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Original Article

A clinical study of the CALLY index and HALP score for evaluating response to FOLFOX in colorectal cancer with lung metastases

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Abstract: Objectives: To evaluate the predictive value of the C-reactive protein-albumin-lymphocyte (CALLY) index and the hemoglobin-albumin-lymphocyte-platelet (HALP) score for chemotherapy response and survival outcomes in colorectal cancer (CRC) patients with pulmonary metastases treated with FOLFOX chemotherapy. Methods: This retrospective study included CRC patients with lung metastases who received first-line FOLFOX-based chemotherapy. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cutoff values for CALLY and HALP in predicting objective response. Logistic regression analyses were performed to identify factors associated with objective response. Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method and Cox proportional hazards models. Combined risk stratification based on CALLY and HALP was further evaluated. Results: Both CALLY and HALP scores were significantly higher in patients achieving objective response than those in non-responders. In multivariable logistic regression, CALLY and HALP were independent protective factors for objective response. Survival analyses demonstrated that low CALLY and low HALP were associated with significantly shorter PFS and OS. In multivariable Cox analyses, HALP remained an independent predictor for both PFS and OS, whereas CALLY was independently associated with PFS and showed a borderline association with OS. Combined stratification based on CALLY and HALP further improved prognostic discrimination. Time-dependent ROC analysis showed that the combined score achieved the highest predictive accuracy at 24 months. Conclusions: CALLY and HALP scores are effective predictors of chemotherapy response and survival in CRC patients with pulmonary metastases receiving FOLFOX. Their combined application enhances risk stratification and may assist in individualized treatment decision-making.

Keywords: CALLY index, HALP score, colorectal cancer, lung metastasis, FOLFOX

Introduction

Colorectal cancer (CRC) remains a major global health burden, and recent statistics show that its incidence and mortality are still high [1]. Management of metastatic CRC has moved toward integrated care that blends molecular profiling, systemic therapy, and local treatment. Current guidelines commonly recommend oxaliplatin-based doublet chemotherapy, such as FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin), as a key first-line backbone, with individualized choices guided by biomarkers and patient condition [2, 3]. Even so, real-world outcomes vary widely. Patients who receive similar strategies can show very different response patterns and long-term survival [4]. This leaves a practical question. Before treatment starts, how can

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we stratify response and prognosis using markers that are accessible, low cost, and repeatable?

Among metastatic patterns, lung metastasis is a frequent distant site in CRC. For patients with limited lung metastases, local approaches such as pulmonary metastasectomy and stereotactic body radiotherapy (SBRT) can offer survival benefit in selected groups. The benefit, however, depends heavily on patient selection and the overall burden of systemic disease [5, 6]. Prior work suggests that surgery and stereotactic ablative radiotherapy (SABR) may yield similar overall survival in some oligometastatic settings, yet local control, PFS, and recurrence patterns can differ. That contrast reinforces how much treatment choice depends on careful risk stratification [7]. Traditional oncology variables, including CEA, maximum lesion size, lesion count, and stage, help to some extent, but they often miss two key dimensions. One is systemic inflammation and immune competence. The other is nutritional reserve. Both shape chemotherapy tolerance, antitumor immune effects, and the tendency toward metastatic progression.

Growing evidence supports a shared role of systemic inflammation and malnutrition in CRC metastasis and treatment response. This has pushed composite inflammation-nutrition scores into the spotlight. The C-reactive protein, albumin and lymphocyte (CALLY) index has been reported to correlate with survival in CRC cohorts and has been used for risk stratification [8-11]. The hemoglobin, albumin, lymphocyte and platelet (HALP) score integrates anemia and nutrition with immune cell status and platelet-related inflammatory activation. Across several tumor types, HALP shows prognostic value, and recent reviews and clinical studies support its association with prognosis and survival [12, 13]. In CRC, HALP has also been linked to postoperative outcomes and sarcopenia risk, which supports its role as a marker of host condition [14]. Still, most studies of CALLY and HALP focus on surgical populations or broader CRC cohorts. Evidence is thinner for a setting that clinicians struggle with every day: CRC lung metastases treated with FOLFOX, especially when objective response and follow-up outcomes are evaluated together.

With this in mind, we studied patients with CRC lung metastases who received FOLFOX and built an analysis framework that connects objective response, survival outcomes (PFS and OS), and risk stratification using CALLY, HALP, and their combination. We examined how CALLY and HALP distribute across response categories and how they relate to tumor-burden measures. We then tested whether these scores remain associated with objective response, PFS, and OS after accounting for stage, metastatic burden, and chemotherapy line. Finally, we assessed whether combined stratification adds clinically useful separation. Our goal was straightforward. By using simple inflammation-nutrition composite indices that come from routine tests, we aimed to provide evidence that better matches real-world decision-making for FOLFOX-treated CRC lung metastases.

Materials and methods

Sample size calculation

Sample size was calculated using the Schoenfeld formula for survival analysis. Based on a systematic review and meta-analysis by Xu et al. [12], which included 13,038 patients across various solid tumors, the HALP score was associated with overall survival with hazard ratios ranging from 1.44 to 1.81. With a two-sided significance level of 0.05, statistical power of 80%, equal group allocation, and an anticipated event rate of 60%, the required sample size ranged from 169 to 339 patients after accounting for a 10% dropout rate [14, 15]. Our final sample of 330 patients met this requirement, ensuring adequate statistical power for the primary survival analyses.

Clinical data collection

This retrospective cohort study collected clinical data from CRC patients with pulmonary metastasis who received FOLFOX chemotherapy at our institution's oncology department between February 2017 and February 2022. A total of 330 patients were enrolled. The study was approved by The First People's Hospital of Lanzhou City medical ethics committee, and informed consent was waived.

Inclusion criteria: (1) pathologically confirmed colorectal adenocarcinoma; (2) pulmonary me-

tastasis confirmed by imaging (chest computed tomography [CT] or positron emission tomography-CT [PET-CT]); (3) at least 4 cycles of FOLFOX (5-fluorouracil + leucovorin + oxaliplatin) chemotherapy; (4) complete baseline laboratory data before chemotherapy; (5) evaluable imaging follow-up data; (6) age ≥18 years.

Exclusion criteria: (1) other primary malignancies; (2) severe infection, autoimmune disease, or hematological disorders; (3) glucocorticoid or immunosuppressant use within 2 weeks before chemotherapy; (4) incomplete clinical or follow-up data; (5) severe hepatic or renal dysfunction before chemotherapy.

Collected clinical data included: (1) Demographics: sex and age. (2) Tumor characteristics: primary tumor location (left colon/right colon/rectum), histological differentiation (well/moderate/poor), number of pulmonary metastases (solitary/multiple), maximum diameter of pulmonary metastases (cm), concurrent liver metastasis, RAS mutation status (wild-type/mutant), and combined targeted therapy. (3) Treatment-related factors: chemotherapy line (first-line/second-line) and Eastern Cooperative Oncology Group (ECOG) performance status. (4) Laboratory parameters: hemoglobin (Hb), albumin (ALB), lymphocyte count (LYM), platelet count (PLT), C-reactive protein (CRP), and carcinoembryonic antigen (CEA).

Laboratory testing

All laboratory parameters were measured from fasting venous blood collected within 1 week before chemotherapy. Complete blood count including hemoglobin, lymphocyte count, and platelet count was performed using the Sysmex XN-9000 automated hematology analyzer (Sysmex Corporation, Japan). Serum albumin was measured by the bromocresol green method using the Beckman Coulter AU5800 automated biochemistry analyzer (Beckman Coulter, USA). Serum CRP was measured by immunoturbidimetry on the same analyzer. Serum CEA was measured by electrochemiluminescence using the Roche Cobas e801 immunoassay analyzer (Roche, Switzerland). All tests were performed strictly following instrument operating procedures and reagent kit instructions. Quality control samples were included in each batch.

Immune-nutritional score calculation

The following immune-nutritional scores were calculated from baseline laboratory parameters before chemotherapy: (1) CALLY score (C-reactive protein-albumin-lymphocyte-platelet score) = [albumin (g/L) × lymphocyte count ($\times 10^9$/L)]/CRP (mg/L); (2) HALP score (hemoglobin-albumin-lymphocyte-platelet score) = [hemoglobin (g/L) × albumin (g/L) × lymphocyte count ($\times 10^9$/L)]/platelet count ($\times 10^9$/L).

Imaging assessment

All patients underwent contrast-enhanced chest CT before chemotherapy and after every 2 cycles, using GE Revolution CT or Siemens SOMATOM Definition AS+ CT scanners. Two radiologists with more than 5 years of experience independently reviewed the images and measured the maximum diameter of pulmonary metastases. Treatment response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

Functional status assessment

Patient functional status was evaluated using the ECOG performance status scale, ranging from 0 to 5. A score of 0 indicates fully active with no restrictions. A score of 1 indicates ambulatory and capable of light work. A score of 2 indicates ambulatory and capable of self-care but unable to work, with more than 50% of waking hours spent out of bed. This study included patients with ECOG scores of 0 to 2.

