Inflammation-based prognostic scoring system for predicting the prognosis of advanced small cell lung cancer patients receiving anlotinib monotherapy

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Abstract

**Background:** According to the randomized multicenter phase II trial (ALTER1202), anlotinib has been approved as a third-line therapy for advanced small-cell lung cancer (SCLC). Some studies showed the predictive function of inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) in the different cancers treated with anti-vascular targeting drugs. However, none of the studies showed the roles of NLR, PLR, and LMR in SCLC patients receiving anlotinib. Thus, our objective was to establish a scoring system based on inflammation to individuate patient stratification and selection based on NLR, PLR, and LMR.

**Methods:** NLR, PLR, and LMR and their variations were calculated in 53 advanced SCLC patients receiving anlotinib as a third- or further-line treatment at Ningbo Medical Center Lihuili Hospital between January 2019 and December 2021. Kaplan–Meier curves were plotted. Both univariate and multivariate Cox regressions were used to identify predictors of survival.

**Results:** Disease control rate was related to pre-NLR, pre-PLR, pre-LMR, post-NLR elevation, post-PLR elevation, and post-LMR elevation. The multivariate analysis determined post-NLR elevation, pre-PLR > 240.56, and pre-LMR ≤1.61 to be independently associated with progression-free survival, not overall survival. The inflammation-based prognostic scoring system demonstrated favorable predictive ability from the receiver operating characteristic curve (AUC: 0.791, 95% CI: 0.645–0.938).

**Conclusions:** Post-NLR variation, pre-PLR, and pre-LMR were independent prognostic factors for PFS in advanced SCLC receiving anlotinib monotherapy. The inflammation-based prognostic scoring system can accurately predict effectiveness and survival.

**Keywords**

anlotinib, neutrophil to lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), prognostic scoring system, small-cell lung cancer (SCLC)
1 | BACKGROUND

Lung cancer is one of the most common malignancies and a leading cause of cancer-related deaths worldwide. Although small-cell lung cancer (SCLC) accounts for only 15% of all cases, most patients were diagnosed at an advanced stage or with multiple metastases due to its rapid growth ability. The 5-year survival rate is lower than 5%. Recent reports revealed that the longest median overall survival (mOS) of SCLC was 12.9 months. In terms of treatments for advanced SCLC, we are entering the third generation of no breakthrough progress. However, immunotherapy and anti-vascular therapy have prolonged the survival period to a limited extent. In China, anlotinib is one of the most influential anti-vascular targeting drugs. Chinese Society of Clinical Oncology (CSCO) guidelines have approved it as a third-line therapy for advanced SCLC. The tyrosine kinase inhibitor (TKI) anlotinib acts on tumor angiogenesis and proliferation signaling by targeting multiple tyrosine kinases. Several growth factors are targeted by this receptor, including the vascular endothelium growth factor receptors, epidermal growth factor receptor (EGFR), the fibroblast growth factor receptors, the immune-derived growth factor receptor, and the stem cell factor receptor. During the randomized multicenter phase II trial (ALTER1202), disease control rate (DCR) was reported at 71.6%, median progression-free survival (mPFS) was 4.1 months, and mOS was 7.3 months. It works similarly to non-small-cell lung cancer (NSCLC), but its response duration widely varies between people.

Our previous research shows that the predicted model for NSCLC treated with anlotinib based on the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) could screen out patients who may benefit most from anlotinib therapy. Recently, several factors have been identified that may predict the effectiveness of anlotinib. Some adverse reactions to anlotinib treatment, such as hypertension, hand-foot syndrome, and tumor cavitation, may act as prognostic factors in SCLC, which resembles NSCLC. Besides that, studies pointed out that some hematological indicators of inflammation and nutrition are connected with the efficacy of SCLC treatment, including NLR and prognostic nutritional index (PNI). Anlotinib presents some good responses in SCLC and NSCLC and shares several predicted factors, such as NLR. A prognostic scoring system from our earlier research based on NLR and PLR illustrated the different prognoses in NSCLC patients treated with anlotinib. However, none of the studies demonstrated the roles of inflammatory signs, such as PLR and lymphocyte-to-monocyte ratio (LMR), in SCLC patients receiving anlotinib, nor prognostic scoring systems based on different types of efficient biomarkers to predict treatment prognosis better.

