

PROGNOSTIC SIGNIFICANCE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO AND PLATELET-TO-LYMPHOCYTE RATIO IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma, and despite rituximab-based immuno-chemotherapy, up to 40% of patients experience treatment failure. The International Prognostic Index (IPI) remains the standard prognostic tool, but its discriminatory power is limited, prompting interest in inflammation-based biomarkers such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). This retrospective study aimed to evaluate the prognostic significance of pre-treatment and post-treatment NLR and PLR for overall survival (OS) and progression-free survival (PFS) in patients with DLBCL. Forty-six patients treated at the Clinic of Oncology, University Clinical Centre Niš, were included. NLR and PLR were calculated at baseline and after treatment completion; median values were used as cut-offs given limited ROC-based discrimination. Kaplan-Meier analysis, log-rank testing, and univariate and multivariate Cox regression (adjusted for IPI and Hans classification) were performed. High pre-treatment NLR was associated with significantly shorter OS (HR = 2.990, 95% CI: 1.399–6.390, $p = 0.005$) and PFS (HR = 2.994, 95% CI: 1.401–6.398, $p = 0.005$), whereas pre-treatment PLR and post-treatment NLR/PLR showed no significant associations. In multivariate models, high pre-treatment NLR retained only a nonsignificant trend toward poorer OS and PFS, and neither IPI nor cell-of-origin subtype was an independent predictor. Pre-treatment NLR appears to be a promising, low-cost prognostic marker in DLBCL, but this study was underpowered to confirm its independent prognostic value; larger, prospective studies are warranted.

Keywords: lymphoma, large b-cell, diffuse, neutrophils, lymphocytes, blood platelets, prognosis

Prognostički značaj odnosa neutrofila i limfocita i odnosa trombocita i limfocita kod pacijenata sa difuznim krupnoćelijskim B-limfomom

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Difuzni krupnoćelijski B-limfom (DLBCL) je najčešći agresivni non-Hodgkin limfom, i uprkos imunohemioterapiji zasnovanoj na rituksimabu, i do 40% bolesnika ima neuspeh lečenja. Internacionalni prognostički indeks (IPI) ostaje standardni prognostički alat, ali je njegova diskriminatorska moć ograničena, što je podstaklo interesovanje za biomarkere zasnovane na zapaljenju, kao što su odnos neutrofila i limfocita (NLR) i odnos trombocita i limfocita (PLR). Cilj ove retrospektivne studije bio je procena prognostičkog značaja pretretmanskog i posttretmanskog NLR i PLR za ukupno preživljavanje (OS) i preživljavanje bez progresije bolesti (PFS) kod bolesnika sa DLBCL. Analizirano je 46 pacijenata lečenih na Klinici za onkologiju Univerzitetskog kliničkog centra Niš. NLR i PLR su izračunati na početku i po završetku lečenja; s obzirom na ograničenu diskriminatorsku moć ROC analize, kao granične vrednosti korišćene su medijalne vrednosti. Sprovedene su Kaplan-Majerova analiza, log-rank test, kao i univarijantna i multivarijantna Koksova regresija (prilagođena za IPI i Hansovu klasifikaciju). Visok pretretmanski NLR bio je povezan sa značajno kraćim OS (HR = 2.990, 95% CI: 1.399–6.390, p = 0.005) i PFS (HR = 2.994, 95% CI: 1.401–6.398, p = 0.005), dok pretretmanski PLR i posttretmanski NLR/PLR nisu pokazali značajnu povezanost. U multivarijantnim modelima, visok pretretmanski NLR zadržao je samo statistički neznačajan trend ka lošijem OS i PFS, a ni IPI ni podtip prema ćelijskom poreklu nisu bili nezavisni prediktori. Pretretmanski NLR se pokazuje kao obećavajući, jeftin prognostički marker kod DLBCL, ali je ova studija bila nedovoljne snage da potvrdi njegovu nezavisnu prognostičku vrednost; potrebne su veće, prospektivne studije.

Ključne reči: limfom, krupnoćelijski B, difuzni, neutrofili, limfociti, trombociti, prognoza

INTRODUCTION

Among non-Hodgkin lymphomas, DLBCL represents the most frequently diagnosed subtype, accounting for approximately one-third to more than half of all cases, with an estimated European incidence of about 3.8 per 100,000 (1). Recognized risk factors comprise a positive family history of lymphoma, underlying autoimmune disease, HIV or HCV seropositivity, elevated body mass during young adulthood, and certain occupational exposures (2). DLBCL has been characterized by high heterogeneity in clinical presentation, although predominantly it has an aggressive clinical course. However, curability rate exceeds almost two thirds of cases, but 35–40% of patients fare poorly (3).

Various prognostic indicators have been evaluated in DLBCL, including biochemical, clinical, immunohistochemical (4) or other, all of which have been proven to have certain significance as a prognostic tool. Nevertheless, perhaps one of the most known is the International Prognostic Index (IPI) which has incorporated several well-recognized risk factors, such as age, disease stage, LDH value, performance status, and the number of involved extranodal sites. Both the IPI and its age-adjusted counterpart (aaIPI, applied to patients aged 60 years or younger) were originally validated during the pre-rituximab era across nearly every DLBCL subtype, with the notable exception of primary mediastinal large B-cell lymphoma (PMLBCL) (5). After introduction of rituximab as regular component to the CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) regimen, its significance declined. Subsequent modifications, including the revised IPI (R-IPI) and the National Comprehensive Cancer Network IPI (NCCN-IPI), provided only modest improvement (6). A new era has brought molecular biomarkers into DLBCL prognostication, which have not yet been validated (6).

