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**RESEARCH ARTICLE**

**TRANSLATIONAL AND CLINICAL RESEARCH**



# Prognostic value of immunotherapy in advanced non-small cell lung cancer based on baseline and dynamic changes in hemoglobin, albumin, and platelets

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**ABSTRACT**

Immune checkpoint inhibitors enhance the tumor-killing ability of T-cells in non-small cell lung cancer (NSCLC), thereby boosting overall survival (OS) and transforming treatment for advanced stages. However, challenges persist, including low response rates and the absence of effective markers for candidate selection. This study evaluated the impact of hemoglobin, albumin, and platelet (HALP), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) on immunotherapy efficacy and survival in advanced NSCLC. Furthermore, the study aimed to develop a nomogram based on these parameters. Clinical and hematological data from patients diagnosed with NSCLC who received immunotherapy were analyzed. Efficacy was assessed using the immune Response Evaluation Criteria in Solid Tumors (iRECIST), and progression-free survival (PFS) and OS were analyzed. Prediction models were based on baseline and post-treatment HALP, NLR, and PLR. The 203 included patients had a median follow-up of 16 months, a median PFS (mPFS) of 7 months (6.0 – 8.0), while the median OS (mOS) was not available (24.0 – not available). The PLR before treatment ($PLR_0$) was linked to a higher disease control rate (DCR) (odds ratio [OR] = 0.258), while initial immunotherapy and NLR after four cycles of treatment ($NLR_{4C}$) significantly boosted the objective response rate (ORR). Cox regression showed that HALP before treatment ($HALP_0$), HALP after four cycles of treatment ($HALP_{4C}$), and NLR before treatment ($NLR_0$) significantly influenced PFS. Additionally, $HALP_0$, $NLR_0$, and PLR after four cycles of treatment ($PLR_{4C}$) were associated with OS. The C-indices for PFS and OS were 0.823 and 0.878, respectively, indicating good prediction accuracy. HALP, NLR, and PLR at various time

points effectively predicted immunotherapy response in advanced NSCLC patients. Low HALP with high NLR and PLR indicated a poor prognosis. The findings can provide the basis for stratified randomized controlled trials (RCTs) in the future.

**Keywords:** Non-small cell lung cancer; immune checkpoint inhibitors; HALP, NLR, PLR, dynamics.

## INTRODUCTION

According to the latest estimates from the International Agency for Research on Cancer, close to 20 million new cases of cancer were diagnosed in 2022 (including non-melanoma skin cancers [NMSCs]) [1]. Lung cancer was the most commonly diagnosed cancer, with nearly 2.5 million new cases (12.4% of all cancers worldwide). It was also the leading cause of cancer-related death, with an estimated 1.8 million deaths (18.7%) [1]. Most patients with lung cancer are diagnosed at an advanced stage, and the 5-year survival rate of patients with advanced-stage disease is only 19% [2]. The development of immunotherapies in recent years has improved the prognosis of patients with NSCLC to a certain extent [3]. Immunotherapy, represented by programmed cell death 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs), has a significant effect on patients with NSCLC. Immunotherapy has also become the first-line standard treatment for patients with driver-negative advanced NSCLC [4-7]. However, immunotherapy can cause serious immune-related adverse reactions. Therefore, accurate and effective biomarkers are critical to determine whether immunotherapy is beneficial. Currently, PD-L1 and tumor mutation burden (TMB) are the most common biomarkers for predicting the efficacy of NSCLC immunotherapy [8]. However, detecting PD-L1 and TMB expression still faces many challenges. For example, the existing detection platform, scoring system, and interpretation criteria for PD-L1 differ, so it remains difficult to form a consistent standard. Moreover, there are various reasons for the upregulation of PD-L1 expression. Due to the heterogeneity or dynamics of PD-L1 protein expression in tumors, the true status of PD-L1 expression is difficult to determine. In addition,

even in patients with negative PD-L1 expression, 10% to 20% of patients experience remission after treatment with ICIs [9]. TMB evaluation methods include whole exome sequencing and targeted gene sequencing. The clinical application of whole exon sequencing is limited due to its complexity, cost, time consumption, and stringent requirements for tumor tissue samples. Moreover, the FDA has not yet approved the integration of targeted gene sequencing panel testing for TMB into clinical practice. Hence, the application of such detection methods still falls mainly into laboratory or clinical research. Therefore, there is a need for easily accessible biomarkers to select potential beneficiaries of immunotherapy.

In recent years, many inflammatory indicators have been found to be predictive in oncology, and several hematological inflammatory indicators have been proven to be prognostic markers of NSCLC. For example, the NLR, PLR, systemic immune-inflammation index (SII) [10], and prognostic nutritional index (PNI) are significantly correlated with malignancy, providing important information for predicting patient prognosis [11-15]. Furthermore, the HALP has been shown to be associated with the prognosis of various malignancies such as kidney cancer [16], esophageal cancer [17], pancreatic cancer [18], small cell lung cancer [19-20], bladder cancer [21], and prostate cancer [22]. However, the clinical significance of these values at baseline and at different time points after treatment remains controversial. Therefore, this study aimed to explore the clinical value of the baseline HALP, NLR, and PLR values and their dynamic changes in the prognosis of patients with NSCLC and establish a nomogram to provide a reference for the prognostic risk assessment of these patients.

## MATERIALS AND METHODS

### Clinical data

Data from patients with advanced NSCLC who received ICIs between August 2019 and November 2022 were retrospectively collected. The inclusion criteria were as follows: (1) pathological diagnosis of NSCLC; (2) clinical stage III, which is inoperable, or stage IV; (3) received immunotherapy or combination immunotherapy; (4) had complete medical records and imaging data available to evaluate efficacy. The exclusion criteria were as follows: (1) pathological diagnosis includes small-cell lung cancer, (2) autoimmune diseases, (3) symptomatic pulmonary interstitial disease and other serious comorbidities, and (4) blood system diseases. In total, 203 patients were enrolled in this study. The requirement for written informed consent was waived due to the retrospective and anonymous study design.

Clinicopathological features of the included patients, including sex, age, pathological type, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score, tumor, node, metastasis (TNM) staging, type of driver gene mutation, smoking and drinking history, number of treatment lines, and treatment options, were evaluated. Hematological parameters, such as hemoglobin, neutrophils, albumin, lymphocytes, and platelets, were measured before treatment, after two cycles of treatment, and after four cycles of treatment.

### Methods

### Treatment options

In the immunotherapy regimen, patients received 200 mg pembrolizumab, 200 mg tislelizumab, 200 mg camrelizumab, 200 mg sintilimab, or 240 mg toripalimab intravenously once every

three weeks. Combination regimens include immunotherapy combined with chemotherapy or anti-angiogenic drugs. For patients who possess EGFR mutations, immunotherapy serves as a posterior-line therapy for them.

**Definitions**

HALP = hemoglobin (g/L) × albumin (g/L) × lymphocytes ($10^9$/L)/platelets ($10^9$/L); NLR= ratio of neutrophil count($10^9$/L) to lymphocyte count ($10^9$/L); PLR = ratio of platelet count ($10^9$/L) to lymphocyte count($10^9$/L).

**Assessment**

Follow-up included outpatient or inpatient reviews and telephone interviews. Follow-ups included the treatment response, recurrence, and time of death. The iRECIST criteria were used to evaluate the patients' response to treatment. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were used as metrics. The objective response rate (ORR) and disease control rate (DCR) were used to evaluate treatment efficacy. The PFS and OS were used to assess survival. The ORR was defined as the sum of CR and PR, while the DCR was defined as the sum of CR, PR, and SD. PFS was defined as the duration from the start of immunotherapy to disease progression or death. OS was defined as the interval from disease onset to death from any cause or the last follow-up, whichever occurred first.

**Ethical statement**

This study was approved by the Ethical Committee of Liaocheng People's Hospital (approval number: 2023246). The requirement for written informed consent was waived because of the retrospective study design.