Host inflammatory responses contribute significantly to tumor initiation, progression, and symptom response. The predictive value of many clinical inflammation markers has been proven in various tumors, including the most widely discussed NLR and PLR. Recently, some studies exhibited the predictive function of inflammatory markers, including NLR and PLR, in different cancers treated with different anti-vascular targeting drugs. An inflammatory biomarker called LMR was discovered to act with potential predictive value in SCLC. However, no studies have described the predictive value of NLR, PLR, or LMR in SCLC patients receiving anlotinib therapy.

This study performed a retrospective analysis of NLR, PLR, and LMR in advanced SCLC patients given anlotinib as a third or further line of treatment. Furthermore, a related prognostic scoring system was established to screen different benefit groups.

2 | METHODS

2.1 | Patient selection

A retrospective review of anlotinib-treated patients with advanced SCLC was conducted at Ningbo Medical Center Lihuili Hospital from January 2019 to December 2021. The inclusion criteria were as follows: (i) a pathology diagnosis of metastatic or recurrent SCLC at an extensive stage; (ii) had received at least two kinds of chemotherapy previously; (iii) monotherapy with anlotinib for more than 1 cycle; (iv) the data of routine blood test acquisition were taken 2 weeks

| TABLE 1 Patients' basic characteristics | Patients (%) |
|-----------------------------------------|--------------|
| **Characteristics**                     | **Patients (%)** |
| Age (years)                             |               |
| Median                                  | 67 years      |
| Range                                   | 48–80         |
| < 65                                    | 22 (41.5%)    |
| ≥ 65                                    | 31 (58.5%)    |
| Gender                                  |               |
| Male                                    | 51 (96.2%)    |
| Female                                  | 2 (3.8%)      |
| Performance status (ECOG)               |               |
| 0–1                                     | 33 (62.3%)    |
| 2–3                                     | 20 (37.7%)    |
| Smoking history                         |               |
| Yes                                     | 2 (3.8%)      |
| No                                      | 51 (96.2%)    |
| Brain metastases                        |               |
| Yes                                     | 18 (34.0%)    |
| No                                      | 35 (66.0%)    |
| History of thoracic radiotherapy        |               |
| Yes                                     | 30 (56.6%)    |
| No                                      | 23 (43.4%)    |
| History of immunotherapy                |               |
| Yes                                     | 14 (26.4%)    |
| No                                      | 39 (73.6%)    |
| Treatment line of anlotinib             |               |
| 3                                       | 37 (69.8%)    |
| > 3                                     | 16 (30.2%)    |
## TABLE 2  
Associations of NLR, PLR, LMR, and their variations with clinicopathological characteristics

