High neutrophil, low lymphocyte and hemoglobin unfavorably impact survival in non-small cell lung cancer patients with brain metastases

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Research

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Abstract

Background

Brain metastases (BM) from NSCLC has emerged as an increasingly corresponding clinical problem. Precise prognostic evaluation is the basis for personalized medicine. This study sought to investigate prognostic values of clinical and hematological indicators for NSCLC patients with BM in the real world, which could further help guide survivorship care in the actual clinical setting and clinical trials.

Materials and Methods

We retrospectively reviewed the clinical and hematological indicators of NSCLC patients with BM treated with whole-brain radiotherapy. Receiver operating characteristic curve was performed to evaluate the optimal cut-off point. Kaplan–Meier survival analysis and Cox regression analyses were used to evaluate survival.

Results

105 patients were included and median survival was 21 months (range: 1–64 months). Univariate analyses demonstrated that favorable survival was associated with resection history of NSCLC (P = 0.015), absent of intracranial symptom (P = 0.044), lymphocyte ≥ $1.54*10^9$/L(P < 0.001), neutrophil < $4.64*10^9$/L (P = 0.016), hemoglobin ≥ 117.5 g/L (P < 0.001), BSBM scores of 2–3 (P = 0.033) and Lung-molGPA scores of 2.5-4 (P < 0.001). Cox regression analysis showed that lymphocyte (HR 3.390, 95% CI 1.869–6.151, P < 0.001), neutrophil (HR 0.517, 95% CI 0.286–0.934, P = 0.029), hemoglobin (HR 3.215, 95% CI 1.748–5.911, P < 0.001), resection history of NSCLC(HR 2.813, 95% CI 1.375–5.754, P = 0.005), intracranial symptom(HR 0.251, 95% CI 0.113–0.561, P = 0.001), and Lung-molGPA(HR 2.317, 95% CI 1.186–4.527, P = 0.014) were independent prognostic factors for NSCLC patients with BM.

Conclusions

High neutrophil, low lymphocyte and hemoglobin, absent of resection history of NSCLC, present of intracranial symptom, and Lung-molGPA scores of 0–2 may provide valuable information for indicating poor prognosis in NSCLC patients with BM .

Background

Lung cancer has a high morbidity and cancer-related mortality, and Non-small cell lung cancer (NSCLC) is the most common pathological subtype(1). Accompanying dramatic improvements in imaging technology and systemic disease control rate, NSCLC patients have a particularly high propensity to

develop brain metastases (BM), about 40%(2). Potentially curative treatment strategies for BM are limited and mainly base on local approaches including surgical resection, whole-brain radiotherapy (WBRT) and stereotactic radiosurgery-stereotactic radiotherapy (SRS-SRT). Previous studies have demonstrated that the median overall survival (mOS) after the diagnosis of BM for patients with untreated and treated NSCLC was about 4–11 weeks and 4–15 months, respectively[3, 4]. With the advent and wide application of targeted agents and immune checkpoint inhibitors, long-term survival has become increasingly common in NSCLC patients with BM(5). What's more, the quality of life after treatment for BM (QUARTZ) trial has shown that WBRT provided limited benefit compared with best supportive care in poor-prognosis NSCLC patients with asymptomatic BM[6]. Due to the risks of neurocognitive impairment, it is remains controversial whether SRS-SRT could replace the application of WBRT[7]. Furthermore, several studies have suggested that optimised WBRT could lead to more individual strategies, when it was given to appropriate patients at the right time[8, 9].

Thus, only by identifying prognostic indicators, separating subgroups of patients and then choosing personalized medicine can the therapeutic effect be maximized and the excessive medicine be avoided. Several standard prognostic scores have been widely adopted to provide valuable information for clinical decision making and trial eligibility, such as the Radiation Therapy Oncology Group—recursive partitioning analysis (RTOG-RPA), proposed basic score for brain metastases(BSBM) and Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA) [10–13]. However, such prognostic scores are of relative efficacy, and it is still controversial which prognostic score is the most appropriate to use (14, 15). In addition, standard clinical blood indicators derived from routinely clinical practice have been demonstrated to correlate with patient outcome in patients with BM(16, 17). Therefore, more advanced prognostic scores are needed to facilitate clinical decision making, as combining hematological indicators.

The purpose of the present study was to investigate the prognostic values of clinical and hematological indicators routinely evaluated at the clinical course of BM. We hypothesized that the indicators of chronic inflammation and nutrition have significant prognostic relevance in NSCLC patients with BM. Therefore, we evaluated the hematological indicators in 105 NSCLC patients with BM. The relationship between lymphocyte, neutrophil, hemoglobin, clinicopathologic features, and prognosis were assessed to comfirm whether lymphocyte, neutrophil and hemoglobin are predictor for survival in NSCLC patients with BM. The comfirmation of prognostic factors could further facilitate improvement of prognostic scores or establishment of new scores, and better inform of BM patient outcomes and helping guide survivorship care in the actual clinical setting and clinical trials.

Materials And Methods

Patient selection

The protocol of this research was approved by Liaoning Cancer Hospital Institutional Review Board. This study was a retrospective study, so the inform consent could be granted a waiver. We retrospectively reviewed hospital records from patients received treatment for NSCLC or BM at radiotherapy department of Liaoning Cancer Hospital during 2018. The exclusion criteria were as follows: did not complete WBRT for BM; history of other malignant tumors; incomplete chart information; had a past radiation therapy history of BM at other institution. Ultimately, we identified 105 consecutive patients with biopsy-proven primary NSCLC and biopsy-proven and/or radiologically confirmed BM treated with WBRT using either three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiation therapy (IMRT) at our institution. Last follow-up for vital status was conducted during December 30–31, 2019.

Data collection

The baseline clinical information included: age, sex, histologic subtype, smoking history, drinking history, family history, previous treatment, intracranial symptom, Karnofsky Performance Status(KPS), extracranial metastases (ECM), primary tumor status, resection of BM, radiotherapy plan, RTOG-RPA, BSBM, and Lung-molGPA score.

The following hematological indicators were recorded between 2 weeks before the WBRT and the first day of WBRT under conditions without steroid therapy: absolute lymphocyte count, absolute neutrophil count, hemoglobin, mean corpuscular volume (MCV), and platele.

Cranial magnetic resonance imaging (MRI) or cranial computed tomography (CT) was performed for evaluation of intracranial disease in the light of institutional practice at the time of initial diagnosis, routine review, systemic disease progression or the development of new neurological symptom or signs. The following information were evaluated by cranial MRI/CT: number of lesions, size of BM in diameter. Status of NSCLC at BM diagnosis was evaluated by chest CT or PET-CT.

Statistical Analysis

The hematological indicators were initially recorded as continuous variables. Then, absolute lymphocyte count, absolute neutrophil count, hemoglobin, MCV, and platele were transformed into categorical variables according to the best cutoff point determined using the receiver operating characteristic (ROC) curve analysis, which calculates maximum joint sensitivity and specificity.

