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Clinical predictors of leptomeningeal metastasis from lung adenocarcinoma based on retrospective analysis

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Abstract. Leptomeningeal metastasis (LM) is common in patients with lung adenocarcinoma, leading to high mortality rates. The predictors of systematic survival in patients with LM and lung adenocarcinoma remain poorly understood. The present study retrospectively analyzed 78 lung adenocarcinoma patients with or without LM treated at Ningbo Medical Center, Lihuili Hospital (Ningbo, China) between November 2016 and August 2024. Clinical characteristics and baseline hematological parameters obtained at LM diagnosis were evaluated for their associations with overall survival (OS). Median OS was 9.0 months (range: 0.2-48.9 months) in patients with LM. Univariate analysis identified age <60 years, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2, receipt of brain radiotherapy after a diagnosis of LM, no extracranial metastasis, epidermal growth factor receptor (EGFR) 19 mutation, receipt of third-generation EGFR tyrosine kinase inhibitor therapy before a diagnosis of LM, neutrophil-to-lymphocyte ratio <7.5755, platelet-to-lymphocyte ratio (PLR) <156.035 and a molecular graded prognostic assessment >1.5 to be significant predictors of superior OS. According to multivariate analysis, extracranial metastasis [hazard ratio (HR)=2.291; 95% CI, 1.074-4.888; P=0.032], PLR <156.035 (HR=0.233; 95% CI, 0.123-0.442; P<0.001) and ECOG PS 0-2 (HR=0.302; 95% CI, 0.152-0.599; P=0.001) remained predictive of OS. In conclusion, extracranial metastasis, PLR and ECOG PS were identified to be prospective independent clinical prognostic indicators of survival in patients with lung adenocarcinoma and LM. Overall, the present study highlighted the potential use of clinical characteristics and hematological variables before treatment to predict the outcomes of patients with lung adenocarcinoma complicated with LM.

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Introduction

Leptomeningeal metastasis (LM) is a type of central nervous system metastasis defined by the infiltration and spread of tumor cells in the leptomeninges or spinal leptomeninges. Clinically, it can present with a broad spectrum of symptoms, including headache, vomiting, mental and behavioral changes, seizures, hearing loss, visual disturbances, limb weakness and paresthesia (1,2). LM represents 11-20% of central nervous system metastases, with the highest rates reported in melanoma and lung cancer (2). LM is associated with a notably poor prognosis and short survival time, with median overall survival (OS) ranging from 3.6 weeks to 11 months (1). LM develops in 5-10% all patients with solid tumors and 3-5% patients with non-small cell lung cancer (NSCLC) (2-4). The development of LM is a complex, multi-step process that is driven by tumor cells acquiring capabilities for invasion and migration. These capabilities are supported by dynamic cytoskeletal reorganization and the activation of conserved pro-metastatic signaling pathways, such as the SPP1-CD44 axis and CXCL2/CCL2 chemokines (5). In the absence of treatment, patients with LM can succumb within 4-6 weeks. Conversely, the median duration of survival with treatment ranges from 3.6 to 4.5 months (6,7). Because of the blood-brain barrier (BBB), the majority of drugs cannot enter the meningeal cavity; therefore the meningeal cavity serves as a sanctuary site for tumor cells, allowing them to evade systemic therapies. However, due to advancements in imaging and systemic disease control, LM is increasingly diagnosed in patients with lung adenocarcinoma (8,9). With improvements in therapy, including targeted therapy, radiotherapy and intrathecal therapy, OS in patients with NSCLC and LM has improved, increasing from 1-3 to a current range of 11.0-20.4 months (10-12).

A single-arm phase II clinical study previously revealed that intrathecal therapy was efficient and safe in patients with LM from epidermal growth factor receptor (EGFR) mutation-positive NSCLC. Using the Response Assessment in Neuro-Oncology (RANO) criteria, the response rate was high at ~80.3%, but certain patients (19.7%) did not respond to treatment (10). In the BLOOM trial of patients with EGFR mutation-positive NSCLC and LM, a double dose of osimertinib produced an effective response with an objective response rate (ORR) of 62% and a median duration of response of 15.2 months, according to a neuroradiological blinded central independent review (11). Similarly, in 80 patients with EGFR or anaplastic lymphoma kinase (ALK) mutation-positive lung adenocarcinoma, median OS was 10.4 months, compared with 3.8 months in patients with wild-type lung adenocarcinoma (13). Furthermore, a retrospective study of patients with lung adenocarcinoma and LM revealed that brain radiotherapy could prolong survival, with median OS of 6.2 months (95% CI, 4.4-12.4) (13). This outcome was achieved because brain radiotherapy could damage the BBB, thereby increasing the intracranial antitumor drug concentration (14). Although a growing number of therapeutic methods have led to improvements in OS and ORR among patients with LM from lung adenocarcinoma, the existence of non-responders highlights the need to identify the factors influencing treatment outcomes.

The present retrospective study aimed to identify prognostic factors for advanced lung adenocarcinoma with LM to enhance the efficacy of novel therapies by Kaplan-Meier method.

Materials and methods

Patients. The present study was approved by the Ethics Committee of the Ningbo Medical Center, Lihuili Hospital (approval no. KY2024SL297-01). Requirement for informed consent was waived by the Ethics Committee of Ningbo Medical Center Lihuili Hospital since this is a retrospective study. All patients were treated between November 2016 and August 2024.