The role of inflammation and its impact on disease outcome have been demonstrated in various malignancies, including DLBCL. A number of investigations have specifically addressed whether the neutrophil-to-lymphocyte ratio (NLR) holds prognostic relevance in the DLBCL population (7).

NLR is an inflammatory biomarker which was found to be elevated in various conditions involving tissue damage, including bacterial and fungal infections, myocardial infarction, and different types of cancer (8). The platelet-to-lymphocyte ratio (PLR) is another representative biomarker of inflammation whose prognostic value has been evaluated in ovarian, colorectal, and other malignancies (9). Although elevated NLR and PLR values are associated with poor prognosis in

various cancers, they have been rarely considered as prognostic biomarkers in DLBCL (10). Given the high availability and low cost, examining whether NLR and PLR are linked to overall survival (OS) and progression-free survival (PFS) in DLBCL represents a particularly promising research direction. Considering the facts discussed above we conducted a study of these two inflammatory biomarkers in our patient cohort.

AIM

The aim of the study was to determine whether NLR and PLR are associated with OS and PFS among DLBCL patients treated in Southeastern Serbia.

METHODS

Neutrophil, platelet, and lymphocyte counts were measured at the Center for Clinical and Medical Biochemistry at the University Clinical Centre Niš. NLR was defined as the ratio of the absolute neutrophil count to the absolute lymphocyte count, whereas PLR was defined as the ratio of the absolute platelet count to the absolute lymphocyte count.

Patients were treated with rituximab-based immunochemotherapy regimens according to institutional protocols. The majority of patients received R-CHOP-based therapy, while smaller subsets were treated with R-CVP, R-CHOEP, R-CEOP, DA-EPOCH-R, or modified regimens depending on age, comorbidities, disease characteristics, and treating physician assessment. Some patients additionally received consolidative radiotherapy.

ROC analysis was explored for determination of optimal cut-off values; however, discriminatory performance was limited, likely due to the relatively small cohort size and low number of events (Table 1). Therefore, median values of the respective markers were used as predefined cut-off values for exploratory analyses: NLR > 2.62 and PLR > 146.0 at the beginning of treatment, and NLR > 2.80 and PLR > 235.0 at the end of treatment.

Ethical approval for this study was obtained from the University Clinical Center Niš Ethics Committee (approval no. 6043, February 2026).

Statistical Analysis

Data were analyzed using IBM SPSS v27.0 (IBM Corp., Armonk, NY, USA). Measures of central tendency and variability were calculated. Shapiro-Wilk test was used to assess the normality of data distribution. Mann-Whitney U test was used for group comparisons. Survival curves were estimated using the Kaplan-Meier method and compared with the Log-rank test; Cox regression analyses were performed to determine statistical significance at $p < 0.05$.

RESULTS

The study included 46 patients treated at the Oncology Clinic of the University Clinical Center in Niš between 2018 and 2023. Of the total number of patients, 20 were male (43.5%) and 26 female (56.5%). The average age of patients in our study was 63.20 ± 12.22 years. No statistically significant age difference was found between genders ($p > 0.05$).

Of the total number of patients, 22 (47.8%) were classified as non-GCB, 23 (50%) as GCB, and 1 (2.2%) was unclassifiable (NU). DLBCL, not otherwise specified (DLBCL, NOS) was the most frequent subtype, observed in 38 patients (82.6%), followed by T-cell-rich DLBCL, testicular DLBCL, and DLBCL with double-expressor phenotype, each occurring in 2 patients (4.3%). Less common subtypes were DLBCL with double-hit features and primary mediastinal large B-cell lymphoma (PMLBCL), each seen in one patient (2.2%).

Among the 46 patients, the most common IPI scores were 2 (37.0%) and 1 (30.4%). Higher-risk scores of 3, 4, and 5 were observed in 21.7%, 4.3%, and 2.2% of patients, respectively, while 4.3% of patients had an IPI score of 0.

During the observation period, 8 deaths (17.4%) and 8 documented progression events (17.4%) were recorded. Treatment heterogeneity reflected real-world clinical practice in a tertiary referral center.

ROC analysis of pre-treatment and post-treatment NLR and PLR showed only limited discriminatory performance for both OS and PFS (AUC range 0.526-0.684; Table 1). Our results showed that patients with high pretreatment NLR had nearly three times higher risk of death ($HR = 2.990$, 95% CI: 1.399–6.390, $p = 0.005$). PFS was also significantly shorter in patients with high compared to low pretreatment NLR ($HR = 2.994$, 95% CI: 1.401–6.398, $p = 0.005$) (Figures

1 and 2). There were no significant differences in OS (HR = 1.335, 95% CI: 0.690–2.582, $p = 0.388$) and PFS (HR = 1.336, 95% CI: 0.691–2.586, $p = 0.389$) between groups with low and high baseline PLR (Figures 3 and 4).

Post-treatment NLR did not significantly influence OS (HR = 0.916, 95% CI: 0.471–1.785, $p = 0.797$) or PFS (HR = 1.917, 95% CI: 0.457–8.040, $p = 0.373$) (Figures 5 and 6). Similarly, OS (HR = 1.450, 95% CI: 0.726–2.895, $p = 0.292$) and PFS (HR = 1.452, 95% CI: 0.727–2.899, $p = 0.291$) did not differ in low and high post-treatment PLR groups (Figures 7 and 8).