Brain metastatic free survival (BMFS) was defined as time from diagnosis of biopsy-proven primary NSCLC to biopsy-proven and/or radiologically confirmed BM. OS was performed from the initial diagnosis of BM to the emergence of the death or last follow-up. Synchronous diagnosis, defined as diagnosis of primary NSCLC and BM within 30 days.

Comparisons between groups were done utilising contingency tables with Pearson’s chi-squared test and two-sided Fisher’s exact tests for categorical parameters. Relationship between hematological indicators were done utilising Pearson’s correlation coefficient analysis.The Kaplan–Meier method and log-rank test were performed for survival estimations. All of the statistically significant variables identified in the

univariate analyses were included in the multivariate survival analysis using the Cox proportional hazard model. All analyses were performed using SPSS Version 24.0 and GraphPad Prism Version 6.0. A two-sided p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

Table 1 lists the clinicalpathologic characteristics of all patients. 105 patients (male 57/105 (54.3%); female 48/105 (45.7%)) with newly diagnosed NSCLC BM were available for further analysis. Median age at diagnosis of BM was 59 years (range 35–79 years). All patients was treated with WBRT, while 10/105 (9.5%) patients were treated with resection of BM as initial therapy for BM. Of these, there are more patients diagnosed with singular BM (80% vs. 20%) and BM ≥ 3 cm in diameter (80% vs. 20%) compared to patients performed radiotherapy as initial therapy for BM ($\chi2 = 8.132$; $P = 0.01$; $\chi2 = 9.989$; $P = 0.002$). In term of the size of BM in diameter, less patients were suffered from intracranial symptom among patients diagnosed with BM < 3 cm in diameter (40/59; 67.8%) compared to patients diagnosed with BM > 2 cm in diameter (25/27; 92.6%; $\chi2 = 6.171$; $P = 0.013$).

Relationship between lymphocyte, neutrophil, hemoglobin and clinicopathologic features in patients with BM and NSCLC

We assessed various hematological indicators in our patient cohort. The statistically determined appropriate cut-off values based on the results of ROC curve analysis were as follows: $1.54*10^9$/L for lymphocyte, $4.64*10^9$/L for neutrophil, 117.5 g/L for hemoglobin, 94.85fL for MCV, and $289*10^9$/L for platele (Fig. 1).

Lymphocyte was reduced (lower than 1.54) in 50.5% (53/105) of patients (Table 1). Median lymphocyte was 1.55 (range, 0.27–3.45) in pretreated patients. Patients with low lymphocyte were more likely to be treated with previous surgery, radiotherapy and/or targeted therapy for NSCLC before WBRT ($\chi2 = 5.192$; $P = 0.023$; $\chi2 = 7.151$; $P = 0.007$; $\chi2 = 4.110$; $P = 0.043$). Of note, lymphopenic status was not significantly impacted by previous chemotherapy ($\chi2 = 1.155$; $P = 0.283$). The association between lymphocyte and the drinking status was evident ($\chi2 = 5.158$; $P = 0.023$). Moreover, patients with ECM demonstrated a slightly lower level of lymphocyte contrasted with those without ECM ($\chi2 = 7.389$; $P = 0.007$).

Neutrophil was increased (higher than 4.64) in 49.5% (52/105) of patients (Table 2). Median neutrophil was 5.68 (range, 0.20–51.6) in pretreated patients. Gene status was associated with neutrophil, patients with mutation of *epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK)* had a significantly lower neutrophil than wild-type patients ($\chi2 = 6.011$; $P = 0.014$). Furthermore, a significant association between NLR and prognostic scores for BM was observed. In term of Lung-molGPA ($\chi^2 = 5.658$; $P = 0.017$), patients with low neutrophil may have a better prognosis than patients with high NLR.

Hemoglobin was reduced (< 117.5 g/L) in 21% (22/105) of patients (Table 3). Median hemoglobin was 134.18 (range, 73–323) in pretreated patients. The association between hemoglobin and previous chemotherapy was evident (χ^2 = 8.573; P = 0.003). In addition,the prognostic scores were correlated with hemoglobin as well, including BSBM (χ^2 = 5.608; P = 0.018) and Lung-molGPA (χ^2 = 4.454; P = 0.035).

Relationship between hematological indicators

We observed a linear correlation between platele and lymphocyte or neutrophil in patients with BM and NSCLC (R^2 = 0.067, P = 0.008; R^2 = 0.124, P < 0.001). We found a similar correlation between hemoglobin and lymphocyte or MCV (R^2= 0.060, P = 0.012; R^2 = 0.073, P = 0.005), as shown in Fig. 2. The correlation between other hematological indicators was not significant.

Brain metastases free survival

Among 105 NSCLC patients, 44 (41.9%) did not undergo any tumor related treatment before the diagnosis of BM due to synchronous diagnosis. Median BMFS of the 61/95 (58.1%) patients with asynchronous diagnosis was 15 months (range 1–56). Patients with asynchronous diagnosis had significantly higher level of hemoglobin than patients diagnosed asynchronously (χ^2 = 4.204; P = 0.004; Fig. 3A). 17/61(27.9%) patients with low hemoglobin showed a median BMFS of 17 months (range 2–213) while 44/61 (72.1%) patients with high hemoglobin showed a median BMFS of 14 months (range 2–52; p = 0.047; log-rank test; Fig. 3B). This phenomenon may be explained by the consumption of the tumor and the treatment-related blood toxicity. Moreover, according to RTOG-RPA(P < 0.001; Fisher Exact test) and BSBM (χ^2 = 9.238; P = 0.002), patients with asynchronous diagnosis may have a better prognosis than patients with synchronous diagnosis, which requires further survival analysis to comfirm.

Overall survival

All 105 patients were strictly followed up, and the median follow-up time was 22 months (range: 1–64 months). In the entire cohort, mOS was 21 months (range: 1–64 months) and the 1- year, 2-year and 5-year survival rates were 69.3%, 47.2% and 16.3%, respectively. Median survival from BM diagnosis was no statistically significant difference in patients with asynchronous diagnosis (22 months) compared to patients with synchronous diagnosis (21 months; p = 0.885; Table 4; Fig. 4A).

There was a associaton with survival was found when patients were divided into lymphocyte low and high groups by the cut-off value of 1.54. Patients with elevated lymphocyte had significantly longer OS, 37 months vs. 14months (P < 0.001; Fig. 4B). Moreover, when patients were divided into low neutrophil and high neutrophil groups by the cut-off value of 4.64, patients with low neutrophil showed longer OS compared with those with high neutrophil (mOS, 28months vs. 15months, P = 0.016; Fig. 4C). Similarly, high hemoglobin was also significantly correlated with better prognosis(mOS, 27months vs. 11months, P < 0.001; Fig. 4D). While, other laboratory parameters—MCV and platele did not significantly correlated with patient survival (Table 4).

Data needed for RTOG-RPA, BSBM and Lung-molGPA calculation including age, KPS, and number of BM were significantly associated with survival. However, non-significant differences were observed between ECM, gene status, primary tumor status and OS (Supplementary Table S1).

