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Research Article

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Abstract

Background and objective:

In modern clinical medicine, the most prevalent category of cancer is lung cancer, and the brain is a routine organ of metastasis for lung cancer. Recently, researchers have evaluated hematologic indicators such as neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) and confirmed that they are valid indices for predicting outcome of lung cancer patients. However, the prognostic significance for lung cancer patients who have progressed to brain metastasis has not been clarified. In our study, a meta-analysis which focus on the association of pre-treatment NLR, PLR and overall survival (OS) in lung cancer patients with brain metastasis was performed and reported.

Methods

PubMed, Embase and CNKI databases were the scope of our search, and the search methodology was derived from PRISMA. Meta-analyses of OS were performed using random effects models due to significant heterogeneity. This study has been registered on PROSPERO (CRD42022329590).

Results

We finally included 11 articles to evaluate NLR and PLR in 1977 eligible patients. The NLR group consisted of 11 studies whose meta-analysis showed that OS was significantly shorter in high-NLR patients than low-NLR patients (pooled HR = 1.84 (95% CI: 1.47–2.31)). Five studies were included in the PLR group, and the result suggested that OS was significantly shorter in high-PLR patients than low-PLR patients (pooled HR = 1.53 (95% CI: 1.07–2.20)).

Conclusions

Meta-analysis showed that association of pre-treatment NLR, PLR and OS are statistically significant. Pre-treatment lower NLR and PLR predict better OS.

1. Introduction

In modern clinical medicine, pulmonary malignant tumors is the most prevalent category of cancer (11.6%) and the major source of cancer-derived deaths (18.4%) (1). The brain is a routine organ of metastasis in lung cancer patients, whose incidence is as high as 18.9% (2) and 19.9% (3) in early and advanced lung cancer patients, respectively. In addition, 6.3–15.6% of patients progressed to BM after curative surgery (4–6). Among the primary lung cancer types with brain metastasis, adenocarcinoma accounted for 44%, squamous cell carcinoma for 26%, small cell carcinoma for 16%, and large cell carcinoma for 14% (7). Due to the development of IT and TT, the prognosis of lung cancer has improved significantly (8, 9). However, the overall prognosis of patients with BM is still not promising, and the treatment of such patients still faces great challenges (10). It is also an urgent task to find a way to predict the outcome of such patients effectively.

Although many models, which are used to predict the outcome of BM patients effectively are available, such as RTOG-RPA, SIR, BSBM and GPA (11–13), they have certain shortcomings, such as some of the more subjective scoring items can cause instability for posterior prediction. In subsequent updates, diagnosis-specific GPA and the modified BSBM place greater emphasis on the primary site and brain factors (14, 15). Then later, the newly proposed BM-Score focused for the first time on patients with small cell lung cancer (16). However, they still have limitations, such as the requirement that patients receive a specific treatment (SRS or WBRT), which certainly narrows the predictive range of these metrics.

In order to address the problems with these methods and because the association between the severity of inflammation and prognosis of cancer has been universally recognized (17), investigators have turned their attention to hematological indicators. NLR and PLR have been routinely and widely collected in clinical settings as data that can be easily collected and tested, and it also overcomes the problem of subjectivity of the above models. Although increasing trials have demonstrated the predictive value of outcomes possessed by NLR and PLR before treatment in lung cancer patients (18–22), the findings in patients with advanced BM are still controversial. The retrospective study of Cho noted that higher NLR and PLR were associated with longer OS (HR for NLR = 1.817, 95% CI 1.301-2.539, P < 0.001; HR for PLR = 1.654, 95% CI 1.178-2.322, P = 0.004) (23), but the opposite conclusion was reached in the study of Liu (HR for NLR = 0.921, 95% CI 0.658-1.290, P = 0.633; HR for PLR = 0.884, 95% CI 0.659-1.186, P = 411) (24). Therefore, our study aimed to collect the available experimental data to clarify whether there is an association between NLR, PLR and OS of patients who have developed BM of lung cancer, and if so, what kind of association exists.