Study outcomes

Primary outcomes: (1) Objective response rate (ORR), defined as the proportion of patients achieving CR or PR; (2) Progression-free survival (PFS), defined as the time from chemotherapy initiation to disease progression or death from any cause.

Secondary outcome: Overall survival (OS), defined as the time from chemotherapy initiation to death from any cause. The follow-up cutoff date was February 28, 2025. The mean follow-up time was 22.6 months (range, 3-48 months). Thirteen patients (3.9%) were lost to follow-up and were censored at the date of last contact.

For patients still alive or lost to follow-up at this date, survival was censored at the last contact.

Statistical analysis

Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were presented as mean ± standard deviation or median with interquartile range, as appropriate, and compared using the independent-samples T test or the Mann-Whitney U test. Categorical variables were expressed as counts (percentages) and compared using the chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of CALLY and HALP scores to predict objective response, and the optimal cutoff values were determined based on the maximum Youden index. The optimal cutoff values were 0.61 for the CALLY score and 30.21 for the HALP score. Univariate and multivariable logistic regression analyses were used to identify factors associated with objective response, with odds ratios (ORs) and 95% confidence intervals (CIs) reported. In logistic regression analyses, CALLY and HALP were entered as continuous variables to preserve their full quantitative information and to assess their independent associations with treatment response without information loss due to categorization. For survival analyses, PFS and OS were estimated using the Kaplan-Meier method and compared between the groups using the log-rank test. Univariate and multivariable Cox proportional hazards regression models were applied to identify prognostic factors for PFS and OS, with hazard ratios (HRs) and 95% CIs calculated. For these analyses, CALLY and HALP were categorized into high and low groups according to the ROC-derived cutoff values to facilitate clinical interpretability and risk stratification. Variables with P<0.10 in univariate analyses were entered into the corresponding multivariable models. Combined risk stratification was further performed based on CALLY and HALP categories, classifying patients into low-risk (both high), intermediate-risk (one high and one low), and high-risk (both low) groups. In addition, for the time-dependent ROC analyses, a combined CALLY-HALP score was constructed as a weighted risk score. Specifically, CALLY and HALP were first dichotomized using the ROC-derived cutoff values (CALLY <0.61; HALP <30.21), and two binary indicators were defined (1 = low, 0 = high). The combined score was then calculated as a weighted linear combination of these indicators using the regression coefficients (β) derived from the multivariable Cox proportional hazards model, according to the following formula: Combined score = βCALLY × CALLYlow + βHALP × HALPlow. All statistical tests were two-sided, and a *P* value <0.05 was considered statistically significant.

Results

Baseline clinical characteristics

A total of 330 CRC patients with pulmonary metastasis receiving FOLFOX chemotherapy were enrolled and divided into non-objective response and objective response groups. The two groups showed no significant differences in age, body mass index (BMI), sex, smoking history, ECOG performance status, primary tumor location, histological differentiation, primary tumor resection, KRAS/NRAS status, or microsatellite instability (MSI)/mismatch repair (MMR) status (all P>0.05).

For laboratory parameters, CEA (P<0.001), hemoglobin (P<0.001), albumin (P<0.001), lymphocyte count (P<0.001), platelet count (P< 0.001), and CRP (P<0.001) all differed significantly between the groups. Imaging and disease burden indicators also showed significant differences: maximum pulmonary metastasis diameter (P<0.001), number of pulmonary metastases (P = 0.006), and initial tumor-node-metastasis (TNM) stage (P<0.001). CALLY scores (P<0.001) and HALP scores (P<0.001) were significantly higher in the objective response group compared with the non-objective response group. Chemotherapy line also differed significantly between the groups (P = 0.002) (**Table 1**).

CALLY and HALP score differences across response categories

Patients were classified into CR, PR, SD, and PD categories according to RECIST criteria. CALLY scores differed significantly across these categories (overall P<0.001). Pairwise comparisons showed significant differences between

Table 1. Comparison of baseline clinical characteristics between non-objective response and objective response groups

Variable	Total (n = 330)	Non-OR Group (n = 168)	OR Group (n = 162)	Statistic	*P* Value	OR (95% CI)
Age (years)	60.00 (51.00, 67.00)	60.00 (53.00, 67.00)	58.00 (51.00, 66.00)	1.357	0.175	1.012 (0.991-1.033)
BMI (kg/m^2)	23.93 (21.86, 25.67)	24.02 (21.62, 25.55)	23.85 (21.98, 25.74)	0.634	0.526	0.974 (0.903-1.05)
CEA (ng/mL)	35.85 (20.97, 54.45)	48.25 (29.93, 64.22)	28.70 (14.50, 43.00)	6.436	<0.001	1.034 (1.023-1.046)
Max lung met diameter (cm)	3.30 (2.40, 4.27)	3.80 (2.80, 4.70)	2.90 (2.30, 3.80)	5.052	<0.001	1.586 (1.322-1.903)
Hemoglobin (g/L)	124.66±15.32	120.43±15.40	129.04±14.00	5.308	<0.001	0.961 (0.945-0.976)
Albumin (g/L)	39.63±4.59	38.08±4.73	41.25±3.82	6.664	<0.001	0.839 (0.791-0.889)
Lymphocyte (×10^9/L)	1.64±0.49	1.50±0.46	1.79±0.49	5.543	<0.001	0.274 (0.166-0.45)
Platelet (×10^9/L)	288.77±73.79	305.76±72.23	271.15±71.43	4.375	<0.001	1.007 (1.004-1.01)
CRP (mg/L)	13.00±5.03	14.20±5.74	11.76±3.81	4.529	<0.001	1.109 (1.058–1.163)
CALLY score	0.52 (0.37, 0.72)	0.42 (0.30, 0.54)	0.62 (0.48, 0.86)	7.437	<0.001	0.117 (0.05-0.274)
HALP score	26.71 (19.64, 38.84)	22.58 (17.06, 27.96)	34.73 (25.21, 47.66)	8.308	<0.001	0.929 (0.91-0.948)
Sex				0.364	0.546	
Male	201 (60.9%)	105 (62.5%)	96 (59.3%)			0.873 (0.561-1.358)
Female	129 (39.1%)	63 (37.5%)	66 (40.7%)			
Smoking history				0.427	0.514	
Yes	124 (37.6%)	66 (39.3%)	58 (35.8%)			0.862 (0.552-1.347)
No	206 (62.4%)	102 (60.7%)	104 (64.2%)			
ECOG PS				3.654	0.056	
0-1	254 (77.0%)	122 (72.6%)	132 (81.5%)			1.659 (0.985-2.795)
2	76 (23.0%)	46 (27.4%)	30 (18.5%)			
Primary tumor site				0.071	0.790	
Colon	187 (56.7%)	94 (56.0%)	93 (57.4%)			1.061 (0.686-1.640)
Rectum	143 (43.3%)	74 (44.0%)	69 (42.6%)			
Histological differentiation				2.291	0.130	
Well/Moderate	238 (72.1%)	115 (68.5%)	123 (75.9%)			1.454 (0.895-2.362)
Poor/Undifferentiated	92 (27.9%)	53 (31.5%)	39 (24.1%)			
Initial TNM stage				11.434	<0.001	
IVA	206 (62.4%)	90 (53.6%)	116 (71.6%)			2.186 (1.384-3.451)
IVB	124 (37.6%)	78 (46.4%)	46 (28.4%)			
Number of lung metastases				7.484	0.006	
Solitary	138 (41.8%)	58 (34.5%)	80 (49.4%)			1.850 (1.188-2.881)
Multiple	192 (58.2%)	110 (65.5%)	82 (50.6%)			
Primary tumor resection				2.930	0.087	
Yes	213 (64.5%)	101 (60.1%)	112 (69.1%)			1.486 (0.943-2.341)
No	117 (35.5%)	67 (39.9%)	50 (30.9%)			
Chemotherapy line				10.041	0.002	
First-line	208 (63.0%)	92 (54.8%)	116 (71.6%)			2.083 (1.319-3.290)
Second-line	122 (37.0%)	76 (45.2%)	46 (28.4%)			
KRAS/NRAS status				0.152	0.697	
Mutant	138 (41.8%)	72 (42.9%)	66 (40.7%)			0.917 (0.592-1.420)
Wild-type	192 (58.2%)	96 (57.1%)	96 (59.3%)			
MSI/MMR status				0.125	0.724	
MSI-H/dMMR	22 (6.7%)	12 (7.1%)	10 (6.2%)			0.855 (0.359-2.038)
MSS/pMMR	308 (93.3%)	156 (92.9%)	152 (93.8%)			

Note: BMI, body mass index; CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; TNM, tumor-node-metastasis; MSI, microsatellite instability; MMR, mismatch repair; dMMR, deficient mismatch repair; pMMR, proficient mismatch repair; CALLY, C-reactive protein-albumin-lymphocyte score; HALP, hemoglobin-albumin-lymphocyte-platelet score; OR, objective response; CI, confidence interval.

