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Original Article

Relationship between lymphocyte to monocyte ratio and brain metastasis in non-smalll cell lung cancer patients

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Abstract: Objective: To observe whether there is an association between the lymphocyte/monocyte ratio (LMR) and the occurrence of brain metastases in non-small cell lung cancer (BM-NSCLC) patients. Method: Retrospective collection of patients' information meeting the standards of nano-excretion, was done from January 2016 to September 2021. We calculated the odds ratio (OR) and 95% confidence interval (CI) of LMR versus BM-NSCLC using multivariate logistic regression, and stratified analysis was performed. The linear or nonlinear relationships that exist between the two were explored by generalized additive model and smoothed curve fitting. Results: In all three models, LMR was negatively associated with BM-NSCLC (Model 1: OR, 0.72; 95% CI, 0.57-0.9; P=0.0037. Model 2: OR, 0.64; 95% CI, 0.50-0.82; P=0.0005. Model 3: OR, 0.62; 95% CI, 0.47-0.81; P=0.0005). This negative association was shown to be significant in patients with adenocarcinoma (ADC), who were, female, and in T2-T4 stages, and N1-N3 stages (ADC: OR, 0.59; 95% CI, 0.44-0.80; P=0.0006. female: OR, 0.37; 95% CI, 0.20-0.68; P=0.0013. T2-T4: OR, 0.59; 95% CI, 0.43-0.82; P=0.0014; N1-N3: OR, 0.62; 95% CI, 0.45-0.86; P=0.0042), according to subgroup analysis. Conclusion: After controlling for relevant confounders, this study demonstrated that increased LMR levels in NSCLC patients were substantially and inversely connected to their likelihood of BM, particularly in patients with ADC, who were female, or had T2-T4, and N1-N3 stages.

Keywords: Non-small cell lung cancer, brain metastasis, lymphocyte to monocyte ratio, tumor immunity and microenvironment, linear regression

Introduction

Lung cancer is a common malignant tumor of the respiratory system in clinical practice, and its incidence and mortality rate rank first among malignant tumors, with up to 85% of patients having non-small cell lung cancer (NSCLC) among various lung cancer types [1]. Among them, brain metastases (BM) occur in 10% to 25% [2-4], but there is no effective early warning sign. Moreover, the prognosis of patients with brain metastases from NSCLC is not satisfactory. Whole-brain radiotherapy can reduce the local recurrence rate to some extent, but it is hardly useful to improve the survival of patients. Therefore, it is essential to analyze the correlation between proven biomarkers and brain metastasis of NSCLC (BM-NSCLC) in order to further explore the pathologic mechanism and identify patients at risk for brain metastasis.

The inflammatory response is involved in the development of tumors. The relationship between inflammation and cancer was first described by Virchow [5] in 1863, and the role played by inflammation in promoting the development, progression, and metastasis of tumors is increasingly accepted. Previous studies had pointed out that inflammatory indicators in peripheral blood, such as neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to lymphocyte ratio (PLR), can better reflect the prognosis of

lung cancer, breast cancer, and gastric cancer than single indicators [6-8]. Most studies have focused on the value played by NLR in baseline serum; and in patients with adrenocortical carcinoma (ACC), overall survival (OS) was significantly lower in the higher NLR group than in the lower NLR group (P=0.032) [9]. High NLR values also independently predict poorer survival in patients with advanced NSCLC treated by immune checkpoint blockade (ICB) [10]. However, the role of tumor-associated monocytes cannot be ignored. Studies have shown that [11] higher LMR is regarded as one of the indicators of good prognosis. Compared to patients with LMR ≥3.8, lower LMR (<3.8) patients seem to have a lower complete remission rate (26% vs. 90%, P<0.001), 2-year progression-free survival (18% vs. 82%, P< 0.001), and 3-year overall survival (24% vs. 86%, P<0.001).