2. Materials And Methods

2.1 Literature Search

Articles about the prognostic significance of pre-treatment NLR or PLR in patients with BM from lung cancer were searched on PubMed, Embase and CNKI from the time of database creation until June 18, 2022. The search program was based on PRISMA (25). Searches were conducted using the following keywords, including lung tumors, lung cancer, brain metastasis, BM, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, NLR, PLR. The search was done by two investigators without mutual communication. When disagreements arose, a third reviewer steps in to discuss and make the final decision.

2.2 Inclusion and exclusion criteria
A study is considered qualified if it meets the following criteria: (1) Studies in lung cancer patients with a clinical or histological diagnosis of BM. (2) Studies that assess the association of NLR or PLR and OS. (3) Studies in which NLR, PLR and their cut-off values are adequately and accurately defined (4) Studies in which NLR and PLR values were recorded prior to any treatment of BM.

Exclusion criteria: (1) letters, reviews, expert opinions, comments, meetings or reports summaries. (2) overlapping or duplicated studies. (3) insufficient information to assess HR with 95% CI.

2.3 Data extraction and quality assessment

Two investigators independently extracted and recorded documentary features: first author, country, publication time, duration, design of study, size of sample, age, sex, follow up time, pathological type, cancer type, treatment and survival outcomes. If available, we used the HR and 95% CI explicitly stated in the paper. Otherwise, the investigators extracted relevant data from Kaplan-Meier survival curves(26). Results are preferred for multivariate analysis, if not then univariate analysis results are used.

We used the NOS scale to assess the overall quality of the included studies(27). Each study has three main areas to assess in the NOS scale, namely the selection of study groups (scores 0–4), comparability between groups (scores 0–2), and for case-control or cohort studies, exposure or outcome of interest was determined separately (scores 0–3), with full score of 9 points. High-quality studies had NOS scores greater than 7, moderate-quality studies had scores between 5 and 7, and low-quality studies had scores less than 5 and needed to be excluded.

2.4 Statistical analysis

We used Stata 12.0 software for statistical analysis of the data. HR and its associated 95% CI were used as statistical effect indicators. Heterogeneity was tested using Q-test and $I^2$ statistic before meta-analysis. When $P > 0.1$ and $I^2 < 50\%$, heterogeneity was deemed insignificant and a fixed-effects model was applied for the analysis. When $P \leq 0.1$ and $I^2 > 50\%$, significant heterogeneity was deemed to be present in the incorporated studies and a random effects model was applied for analysis(28). When there was significant heterogeneity among the included studies, sensitivity analyses were conducted to look for potential sources. The magnitude of publication bias was estimated using funnel diagram, Begg's and Egger's test. In all analyses, $P < 0.05$ was defined as a sign of the presence of statistical significance.

3. Result

3.1 Literature selection results

Based on the above search strategy, 118 articles were searched. After the first browse, 97 of these articles were discarded because of the type of literature, duplicate publications, unclear diagnosis and poor relevance. After reading the full text, 10 of the articles were further excluded due to unavailability of data, resulting in a total of 11 articles(23, 24, 29–37) included (Fig. 1). The above studies involved a total of 1977 cases. All studies reported the association between pre-treatment NLR or PLR and OS. The basic characteristics of the included studies and the results of the quality assessment are presented in Table 1.

3.2 Results of meta-analysis

Eleven studies(23, 24, 29–37) reported the association of NLR and OS in lung cancer patients with BM. The random effects model was applied because the test for heterogeneity showed significant heterogeneity among the included studies ($P = 0.016, I^2 = 54.0\%$). The HR was 1.84 (95% CI: 1.47–2.31, $p < 0.001$), suggesting that there is a statistically significant association of NLR and OS in lung cancer patients with BM (Fig. 2).

