

Pretreatment Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte ratio, and Lymphocyte-to-Monocyte Ratio in Extramammary Paget's Disease: A Retrospective Study

Wen-Hsin YU¹, Che-Chia HSU² , Yi-Hua LIAO² , Chia-Yu CHU² , and Yi-Shuan SHEEN^{2*} 

¹Department of Medical Education, National Taiwan University Hospital, Taipei, and ²Department of Dermatology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan. *E-mail: sheenyishuan@gmail.com

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Extramammary Paget's disease (EMPD) is a rare intraepithelial malignancy arising in apocrine gland-rich areas, most often affecting individuals aged 60–80 years. It shows higher prevalence in Caucasian females and Asian males (1). Reported prognostic factors include tumour thickness, invasion depth, nodularity, lymphovascular invasion, perianal location, nodal metastasis, and advanced age (1–4).

Systemic inflammatory markers – such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-neutrophil ratio (PNR) – have been associated with prognosis in various malignancies (5–7), but their relevance in EMPD remains unclear. This study evaluated the prognostic significance of pretreatment inflammatory markers for disease-specific survival (DSS) in EMPD.

MATERIALS AND METHODS

This retrospective single-centre study included 85 patients with histologically confirmed, treatment-naïve EMPD who underwent pretreatment blood testing at National Taiwan University Hospital between 1 January 1994, and 31 December 2022. Exclusion criteria were active infections, autoimmune or haematological disorders, other malignancies, prior immunosuppressive or anticancer treatments, secondary Paget's disease, and treatment at other institutions. The patient selection process is detailed in Fig. S1.

Clinical data and inflammatory markers (NLR, PLR, LMR, and PNR) were collected. This study was approved by the Research Ethics Committee of National Taiwan University Hospital (202312042RINA); informed consent was waived.

Statistical analysis included χ^2 , Fisher's exact, and Mann–Whitney *U* tests. The receiver operating characteristic (ROC) curve determined DSS-based cutoffs. Kaplan–Meier curves and log-rank tests assessed survival, and Cox regression identified prognostic factors. Variables with $p < 0.10$ in univariate analysis were included in multivariate models. Statistical significance was defined as $p < 0.05$. Given limited DSS events, Firth's penalized likelihood method was applied. Additional overall survival (OS)-based analyses are provided in Table SII, Table SIV and Fig. S5.

Among 85 patients, the mean age was 68.98 years, and 79% were male (Table I). Median tumour size was 52 cm². Perianal location, nodularity, ulceration, lymphovascular invasion, dermal invasion, and lymph node metastasis were present in 11%, 6%, 4%, 5%, 21%, and 6%, respectively. Most patients (84%) received surgery alone. Recurrence occurred in 28%, and 13% died from EMPD. Disease-specific survival was the primary endpoint due to the proportion of non-disease-related deaths. Median NLR, PLR, LMR, and PNR were 2.15, 129, 4.67, and 55.6, respectively.

Higher NLR was associated with older age, nodularity, ulceration, lymphovascular invasion, and nodal metastasis. Elevated PLR was linked to older age and lymphovascular invasion. Lower

LMR was correlated with older patients, perianal location, and those with lymph node or distant metastasis. These associations are summarized in Table I.

Receiver operating characteristic analysis identified optimal cutoff values for DSS as follows: NLR 2.54, PLR 117, LMR 3.69, and PNR 55.6 (Fig. S2). Cutoff values based on OS are presented in Fig. S3. Kaplan–Meier analysis revealed significantly poorer DSS in patients with high NLR, high PLR, low LMR, or low PNR ($p < 0.05$) (Fig. S4), with OS-based survival curves shown in Fig. S5.

Univariate Cox regression analysis identified age, level of invasion, metastasis, treatment, and inflammatory markers (NLR, PLR, and LMR) as significant predictors of DSS (Table II). Given the limited number of DSS events, our analysis primarily emphasizes univariate findings. Corresponding multivariate results are provided in Table SI, and Cox regression findings for OS are detailed in Table SII.

Clinical features stratified by DSS-based inflammatory marker cutoffs are presented in Table SIII. High NLR was significantly associated with ulceration, lymphovascular invasion, and metastasis. High PLR and low LMR were both associated with older age, while low LMR was additionally linked to perianal tumour location. All associations had p -values < 0.05 . Analyses based on OS-derived cutoffs are provided in Table SIV.

DISCUSSION

This study demonstrated, through univariate analysis, that elevated NLR (≥ 2.54) and PLR (≥ 117), as well as reduced LMR (< 3.69), were significantly associated with poorer DSS in patients with EMPD. The prognostic significance of several inflammatory markers has been reported in various malignancies. For example, Wang et al. (5) found that NLR > 3.07 , PLR > 118.70 , and LMR ≤ 7.38 predicted poorer OS in mucosal melanoma, while Maeda et al. (7) reported that NLR ≥ 3 was associated with worse DSS in cutaneous squamous cell carcinoma. Specifically in EMPD, Maeda et al. (8) reported that higher NLR was correlated with poorer OS.