LMR in peripheral blood can partially express changes between host immunity and tumor microenvironment, and can be easily, and at low-cost, determined from complete blood count. A high LMR represents a higher lymphocyte count and a lower monocyte count. Lymphocytes are immune response cells that can participate in cell death and inhibit tumor cell proliferation and migration, and can stimulate anti-tumor immune activity to inhibit malignant tumor progression. Lymphopenia usually indicates a severe disease and is linked to a poor prognosis in cancer [12]. Conversely, monocytes suppress the host's anti-tumor immune response and strengthen tumor progression and metastasis. Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-1 secreted by monocytes are linked to poor prognosis in cancer patients [13-14]. Hiren Mandaliya [15] et al. showed that low LMR predicts worse OS. Studies have mostly examined the significance of LMR levels in determining prognosis for NSCLC patients, but there are fewer studies that investigate the relationship between LMR levels and BM-NSCLC, and the effects brought by confounding factors have not been taken into account, and special populations have not been defined by stratified analysis. Neither was a linear or nonlinear relationship between the two explored using a smooth curve fit. Based on the issues found in clinical practice, our study aimed to determine whether LMR is related to BM and provide clinical evidence for further research.

Methods

Study population

The information of patients with NSCLC diagnosed and treated in Cancer Hospital of Anhui University of Science and Technology from January 2016 to September 2021 was collected retrospectively, and the target population was screened according to the nano-emission standard.

Inclusion criteria: 1. Histopathology or cell chemistry diagnosis of NSCLC and no other primary tumor present. 2. Metastasis to the bones is defined as a systemic bone image and assessment by CT or MRI to prove typical bone metastasis. 3. Image analysis (CT or MRI) is required for the diagnosis of brain metastasis. 4. The patient was not treated (radiation, chemotherapy, targeted therapy, surgery, etc.) within 15 days prior to the time of hematology data collection. 5. Patients with bone or brain metastases were diagnosed to have metastases at the time of first admission for routine examination, without obvious inflammatory symptoms.

Exclusion criteria: 1. Patients with incomplete clinical information regarding Age, Sex, Type, T, N stage, and smoking. 2. Types of pathology other than adenocarcinoma (ADC), or squamous cell carcinoma (SCC). 3. Patients with ≥2 sites of metastasis.

Finally, 228 patients were screened out, among which 109 cases had no metastasis, 63 cases had brain metastasis, and 56 cases had bone metastasis. Before we collected and use the information of our patients, we received their consent. This ensures that the information is treated as confidential and that it is kept secure. Moreover, the application to the Ethics Committee of the hospital was approved (2022-KY-FZZX-01).

Study variables

The complete hematocrit was obtained from the patient on admission, and NLR refers to neutrophils-to-lymphocytes ratio, PLR refers to platelets-to-lymphocyte ratio, and LMR refers to lymphocytes-to-monocyte ratio. In a multiple regression model, Age, Sex, Type, T, N stage, and smoking has been adjusted for as potential confounder.

Table 1. Description of the study population

Exposure	No metastasis n=109	Bone metastasis n=56	Brain metastasis n=63
NLR (mean ± SD)	3.46±2.61	4.11±3.30	5.68±4.25
PLR (mean ± SD)	176.54±108.56	197.25±119.94	212.51±97.5
LMR (mean ± SD)	3.41±1.92	3.27±1.35	2.59±1.20
Sex n (%)			
Male	81 (74.31%)	26 (46.43%)	35 (55.56%)
Female	28 (25.69%)	30 (53.57%)	28 (44.44%)
Age n (%), years			
<60	18 (16.51%)	18 (32.14%)	27 (42.86%)
≥60	91 (83.49%)	38 (67.86%)	36 (57.14%)
Type n (%)			
ADC	64 (58.72%)	44 (78.57%)	57 (90.48%)
SCC	45 (41.28%)	12 (21.43%)	6 (9.52%)
T Stage n (%)			
Tis-T1	21 (19.27%)	8 (14.29%)	15 (23.81%)
T2-T4	88 (80.73%)	48 (85.71%)	48 (76.19%)
N Stage n (%)			
N0	38 (34.86%)	5 (8.93%)	13 (20.63%)
N1-N3	71 (65.14%)	51 (91.07%)	50 (79.37%)
Smoking n (%)			
YES	13 (11.93%)	12 (21.43%)	7 (11.11%)
NO	96 (88.07%)	44 (78.57%)	56 (88.89%)

Note: ADC: adenocarcinoma; SCC: squamous cell carcinoma; NLR: neutrophils/lymphocytes; PLR: platelets/lymphocytes; LMR: lymphocytes/monocytes.