**Statistical analysis**

IBM SPSS, X-tile, and R were used for the statistical analyses and displays. X-tile was used to determine the optimal cutoff values for HALP, NLR, and PLR. X-tile software selects the best segmentation point by selecting the highest $\chi 2$ value to group the research subjects and using the log-rank test to calculate the minimum P-value [23]. We put the outcome state into the censor status column, survival time into the Survival Time column, and research factors HALP/NLR/PLR into the Marker1 column. Finally, the best truncation values were obtained. The chi-square test and logistic regression analysis were employed to identify significant variables influencing the DCR and ORR. Kaplan–Meier survival analysis and the log-rank test were utilized to compare the OS and PFS across different groups. Cox regression analysis (stepwise, bidirectional) was conducted to evaluate the prognostic factors. A nomogram of the prediction model was constructed from the independent predictors. Bootstrap sampling verification was carried out on the nomogram, and rms packets (1000 bootstrap resamples) were used to correct overfitting. A bootstrapping method is a nonparametric data-generating method in which new datasets are repeatedly generated from an original dataset and created by random drawing from the sample with replacement. The C-index and the calibration curve method were used to assess the accuracy of the prediction model. All tests were conducted using a two-sided approach, with statistical significance established at $P < 0.05$.

**RESULTS**

**Clinical characteristics of the patients**

A total of 203 patients were included in this study. The mean age at the time of diagnosis was

64.3 years. Most patients were male (77.83%; n=158). Their ECOG-PS score was predominantly 0-1 (91.63%; n=186). Squamous cell carcinoma constituted 45.81% of the cases, while non-squamous cell carcinoma comprised 54.19%. Patients with stage III and IV disease represented 42.86% and 57.14% of the patients, respectively. Mutations (including EGFR, KRAS, ALK, ROS-1, and BRAF) were detected in 48 cases (23.64%) but not in 106 cases (52.22%). There were 83 cases (40.89%) treated with monotherapy and 120 patients (59.11%) treated with combination therapy. A total of 125 patients (61.58%) were initially treated, and 78 patients (38.42%) were retreated (Table 1).

**Optimal cutoff**

The optimal cutoff values for HALP, NLR, and PLR to predict PFS and OS were established using X-tile as 13.99 (Figure 1A), 6.23 (Figure 1B), 305.21 (Figure 1C), and 13.99 (Figure 1D), 6.23 (Figure 1E), 251.19 (Figure 1F), respectively. The patients were then categorized based on these optimal cutoff values.

**Assessment**

The $\chi 2$ test was used to analyze the influencing factors. The results showed that $HALP_0$, $HALP_{2C}$, $HALP_{4C}$, $NLR_0$, $NLR_{2C}$, $NLR_{4C}$, $PLR_0$, and $PLR_{4C}$ affected the DCR. The ECOG-PS score, number of immunotherapy lines, and $HALP_0$, $HALP_{4C}$, $NLR_0$, $NLR_{4C}$, and $PLR_0$ levels were correlated with the ORR. Multivariate logistic regression analysis demonstrated that $PLR_0 \leq 305.21$ was associated with a higher DCR (OR = 0.258, 95% CI: 0.070–0.946), and that immunotherapy as the initial treatment (OR = 2.697, 95% CI: 1.430–5.089) along with $NLR_{4C}$ (OR = 4.273, 95% CI: 1.039–17.582) were significantly associated with a higher ORR (Table

2).

**Survival analysis**

Kaplan-Meier survival curves and log-rank tests showed that low $HALP_0$, $HALP_{2C}$, and $HALP_{4C}$ and high $NLR_0$, $NLR_{4C}$, $PLR_0$, and $PLR_{4C}$ levels were associated with shorter PFS (Figure 2A-2I). Low $HALP_0$ and $HALP_{4C}$ levels and high $NLR_0$, $NLR_{4C}$, $PLR_0$, and $PLR_{4C}$ levels were associated with a shorter OS (Figure 2J-2R).

Univariate Cox analysis showed that age, TNM stage, treatment regimen, $HALP_0$, $HALP_{2C}$ $HALP_{4C}$, $NLR_0$, $NLR_{4C}$, $PLR_0$, and $PLR_{4C}$ were correlated with PFS. Multivariate Cox analysis showed that age ≥65 years (HR=2.05, 95%CI: 1.48–2.84, P<0.001), $HALP_0$≤13.99 (HR=0.19, 95%CI: 0.11–0.32, P<0.001), $HALP_{4C}$≤13.99 (HR=0.38, 95%CI: 0.18–0.79, P=0.01), and $NLR_0$>6.23 (HR=5.11, 95%CI: 3.05–8.55, P<0.001) increased the risk of disease progression. The TNM stage (HR = 1.62, 95% CI: 1.16–2.25, P = 0.004) was also an independent predictor of PFS, and patients with stage IV disease had a higher risk of disease progression than those with stage III disease (Table 3).

Univariate Cox analysis demonstrated that the age, TNM stage, treatment regimen, $HALP_0$, $HALP_{4C}$, $NLR_0$, $NLR_{4C}$, $PLR_0$, and $PLR_{4C}$ were correlated with OS. Multivariate Cox analysis showed that age ≥65 years (HR=3.17, 95%CI: 1.80–5.60, P < 0.001), $HALP_0$≤13.99 (HR=0.34, 95%CI: 0.15–0.80, P=0.013), $NLR_0$>6.23 (HR=2.99, 95%CI: 1.27–7.01, P=0.012), and $PLR_{4C}$>251.19 (HR=3.00, 95%CI: 1.67–5.40, P<0.001) increased the risk of death. In addition, the TNM stage (HR = 2.22, 95% CI: 1.18–4.19, P = 0.013) and treatment regimen (HR = 0.24, 95% CI: 0.13–0.47, P < 0.001) were also independent predictors of OS (Table 4).

**Establishment of a nomogram and predictive models**

A nomogram for PFS and OS was constructed based on the Cox multifactor results. The C-indices of the established nomogram were 0.823 (95% CI: 0.799–0.848) and 0.878 (95% CI: 0.845–0.912), respectively, showing that it had good prediction accuracy (Figure 3).

**DISCUSSION**

ICIs are highly effective treatments for patients with advanced NSCLC and PD-L1 TPS ≥ 50%, compared with conventional chemotherapy. In addition, several studies on ICI therapy for NSCLC have shown significant benefits regardless of PD-L1 expression status [4-7] without side effects or financial burden for patients. Efficient, inexpensive, and convenient markers are needed to help characterize patients who may potentially benefit from ICI therapy. The HALP, NLR, and PLR values are calculated based on hematological indicators and are cost-effective and easy to obtain. Moreover, the nomogram we established is a simple and convenient prediction model. It can be used in the clinic to estimate the survival status of patients, identify whether they are high-risk, and inform early interventions to improve their quality of life. In our study, the HALP, NLR, and PLR values at various time points effectively predicted immunotherapy response in patients with advanced NSCLC, where low HALP with high NLR and PLR values indicated poor prognosis. Hence, our data can serve as a reference for patient stratification in future RCTs of treatments in NSCLC or other related diseases.

Studies have shown that the occurrence, progression, and metastasis of malignant tumors are closely related to the nutritional, inflammatory, and immune status of the body [24]. A low HALP value could be attributed to low hemoglobin counts, low hemoglobin counts, low

lymphocytes counts or high platelets counts. Meanwhile, a high NLR value could be attributed to high neutrophil counts, or low lymphocyte counts, and a high PLR could be attributed to high platelet counts, or low lymphocyte counts. Most patients with advanced cancer have varying degrees of anemia, which can lead to an increased risk of death from various tumors [25]. Neutrophils are the first responders to inflammation and infection in the body and are the main factors connecting inflammation and tumors, inhibiting or promoting cancer [26-27]. Human blood albumin levels also reflects the nutritional state of the body; as a negative acute-phase protein, it can also reflect the body's inflammatory state [28]. Platelets can release transformational growth factor-β1, vascular epidermal growth factor, and other cytokines, which play an important role in tumor cell growth, metastasis, angiogenesis, and immune escape [29]. Lymphocytes initiate a cytotoxic immune response to inhibit the proliferation, invasion, and metastasis of tumor cells and are key cells in the immune response against tumor cells [30]. Therefore, low HALP values with high NLR and PLR values could be applied as a reliable biomarker of tumor progression and poor prognosis. Compared with the application of single indicators, a composite indicator involving the HALP, NLR, and PLR integrates multiple parameters, which can more comprehensively and objectively reflect the activation of the inflammatory response, immune response, and nutritional status. Composite indicators have been used to evaluate the prognosis of various malignant tumors. To the best of our knowledge, this is the first study to describe the prognostic value of incorporating baseline and dynamic changes in a range of inflammatory markers to predict the response to full-line immunotherapy in NSCLC.