The inclusion criteria were as follows: i) Age of 18-85 years; ii) confirmation of lung adenocarcinoma by pathology; iii) LM diagnosis by cerebrospinal fluid (CSF) cytology or MRI using previous Chinese expert consensus (15); iv) peripheral blood testing within 7 days of an LM diagnosis and before treatment; and v) receipt of third-generation EGFR tyrosine kinase inhibitor (TKI) therapy, intrathecal therapy or brain radiotherapy after the LM diagnosis. The exclusion criteria were as follows: i) Immunodeficiency; ii) diagnosis of other carcinoma; iii) presence of serious co-morbidities (such as heart disease, infection or renal failure); iv) inadequate laboratory information and clinical data; v) pregnancy; vi) received corticosteroid therapy or had an infection within the 7 days preceding enrollment; and vii) gene mutations (including ALK, RET, HER2 and ROS1) other than EGFR exon 19 or 21 mutations, because for other mutations, either the patient population was small or there were no definitively effective targeted drugs established for leptomeningeal metastasis.

Clinical data collected included the following: i) Age; ii) sex; iii) smoking status; iv) ECOG PS (16); v) Karnofsky performance status (KPS) (17); vi) receipt of chemotherapy or brain radiotherapy before a diagnosis of LM; vii) receipt of brain radiotherapy after a diagnosis of LM (clinical data indicated that there were no standard guidelines prior to 2025; the decision to proceed with brain radiotherapy following LM was based on physician clinical experience rather than solely on patient condition); viii) CSF cytology; ix) brain MRI; x) driver gene mutation status; xi) brain metastasis (BM); xii) extracranial metastasis; xiii) receipt of third-generation EGFR TKI therapy before a LM diagnosis; xiv) receipt of intrathecal therapy; and xv) neurological symptoms (such as dizziness and headache). Peripheral blood test variables included the neutrophil ($x10^9$/l), platelet ($x10^9$/l) and lymphocyte counts ($x10^9$/l) within 7 working days until participants received brain radiotherapy, intrathecal therapy or targeted therapy after the LM diagnosis.

Response evaluation. Typically, the treatment response of LM is evaluated according to the RANO and European Association of Neuro-Oncology-European Society for Medical Oncology guidelines based on the clinical neurological examination, CSF pathology and MRI (18,19). However, the relevant data were characterized by incomplete recording, inconsistent documentation and a lack of standardization among patients. Consequently, LM-specific endpoints (neurological PFS, CSF cytology clearance and intracranial control) were not reliably assessable in the present study. Therefore, OS, defined as the time from the initial diagnosis of LM to death or the last follow-up, was the primary endpoint of this study.

Statistical analysis. The results were presented as the median, range and proportion. The Kaplan-Meier method was used for survival analysis. Univariate analysis and multivariate Cox regression analysis were performed to identify the factors independently predictive of survival. If predictors exhibited potential multicollinearity, appropriate factors would be selected through association analysis whilst considering data balance. All tests were two-sided, where $P<0.05$ was considered to indicate a statistically significant difference. The cut-offs of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were determined by receiver operating characteristic (ROC) curve analysis and the Youden index. Based on previous studies, the molecular graded prognostic assessment (molGPA) score was calculated following the established criteria (Table I), which involved summing the individual scores for KPS, extracranial metastasis and EGFR mutation status. This score was then investigated as a predictive factor (20-22). SPSS 20.0 (IBM Corp.) was used to analyze all statistical data.

Results

Characteristics of patients. From November 2016 to August 2024, LM from lung adenocarcinoma was confirmed by CSF cytology or MRI in 78 patients. The clinical information of patients is summarized in Table II. The median age of the patients was 64 years (range, 37-83). The cohort included 39 patients <60 years old, where 44 patients were male. The majority of patients were non-smokers (73.1%) and most patients had ECOG PS 0-2 (79.5%). A total of 12 patients (15.4%) received brain radiotherapy before the LM diagnosis and 24 patients (30.8%) underwent brain radiotherapy after LM was detected. In addition, 49 patients (62.8%) had BM and 58 patients (74.4%) exhibited extracranial metastasis. In addition, 69 patients (88.5%)

Table I. Scoring standard of molGPA for LM.

	molGPA for LM		
Predictor	0	0.5	1
Karnofsky performance score	<60	60-70	80-100
Extracranial metastasis	Present	Absent	-
Epidermal growth factor receptor	No sensitive mutation	Sensitive mutation	-

molGPA, molecular graded prognostic assessment; LM, leptomeningeal metastasis.

Table II. Clinical characteristics of patients (n=78).