On univariate analysis, patients with resection of NSCLC had longer OS than those without resection of NSCLC (mOS, 42 months vs. 18months, P = 0.015; Supplementary Figure S1A; Table 4). Besides, patients without intracranial symptom had a comparable survival times than symptomatic patients (median, 28 months vs. 16months, P = 0.044; Supplementary Figure S1B). Moreover, univariate analysis demonstrated that the Lung-molGPA was significantly associated with survival (P < 0.001; Supplementary Figure S1C).

After multivariate analyses, the remaining independent prognostic factors for OS were lymphocyte (HR 3.390, 95% CI 1.869–6.151, P < 0.001), neutrophil (HR 0.517, 95% CI 0.286–0.934, P = 0.029), hemoglobin(HR 3.215, 95% CI 1.748–5.911, P < 0.001), resection history of NSCLC(HR 2.813, 95% CI 1.375–5.754, P = 0.005), intracranial symptom (HR 0.251, 95% CI 0.113–0.561, P = 0.001), and Lung-molGPA(HR 2.317, 95% CI 1.186–4.527, P = 0.014; Table 5).

Discussion

The selective barrier function of blood-brain barrier (BBB) has ability to prevent inflammatory cells, immunoglobulin and cytotoxic substances in the blood from entering the brain, resulting in immunosuppression of tumor microenvironment (TME) in early brain tumors. However, BM could break the strict "immune-tolerant" environment by disrupting the BBB, and then allowing inflammatory cells to exert anti-tumor effects. Inflammatory cells, including neutrophils, lymphocytes and so on, have been identified and validated the association with prognosis for BM. Recently, several studies have reported that the high NLR before SRS-SRT, operation or immunotherapy inversely predicts OS in patients with BM, which was detected in circumstances of the high neutrophil and the low lymphocyte(18–20). Similar results have been observed in our study, in which lymphocyte and neutrophil collected before WBRT, were independent prognostic factors for BM from NSCLC. While the biologic basis of the phenomenon is not thoroughly comprehend. It may interrelate with elevated neutrophil-dependent inflammation and decreased lymphocyte mediated anti-tumor response. Inflammation, serving as a hallmark of cancer, has been reported to promote tumorigenesis and progression of cancer(21). Circulating neutrophils, mediated systemic inflammation, has been shown to promote DNA damage response, angiogenesis and tumor invasion by secreting tumor necrosis factors, vascular endothelial growth factors and some cytokines(22). Neutrophilia as an inflammatory response inhibits the cytolytic activity of lymphocytes, activated T cell and natural killer cells, which could promote cancer progression and affect clinical outcome[23]. Lymphocyte plays a crucial role in host anti-tumor immunity response, and could eradicate tumor cells by cytokine secretion and cytotoxic cell death. Worth to mention, the post-treatment NLR was associated with poor prognosis as well(24, 25). While the biologic basis of the relationship between post-treatment NLR and success of treatment is quite complex. It is true that lymphopenia is correlated with a poor prognosis, while a preclinical study found that activated T cells could facilitate BM through inducing an elevated expression of Guanylate-Binding Protein 1 (GBP1) by the cancer cells(26). Moreover, neutropenia increase the risk of infections. In term of our median values of neutrophil and lymphocyte

within the normal range, we consider that the prognostic values of neutrophil and lymphocyte should be within a certain range, and the the biologic basis requires further research.

In addition to inflammatory cells, hemoglobin is regarded as a both nutritional and inflammation-related indicator, which has a significant prognostic relevance of BM and NSCLC(27, 28). Our results are consistent with the prognostic effect of hemoglobin for survival in NSCLC BM. In a systematic review and meta-analysis, even if the continuous variable hemoglobin level was in the normal range, a decreased hemoglobin level was significantly related to worse survival for lung cancer patients(29). The mechanism underlying the prognostic value of hemoglobin can be explained from several perspectives. Hemoglobin reduction causes hypoxia of tumor, which then promotes tumor growth and resistant to chemoradiotherapy by modulating the gene expression and cell-cycle position, subsequently leads to the cancer progression and poor survival(30). The potential cause of these differences remains unclear, the determination and the best cut-off values of neutrophil, lymphocyte and hemoglobin should enroll in further randomized controlled trials to confirm their relevance in the incidence of BM and prognosis, which may help build a easy-to-calculate laboratory score for BM from NSCLC. Additionally, previous reports indicated that the serum markers such as peripheral blood cell counts can be used as a predictor for response to immunotherapy(31). Therefore, the in-depth study about prognostic values of neutrophil, lymphocyte and hemoglobin will help us to further understand the immune mechanism of NSCLC BM, and ultimately help us to make better clinical decisions in circumstances such as facing moderate-to-severe irAEs and distinguishing tumor flares (or pseudoprogressions) from true progressions.

Among patients with asynchronous diagnosis, patients originally treated with surgical resection for NSCLC experienced prolonged BMFS and OS. Our findings are well in line with other studys comfirming the clinical significance of surgical resection for NSCLC(32). While randomized controlled data has not suggested that surgical resection provides a significant survival benefit for all stage NSCLC patients, present nationwide guidelines nevertheless underline the significance of offering surgical resection for resectable patients given potential chance for cure. However, the choice of surgical approach and surgical intervention is still debatable(33, 34). We could await direction from further studies.

In our study, we have confirmed that patients with neurological symptom presented with poor prognosis. Besides, the Neurologic Assessment in Neuro-Oncology (NANO) scale objectifying the symptomatic burden, has been a standard part in the response assessment of primary brain tumors(35, 36). While symptom evaluation has not been included in the prognostic assessment in newly diagnosed BM so far. Moreover, we have confirmed the utility of the Lung-molGPA score.

Although we were able to investigate potential prognostic indicators for NSCLC patients with BM in a real-life cohort, some limitations have to be considered in the explanation of our results, including its retrospective study, relatively small sample size and heterogeneous patient characteristics. Because our data was collected in the radiotherapy department, this study only included patients receiving WBRT for BM to avoid selection bias. Both before and after the diagnosis of BM, the treatment strategy varied widely thus precluding the capability to assess the impact of these agents on the laboratory indicators

and study patients. Moreover, the predictive versus prognostic value of clinical factors and hematological indicators evaluated cannot be determined owing to lack of a control arm. For these reasons, our results ought to be considered hypothesis generating.

Conclusion

In summary, our data show that neutrophil, lymphocyte and hemoglobin before WBRT were independent prognostic factors for NSCLC patients with BM. Furthermore, our data stressed the importance to evaluate symptomatic and asymptomatic patients separately because of the differing survival prognosis. Further validation in larger cohorts and prospective studies is required, which may help clinical decision-making and patient risk stratification for NSCLC BM.

