

ORIGINAL RESEARCH ARTICLE

Systemic inflammation and risk stratification
in pheochromocytoma: Insights from PASS
components, TNM stage, and the tumor
immune microenvironment

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Abstract

Introduction: The Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) and Tumor–Node–Metastasis (TNM) staging capture histopathological and anatomical risk features in adrenal pheochromocytoma, but do not incorporate systemic inflammation.

Objectives: To investigate the associations of preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) with individual PASS components and American Joint Committee on Cancer TNM stage in adrenal pheochromocytoma.

Methods: We retrospectively screened 62 patients; after predefined exclusions, 55 patients with adrenal pheochromocytoma were included. Clinical characteristics, tumor size, urinary metanephrine and normetanephrine levels, PASS components, TNM stage, and preoperative blood counts were recorded. Associations of NLR and PLR with PASS components were assessed using univariate logistic regression, with Benjamini–Hochberg correction across the 12 component-level analyses. NLR and PLR were also compared between Stage I/II and Stage III/IV disease.

Results: After Benjamini–Hochberg correction, associations of NLR with vascular invasion and high cellularity were attenuated, whereas those with capsular invasion, large nests or diffuse growth, tumor necrosis, atypical mitosis, and mitotic activity > 3/10 high-power fields remained significant. NLR was higher in Stage III/IV than Stage I/II disease (median: 3.85; range: 2.17–6.73 vs. median: 2.59; range: 1.52–5.48, $p = 0.019$). PLR was associated with PASS ≥ 6 in the unadjusted analysis but not with individual PASS components and did not differ by stage.

Conclusion: Higher preoperative NLR was associated with selected PASS components and Stage III/IV disease in adrenal pheochromocytoma. These exploratory findings require validation in larger multicenter cohorts and should not be interpreted as evidence of independent prognostic value.

Keywords: Pheochromocytoma; Paraganglioma; Tumor microenvironment; Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Pheochromocytoma of the Adrenal Gland Scaled Score; Tumor–Node–Metastasis classification

1. Introduction

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors originating from chromaffin cells of the adrenal medulla and extra-adrenal paraganglia, respectively. Despite advances in understanding their molecular and histopathological characteristics, no definitive single biomarker or histological parameter can reliably predict malignancy in the absence of metastasis.¹ Consequently, numerous investigations have evaluated various histopathological and molecular markers to improve the prediction of metastasis and prognosis in PPGL patients, even before the widespread adoption of the Pheochromocytoma of the Adrenal Gland Scaled Score (PASS).^{2,3} Following the introduction of PASS, markers such as the Ki-67 index and immunohistochemical staining for succinate dehydrogenase B and PS 100 have been integrated into subsequent prognostic assessments. These markers have contributed to the development of refined scoring systems, including the Grading System for Adrenal Pheochromocytoma and Paraganglioma (GAPP), the modified GAPP, and the Composite Pheochromocytoma/Paraganglioma Prognostic Score (COPPS).⁴ Together with histopathological features such as cellularity, comedo-type necrosis, capsular and vascular invasion, growth pattern, and catecholamine phenotype, these systems provide complementary information on tumor biology and the tumor microenvironment (TME).^{5,6} Given the interobserver variability associated with PASS, subsequent scoring systems, including GAPP and COPPS, have been proposed to improve risk stratification. Nevertheless, the prediction of metastatic potential and survival remains challenging because PPGLs exhibit highly variable clinical behavior.^{7,8}

The 2017 and 2022 World Health Organization classifications recommend that all PPGLs be regarded as potentially malignant tumors and endorse the tumor–node–metastasis (TNM) system established by the American Joint Committee on Cancer (AJCC) for prognostic staging.^{1,9} Nevertheless, uncertainty persists within the current TNM framework. The distinction between T1 and T2 categories remains debated, and survival outcomes may overlap within stage pairs, particularly between Stages I and II and between Stages III and IV, indicating a need for additional reliable markers that may improve risk stratification.^{10,11}

These uncertainties are especially relevant when a study focuses on tumor-level features rather than long-term survival. In routine practice, many pheochromocytomas are completely resected with no evidence of metastasis, leaving clinicians with histopathological and anatomical findings that suggest risk but do not establish malignancy. PASS, GAPP, COPPS, and TNM staging address this uncertainty from different perspectives; however, none of these systems fully captures the interaction between tumor morphology, host response, and systemic inflammation. For this reason, evaluating inflammatory markers alongside established morphological and staging variables may provide a complementary perspective on tumor biology at the time of initial diagnosis.

Accordingly, the present study did not evaluate malignancy as a binary histological outcome or examine long-term prognosis. Instead, it investigated the associations of preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) with individual PASS components and AJCC TNM staging, including a comparison of Stage I/II with Stage III/IV disease.

In this context, systemic inflammatory markers may provide complementary biological insight because inflammation is linked to tumor behavior and prognosis across various cancers.¹² Inflammation within the TME is a hallmark of cancer. Components of the TME, including cancer-associated fibroblasts, tumor-associated macrophages, and inflammatory cytokines, can promote tumor growth, angiogenesis, invasion, and tumor survival.¹³

Peripheral inflammatory indices such as NLR and PLR are attractive in this setting because they are inexpensive, routinely available before surgery, and reflect different aspects of systemic inflammation. NLR may represent the balance between neutrophil-associated inflammatory activity and lymphocyte-mediated immune surveillance, whereas PLR may reflect platelet-related inflammatory and pro-angiogenic signaling in addition to lymphocyte status. These indices are nonspecific and may be influenced by several non-tumor conditions; nevertheless, when interpreted carefully, they may provide hypothesis-generating information on tumor–host interactions. We therefore examined NLR and PLR as accessible systemic correlates of established histopathological and anatomical

features rather than as stand-alone prognostic biomarkers.