Characteristic	Patients
Median age, years (range)	64.0 (37-83)
Age, years, N (%)	
<60	39 (50.0)
≥60	39 (50.0)
Sex, N (%)	
Male	44 (56.4)
Female	34 (43.6)
Smoking, N (%)	
Yes	21 (26.9)
No	57 (73.1)
Eastern Cooperative Oncology Group performance status, N (%)	
0-2	62 (79.5)
3-4	16 (20.5)
Chemotherapy before LM, N (%)	
Yes	42 (53.8)
No	36 (46.2)
Brain radiotherapy before LM, N (%)	
Yes	12 (15.4)
No	66 (84.6)
Brain radiotherapy after LM, N (%)	
Yes	24 (30.8)
No	54 (69.2)
Brain metastasis, N (%)	
Yes	49 (62.8)
No	29 (37.2)
Extracranial metastasis, N (%)	
Yes	58 (74.4)
No	20 (25.6)
Neurological symptoms, N (%)	
Yes	69 (88.5)
No	9 (11.5)
Gene mutation, N (%)	
EGFR 19 mutation	26 (33.3)
EGFR 21 mutation	30 (38.5)
EGFR wild-type	22 (28.2)
Third-generation EGFR tyrosine kinase inhibitor therapy before LM, N (%)	
Yes	47 (60.3)
No	31 (39.7)
Modality of LM diagnosis, N (%)	
MRI	27 (34.6)
Cerebrospinal fluid cytology	20 (25.6)
Both	31 (39.8)
Neutrophil-to-lymphocyte ratio (%)	
<7.5755	61 (78.2)
≥7.5755	17 (21.8)
Platelet-to-lymphocyte ratio, N (%)	
<156.035	35 (44.9)
≥156.035	43 (55.1)
Intrathecal therapy (%)	
Yes	36 (46.2)
No	42 (53.8)
Molecular graded prognostic assessment (%)	
0.0	13 (16.7)
0.5-1.0	58 (74.4)
1.5-2.0	7 (8.9)

LM, leptomeningeal metastasis. EGFR, epidermal growth factor receptor.

had neurological symptoms, whilst 36 patients (46.2%) received intrathecal therapy and 47 patients (60.3%) received third-generation EGFR TKI therapy before LM was detected. EGFR mutational profiling identified exon 19 deletions in 26 patients (33.3%) and the L858R mutation (exon 21) in 30 patients (38.5%), whilst 22 (28.2%) were EGFR wild-type. Furthermore, nine EGFR-wild-type patients underwent next-generation sequencing testing, which confirmed no EGFR mutations but revealed alterations in other genes, including KRAS, TP53 and PIK3CA. The modalities used to diagnose LM were MRI alone (27 patients; 34.6%), CSF cytology alone (20 patients; 25.6%) and MRI + CSF

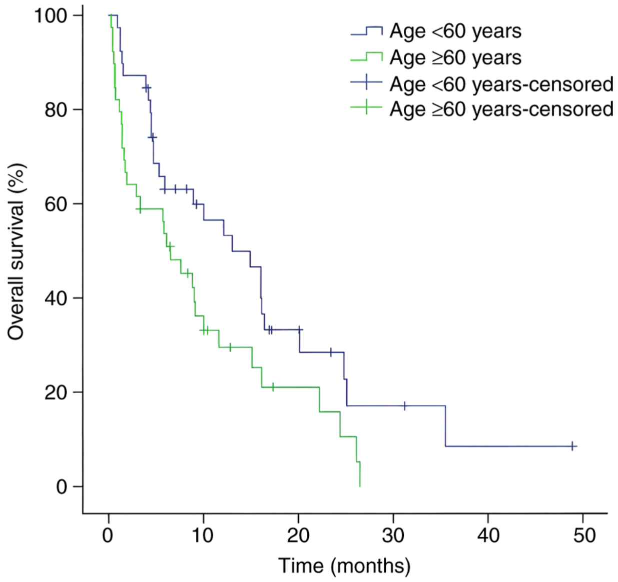

Figure 1. Kaplan-Meier curve analysis of overall survival among patients with lung adenocarcinoma and leptomeningeal metastasis in relation to age.

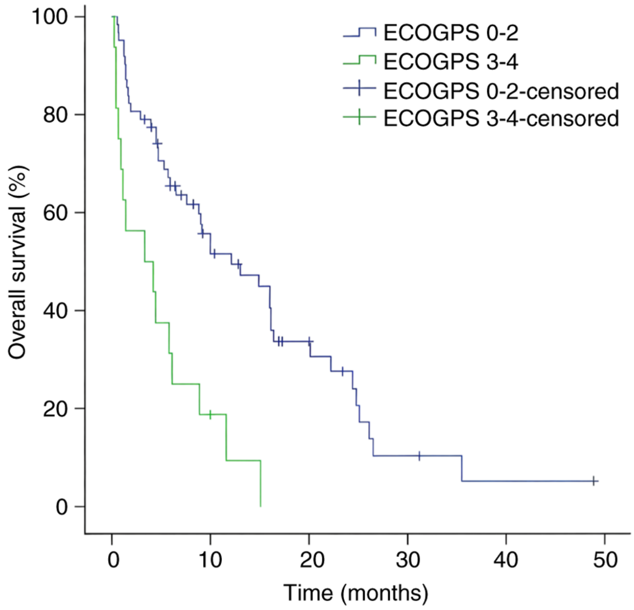

Figure 2. Kaplan-Meier curve analyses of overall survival among patients with lung adenocarcinoma and leptomeningeal metastasis in relation to Eastern Cooperative Oncology Group performance status.

cytology (31 patients; 39.8%). The molGPA score was 0 in 13 patients (16.7%), 0.5-1.0 in 58 patients (74.4%) and 1.5-2.0 in 7 patients (8.9%).

Optimal cut-offs for NLR and PLR. In the present study, ROC curve analysis was used to select the appropriate cut-offs for NLR and PLR. For NLR, the optimal cut-off was 7.5755, which had an area under curve (AUC) of 0.599. Further, the optimal cut-off for PLR was 156.035 (AUC=0.654).