In this retrospective study, we assessed the clinical characteristics and prognosis of 203 patients with NSCLC, forecasting their clinical outcomes by analyzing peripheral blood inflammatory and nutritional markers potentially linked to NSCLC. Unlike previous studies, this work developed multiple models using HALP, NLR, and PLR data across different time points (0, 2c, 4c) to dynamically predict treatment efficacy and patient survival rates. Diverging from a prior study [31], which was limited to patients receiving first-line immunotherapy only, our study included patients across all lines of immunotherapy, including those beyond the first line. An earlier study [31] only included patients with wild-type EGFR, ALK, and ROS-1, as opposed to our current study, which included patients with both mutated and wild-type genes. Patients with gene mutations were administered targeted therapy as the first line, and immunotherapy was applied as the backline. The third distinction was that this previous study [31] employed the interquartile range for grouping, which may introduce a larger error margin. The optimal cutoff for these indices might vary between PFS and OS, as determined using X-tile. Both HALR and NLR displayed identical optimal cutoffs for PFS and OS (HALP = 13.99, NLR = 6.23), whereas the optimal cutoff for PLR differed (PLR = 251.19 for OS, PLR = 305.21 for PFS); hence, the algorithm was deemed more robust. Furthermore, our data indicate that $HALP_0 > 13.99$ and $NLR_0 \leq 6.23$ are associated with longer PFS and OS, $HALP_{4C} > 13.99$ correlates with longer PFS, and $PLR_{4C} \leq 251.19$ correlates with longer OS.

NLR and PLR are markers for the general immune response to various stress conditions [32]. A previous review [33] described several experiments to confirm that inflammatory biomarkers can predict clinical outcomes in NSCLC treated with ICIs. Qi Yuan et al. [34] analyzed low

baseline NLR and PLR values and showed a strong association with both better PFS (P = 0.011 and 0.027, respectively) and longer OS (P = 0.042 and 0.039, respectively) in patients with advanced NSCLC treated with ICIs. Jianxin Chen et al. [35] observed that immunotherapy in patients with NSCLC with a baseline NLR ≤ 4 was associated with improved PFS (5.7 vs. 2.0 months, P = 0.0083) and OS (21.3 vs. 5.0 months, P = 0.0163). Further investigation revealed that even those harboring EGFR-sensitive mutations could benefit from anti-PD-1 inhibitors as further line treatment after progression to EGFR-TKIs, which supports our finding in the current study. However, most of these studies were based on baseline data only. Yohei Asano et al. [36] showed that NLR and PNI dynamics were independent predictors of BoMRR and OS, which were demonstrated as biomarkers of treatment response and prognosis in the ICI treatment of patients with NSCLC with bone metastases. Unlike our study, we did not individually stratify patients with bone metastases from NSCLC. Polat Olgun et al. [37] revealed that high post-treatment NLRs ≥ 5 (p = 0.004) and PLRs ≥ 170 (p ≤ 0.001) were independent prognostic factors for shorter OS. The above two experiments are similar to our study, which dynamically observed changes in the corresponding indicators. The above conclusions also apply to SCLC [38].

The HALP score has been shown to be associated with the prognosis of various malignancies; however, there are few studies on HALP in NSCLC, with only two articles available so far. In 2022, Wei et al. [39] conducted a retrospective analysis of 362 NSCLC patients receiving adjuvant chemotherapy. The optimal cutoff value determined using X-tile was 48.2; HALP scores below 48.2 were associated with poorer OS (P = 0.02) and DFS (P < 0.01). However, it

is important to note that it included NSCLC patients receiving adjuvant chemotherapy, which was different from ours. Fang et al. [31] examined patients with inoperable NSCLC undergoing first-line immunotherapy in combination with chemotherapy and noted that the HALP scores did not significantly predict PFS ($p = 0.771$) or OS ($p = 0.996$), which was different from ours. High pretreatment PLR (OR = 2.612) and increased NLR during follow-up (OR = 2.516) were significantly linked to a lower ORR. Furthermore, high pretreatment PLR (HR = 2.319) predicted shorter PFS, while high pretreatment NLR (HR=1.635) and increased NLR (HR = 1.663) and PLR (HR = 1.691) predicted poorer OS.

To evaluate the accuracy of our predictive model, we constructed a nomogram, calculated the agreement index, and plotted a calibration curve. Internal verification results showed that the C-index of the model for PFS and OS was 0.823 (95% CI: 0.799–0.848) and 0.878 (95% CI: 0.845–0.912), respectively, indicating that the accuracy of the model is high.

Our study has several limitations. First, it was a single-center retrospective study with a limited sample size, which requires further expansion of the sample size in multiple centers for verification. Second, changes in hematological markers may have been caused by chemotherapy alone, requiring a control group of patients receiving chemotherapy only. We were unable to recruit a sufficient number of patients as controls because chemotherapy alone is rare in current clinical practice. Despite these limitations, the role of immune cells in responding to the immune inflammatory state of the body during tumor immunotherapy cannot be overlooked, which is the mechanism underlying this study [31]. Third, there is no clear consensus on the optimal cutoff values for the parameters we investigated. In the future, the

application value of the above indices in the immunotherapy of advanced NSCLC should be further explored through a larger sample size or meta-analysis.

## CONCLUSION

The HALP, NLR, and PLR values at various time points effectively predicted immunotherapy response in patients with advanced NSCLC, where low HALP with high NLR and PLR values indicated poor prognosis. Our data can serve as a designing reference for stratification in later RCTs.

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## Data availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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## TABLES AND FIGURES WITH LEGENDS

### TABLE 1. Baseline characteristics of the patients

| Characteristics | | n | Percentage (%) |
|---|---|---|---|
| Sex | Male | 158 | 77.83 |
| | Female | 45 | 22.17 |
| Age | < 65 | 99 | 48.77 |
| | ≥ 65 | 104 | 51.23 |
| Smoking | No | 75 | 36.95 |
| | Yes | 128 | 63.05 |
| Drinking | No | 129 | 63.55 |
| | Yes | 74 | 36.45 |
| ECOG-PS | 0 - 1 | 186 | 91.63 |
| | 2 | 17 | 8.37 |
| Histology | Non-squamous carcinoma | 110 | 54.19 |
| | Squamous carcinoma | 93 | 45.81 |
| TNM stage | III | 87 | 42.86 |
| | IV | 116 | 57.14 |
| Gene mutation | No | 49 | 24.14 |
| | Yes | 48 | 23.64 |
| | Unknown | 106 | 52.22 |
| Option of treatment | Monotherapy | 83 | 40.89 |
| | Combination therapy | 120 | 59.11 |

| Characteristics | | n | Percentage (%) |
|---|---|---|---|
| Lines of treatment | 1 | 125 | 61.58 |
| | ≥ 2 | 78 | 38.42 |

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; TNM stage: Tumor node metastasis stage.