In the pre-treatment NLR Cox regression model, high pre-treatment NLR showed a trend toward shorter OS (HR = 4.19, 95% CI: 0.79–22.22, $p = 0.093$) and PFS (HR = 4.15, 95% CI: 0.78–22.11, $p = 0.096$). Neither IPI (OS: HR = 0.53, 95% CI: 0.115–2.451, $p = 0.417$; PFS: HR = 0.52, 95% CI: 0.114–2.395, $p = 0.403$) nor Hans subtype (OS: HR = 0.35, 95% CI: 0.068–1.809, $p = 0.211$; PFS: HR = 0.38, 95% CI: 0.074–1.939, $p = 0.244$) was a significant predictor of disease outcome.

There were no statistically significant predictors present in the pre-treatment PLR model. For OS, high PLR was associated with poorer survival (HR = 2.17, 95% CI: 0.514–9.196, $p = 0.291$), non-GCB subtype with worse outcome (HR = 3.11, 95% CI: 0.62–15.67, $p = 0.169$), and high IPI with increased risk (HR = 2.13, 95% CI: 0.472–9.567, $p = 0.326$). For PFS, high PLR (HR = 2.19, 95% CI: 0.518–9.274, $p = 0.286$), non-GCB (HR = 2.95, 95% CI: 0.587–14.794, $p = 0.189$), and high IPI (HR = 2.20, 95% CI: 0.490–9.908, $p = 0.303$) showed similar nonsignificant trends.

No significant predictors were identified in the post-treatment NLR model. Low post-treatment NLR trended toward longer OS (HR = 0.52, 95% CI: 0.12–2.24, $p = 0.377$) and longer PFS (HR = 0.52, 95% CI: 0.12–2.23, $p = 0.119$). Non-GCB subtype (OS: HR = 2.76, 95% CI: 0.56–13.70, $p = 0.213$; PFS: HR = 2.61, 95% CI: 0.525–12.936, $p = 0.241$) and high IPI (OS: HR = 1.87; 95% CI: 0.411–8.482, $p = 0.419$; PFS: HR = 1.90, 95% CI: 0.419–8.645, $p = 0.405$) were associated with poorer outcomes, although not significant.

Similarly, no statistically significant predictors were observed in the post-treatment PLR model. High post-treatment PLR was associated with worse OS (HR = 1.75, 95% CI: 0.41–7.41, $p =$

0.447) and PFS (HR = 1.73, 95% CI: 0.41–7.29, $p = 0.458$). Non-GCB (OS: HR = 2.60; 95% CI: 0.519–13.021, $p = 0.245$; PFS: HR = 2.51, 95% CI: 0.409–7.286, $p = 0.458$) and high IPI (OS: HR = 2.09, 95% CI: 0.466–9.335, $p = 0.336$; PFS: HR = 2.13, 95% CI: 0.477–9.535, $p = 0.322$) showed trends toward poorer outcomes which were not significant.

DISCUSSION

Previous studies regarding this topic have highlighted the association between high NLR and shorter OS and PFS in DLBCL patients (10). One of the possible contributing factors is proinflammatory cytokines which promote tumor-supportive inflammation within the tumor microenvironment (11). Elevated NLR indicates increased neutrophil counts and higher levels of vascular endothelial growth factor (VEGF), which is produced by neutrophils (12). VEGF plays a key role in angiogenesis and tumor growth, explaining the shorter survival of patients with high NLR. High NLR shows an imbalance between the proinflammatory and antitumor immune responses. In addition to VEGF, neutrophils secrete reactive oxygen species (ROS), elastase, and metalloproteinases that degrade the extracellular matrix, facilitating tumor invasion. Neutrophils may also inhibit cytotoxic T lymphocyte activation through secretion of arginase-1, further weakening antitumor immunity (13).

In contrast, low lymphocyte count, which is present in high NLR and PLR, suggests a decreased number of effector T-cells (e.g., CD8+ and NK-cells) that are essential for identifying and eliminating malignant cells. Because of this, NLR and PLR represent indirect biomarkers of immune response in DLBCL. Their simplicity, low cost, and high availability make them attractive prognostic biomarkers in clinical practice (12).

The potential application of these markers could involve early identification of high-risk patients who may benefit from closer monitoring or personalized therapies, including immunomodulatory or anti-inflammatory treatments. Our Log-rank analyses showed that both OS and PFS were significantly longer in patients with low pretreatment NLR, consistent with the results of Wang et al. (12).

Previous experimental and clinical studies suggest that inflammation in DLBCL may involve cytokines such as IL-3, IL-6, and IL-10, which may stimulate megakaryocyte proliferation and contribute to increased platelet counts (14,15). Cytokines were not directly analyzed in the

present study. Activated platelets can secrete various biomolecules that promote angiogenesis within the tumor microenvironment (16). Through secretion of transforming growth factor-beta (TGF- β 1), platelets facilitate epithelial-mesenchymal transition and metastasis (17). Elevated PLR may also result from decreased lymphocyte counts, which are essential for antitumor immunity. Tumor-infiltrating CD3+ and CD8+ Th1 T-cells can inhibit tumor proliferation and metastasis (18). Chen et al. conducted a meta-analysis of eight studies involving 1931 patients and concluded that high PLR was a significant prognostic marker for shorter OS in DLBCL patients (HR = 1.73, 95% CI = 1.29–2.31, $p < 0.001$) (19). Given that the studies included patients from both Asia and Europe, Chen et al. divided the participants into subgroups. In the Asian group, elevated PLR was a significant marker for shorter OS (HR = 1.95, 95% CI = 1.34–2.84, $p < 0.001$), while in the European group (Austria and Croatia), PLR was not a significant prognostic marker (HR = 1.32, 95% CI = 0.95–1.84, $p = 0.103$). Analysis of seven studies with 1416 participants showed that PLR did not significantly affect PFS (HR = 0.85, 95% CI = 0.57–1.27, $p = 0.438$) (19). Our results revealed that PLR was not a significant prognostic marker for OS or PFS, aligning with the findings of the previously mentioned study. The lack of significance of PLR in our study may indicate differences in its prognostic value based on ethnic background.