| Characteristics                  | Pre-NLR | Post-NLR variation | Pre-PLR | Post-PLR variation | Pre-LMR | Post-LMR variation |
|----------------------------------|---------|--------------------|---------|--------------------|---------|--------------------|
|                                  | ≤ 3.62 | > 3.62             | p-Value | ≤ 240.56           | > 240.56| p-Value            |
| Age (years)                      |         |                    |         |                    |         |                    |
| < 65                             | 12      | 10                 | 0.983   | 11                 | 9       | 0.908              |
|                                  | (22.6%) | (18.9%)            |         | (20.8%)            | (17.0%) |                    |
| ≥ 65                             | 17      | 14                 | 0.591   | 15                 | 16      | 0.553              |
|                                  | (32.1%) | (26.4%)            |         | (28.3%)            | (30.2%) |                    |
| Performance status               |         |                    |         |                    |         |                    |
| < 0.5                            | 19      | 14                 | 0.591   | 15                 | 18      | 0.500              |
|                                  | (35.8%) | (26.4%)            |         | (28.3%)            | (34.0%) |                    |
| ≥ 0.5                            | 10      | 10                 | 0.691   | 16                 | 11      | 0.693              |
|                                  | (18.9%) | (24.5%)            |         | (22.6%)            | (20.8%) |                    |
| Brain metastases                 |         |                    |         |                    |         |                    |
| Yes                              | 7       | 11                 | 0.097   | 9                  | 9       | 0.922              |
|                                  | (13.2%) | (20.8%)            |         | (17.0%)            | (17.0%) |                    |
| No                               | 22      | 13                 | 0.611   | 16                 | 11      | 0.973              |
|                                  | (41.5%) | (24.5%)            |         | (30.2%)            | (22.6%) |                    |
| History of thoracic radiotherapy |         |                    |         |                    |         |                    |
| Yes                              | 19      | 11                 | 0.150   | 14                 | 16      | 0.693              |
|                                  | (35.8%) | (20.8%)            |         | (26.4%)            | (30.2%) |                    |
| No                               | 10      | 13                 | 0.832   | 12                 | 11      | 1.000^              |
|                                  | (18.9%) | (24.5%)            |         | (22.6%)            | (20.8%) |                    |
| History of immunotherapy         |         |                    |         |                    |         |                    |
| Yes                              | 8       | 6                  | 0.383   | 8                  | 6       | 0.480              |
|                                  | (15.1%) | (11.3%)            |         | (15.1%)            | (11.3%) |                    |
| No                               | 21      | 18                 | 0.480   | 10                 | 7       | 0.679              |
|                                  | (39.6%) | (34.0%)            |         | (7.5%)             | (7.5%)  |                    |
| Treatment line of anlotinib      |         |                    |         |                    |         |                    |
| 3                                | 21      | 16                 | 0.650   | 19                 | 18      | 0.611              |
|                                  | (39.6%) | (30.2%)            |         | (35.8%)            | (34.0%) |                    |
| > 3                              | 8       | 15                 | 0.193   | 9                  | 9       | 0.000              |
|                                  | (15.1%) | (15.1%)            |         | (17.0%)            | (17.0%) |                    |
| Treatment response               |         |                    |         |                    |         |                    |
| DCR                              | 23      | 12                 | 0.025   | 22                 | 13      | 0.005              |
|                                  | (43.4%) | (22.6%)            |         | (41.5%)            | (24.5%) |                    |
| PD                               | 6       | 12                 | 0.005   | 29                 | 6       | 0.004              |
|                                  | (11.4%) | (22.6%)            |         | (15.1%)            | (11.1%) |                    |

^Analyzed with Fisher; the rest analyzed by chi-square test.
before treatment and within 2–4 weeks after treatment; and (v) at least one measurable lesion could be used to evaluate the efficacy following the response evaluation criteria in solid tumors (RECIST 1.1). The exclusion criteria were as follows: (i) clear signs of infection and inflammation and using steroids within the last 2 weeks; (ii) history of liver cirrhosis and autoimmune diseases; and (iii) lack of efficacy evaluation and follow-up information. In the end, 53 patients were enrolled.

2.2 Data collection

Basal clinical characteristics and pathological information were recorded. The routine blood test acquisition data were taken 2 weeks before and within 2–4 weeks after treatment. The NLR was considered as a neutrophil count divided by lymphocyte count, PLR as a platelet count divided by lymphocyte count, and LMR as a lymphocyte count divided by monocyte count. Pre-treatment NLR (pre-NLR) was defined 2 weeks before treatment, while post-treatment NLR (post-NLR) within 2–4 weeks after treatment. Similarly, pre-treatment PLR (pre-PLR), pre-treatment LMR (pre-LMR), post-treatment PLR (post-PLR), and post-treatment LMR (post-LMR) were calculated.

2.3 Clinical assessments and follow-up

Anlotinib was taken daily for 2 weeks, then stopped for 1 week in each cycle. There was no change in treatment until the disease progressed. B-ultrasound imaging and computed tomography scanning were performed as follow-up evaluations every two treatment cycles based on the RECIST1.1. A diagnostic examination was conducted whenever there was a suspicion of recurrence. DCR was calculated as the percentage of patients who had a complete response (CR), a partial response (PR), or stable disease (SD). The percentage of CR and PR was used to calculate the objective response rate (ORR). The period between the beginning of therapy and the last follow-up visit or progression was defined as progression-free survival (PFS). The overall survival (OS) is the period between the start of treatment and the time of death (irrespective of the cause). Our final follow-up date was June 30, 2022.

