Lower lymphocyte percentage and higher platelet count as poor prognostic factors for patients with epidermal growth factor receptor–mutated lung adenocarcinoma receiving tyrosine kinase inhibitors as first-line treatment

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Abstract

Background

This study evaluated the effect of clinical factors on the treatment outcomes of patients with lung adenocarcinoma with active epidermal growth factor receptor (EGFR) mutations who received tyrosine kinase inhibitors (TKIs) as first-line treatment.

Methods

Patients with stage IIIb or IV lung adenocarcinoma with mutated EGFR were enrolled retrospectively between March 2010 and December 2017. The effects of various clinical features and hematologic markers on progression-free survival (PFS) and overall survival (OS) were analyzed.

Results

A total of 190 patients were enrolled in this study. In univariate analysis, the male sex, smoking history, EGFR mutation with L858R, and presentation with malignant pleural effusion at initial diagnosis were significantly associated with shorter PFS or OS. Among hematologic markers, lower lymphocyte percentage and higher platelet count were associated with significantly poor PFS and OS. Stepwise multivariate Cox regression analysis showed that smoking history, EGFR mutation with L858R, and lower lymphocyte percentage were independent poor prognostic factors for PFS and OS. Presentation with malignant pleural effusion and higher platelet count was an independent poor prognostic factor for OS only.

Conclusion

Patients with lung adenocarcinoma receiving TKIs as the first-line treatment and having hematologic markers with lower lymphocyte percentage, and higher platelet count had poorer prognoses compared with other patients. Additional studies are warranted to elucidate the underlying mechanisms.

Background

By the World Health Organization, lung cancers are the leading causes of cancer mortality and disability-adjusted life years[1]. Treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) as the first-line therapy for EGFR-mutant lung adenocarcinoma improved the
response rates, progression-free survival (PFS) and overall survival (OS) significantly [2]. Although the response rate of EGFR TKIs as first-line treatment is high, there are still some patients with a dismal prognosis. Several biomarkers by previous reports, including CEACAM (carcinoembryonic antigen-related cell adhesion molecule), CA125 (cancer antigen 125), CYFRA21-1 (cytokeratin-19 fragments), neuron-specific enolase, and et al., all showed limited sensitivity and specificity [3]. Evidence by previous studies had been showed changes in blood components and blood cells, including a white blood count and platelet, in cancer patients associated with the disease severity and survival [4–8]. By the previous study, lymphocytes played critical roles in promoting systemic immune responses against tumors, and lymphocytopenia is associated with poor outcomes in many malignancies [9–11]. High expression of CD8+ T lymphocytes, which predicts a favorable prognosis in lung adenocarcinoma was reported [12]. Platelet also played another important role in cancer prognosis. Thrombocytosis has been found which is associated with poorer cancer prognosis. Shorter OS rates observed for patients with many cancers, included ovarian cancer [4], lung cancer [5], and breast cancer [6] which was related to thrombocytosis at the time of diagnosis, and poor prognoses of patients with colorectal cancer [7] and renal cancer [8] before surgical therapy are related to high platelet counts. Sylman et al. reported that platelet count is also a predictor of metastasis and venous thromboembolism in patients with cancer [13].

On the other hand, systemic inflammation also plays a role in cancer prognosis [14]. Inflammatory mediators are involved in cancer progression with apoptosis, angiogenesis, and DNA damage [15]. Numerous studies have shown the relationship between inflammation and cancer prognosis [16, 17]. The markers included the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Higher NLR or PLR has been reported to predict shorter progression-free survival (PFS) and OS in many solid cancers [18–21].

Awareness of newer prognostic factors might provide a potential direction for further improvement in treatment for EGFR-mutated non-small-cell lung cancer (NSCLC), especially adenocarcinoma, but no study has focused on hematologic and inflammatory markers in EGFR-mutant lung adenocarcinoma. In this study, we evaluated the effects of hematologic and inflammatory factors on the treatment
outcomes of patients with advanced or metastatic lung adenocarcinoma with active EGFR mutations. All patients received TKIs as the first-line treatment.