Besides univariate analyses, in this study, we evaluated the significance of pretreatment and post-treatment NLR and PLR as independent prognostic markers in patients with DLBCL, after adjustment for IPI and cell-of-origin (Hans classification). Although high pretreatment NLR demonstrated the strongest association with poor OS and PFS in our cohort, this effect did not reach statistical significance, and wide confidence intervals reflect imprecision. Pretreatment PLR, as well as post-treatment NLR and PLR, also showed nonsignificant trends toward worse survival. Neither IPI nor Hans subtype retained significance in any of the Cox regression models. Taken together, our findings suggest that systemic inflammatory markers may have potential prognostic relevance beyond traditional indices; however, the present study was underpowered to confirm independent statistical significance.

Our results are directionally consistent with a large body of evidence showing that elevated pre-treatment NLR is associated with poor outcomes in DLBCL. A meta-analysis including over 2500 patients showed that elevated NLR was significantly associated with poorer OS (HR = 1.83, 95% CI: 1.24–2.69) and PFS (HR = 1.59, 95% CI: 1.12–2.25) (20).

Similarly, Beltrán et al.'s multi-institutional validation in Latin American cohorts (n = 597) demonstrated that $\text{NLR} \geq 4$ was an adverse prognostic factor for survival, independent of IPI / NCCN-IPI (21).

Our HR estimates for pre-treatment NLR were higher than those reported in prior studies. However, the association did not reach statistical significance. Differences in cohort size, cut-off values, treatment regimens, and modeling strategies may explain variability across studies. Importantly, our analysis included both IPI and Hans subtype in the same Cox models, an approach not uniformly adopted in literature.

Despite these limitations, our findings support the biological rationale that systemic inflammation contributes to adverse outcomes in DLBCL. Pre-treatment NLR, in particular, showed the most consistent association with prognosis in our models, even if not statistically conclusive. Future studies with larger patient populations are needed to validate whether changes in NLR and PLR after therapy, in addition to baseline values, provide incremental prognostic information beyond established indices. Incorporating these easily measurable blood-based markers into prognostic models could refine risk stratification, especially when combined with molecular subtyping.

The present study has several limitations that should be acknowledged. First, the retrospective single-center design and relatively small sample size reduce statistical power and limit generalizability of the findings. Second, inclusion of multiple DLBCL subtypes and heterogeneous treatment regimens introduced biological and therapeutic heterogeneity. Third, the low number of OS and PFS events limited the robustness of multivariate Cox regression analyses and increased the possibility of model overfitting. Additionally, progression and death occurred in a largely overlapping subset of patients in this cohort, which explains the identical ROC/AUC estimates for OS and PFS in Table 1. Finally, cut-off values for NLR and PLR were determined using median values rather than ROC-derived thresholds due to limited discriminatory performance in ROC analyses. This reliance on cohort-specific median values, rather than externally validated thresholds, limits direct comparability of our results with previously published studies that applied fixed or ROC-derived cut-offs, and should be taken into account when interpreting the reported effect sizes. Therefore, the present findings should be considered exploratory and hypothesis-generating.

CONCLUSION

In this cohort of patients with DLBCL from Southeastern Serbia, elevated pre-treatment NLR was associated with shorter OS and PFS in univariate analyses. Although pre-treatment NLR demonstrated the strongest association with adverse outcomes in multivariate models, independent prognostic significance could not be confirmed after adjustment for IPI and Hans subtype. Pre-treatment and post-treatment PLR did not show significant prognostic value in this cohort. Given its simplicity, low cost, and wide availability from routine complete blood counts, pre-treatment NLR could, pending further validation, be incorporated as a low-burden adjunct to existing risk-stratification tools such as the IPI, helping to flag patients who may warrant closer follow-up rather than replacing established indices. Larger prospective studies are required to validate these findings and establish standardized cut-off values for clinical application.

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APPENDICES

Table 1 Receiver operating characteristic (ROC) analysis of pre-treatment and post-treatment NLR and PLR for predicting overall survival (OS) and progression-free survival (PFS)

Outcome	Biomarker	Timing	AUC	95 % CI	p
Overall survival (OS)	NLR	Pre-treatment	0.684	0.519–0.849	.105
Overall survival (OS)	PLR	Pre-treatment	0.641	0.444–0.838	.213
Overall survival (OS)	NLR	Post-treatment	0.582	0.362–0.803	.469
Overall survival (OS)	PLR	Post-treatment	0.526	0.309–0.744	.817
Progression-free survival (PFS)	NLR	Pre-treatment	0.684	0.519–0.849	.105
Progression-free survival (PFS)	PLR	Pre-treatment	0.641	0.444–0.838	.213
Progression-free survival (PFS)	NLR	Post-treatment	0.582	0.362–0.803	.469
Progression-free survival (PFS)	PLR	Post-treatment	0.526	0.309–0.744	.817