2.4 Statistical analysis

Receiver operating characteristic (ROC) curve analysis was used to determine the best cutoff values for NLR, PLR, and LMR based on the maximum Youden index. Furthermore, they could differentiate between DCR and progressive disease (PD) based on sensitivity and specificity. Fisher’s exact and chi-square tests were applied. The Kaplan–Meier method was used to draw survival curves. The log-rank test was used to determine any differences. Hazard ratios (HRs) and 95% CIs were calculated. The 5-fold cross-validation validated the multivariable logistic regression model. Statistical significance was defined as \( p < 0.05 \). All analyses were conducted using SPSS (version 26.0, IBM) and R version 4.0.1 (R Foundation for Statistical Computing).

3 RESULTS

3.1 Patient characteristics

Table 1 summarizes the basic characteristics of patients. In total, 45 (84.9%) patients were initially treated with 12 mg/day of anlotinib. There were 53 patients ranging in age from 48 to 80 years old, with a median age of 67. Among them, seven patients were diagnosed as IVA stage and the rest were IVB stage. Eighteen (34.0%) of them were diagnosed with brain metastases, 16 (30.2%) of whom had received fourth-line therapy or higher, 14 (26.4%) of them had previously received immunotherapy, and 32 (60.4%) had previously accepted thoracic radiotherapy. In addition, all the patients with brain metastases underwent whole brain radiotherapy.

The best cutoff values of pre-NLR, pre-PLR, and pre-LMR were 3.62, 240.56, and 1.61, respectively. The area under the curve (AUC) of them were 0.692 (95% CI: 0.546–0.838; Figure S1A,B), 0.683 (95% CI: 0.524–0.841) (Figure S1C,D), and 0.697 (95% CI: 0.544–0.849; Figure S1E,F). In total, 24 (45.3%) patients had a high pre-NLR > 3.62 and 29 (54.7%) had a low pre-NLR ≤ 3.62. Moreover, 16 (30.2%) patients had a high pre-PLR > 240.56 and 37 (69.8%) had a low pre-PLR ≤ 240.56. Furthermore, 33 (62.3%) patients had a high pre-LMR > 1.61, and 20 (37.7%) had a low pre-LMR ≤ 1.61. Post-NLR elevation, post-PLR elevation, and post-LMR elevation were 27 (50.9%) patients, 24 (45.3%) patients, and 24 (45.3%) patients, respectively. A median follow-up time of 20.8 months was observed (0.8 to 25.4 months). All the patients ended up with a progressive disease. Neither of them achieved CR. Moreover, 4 (7.5%), 31 (58.5%), and 18 (34.0%) patients achieved PR, SD, and PD, respectively. In the entire cohort of patients, mPFS and mOS were 3.0 and 7.2 months, respectively.

3.2 Relevance between NLR, PLR, and LMR and their variations with clinicopathological parameters and treatment response

There was no correlation between NLR, PLR, or LMR and their variations with clinicopathological parameters, including performance status (PS) scores, the history of chest radiotherapy or immunotherapy, brain metastases or not, and the lines of treatment. Interestingly, the optimal cutoff value of ROC curve shows that a low DCR was associated with a high pre-NLR \( (p = 0.025) \), high pre-PLR \( (p = 0.004) \), low pre-LMR \( (p = 0.012) \), post-NLR elevation...
(p = 0.005), post-PLR elevation (p = 0.025), and post-LMR elevation (p = 0.016) (Table 2).