CR and PR, SD, and PD groups (all P<0.001). PR versus SD (P<0.001), PR versus PD (P< 0.001), and SD versus PD (P = 0.0095) comparisons were also significant (**Figure 1A**).

For HALP scores, overall differences across response categories were also significant (P< 0.001). Pairwise comparisons revealed significant differences between CR and SD (P =

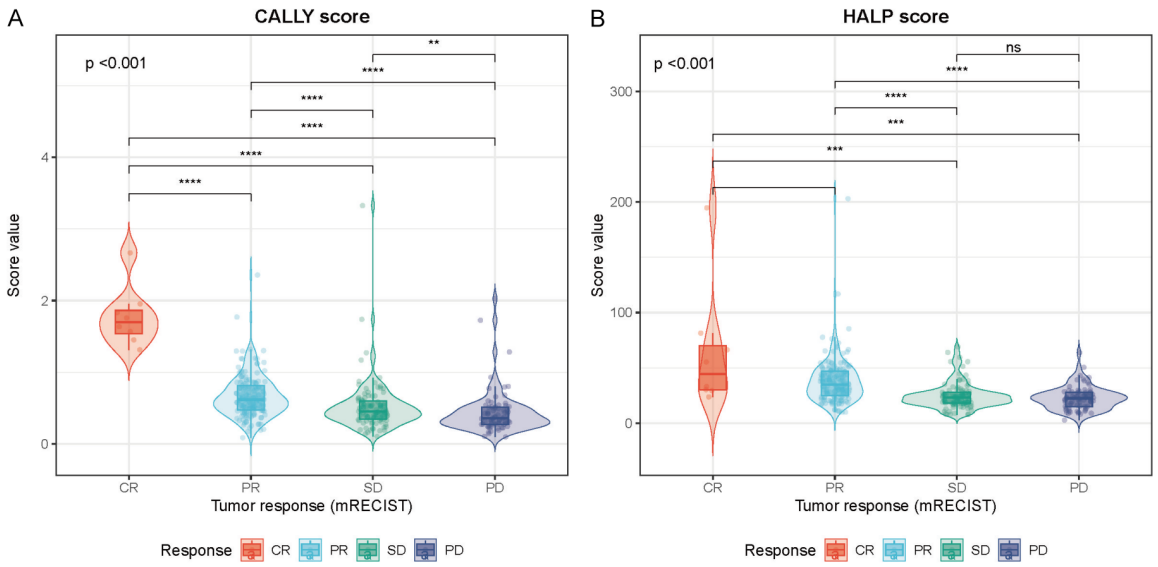

Figure 1. Distribution of CALLY and HALP scores across different response categories. A. Distribution of CALLY scores among patients with different treatment responses (CR, PR, SD, PD). B. Distribution of HALP scores among patients with different treatment responses (CR, PR, SD, PD). Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; CALLY, C-reactive protein-albumin-lymphocyte score; HALP, hemoglobin-albumin-lymphocyte-platelet score. NsP>0.05, **P<0.01, ***P<0.001, ****P<0.0001.

0.0011), CR and PD (P = 0.0007), PR and SD (P<0.001), and PR and PD (P<0.001). However, CR versus PR (P = 0.1592) and SD versus PD (P = 0.424) did not reach significance (**Figure 1B**).

Correlation analysis between clinical variables and CALLY/HALP scores

Correlation analysis assessed relationships among baseline clinical variables and their associations with CALLY and HALP scores. CEA positively correlated with maximum pulmonary metastasis diameter (P<0.001) and showed significant correlations with HALP score (P< 0.001) and TNM stage (P = 0.015). Among hematological and inflammatory parameters, hemoglobin, albumin, lymphocyte count, platelet count, and CRP all showed varying degrees of significant correlation with CALLY or HALP scores (all P<0.05). CALLY and HALP scores were significantly positively correlated with each other (P<0.001).

Given the significant correlations between hemoglobin, albumin, lymphocyte count, platelet count, CRP and CALLY or HALP scores, these variables were excluded from subsequent regression analyses to avoid potential collinearity. No significant correlations were observed among other clinical variables (P>0.05). The overall correlation pattern is shown in **Figure 2**.

Variable assignment, collinearity diagnostics, and logistic regression results

Variables included in the regression model were categorically assigned, and collinearity diagnostics were performed. Variance inflation factors for all variables were low, indicating no substantial multicollinearity and suitability for regression analysis (**Table 2**).

In univariate logistic regression, CEA (OR = 1.034), maximum pulmonary metastasis diameter (OR = 1.586), TNM stage (OR = 2.186), number of pulmonary metastases (OR = 1.850), and chemotherapy line (OR = 2.083) were significantly associated with increased risk of non-objective response. CALLY (OR = 0.117) and HALP (OR = 0.929) were significantly associated with reduced risk. In multivariate logistic regression, CEA (OR = 1.030), maximum pulmonary metastasis diameter (OR = 1.455), TNM stage (OR = 2.298), number of pulmonary metastases (OR = 1.883), and chemotherapy line (OR = 2.575) remained as independent risk factors for non-objective response. CALLY (OR = 0.406) and HALP (OR = 0.935) remained

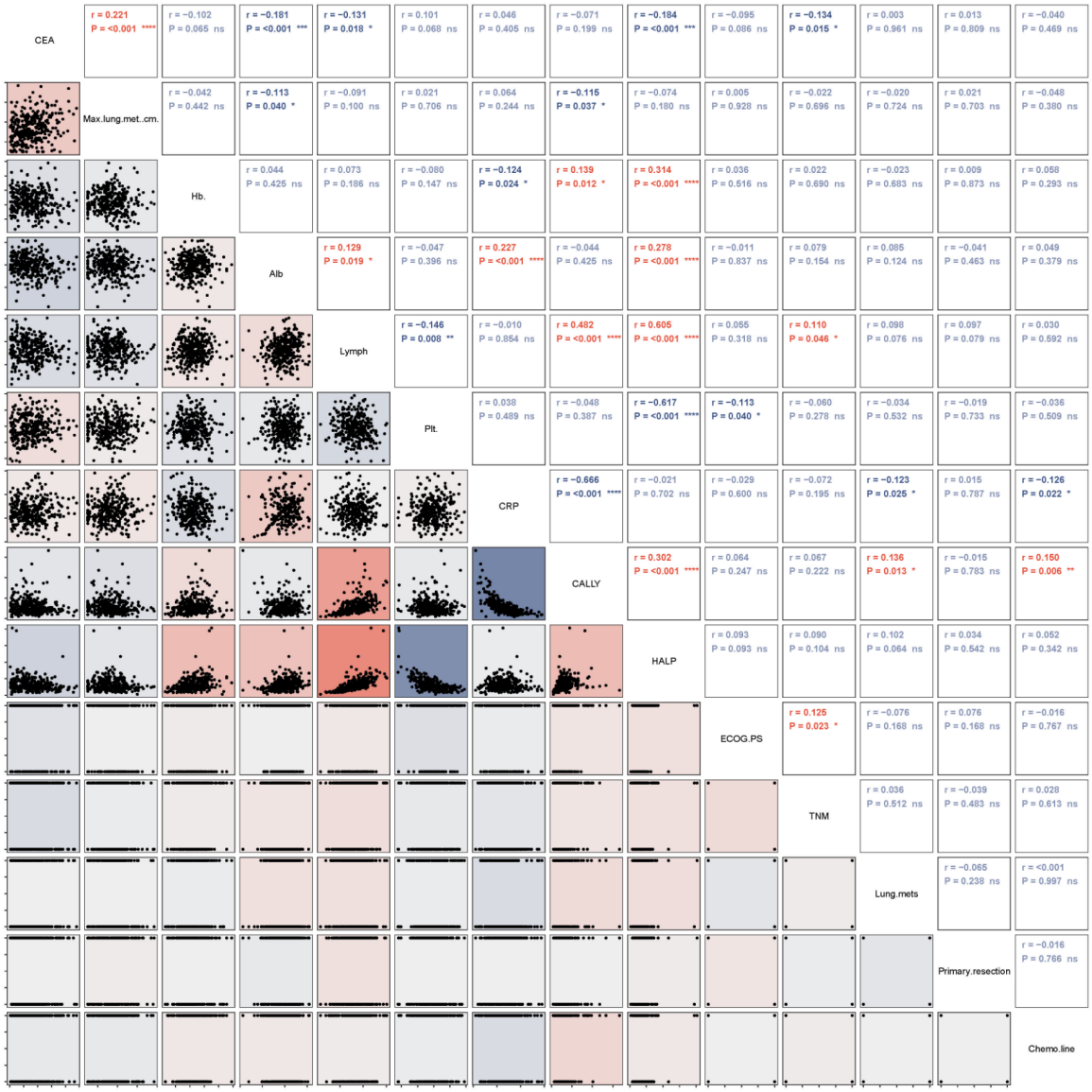

Figure 2. Correlation matrix analysis between clinical variables and CALLY/HALP scores. Note: CEA, carcinoembryonic antigen; Max lung met, maximum diameter of lung metastasis; Hb, hemoglobin; Alb, albumin; Lymph, lymphocyte count; Plt, platelet count; CRP, C-reactive protein; CALLY, C-reactive protein-albumin-lymphocyte score; HALP, hemoglobin-albumin-lymphocyte-platelet score; ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis staging system (AJCC 8th edition); Lung mets, number of lung metastases; Primary resection, primary tumor resection; Chemo line, line of chemotherapy.

independently associated with lower risk of non-objective response (**Table 3**).