Methods

Patients and data collection

Patients with diagnosis as stage IIIb or IV lung adenocarcinoma in Buddhist Tzu Chi General Hospital, Hualien, Taiwan, from March 1, 2010, to December 31, 2017, and harbored mutated EGFR were enrolled in this retrospective study. According to the World Health Organization pathology classification, lung adenocarcinoma was confirmed pathologically. All patients received serial imaging studies at the initial diagnosis for staging, including computed tomography (CT), whole-body bone scan, positron emission tomography scan (PET), and brain imaging. Tumor staging was recorded by the seventh American Joint Committee on Cancer staging system. All the patients had an EGFR mutation examination of the tumor specimen, and the results showed active EGFR mutations in exons 18, 19, 20, or 21 in all patients. And then they received EGFR TKIs as first-line therapy, including afatinib, erlotinib, or gefitinib. The choice of EGFR TKI was by the discretion of their attending physicians. Patients were excluded if they had previously undergone palliative chemotherapy.

Baseline clinical characteristics were determined through a retrospective chart review, including age at diagnosis, sex, staging, smoking status, mutation type, and TKIs used. Smoking status was categorized to ever smoker or never smoker. Malignant pleural effusion was diagnosed by either pleural effusion cytology or a pleural biopsy. Complete blood counts, including total leukocyte counts with a different count, hemoglobin, and platelet count, were also recorded. NLR and PLR were also calculated from the data of complete blood counts.

Mutational analysis of EGFR gene was done as described in a previous study [22]. Briefly, formalin-fixed, paraffin-embedded tissues of histologically were used for confirming NSCLC. An EGFR RGQ Kit (Qiagen, Hilden, Germany) was used for the analysis of mutations in EGFR, which utilizes amplification refractory mutation-specific polymerase chain reaction and Scorpion technologies for detection and direct sequencing.

PFS was recorded as the duration between the start of TKI treatment and the date of progression. And
OS was defined as the duration from the start of TKI treatment to the time of all-cause death. All enrolled patients were followed up until death or the end of December 2018. This retrospective study was approved by the Institutional Review Board of Buddhist Tzu Chi General Hospital (IRB108–48-B). Informed written consent was waived because the study was a retrospective data analysis.

Statistical analyses

Data were analyzed by MedCalc (Mariakerke, Belgium) with median and hazard ratios (HRs) and their 95% confidence intervals (CIs). PFS and OS were analyzed using Kaplan–Meier curves and the log-rank test. Univariate and multivariate analyses were executed using Cox proportional-hazards regression. All variables were included for multivariate analysis to assess the effect of each variable after univariate analyses. Stepwise variable selection was used to develop a reduced multivariate model, including variables with P < 0.1 and removing variables with P > 0.2. Two-sided with the level of statistical significance set at P < 0.05 was used in all results.

Results

Clinical features of patients

Overall, 190 patients [87 (45.8%) male and 103 (54.2%) female patients] were enrolled in this study. The median follow-up duration was 17.9 months (range, 0.5–91.3 months). The clinical features of this study population, such as age, sex, smoking history, stage, EGFR mutation, drugs used, malignant pleural effusion, and brain metastasis, are summarized in Table 1. The median age at diagnosis was 70 (range, 42–95) years. In all patients, adenocarcinoma was confirmed pathologically. Twenty-one (11.1%) and 169 (88.9%) patients were at TNM stages IIIb and IV, respectively. As the type of EGFR mutation, 89 (46.8%) patients had L858R, 89 (46.8%) had exon 19 deletions, and the remaining 12 (6.3%) had other mutations that were sensitive to TKI treatment by previous reports. The 12 uncommon active mutations of EGFR were 7 for L871Q in exon 21, 1 for L858M, 1 for S768I in exon 20, 1 for G719X in exon 18, and 2 for two-point mutations with E709G/L858R and G719X/L861Q. The TKIs used were gefitinib in 91 (47.9%) patients, erlotinib in 54 (28.4%), and afatinib in 45 (23.7%). Most patients reported being never smokers (66.8%). Malignant pleural effusion at initial diagnosis was observed in 48 (25.3%) patients. Among the patients, 152 (80%) had disease
progression, and 110 (57.9%) died during follow-up.