Statistical analysis

One-way analysis of variance (ANOVA) or Kruskal-Wallis test was used for continuous variables, and X^2 test was used for categorical variables. Single and multifactor analysis were performed to detect risk factors associated with BM-NSCLC. A weighted generalized summation model, adjusting for different variables, was used to observe the trend in LMR, and an analysis of the nonlinear relationship between LMR and BM was carried out with smoothed curve fitting. All examinations were bilateral and *P*-values less than 0.05 were considered significant. All statistical analyses were conducted using the Empower-Stats software (http://www.empowerstats.com) based on R language.

Results

Baseline description and univariate and multivariate analysis

228 NSCLC patients were included based on the nadir criteria, including 109 patients who did not have metastases, 56 patients who had bone metastases, and 63 patients who had brain metastases (**Table 1**). Three groups of people were compared (**Figure 1**). There was a significant difference in LMR levels between patients with nonmetastatic NSCLC and patients with BMNSCLC (P= 0.0089). However, there was no significant difference in LMR levels between patients without metastasis and those with bone metastasis (P= 0.77). Univariate and multivariate analyses showed that age (P=0.0054), tumor type (P= 0.0004), NLR (P=0.0083), and LMR (P=0.0179) were independent risk factors for BM-NSCLC (**Table 2**).

Multiple regression analysis of the LMR level and BM

The multiple regression analysis (**Table 3**) showed that LMR was negatively associated with BM-NSCLC without adjusting for confounders in model 1 (OR, 0.72; 95% CI, 0.57-0.90; P=0.0037), and each unit increase in LMR was associated with a 28% reduction in the risk of BM-NSCLC in the patients. When demographic factors (age and sex) were corrected for in model 2, each unit increase in LMR was associated with a 36% reduction in the risk of BM-NSCLC (OR, 0.64; 95% CI, 0.50-0.82; P=0.0005). The results of model 3 showed that for models that adjusted for all potential confounders (age, sex, type, T and N stage and smoking), each unit increase in LMR resulted in a 38% reduction in the incidence of BM (OR, 0.62; 95% CI, 0.47-0.81; P=0.0005). As a result of converting LMR from a continuous variable to a categorical variable (tertiles), a high LMR (3.56-10.12) was significantly associated with a lower risk of BM than a low LMR (0.76-2.02) (P=0.0062), and this trend was significant (P=0.0061).

Subgroup analysis

Subgroup analysis is shown in **Table 4**, and after stratification by age (<60 or ≥60 years),