Our findings align with these previous reports regarding NLR and further suggest that PLR and LMR may also hold prognostic value in EMPD. To the best of our knowledge, this is one of the first studies to demonstrate a significant association of PLR and LMR with DSS outcomes in EMPD. These findings merit further validation in larger, independent cohorts.

Several mechanisms may underlie the observed associations. Neutrophils promote tumour progression by enhancing cellular proliferation, inducing DNA damage, suppressing T-cell-mediated immune responses, promoting angiogenesis, and facilitating metastasis (9). In contrast, lymphocytes

Table I. Patient characteristics and median values of NLR, PLR, and LMR according to clinical features in 85 patients with extramammary Paget's disease

Characteristics		NLR		PLR		LMR	
		Median NLR	p-value	Median PLR	p-value	Median LMR	p-value
Number of patients	85						
Age, years, mean±SD	68.98±12.85						
< 70 years, n (%)	50 (59%)	2.05 (1.43–2.53)	0.016*	115 (87.1–148)	0.046*	5.51 (3.97–6.84)	0.002*
≥ 70 years, n (%)	35 (41%)	2.40 (1.82–2.99)		142 (112–163)		4.02 (3.15–5.02)	
Sex, n (%)							
Female	18 (21%)	2.12 (1.84–2.47)	0.792	143 (113–170)	0.083	4.66 (3.28–7.08)	0.855
Male	67 (79%)	2.29 (1.61–2.65)		124 (89.3–151)		4.67 (3.64–6.05)	
Primary tumour site, n (%)							
Non-perianal ^a	76 (89%)	2.11 (1.60–2.63)	0.130	123 (90.7–152)	0.087	4.86 (3.82–6.67)	0.012*
Perianal	9 (11%)	2.35 (2.18–2.97)		142 (129–167)		3.36 (2.89–4.80)	
Tumour, cm ² , median (IQR)	52 (35–80)						
< 52, n (%)	42 (49%)	2.03 (1.58–2.56)	0.092	120 (86.5–151)	0.147	5.12 (3.91–6.84)	0.071
≥ 52, n (%)	43 (51%)	2.35 (1.77–2.93)		138 (108–156)		4.23 (3.52–5.59)	
Tumour nodule, n (%)							
Absent	80 (94%)	2.12 (1.62–2.58)	0.033*	129 (95.6–153)	0.605	4.68 (3.62–6.53)	0.147
Present	5 (6%)	2.64 (2.43–3.54)		134 (110–164)		3.86 (1.80–5.29)	
Tumour ulceration, n (%)							
Absent	82 (96%)	2.14 (1.65–2.58)	0.016*	129 (96.0–151)	0.242	4.68 (3.63–6.32)	0.091
Present	3 (4%)	3.00 (2.69–4.22)		155 (112–235)		2.80 (2.71–4.85)	
Lymphovascular invasion, n (%)							
Absent	81 (95%)	2.12 (1.63–2.57)	< 0.001*	126 (95.6–151)	0.028*	4.70 (3.62–6.43)	0.195
Present	4 (5%)	3.61 (3.33–3.89)		166 (144–200)		3.52 (2.32–5.57)	
Invasive level, n (%)							
Non-dermal invasion	67 (79%)	2.15 (1.66–2.57)	0.224	126 (89.3–151)	0.292	4.70 (3.64–6.22)	0.355
Dermal invasion	18 (21%)	2.35 (1.70–3.64)		139 (109–161)		4.21 (2.70–6.17)	
Lymph node metastasis, n (%)							
Absent	80 (94%)	2.14 (1.67–2.58)	0.022*	129 (96.6–153)	0.821	4.86 (3.66–6.53)	0.029*
Present	5 (6%)	3.60 (2.31–4.05)		137 (88.1–188)		3.44 (2.05–4.21)	
Distant metastasis, n (%)							
Absent	84 (99%)	2.15 (1.67–2.63)	0.141	129 (96.6–153)	0.941	4.68 (3.62–6.20)	0.024*
Present	1 (1%)	3.60		124		1.39	
Treatment, n (%)							
Surgery only	71 (84%)	2.15 (1.66–2.58)	0.276	126 (96.3–152)	0.343	4.92 (3.74–6.22)	0.082
Surgery + other treatments ^b	14 (16%)	2.38 (1.70–3.67)		139 (111–196)		3.94 (2.92–4.96)	
NLR, median (IQR)	2.15 (1.69–2.65)						
PLR, median (IQR)	129 (96.9–153)						
LMR, median (IQR)	4.67 (3.57–6.18)						
PNR, median (IQR)	55.6 (47.7–73.4)						
Recurrence, n (%)	24 (28%)						
Death, n (%)	18 (21%)						
Disease-specific deaths, n (%)	11 (13%)						