**TABLE 2. Response to treatment**

| Clinical indices | Disease control rate | | | Overall response rate | | |
|---|---|---|---|---|---|---|
| | n | Percentage | P value | n | Percentage | P value |
| **Sex** | | | | | | |
| Male | 136/158 | 86.08% | 0.919 | 84/158 | 53.16% | 0.777 |
| Female | 39/45 | 86.67% | | 25/45 | 55.56% | |
| **Age** | | | | | | |
| <65 | 89/99 | 89.90% | 0.137 | 48/99 | 48.48% | 0.146 |
| ≥65 | 86/104 | 82.69% | | 61/104 | 58.65% | |
| **Smoking** | | | | | | |
| No | 67/75 | 89.33% | 0.323 | 45/75 | 60.00% | 0.168 |
| Yes | 108/128 | 84.38% | | 64/128 | 50.00% | |
| **Drinking** | | | | | | |
| No | 113/129 | 87.60% | 0.448 | 68/129 | 52.71% | 0.711 |
| Yes | 62/74 | 83.78% | | 41/74 | 55.41% | |
| **ECOG-PS** | | | | | | |
| 0-1 | 162/186 | 87.10% | 0.224 | 96/186 | 51.61% | 0.049 |
| 2 | 13/17 | 76.47% | | 13/17 | 76.47% | |
| **Histology** | | | | | | |
| Non-squamous carcinoma | 92/110 | 83.64% | 0.248 | 66/110 | 60.00% | 0.050 |
| Squamous carcinoma | 83/93 | 89.25% | | 43/93 | 46.24% | |
| **TNM stage** | | | | | | |
| III | 73/87 | 83.91% | 0.411 | 48/87 | 55.17% | 0.715 |
| IV | 102/116 | 87.93% | | 61/116 | 52.59% | |
| **Gene mutation** | | | | | | |
| No | 41/49 | 83.67% | | 25/49 | 51.02% | |
| Yes | 41/48 | 85.42% | 0.780 | 28/48 | 58.33% | 0.745 |
| Unknow | 93/106 | 87.74% | | 56/106 | 52.83% | |
| **Option of treatment** | | | | | | |
| Monotherapy | 73/83 | 87.95% | 0.549 | 38/83 | 45.78% | 0.060 |
| Combination therapy | 102/120 | 85% | | 71/120 | 59.17% | |
| **Lines of treatment** | | | | | | |

| Clinical indices | Disease control rate | | | Overall response rate | | |
|---|---|---|---|---|---|---|
| | n | Percentage | P value | n | Percentage | P value |
| 1 | 109/125 | 87.20% | 0.603 | 56/125 | 44.80% | 0.001 |
| ≥2 | 66/78 | 84.62% | | 53/78 | 67.95% | |
| **$HALP_0$ (PFS and OS)** | | | | | | |
| ≤13.99 | 55/82 | 67.07% | ＜0.001 | 57/82 | 69.51% | ＜0.001 |
| >13.99 | 120/121 | 99.17% | | 52/121 | 42.98% | |
| **$HALP_{2C}$ (PFS and OS)** | | | | | | |
| ≤13.99 | 21/32 | 65.63% | ＜0.001 | 21/32 | 65.63% | 0.140 |
| >13.99 | 154/171 | 90.06% | | 88/171 | 51.46% | |
| **$HALP_{4C}$ (PFS and OS)** | | | | | | |
| ≤13.99 | 20/34 | 58.82% | ＜0.001 | 24/34 | 70.59% | 0.030 |
| >13.99 | 155/169 | 91.72% | | 85/169 | 50.30% | |
| **$NLR_0$ (PFS and OS)** | | | | | | |
| ≤6.23 | 120/122 | 98.36% | ＜0.001 | 52/122 | 42.62% | ＜0.001 |
| >6.23 | 55/81 | 67.90% | | 57/81 | 70.37% | |
| **$NLR_{2C}$ (PFS and OS)** | | | | | | |
| ≤6.23 | 164/187 | 87.70% | 0.035 | 98/187 | 52.41% | 0.208 |
| >6.23 | 11/16 | 68.75% | | 11/16 | 68.75% | |
| **$NLR_{4C}$ (PFS and OS)** | | | | | | |
| ≤6.23 | 160/177 | 90.40% | ＜0.001 | 88/177 | 49.72% | 0.003 |
| >6.23 | 15/26 | 57.69% | | 21/26 | 80.77% | |
| **$PLR_0$ (PFS)** | | | | | | |
| ≤305.21 | 133/137 | 97.08% | ＜0.001 | 67/137 | 48.91% | 0.049 |
| >305.21 | 42/66 | 63.64% | | 42/66 | 63.64% | |
| **$PLR_{2C}$ (PFS)** | | | | | | |
| ≤305.21 | 152/173 | 87.86% | 0.101 | 90/173 | 52.02% | 0.251 |
| >305.21 | 23/30 | 76.67% | | 19/30 | 63.33% | |
| **$PLR_{4C}$ (PFS)** | | | | | | |
| ≤305.21 | 156/174 | 89.66% | ＜0.001 | 89/174 | 51.15% | 0.075 |
| >305.21 | 19/29 | 65.52% | | 20/29 | 68.97% | |
| **$PLR_0$ (OS)** | | | | | | |
| ≤251.19 | 115/116 | 99.14% | ＜0.001 | 53/116 | 45.69% | 0.008 |

| Clinical indices | Disease control rate | | | Overall response rate | | |
|---|---|---|---|---|---|---|
| | n | Percentage | P value | n | Percentage | P value |
| >251.19 | 60/87 | 68.97% | | 56/87 | 64.37% | |
| **$PLR_{2C}$ (OS)** | | | | | | |
| ⩽251.19 | 135/153 | 88.24% | 0.143 | 81/153 | 52.94% | 0.706 |
| >251.19 | 40/50 | 80.00% | | 28/50 | 56.00% | |
| **$PLR_{4C}$ (OS)** | | | | | | |
| ⩽251.19 | 136/150 | 90.67% | 0.002 | 76/150 | 50.67% | 0.146 |
| >251.19 | 39/53 | 73.58% | | 33/53 | 62.26% | |

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; TNM stage: Tumor node metastasis stage; PFS: Progression free survival; OS: Overall survival; $HALP_0$: Hemoglobin, albumin, and platelet before treatment; $HALP_{2C}$: Hemoglobin, albumin, and platelet after 2 cycles of treatment; $HALP_{4C}$: Hemoglobin, albumin, and platelet after 4 cycles of treatment; $NLR_0$: Neutrophil-to-lymphocyte ratio before treatment; $NLR_{2C}$: Neutrophil-to-lymphocyte ratio after 2 cycles of treatment; $NLR_{4C}$: Neutrophil-to-lymphocyte ratio after 4 cycles of treatment; $PLR_0$: Platelet-to-lymphocyte ratio before treatment; $PLR_{2C}$: Platelet-to-lymphocyte ratio after 2 cycles of treatment; $PLR_{4C}$: Platelet-to-lymphocyte ratio after 4 cycles of treatment.

**TABLE 3. Univariate and multivariate analysis of progression free survival**

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| Clinical indexes | HR (95%CI) | P value | HR (95%CI) | P value |
| **Sex** | | | | |
| Male | | | | |
| Female | 1.06 (0.74, 1.51) | 0.752 | | |
| **Age** | | | | |
| <65 | | | | |
| ≥65 | 1.40 (1.03, 1.91) | 0.029 | 2.05 (1.48, 2.84) | <0.001 |
| **Smoking** | | | | |
| No | | | | |
| Yes | 1.07 (0.78, 1.46) | 0.673 | | |
| **Drinking** | | | | |
| No | | | | |
| Yes | 0.91 (0.67, 1.25) | 0.566 | | |
| **ECOG-PS** | | | | |
| 0-1 | | | | |
| 2 | 0.80 (0.44, 1.49) | 0.487 | | |
| **Histology** | | | | |
| Non-squamous carcinoma | | | | |
| Squamous carcinoma | 0.91 (0.67, 1.23) | 0.545 | | |
| **TNM stage** | | | | |
| III | | | | |
| IV | 1.47 (1.08, 2.01) | 0.014 | 1.62 (1.16, 2.25) | 0.004 |
| **Gene mutation** | | | | |
| No | | | | |
| Yes | 0.89 (0.58, 1.37) | 0.604 | | |
| Unknow | 0.88 (0.61, 1.26) | 0.478 | | |
| **Option of treatment** | | | | |
| Monotherapy | | | | |
| Combination therapy | 0.55 (0.41, 0.75) | <0.001 | | |
| **Lines of treatment** | | | | |
| 1 | | | | |
| ≥2 | 1.13 (0.83, 1.54) | 0.427 | | |
| **$HALP_0$** | | | | |
| ≤13.99 | | | | |
| >13.99 | 0.09 (0.06, 0.13) | <0.001 | 0.19 (0.11, 0.32) | <0.001 |
| **$HALP_{2C}$** | | | | |
| ≤13.99 | | | | |
| >13.99 | 0.42 (0.29, 0.63) | <0.001 | 1.56 (0.97, 2.51) | 0.066 |
| **$HALP_{4C}$** | | | | |