Clinical features versus lung adenocarcinoma under TKI treatment

Univariate analysis results revealed that the male sex (median PFS: 10.4 vs 15.17 months, P = 0.0036; median OS: 18.2 vs 35.37 months, P = 0.0016) and ever smoking (median PFS: 9.63 vs 15.33 months, P = 0.0001; median OS 15.63 vs 33.8 months, P < 0.0001) were associated with poor PFS and OS. With respect to EGFR mutation types, exon 19 deletion had better PFS and OS than L858R or others did (median PFS: 14.73, 11.27, vs 6.43 months, P = 0.0271; median OS: 30.47, 20.43, vs 9.97 months, P < 0.0001). Malignant pleural effusion at the time of initial diagnosis was associated with poor OS only (median PFS: 10.4 vs 12.33 months, P = 0.0573; median OS: 16.33 vs 28.07 months, P = 0.0099).

Multivariate analysis with a stepwise model revealed that ever smoking was independent poor prognostic factors for PFS and OS (PFS: HR = 0.56, 95% CI: 0.40–0.79, P = 0.0011; OS: HR = 0.55, 95% CI: 0.37–0.83, P = 0.0042). EGFR exon 19 deletion was independent better prognostic factors for PFS and OS (PFS: HR = 1.35, 95% CI: 1.03–1.76, P = 0.0292; OS: HR = 1.65, 95% CI: 1.20–2.29, P = 0.0024). Malignant pleural effusion at the time of initial diagnosis was associated with poor OS still (OS: HR = 0.63, 95% CI: 0.42–0.95, P = 0.02887). The detailed data are presented in Tables 1-3.

Hematologic markers versus lung adenocarcinoma under TKI treatments

At the time of diagnosis, lower total leukocyte count (lower than 7350/μL vs higher, median PFS: 14.73 vs 11.73 months, P = 0.0018; median OS: 35.07 vs 19.4 months, P = 0.0059), lower platelet count (lower than 250,000/μL vs higher, median PFS: 14.43 vs 10.73 months, P = 0.0478; median OS: 27.3 vs 20.17 months, P = 0.0059), and lower neutrophil percentage (lower than 68.7% vs higher, median PFS: 15.33 vs 10.73 months, P = 0.0190; median OS: 40.3 vs 18.2 months, P < 0.0001) were significantly associated with a better prognosis in the univariate analysis. Higher lymphocyte percentage (higher than 20.8% vs lower, median PFS: 16.3 vs 9.9 months, P = 0.0009; median OS: 47.63 vs 18.07 months, P < 0.0001) was also significantly associated with better PFS and OS (Figure 1). In the univariate analysis, the cutoff levels of NLR and PLR were established based on median values: 3.2 and 12200, respectively. Lower NLR (median PFS: 15.63 vs 9.97 months, P = 0.0030;
median OS: 40.8 vs 18.07 months, P < 0.0001) and lower PLR (median PFS: 15.17 vs 10.73 months, P = 0.0113; median OS: 35.27 vs 17.83 months, P < 0.0001) were associated with better PFS and OS. In the multivariate analysis with a stepwise model, only higher lymphocyte percentage was significantly associated with better prognosis in PFS (HR = 1.50, 95% CI: 1.08–2.09, P = 0.0159). Regarding OS, higher lymphocyte percentage (HR = 2.10, 95% CI: 1.39–3.17, P = 0.0004) was also associated with a better prognosis, but higher platelet count (HR = 0.63, 95% CI: 0.43–0.93, P = 0.0211) was associated with a significantly poorer prognosis.