PFS comparison by CALLY and HALP stratification

At the time of analysis, the mean follow-up duration was 22.6 months (range, 3-48 months), and 13 patients (3.9%) were lost to follow-up. After stratification based on unified cutoffs, both CALLY and HALP scores significantly distinguished populations with different PFS outcomes (both P<0.001).

In CALLY stratification, the high-score group had better PFS than the low-score group (**Figure 3A**). At 12 months, PFS rates were 53.8% (95% CI: 45.5%-63.5%) for the high-score group and 27.5% (95% CI: 22.1%-34.2%) for the low-score group. Corresponding 12-month cumulative progression rates were 46.2% (95% CI: 36.5%-54.5%) and 72.5% (95% CI: 65.8%-

Table 2. Variable assignment and collinearity diagnostics (VIF)

Variable	Assignment	VIF
CEA (ng/mL)	Continuous	1.040
Max lung met (cm)	Continuous	1.069
CALLY	Continuous	1.075
HALP	Continuous	1.091
ECOG PS	0-1 = 0, 2 = 1	1.032
TNM	IVA = 0, IVB = 1	1.052
Lung mets	Solitary = 0, Multiple = 1	1.051
Primary resection	No = 0, Yes = 1	1.022
Chemo line	First-line = 0, Second-line = 1	1.057

Note: VIF, variance inflation factor; CEA, carcinoembryonic antigen; Max lung met, maximum diameter of lung metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis staging system (AJCC 8th edition); Lung mets, number of lung metastases; Primary resection, primary tumor resection; Chemo line, line of chemotherapy.

77.9%), respectively. At 24 months, cumulative progression rates were 84.0% (95% CI: 75.9%-89.4%) for the high-score group and 95.3% (95% CI: 91.3%-97.4%) for the low-score group (**Figure 3A**).

HALP stratification showed a consistent pattern. The high-score group had better PFS outcomes (**Figure 3B**). At 12 months, PFS rates were 52.7% (95% CI: 44.8%-62.1%) versus 26.9% (95% CI: 21.4%-33.7%), with cumulative progression rates of 47.3% (95% CI: 37.9%-55.2%) versus 73.1% (95% CI: 66.3%-78.6%). At 24 months, cumulative progression rates were 88.4% (95% CI: 81.3%-92.8%) versus 93.0% (95% CI: 88.5%-95.8%) (**Figure 3B**).

Multivariate cox regression for PFS

In univariate Cox regression, CEA (HR = 1.013, P<0.001), maximum pulmonary metastasis diameter (HR = 1.252, P<0.001), CALLY stratification (HR = 1.788, P<0.001), HALP stratification (HR = 1.653, P<0.001), ECOG performance status (HR = 1.335, P = 0.031), and chemotherapy line (HR = 1.687, P<0.001) were significantly associated with PFS. Other variables were not significant (all P>0.05) (**Table 4**).

Multivariate Cox regression confirmed that CEA (HR = 1.006, 95% CI: 1.001-1.011, P = 0.016), maximum pulmonary metastasis diameter (HR = 1.155, 95% CI: 1.050-1.270, P = 0.003), low CALLY score (HR = 1.344, 95% CI: 1.037-1.742, P = 0.025), low HALP score (HR = 1.457, 95% CI: 1.142-1.859, P = 0.002), ECOG score of 2 (HR = 1.315, 95% CI: 1.008-1.716, P = 0.043), and second-line chemotherapy (HR = 1.515, 95% CI: 1.193-1.924, P<0.001) remained independently associated with PFS (**Table 4**).

OS comparison by CALLY and HALP stratification

After stratification, both scores significantly distinguished populations with different OS outcomes (CALLY: P<0.001; HALP: P = 0.001).

In CALLY stratification, the high-score group had better OS (**Figure 4A**). At 12 months, OS rates were 87.4% (95% CI: 81.6%-93.6%) versus 73.8% (95% CI: 68.1%-80.0%). At 24 months, OS rates were 61.3% (95% CI: 53.1%-70.7%) versus 42.8% (95% CI: 36.5%-50.2%) (**Figure 4A**).

HALP stratification showed similar results (**Figure 4B**). At 12 months, OS rates were 88.4% (95% CI: 83.0%-94.1%) versus 72.5% (95% CI: 66.6%-79.0%). At 24 months, OS rates were 60.9% (95% CI: 53.0%-70.0%) versus 42.2% (95% CI: 35.8%-49.8%) (**Figure 4B**).

Multivariate cox regression for OS

In univariate Cox regression, CEA (HR = 1.007, 95% CI: 1.002-1.013, P = 0.004), maximum pulmonary metastasis diameter (HR = 1.216, 95% CI: 1.101-1.343, P<0.001), low CALLY score (<0.61) (HR = 1.682, 95% CI: 1.268-2.231, P<0.001), low HALP score (<30.21) (HR = 1.566, 95% CI: 1.191-2.059, P = 0.001), ECOG score of 2 (HR = 1.402, 95% CI: 1.037-1.894, P = 0.028), and second-line chemotherapy (HR = 1.707, 95% CI: 1.301-2.239, P<0.001) were significantly associated with OS. Other variables were not significant (all P>0.05).

In multivariate Cox regression, maximum pulmonary metastasis diameter (HR = 1.149, 95% CI: 1.037-1.273, P = 0.008), low HALP score (HR = 1.394, 95% CI: 1.047-1.857, P = 0.023), ECOG score of 2 (HR = 1.398, 95% CI: 1.034-1.890, P = 0.030), and second-line chemotherapy (HR = 1.539, 95% CI: 1.168-2.028, P = 0.002) remained independently associated with OS. CEA was no longer significant (HR = 1.002, P = 0.590), and low CALLY score showed

Table 3. Univariate and multivariate logistic regression analysis of factors associated with objective response

Variable	Univariate OR	*P* Value	95% CI	Multivariate OR	*P* Value	95% CI
CEA (ng/mL)	1.034	<0.001	1.023-1.046	1.030	<0.001	1.017-1.044
Max lung met (cm)	1.586	<0.001	1.322-1.903	1.455	0.001	1.164-1.841
CALLY	0.117	<0.001	0.05-0.274	0.406	0.022	0.178-0.857
HALP	0.929	<0.001	0.91-0.948	0.935	<0.001	0.913-0.955
ECOG PS	1.659	0.057	0.985-2.795	NA	NA	NA
TNM	2.186	<0.001	1.384-3.451	2.298	0.006	1.278-4.211
Lung mets	1.850	0.006	1.188-2.881	1.883	0.030	1.067-3.367
Primary resection	1.486	0.088	0.943-2.341	NA	NA	NA
Chemo line	2.083	0.002	1.319-3.290	2.575	0.002	1.428-4.745

Note: CEA, carcinoembryonic antigen; Max lung met, maximum diameter of lung metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis staging system (AJCC 8th edition); Lung mets, number of lung metastases; Primary resection, primary tumor resection; Chemo line, line of chemotherapy; OR, odds ratio; CI, confidence interval; NA, not applicable.

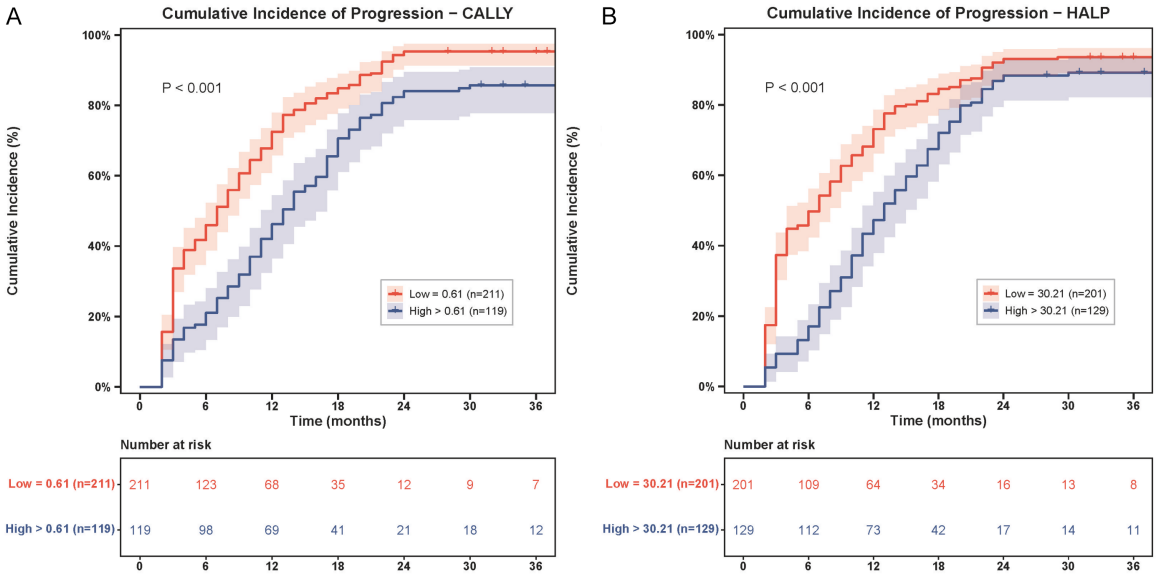

Figure 3. Comparison of PFS by CALLY and HALP score stratification. A. Cumulative incidence curves of progression for patients stratified by CALLY score. B. Cumulative incidence curves of progression for patients stratified by HALP score. Note: CALLY, C-reactive protein-albumin-lymphocyte score; HALP, hemoglobin-albumin-lymphocyte-platelet score; PFS, progression-free survival.

only a borderline trend (HR = 1.315, P = 0.078) (**Table 5**).