| | | | | |
|---|---|---|---|---|
| ≤13.99 | | | | |
| >13.99 | 0.30 (0.20, 0.44) | <0.001 | 0.38 (0.18, 0.79) | 0.010 |
| **$NLR_0$** | | | | |
| ≤6.23 | | | | |
| >6.23 | 8.46 (5.93, 12.06) | <0.001 | 5.11 (3.05, 8.55) | <0.001 |
| **$NLR_{2C}$** | | | | |
| ≤6.23 | | | | |
| >6.23 | 1.33 (0.78, 2.27) | 0.295 | | |
| **$NLR_{4C}$** | | | | |
| ≤6.23 | | | | |
| >6.23 | 4.00 (2.57, 6.25) | <0.001 | | |
| **PLR0** | | | | |
| ≤305.21 | | | | |
| >305.21 | 5.31 (3.78, 7.45) | <0.001 | | |
| **$PLR_{2C}$** | | | | |
| ≤305.21 | | | | |
| >305.21 | 1.46 (0.97, 2.19) | 0.070 | | |
| **$PLR_{4C}$** | | | | |
| ≤305.21 | | | | |
| >305.21 | 2.16 (1.43, 3.28) | <0.001 | 0.54 (0.25, 1.18) | 0.120 |

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; TNM stage: Tumor node metastasis stage; $HALP_0$: Hemoglobin, albumin, and platelet before treatment; $HALP_{2C}$: Hemoglobin, albumin, and platelet after 2 cycles of treatment; $HALP_{4C}$: Hemoglobin, albumin, and platelet after 4 cycles of treatment; $NLR_0$: Neutrophil-to-lymphocyte ratio before treatment; $NLR_{2C}$: Neutrophil-to-lymphocyte ratio after 2 cycles of treatment; $NLR_{4C}$: Neutrophil-to-lymphocyte ratio after 4 cycles of treatment; $PLR_0$: Platelet-to-lymphocyte ratio before treatment; $PLR_{2C}$: Platelet-to-lymphocyte ratio after 2 cycles of treatment; $PLR_{4C}$: Platelet-to-lymphocyte ratio after 4 cycles of treatment.

**TABLE 4. Univariate and multivariate analysis of overall survival**

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| Clinical indexes | HR (95%CI) | P-value | HR (95%CI) | P-value |
| **Sex** | | | | |
| Male | | | | |
| Female | 0.77 (0.40, 1.49) | 0.440 | | |
| **Age** | | | | |
| <65 | | | | |
| ≥65 | 2.19 (1.28, 3.74) | 0.004 | 3.17 (1.80, 5.60) | <0.001 |
| **Smoking** | | | | |
| No | | | | |
| Yes | 1.50 (0.86, 2.60) | 0.153 | | |
| **Drinking** | | | | |
| No | | | | |
| Yes | 1.32 (0.79, 2.21) | 0.284 | | |
| **ECOG-PS** | | | | |
| 0-1 | | | | |
| 2 | 1.85 (0.84, 4.08) | 0.127 | | |
| **Histology** | | | | |
| Non-squamous carcinoma | | | | |
| Squamous carcinoma | 0.63 (0.37, 1.07) | 0.084 | | |
| **TNM stage** | | | | |
| III | | | | |
| IV | 2.81 (1.54, 5.11) | 0.001 | 2.22 (1.18, 4.19) | 0.013 |
| **Gene mutation** | | | | |
| No | | | | |
| Yes | 0.75 (0.37, 1.52) | 0.421 | | |
| Unknown | 0.76 (0.42, 1.37) | 0.367 | | |
| **Option of treatment** | | | | |
| Monotherapy | | | | |
| Combination therapy | 0.18 (0.10, 0.33) | <0.001 | 0.24 (0.13, 0.47) | <0.001 |
| **Lines of treatment** | | | | |
| 1 | | | | |
| ≥2 | 1.03 (0.61, 1.74) | 0.903 | | |
| **$HALP_0$** | | | | |
| ≤13.99 | | | | |
| >13.99 | 0.10 (0.06, 0.19) | <0.001 | 0.34 (0.15, 0.80) | 0.013 |
| **$HALP_{2C}$** | | | | |
| ≤13.99 | | | | |
| >13.99 | 0.58 (0.29, 1.14) | 0.115 | | |
| **$HALP_{4C}$** | | | | |

| | | | | |
|---|---|---|---|---|
| ≤13.99 | | | | |
| >13.99 | 0.33 (0.18, 0.61) | <0.001 | | |
| **$NLR_0$** | | | | |
| ≤6.23 | | | | |
| >6.23 | 8.29 (4.60, 14.93) | <0.001 | 2.99 (1.27, 7.01) | 0.012 |
| **$NLR_{2C}$** | | | | |
| ≤6.23 | | | | |
| >6.23 | 0.81 (0.25, 2.58) | 0.719 | | |
| **$NLR_{4C}$** | | | | |
| ≤6.23 | | | | |
| >6.23 | 3.42 (1.69, 6.93) | 0.001 | | |
| **$PLR_0$** | | | | |
| ≤251.19 | | | | |
| >251.19 | 6.05 (3.47, 10.55) | <0.001 | | |
| **$PLR_{2C}$** | | | | |
| ≤251.19 | | | | |
| >251.19 | 0.91 (0.50, 1.66) | 0.763 | | |
| **$PLR_{4C}$** | | | | |
| ≤251.19 | | | | |
| >251.19 | 1.95 (1.15, 3.32) | 0.014 | 3.00 (1.67, 5.40) | <0.001 |

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; TNM stage: Tumor node metastasis stage; $HALP_0$: Hemoglobin, albumin, and platelet before treatment; $HALP_{2C}$: Hemoglobin, albumin, and platelet after 2 cycles of treatment; $HALP_{4C}$: Hemoglobin, albumin, and platelet after 4 cycles of treatment; $NLR_0$: Neutrophil-to-lymphocyte ratio before treatment; $NLR_{2C}$: Neutrophil-to-lymphocyte ratio after 2 cycles of treatment; $NLR_{4C}$: Neutrophil-to-lymphocyte ratio after 4 cycles of treatment; $PLR_0$: Platelet-to-lymphocyte ratio before treatment; $PLR_{2C}$: Platelet-to-lymphocyte ratio after 2 cycles of treatment; $PLR_{4C}$: Platelet-to-lymphocyte ratio after 4 cycles of treatment.