**Discussion**

Lung cancer is a prominent global health burden that causes approximately 1.5 million annual deaths by previous reports[23]. The prognosis of patients with advanced-stage lung adenocarcinoma with genotype-driven mutations has improved owing to target therapy administration [24, 25], including in-frame deletions in exon 19 (Del19) or exon 21 substitution of leucine for arginine (L858R) [24–27]. Patients with lung adenocarcinoma who harbor these classical mutations have high objective response rates to the first-generation reversible adenosine triphosphate-competitive EGFR TKIs, including gefitinib and erlotinib, and second-generation irreversible TKI, including afatinib. Despite the high response rates (52.7%–83%) of TKIs used in treating patients with stage IIIb or IV lung cancer with active EGFR mutations, such patients eventually succumb to this disease; To further improve the outcome, more aggressive treatment might be necessary for some patients. Therefore, methods for predicting prognosis have become increasingly critical. In this study, we demonstrated that lower lymphocyte percentage predicted poor PFS and OS and higher platelet count predicted poor OS in patients with active EGFR mutations receiving TKIs as the first-line treatment.

Several retrospective studies have shown longer PFS after TKI treatment in patients harboring EGFR with exon 19 deletions than in those with exon 21 mutations. Won et al. reported that 87 patients with exon 19 deletions had longer PFS following EGFR TKI treatment [28]. Zhou et al. also reported that 219 patients with exon 19 deletions had longer survival times significantly [29]. In our data, the patients with exon 19 deletions had better PFS and OS than did those with L858R. Previous studies have shown that malignant pleural effusion at initial diagnosis [30, 31] is associated with poor OS in
lung cancer patients. A recent study proposed that cancer stem cells in pleural effusion contribute to the metastatic cascade through the epithelial-mesenchymal transition, anoikis, and adaptation in the microenvironment. This result may explain the high therapeutic failure rates if the patients have malignant pleural effusion [32]. Our results also showed the patients with malignant pleural effusion would have a poor prognosis. In addition to malignant pleural effusion and EGFR mutation sites, some patient features have been found to predict EGFR TKI treatment outcomes, including smoking history, size, and metastatic sites [33, 34]. Sex and smoking history are common prognostic factors in cancers. Our results show that male and a smoker were positively associated with poor prognosis by univariate analysis but not by multivariate analysis [22].

In our study, an increase in lymphocyte percentage along with a related increase in leukocyte count and decrease in neutrophil percentage was associated with a better prognosis. Because lymphocytes are critical in promoting systemic immune responses against tumors, lymphocytopenia is associated with poor outcomes in many solid cancers [9–11]. Cytotoxic T lymphocytes elicit adaptive cellular immunity against tumor cells [35], and Ye et al. found that high expression of CD8+ T lymphocytes predicts better prognosis in patients with lung adenocarcinoma [12]. In our study, patients with a lymphocyte percentage of >20.8% had a better prognosis than did other patients. Higher lymphocyte percentage and lower lymphocyte percentage were associated with median OS periods of 40.63 and 18.07 months, respectively, and these were significantly different between univariate and multivariate analyses.

High platelet count has been reported with a poor prognosis in various cancers [11, 36]. The mechanism may be related to thymidine phosphorylase, which is a platelet-derived endothelial cell growth factor with potent angiogenic activity. An increase in thymidine phosphorylase levels may be associated with a poor prognosis in various solid tumor tissues [37]. Thrombocytosis with a negative prognostic value in lung cancer has been reported before [38, 39]. However, no study has found that higher platelet count is associated with a poorer prognosis in only lung adenocarcinoma with EGFR mutations under TKI treatment. In our results, 190 patients with EGFR-mutated lung adenocarcinoma under TKI treatment demonstrated that patients with higher pretreatment platelet counts had shorter
PFS and OS. Notably, under multivariate analysis, higher platelet count was found to affect only OS and not PFS. TKI treatment may be able to overcome the effects of platelet count; additional studies are required to elucidate this hypothesis.

