PSCC cohorts, PLR elevation is associated with worse OS, complementing the picture presented by NLR but with a slightly different biological emphasis, capturing platelet-driven microenvironment changes coupled with adaptive immune suppression. While precise cut-off thresholds vary across reports due

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to population and assay differences, values exceeding 133.5 have been proposed via receiver operating characteristic curve analysis for stratifying risk before surgical intervention (13).

While the systemic indices discussed earlier capture host inflammatory status in a relatively accessible way, they remain indirect proxies for intratumorally events. Recent advances in molecular pathology have reclassified penile neoplasms into discrete biological subtypes based on HPV status, gene mutations, and protein expression profiles (12). By overlaying CBC- or CRP-derived inflammatory metrics onto these molecular categories, it becomes possible to examine whether specific genomic contexts consistently produce certain systemic inflammatory phenotypes. For example, an elevated neutrophil-to-lymphocyte ratio (NLR) might align more with TP53-mutated, HPV-negative tumors characterized by high PD-L1 expression, reflecting immunosuppressive microenvironments that weaken adaptive immune surveillance (22).

## CONCLUSIONS

Penile squamous cell carcinoma presents unique challenges due to its multifactorial etiology and the intricate interplay between tumor biology and host immune responses. The integration of complete blood count-derived inflammatory markers such as NLR, platelet-to-lymphocyte ratio, and MLR, alongside C-reactive protein measurements, offers a promising avenue for enhancing prognostic assessment and clinical management. These biomarkers provide accessible, minimally invasive, and cost-effective tools that reflect systemic inflammation and immune dysregulation associated with tumor progression, nodal metastasis, and survival outcomes.

## CONFLICT OF INTEREST AND FUNDING

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