Abbreviations

NSCLC, non-small cell lung cancer; BM, brain metastases; WBRT, whole-brain radiotherapy; SRS-SRT, stereotactic radiosurgery-stereotactic radiotherapy; mOS, median overall survival; QUARTZ, quality of life after treatment for BM; RTOG-RPA, Radiation Therapy Oncology Group
recursive partitioning analysis; BSBM, basic score for brain metastases; Lung-molGPA, Graded Prognostic Assessment for Lung Cancer Using Molecular Markers; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; KPS, Karnofsky Performance Scale; ECM, extracranial metastases; MCV, mean corpuscular volume; MRI, magnetic resonance imaging; CT, computed tomography; ROC, receiver operating characteristic; BMFS, Brain metastatic free survival; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; HRs, hazard ratios; CIs, confidence intervals; BBB, blood-brain barrier; TME, tumor microenvironment; GBP1, Guanylate-Binding Protein 1; NANO, Neurologic Assessment in Neuro-Oncology;

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no potential conflicts of interest.

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Authors' contributions

Wang Li: writing, review and revision of the manuscript. Yanli Qu: study supervision. Fengyun Wen: interpretation of data. Xiaoyi He: acquisition of data. Hongying Jia: material support. Hangyu Liu: analysis of data. Hong Yu: conception, design and revision of the manuscript.

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Tables

Table 1. The relationship between lymphocyte and clinicopathologic features of non-small cell lung cancer patients with brain metastases

Variable	Patients (n = 105)	Lymphocyte <1.54*10^9/L (n=53,50.5%)	Lymphocyte ≥1.54*10^9/L (n=52,49.5 %)	c2	p value
Age (years)	59 (35-79)			3.626	0.057
<65	76(72.4)	34(64.2)	42(80.8)		
≥65	29(27.6)	19(35.8)	10(19.2)		
Sex				0.232	0.630
Female	48(45.7)	23(43.7)	25(48.1)		
Male	57(54.3)	30(56.6)	27(51.9)		
Pathology				0.038	0.845
AC [a)]	84(80.0)	42(79.2)	42(80.8)		
NAC [b)]	21(20.0)	11(20.8)	10(19.2)		
Resection history of NSCLC [c)]				5.192	**0.023**
No	64(61.0)	38(71.7)	26(50.0)		
Yes	41(39.0)	15(28.3)	26(50.0)		
Smoking history				0.264	0.607
No	62(59.0)	30(56.6)	32(61.5)		
Yes	43(41.0)	23(43.4)	20(38.5)		
Drinking history				5.518	**0.023**
No	81(77.1)	36(67.9)	45(86.5)		
Yes	24(22.9)	17(32.1)	7(13.5)		
Family history				0.102	0.750
No	90(85.7)	46(86.8)	44(84.6)		
Yes	15(14.3)	7(13.2)	8(15.4)		
Gene status*				2.787	0.095
Negative/unknown	56(53.3)	24(45.3)	32(61.5)		
Positive	49(46.7)	29(54.7)	20(38.5)		
Previous chemotherapy				1.155	0.283
No	53(50.5)	24(45.3)	29(55.8)		
Yes	52(49.5)	29(54.7)	23(44.2)		
Previous radiotherapy				7.151	**0.007**
No	89(84.8)	40(75.5)	49(94.2)		
Yes	16(15.2)	13(24.5)	3(5.8)		
Previous target therapy				4.110	**0.043**
No	87(82.9)	40(75.5)	47(90.4)		
Yes	18(17.1)	13(24.5)	5(9.6)		

ECM [d]				7.389	**0.007**
Absent	74(70.5)	31(58.5)	43(82.7)		
Present	31(29.5)	22(41.5)	9(17.3)		
Primary tumor status				0.012	0.914
Control	47(44.8)	24(45.3)	23(44.2)		
Uncontrol	58(55.2)	29(54.7)	29(55.8)		
Synchronous diagnosis#				0.229	0.632
Yes	44(41.9)	21(39.6)	23(44.2)		
No	61(58.1)	32(60.4)	29(55.8)		
Intracranial symptoms				0.003	0.958
No	24(22.9)	12(22.6)	12(23.1)		
Yes	81(77.1)	41(77.4)	40(76.9)		
Number of BM [e]				0.797	0.372
1	36(34.3)	16(302)	20(38.5)		
>1	69(65.7)	37(69.8)	32(61.5)		
Size of BM in diameter(cm)				0.275	0.600
<3	59(68.6)	32(71.1)	27(65.9)		
≥3	27(31.4)	13(28.9)	14(34.1)		
Resection of BM				0.401	0.527
No	95(90.5)	47(88.7)	48(92.3)		
Yes	10(9.5)	6(11.3)	4(7.7)		
RTOG-PRA [f]				0.922	0.337
I	26(24.8)	11(20.8)	15(28.8)		
II	79(75.2)	42(79.2)	37(71.2)		
BSBM [g]				3.469	0.063
0-1	31(29.5)	20(37.7)	11(21.2)		
2-3	74(70.5)	33(62.3)	41(78.8)		
Lung-molGPA [h]				0.970	0.325
I/II	33(31.4)	19(35.8)	14(26.9)		
III/IV	72(68.6)	34(64.2)	38(73.1)		

*Epidermal growth factor receptor(EGFR) and anaplastic lymphoma kinase (ALK);

#Synchronous diagnosis, defined as diagnosis of primary NSCLC and BM within 30 days;

Abbreviations: a) AC, adenocarcinoma; b) NAC, non-adenocarcinoma; c) NSCLC, non-small cell lung cancer; d) ECM, extracranial metastases; e) BM, brain metastases; f) RTOG-RPA, Radiation Therapy Oncology Group—recursive partitioning analysis; g) BSBM, proposed basic score for brain metastases; h) Lung-molGPA, Graded Prognostic Assessment for Lung Cancer Using Molecular Markers.

Table 2. The relationship between neutrophil and clinicopathologic features of non-small cell lung cancer patients with brain metastases

Variable	Patients (n = 105)	Neutrophil <4.64*10^9/L (n=53,50.5%)	Neutrophil ≥4.64*10^9/L (n=52,49.5 %)	c2	p value
Age (years)				2.522	0.112
<65	76(72.4)	42(79.2)	34(65.4)		
≥65	29(27.6)	11(20.8)	18(34.6)		
Sex				0.091	0.762
Female	48(45.7)	25(47.2)	23(44.2)		
Male	57(54.3)	28(52.8)	29(55.8)		
Pathology				0.610	0.435
AC [a)]	84(80.0)	44(83.0)	40(76.9)		
NAC [b)]	21(20.0)	9(17.0)	12(23.1)		
Resection history of NSCLC [c)]				2.966	0.085
No	64(61.0)	28(52.8)	36(69.2)		
Yes	41(39.0)	25(47.2)	16(30.8)		
Smoking history				3.487	0.062
No	62(59.0)	36(67.9)	26(50.0)		
Yes	43(41.0)	17(32.1)	26(50.0)		
Drinking history				0.768	0.381
No	81(77.1)	39(73.6)	42(80.8)		
Yes	24(22.9)	14(26.4)	10(19.2)		
Family history				3.657	0.056
No	90(85.7)	42(79.2)	48(92.3)		
Yes	15(14.3)	11(20.8)	4(7.7)		
Gene status*				6.011	**0.014**
Negative/unknown	56(53.3)	22(41.5)	34(65.4)		
Positive	49(46.7)	31(58.5)	18(34.6)		
Previous chemotherapy				2.146	0.143
No	53(50.5)	23(43.4)	30(57.7)		
Yes	52(49.5)	30(56.6)	22(42.3)		
Previous radiotherapy				1.092	0.296
No	89(84.8)	43(81.1)	46(88.5)		
Yes	16(15.2)	10(18.9)	6(11.5)		
Previous target therapy				0.983	0.321
No	87(82.9)	42(79.2)	45(86.5)		
Yes	18(17.1)	11(20.8)	7(13.5)		