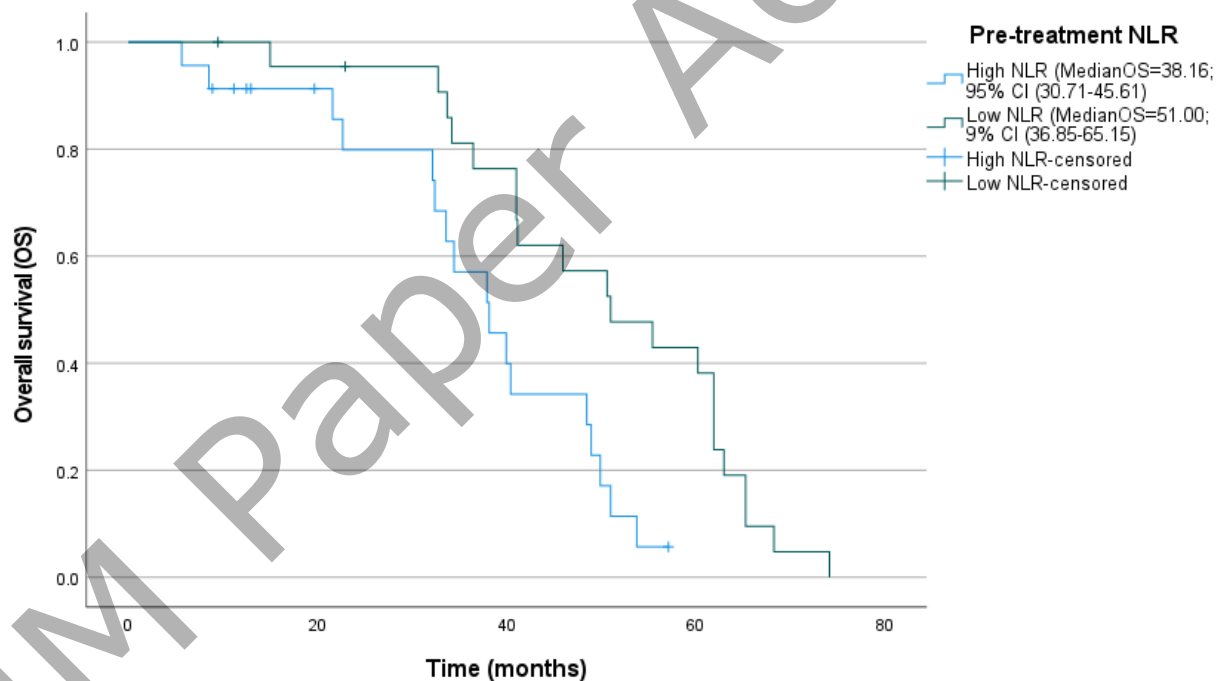


Figure 1. Overall survival (OS) by pre-treatment NLR

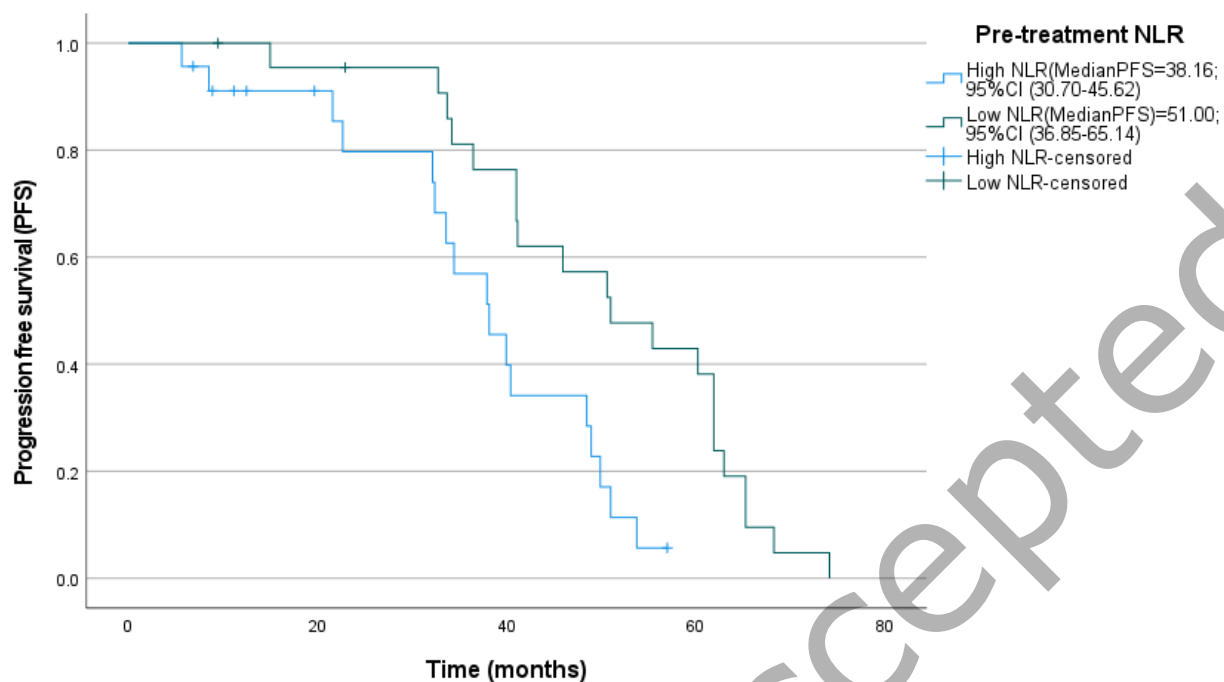


Figure 2. Progression free survival (PFS) by pre-treatment NLR