^aNon-perianal regions include genital, pubic, and axillary area. ^bOther treatments include topical medicine (imiquimod or fluorouracil), chemotherapy, or radiotherapy. SD: standard deviation; IQR: interquartile range; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PNR: platelet-to-neutrophil ratio. *Statistically significant.

play an antitumour role by inducing apoptosis and activating immune activation (10). Previous studies have shown that IL-17 indirectly promotes the differentiation of monocytes into M2-like macrophages, which accumulate in invasive EMPD and contribute to a tumour-supportive microenvi-

ronment that may accelerate disease progression (11, 12). Platelets also facilitate tumour development through both contact-dependent and contact-independent interactions with tumour cells (13). Collectively, these mechanisms may explain the prognostic relevance of systemic inflammatory markers observed in this study.

Although PNR did not reach statistical significance in the univariate Cox model for DSS ($p=0.052$), Kaplan–Meier analysis revealed a significant association ($p=0.048$), suggesting possible relevance. The observed positive association between PNR and DSS may indicate that neutrophils exert a relatively greater influence than platelets on EMPD prognosis. However, this hypothesis requires further validation through mechanistic studies.

In our study, elevated NLR and PLR, along with decreased LMR, were significantly associated with adverse clinicopathological features – including older age, nodularity, lymphovascular invasion, perianal involvement, and metastasis – supporting their potential utility as indicators of tumour aggressiveness in EMPD.

While this study focused on DSS, previous research, such as that by Ebata et al. (14), has shown that inflam-

Table II. Univariate Cox regression analysis for prediction of disease-specific survival of 85 patients with extramammary Paget's disease

Characteristics	Univariate analysis	
	HR (95% CI)	p-value
Sex (male vs female)	1.99 (0.33–12.0)	0.392
Age (years old) (≥ 70 vs < 70)	19.6 (3.01–128)	< 0.001*
Primary tumour site (perianal vs non-perianal ^a)	1.64 (0.27–10.1)	0.598
Tumour size (cm ²) (≥ 52 vs < 52)	1.61 (0.46–5.70)	0.433
Tumour nodule (yes vs no)	6.30 (0.92–42.9)	0.098
Tumour ulceration (yes vs no)	8.84 (1.63–47.2)	0.060
Lymphovascular invasion (yes vs no)	4.82 (0.76–30.4)	0.141
Invasive level (dermal vs non-dermal)	5.76 (1.73–19.2)	0.004*
Metastasis (yes vs no)	29.9 (4.98–180)	< 0.001*
Treatment (surgery + other treatments ^b vs surgery only)	5.82 (1.61–21.1)	0.010*
NLR (≥ 2.54 vs < 2.54)	17.5 (2.89–106)	< 0.001*
PLR (≥ 117 vs < 117)	21.7 (1.08–436)	< 0.001*
LMR (≥ 3.69 vs < 3.69)	0.11 (0.03–0.41)	< 0.001*
PNR (≥ 55.6 vs < 55.6)	0.28 (0.06–1.22)	0.052

^aNon-perianal regions include genital, pubic, and axillary area. ^bOther treatments include topical medicine (imiquimod or fluorouracil), chemotherapy, or radiotherapy. CI: confidence interval; HR: hazard ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PNR: platelet-to-neutrophil ratio. *Statistically significant.

matory markers, particularly NLR, may also predict lymph node metastasis in EMPD, highlighting their potential utility in identifying candidates for sentinel lymph node biopsy. Other biomarkers, including serum carcinoembryonic antigen and cytokeratin 19 fragments, have also been proposed for nodal detection (15). Our findings suggest that NLR, PLR, and LMR may serve as complementary markers to these established tools in enhancing prognostic assessment in EMPD (8).

This study has several limitations. The small sample size and retrospective design may have limited the statistical power and generalizability of our findings. The low number of disease-specific events likely reflects not only the rarity of EMPD but also its generally favourable prognosis and low disease-specific mortality. Moreover, the proposed cutoff values for inflammatory markers require external validation in independent cohorts. Sentinel lymph node biopsy was not routinely performed at our institution, limiting our ability to directly correlate biomarker levels and nodal status.

In conclusion, this study identified elevated NLR and PLR, as well as decreased LMR, as significant prognostic markers associated with poorer DSS in patients with EMPD. These readily available systemic inflammatory markers may serve as useful adjuncts to established clinicopathological parameters, supporting prognostic assessment and informing clinical decision-making in EMPD.

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