The focus on adrenal pheochromocytoma was intentional. Because PASS was developed specifically for adrenal pheochromocytoma, and AJCC T-category definitions differ between adrenal pheochromocytoma and sympathetic paraganglioma, NLR and PLR were evaluated as complementary markers of systemic inflammation in relation to pheochromocytoma-specific pathological and anatomical features, rather than as generic neuroendocrine tumor biomarkers or direct measures of the local tumor immune microenvironment.

Previous studies in pheochromocytoma have reported associations between prognosis and a heightened systemic inflammatory state; however, evidence relating peripheral inflammatory markers to clinical outcomes in PPGLs remains limited.^{14,15} In our previous retrospective two-center cohort study, 88 patients were screened, and 74 patients with histologically confirmed pheochromocytoma or paraganglioma were included, with a median follow-up of 84 months. Prognostic cutoffs of $\text{NLR} > 3.43$ and $\text{PLR} > 193.1$ were identified, and combinations of $\text{PASS} \geq 6$ with elevated NLR or PLR were associated with adverse outcomes.¹⁶ In contrast, the present study included 55 patients with adrenal pheochromocytoma and examined the associations of these inflammatory indices with individual PASS components and with AJCC TNM stage, rather than with prognosis.

Given the limited evidence regarding the relationships between NLR and PLR and individual PASS components and TNM stage, we aimed to investigate these associations in adrenal pheochromocytoma. We hypothesized that higher preoperative NLR and PLR would be associated with selected histopathological features and a more advanced TNM stage.

2. Materials and methods

2.1. Study design and population

Patients with histologically confirmed PPGLs diagnosed between 2007 and 2024 were retrospectively screened. After excluding patients with paragangliomas ($n = 3$), long-term glucocorticoid use ($n = 1$), preoperative infection ($n = 1$), incomplete PASS data, or unavailable data required for TNM staging ($n = 2$), the final analytic cohort comprised 55 patients with adrenal pheochromocytoma.

Long-term glucocorticoid exposure was excluded because it may cause neutrophilia and lymphopenia, thereby artificially increasing NLR independently of tumor-associated inflammation. Preoperative infection was also excluded because it may alter inflammatory indices independently of tumor biology. Similarly, excluding cases

with incomplete PASS or TNM information ensured that all included patients contributed to the component-level and stage-based analyses.

This retrospective study used an all-eligible-case design. The sample size was determined by the number of patients treated during the predefined 2007–2024 study period who met the eligibility criteria and had complete data for the principal analyses. No a priori power analysis was performed to define a prospective recruitment target. All eligible cases were included because pheochromocytoma is rare, and the available number of patients with complete pathological, preoperative hematological, and staging data was limited. A post hoc sensitivity analysis was subsequently performed to characterize the detectable effect size for the Stage I/II versus Stage III/IV comparison, as described in Section 2.3.

All data were collected from the electronic clinical database. Patient demographics, laboratory, radiological, and histopathological variables were recorded. Complete blood counts, including absolute neutrophil, platelet, and lymphocyte counts, were obtained within one month before surgery. Metastatic disease was defined by radiological confirmation on computed tomography and/or magnetic resonance imaging at diagnosis or during follow-up. PASS components were extracted from the original pathology reports. Archival slides were not formally re-reviewed by a study pathologist blinded to NLR and PLR; consequently, interobserver agreement statistics were unavailable.

Pathology reports were reviewed to extract both the total PASS score and the presence or absence of each individual PASS component. When available, operative, radiological, and follow-up records were cross-checked to assign anatomical stage and document local recurrence, metastatic recurrence, and disease-specific mortality. This approach allowed evaluation of the inflammatory indices against predefined pathological and anatomical variables rather than against nonspecific clinical outcomes alone. No additional immunohistochemical or tissue-based immune analyses were performed on archival samples.

The study protocol was approved by the Ethics Committee of Katip Çelebi University in Izmir, Turkey, and complied with the Declaration of Helsinki (approval no. 0117; September 19, 2024). The Institutional Review Board (IRB) waived the requirement for informed consent because of the retrospective design. Data were extracted from hospital records and anonymized before analysis.

2.2. Method

Paragangliomas were excluded to maintain a homogeneous adrenal pheochromocytoma cohort. In adrenal pheochromocytoma, the T1/T2 distinction is based

on a 5-cm tumor size threshold, whereas sympathetic paraganglioma is classified as T2 irrespective of size in the absence of invasion. This was particularly important because the present study also focused on the AJCC TNM stage. Including paragangliomas in the analysis could therefore have introduced staging heterogeneity despite their common classification with pheochromocytomas as PPGLs. The remaining exclusions are described in Section 2.1.

Preoperative NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Preoperative PLR was calculated by dividing the platelet count by the absolute lymphocyte count; all component counts were expressed in $\times 10^3/\mu\text{L}$.

Clinical variables were age, gender, primary tumor size and localization, and urinary metanephrine and normetanephrine levels. Tumor size was defined as the largest macroscopic diameter of the gross surgical specimen recorded in the final pathology report. The total PASS score, individual PASS components, and TNM stage were recorded. In accordance with the PASS system, high mitotic activity was defined as > 3 mitotic figures per 10 high-power fields (HPFs). Patients with metastasis on imaging at diagnosis or during follow-up were considered as having malignant disease, irrespective of PASS score. The PASS components and scoring system are summarized in [Table A1](#), and the AJCC TNM categories and stage grouping used in this study are summarized in [Table A2](#).