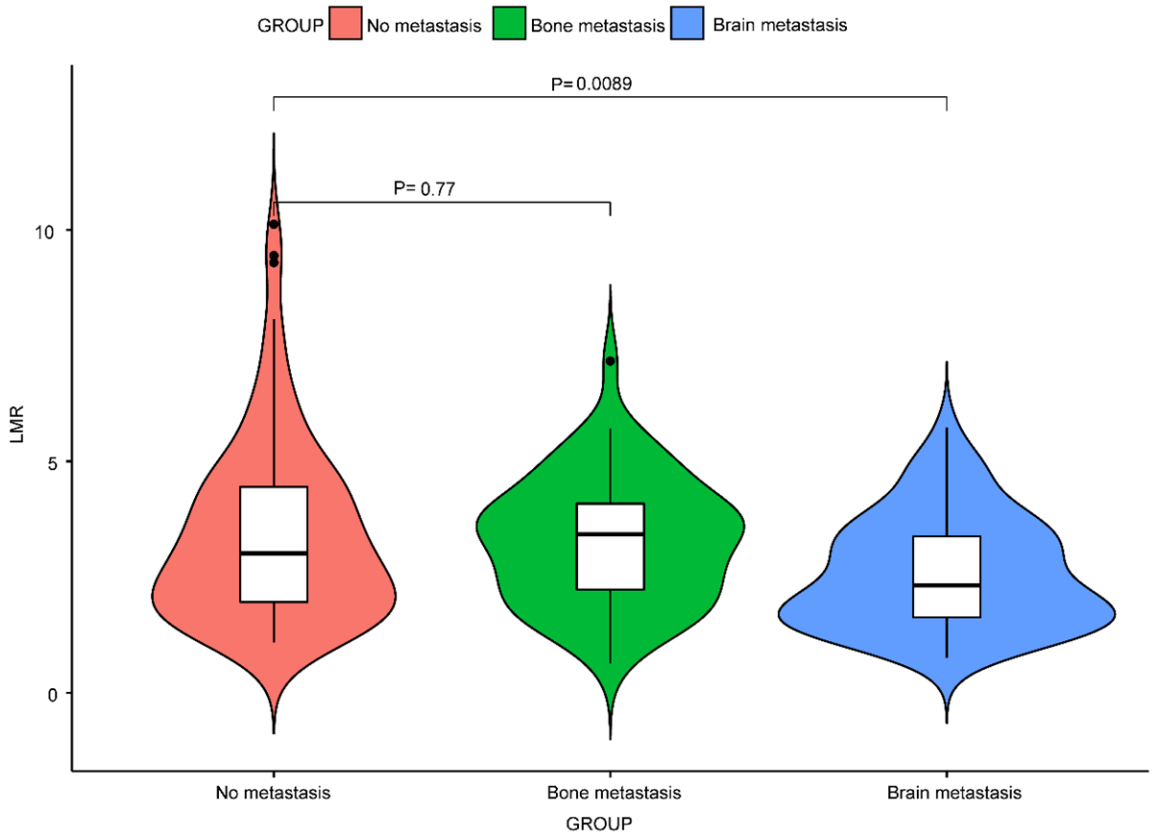

Figure 1. Distribution of LMR in different groups.

LMR level was negatively correlated with BM risk, Age <60 years (OR, 0.36; 95% CI, 0.16-0.79; P=0.0107) Age ≥60 years (OR, 0.67; 95% CI, 0.48-0.95; P=0.0250). After stratification by sex, this negative association was significant in females (OR, 0.37; 95% CI, 0.20-0.68; P=0.0013), while it was not significant in males (OR, 0.85; 95% CI, 0.61-1.18; P=0.3184). This negative correlation was also present in ADC patients (OR, 0.59; 95% CI, 0.44-0.80; P=0.0006), while there was no significant correlation in SCC patients (OR, 0.73; 95% CI, 0.33-1.63; P=0.4420). Stratification by T-stage showed a significant correlation with T2-T4 staging (Tis-T1: OR, 0.58; 95% CI, 0.28-1.18; P=0.1328. T2-T4: OR, 0.59; 95% CI, 0.43-0.82; P=0.0014). In the results of the analysis of N-stage stratification, there was a negative correlation of LMR and BM with N1-N3 stage, but not significantly so in patients with N0 stage (N0: OR, 0.57; 95% CI, 0.32-1.04; P=0.0685. N1-N3: OR, 0.62; 95% CI, 0.45-0.86; P=0.0042). **Figures 2-4** demonstrate that a negative correlation exists between LMR and BM using the generalized additive model and smoothed curve fitting.

Discussion

By analyzing levels of LMR among patients without metastasis, with brain metastasis, and bone metastasis, a difference in LMR was found only in patients without metastasis and with BM. Therefore, we focused on the potential relationship between LMR and BM. This study showed that after adjusting for possible confounding factors that may lead to BM formation, a high LMR level was negatively correlated with BM. This negative correlation was significant in females, ADC, stage T2-T4 and N1-N3 patients, but not in males, SCC, or stage Tis-T1 and N0 patients.