### 3.3 | Factors associated with prognosis

Except for post-LMR elevation, univariate analysis revealed that it was unrelated to FPS (p = 0.093) (Figure 1A) or OS (p = 0.140) (Figure 1B). The below elements, including pre-NLR > 3.62, post-NLR elevation, pre-PLR > 240.56, post-PLR elevation, and post-LMR ≤ 1.61, were significant risk factors for a poor PFS or OS (Table 3). In patients with pre-NLR > 3.62, mPFS and mOS were markedly shorter than the others (2.0 months vs. 3.5 months, HR: 2.015, 95% CI: 1.141–3.558, p = 0.016 [Figure 2A]; 4.5 months vs. 7.8 months, HR: 2.270, 95% CI: 1.123–4.175, p = 0.008 [Figure 2B]). mPFS and mOS in elevated post-NLR patients were significantly shorter than those in non-elevated patients (2.0 months vs. 4.5 months, HR: 2.576, 95% CI: 1.419–4.677, p < 0.001 [Figure 3A]; 3.9 months vs. 8.4 months, HR: 2.307, 95% CI: 1.268–4.196, p = 0.005 [Figure 3B]). Among patients with pre-PLR > 240.56, mPFS and mOS were significantly less in patients with lower values (1.5 months vs. 4.0 months, HR: 2.756, 95% CI: 1.419–4.677, p < 0.001 [Figure 4A]; 3.0 months vs. 7.6 months, HR: 2.134, 95% CI: 1.145–3.979, p = 0.014 [Figure 4B]). For elevated post-PLR, mPFS and mOS were markedly less than their non-elevated counterparts (2.5 months vs. 4.0 months, HR: 1.943, 95% CI: 1.085–3.479, p = 0.017 [Figure 5A]; 3.9 months vs. 8.4 months, HR: 2.645, 95% CI: 1.395–5.014, p = 0.002 [Figure 5B]). In patients with pre-LMR ≤ 1.61, mPFS and mOS were significantly longer than patients with lower values (4.5 months vs. 1.5 months, HR: 0.274, 95% CI: 0.140–0.536, p < 0.001 [Figure 6A]; 8.2 months vs. 3.9 months, HR: 0.381, 95% CI: 0.202–0.720, p = 0.002 [Figure 6B]). In addition, post-NLR elevation and pre-PLR > 240.56 were independent risk factors for poor PFS by multivariate analysis, and pre-LMR ≤ 1.61 was an independent protective factor for PFS by multivariate analysis, but unfortunately not for OS (Table 4).