Combined CALLY and HALP stratification analysis

Four subgroups were constructed based on high/low CALLY and HALP stratification. Treatment response distribution differed significantly across groups (P<0.001). For survival outcomes, PFS and OS showed clear separation among the four groups (both P<0.001) (**Figure 5A**, **5B**).

Cox regression with CALLY-H/HALP-H as reference showed that for PFS, the CALLY-L/HALP-L group had significantly elevated progression risk (HR = 2.296, 95% CI: 1.695-3.111, P< 0.001). CALLY-H/HALP-L (P = 0.268) and CALLY-L/HALP-H (P = 0.064) did not differ significantly from reference (**Figure 5A**). For OS, the CALLY-L/HALP-L group also had significantly elevated mortality risk (HR = 2.168, 95% CI: 1.499-3.136, P<0.001). CALLY-H/HALP-L (P = 0.165) and CALLY-L/HALP-H (P = 0.061) did not differ significantly from the reference (**Figure 5B**).

Table 4. Univariate and multivariate cox regression analysis of factors associated with PFS

Variable	Univariate			Multivariate		
	β	*P* Value	HR (95% CI)	β	*P* Value	HR (95% CI)
Age (years)	0.003	0.594	1.003 (0.992-1.014)			
BMI (kg/m^2)	-0.003	0.872	0.997 (0.959-1.036)			
CEA (ng/mL)	0.013	<0.001	1.013 (1.009-1.018)	0.006	0.016	1.006 (1.001-1.011)
Max lung met diameter (cm)	0.224	<0.001	1.252 (1.143-1.370)	0.144	0.003	1.155 (1.050-1.270)
CALLY score						
≥0.61 (ref)						
<0.61	0.581	<0.001	1.788 (1.406-2.275)	0.296	0.025	1.344 (1.037-1.742)
HALP score						
≥30.21 (ref)						
<30.21	0.503	<0.001	1.653 (1.310-2.087)	0.377	0.002	1.457 (1.142-1.859)
Sex						
Female (ref)						
Male	0.160	0.172	1.174 (0.932-1.478)			
Smoking history						
No (ref)						
Yes	-0.107	0.367	0.899 (0.712-1.134)			
ECOG PS						
0-1 (ref)						
2	0.289	0.031	1.335 (1.026-1.737)	0.274	0.043	1.315 (1.008-1.716)
Primary tumor site						
Rectum (ref)						
Colon	-0.098	0.398	0.907 (0.722-1.138)			
Histological differentiation						
Poor/Undifferentiated (ref)						
Well/Moderate	0.011	0.930	1.011 (0.785-1.303)			
Initial TNM stage						
IVB (ref)						
IVA	0.131	0.270	1.140 (0.903-1.438)			
Number of lung metastases						
Multiple (ref)						
Solitary	-0.096	0.409	0.908 (0.723-1.141)			
Primary tumor resection						
No (ref)						
Yes	0.101	0.401	1.106 (0.874-1.399)			
Chemotherapy line						
First-line (ref)						
Second-line	0.523	<0.001	1.687 (1.334-2.132)	0.416	<0.001	1.515 (1.193-1.924)
KRAS/NRAS status						
Wild-type (ref)						
Mutant	-0.113	0.331	0.893 (0.711-1.122)			
MSI/MMR status						
MSS/pMMR (ref)						
MSI-H/dMMR	-0.168	0.457	0.845 (0.542-1.317)			

Note: CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis staging system (AJCC 8th edition); MSI, microsatellite instability; MMR, mismatch repair; dMMR, deficient mismatch repair; pMMR, proficient mismatch repair; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; ref, reference category.

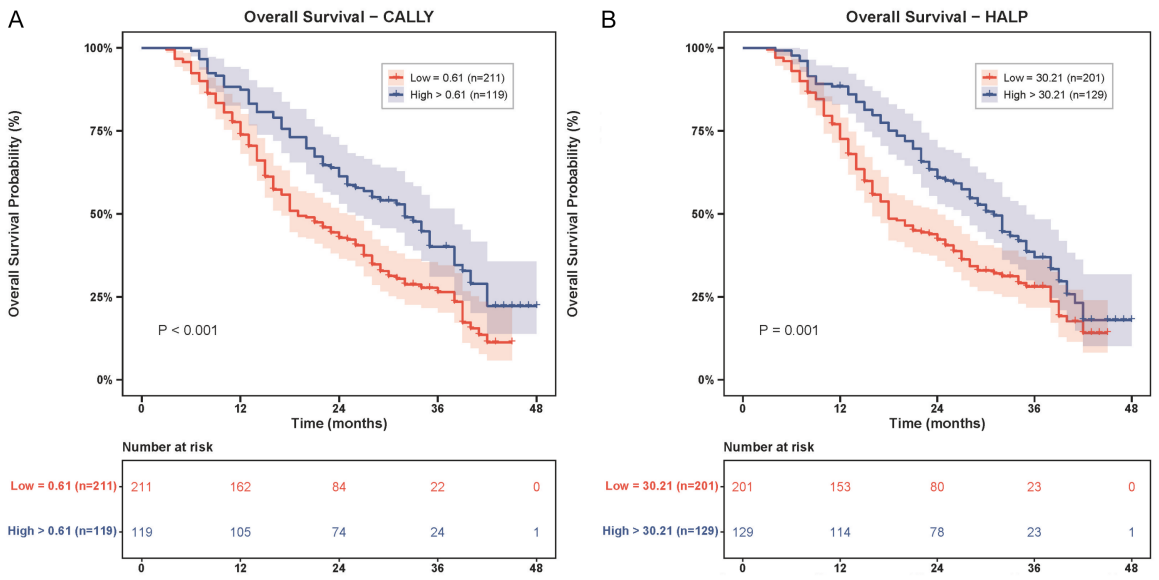

Figure 4. Comparison of OS by CALLY and HALP score stratification. A. Kaplan-Meier OS curves for patients stratified by CALLY score. B. Kaplan-Meier OS curves for patients stratified by HALP score. Note: CALLY, C-reactive protein-albumin-lymphocyte score; HALP, hemoglobin-albumin-lymphocyte-platelet score; OS, overall survival.

Table 5. Univariate and multivariate cox regression analysis of factors associated with OS

Variable	Univariate			Multivariate		
	β	*P* Value	HR (95% CI)	β	*P* Value	HR (95% CI)
Age (years)	-0.002	0.800	0.998 (0.986-1.011)			
BMI (kg/m^2)	0.015	0.505	1.015 (0.971-1.061)			
CEA (ng/mL)	0.007	0.004	1.007 (1.002-1.013)	0.002	0.590	1.002 (0.996-1.007)
Max lung met diameter (cm)	0.195	<0.001	1.216 (1.101-1.343)	0.139	0.008	1.149 (1.037-1.273)
CALLY score						
≥0.61 (ref)						
<0.61	0.520	<0.001	1.682 (1.268-2.231)	0.273	0.078	1.315 (0.970-1.782)
HALP score						
≥30.21 (ref)						
<30.21	0.448	0.001	1.566 (1.191-2.059)	0.332	0.023	1.394 (1.047-1.857)
Sex						
Female (ref)						
Male	0.172	0.203	1.188 (0.911-1.549)			
Smoking history						
No (ref)						
Yes	-0.079	0.566	0.924 (0.706-1.210)			
ECOG PS						
0-1 (ref)						
2	0.338	0.028	1.402 (1.037-1.894)	0.335	0.030	1.398 (1.034-1.890)
Primary tumor site						
Rectum (ref)						
Colon	-0.149	0.273	0.861 (0.660-1.125)			
Histological differentiation						
Poor/Undifferentiated (ref)						
Well/Moderate	0.143	0.333	1.154 (0.863-1.543)			

Initial TNM stage						
IVB (ref)						
IVA	0.022	0.874	1.022 (0.779-1.341)			
Number of lung metastases						
Multiple (ref)						
Solitary	-0.127	0.348	0.881 (0.676-1.148)			
Primary tumor resection						
No (ref)						
Yes	0.213	0.127	1.237 (0.941-1.626)			
Chemotherapy line						
First-line (ref)						
Second-line	0.535	<0.001	1.707 (1.301-2.239)	0.431	0.002	1.539 (1.168-2.028)
KRAS/NRAS status						
Wild-type (ref)						
Mutant	-0.177	0.191	0.838 (0.643-1.092)			
MSI/MMR status						
MSS/pMMR (ref)						
MSI-H/dMMR	-0.251	0.309	0.778 (0.480-1.262)			

Note: BMI, body mass index; CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis staging system (AJCC 8th edition); MSI, microsatellite instability; MMR, mismatch repair; dMMR, deficient mismatch repair; pMMR, proficient mismatch repair; HR, hazard ratio; CI, confidence interval; OS, overall survival; ref, reference category.