Survival outcomes. Median OS for all patients was 9.0 months. OS was improved in patients <60 years old compared with those aged ≥60 years (Fig. 1) as well as in patients with an ECOG PS of 0-2 versus 3-4 (Fig. 2). The data indicated that brain radiotherapy after the diagnosis of LM can improve the OS relative to no brain radiotherapy (Fig. 3). Concerning gene mutations, OS was improved in patients with EGFR 19 exon deletion compared with those with an EGFR exon 21 mutation or EGFR wild-type (Fig. 4). Furthermore, OS was improved among patients who received third-generation EGFR TKI therapy before the diagnosis of LM compared with those who received non-third-generation EGFR TKIs (Fig. 5). By contrast, NLR ≥7.5755 vs. <7.5755 (Fig. 6) and PLR ≥156.035 vs. <156.035 (Fig. 7) were predictive of shorter OS. In addition, extracranial metastasis was associated with shorter OS vs. extracranial metastasis (Fig. 8). According to the molGPA classification, patients with a score of 0.0 had worse OS compared with those with score of 0.5-1.0 and 1.5-2.0 (Fig. 9). However, sex, smoking status, the receipt of chemotherapy before the diagnosis of LM, the receipt of brain radiotherapy before the diagnosis of LM, BM, neurological symptoms, the modality used to diagnose LM diagnosis and the receipt of intrathecal therapy were not significantly associated with OS (Table III).

Since NLR and PLR share lymphocyte counts and may exhibit collinearity, which could lead to unstable estimates if both were included in the multivariable model, only PLR was selected for inclusion in the model. Multivariate analysis identified non-extracranial metastasis [vs. extracranial metastasis; hazard ratio (HR)=2.291; 95% CI, 1.074-4.888; P=0.032], PLR<156.035 (vs. ≥156.035; HR=0.233; 95% CI, 0.123-0.442) and ECOG PS 0-2 (vs. 3-4; HR=0.302; 95% CI, 0.152-0.599) as meaningful clinical characteristics associated with OS (Table III), whereas the remaining factors were not predictive of outcomes.

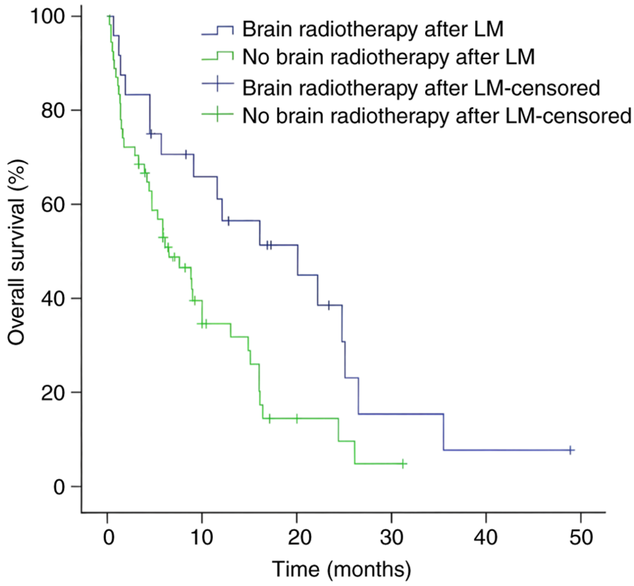

Figure 3. Kaplan-Meier curve analyses of overall survival among patients with lung adenocarcinoma and LM in relation to the receipt of brain radiotherapy after the LM diagnosis. LM, leptomeningeal metastasis.

Discussion

The selection of treatment for patients with lung adenocarcinoma and LM is a difficult clinical challenge. Although the

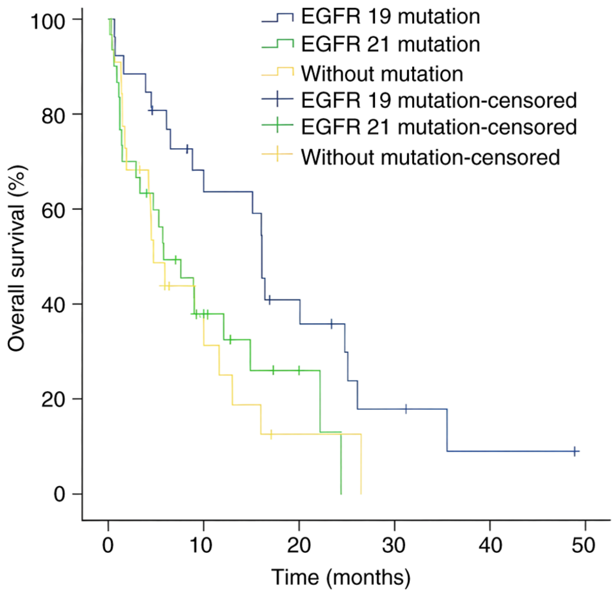

Figure 4. Kaplan-Meier curve analyses of overall survival among patients with lung adenocarcinoma and leptomeningeal metastasis in relation to the gene mutation status. EGFR, epidermal growth factor receptor.