Some studies showed lower NLR, or PLR ratio exhibited better PFS and OS in NSCLC patients [20, 40, 41]. Inflammation may contribute to tumor initiation through genetic mutations, genomic instability, and epigenetic modifications. Inflammation may also stimulate angiogenesis, causes immunosuppression, and promotes the formation of microenvironments in which malignant cells can survive, and metastatic spread [42]. Accordingly, the close association between increased systemic inflammatory responses, including NLR and PLR, and poor prognosis identified in our study may be associated with inflammatory in cancer cells.

Conclusions
In our study of patients with stage IIIb or IV lung adenocarcinoma with EGFR mutations who received TKIs as the first-line treatment, a lower lymphocyte percentage and higher platelet counts were significantly associated with shorter PFS and OS. Stepwise multivariate Cox regression analysis also showed that lower lymphocyte percentage was an independent poor prognostic factor for both PFS and OS, but a higher platelet count was only for OS. Further research is necessary to confirm the possible mechanism of poor prognoses.

Abbreviations
CA125: Cancer Antigen 125
CEACAM: Carcinoembryonic Antigen-related Cell Adhesion Molecule
CIs: Confidence Intervals
CYFRA21-1: Cytokeratin-19 Fragments
Del 19: In-frame Deletions in Exon 19
EGFR: Epidermal Growth Factor Receptor
HR: Hazard Ratios
NLR: Neutrophil-to-lymphocyte Ratio
NSCLC: Non-small-cell Lung Cancer
OS: Overall Survival

PFS: Progression-Free Survival

PLR: Platelet-to-lymphocyte Ratio

TKI: Tyrosine Kinase Inhibitors

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board of Buddhist Tzu Chi General Hospital (IRB108–48-B).

Consent for publication

Informed written consent was waived by the Institutional Review Board of Buddhist Tzu Chi General Hospital because the study was a retrospective data analysis.

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 that they have no competing interests

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Authors’ contributions

The contributions of authors included: YF Wu: the conception and design of the study, analysis and interpretation of data, drafting the article; CB Lin, SC Chu, WH Huang, JJ Lee, GG Yang, TF Wang: acquisition of data; CC Li: final approval of the version to be submitted.