Five studies(23, 24, 32, 33, 37) reported the association between PLR and OS in lung cancer patients with BM. The random effects model was applied because the test for heterogeneity showed significant heterogeneity among the included studies ($P = 0.003, I^2 = 75.4\%$). The HR was 1.53 (95% CI: 1.07–2.20, $p = 0.020$), indicating the association of PLR and OS exhibited statistically significant (Fig. 3).

3.3 Subgroup analysis

Subgroup analysis was conducted to further investigate the relation of NLR, PLR and OS. In the group of NLR, the results suggested that high-NLR patients had short OS regardless of the area (east Asia or non-east Asia), sample size (>150 or <150), the cut-off (>3 or <3) and design of study (single-center or multi-center). In the subgroups analysis of cancer types (NSCLC or SCLC or both of them), the association of NLR and OS in the SCLC group showed no significance in statistical terms (HR = 1.45, 95% CI 0.81–2.59, $p = 0.212$). There was significant heterogeneity in the area of east Asia ($I^2 = 67.0\% p = 0.006$), sample size larger than 150 ($I^2 = 72.8\%, P = 0.002$), cut-off value lower than 3 ($I^2 = 75.9\% p = 0.002$), SCLC ($I^2 = 70.8\% p = 0.033$) and the study design of single-center ($I^2 = 58.1\% p = 0.011$) (Table 2).

And further subgroup analysis of PLR group was performed to assess the effect of cut-off, cancer types and design of study on the prognostic predictive power of PLR, and the detailed results are shown in Table 3. The association of PLR and OS in the corresponding subgroups showed no significance in statistical terms when the cut-off was less than 200 (HR = 1.32, 95% CI 0.84–2.08, $p = 0.223$), the cancer type was SCLC (HR = 1.24, 95% CI 0.56–2.76, $p = 0.599$) and the study design was single-center (HR = 1.51, 95% CI 0.97–2.36, $p = 0.067$). A high level of heterogeneity was found in the cut-off value lower than 200 ($I^2 = 78.9\% p = 0.009$), SCLC ($I^2 = 74.8\% p = 0.046$) and the study design of single-center ($I^2 = 80.9\% p = 0.001$).

3.4 Publishing bias and sensitivity analysis
For NLR and PLR, HRs for OS and their associated 95% CIs were combined and evaluated. The results of publication bias are shown in Fig. 4. The funnel diagram looks roughly symmetrical, and the results of the Egger’s and Begg's test also indicated a low degree of bias in our study (all P values > 0.05). Sensitivity analysis showed that there was no significant effect of any of the studies on the effect values (Fig. 5).

4. Discussion

Globally, pulmonary malignant tumors is the major source of cancer-derived deaths for the last several decades(1). With the advent of IT and TT, a large proportion of patients with advanced lung cancer also have effective treatment strategies and have reaped good outcomes(38). However, the treatment options for patients who have been clinically or histologically diagnosed with BM from lung cancer remain inconclusive and still need to be determined based on the patient's prognosis estimate(39). This often results in delayed treatment or waste of medical resources, therefore, the early use of simple hematological indicators to determine patient prognosis is of great significance in clinical work. Our meta-analysis confirms that NLR and PLR before treatment were statistically associated with OS in lung cancer patients with BM.

NLR and PLR are very common hematological indicators in laboratory tests. Many studies have confirmed the association among these indicators and the outcome of solid tumors(40). According to a retrospective study conducted by Liu et al. High NLR and PLR signified shorter PFS (For NLR: HR = 2.17, 95%CI 1.01-4.55, P = 0.048; For PLR: HR = 2.56, 95%CI 1.06-5.88, P = 0.025) and shorter OS (For NLR: HR = 5.00, 95%CI 1.61-16.67, P = 0.002; For PLR: HR = 5.00, 95%CI 1.37-16.67, P = 0.008) in advanced NSCLC, suggesting the adverse prognosis of high NLR and PLR in cancer patients(41). For lung cancer that has progressed to the appearance of BM, the study by Cho et al. also demonstrated that OS was shorter in the NLR-increased group than NLR-not-increased group (HR: 1.817; 95%CI = 1.301–2.539, p < 0.001), and the same results were found in the PLR group (HR: 1.654; 95%CI = 1.178–2.322; p = 0.004)(23). This also confirms that in patients with BM, these hematological indicators have similar significance.