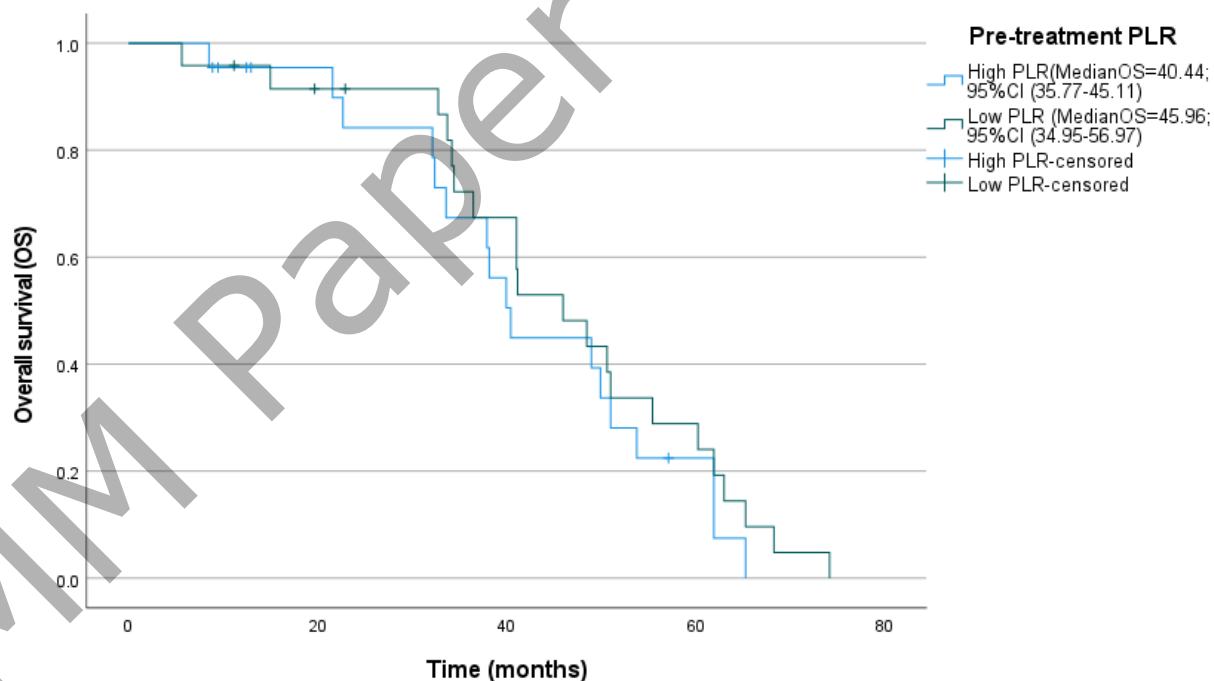


Figure 3. Overall survival (OS) by pretreatment PLR

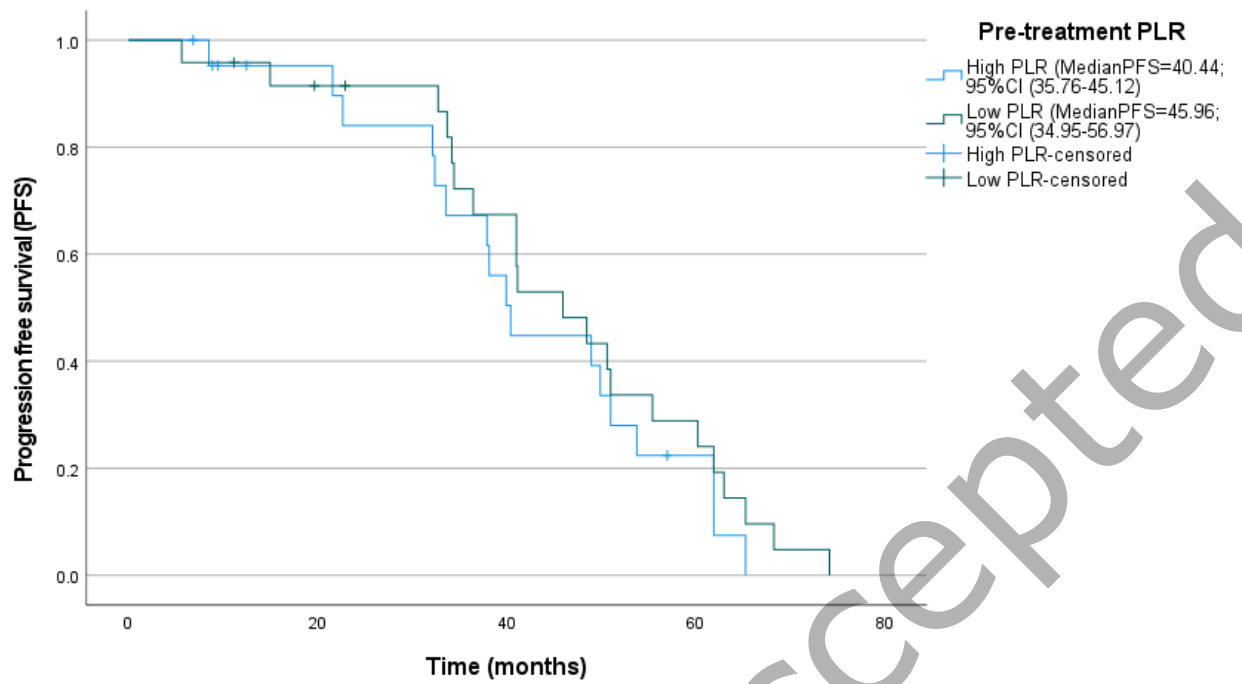


Figure 4. Progression free survival (PFS) by pretreatment PLR