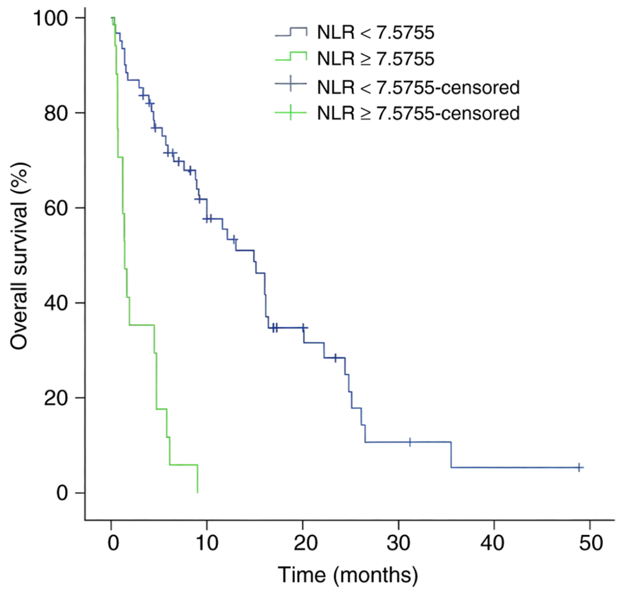

Figure 6. Kaplan-Meier curve analyses of overall survival among patients with lung adenocarcinoma and leptomeningeal metastasis in relation to NLR. NLR, neutrophil-to-lymphocyte ratio.

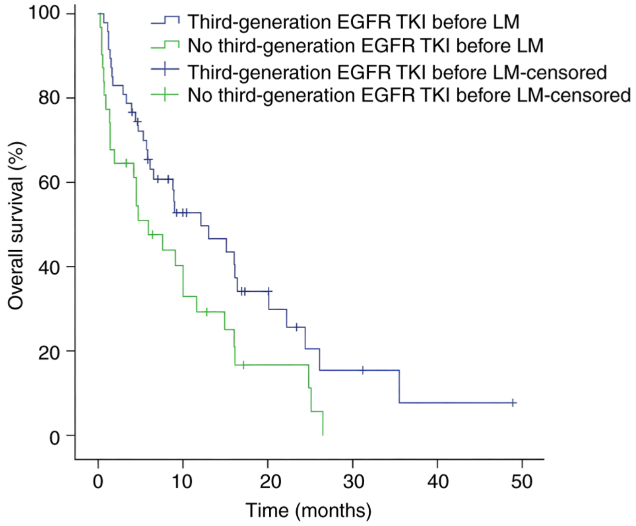

Figure 5. Kaplan-Meier curve analysis of overall survival among patients with lung adenocarcinoma and LM in relation to the receipt of receiving third-generation EGFR TKI therapy before the LM diagnosis. LM, leptomeningeal metastasis; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

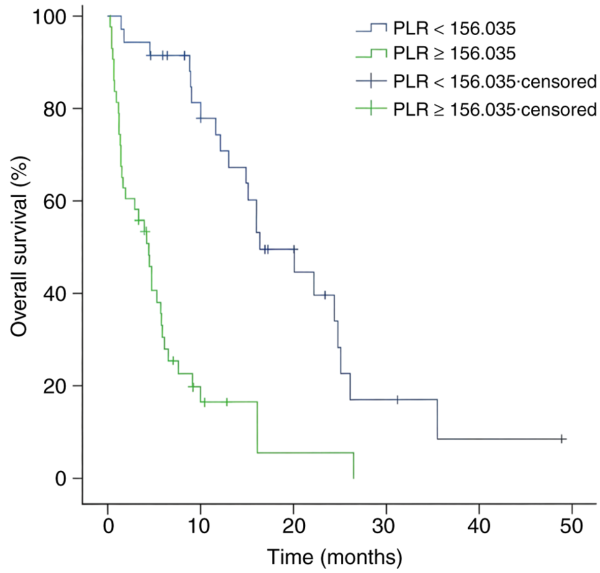

Figure 7. Kaplan-Meier curve analyses of overall survival among patients with lung adenocarcinoma and leptomeningeal metastasis in relation to PLR. PLR, platelet-to-lymphocyte ratio.

overall prognosis is grave, significant heterogeneity in survival exists, underscoring the critical need for reliable prognostic biomarkers to guide personalized management. While prior research has established several prognostic factors, including ECOG PS, intrathecal therapy and antiangiogenic therapy following LM, the integrative role of routinely available hematological indices, such as NLR and PLR, in combination with established clinical parameters, within the framework of contemporary multimodal treatment strategies (involving third-generation EGFR-tyrosine kinase inhibitors and radiotherapy), remains to be further validate (10,23). The present study aimed to address this gap by comprehensively evaluating a panel of pre-treatment clinical and hematological variables. The prognostic significance of several established factors in univariate analysis were assessed, where non-extracranial metastasis, a low PLR (<156.035) and a good performance status (ECOG PS 0-2) were identified as independent predictors of longer OS in the multivariate model. This integrative approach provides a practical and robust framework for risk stratification in this patient population.