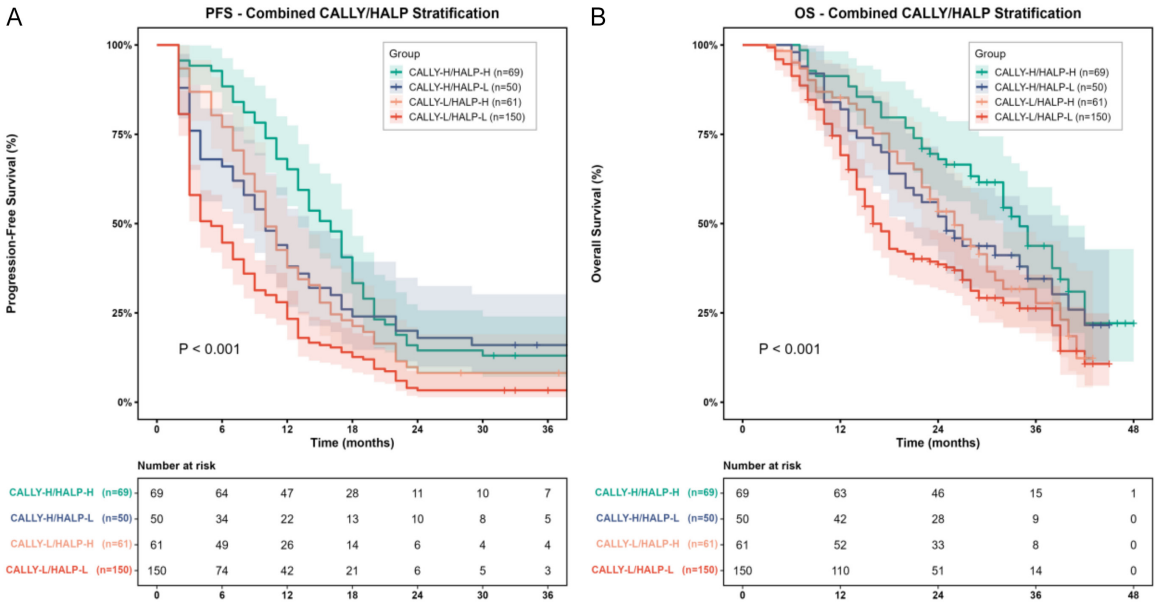

Figure 5. PFS and OS comparison by combined CALLY and HALP stratification (Four-Group Analysis). A. PFS curves for the four combined stratification groups. B. OS curves for the four combined stratification groups. Note: CALLY, C-reactive protein-albumin-lymphocyte score; HALP, hemoglobin-albumin-lymphocyte-platelet score; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

When patients were reclassified into low-risk (both high), intermediate-risk (one high and one low), and high-risk (both low) groups, PFS and OS showed clear gradient separation (both P< 0.001) (**Figure 6A**, **6B**). Using the low-risk group as the reference, Cox regression showed that for PFS, the high-risk group had significantly increased progression risk (HR = 2.295, 95%

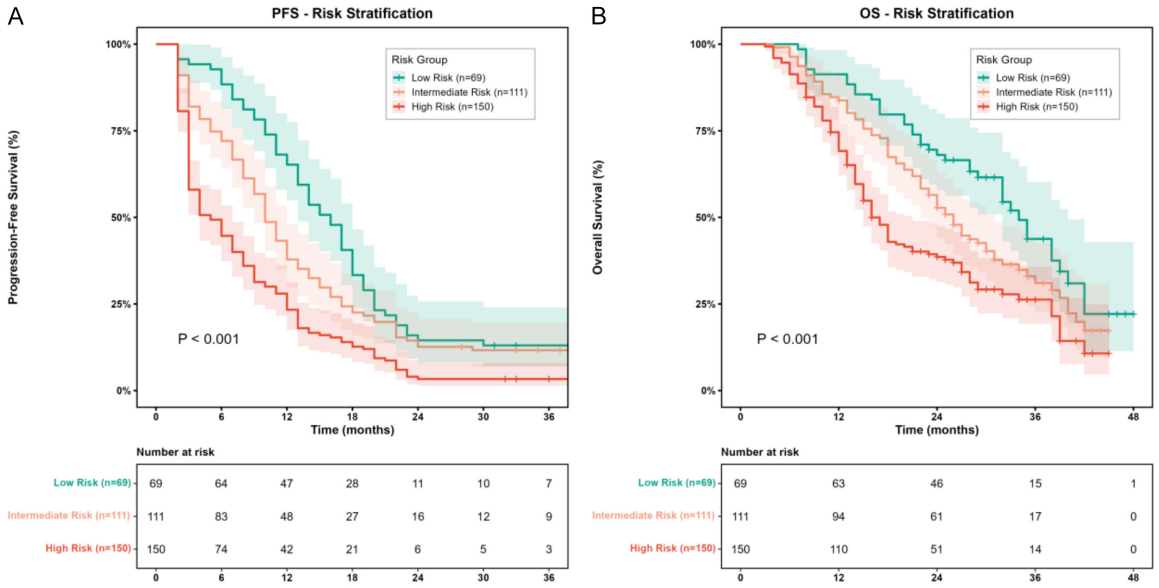

Figure 6. PFS and OS comparison by combined risk stratification (three-group analysis). A. PFS curves for the three risk stratification groups. B. OS curves for the three risk stratification groups. Note: CALLY, C-reactive protein-albumin-lymphocyte score; HALP, hemoglobin-albumin-lymphocyte-platelet score; Low Risk, both CALLY and HALP high; Intermediate Risk, one high and one low; High Risk, both CALLY and HALP low; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

CI: 1.694-3.109, P<0.001), while the intermediate-risk group did not differ significantly (HR = 1.338, P = 0.076) (**Figure 6A**). For OS, the high-risk group had significantly increased mortality risk (HR = 2.167, 95% CI: 1.498-3.135, P< 0.001), while the intermediate-risk group did not differ significantly (HR = 1.456, P = 0.057) (**Figure 6B**).

Predictive performance of CEA, CALLY, HALP, and combined score for PFS and OS at 12 and 24 months

At 12 months, all four indicators showed moderate discrimination for PFS, with the combined score achieving the highest area under the curve (AUC). DeLong tests showed no significant differences between the combined score and CEA (P = 0.175), CALLY (P = 0.117), or HALP (P = 0.115) (**Figure 7A**). For 12-month OS, the combined score also had a relatively high AUC and demonstrated better discrimination than CALLY alone (P = 0.041). Differences from CEA (P = 0.267) and HALP (P = 0.976) were not significant (**Figure 7B**).

At 24 months, CEA showed the highest discrimination for PFS. DeLong tests indicated that CEA's AUC was significantly better than HALP (P<0.001). CALLY also outperformed HALP (P = 0.015), as did the combined score (P = 0.003). No significant differences were found between CEA and CALLY (P = 0.394) or between CEA and the combined score (P = 0.383) (**Figure 8A**). For 24-month OS, the combined score had the highest AUC, but differences from CEA (P = 0.093), CALLY (P = 0.070), and HALP (P = 0.495) did not reach significance (**Figure 8B**).

Discussion

This study focused on CRC patients with pulmonary metastasis receiving FOLFOX chemotherapy and systematically evaluated the clinical value of CALLY and HALP scores in predicting treatment response and survival outcomes. Our findings indicate that both scores effectively distinguish patients achieving objective response from those who do not. Both are significantly associated with PFS and OS. Combined stratification further strengthens prognostic risk classification, providing new reference points for clinical decision-making.