ECM [d]				0.497	0.481
Absent	74(70.5)	39(73.6)	35(67.3)		
Present	31(29.5)	14(26.4)	17(32.7)		
Primary tumor status				1.654	0.198
Control	47(44.8)	27(50.9)	20(38.5)		
Uncontrol	58(55.2)	26(49.1)	32(61.5)		
Synchronous diagnosis#				0.764	0.382
Yes	44(41.9)	20(37.7)	24(46.2)		
No	61(58.1)	33(62.3)	28(53.8)		
Intracranial symptoms				1.799	0.180
No	24(22.9)	15(28.3)	9(17.3)		
Yes	81(77.1)	38(71.7)	43(82.7)		
Number of BM [e]				2.479	0.115
1	36(34.3)	22(41.5)	14(26.9)		
>1	69(65.7)	31(58.5)	38(73.1)		
Size of BM in diameter(cm)				1.711	0.191
<3	59(68.6)	33(75.0)	26(61.9)		
≥3	27(31.4)	11(25.0)	16(38.1)		
Resection of BM				3.854	0.050
No	95(90.5)	45(84.9)	50(96.2)		
Yes	10(9.5)	8(15.1)	2(3.8)		
RTOG-PRA [f]				3.073	0.080
I	26(24.8)	17(32.1)	91(17.3)		
II	79(75.2)	36(67.9)	43(82.7)		
BSBM [g]				1.284	0.257
0-1	31(29.5)	13(24.5)	18(34.6)		
2-3	74(70.5)	40(75.5)	34(65.4)		
Lung-molGPA [h]				5.658	**0.017**
I/II	33(31.4)	11(20.8)	22(42.3)		
III/IV	72(68.6)	42(79.2)	30(57.7)		

*Epidermal growth factor receptor(EGFR) and anaplastic lymphoma kinase (ALK);

#Synchronous diagnosis, defined as diagnosis of primary NSCLC and BM within 30 days;

Abbreviations: a) AC, adenocarcinoma; b) NAC, non-adenocarcinoma; c) NSCLC, non-small cell lung cancer; d) ECM, extracranial metastases; e) BM, brain metastases; f) RTOG-RPA, Radiation Therapy Oncology Group—recursive partitioning analysis; g) BSBM, proposed basic score for brain metastases; h) Lung-molGPA, Graded Prognostic Assessment for Lung Cancer Using Molecular Markers.

Table 3. The relationship between hemoglobin and clinicopathologic features of non-small cell lung cancer patients with brain metastases

Variable	Patients (n = 105)	Hemoglobin <117.5 g/L (n=22,21.0%)	Hemoglobin ≥ 117.5 g/L (n=83,73.0 %)	c2	p value
Age (years)				0.245	0.620
<65	76(72.4)	15(68.2)	61(73.5)		
≥65	29(27.6)	7(31.8)	22(22.9)		
Sex				0.206	0.650
Female	48(45.7)	11(50.0)	37(44.6)		
Male	57(54.3)	11(50.0)	46(55.4)		
Pathology				0.997	0.318
AC [a)]	84(80.0)	16(72.7)	68(81.9)		
NAC [b)]	21(20.0)	6(27.3)	15(18.1)		
Resection history of NSCLC [c)]				0.084	0.772
No	64(61.0)	14(63.6)	50(60.2)		
Yes	41(39.0)	8(36.4)	33(39.8)		
Smoking history				0.000	0.996
No	62(59.0)	13(59.1)	49(59.0)		
Yes	43(41.0)	9(40.9)	34(41.0)		
Drinking history				1.342	0.247
No	81(77.1)	19(86.4)	62(74.7)		
Yes	24(22.9)	3(13.6)	21(25.3)		
Family history				1.267	0.260
No	90(85.7)	21(95.5)	69(83.1)		
Yes	15(14.3)	1(4.5)	14(16.9)		
Gene status*				0.371	0.543
Negative/unknown	56(53.3)	13(59.1)	43(51.8)		
Positive	49(46.7)	9(40.9)	40(48.2)		

Previous chemotherapy				8.573	**0.003**
No	53(50.5)	5(22.7)	48(57.8)		
Yes	52(49.5)	17(77.3)	35(42.2)		
Previous radiotherapy				2.053	0.152
No	89(84.8)	16(72.7)	73(88)		
Yes	16(15.2)	6(27.3)	10(12)		
Previous target therapy				<0.001	1.000
No	87(82.9)	18(81.8)	69(83.1)		
Yes	18(17.1)	4(18.2)	14(16.9)		
ECM [d)]				1.734	1.188
Absent	74(70.5)	13(59.1)	69(73.5)		
Present	31(29.5)	9(40.9)	22(26.5)		
Primary tumor status				0.309	0.578
Control	47(44.8)	11(50)	36(43.4)		
Uncontrol	58(55.2)	11(50)	47(56.6)		
Synchronous diagnosis#				4.204	**0.040**
Yes	44(41.9)	5(22.7)	39(47.0)		
No	61(58.1)	17(77.3)	44(53.0)		
Intracranial symptoms				0.345	0.557
No	24(22.9)	4(18.2)	20(24.1)		
Yes	81(77.1)	18(81.8)	63(75.9)		
Number of BM [e)]				1.650	0.199
1	36(34.3)	5(22.7)	31(37.3)		
>1	69(65.7)	17(77.3)	52(62.7)		
Size of BM in diameter(cm)				1.859	0.173
<3	59(68.6)	4(82.4)	45(65.2)		
≥3	27(31.4)	3(17.6)	24(34.8)		

Resection of BM				0.236	0.627
No	95(90.5)	21(95.5)	74(89.2)		
Yes	10(9.5)	1(4.5)	9(10.8)		
RTOG-PRA [f)]				0.062	0.804
I	26(24.8)	5(22.7)	21(25.3)		
II	79(75.2)	17(77.3)	62(74.7)		
BSBM [g)]				5.608	**0.018**
0-1	31(29.5)	11(50.0)	20(24.1)		
2-3	74(70.5)	11(50.0)	63(75.9)		
Lung-molGPA [h)]				4.454	**0.035**
I/II	33(31.4)	11(50)	22(26.5)		
III/IV	72(68.6)	11(50)	61(73.5)		

*Epidermal growth factor receptor(EGFR) and anaplastic lymphoma kinase (ALK);

#Synchronous diagnosis, defined as diagnosis of primary NSCLC and BM within 30 days;

Abbreviations: a) AC, adenocarcinoma; b) NAC, non-adenocarcinoma; c) NSCLC, non-small cell lung cancer; d) ECM, extracranial metastases; e) BM, brain metastases; f) RTOG-RPA, Radiation Therapy Oncology Group—recursive partitioning analysis; g) BSBM, proposed basic score for brain metastases; h) Lung-molGPA, Graded Prognostic Assessment for Lung Cancer Using Molecular Markers.