Neutrophils, platelets and lymphocytes are commonly investigated as peripheral blood indicators in laboratory examination. The independent prognostic value of NLR and PLR in the present cohort underscores the pivotal role of the

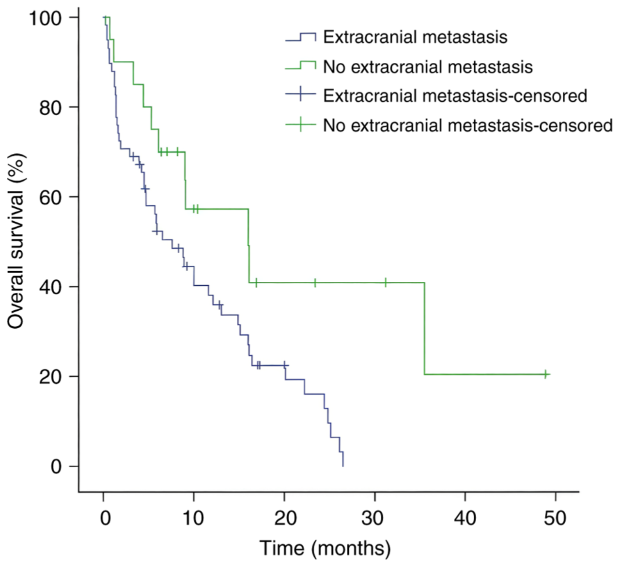

Figure 8. Kaplan-Meier curve analyses of overall survival among patients with lung adenocarcinoma and leptomeningeal metastasis in relation to extracranial metastasis.

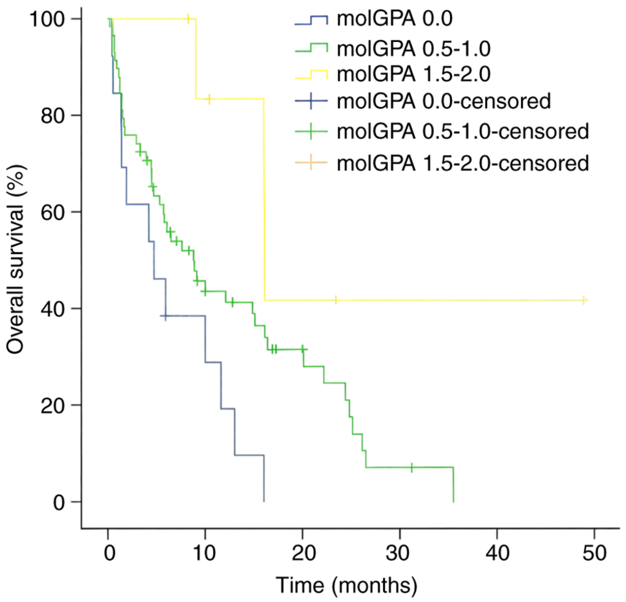

Figure 9. Kaplan-Meier curve analyses of overall survival among patients with lung adenocarcinoma and leptomeningeal metastasis in relation to molGPA. molGPA, molecular graded prognostic assessment.

systemic inflammatory response and tumor immune microenvironment in LM pathogenesis. Consistent with the results of *ex post facto* studies, NLR and PLR, as projected factors of lung cancer mortality, can influence the tumor inflammatory microenvironment, particularly in patients with BM and LM (18,19,21). NLR >3.83 (HR=2.66; 95% CI 1.17-6.01; P=0.019) indicated poor survival in a consecutive cohort of patients with BM (24). In a previous systematic review and meta-analysis of patients with BM from lung cancer, 11 studies revealed that high NLR (HR=1.84; 95% CI, 1.47-2.31; P<0.001) was significantly associated with shorter OS, where an analysis of five studies indicated that high PLR was predictive of shorter OS (HR=1.53; 95% CI, 1.07-2.20; P=0.020) (25). In addition, low NLR (HR=0.49; 95% CI, 0.28-0.86; P=0.012) was associated with longer OS in patients with lung cancer and LM. Patients with pre-treatment PLR <145.44 (P=0.031) had longer OS according to a univariate analysis (20). Similarly, in a multivariate analysis of the whole cohort, a pre-treatment PLR cut-off of 209.77 was associated with a significant difference in median OS (8.0 vs. 14.5 months; P=0.047). In addition, post-treatment NLR >3.57 (HR=2.203; 95% CI, 1.060-4.578; P=0.034) was a useful prognostic factor for patients with lung cancer and LM according to a multivariate analysis (26).

Previously, Berghoff *et al* (27) reported that the brain is not a completely independent organ. Inflammatory cells can stimulate the release of certain substances, such as reactive oxygen species, affecting neighboring cancer cells (28). The inflammatory microenvironment mainly consists of neutrophils, platelets and lymphocytes. As key factors in the tumor response, neutrophils are positioned in the glycolytic and hypoxic tumor core, where they can promote angiogenesis to support tumor cell proliferation (29). Neutrophils represent the most common immune cell type in human blood, where they can regulate cancer initiation, growth and metastasis (29). Other cells, such as T cells and macrophages, can interact with neutrophils in the tumor microenvironment (30). By contrast, platelets can promote epithelial-mesenchymal transition to facilitate cancer cell proliferation and invasiveness. Activated platelets can help cancer cells avoid immune system surveillance and anoikis. Therefore, platelets have an important role in tumor metastasis (31). Lymphocytes inhibit tumor cell proliferation and provoke cancer cell killing by T cells (32). Studies have identified NLR and PLR as key predictors of clinical outcomes in various tumors, such as breast and colon cancer (33,34). In the unique sanctuary of the central nervous system, the value of these ratios may be amplified. Inflammatory crosstalk at the blood-CSF barrier can modulate the permeability of this barrier and create a permissive niche for tumor cell colonization and proliferation. Therefore, elevated NLR and PLR likely reflect a heightened systemic and potentially local pro-metastatic milieu that is permissive for the establishment and progression of LM, explaining their potent prognostic power in the present analysis.