The T categories (T1–T3) describe grading features of the primary tumor, whereas stage groups (I–IV) describe the anatomical extent of disease. Periadrenal adipose tissue invasion was classified as T3 according to the AJCC TNM system, whereas a tumor diameter of 5 cm was used as the cutoff for distinguishing T1 from T2 tumors. For analysis, patients were grouped into Stage I/II or Stage III/IV based on the presence of invasion, nodal disease, or distant metastasis.¹⁰

Stages I and II, which differed only in tumor size and in the absence of local invasion, nodal disease, or distant metastasis, comprised the non-invasive group. Stages III and IV, defined by local invasion and/or nodal or distant metastatic disease, comprised the invasive/metastatic group. Metastatic disease was confirmed using computed tomography and/or magnetic resonance imaging at diagnosis or during follow-up. Available urinary catecholamine metabolite measurements and follow-up imaging findings were recorded.

2.3. Statistical analysis

Patients with missing data for the core analytic variables, including preoperative blood counts, PASS components,

or TNM stage, were excluded. Variables that were not systematically available across the entire cohort, such as genetic testing, were presented descriptively and excluded from inferential analyses.

Variable distributions were assessed using the Kolmogorov–Smirnov test. Continuous variables were presented as median (range) when non-normally distributed and mean $\pm$ standard deviation when normally distributed. Categorical variables were presented as n (%). Continuous variables were compared using the Mann–Whitney U test or independent-samples t test, as appropriate, and categorical variables using the χ^2 test or Fisher's exact test, as appropriate. Univariate logistic regression was used to assess the associations between NLR and PLR and individual PASS components and composite PASS thresholds.

The primary analyses were exploratory and evaluated the associations of preoperative inflammatory indices with individual PASS components and AJCC TNM stage. Longitudinal outcomes, such as subsequent metastasis, recurrence, disease-specific mortality, and survival, were not modeled. A multivariable model for Stage III/IV disease was not performed because only eight patients were in this group; including NLR alongside age, tumor size, and other covariates would have created a substantial risk of overfitting and unstable estimates. The small total cohort also precluded a reliable and uniform adjusted modeling strategy across multiple component-specific analyses. Accordingly, the PASS-component findings were reported as unadjusted associations and should not be interpreted as evidence that NLR or PLR is independently associated with pathological features or has prognostic value.

Because no a priori sample size calculation was performed, a post hoc sensitivity analysis was conducted to characterize the between-group difference detectable with the available sample size. With 47 patients in the Stage I/II and 8 in the Stage III/IV, assuming a two-sided α of 0.05 and 80% power, the study could detect a standardized effect size of approximately Cohen's $d = 1.09$. Thus, the stage-group comparison could detect only a large between-group difference. This calculation applied only to the stage-group comparison and not to the individual PASS-component logistic regression analyses. A statistically significant p -value in this setting indicated a detectable within-cohort difference, but did not ensure that the magnitude of the association was precise or reproducible, whereas a nonsignificant p -value cannot exclude a small-to-moderate association.

To control the false discovery rate across individual PASS-component analyses, the Benjamini–Hochberg procedure was applied separately to the 12 NLR and 12

PLR comparisons. Both unadjusted p -values and adjusted q -values were reported. Composite PASS thresholds were excluded from this correction because they are derived summary cutoffs rather than individual histopathological components. A two-sided $p < 0.05$ was considered statistically significant in unadjusted analyses, and $q < 0.05$ after Benjamini–Hochberg correction.

3. Results

3.1. Study population

Because paragangliomas were excluded, the term pheochromocytoma was used exclusively to refer to adrenal medullary tumors in this cohort; PPGL was used only when discussing broader classifications or previous studies that included both tumor types.

The study cohort consisted of 55 patients diagnosed with pheochromocytoma. The median age was 48 years, with a slight predominance of female patients (58.1%). Hypertension was present in 41 patients (74.5%). Median tumor size was 60 mm, and median PASS score was 4. The majority of the patients had a Stage II tumor according to the TNM classification (58.2%). Metastatic disease at diagnosis was present in 3.6% of patients. Metastatic recurrence (1.8%) and local recurrence (1.8%) each occurred in one patient (Table 1).

Overall, the cohort was dominated by non-invasive disease, with a small number of patients classified as Stage III or Stage IV. This distribution is consistent with the clinical frequency that invasive or metastatic pheochromocytoma is uncommon, limiting the precision of stage-based comparisons. Accordingly, the stage-based findings were interpreted together with the individual PASS-component analyses rather than as independent prognostic evidence.

Pheochromocytoma-related mortality was defined as death directly attributable to progressive or metastatic pheochromocytoma or to perioperative complications of adrenalectomy for pheochromocytoma. All deaths, regardless of cause, were included in all-cause mortality.

During a median follow-up of six years, nine patients (16.3%) died. Causes included gastric, endometrial, lung, and breast malignancies; urosepsis; cardiovascular disease; and postoperative complications after hemangioblastoma resection in a patient with von Hippel–Lindau disease. Two deaths (3.6% of the cohort; 22.2% of all deaths) were pheochromocytoma-related: one followed postoperative complications of adrenalectomy, and the other resulted from progression of residual invasive pheochromocytoma after partial resection.

Table 1. Characteristics of the patients

Characteristics	Value
Total patients (n)	55
Age (years [median], range)	48 (19–79)
Sex (female/male)	32/23
Tumor size (mm)	60 (24–140)
PASS score	4 (0–19)
AJCC TNM stage	
Stage I (n , %)	15 (27.3%)
Stage II (n , %)	32 (58.2%)
Stage III (n , %)	6 (10.9%)
Stage IV (n , %)	2 (3.6%)
Metastasis at diagnosis (n , %)	2 (3.6%)
Metastatic recurrence (n , %)	1 (1.8%)
Local recurrence (n , %)	1 (1.8%)
All-cause mortality (n , %)	9 (16.3%)
Follow-up, median years (range)	6 (0–17)
Urinary normetanephrine, median (range), $\mu\text{g/day}$	5,313 (247–25,412)
Urinary metanephrine, median (range), $\mu\text{g/day}$	3,736 (24–29,458)
	MEN2A (7)
Available genetic/syndromic findings ($n = 10$)	<i>NFI</i> (1)
	<i>VHL</i> (1)
	<i>ATRX</i> mutation (1)
History of hypertension (n , %)	41 (74.5%)

Notes: The TNM stage was assigned at the time of primary tumor diagnosis according to the AJCC criteria;¹ genetic and syndromic findings are reported from available clinical and genetic records; genetic testing was not performed systematically; therefore, these findings are descriptive.