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Tables

Table 1. Median progression-free survival and overall survival of patients with specific clinical features
| Clinical features          | Numbers (n) | Median PFS (months) | P-value (PFS) | Med (r) |
|---------------------------|-------------|---------------------|---------------|---------|
| All patients              | 190         | 12.0                |               |         |
| Age                       |             |                     |               |         |
| >70 years                 | 96          | 11.43               | 0.3565        |         |
| ≤70 years                 | 94          | 14.77               |               |         |
| Gender                    |             |                     |               |         |
| Male                      | 87          | 10.4                | 0.0036**      |         |
| Female                    | 103         | 15.17               |               |         |
| Smoking                   |             |                     |               |         |
| Ever                      | 63          | 9.63                | 0.0001**      |         |
| Never                     | 127         | 15.33               |               |         |
| Stage                     |             |                     |               |         |
| IIIb                      | 21          | 15.33               | 0.0639        |         |
| IV                        | 169         | 12                  |               |         |
| Mutation                  |             |                     |               |         |
| Deletion 19               | 89          | 14.73               | 0.0271*       |         |
| L858R                     | 89          | 11.27               |               |         |
| Others                    | 12          | 6.43                |               |         |
| Drugs                     |             |                     |               |         |
| Afatinib                  | 45          | 16.13               | 0.1005        |         |
| Erlotinib                 | 54          | 13.1                |               |         |
| Gefitinib                 | 91          | 11.43               |               |         |
| Malignant pleural effusion|             |                     |               |         |
| Yes                       | 48          | 10.4                | 0.0573        |         |
| No                        | 142         | 12.33               |               |         |
| Brain metastasis          |             |                     |               |         |
| Yes                       | 45          | 13.57               | 0.4904        |         |
| No                        | 145         | 11.93               |               |         |
| Hematologic markers       |             |                     |               |         |
| WBC count                 |             |                     |               |         |
| >7350/μL                  | 95          | 11.03               | 0.0018**      |         |
| ≤7350/μL                  | 95          | 14.73               |               |         |
| Hb                        |             |                     |               |         |
| >12.3g/dL                 | 93          | 12.63               | 0.9277        |         |
| ≤12.3g/dL                 | 97          | 11.53               |               |         |
| Platelet count            |             |                     |               |         |
| >250K/μL                  | 95          | 10.73               | 0.0478*       |         |
| ≤250K/μL                  | 95          | 14.43               |               |         |
| MPV$                      |             |                     |               |         |
| >9.6fL                    | 93          | 11.8                | 0.6242        |         |
| ≤9.6fL                    | 93          | 14.4                |               |         |
| Neutrophil%               |             |                     |               |         |
| >68.7%                    | 96          | 10.73               | 0.0190*       |         |
| ≤68.7%                    | 94          | 15.33               |               |         |
| Lymphocyte%               |             |                     |               |         |
| >20.8%                    | 95          | 16.3                | 0.0009**      |         |
| ≤20.8%                    | 95          | 9.9                 |               |         |
| Neutrophil-to-lymphocyte ratio |         |                     |               |         |
| >3.2                      | 96          | 9.97                | 0.0030**      |         |
| ≤3.2                      | 94          | 15.63               |               |         |
| Platelet-to lymphocyte% ratio |         |                     |               |         |
| >12200                    | 95          | 10.73               | 0.0113*       |         |
| ≤12200                    | 95          | 15.17               |               |         |
Only 186 patients had mean platelet volume (MPV) data; PFS: progression-free survival; OS: overall survival

* P-value < 0.05; ** P-value < 0.01

Table 2. Analyses for the relationship between clinical features and progression-free survival

| Clinical features                                      | Univariate                     | Multivariate (Stepwise mode) |
|--------------------------------------------------------|--------------------------------|-------------------------------|
|                                                        | HR (95% CI)                    | P-value                       | HR (95% CI)                  |
| Age (>70 years vs ≤70 years)                           | 0.86 (0.62-1.19)               | 0.3565                        |                                |
| Gender (male vs female)                                | 0.63 (0.44-0.85)               | 0.0036**                      |                                |
| Smoking (ever vs never)                                | 0.53 (0.32-0.69)               | 0.0001**                      | 0.56 (0.40-0.79)              |
| Stage (IIIb vs IV)                                     | 0.59 (0.40-1.03)               | 0.0639                        |                                |
| Mutation (Del 19 vs L858R vs others)                   | -                              | 0.0271*                       | 1.35 (1.03-1.76)              |
| Drugs (Afatinib vs Erlotinib vs Gefitinib)             | -                              | 0.1005                        |                                |
| Malignant pleural effusion (Yes vs No)                 | 0.71 (0.47-1.12)               | 0.0573                        |                                |
| Brain metastasis (Yes vs No)                           | 1.14 (0.79-1.63)               | 0.4904                        |                                |
| Hematologic markers                                    |                                |                               |                                |
| WBC count (>7350/μL vs ≤7350/μL)                       | 0.61 (0.43-0.82)               | 0.0018**                      |                                |
| Hb (>12.3g/dL vs ≤12.3g/dL)                            | 1.01 (0.74-1.40)               | 0.9277                        |                                |
| Platelet count (>250K/μL vs ≤250K/μL)                  | 0.73 (0.53-1.00)               | 0.0478*                       |                                |
| MPV (>9.6fL vs ≤9.6fL)                                 | 0.92 (0.67-1.27)               | 0.6242                        |                                |
| Neutrophil% (>68.7% vs ≤68.7%)                         | 0.69 (0.49-0.94)               | 0.0190*                       |                                |
| Lymphocyte% (>20.8% vs ≤20.8%)                         | 1.70 (1.26-2.40)               | 0.0009**                      | 1.50 (1.08-2.09)              |
| Neutrophil-to-lymphocyte ratio (>3.2 vs ≤3.2)         | 0.62 (0.44-0.85)               | 0.0030**                      |                                |
| Platelet-to-lymphocyte% ratio (>12200 vs ≤12200)      | 0.67 (0.48-0.91)               | 0.0113*                       |                                |