The persistence of ECOG PS as an independent prognostic factor reasserts the fundamental importance of the physiological status of the patient. A poor performance status frequently mirrors a higher systemic tumor burden, increased cancer-related symptomatology and diminished physiological capacity to tolerate aggressive therapies (23). The present findings suggest that ECOG PS captures elements of disease aggressiveness and patient frailty that are not fully explained by laboratory values or mutation status alone. This finding aligns with that by Wang *et al* (26), who reported a significant difference in median OS (4 vs. 15 months) based on ECOG PS. Other studies have illustrated that patients with low ECOG PS have longer survival, consistent with the findings in the present study (10,20). Consequently, performance status remains an indispensable, non-redundant tool for initial prognostication and clinical decision-making in neuro-oncology.

The present univariate analysis suggested a survival benefit associated with brain radiotherapy administered after LM diagnosis. Although this effect was attenuated in

Table III. Uni- and multivariate analyses for overall survival of patients with LM.

		Univariate			Multivariate		
Characteristic	N	Median, months	95% CI	P-value	Hazard ratio	95% CI	P-value
Age, years				0.029	0.844	0.474-1.502	0.563
<60	39	13.0	6.96-19.04				
≥60	39	6.5	3.00-10.00				
Sex				0.742			
Male	44	7.6	1.68-13.52				
Female	34	10.0	5.79-14.21				
Smoking				0.687			
Yes	21	9.1	0.00-22.96				
No	57	9.0	5.95-12.05				
Eastern Cooperative Oncology Group performance status				<0.001	0.302	0.152-0.599	0.001
0-2	62	12.1	4.97-19.23				
3-4	16	3.3	0.00-8.79				
Chemotherapy before LM				0.314			
Yes	42	11.6	6.61-16.59				
No	36	7.6	3.25-11.95				
Brain radiotherapy before LM				0.514			
Yes	12	5.8	4.18-7.42				
No	66	10.0	6.69-13.31				
Brain radiotherapy after LM				0.012	0.509	0.253-1.026	0.059
Yes	24	20.1	5.02-35.18				
No	54	6.5	2.73-10.28				
Brain metastasis				0.260			
Yes	49	7.6	3.92-11.28				
No	29	16.0	9.51-22.49				
Extracranial metastasis				0.012	2.291	1.074-4.888	0.032
Yes	58	7.6	3.99-11.21				
No	20	16.0	5.47-26.53				
Neurological symptoms				0.110			
Yes	69	7.6	3.58-11.62				
No	9	9.1	/				
Gene mutation				0.019	1.050	0.711-1.552	0.806
EGFR 19 mutation	26	16.1	14.64-17.56				
EGFR 21 mutation	30	5.8	1.34-10.26				
Without mutation	22	4.7	2.51-6.89				
Third-generation EGFR tyrosine kinase inhibitor therapy before LM				0.035	0.958	0.478-1.920	0.904
Yes	47	12.1	4.20-20.00				
No	31	5.9	2.39-9.41				
Modality of LM diagnosis				0.666			
MRI	27	9.0	2.18-15.83				
Cerebrospinal fluid cytology	20	9.1	6.18-12.02				
Both	31	10.0	2.08-17.92				
Neutrophil-to-lymphocyte ratio				<0.001			
<7.5755	61	14.9	10.53-19.27				
≥7.5755	17	1.4	0.86-1.94				

Table III. Continued.

		Univariate			Multivariate		
Characteristic	N	Median, months	95% CI	P-value	Hazard ratio	95% CI	P-value
Platelet-to-lymphocyte ratio				<0.001	0.233	0.123-0.442	<0.001
<156.035	35	16.4	10.56-22.24				
≥156.035	43	4.4	3.01-5.80				
Intrathecal therapy				0.880			
Yes	36	10.0	3.70-16.30				
No	42	8.8	4.25-13.35				
Molecular graded prognostic assessment				0.008	0.625	0.268-1.458	0.277
0.0	13	4.7	0.00-9.40				
0.5-1.0	58	8.8	4.61-12.99				
1.5-2.0	7	16.1	15.89-16.31				

LM, leptomeningeal metastasis; OS, overall survival; EGFR, epidermal growth factor receptor.

the multivariate model, it hints at the potential role of brain radiotherapy in disrupting the BBB (14). Evidence from the literature suggests that brain radiotherapy is beneficial for patients with NSCLC and LM (35). In a previous retrospective study, univariate analysis illustrated that brain radiotherapy can prolong OS compared with non-brain radiotherapy (median OS: 11.4 vs. 5.0 months; P=0.051) in 80 patients with LM from NSCLC (36). Consistent with the present findings, brain radiotherapy after the diagnosis of LM was associated with longer OS (median OS=20.1 months; P=0.012) according to a univariate analysis. Although multivariate analysis did not confirm this finding-likely due to the limited number of patients who received brain radiotherapy-this treatment modality following the diagnosis of LM may still be predictive of OS in patients with NSCLC and LM (HR=0.580; P=0.132).

According to multivariate analysis, extracranial metastasis negatively influenced OS (P=0.032) in patients with LM from NSCLC in the present study. Previous studies identified extracranial metastasis as a survival biomarker. In patients with LM from NSCLC, univariate analysis illustrated that patients with extracranial metastasis had shorter OS (HR=2.09; P<0.01) regardless of the EGFR status (37). Multivariate analysis in another retrospective study also demonstrated that extracranial metastasis was an independent predictor for poorer survival compared with the absence of extracranial metastasis (median OS: 10.0 vs. 20.0 months; P=0.023) (38). In summary, extracranial metastasis portended inferior outcomes among patients with NSCLC and LM.