Value of CALLY and HALP scores in predicting chemotherapy response

We found that patients in the objective response group exhibited significantly higher CALLY and HALP scores compared to those in the

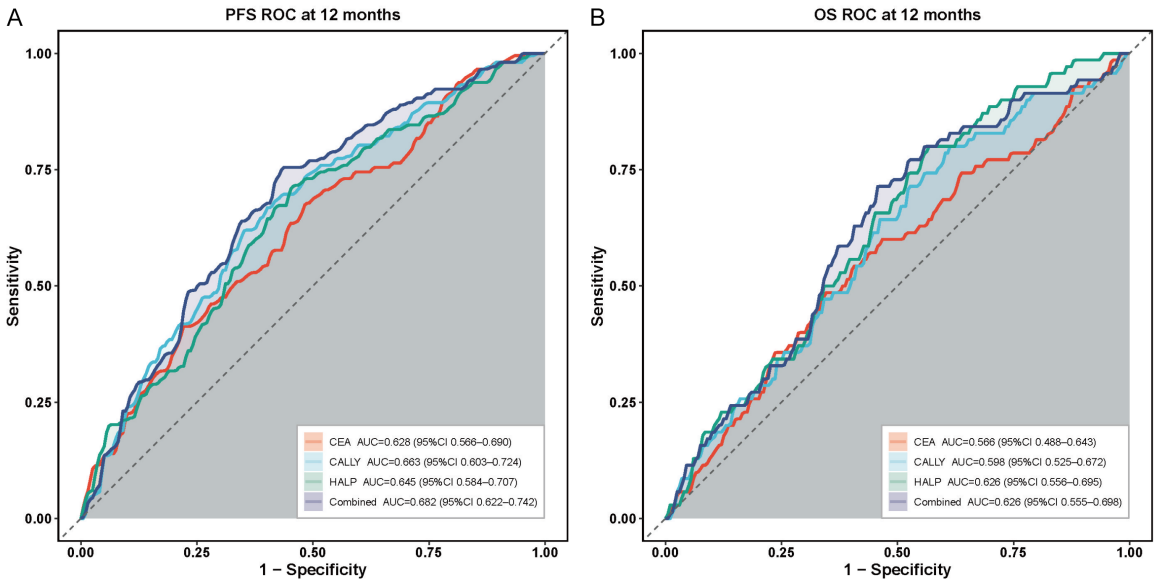

Figure 7. ROC curves comparing CEA, CALLY, HALP, and combined score for PFS and OS prediction at 12 months. A. Time-dependent ROC curves for 12-month PFS. B. Time-dependent ROC curves for 12-month OS. Note: CEA, carcinoembryonic antigen; CALLY, C-reactive protein-albumin-lymphocyte score; HALP, hemoglobin-albumin-lymphocyte-platelet score; Combined, combined score; PFS, progression-free survival; OS, overall survival; ROC, receiver operating characteristic curve; AUC, area under the curve; CI, confidence interval; DeLong, DeLong test.

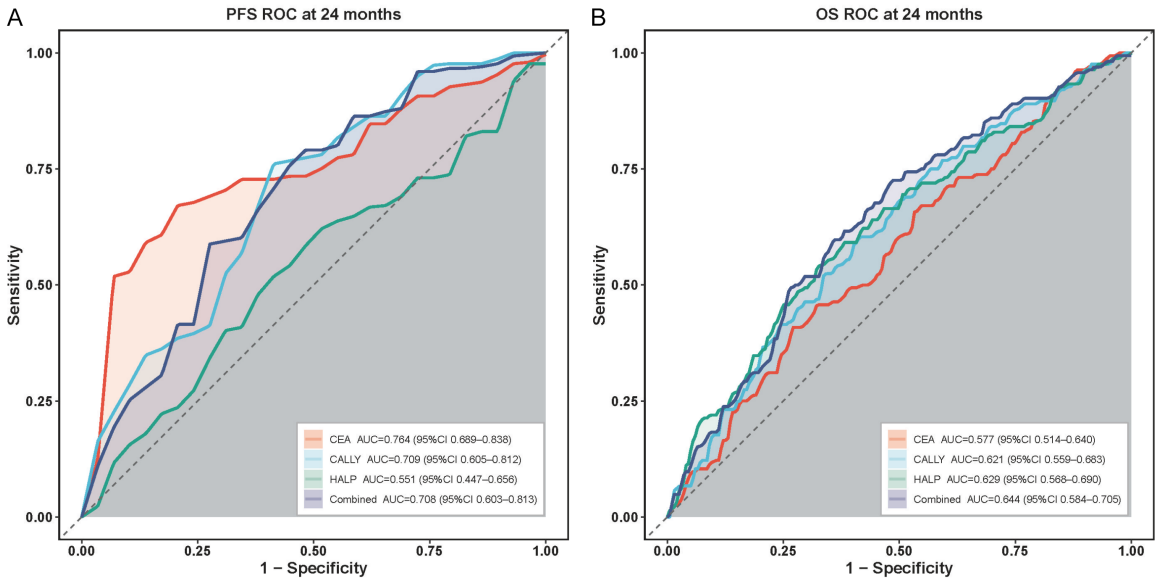

Figure 8. ROC curves comparing CEA, CALLY, HALP, and combined score for PFS and OS prediction at 24 months. A. Time-dependent ROC curves for 24-month PFS. B. Time-dependent ROC curves for 24-month OS. Note: CEA, carcinoembryonic antigen; CALLY, C-reactive protein-albumin-lymphocyte score; HALP, hemoglobin-albumin-lymphocyte-platelet score; Combined, combined score; PFS, progression-free survival; OS, overall survival; ROC, receiver operating characteristic curve; AUC, area under the curve; CI, confidence interval; DeLong, DeLong test.

non-objective response group. Both scores demonstrated a distinct gradient distribution across the categories of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Multivariate logistic regression analysis confirmed that CALLY (odds ratio [OR] = 0.406) and HALP (OR = 0.935) are independent protective factors for achieving an objective response. These findings are consistent with previous reports. Yang

et al. [8] analyzed data from 1,260 colorectal cancer (CRC) patients in the INSCOC study and found that the CALLY index was independently associated with overall survival (OS) (hazard ratio [HR] = 0.91, P<0.001). The prognostic predictive value of the CALLY index (C-index = 0.666) surpassed that of traditional inflammatory markers such as the modified Glasgow Prognostic Score (mGPS), neutrophil-to-lymphocyte ratio (NLR), systemic inflammation index (SII), and platelet-to-lymphocyte ratio (PLR). Another study [16] demonstrated that in patients undergoing hepatectomy for colorectal liver metastases, a low CALLY index independently predicted OS and was significantly correlated with an increase in postoperative complications. Regarding HALP, a meta-analysis conducted by Xu et al. [12] included 28 studies encompassing 13,110 patients with solid tumors and revealed that a low HALP score was significantly associated with decreased OS (HR = 1.61), cancer-specific survival (HR = 1.80), and PFS/DFS/RFS (HR = 1.61) [12]. Evidence also suggests that the HALP score predicts OS, PFS, and treatment response across multiple tumor types, including gastric cancer, CRC, bladder cancer, and lung cancer [12].

From a biological mechanism perspective, the CALLY score integrates C-reactive protein (CRP), albumin, and lymphocyte count. These three components reflect systemic inflammation, nutritional reserves, and cellular immune function, respectively. Burgos-Molina et al. [17] reviewed how chronic inflammation promotes CRC development through the activation of NF-κB, MAPK, and other signaling pathways. Inflammatory cells and their secreted pro-inflammatory cytokines, such as IL-6, TNF-α, and IL-1β, regulate the tumor microenvironment, thereby promoting tumor proliferation, survival, and invasion [18]. Hypoalbuminemia not only reflects malnutrition but also correlates closely with increased chemotherapy-induced toxicity, including higher rates of anemia, fatigue, and appetite loss [19]. Ikeda et al. [20] further confirmed that in elderly patients with advanced non-small cell lung cancer, hypoalbuminemia was significantly associated with early chemotherapy discontinuation and independently predicted survival. Lymphocytes serve as core effector cells in antitumor immunity; their number and functional status directly influence the body's immune surveillance capacity. Research indicates that tumor-infiltrating lymphocyte density and functional status correlate with prognosis and immunotherapy response across multiple solid tumors [21]. Peripheral blood lymphocyte count can reflect overall immune status to some extent. Therefore, patients with low CALLY scores may simultaneously experience inflammatory activation, nutritional depletion, and immune suppression, which reduces their responsiveness to chemotherapy.

The HALP score incorporates hemoglobin and platelet count alongside albumin and lymphocyte components. Anemia is prevalent among cancer patients and can lead to tumor tissue hypoxia, adversely affecting the cytotoxic efficacy of chemotherapy drugs. Harrison and Blackwell [22] reviewed the exacerbating role of anemia in intratumoral hypoxia. Hypoxia diminishes the sensitivity to chemoradiotherapy through various mechanisms, including reduced free radical generation, induction of drug resistance genes, and the promotion of tumor invasion and metastasis [22]. Evidence indicates that tumor hypoxia is characteristic of locally advanced solid tumors and plays a key role in treatment resistance [23]. Patients with anemia, particularly those with low hemoglobin levels, experience more pronounced tumor hypoxia and a higher risk of treatment resistance [22, 23]. Platelets not only contribute to tumor-associated thrombosis but also facilitate tumor proliferation and metastasis by releasing platelet-derived growth factor and transforming growth factor-β. Consequently, the HALP score provides a more comprehensive assessment of host status, offering supplementary insights for predicting chemotherapy response [12].