Abbreviations: AJCC: American Joint Committee on Cancer; MEN2A: Multiple endocrine neoplasia type 2A; PASS: The Pheochromocytoma of the Adrenal Gland Scaled Score; TNM: Tumor–node–metastasis.

Among the 10 patients with available genetic or syndromic data, seven had multiple endocrine neoplasia type 2A, one had neurofibromatosis type 1, one had von Hippel–Lindau disease, and one had an *ATRX* mutation.

3.2. Associations of preoperative neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with PASS components

Univariate logistic regression analysis was used to assess

the associations of NLR and PLR with PASS components. In unadjusted analyses, higher NLR was significantly associated with vascular invasion (odds ratio [OR]: 1.8, 95% confidence interval [CI]: 1.0–3.2, $p = 0.042$), capsular invasion (OR: 2.1, 95% CI: 1.2–3.7, $p = 0.012$), high cellularity (OR: 1.8, 95% CI: 1.0–3.0, $p = 0.037$), large nests or diffuse growth (OR: 2.0, 95% CI: 1.1–3.6, $p = 0.016$), tumor necrosis (OR: 2.6, 95% CI: 1.3–5.4, $p = 0.010$), atypical mitosis (OR: 3.0, 95% CI: 1.2–7.2, $p = 0.013$), and mitotic activity $> 3/10$ HPF (OR: 2.3, 95% CI: 1.2–4.1, $p = 0.009$). After Benjamini–Hochberg correction across the 12 individual component analyses, associations with capsular invasion, large nests or diffuse growth, tumor necrosis, atypical mitosis, and mitotic activity $> 3/10$ HPF remained significant (all $q = 0.038$), whereas associations with vascular invasion and high cellularity were attenuated (both $q = 0.072$). Higher NLR was also associated with PASS thresholds of ≥ 4 , ≥ 5 , and ≥ 6 in unadjusted analyses. PLR was not associated with any individual PASS component after correction but was associated with PASS ≥ 6 in the unadjusted analysis (OR: 1.01, 95% CI: 1.00–1.02, $p = 0.010$) (Table 2).

The correction for multiple comparisons, therefore, narrowed the most robust NLR-related signals to selected PASS components reflecting invasion, growth pattern, necrosis, and mitotic activity. This distinction was important for interpretation: the unadjusted associations suggested a broader relationship between NLR and several PASS items, whereas the corrected analyses identified a smaller set of findings that were less likely to reflect false-positive results from multiple testing. Several OR estimates, particularly those for atypical mitosis and the composite PASS thresholds, were accompanied by wide 95% CIs.

3.3. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio according to tumor stage

Age, sex, and urinary metanephrine and normetanephrine levels did not differ significantly between the Stage I/II and Stage III/IV groups. Tumors were larger in the Stage III/IV group ($p = 0.048$) (Table 3). NLR and PLR showed right-skewed distributions in both stage groups, particularly for PLR; however, these patterns should be interpreted descriptively, as only eight patients had Stage III/IV disease.

Figure 1 compares the median and range of inflammatory indices between non-invasive Stage I/II and invasive/metastatic Stage III/IV disease. Median NLR was significantly higher in the Stage III/IV group (3.85 [2.17–6.73] vs. 2.59 [1.52–5.48], $p = 0.019$), whereas median PLR did not differ significantly (224.31 [90.91–413.73] vs. 161.20 [67.25–409.00], $p = 0.396$) (Figure 1A and 1B).

Figure 2 shows median NLR and PLR across individual

TNM stages. Median NLR tended to increase with advancing stage, whereas PLR showed no consistent stage-related pattern (Figure 2A and 2B).

4. Discussion

In the present study, we evaluated the associations among preoperative systemic inflammatory indices and established histopathological and anatomical risk features in patients with adrenal pheochromocytoma. Higher NLR was associated with several individual PASS components in unadjusted analyses. After correction for multiple testing, the associations with capsular invasion, large nests or diffuse growth, tumor necrosis, atypical mitosis, and mitotic activity $> 3/10$ HPF remained significant, whereas the associations with vascular invasion and high cellularity were attenuated. NLR was also significantly higher in patients with Stage III/IV than Stage I/II disease. PLR was associated with PASS ≥ 6 in the unadjusted analysis but not with individual PASS components after correction and did not differ by stage. Because paragangliomas were excluded, these findings apply specifically to adrenal pheochromocytoma.

These findings do not indicate that NLR can diagnose malignant behavior or replace pathological assessment and anatomical staging. Rather, they suggest that systemic inflammatory imbalance may accompany selected tumor features used in pheochromocytoma risk assessment. By examining individual PASS components rather than the total score alone, the study provides a more granular view of the morphological features associated with NLR. The present analysis should be distinguished from a longitudinal prognostic study. Preoperative NLR and PLR were evaluated in relation to pathological features identified in the resected tumor and to the anatomical extent of disease, as represented by the AJCC TNM stage. Longitudinal outcomes—including subsequent metastasis, recurrence, disease-specific mortality, and survival—were not modeled; therefore, the present analysis neither tests nor establishes the prognostic value of NLR or PLR.