The microenvironment of brain tumors has a distinctive cellular composition, histological and anatomical structure, immune environment, and various metabolic constraints that differ significantly from extracranial lesions, exerting unique and profound selective pressures on tumor cells and influencing the process of metastatic and therapeutic response(42). The brain parenchyma contains cell types not found in extracranial organs, such as neurons, astrocytes, microglia, and oligodendrocytes. BBB and BCSFB isolate the brain into a relatively independent environment by sealing the tight connection between brain capillary endothelial cells or specific epithelial cells and meningeal cells, protecting the brain from various pathogenic factors(43).

But when brain metastasis occurs, the situation is different from normal. The brain has long been considered an organ with "immune privilege", meaning that surrounding immune cells are restricted by BBB from entering the brain in large numbers, making the immune environment of the brain very different from that of the external parts of the brain. However, recent research suggests that the brain is not a complete immune sanctuary and that immune cells from the periphery can enter the brain in certain ways, and this is particularly evident in patients who have developed BM(44). During inflammation, immune cells in the peripheral blood such as leukocytes can make the BBB more permeable by secreting IL-1β or by the adhesion proteins ICAM1, VCAM1 or E-selectin(45).

Moreover, when BM occurs, the tumor compromises the structural integrity of the BBB, leading to the creation of a BTB characterized by inhomogeneous permeability and active efflux of molecules(46). From this, we can reasonably speculate that the indicators of peripheral blood circulation in patients with BM can also reflect intracranial lesions to some extent.

We can explain their relationship with patient prognosis by analyzing the composition of NLR and PLR. Neutrophils, platelets, and lymphocytes can represent three physiological or pathological response systems of the body: acute inflammatory response, coagulation response, and acquired immune response, and the tremendous impact of these various cells on the development of tumors is also widely documented. Early in the tumor process, these cells generate an attractive environment for tumor growth, promote genomic instability and foster angiogenesis(47). Neutrophils regulate inflammation through the production of reactive intermediates such as ROS and RNS. They also promote angiogenesis, progression and invasion of tumor by releasing NE and matrix metalloproteinases MMP8/9, which reconfigure the extracellular matrix in the tumor microenvironment. These proteases degrade pro-inflammatory cytokines and reposition the microenvironment of tumor, increasing the oncogenic potential of tumor cells in vivo and vitro, as well as the metastasis initiation potential of cancer cells to enhance tumor progression and aid metastasis(48, 49). Platelets are important for hematogenous metastatic dissemination. Platelets provide large amounts of secreted proteins and alpha particles contents to the adjacent areas, all of which contribute to the initiation and acceleration of the host inflammatory response on the one hand, and on the other hand, its activation creates a tumor-friendly microenvironment that protects tumor cells from shear and NK cell attack, prompting platelet embolization of tumor cells to lodge in the vessel wall. Then, by producing growth factors, tumor cells acquire a mesenchymal-like phenotype and expand the gap between capillary endothelial cells, accelerating extravasation to other organs(50). Lymphocytes can exert extrinsic tumor suppressive effects through cancer immunosurveillance function. The role that immunity plays in the complex interaction between tumor and host has been termed "cancer immune editing(51)". There is growing evidence that finding TILs in a cancer patient's tumor often suggests a better outcome for that patient. Several seminal studies involving patients with primary or metastatic melanoma(52), squamous cell carcinoma or adenocarcinoma of the esophagus(53), and patients with advanced ovarian adenocarcinoma(54) have established strong relationships between the presence of TILs and patient outcome, and has analyzed the prognostic value of various T-cell subsets infiltrating in the lesions.