The brain is one of the common metastatic sites of lung cancer, which often indicates a poor prognosis [16]. Lung tissue is rich in blood and lymphatic supply, so lung cancer cells can easily invade the adjacent blood vessels and lymphatic vessels and reach faraway places

Table 2. Univariate and multivariate analysis of risk factors for brain metastasis in NSCLC

Exposure	No metastasis (n=109)	Brain metastasis (n=63)	Univariate Analysis *P*-value	Multivariate Analysis *P*-value
Sex n (%)				
Male	81 (74.31%)	35 (55.56%)	Reference	
Female	28 (25.69%)	28 (44.44%)	0.0123*	0.0699
Age n (%), years				
<60	18 (16.51%)	27 (42.86%)	Reference	
≥60	91 (83.49%)	36 (57.14%)	0.0002***	0.0054**
Type n (%)				
ADC	64 (58.72%)	57 (90.48%)	Reference	
SCC	45 (41.28%)	6 (9.52%)	<0.0001***	0.0004***
T Stage n (%)				
Tis-T1	21 (19.27%)	15 (23.81%)	Reference	
T2-T4	88 (80.73%)	48 (76.19%)	0.4811	
N Stage n (%)				
N0	38 (34.86%)	13 (20.63%)	Reference	
N1-N3	71 (65.14%)	50 (79.37%)	0.0514	
Smoking n (%)				
YES	13 (11.93%)	7 (11.11%)	Reference	
NO	96 (88.07%)	56 (88.89%)	0.8723	
NLR (mean ± SD)	3.46±2.61	5.68±4.25	0.0003***	0.0083**
PLR (mean ± SD)	176.54±108.56	212.51±97.50	0.0397*	0.0977
LMR (mean ± SD)	3.41±1.92	2.59±1.20	0.0037**	0.0179*

Note: ADC: adenocarcinoma; SCC: squamous cell carcinoma; NLR: neutrophils/lymphocytes; PLR: platelets/lymphocytes; LMR: lymphocytes/monocytes; *P<0.05, **P<0.01, ***P<0.001.

Table 3. Relationship between LMR levels and brain metastasis in NSCLC

Exposure	Model 1, OR (95% CI, *P*)	Model 2, OR (95% CI, *P*)	Model 3, OR (95% CI, *P*)
LMR	0.72 (0.57-0.90) 0.0037**	0.64 (0.50-0.82) 0.0005***	0.62 (0.47-0.81) 0.0005***
LMR tertiles			
Low (0.76-2.02)	Reference	Reference	Reference
Middle (2.03-3.53)	0.93 (0.44-1.95) 0.8500	0.98 (0.44-2.20) 0.9689	0.89 (0.36, 2.17) 0.7961
High (3.56-10.12)	0.41 (0.18-0.90) 0.0272*	0.29 (0.12-0.70) 0.0061**	0.26 (0.10, 0.68) 0.0062**
P for trend	0.65 (0.44-0.96) 0.0291*	0.56 (0.36-0.85) 0.0069**	0.52 (0.32, 0.83) 0.0061**

Note: Model 1: no covariates were adjusted; Model 2: AGE and SEX were adjusted; Model 3: age, sex, type, T and N stage and smoking. *P<0.05, **P<0.01, ***P<0.001.

through the body circulation to form metastasis. Since the blood supply to the brain is enormous, accounting for about 1/6~1/4 of all blood circulation, the brain has a high chance to get cancerous emboli. The process of tumor cell metastasis is complex and involves events related to the occurrence of epithelial mesenchymal transformation, survival of tumor cells in the vasculature, interaction with stromal cells, tumor-associated vascular formation, and the impact of the tumor microenvironment [17]. The development of tumor-specific metastasis is well-explained by the "seed-soil" theory [18]. Overexpression of vascular endothelial growth factor (VEGF) in tumor cells can stimulate angiogenesis, thus promoting the settlement and growth of cancer cells. Therefore, when the expression of VEGF in lung adenocarcinoma cells is inhibited, the incidence of brain metastasis is significantly reduced [19].

Inflammatory cells are key players in the tumor microenvironment and are closely related to

Table 4. Subgroup analysis of the correlation between LMR levels and NSCLC brain metastasis