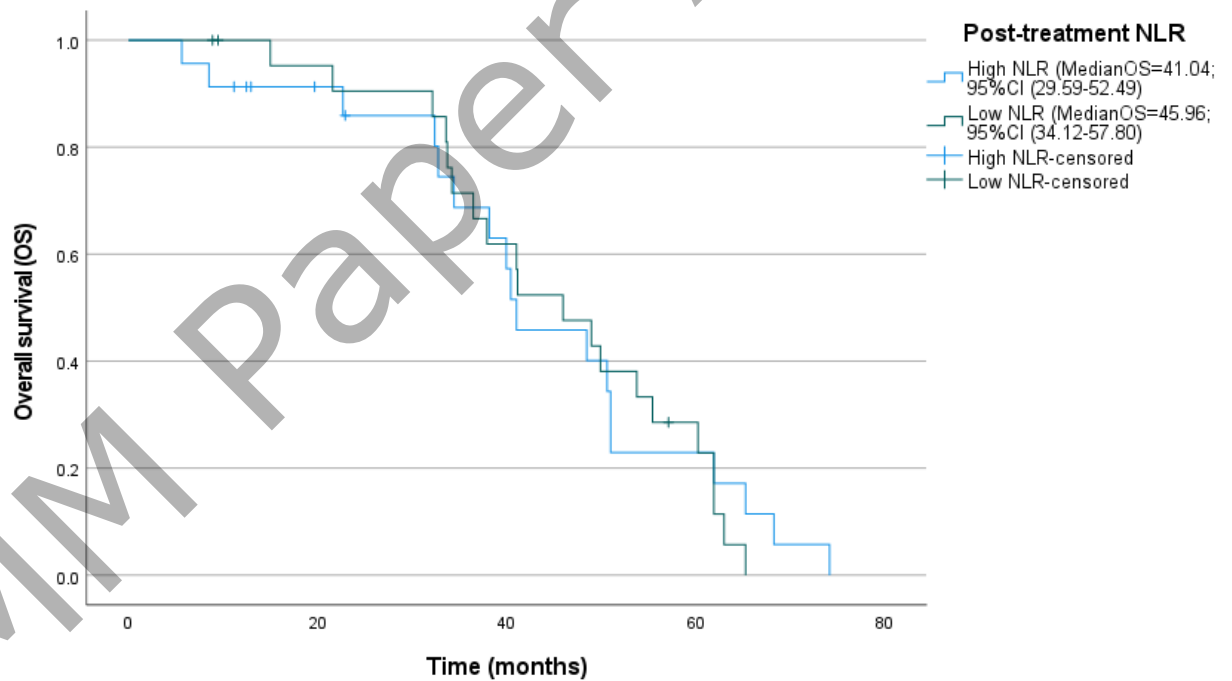


Figure 5. Overall survival (OS) by post-treatment NLR

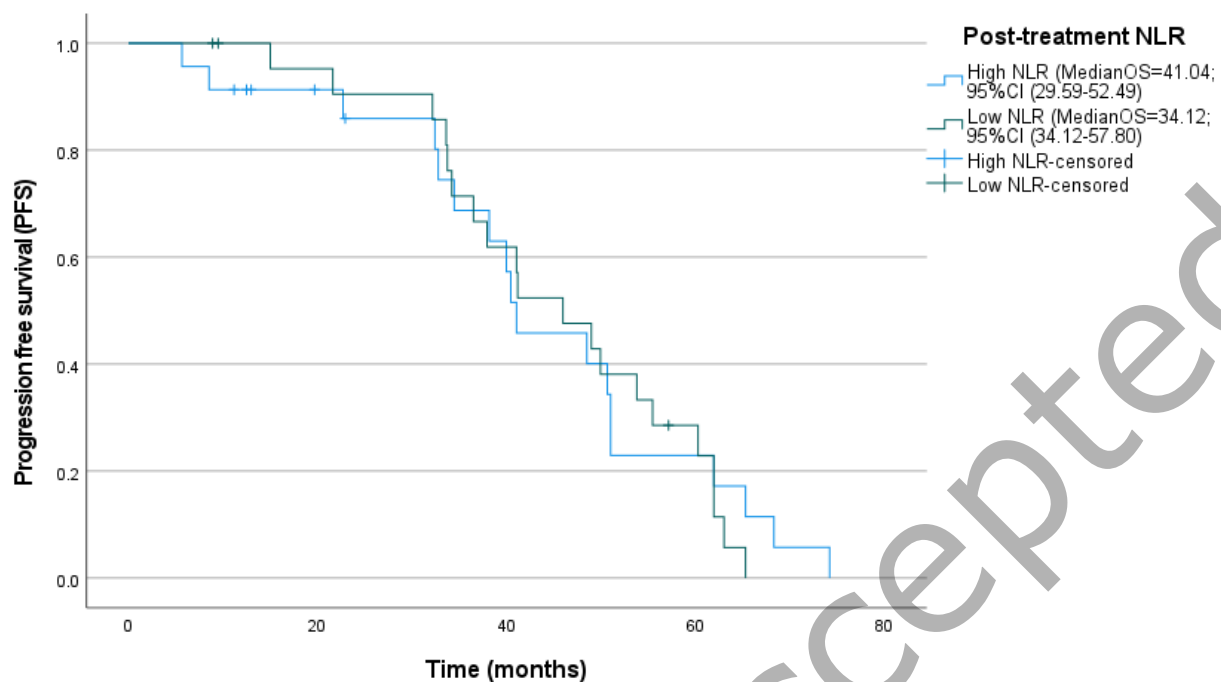


Figure 6. Progression free survival (PFS) by post-treatment NLR