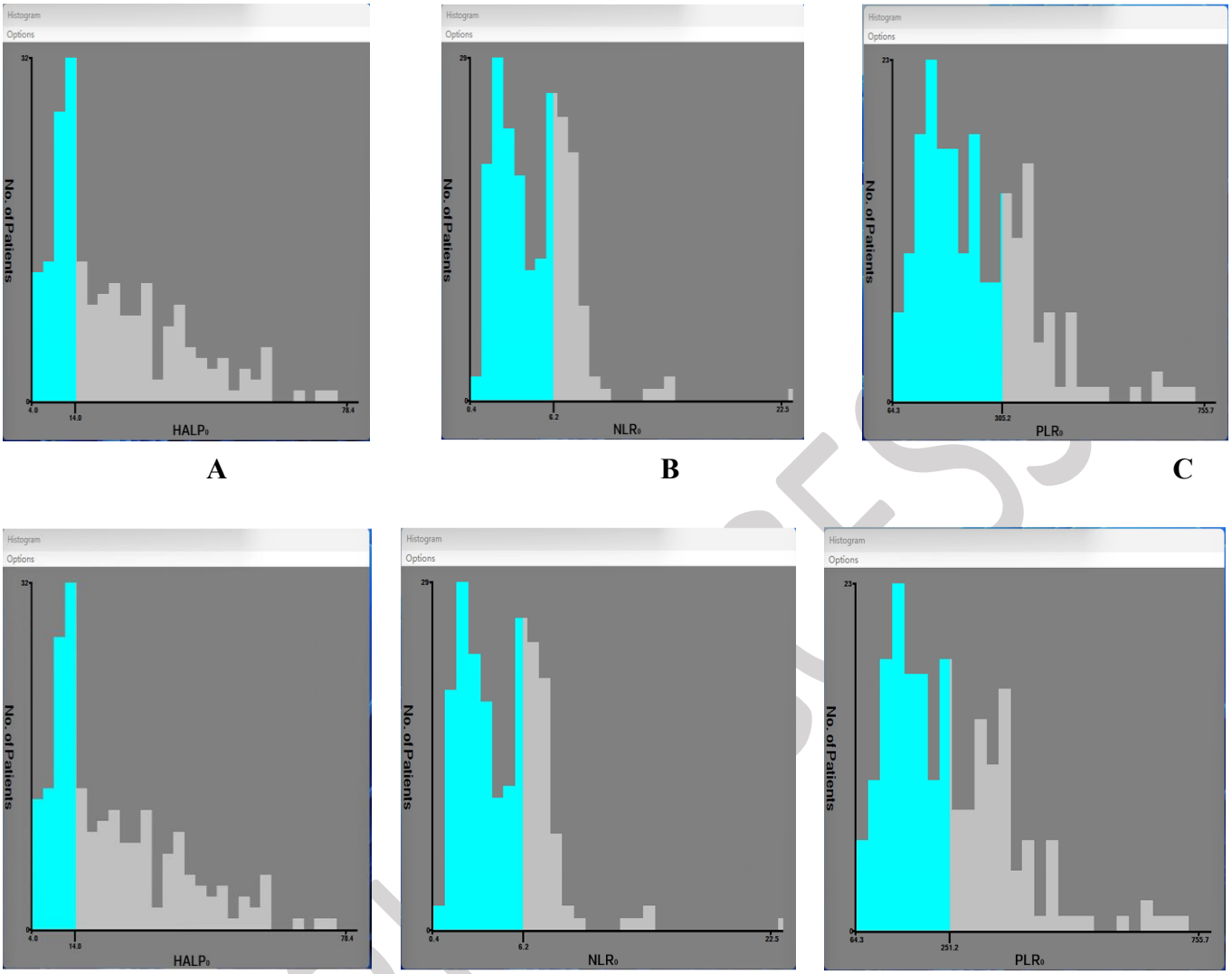
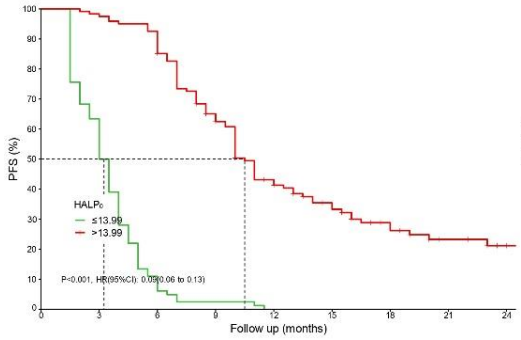
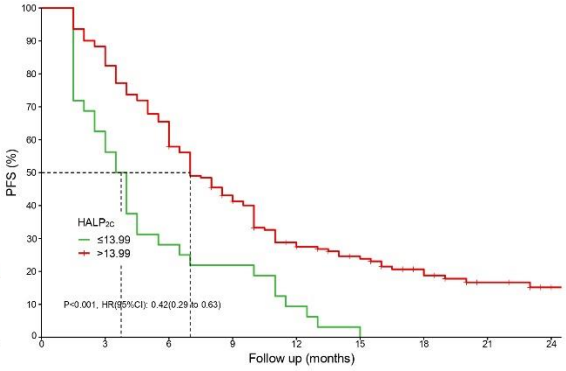



**FIGURE 1. The cutoff points for $NLR_0$/$PLR_0$/$HAPL_0$ of progression free survival and overall survival using the X-tile program**. (A) $HALP_0$ of progression free survival; (B) $NLR_0$ of progression free survival; (C) $PLR_0$ of progression free survival; (D) $HALP_0$ of overall survival; (E) $NLR_0$ of overall survival; (F) $PLR_0$ of overall survival.

**A**

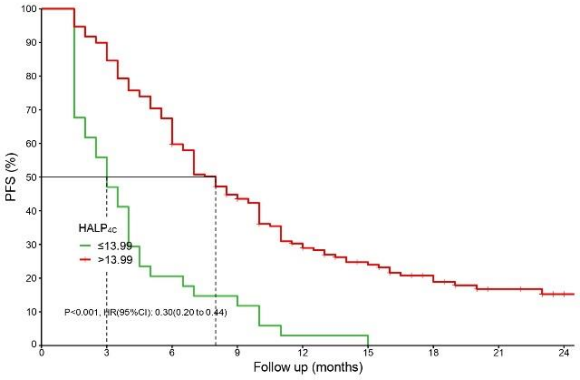

PFS (%)
HALP0
≤13.99
>13.99
P<0.001, HR(95%CI): 0.09(0.06 to 0.13)
Follow up (months)

**B**

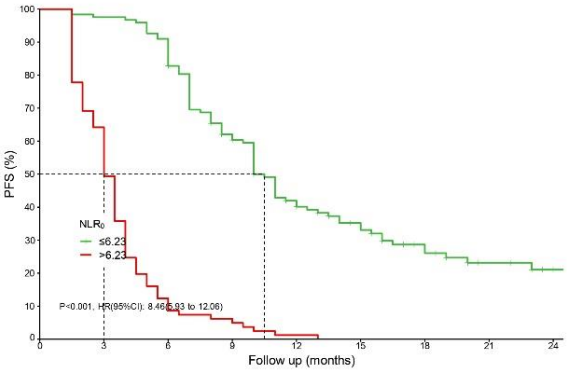

PFS (%)
HALP2C
≤13.99
>13.99
P<0.001, HR(95%CI): 0.42(0.29 to 0.63)
Follow up (months)

:

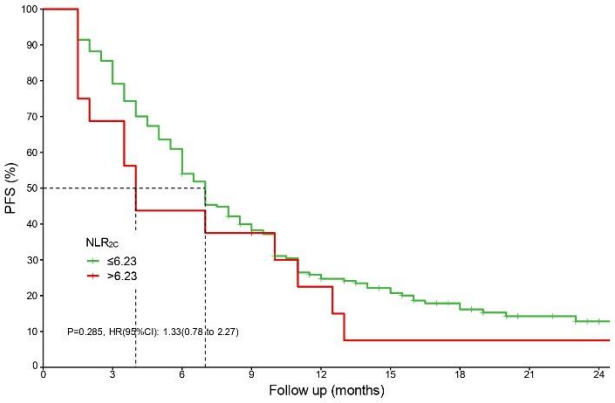
**C**


PFS (%)
HALP4C
≤13.99
>13.99
P<0.001, HR(95%CI): 0.30(0.20 to 0.44)
Follow up (months)

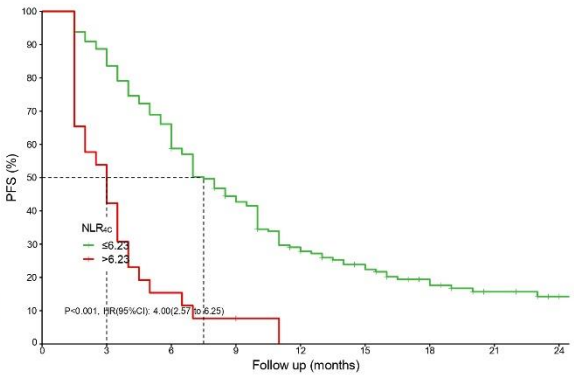
**D**


PFS (%)
NLR0
≤6.23
>6.23
P<0.001, HR(95%CI): 8.46(5.93 to 12.06)
Follow up (months)