Differential performance of CALLY and HALP scores in survival prediction

Our survival analysis showed that both CALLY and HALP scores effectively distinguished populations with different PFS and OS outcomes. Notably, in multivariable Cox regression analyses, the HALP score maintained independent predictive value for both PFS (HR = 1.457, P = 0.002) and OS (HR = 1.394, P = 0.023). In contrast, the CALLY score was independently associated with PFS (HR = 1.344, P = 0.025) but showed only a borderline association with OS (HR = 1.315, P = 0.078).

This differential performance may be explained by the distinct biological components captured by each score and by the intrinsic differences between PFS and OS as clinical endpoints. CRP, a core component of the CALLY score, is an acute-phase reactant that responds rapidly to short-term inflammatory stimuli. As such, it may be more sensitive to near-term tumor-host inflammatory dynamics, early treatment response, and disease progression, which are closely related to PFS. Fan et al. [24] demonstrated that inflammatory-nutritional composite indices effectively predicted treatment response and short-term prognosis in advanced non-small cell lung cancer patients receiving platinum-based chemotherapy, supporting the relevance of inflammation-related markers in short-term prognostic assessment.

In contrast, the HALP score incorporates hemoglobin and platelet count in addition to albumin and lymphocytes, thereby reflecting host reserve, oxygen-carrying capacity, and tumor-platelet interactions. Hemoglobin is closely linked to systemic oxygenation status, and cancer-related anemia can exacerbate intratumoral hypoxia, which has been shown to reduce chemotherapy sensitivity, promote treatment resistance, and facilitate tumor progression [22, 23]. Moreover, platelets are increasingly recognized as active participants in tumor progression and metastasis through the release of growth factors and the promotion of immune evasion. These mechanisms are more likely to exert sustained effects over the disease course, which may explain why HALP demonstrated a more robust and stable association with long-term survival outcomes. Consistent with this interpretation, evidence suggests that the prognostic value of the HALP score for OS remains stable across different tumor types and stages [12], indicating its suitability for long-term prognostic evaluation.

Methodologically, it should also be noted that CALLY and HALP share overlapping components, namely albumin and lymphocyte count, which may introduce partial collinearity in multivariable models. In such settings, variables providing more distinct biological information - such as hemoglobin and platelet count - may retain independent significance, whereas the incremental prognostic contribution of CRP-based information may be attenuated after adjustment. Furthermore, OS is influenced by multiple long-term determinants, including subsequent lines of therapy, comorbidity management, and supportive care. As follow-up duration increases, the impact of short-term inflammatory fluctuations may become diluted, potentially contributing to the borderline significance observed for CALLY in OS analyses.

We also found that CEA independently predicted objective response and PFS but did not retain significance in multivariable OS models. Su et al. [25] reported that changes in CEA were inconsistent with imaging-based treatment response in approximately 50% of patients with stage IV CRC, highlighting the limitations of relying solely on CEA for response evaluation. Moreover, CEA is a non-specific tumor marker with limited sensitivity and can be influenced by smoking and benign conditions [26]. In this context, CALLY and HALP scores may serve as valuable complementary markers to CEA, particularly for prognostic assessment. Notably, our time-dependent ROC analysis demonstrated that the combined CALLY-HALP score achieved the highest AUC at 24 months, suggesting that integrating multiple inflammation-, nutrition-, and anemia-related parameters may outperform single-marker prediction for survival outcomes.

Clinical utility of combined stratification

We constructed a combined stratification model based on CALLY and HALP. The CALLY-L/HALP-L group (both low) exhibited a significantly elevated risk of progression (HR = 2.296) and mortality (HR = 2.168). When patients were categorized into low-risk, intermediate-risk, and high-risk groups, PFS and OS demonstrated clear gradient separation. These findings have significant clinical implications for translation into practice. For high-risk patients with both low CALLY and low HALP, the overall inflammatory-immune-nutritional status is poor. More aggressive treatment strategies may be warranted, including intensified chemotherapy regimens, combined targeted therapy, or immunotherapy [10]. Additionally, enhanced nutritional support and inflammation control should be considered. Zhu et al. [27] conducted a multicenter study demonstrating that a composite immune-inflammatory-nutritional score effectively predicts postoperative prognosis in intrahepatic cholangiocarcinoma, thereby providing guidance for individualized treat-

ment decisions. Conversely, for low-risk patients with both high CALLY and high HALP, chemotherapy tolerance and expected response are favorable. Standard treatment protocols may be appropriate, or maintenance therapy could be considered once disease control is achieved.

Compared to using CALLY or HALP alone, combined stratification integrates information from two dimensions: inflammation (CRP) and anemia/thrombosis (hemoglobin, platelets), allowing for more refined risk classification. Evidence suggests that HALP, when combined with other peripheral blood markers, enhances prognostic prediction accuracy in early breast cancer patients [28]. Furthermore, both CALLY and HALP scores are derived from routine blood test parameters, making them low-cost, easily accessible, and reproducible; thus, they may be suitable for broader clinical application.

Comparison with previous studies

Our findings are generally consistent with previous studies evaluating the prognostic value of CALLY and HALP scores, although several important distinctions should be emphasized. Bahardoust et al. [29] conducted a multicenter study involving 1,447 CRC patients and demonstrated that a higher CALLY index was significantly associated with improved OS and recurrence-free survival. Similarly, Takeda et al. [9] reported that the CALLY index served as a novel prognostic marker in patients undergoing curative surgery for CRC. With respect to HALP, a meta-analysis of digestive system tumors [30] showed that a low HALP score was significantly associated with poorer OS (HR = 1.762), DFS (HR = 1.841), and PFS (HR = 1.444), supporting the broad prognostic relevance of this composite index across gastrointestinal malignancies.

However, several aspects distinguish our study from previous work and highlight its complementary contribution. First, most prior investigations focused on surgical populations or unselected CRC cohorts, often including heterogeneous metastatic sites and treatment strategies. In contrast, our study specifically targeted CRC patients with pulmonary metastasis receiving a uniform FOLFOX-based systemic chemotherapy regimen, thereby addressing a clinically distinct and underrepresented subgroup. Although Bahardoust et al. [29] reported improved survival outcomes in CRC patients undergoing pulmonary metastasectomy in the era of modern chemotherapy, including FOLFOX, their study primarily evaluated surgical outcomes and did not investigate biomarkers for predicting chemotherapy response or survival in non-surgical lung metastasis populations. Similarly, while FOLFOX or FOLFIRI doublet regimens are recognized as standard first-line treatments for metastatic CRC [10], biomarker-based stratification tools specifically validated in patients with lung metastases treated with systemic chemotherapy remain scarce.

Second, our study simultaneously assessed ORR and long-term survival outcomes (PFS and OS), thereby constructing an integrated analytical framework that captures both short-term treatment efficacy and long-term prognosis. Most previous studies primarily focused on survival endpoints alone, without systematically evaluating treatment response. Third, by exploring the combined stratification value of CALLY and HALP, we proposed a practical risk classification model that integrates inflammatory, nutritional, and anemia-related information. This combined approach may offer improved clinical applicability compared with the use of either index alone, particularly in guiding treatment decision-making and follow-up strategies for CRC patients with pulmonary metastases receiving systemic chemotherapy.

Limitations and future directions

This study has several limitations. First, as a single-center retrospective study, it may be subject to selection bias, necessitating validation of our conclusions through multicenter prospective studies. Second, we did not include molecular and immune markers such as circulating tumor DNA (ctDNA) and tumor-infiltrating lymphocytes, suggesting that future research could explore integrated models that combine CALLY/HALP with these novel biomarkers. Third, the optimal cutoff values for CALLY and HALP were derived from our cohort and require external validation. Fourth, we did not perform a subgroup analysis comparing FOLFOX alone versus combined targeted therapy; future studies could further investigate the predictive value of both scores under different treatment

modalities. Finally, CALLY and HALP scores share albumin and lymphocyte count as components, which introduces some degree of collinearity that may affect the estimation of their independent effects.

Future research directions include conducting multicenter prospective validation studies, exploring interactions between CALLY/HALP and molecular subtypes such as RAS/BRAF/MSI status, evaluating the predictive value of dynamic changes in CALLY/HALP before and after chemotherapy, constructing multidimensional prognostic models that integrate clinical, radiomic, and liquid biopsy data, and comparing predictive performance among patients with different metastatic sites (pulmonary versus hepatic metastasis).

Conclusion

In summary, CALLY and HALP scores effectively reflect the inflammatory-immune-nutritional status of CRC patients with pulmonary metastasis before FOLFOX chemotherapy. Both scores are closely associated with objective response and survival outcomes. Their combined stratification further enhances prognostic risk classification and holds potential clinical utility. As convenient scoring tools based on routine blood parameters, CALLY and HALP can serve as reference indicators for clinical treatment decisions and follow-up management.

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Disclosure of conflict of interest

None.

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