Exposure	Model 1, OR (95% CI, P)	Model 2, OR (95% CI, P)	Model 3, OR (95% CI, P)
Stratified by sex			
SEX = Male	0.86 (0.64, 1.15) 0.3154	0.82 (0.61, 1.11) 0.2033	0.85 (0.61, 1.18) 0.3184
SEX = Female	0.43 (0.27, 0.70) 0.0006***	0.40 (0.23, 0.69) 0.0011**	0.37 (0.20, 0.68) 0.0013**
Stratified by Age			
AGE <60	0.66 (0.45, 0.97) 0.0340*	0.63 (0.41, 0.96) 0.0330*	0.36 (0.16, 0.79) 0.0107*
AGE ≥60	0.70 (0.52, 0.95) 0.0223*	0.66 (0.48, 0.90) 0.0093**	0.67 (0.48, 0.95) 0.0250*
Stratified by Type			
ADC	0.64 (0.49, 0.83) 0.0007***	0.57 (0.43, 0.77) 0.0002***	0.59 (0.44, 0.80) 0.0006***
SCC	0.77 (0.37, 1.59) 0.4827	0.72 (0.33, 1.58) 0.4177	0.73 (0.33, 1.63) 0.4420
Stratified by T stage			
T = Tis-T1	0.81 (0.54, 1.22) 0.3151	0.72 (0.43, 1.20) 0.2070	0.58 (0.28, 1.18) 0.1328
T = T2-T4	0.68 (0.52, 0.88) 0.0044**	0.60 (0.44, 0.81) 0.0009***	0.59 (0.43, 0.82) 0.0014**
Stratified by N stage			
N = N0	0.74 (0.48, 1.12) 0.1521	0.58 (0.32, 1.04) 0.0671	0.57 (0.32, 1.04) 0.0685
N = N1-N3	0.73 (0.56, 0.96) 0.0228*	0.66 (0.49, 0.89) 0.0061**	0.62 (0.45, 0.86) 0.0042**

Note: Model 1: no covariates were adjusted; Model 2: age and sex were adjusted; Model 3: age, sex, type, T and N stage and smoking were adjusted. In the subgroup analysis stratified by age, sex, type, T and N stage and the model is not adjusted for the stratification variable itself. *P<0.05, **P<0.01, ***P<0.001.

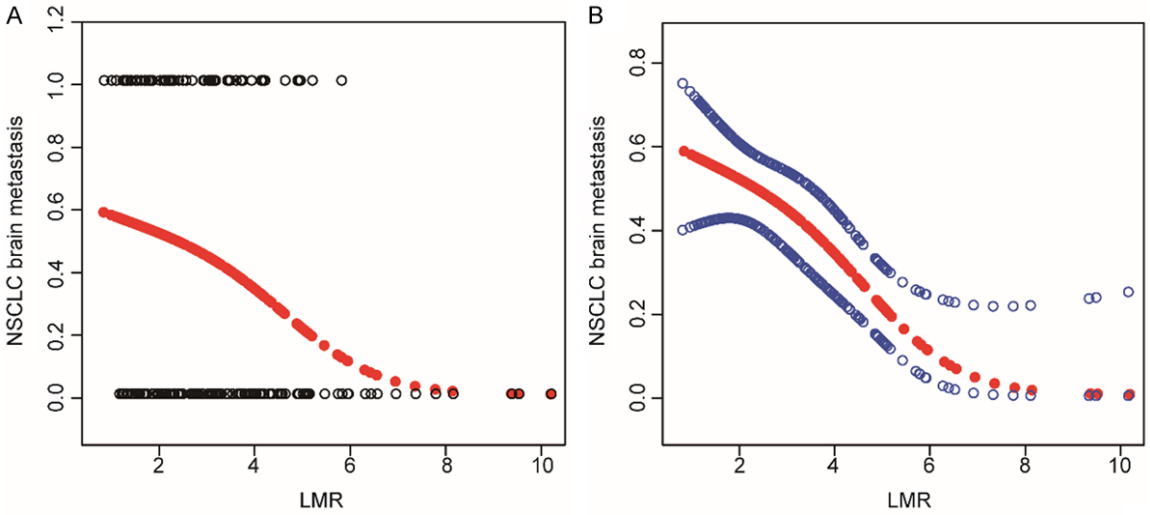

Figure 2. Relationship between LMR levels and brain metastasis in NSCLC. A. Each black dot represents a sample. The vertical coordinate of 0.0 represents that NSCLC has no metastasis, 1.0 represents NSCLC brain metastasis, and the solid line represents the distribution of LMR corresponding to each sample. B. Solid lines represent smoothed curve fits between variables, and the blue bars represent fitted 95% confidence intervals. Adjusted for age, sex, type, T and N stage and smoking.