**E**

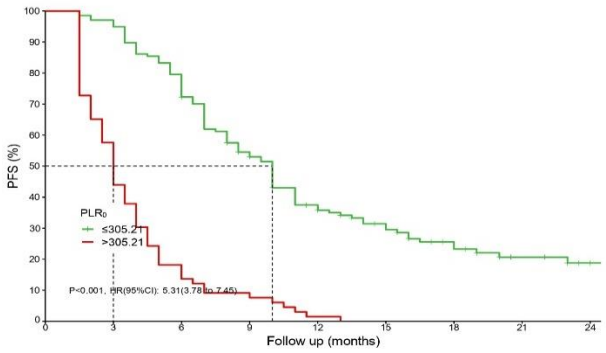

PFS (%)
NLR2C
≤6.23
>6.23
P=0.285, HR(95%CI): 1.33(0.78 to 2.27)
Follow up (months)

**F**

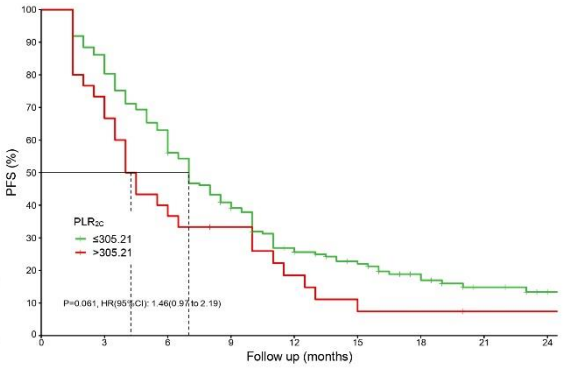

PFS (%)
NLR4C
≤6.23
>6.23
P<0.001, HR(95%CI): 4.00(2.57 to 6.25)
Follow up (months)

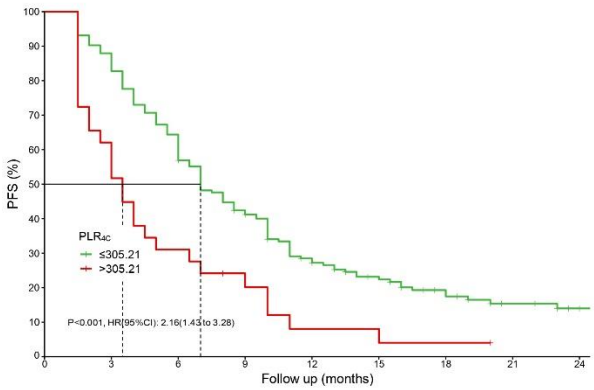
**G**

**H**


PFS (%)
PLR0
≤305.21
>305.21
P<0.001, HR(95%CI): 5.31(3.78 to 7.45)
Follow up (months)

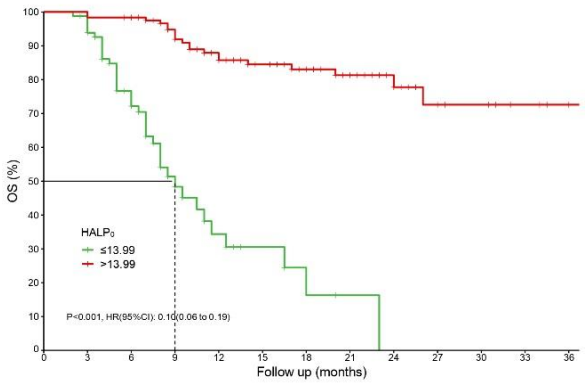
I


PFS (%)
PLR2C
≤305.21
>305.21
P=0.061, HR(95%CI): 1.46(0.97 to 2.19)
Follow up (months)

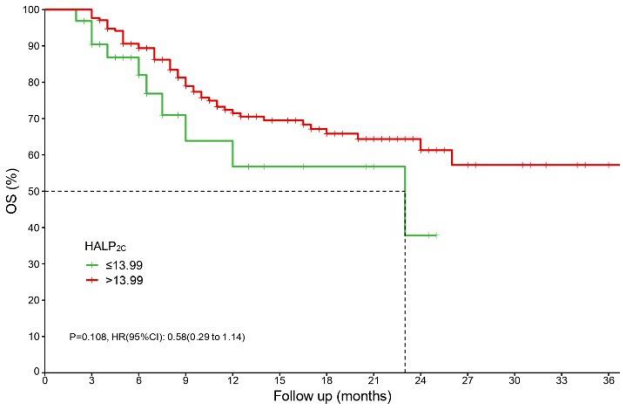

PFS (%)
PLR4C
≤305.21
>305.21
P<0.001, HR(95%CI): 2.16(1.43 to 3.28)
Follow up (months)

J

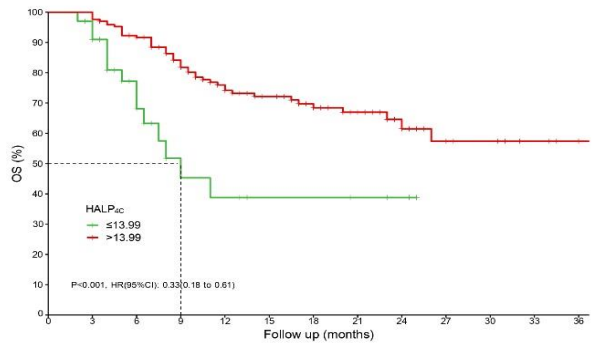
K


OS (%)
HALP0
≤13.99
>13.99
P<0.001, HR(95%CI): 0.10(0.06 to 0.19)
Follow up (months)

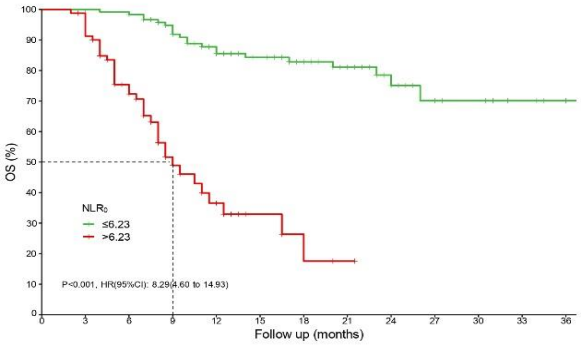
L


OS (%)
HALP2C
≤13.99
>13.99
P=0.108, HR(95%CI): 0.58(0.29 to 1.14)
Follow up (months)

M


OS (%)
HALP4C
≤13.99
>13.99
P<0.001, HR(95%CI): 0.33(0.18 to 0.61)
Follow up (months)

N


OS (%)
NLR0
≤6.23
>6.23
P<0.001, HR(95%CI): 8.29(4.60 to 14.93)
Follow up (months)