Only 186 patients had mean platelet volume (MPV) data; PFS: progression-free survival; OS: overall survival

* P-value < 0.05; ** P-value < 0.01

Table 3. Analyses for the relationship between clinical features and overall survival
| Clinical features                          | Univariate |   |   |
|-------------------------------------------|------------|---|---|
| Age (>70 years vs ≤70 years)              | 0.77 (0.52-1.11) | 0.1560 |
| Gender (male vs female)                   | 0.56 (0.36-0.79) | 0.0016** |
| Smoking (ever vs never)                   | 0.45 (0.24-0.59) | <0.0001** |
| Stage (IIIb vs IV)                        | 0.52 (0.33-1.03) | 0.0642 |
| Mutation (Del 19 vs L858R vs others)      | -          | <0.0001** |
| Drugs (Afatinib vs Erlotinib vs Gefitinib | -          | 0.2042 |
| Malignant pleural effusion (Yes vs No)    | 0.59 (0.34-0.86) | 0.0099** |
| Brain metastasis (Yes vs No)              | 1.15 (0.74-1.76) | 0.5393 |

| Hematologic markers                       |   |   |   |
|-------------------------------------------|------------|---|---|
| WBC count (>7350/μL vs ≤7350/μL)          | 0.59 (0.40-0.86) | 0.0059** |
| Hb (>12.3g/dL vs ≤12.3g/dL)               | 1.14 (0.78-1.66) | 0.4904 |
| Platelet count (>250K/μL vs ≤250K/μL)     | 0.59 (0.40-0.86) | 0.0059** |
| MPV (>9.6fL vs ≤9.6fL)                    | 1.01 (0.69-1.47) | 0.9764 |
| Neutrophil% (>68.7% vs ≤68.7%)            | 0.43 (0.29-0.62) | <0.0001** |
| Lymphocyte% (>20.8% vs ≤20.8%)            | 2.65 (1.84-3.95) | <0.0001** |

| Inflammatory markers                      |   |   |   |
|-------------------------------------------|------------|---|---|
| Neutrophil-to-lymphocyte ratio (>3.2 vs ≤3.2) | 0.40 (0.27-0.58) | <0.0001** |
| Platelet-to-lymphocyte% ratio (>12200 vs ≤12200) | 0.47 (0.31-0.67) | 0.0001** |

$ Only 186 patients had mean platelet volume (MPV) data; PFS: progression-free survival; OS: overall survival

* P-value < 0.05; ** P-value < 0.01

Figures
Kaplan-Meier curves of progression-free survival and overall survival. Kaplan-Meier curves of progression-free survival and (A) and overall survival (B) constructed based on the lymphocyte percentage (PFS, 9.9 vs 16.3 months, P = 0.0009; OS, 18.07 vs 47.63 months, P < 0.0001). Kaplan-Meier curves of PFS (C) and OS (D) constructed based on the platelet count (PFS, 14.43 vs 10.73 months, P = 0.0478; OS, 27.3 vs 20.17 months, P < 0.0059).