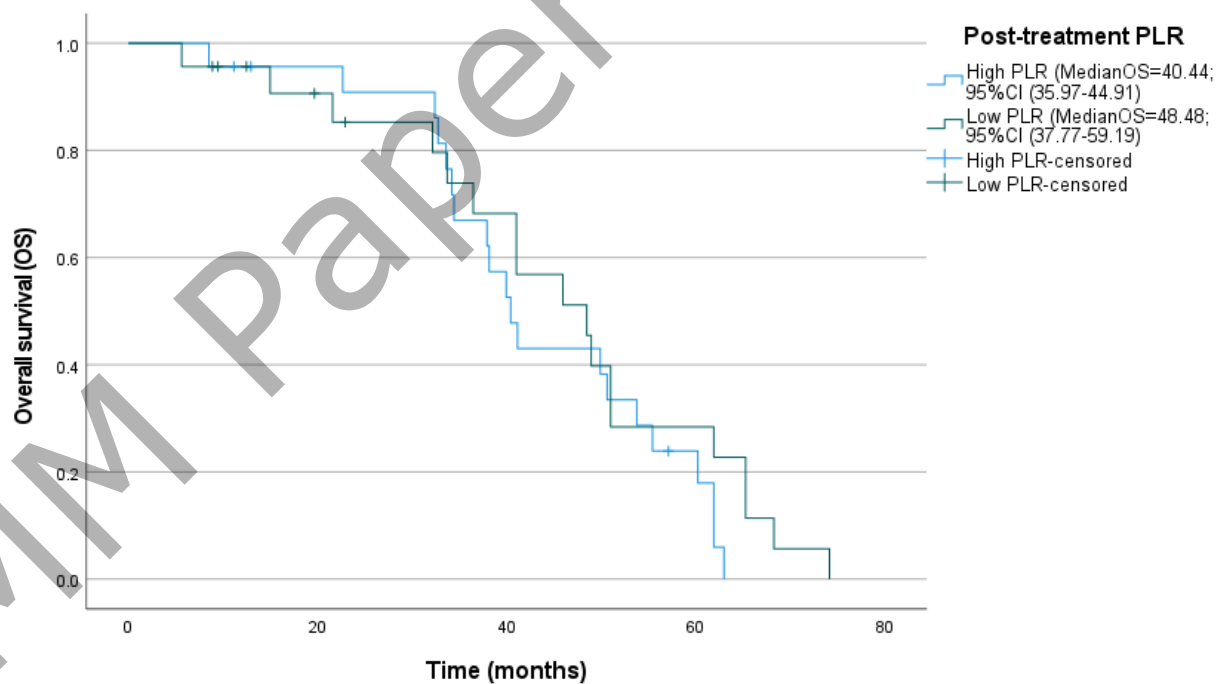


Figure 7. Overall survival (OS) by post-treatment PLR

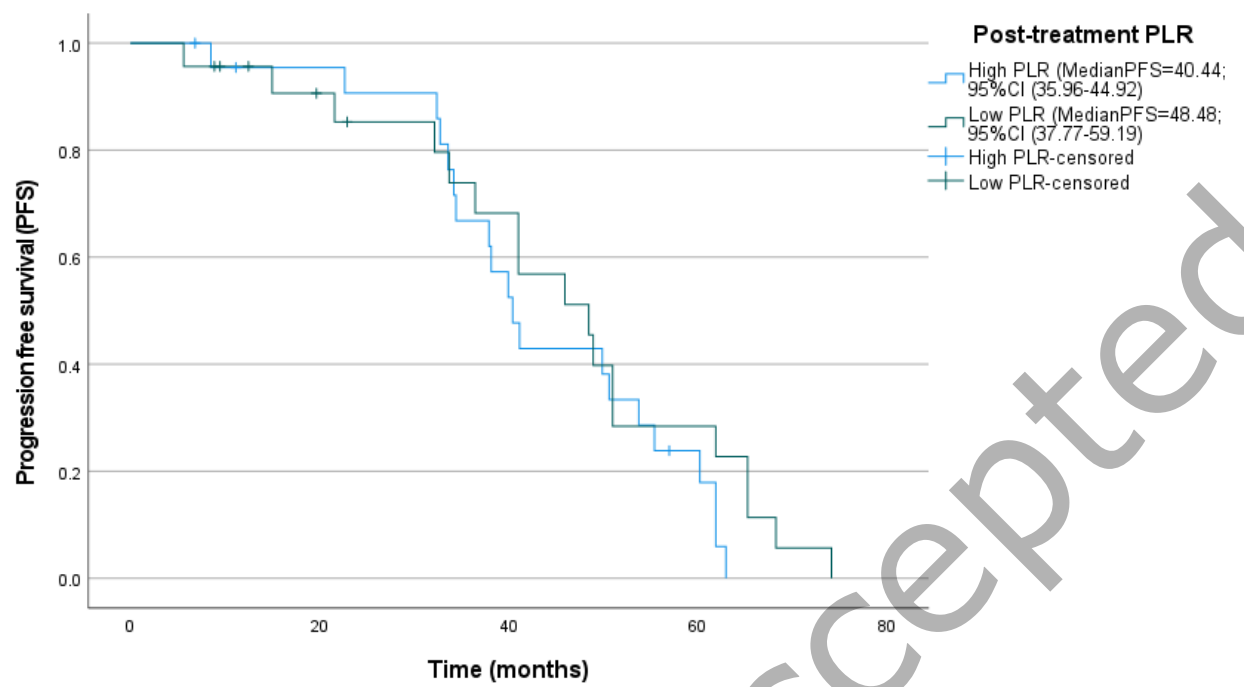


Figure 8. Progression free survival (PFS) by post-treatment PLR