tumor development [20]. Monocytes suppress the host immune response to tumors. Programmed cell death 1 ligand 1 (PD-L1) expression is associated with poor prognosis in various solid tumors, including renal cell carcinoma, pancreatic cancer, and hepatocellular carcinoma [21-23]. This is because PD-L1 can deliver co-inhibitory signals to T cells after binding to programmed cell death protein 1 (PD-1), blocking the recognition of tumor antigens by the immune system, making T cell function impaired and unable to effectively act as killing tumor cells. In contrast, PD-L1 can not only be expressed in human peripheral blood mononuclear cells activated by interferon-γ [24], but also increases its expression in peripheral

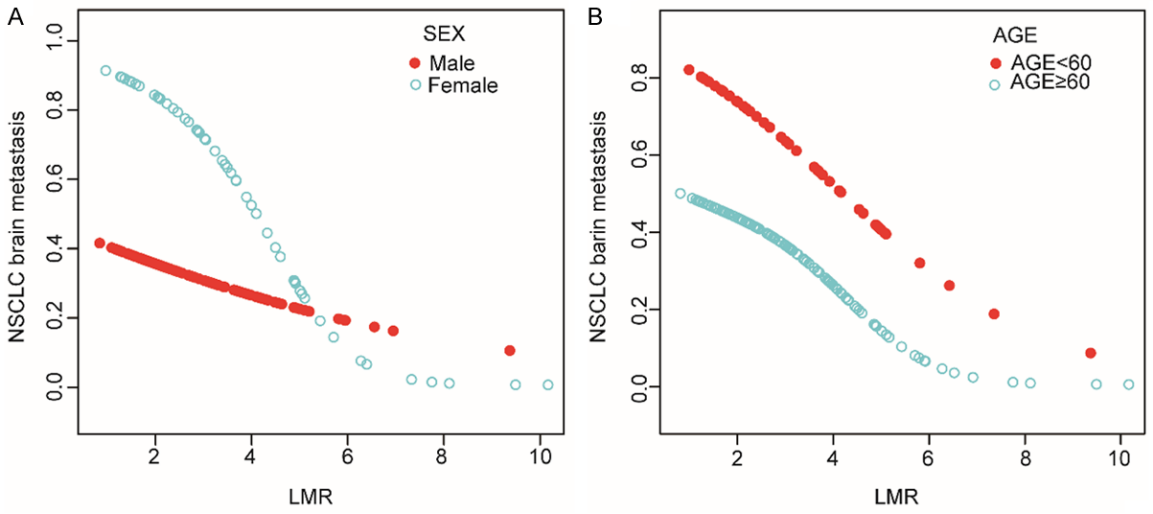

Figure 3. Relationship between LMR and brain metastasis of NSCLC, stratified by demographic factors. A. Stratified by sex, adjustment for age, type, T and N and Smoking. B. Stratified by age, adjustment for sex, type, T and N and Smoking.

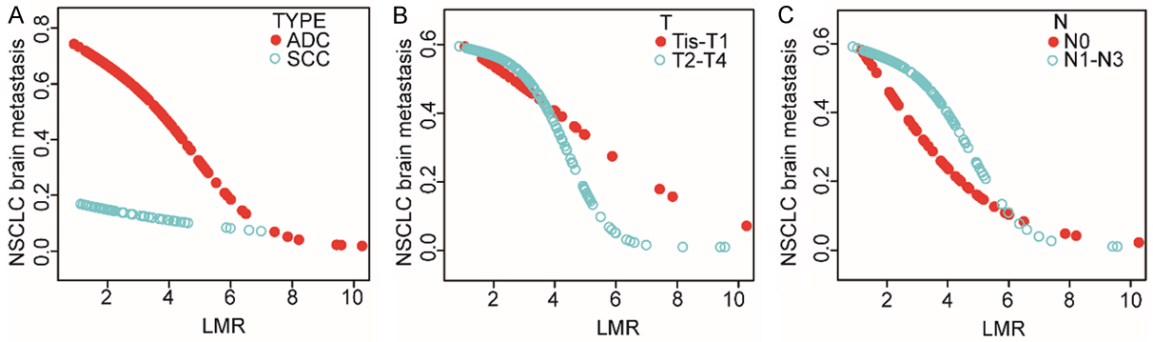

Figure 4. The relationship between LMR and brain metastasis of NSCLC, stratified by clinical characteristics. A. Stratified by TYPE, adjustment for age, sex, T and N and smoking. B. Stratified by T stage, adjustment for age, sex, type, N and smoking. C. Stratified by N stage, adjustment for age, sex, type, T and smoking.