Different EGFR mutations have been associated with differences in OS in patients with LM. In a study by the European Society of Medical Oncology, patients with NSCLC and LM who harbored EGFR exon 19 mutations had superior OS (37). There are two reasons for the distinctions between exon 19 and 21 mutations. The tyrosine phosphorylation structure of EGFR differs between exon 19 deletion and exon 21 mutation in NSCLC cell lines, leading to dissimilar alterations of downstream signaling pathways (38). The other reason is that exon 21 mutation requires asymmetric dimerization for activation and oncogenic transformation, whereas exon 19 mutation is not associated with dimerization activation (39). Therefore, patients with LM and EGFR 19 deletion had prolonged median OS (16.1 months; P=0.019) according to univariate analysis in the present study.

Based on univariate analysis, the receipt of third-generation EGFR TKI therapy before the diagnosis of LM appeared to improve OS in the present study (OS=12.1 months; P=0.035). Third-generation EGFR TKIs have a high rate of entry into the BBB owing to their macrocyclic amide structure and optimized lipophilicity (40-42). However, no difference in OS associated with this variable was observed in the multivariate analysis. This finding could be due to the fact that individual third-generation EGFR TKIs, such as osimertinib, almonertinib, furmonertinib and befotertinib, were not investigated. Therefore, further research is needed to identify the optimal third-generation EGFR TKIs for patients with NSCLC and LM.

Previous studies identified molGPA as a prognosis risk factor for patients with LM (21,22). Zhang *et al* (21) reported that median OS in the low-risk molGPA group was 8.02 months (95% CI, 0.98-38.13), which significantly exceeded the survival duration in the medium- and high-risk groups. In addition, another study reported median OS times of 0.9, 5.8 and 17.7 months for the low-, medium-, and high-risk molGPA groups, respectively (P<0.001) (22). Similarly, the median OS times in these molGPA subgroups in the present study were 4.7, 8.8 and 16.1 months, respectively, with significant differences identified by univariate analysis (P=0.008). These results underscore the potential utility of the molGPA model in optimizing patient management. However, this conclusion is tempered by the small subgroup size (n=7) in the highest molGPA category, which may affect the reliability of the findings. Therefore, further studies are warranted for validation.

The current study had some limitations. It was a retrospective study, within which the small sample size raises the possibility of selection bias. The strong univariate association between post-LM brain radiotherapy and survival was attenuated in the multivariable model. This could be explained if patients receiving radiotherapy had more favorable prognostic factors at baseline, such as superior performance status, lower disease burden or greater fitness for further treatment, all of which independently predict longer survival. In addition, LM was not pathologically confirmed by CSF cytology in all patients. There was also no control group to verify the clinical utility of the cut-offs. The sequence and timing of third-generation EGFR TKI treatment or intrathecal therapy in combination with brain radiotherapy was not standardized. PD-L1 status was also not assessed. Comprehensive next-generation sequencing data was not performed for all patients due to the study's retrospective nature, which may have affected the interpretation of survival and treatment outcomes because of the unknown status of EGFR and other gene mutations. The measured values of NLR and PLR may have been confounded by variations in corticosteroid regimens and occurrence of intercurrent infections. Differences in intrathecal drugs (the doses, fractionation and sites of brain radiotherapy) and third-generation EGFR TKIs could lead to different results. No internal validation was performed when selecting the ROC-based cut-offs, where the data-driven selection of cut-offs can cause overfitting and limited generalizability. The analysis was subject to immortal time bias and confounding by indication due to the retrospective design and timing of therapy administration, which may affect the interpretation of survival benefits associated with therapies, such as radiotherapy and pre-LM TKI use. Despite these limitations, the present study provides evidence for predicting outcomes in patients with lung adenocarcinoma and LM.

In conclusion, the present study identified extracranial metastasis, PLR and ECOG PS as independent predictors of OS in patients with lung adenocarcinoma and LM. In addition, brain radiotherapy, EGFR 19 mutation, the receipt of third-generation EGFR TKI therapy before the diagnosis of LM and molGPA were significantly associated with overall survival. Although intrathecal therapy was associated with negative survival outcomes, EGFR mutation had a crucial influence on survival in the majority of patients. Future studies are needed to delineate the optimal sequencing and combination of radiotherapy, intrathecal therapy and specific TKIs.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YuL was responsible for performing the experiments and collecting data, formal analysis of data, design of the methodology, data curation (managing, cleaning, annotating, and preserving data) and writing the original draft. YiL and XC analyzed data, designing the methodology, data curation (managing, cleaning, annotating, and preserving data), validation and writing the original draft. YZ and HD were responsible for the software (programming, code development, and tool testing), design of the methodology, and reviewing and editing the manuscript. YuL and XC confirm the authenticity of all the raw data. XC edited the manuscript. DJ was responsible for the formal analysis of data, and review and editing the manuscript. GC and XY were responsible for providing resources, conceptualization of the study, reviewing and editing the manuscript, and project administration. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Ningbo Medical Center Lihuili Hospital (approval no. KY2024SL297-01). This study was conducted in accordance with the Declaration of Helsinki. Requirement for informed consent was waived by the Ethics Committee of Ningbo Medical Center Lihuili Hospital since this is a retrospective study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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