In the original clinicopathological and immunophenotypic study of PASS, several histopathological features, including tumor necrosis, atypical mitosis, and mitotic activity $> 3/10$ HPF, were observed in malignant pheochromocytomas, supporting their relevance as morphological indicators of aggressive tumor biology.¹⁷ In the present study, higher preoperative NLR remained significantly associated with capsular invasion, large nests or diffuse growth, tumor necrosis, atypical mitosis, and mitotic activity $> 3/10$ HPF after Benjamini–Hochberg correction. In contrast, the unadjusted associations with vascular invasion and high cellularity were attenuated after

Table 2. Univariate logistic regression analysis of associations of NLR and PLR with PASS parameters, including Benjamini–Hochberg false discovery rate correction

PASS components	NLR				PLR			
	Beta	OR (95% CI)	<i>p</i>	<i>q</i>	Beta	OR (95% CI)	<i>p</i>	<i>q</i>
Vascular invasion	0.59	1.8 (1.0–3.2)	0.042	0.072	0.001	1.00 (0.99–1.01)	0.859	0.859
Capsular invasion	0.73	2.1 (1.2–3.7)	0.012	0.038	0.003	1.00 (0.99–1.01)	0.442	0.589
Profound nuclear polymorphism	0.24	1.3 (0.8–2.1)	0.322	0.341	0.005	1.01 (1.00–1.02)	0.170	0.408
Nuclear hyperchromasia	0.53	1.7 (1.0–2.9)	0.051	0.077	0.006	1.01 (1.00–1.02)	0.120	0.360
High cellularity	0.56	1.8 (1.0–3.0)	0.037	0.072	0.007	1.01 (1.00–1.02)	0.079	0.360
Large nests or diffuse growth	0.71	2.0 (1.1–3.6)	0.016	0.038	0.004	1.00 (0.99–1.01)	0.238	0.420
Cellular monotony	0.34	1.4 (0.7–2.8)	0.341	0.341	0.006	1.01 (1.00–1.02)	0.277	0.420
Tumor cell spindling	0.39	1.5 (0.9–2.5)	0.129	0.172	0.008	1.01 (1.00–1.02)	0.060	0.360
Tumor necrosis	0.96	2.6 (1.3–5.4)	0.01	0.038	0.008	1.01 (1.00–1.02)	0.098	0.360
Atypical mitosis	1.10	3 (1.2–7.2)	0.013	0.038	0.005	1.00 (0.99–1.01)	0.591	0.709
Mitotic activity > 3/10 HPF	0.81	2.3 (1.2–4.1)	0.009	0.038	0.005	1.01 (1.00–1.02)	0.280	0.420
Extension into adipose tissue	0.50	1.7 (1.0–3.3)	0.151	0.181	0.002	1.01 (1.00–1.02)	0.785	0.856
PASS score ≥ 6	1.22	3.4 (1.6–7.0)	0.001	–	0.012	1.01 (1.00–1.02)	0.010	–
PASS score ≥ 5	1.43	4.2 (1.9–9.6)	< 0.001	–	0.006	1.00 (0.99–1.01)	0.130	–
PASS score ≥ 4	1.53	4.6 (1.8–11.9)	00.002	–	0.005	1.00 (0.99–1.01)	0.240	–

Notes: *q* values are Benjamini–Hochberg false discovery rate-adjusted *p*-values calculated separately for NLR and PLR across the 12 individual PASS-component analyses; composite PASS thresholds were not included in this correction because they are derived summary cutoffs rather than individual histopathological components.

Abbreviations: CI: Confidence interval; HPF: High-power field; NLR: Neutrophil-to-lymphocyte ratio; OR: Odds ratio; PASS: The Pheochromocytoma of the Adrenal Gland Scaled Score; PLR: Platelet-to-lymphocyte ratio.

Table 3. Demographic, pathological, and laboratory characteristics according to TNM stage group

Characteristics	Stage I/II (<i>n</i> = 47)	Stage III/IV (<i>n</i> = 8)	<i>p</i>
Age	48 (19–79)	41 (21–75)	0.519
Sex (female/male)	27/20	5/3	>0.999
Tumor size (mm)	55 (24–140)	82 (40–100)	0.048
Normetanephrine (µg/day)	2,604 (310–25,412)	4,478 (247–11,345)	0.637
Metanephrine (µg/day)	956 (45–29,458)	153 (24–3,724)	0.228
PASS score	4 (0–10)	11 (1–19)	<0.001
NLR	2.59 (1.52–5.48)	3.85 (2.17–6.73)	0.019
PLR	161.2 (67.25–409)	224.31 (90.91–413.73)	0.396

Note: TNM stage was assigned at diagnosis of the primary tumor in accordance with the American Joint Committee on Cancer guidelines.¹

Abbreviations: NLR: Neutrophil-to-lymphocyte ratio; PASS: The Pheochromocytoma of the Adrenal Gland Scaled Score; PLR: Platelet-to-lymphocyte ratio; TNM: Tumor–node–metastasis.