Table 4. Univariate survival analyses (log-rank test) in non-small cell lung cancer patients with brain metastases

Variable	Patients (n = 105)	Univariate analysis	
		median OS (months)	P-value
Age (years)			0.185
<65	76(72.4)	25(1-64)	
≥65	29(27.6)	15(4-55)	
Sex			0.345
Female	48(45.7)	27(1-64)	
Male	57(54.3)	20(2-62)	
Pathology			0.246
AC[a)]	84(80.0)	25(1-64)	
NAC [b)]	21(20.0)	15(4-55)	
Resection history of NSCLC [c)]			**0.015**
No	64(61.0)	18(1-64)	
Yes	41(39.0)	42(4-42)	
Smoking history			0.123
No	62(59.0)	28(2-64)	
Yes	43(41.0)	16(1-60)	
Drinking history			0.132
No	81(77.1)	27(1-64)	
Yes	24(22.9)	18(2-60)	
Family history			0.520
No	90(85.7)	21(1-64)	
Yes	15(14.3)	21(5-62)	
Previous chemotherapy			0.613
No	53(50.5)	27(1-62)	
Yes	52(49.5)	20(3-64)	
Previous radiotherapy			0.793

No	89(84.8)	22(2-64)	
Yes	16(15.2)	21(4-64)	
Previous targeted therapy			0.484
No	87(82.9)	22(2-64)	
Yes	18(17.1)	18(1-55)	
Synchronous diagnosis*			0.885
Yes	44(41.9)	21(2-64)	
No	61(58.1)	22(1-62)	
Intracranial symptoms			**0.044**
No	24(22.9)	28(6-62)	
Yes	81(77.1)	16(1-64)	
Size of BM [d] in diameter(cm)			0.256
<3	59(68.6)	21(3-62)	
≥3	27(31.4)	37(2-64)	
Resection of BM			0.188
No	95(90.5)	21(1-62)	
Yes	10(9.5)	42(12-64)	
Lymphocyte (10^9/L)			**<0.001**
<1.54	53(50.5)	14(1-64)	
≥1.54	52(49.5)	37(7-62)	
Neutrophil (10^9/L)			**0.016**
<103.5	53(50.5)	28(2-64)	
≥103.5	52(49.5)	15(1-55)	
Hemoglobin(g/L)			**<0.001**
<117.5	22(21)	11(1-42)	
≥117.5	83(79)	27(2-64)	
MCV(fl) [e]			0.270

<94.85	71(67.6)	27(1-64)	
≥94.85	34(32.4)	16(3-62)	
Platele (10^9/L)			0.114
<289.0	89(84.8)	21(2-64)	
≥289.0	16(15.2)	8(1-49)	
RTOG-PRA [f)]			0.090
I	26(24.8)	37(1-60)	
II	79(75.2)	19(2-64)	
BSBM [g)]			**0.033**
0-1	31(29.5)	14(2-64)	
2-3	74(70.5)	28(1-62)	
Lung-molGPA[h)]			**<0.001**
I/II	33(31.4)	13(2-42)	
III/IV	72(68.6)	35(1-64)	
Radiotherapy technology			0.693
3DCRT [i)]	72(68.6)	21(1-64)	
IMRT [j)]	33(31.4)	22(3-37)	
Radiotherapeutic dose (Gy)			0.170
≤ 30	43(41)	27(1-64)	
> 30	62(59)	18(2-62)	

***** Synchronous diagnosis, defined as diagnosis of primary NSCLC and BM within 30 days;

Abbreviations: a) AC, adenocarcinoma; b) NAC, non-adenocarcinoma; c) NSCLC, non-small cell lung cancer; d) BM, brain metastases; e) MCV, mean corpuscular volume; f) RTOG-RPA, Radiation Therapy Oncology Group—recursive partitioning analysis; g) BSBM, proposed basic score for brain metastases; h) Lung-molGPA, Graded Prognostic Assessment for Lung Cancer Using Molecular Markers; i) 3DCRT, three-dimensional conformal radiotherapy; j) IMRT, intensity-modulated radiation therapy.

Table 5. Multivariate Cox regression analysis for overall survival in non-small cell lung cancer patients with brain metastases

Variable	Multivariate analysis	
	HR (95% CI)	P value
Resection history of NSCLC[a)]		**0.005**
No	1	
Yes	2.813(1.375-5.754)	
Intracranial symptoms		**0.001**
No	1	
Yes	0.251(0.113-0.561)	
Lymphocyte (10^9/L)		**<0.001**
<1.54		
≥1.54	3.390(1.869-6.151)	
Neutrophil (10^9/L)		**0.029**
<103.5	1	
≥103.5	0.517(0.286-0.934)	
Hemoglobin(g/L)		**<0.001**
<117.5	1	
≥117.5	3.215(1.748-5.911)	
BSBM [b)]		0.066
0-1	1	
2-3	0.541(0.282-1.040))	
Lung-molGPA [c)]		**0.014**
0–2	1	
2.5-4	2.317(1.186-4.527)	

Abbreviations: a) NSCLC, non-small cell lung cancer; b) BSBM, proposed basic score for brain metastases; c) Lung-molGPA, Graded Prognostic Assessment for Lung Cancer Using Molecular Markers;

Supplemental Figure

Supplementary Figure S1 Overall survival according to (A) resection history of NSCLC, (B) intracranial symptom, and (C) Lung-molGPA, Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA).