O

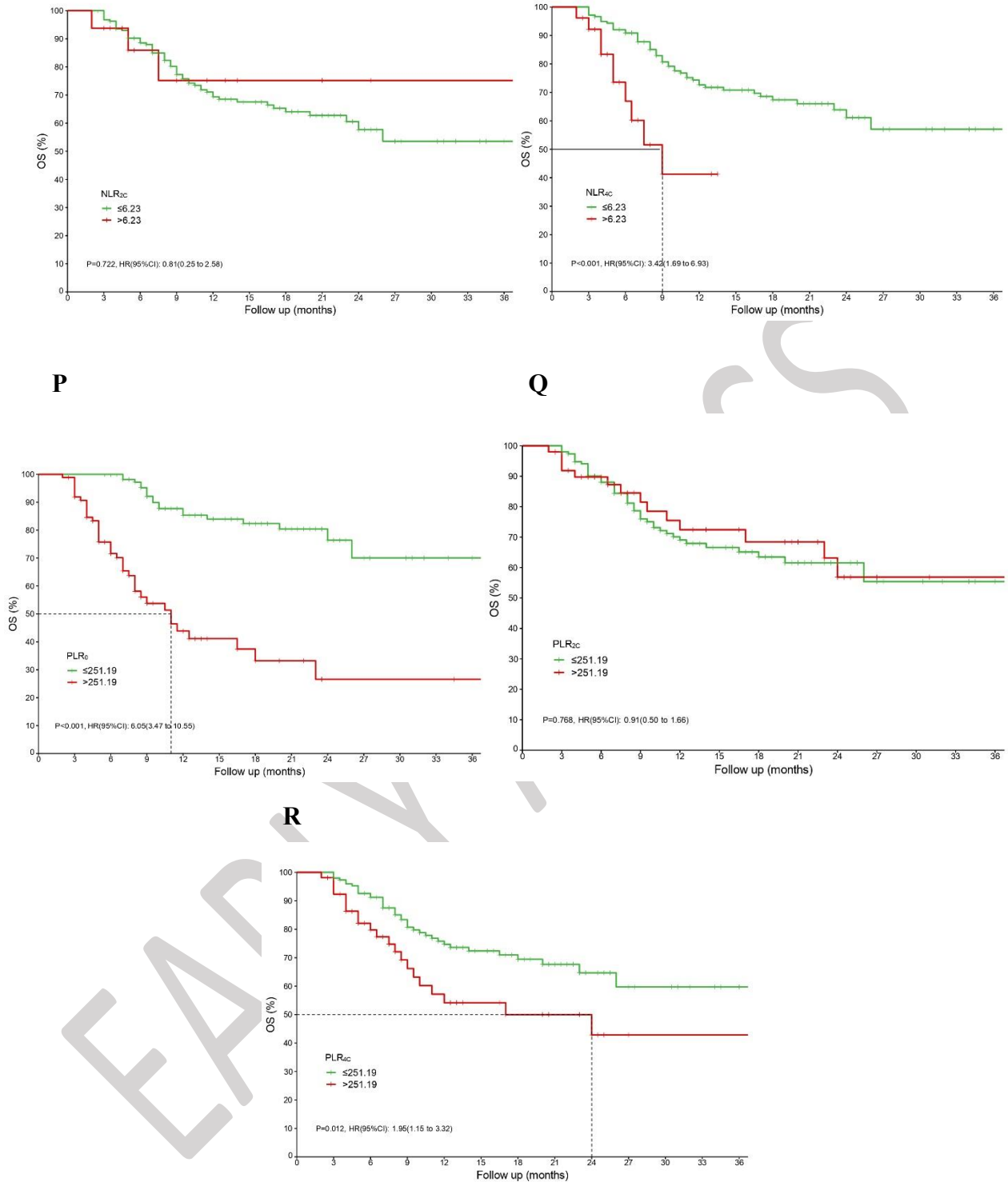



**FIGURE 2. Kaplan–Meier curves for progression free survival and overall survival.** (A and J) Progression free survival and overall survival stratified by the baseline $HALP_0$ index; (B and K) Progression free survival and overall survival stratified by the baseline $HALP_{2C}$ index; (Cand L) Progression free survival and overall survival stratified by the baseline $HALP_{4C}$ index; (D and M) Progression free survival and overall survival stratified by the baseline $NLR_0$ index; (E and N) Progression free survival and overall survival stratified by the baseline $NLR_{2C}$ index; (F and O) PFS

and OS stratified by the baseline $NLR_{4C}$ index; (Gand P) Progression free survival and overall survival stratified by the baseline $PLR_0$ index; (H and Q) Progression free survival and overall survival stratified by the baseline $PLR_{2C}$ index; (I and R) Progression free survival and overall survival stratified by the baseline $PLR_{4C}$ index; PFS: Progression free survival, OS: Overall survival.

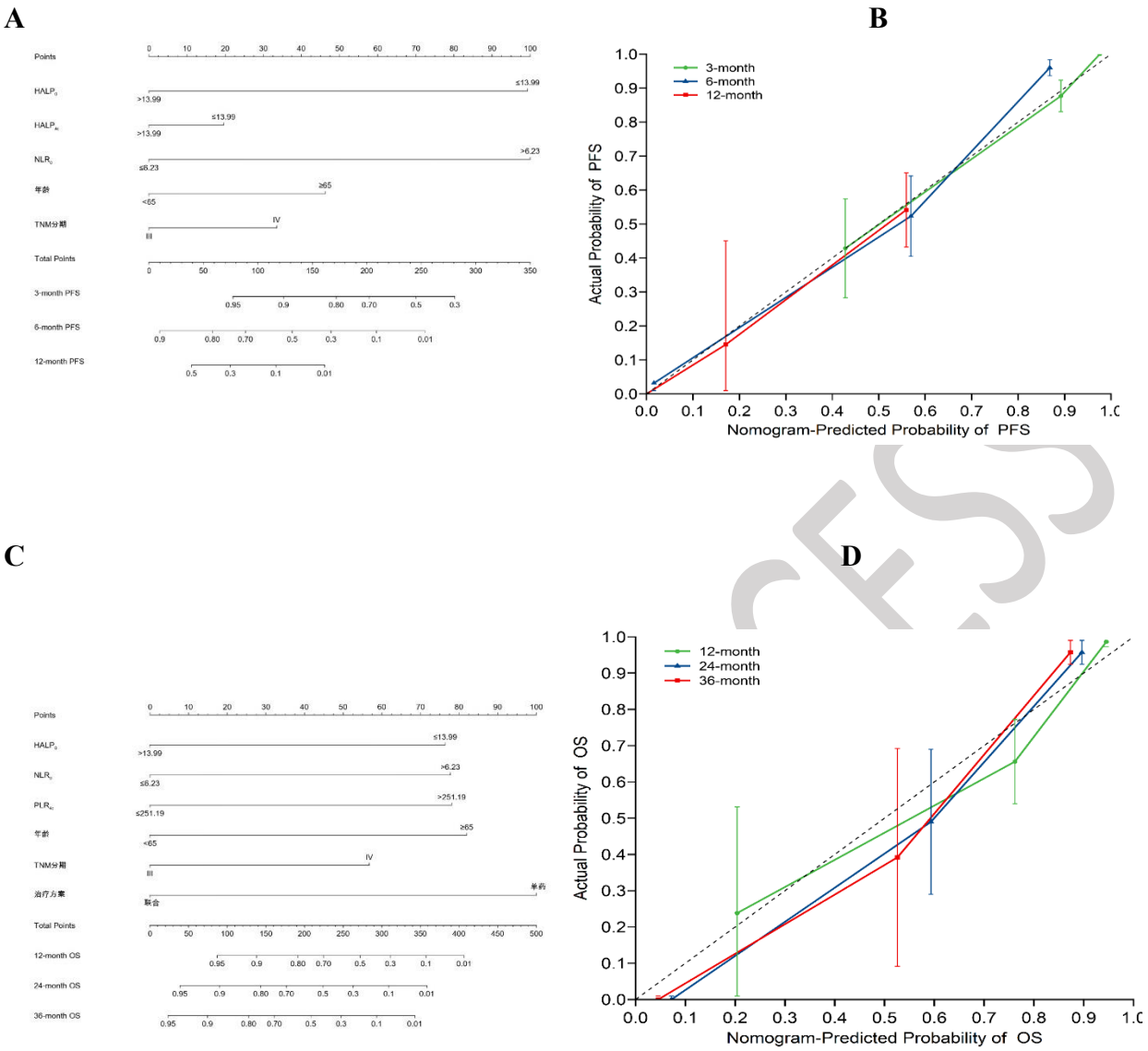



**FIGURE 3. Nomogram predicting the progression free survival and overall survival and calibration plots.** (A) Nomogram predicting the progression free survival; (B) Calibration curve for predicting the probability of 3-months ,6-months and 12-months progression free survival; (C) Nomogram predicting the overall survival; (D) Calibration curve for predicting the probability of 12-months, 24-months, and 36-months overall survival.