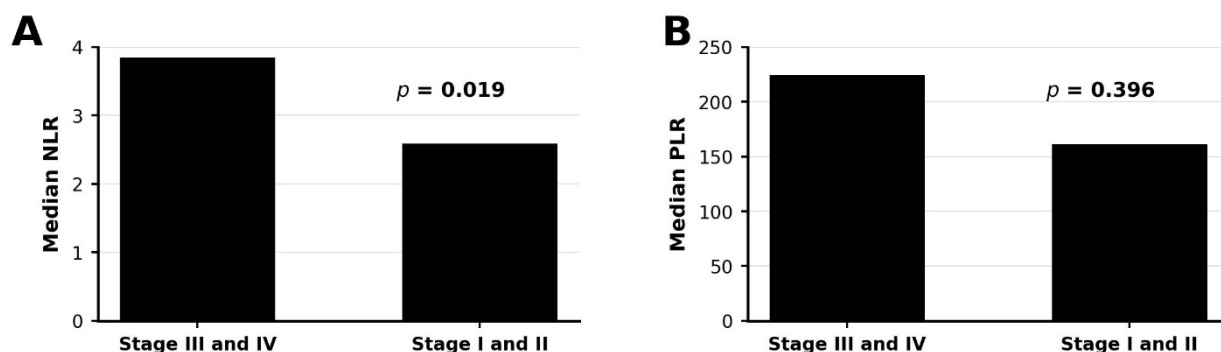


Figure 1. Bar graphs showing median NLR (A) and median PLR (B) according to tumor-node-metastasis stage grouping. NLR was significantly higher in patients with Stage III/IV disease than in those with Stage I/II disease, whereas PLR did not differ significantly. Abbreviations: NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

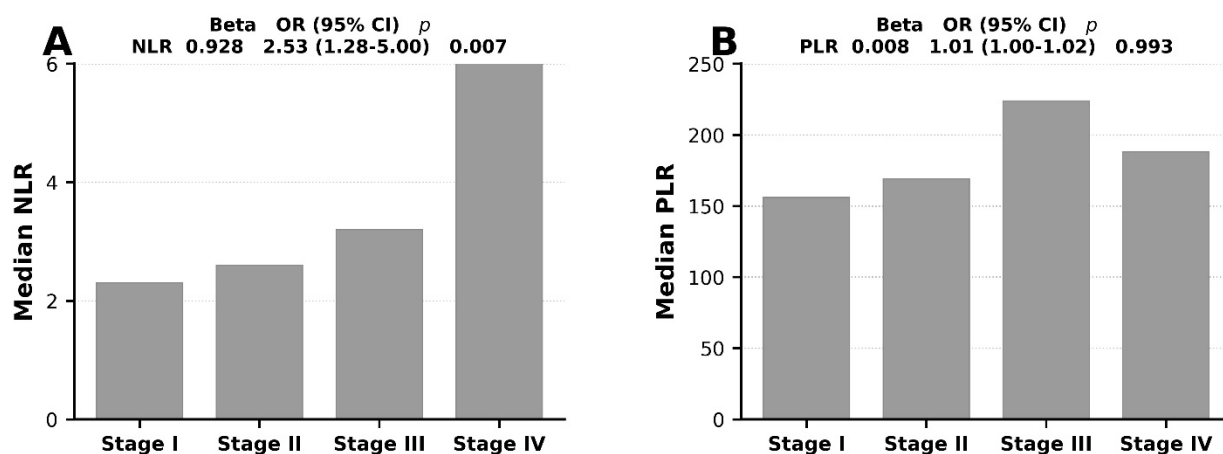


Figure 2. Bar graphs showing median NLR (A) and median PLR (B) across Stage I-IV disease. Median NLR increased with advancing stage, whereas PLR showed no consistent stage-related pattern.

Abbreviations: CI: Confidence interval; NLR: Neutrophil-to-lymphocyte ratio; OR: Odds ratio; PLR: Platelet-to-lymphocyte ratio.

correction. Although these histopathological findings are not direct measures of the TME, features such as necrosis, invasion, diffuse growth, and increased mitotic activity may provide morphological context for tumor-host interactions and local inflammatory processes.

The prognostic assessment of pheochromocytoma remains challenging. Metastatic disease is the only unequivocal evidence of malignancy, and current classifications regard all PPGLs as having metastatic potential rather than dividing them simply into benign and malignant categories.¹ Uncertainty also remains within the TNM framework because T1 and T2 category definitions differ between sympathetic paragangliomas and adrenal pheochromocytomas, while survival outcomes may overlap between Stage I and Stage II, as well as between Stage III and Stage IV.¹⁰ The present study evaluated tumor-

level histopathological and anatomical features rather than survival-based outcomes. NLR should therefore be interpreted as a systemic inflammatory correlate of selected PASS components and TNM stage, not as an independent diagnostic or prognostic biomarker.

Interpretation of PPGL outcomes depends on integrating clinical, operative, pathological, staging, genetic, and follow-up data. The International Collaboration on Cancer Reporting recommends standardized checklist-based reporting to ensure harmonized documentation of elements relevant to management, staging, prognosis, and research.¹⁸ Consistent with this approach, we evaluated preoperative NLR and PLR in relation to routinely reported pathological and anatomical features. Because pheochromocytoma-related mortality occurred in only two patients (3.6%) and genetic data were not systematically

available, mortality-based or genotype-based prognostic analyses were not performed.

From a morphological perspective, the PASS components that remained associated with NLR after correction are biologically plausible. Tumor necrosis may reflect rapid growth, vascular insufficiency, and local tissue injury, which can amplify inflammatory signaling. Atypical mitosis and increased mitotic activity indicate proliferative stress and may coexist with cellular injury or altered immune surveillance. Large nests or diffuse growth patterns may reflect architectural disorganization and expansion of tumor-cell populations, whereas capsular invasion represents interaction with surrounding tissue boundaries. Although these features do not directly demonstrate immune infiltration, their associations with NLR support a possible link between systemic inflammation and aggressive tumor morphology.