This meta-analysis included 11 publications including 1977 patients with lung cancer who developed BM, with no language restrictions. According to the findings of this study, OS was shorter in both the high NLR and high PLR groups, that implies pre-treatment NLR and PLR may be a very promising prognostic predictor for patients with BM from lung cancer. However, according to the subgroup analysis, no statistically significant relationships were found between NLR and OS in BM patients whose primary cancer type was SCLC in the NLR group. The analysis also suggests that the heterogeneity might originate from East Asia, sample size larger than 150, cut-off value less than 3, primary lung cancer type of SCLC and studies with a single-center experimental design. In the PLR group, the association between PLR and OS was also not statistically significant when the primary cancer type was BM with SCLC and the cutoff point was less than 200 when the study type was single-center. The results of the analysis suggest that heterogeneity may arise from studies with cut-off value 200 or less, with primary lung cancer type of SCLC, and with a single-center experimental design. By further analysis, we found that in all studies that included only
SCLC patients, clinicians did not apply immunotherapy to treat patients. However, recent research has shown that the prognostic significance of NLR and PLR for NSCLC needs to be predicated on the treatment of immune checkpoint inhibitors, and high level of NLR and PLR suggest a poor prognosis for such patients(55). Therefore, no statistically significant association was found between PLR, NLR and OS in SCLC patients in the subgroup analysis. Gu et al. found that PLR was significantly associated with PFS and OS at a cutoff value of 180 in patients with Caucasian NSCLC; however, PLR values above 200 were associated with lower prognostic values in Asians(56). While the included literature that analyzed the prognostic value of PLR were from Asia. Therefore, in the subgroup analysis when the PLR as of value is less than 200, there is no statistically significant association between PLR and OS. This suggests that if PLR is used to assess the prognosis of Asian lung cancer patients with BM, then a cut-off value higher than 200 is a better choice. Of course, this should be validated by prospective research with a larger sample capacity. Finally, the limitations of single-center studies also affect the significance in statistical terms of the relationship between PLR and patient OS.

Our study also has other limitations. Firstly, all included studies were retrospective, resulting in less credibility of the evidence than in clinical randomized controlled trials. Secondly, some of the included literature did not mention a clear follow-up time, which may have resulted in bias. Thirdly, each study used a different treatment strategy, which increased the heterogeneity of the included studies. Finally, the cut-off points of NLR and PLR were different in every study, which increased the heterogeneity among studies and made the clinical application more difficult, follow-up studies should establish a better generalizable cut-off value system to guide research and clinical practice.

5. Conclusion

In conclusion, our meta-analysis certified a statistically significant association between pre-treatment NLR, PLR and OS in lung cancer patients with BM, with lower pre-treatment NLR and PLR predicting better OS.

Abbreviations

NLR
Neutrophil to Lymphocyte Ratio
PLR
Platelet to Lymphocyte Ratio
BM
Brain Metastasis
OS
Overall Survival
CNKI
China Knowledge Network
PRISMA
Preferred Reporting Items for Systematic Analysis and Meta-Analysis guidelines
RTOG-RPA
Radiation Therapy Oncology Group–Recursive Partitioning Analysis
SIR
Score Index for Radiosurgery
BSBM
Basic Score for Brain Metastasis
GPA
Graded Prognostic Assessment
SRS
Stereotactic Radiosurgery
WBRT
Whole Brain Radiotherapy
HR
Hazard Ratio
CI
Confidence Interval
TT
Targeted therapy
IT
Immunotherapy
BBB
Blood–brain Barrier
BTB
Blood-tumor Barrier
BCSFB
Blood-cerebrospinal Fluid Barrier
IL-1β
Interleukin-1β
ICAM1
Intercellular Adhesion Molecule 1
VCAM1
Vascular Cell Adhesion Molecule 1
ROS
Reactive Oxygen Species
RNS
Reactive Nitrogen Species
NE
Neutrophil Elastase
TILs
Tumor-infiltrating Lymphocytes.