Figures

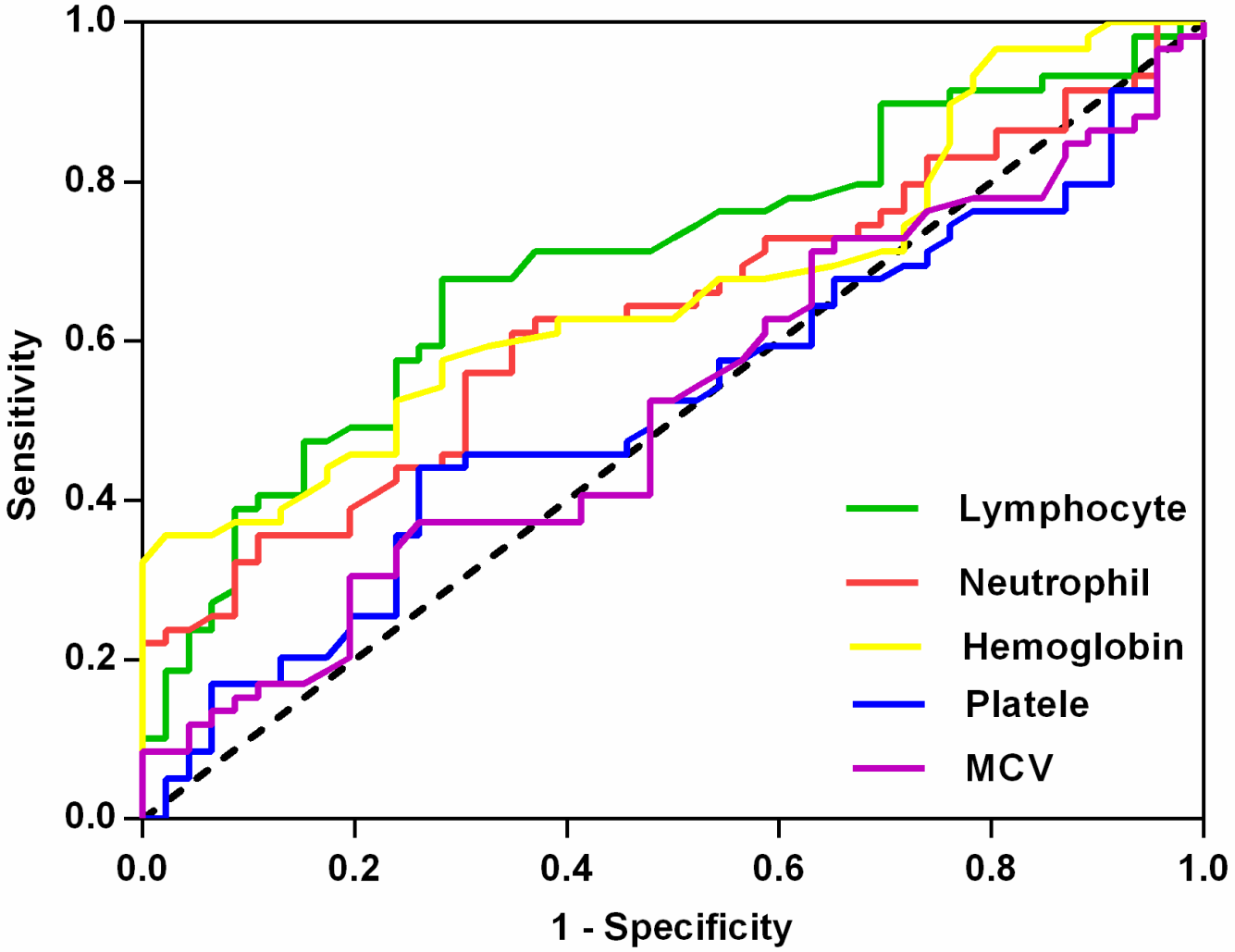

Figure 1

Receiver-operating-characteristic (ROC) and area under the curve (AUC) for optimal cut-off value of lymphocyte (AUC = 0.698; P = 0.786001), neutrophil (AUC = 0.632; P = 0.021), hemoglobin (AUC = 0.666; P = 0.004), mean corpuscular volume (MCV) (AUC = 0.519; P = 0.744), and platele(AUC = 0.520; P = 0.727) before WBRT.

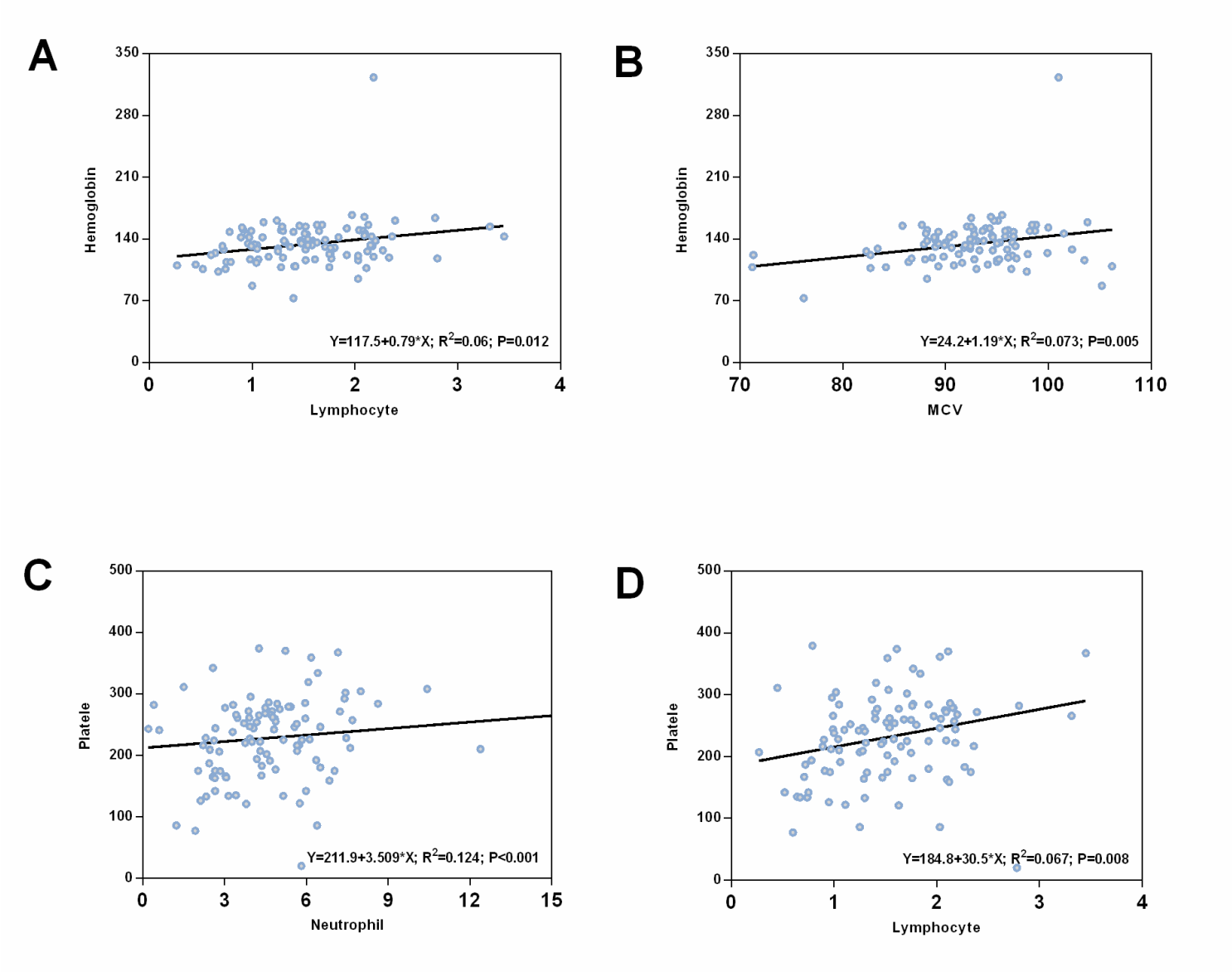

Figure 2

Linear correlations exist between hematological indicators in 105 NSCLC patients with brain metastases. A, correlation between lymphocyte and hemoglobin in 105 NSCLC patients with brain metastases. B, correlation between mean corpuscular volume (MCV) and hemoglobin in 105 NSCLC patients with brain metastases. C, correlation between neutrophil and platele in 105 NSCLC patients with brain metastases. D, correlation between lymphocyte and platele in 105 NSCLC patients with brain metastases.