The biological rationale for these findings may be considered within the broader framework of tumor-associated inflammation. Inflammation is a recognized hallmark of cancer and may contribute to tumor growth, angiogenesis, invasion, immune escape, and metastatic progression.¹⁹ NLR is generally considered to reflect the balance between neutrophil-driven pro-tumor inflammatory activity and lymphocyte-mediated antitumor immune surveillance. Although the TME was not directly evaluated, associations between NLR and selected PASS components may reflect systemic inflammatory correlates of tumor morphology rather than direct evidence of local immune infiltration.²⁰ Mechanistically, elevated NLR may reflect a systemic inflammatory state characterized by neutrophil predominance and relative lymphopenia. Neutrophils can contribute to tumor progression through cytokine release, angiogenic signaling, extracellular matrix remodeling, and suppression of antitumor immune responses, whereas reduced lymphocyte-mediated surveillance may indicate impaired immune surveillance. The associations with necrosis, invasion, diffuse growth, and increased mitotic activity may represent an indirect link between systemic inflammation and aggressive tumor morphology. However, these findings should be interpreted as hypothesis-generating rather than direct evidence of a local immune mechanism in the absence of tissue-based immune profiling.

In many cancers, systemic inflammatory indices such as NLR have been associated with adverse oncological outcomes, although their interpretation remains tumor- and context-dependent.²¹ PPGL-specific immune studies also support the biological plausibility of an interaction between systemic inflammation and tumor behavior. Immune cells can infiltrate the PPGL TME, indicating that

these tumors are not immunologically inert.²² Nevertheless, PPGLs are often described as relatively “cold” tumors, characterized by limited tumor-infiltrating lymphocytes, low antigenicity, and/or immune exclusion, whereas “hot” tumors exhibit more abundant immune-cell infiltration and active local inflammatory signaling.²³ Recent immune-landscape studies have linked aggressive or metastatic PPGLs to differences in macrophage polarization, T-cell composition, and immune signatures.²⁴ NLR, however, measures the balance between circulating neutrophils and lymphocytes and does not directly characterize the local immune context. A pheochromocytoma may therefore remain lymphocyte-poor or immunosuppressive within the tumor while being accompanied by systemic neutrophilia or relative lymphopenia. These PPGL studies provide a biological context rather than direct evidence for the present pheochromocytoma-specific cohort. Paired peripheral and tissue-based immune analyses are needed to clarify whether NLR reflects local tumor–host immune interactions.

Beyond its association with individual PASS components, NLR was also evaluated by TNM stage, which captures the anatomical extent of disease and remains central to PPGL risk assessment. Current TNM staging provides important anatomical information, but several issues remain.²⁵ The prognostic significance of tumor size and the distinction between T1 and T2 categories remains debated, and survival outcomes may overlap between stages I and II and between stages III and IV.²⁶ In contrast, survival and recurrence differ clearly between non-invasive and invasive/metastatic disease.²⁷ In the present cohort, NLR was significantly higher in Stage III/IV than Stage I/II disease (3.85 vs. 2.59, $p = 0.019$), whereas PLR did not differ significantly ($p = 0.396$). Given the small number of advanced-stage cases, this association should be interpreted as exploratory.

The association patterns of NLR and PLR differed in this cohort. NLR was associated with several individual PASS components and Stage III/IV disease, whereas PLR was associated with PASS ≥ 6 but not with individual PASS components after multiple-testing correction or with TNM stage. Our previous study identified prognostic associations for both NLR- and PLR-based PASS combinations, although the estimated association was greater for the NLR-based combination.¹⁶ Comparative studies in other malignancies have also reported differences between the prognostic associations of NLR and PLR, with some showing stronger or more consistent associations for NLR; however, results vary by tumor type, clinical setting, and methodology.^{28–30} Because the present study did not formally compare effect estimates, model performance, or discriminatory ability, it

cannot establish the statistical or biological superiority of either index. These differing association patterns require validation in larger cohorts.

Although pheochromocytoma-specific evidence remains limited, prior PPGL studies suggest that peripheral inflammatory indices may serve as prognostic markers.¹⁵ The present study extends this concept by examining their associations with individual PASS components and TNM stage in adrenal pheochromocytoma.

Future studies should integrate peripheral inflammatory indices with standardized pathology, radiological staging, biochemical phenotype, genetic background, and direct immune profiling. Such an approach is particularly relevant in pheochromocytoma because metastatic behavior may emerge late and cannot always be inferred from a single histological feature at the time of surgery. Larger cohorts should first validate the associations between accessible blood-based markers and tumor morphology and then determine whether these associations correspond to tissue-level immune patterns or long-term outcomes. This would help distinguish nonspecific systemic inflammation from a reproducible biological signal related to tumor–host interaction.

The present study has several strengths. It specifically examined the relationship between preoperative systemic inflammatory indices and individual PASS components, rather than relying solely on the total PASS score, thereby enabling a more detailed assessment of tumor morphology. By evaluating both PASS components and TNM stage, the analysis integrated histopathological and anatomical dimensions of pheochromocytoma risk assessment. The use of routinely available preoperative indices also highlights a potential role for systemic inflammation in a tumor whose malignant potential is often uncertain at initial diagnosis.

The NLR may have a future role as a contextual inflammatory variable rather than an independent decision-making marker. Although the present study did not derive a clinical cutoff, our previous PPGL cohort identified NLR > 3.43 as a threshold associated with adverse prognosis. An elevated value should first be interpreted after excluding infection, glucocorticoid exposure, and other systemic inflammatory conditions. It may then be considered alongside tumor size, biochemical phenotype, genetic background, and findings from conventional computed tomography or magnetic resonance imaging. NLR alone should not trigger functional imaging or alter the surgical plan; however, when imaging is equivocal, or other findings raise concern for invasion or occult metastatic disease, it could reinforce the rationale for otherwise clinically indicated functional imaging, careful perioperative

staging, and standardized pathological assessment of invasion, necrosis, growth pattern, and mitotic activity. This proposed integration remains investigational and is not a validated management algorithm.