**Declarations**

**Ethical Approval and Consent to participate**

Ethics approval and participants consent are not required because this study is a meta-analysis based on the published studies.

**Consent for publication**

All authors consent and approve the manuscript for publication.

**Data availability statement**

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

**Competing interests**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Authors' contributions**

**Bo Yang:** Conception or design of the work, acquisition of data for the work, analysis of data for the work, interpretation of data for the work, drafting the work, critical revision of the work for important intellectual content, and responsibility for overall content as a guarantor. **Yifeng Shao:** Conception or design of the work, analysis of data for the work, interpretation of data for the work, drafting the work, and critical revision of the work for important intellectual content. **Wenyu Zhang:** Conception or design of the work, analysis of data for the work, interpretation of data for the work, drafting the work, and critical revision of the work for important intellectual content. **Wei Cao:** Acquisition of data for the work, analysis of data for the work, interpretation of data for the work, and critical revision of the work for important intellectual content. All authors have given final approval for the version of this article to be published and have agreed to be accountable for all aspects of the work and thereby ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**References**


Tables
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<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Duration</th>
<th>Study design</th>
<th>Total number of patients</th>
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<th>Treatment</th>
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Abbreviation: F: female; M: male; NA: no available; AC: adenocarcinoma; NAC: Non-adenocarcinoma; NSCLC, non-small cell lung cancer; SCLC, small cell lung radiosurgery treatment; IT, immunotherapy; TT, targeted therapy; WBRT: whole-brain radiotherapy; CT: chemotherapy; SRT: stereotactic radiotherapy; SIB: simultaneous integrated boost; NOS: Newcastle-Ottawa Scale; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; OS: overall survival; HR: hazard ratio; CI: confidence interval.
Table 2
Subgroup analyses of the associations between NLR and outcomes

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<td>10</td>
<td>1.84 (1.44–2.35)</td>
<td>&lt;0.001</td>
<td>58.1</td>
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<td>1</td>
<td>2.00 (1.14–3.51)</td>
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Table 3
Subgroup analyses of the associations between PLR and outcomes

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>NO. of studies</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Heterogeneity</th>
<th>Model</th>
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<td></td>
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<td></td>
<td>$I^2$ (%)</td>
<td>Ph</td>
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<tr>
<td>Cut-off</td>
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<tr>
<td>&gt; 200</td>
<td>2</td>
<td>2.03 (1.48–2.76)</td>
<td>&lt;0.001</td>
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<td>0.993</td>
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<tr>
<td>&lt; 200</td>
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<tr>
<td>NSCLC</td>
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<td>1.83 (1.44–2.33)</td>
<td>&lt;0.001</td>
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<tr>
<td>SCLC</td>
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<td>LC</td>
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<td>1.51 (0.97–2.36)</td>
<td>0.067</td>
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<td>1.67 (1.06–2.64)</td>
<td>0.029</td>
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</tr>
</tbody>
</table>

Figures
Figure 1

Flow diagram of study selection.
Figure 2

Meta-analysis of OS in the lung cancer patients with BMs (high NLR groups vs. low NLR groups).
Figure 3

Meta-analysis of OS in the lung cancer patients with BMs (high PLR groups vs. low PLR groups).

Figure 4
Results of publishing bias. A: funnel plot using data of NLR to detect publication bias; B: Egger's test of the NLR group; C: Begg's test of the NLR group; D: funnel plot using data of PLR to detect publication bias; E: Egger's test of the PLR group; F: Begg's test of the PLR group

Figure 5

Results of sensitivity analysis. A: sensitivity analysis with regard to studies included for NLR; B: sensitivity analysis with regard to studies included for PLR