blood mononuclear cells of patients with gastric cancer [25]. Monocytes can also promote the progression of cancer cell metastasis by enhancing tumor cell extravasation and angiogenesis. Regan et al. [26] showed that in a metastatic mouse model, losartan, when used to inhibit the inflammatory response, could reduce the inflammatory monocyte recruitment, as well as the metastasis-related macrophages and tumor angiogenesis, thereby significantly slowing the progression of metastasis. These findings suggest that monocytes are closely linked to an immunosuppressed state in tumor patients, and that elevated levels of monocytes play a pro-tumor role.

While lymphocyte counts may serve as a surrogate marker of host immunity, lymphocytopenia is usually accompanied by an increase in leukocytes, which may lead tumor cells to evade immune surveillance [27]. When lymphocyte counts are relatively reduced and monocyte counts are relatively increased, an imbalance in LMR is strongly associated with poor prognosis in tumor patients. In a study by Li et al. [28], low LMR levels in lung cancer patients were significantly associated with poorer OS (HR, 1.651; 95% CI, 1.306-2.086; P<0.001) and PFS (HR, 1.431; 95% CI, 1.294-1.582; P<0.001). This study revealed that LMR levels were negatively correlated with brain metastases in patients with NSCLC (OR, 0.62; 95% CI, 0.47-0.81; P=0.0005). This may be caused by selective migration of monocytes into the contact between the brain endothelium and the cells, inducing gap formation and then cross-

ing the endothelial cells next to the cells. It is associated with the local disappearance of occludin and the involvement of matrix metalloproteinases (MMP) [29]. After stratified analysis by type, this negative correlation was significant in ADC patients, but SCC patients did not show a significant correlation. Also, one study [30] found that an increase in the percentage of micropapillary subtypes was significantly and positively correlated with an enhancement in the frequency of patients with brain metastases after lung adenocarcinoma resection. This may be related to the high expression of recombinant human C-X-C motif chemokine ligand 14 (CXCL14) in the micropapillary subtype, which can promote proliferation and migration by binding to glycoproteins harboring heparan sulfate proteoglycans and sialic acids [31].

After stratification by sex, this negative association was only present in female patients, which may be related to the role played by estrogen. 17β-estradiol rapidly activates nitric oxide synthase (eNOS), which induces vasodilation to increase tumor blood flow for brain metastasis by promoting nitric oxide (NO) release from endothelial cells through the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway [32]. T refers to the condition of the primary tumor site, N refers to the regional lymph node involvement. The larger the T and N values the more advanced the disease is, the more severe it is, and the more difficult it is to be deal with. In this study, the results of stratified analysis of T and N stages showed that there was a significant negative correlation between LMR and BM with T2-T4 stages, but no difference in patients with Tis-T1 stage, and a negative association in patients with N1-N3 stage, and no significant association in patients with N0 stage.

Compared to the previous research, this study had the advantage of taking into account and adjusting for the effects of confounding factors (age, sex, type, T and N stage, and smoking) to better understand the link between LMR and BM. We also performed a subgroup analysis to examine the correlation between LMR and BM across different populations, and we fitted a smooth curve with the results.

However, our study remains limited: 1. As a retrospective study, there may be some selection bias in this study, despite our efforts to control for potential confounders. 2. Forward-looking data and experiments should be conducted to verify these findings in the future. 3. This study was a single-center study, and there exists the problem of a single study population, so in the future multi-center data will be needed.

Conclusion

In this study, the increase in LMR was negatively correlated with BM, and the relationship varied by sex, type, and T and N stage, which provides a reference for exploring the causal relationship between LMR and BM.

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Disclosure of conflict of interest

None.

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