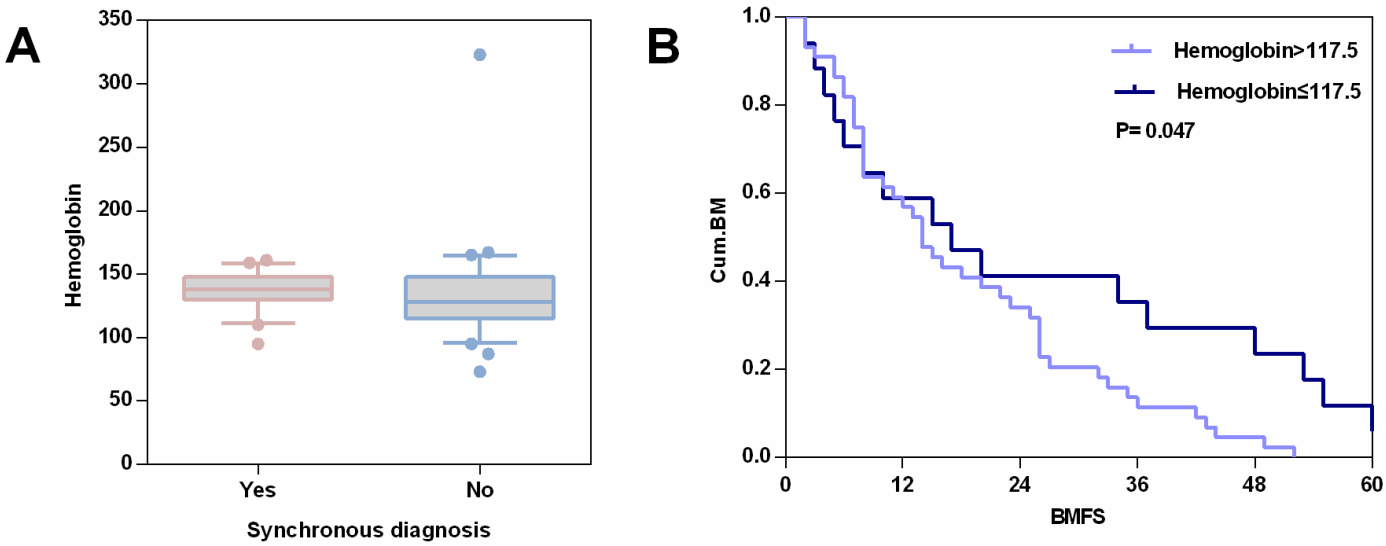

Figure 3

Relationship between hemoglobin and brain metastases free survival (BMFS) in 105 NSCLC patients with brain metastases. A, relationship between hemoglobin and synchronous diagnosis. B, relationship between hemoglobin and BMFS.

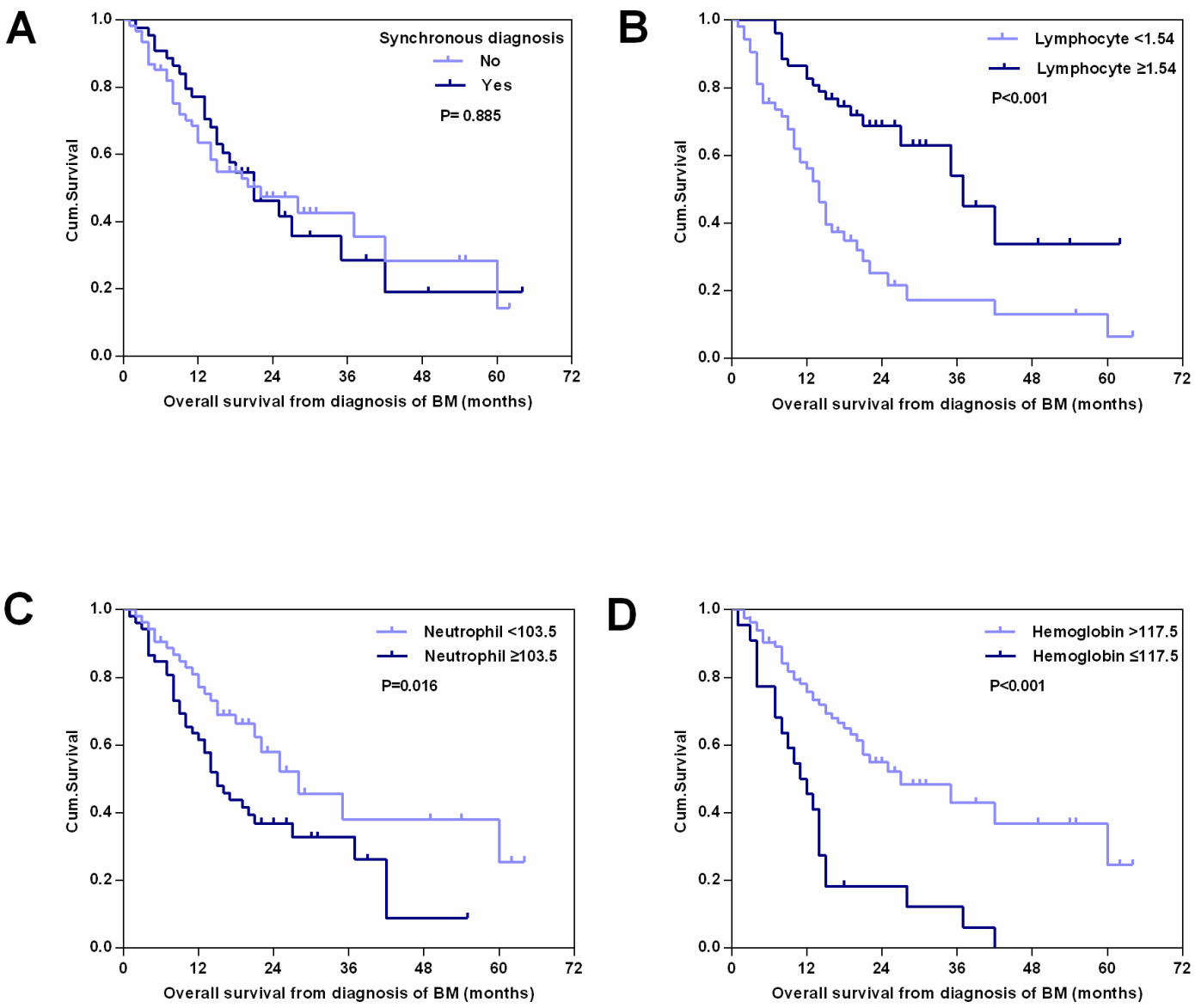

Figure 4

Kaplan-Meier overall survival curves for NSCLC patients with brain metastases. A, overall survival curves according to synchronous diagnosis. B, overall survival curves according to lymphocyte. C, overall survival curves according to neutrophil. D, overall survival curves according to hemoglobin.

Supplementary Files

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