Several limitations should be considered. First, this was a retrospective, single-center, all-eligible-case study of a rare tumor, and no a priori sample-size or power calculation was performed. The final sample was determined by the number of eligible patients treated during the predefined study period who had complete preoperative hematological, pathological, and staging data. A post hoc sensitivity analysis indicated that, with 47 patients in the Stage I/II group and eight in the Stage III/IV group, the available cohort had 80% power to detect only a large standardized difference of approximately Cohen's $d = 1.09$. Therefore, the stage-related analysis was underpowered for small-to-moderate differences. The $p = 0.019$ observed for the NLR comparison should consequently be interpreted as exploratory rather than as a precise and reproducible estimate of the association with advanced-stage disease. Similarly, the nonsignificant PLR result should not be interpreted as evidence of no association, because a potentially relevant small-to-moderate difference may have remained undetected. The limited cohort also precluded reliable multivariable modeling of Stage III/IV disease and a uniform adjusted modeling strategy across multiple PASS-component analyses. A fully adjusted multivariable regression model could not be performed reliably without a substantial risk of overfitting. Because longitudinal events were not analyzed as outcomes, the study cannot determine whether NLR independently predicts future recurrence, metastasis, or disease-specific survival. Therefore, the present findings should be interpreted as exploratory associations between systemic inflammatory indices and tumor-level histopathological or anatomical features, rather than as evidence that NLR independently predicts aggressive pathology or clinical prognosis. Although blood counts were obtained according to predefined methodology, NLR and PLR remain nonspecific systemic inflammatory markers and should not be interpreted as tumor-specific measures. Genetic testing was not performed systematically, and missing data limited the feasibility of genotype-stratified analyses. Future studies should integrate germline and somatic genotyping with standardized pathological assessment and tissue-based characterization of the TME to determine whether genotype-specific immune profiles are associated with particular histopathological features and metastatic potential. Moreover, the tumor immune microenvironment was not directly assessed using tissue-based immune markers, immune-cell quantification, cytokine profiling, or transcriptomic analyses. Although

several NLR associations remained significant after Benjamini–Hochberg correction, they were exploratory and were not fully adjusted for potential confounders. In addition, the wide CIs around several OR estimates indicate limited precision and preclude individualized risk estimation. Finally, PASS components were extracted from routine pathology reports without centralized blinded slide re-review; interobserver-related misclassification may therefore have affected the magnitude and reproducibility of component-level associations.

Despite these limitations, preoperative NLR identified a systemic inflammatory profile associated with selected morphological and anatomical features. Larger multicenter studies integrating standardized pathology, direct immune profiling, genetic background, and longitudinal outcomes are needed to determine its biological and prognostic relevance.

5. Conclusion

Higher preoperative NLR was associated with selected PASS components and Stage III/IV disease in adrenal pheochromocytoma, whereas PLR was associated with $PASS \geq 6$ but not with individual PASS components after multiple-testing correction or with TNM stage. These findings identify a potential link between systemic inflammatory status and morphological and anatomical features relevant to the assessment of pheochromocytoma risk. NLR may provide an inexpensive, context-specific measure that supports careful radiological staging and standardized pathological evaluation; however, the present data do not establish its independent diagnostic or prognostic value or support its use as a direct surrogate for the tumor immune microenvironment. Larger multicenter studies integrating standardized pathology, genetic characterization, longitudinal outcomes, and tissue-based immune profiling are needed to clarify the biological and potential clinical significance of these associations.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Katip Çelebi University in Izmir, Turkey, and complied with the Declaration of Helsinki (Ethical approval number: 0117). The need for consent to participate was waived by the Institutional Review Board (IRB) due to the study's retrospective design. Data were extracted from hospital records and anonymized and de-identified before analysis.

Consent for publication

Not applicable.

Availability of data

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

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Appendix

Table A1. Pheochromocytoma of the Adrenal Gland Scaled Score (PASS)

Histopathological feature	Score if present
Large nests or diffuse growth pattern > 10% of tumor volume	2
Central or confluent tumor necrosis	2
High cellularity	2
Cellular monotony	2
Tumor cell spindling, even focal	2
Mitotic figures > 3/10 high-power fields	2
Atypical mitotic figures	2
Extension into adjacent adipose tissue	2
Vascular invasion	1
Capsular invasion	1
Profound nuclear pleomorphism	1
Nuclear hyperchromasia	1
Maximum possible score	20

Notes: PASS is calculated by summing the points assigned to each histopathological feature; a PASS ≥ 4 has classically been considered suggestive of potentially aggressive biological behavior, although PASS should not be interpreted as a definitive marker of malignancy in isolation; the diagnosis of malignant pheochromocytoma requires metastatic disease; the components and point allocation are based on Thompson's original PASS system.¹⁷

Table A2. AJCC 8th edition TNM classification and stage grouping for pheochromocytoma

Category	Definition
Primary tumor (T category)	
TX	The primary tumor cannot be assessed
T1	Pheochromocytoma < 5 cm in greatest dimension, without extra-adrenal invasion
T2	Pheochromocytoma ≥ 5 cm in greatest dimension, without extra-adrenal invasion
T3	Tumor of any size with invasion into surrounding organs or tissues
Regional lymph nodes (N category)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

(cont'd...)

Table A2. (Continued)

Category	Definition
Distant metastasis (M category)	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Distant metastasis to bone only
M1b	Distant metastasis to distant lymph nodes, liver, or lung only
M1c	Distant metastasis to bone plus multiple other sites
Stage grouping	
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T1, N1, M0; or T2, N1, M0; or T3, any N, M0
Stage IV	Any T, any N, M1

Notes: TNM categories and stage groups were summarized from the *AJCC Cancer Staging Manual*, 8th edition, section on adrenal neuroendocrine tumors;³¹ although the AJCC system applies to pheochromocytoma and sympathetic paraganglioma, paragangliomas were excluded from the present cohort.

Abbreviations: AJCC: American Joint Committee on Cancer; TNM: Tumor–node–metastasis.