### 3.4 | Establishment of the prognostic scoring system

The multivariate analysis led to establishment of a prognostic scoring system based on independent prognostic factors. There was a 1-point increase in risk score for each risk factor. Scores can be assigned from 0 (extremely favorable) to 3 (extremely unfavorable) based on these factors. It was found that different scores led to different treatment responses and prognoses (Table 5). This inflammation-based prognostic scoring system exhibited favorable predictive ability from the ROC curve (AUC: 0.791, 95% CI: 0.645–0.938) (Figure 7). Patients with scores > 1 had a significantly lower DCR (11.3% vs. 54.7%, p < 0.001) compared to patients with score ≤ 1, and patients with score > 2 had a significantly lower DCR (0% vs. 66.0%, p < 0.001) than those with score ≤ 2. However, patients with scores = 0 manifested no difference compared to patients with score > 0 (22.6% vs. 43.4%, p = 0.177). When analyzing PFS according to the inflammation-based prognostic scoring system, patients with at least one score owned a 2.82 times higher risk of disease progression than patients with zero score (mPFS 1.5 vs. 4.5 months, 95% CI: 1.444–5.512, p = 0.001). The patients with at least 2-score owned 5.02 times the risk (mPFS 1.5 vs. 4.5 months, 95% CI: 2.517–10.021, p < 0.001). Moreover,
| Prognostic factors | Progression-free survival | Overall survival |
|--------------------|---------------------------|-----------------|
|                    | HR | 95% CI       | p-Value | HR | 95% CI       | p-Value |
| Age (years)        |    |              |         |    |              |         |
| < 65               | 1  |              |         | 1  |              |         |
| ≥ 65               | 0.582 | 0.322–1.054 | 0.074   | 0.779 | 0.430–1.410 | 0.409   |
| Performance status (ECOG) |    |              |         |    |              |         |
| 0–1                | 1  |              |         | 1  |              |         |
| 2–3                | 1.063 | 0.601–1.880 | 0.835   | 0.976 | 0.536–1.777 | 0.936   |
| Brain metastases   |    |              |         |    |              |         |
| No                 | 1  |              |         | 1  |              |         |
| Yes                | 1.603 | 0.872–2.946 | 0.129   | 1.610 | 0.865–2.998 | 0.133   |
| History of thoracic radiotherapy |    |              |         |    |              |         |
| No                 | 1  |              |         | 1  |              |         |
| Yes                | 0.926 | 0.534–1.606 | 0.785   | 0.684 | 0.382–1.226 | 0.202   |
| History of immunotherapy |    |              |         |    |              |         |
| No                 | 1  |              |         | 1  |              |         |
| Yes                | 0.742 | 0.395–1.394 | 0.353   | 0.686 | 0.347–1.357 | 0.279   |
| Treatment line of anlotinib |    |              |         |    |              |         |
| 3                  | 1  |              |         | 1  |              |         |
| > 3                | 1.363 | 0.733–2.532 | 0.328   | 1.236 | 0.648–2.358 | 0.520   |
| Pre-NLR            |    |              |         |    |              |         |
| ≤ 3.62             | 1  |              |         | 1  |              |         |
| > 3.62             | 2.015 | 1.141–3.558 | 0.016   | 2.270 | 1.234–4.175 | 0.008   |
| Post-NLR variation |    |              |         |    |              |         |
| Decrease           | 1  |              |         | 1  |              |         |
| Rise               | 2.576 | 1.419–4.677 | 0.001   | 2.307 | 1.268–4.196 | 0.005   |
| Pre-PLR            |    |              |         |    |              |         |
| ≤ 240.56           | 1  |              |         | 1  |              |         |
| > 240.56           | 3.335 | 1.718–6.473 | 0.001   | 2.134 | 1.145–3.979 | 0.014   |
| Post-PLR variation |    |              |         |    |              |         |
| Decrease           | 1  |              |         | 1  |              |         |
| Rise               | 1.943 | 1.085–3.479 | 0.017   | 2.645 | 1.395–5.014 | 0.002   |
| Pre-LMR            |    |              |         |    |              |         |
| ≤ 1.61             | 1  |              |         | 1  |              |         |
| > 1.61             | 0.274 | 0.140–0.536 | 0.001   | 0.381 | 0.202–0.720 | 0.002   |
| Post-LMR variation |    |              |         |    |              |         |
| Decrease           | 1  |              |         | 1  |              |         |
| Rise               | 0.636 | 0.364–1.111 | 0.093   | 0.645 | 0.357–1.166 | 0.140   |

**TABLE 3** Univariate analysis of factors associated with progression-free survival and overall survival.
the patients with 3-score were 8.75 times higher in risk (mPFS 0.8 vs. 3.5 months, 95% CI: 3.156–24.254, p < 0.001) (Figure 8). Assessing OS similarly, patients with at least one score manifested 2.56 times risk of death compared to patients with zero score (mOS 4.6 vs. 11.4 months, 95% CI: 1.245–5.257, p = 0.008). The patients with at least a 2-score manifested a 3.47 times higher risk of death than those with a below 2-score (mOS 3.0 vs. 8.2 months, 95% CI: 1.838–6.546, p < 0.001), and the patients with three score owned 3.14 times higher the risk (mOS 2.5 vs. 7.3 months, 95% CI: 1.367–7.189, p = 0.004) (Figure 9).

4 | DISCUSSION

The PFS resulting from this research was similar to another related retrospective study (mPFS: 2.6 months). However, while...
comparing it with ALTER-1202, we found a slight difference in the treatment response (DCR 66.0% compared to 71.6%, PFS 3.0 vs. 4.1, OS 7.2 vs. 7.3). We researchers came to the following conclusions. The first is that the clinical inclusion criteria were less stringent than the written statement. This factor resulted in differences in basal characteristics. All the patients in this study were diagnosed with stage IV, while only 13.6% of ALTER1202 patients were diagnosed with stage I-III. In addition, 37% of our patients were evaluated with more than 2-score in PS score, and 34% had brain metastasis. However, only 4.9% of patients got more than 2-score, and 24.7% experienced brain metastasis in ALTER1202. Second, we evaluated the curative effect of imaging soon after the first cycle of anlotinib treatment in patients with some discomfort symptoms, reducing PFS time by detecting PD cases in time. Finally,
as a third- or further-line treatment for advanced SCLC patients, anlotinib exhibits a moderate but indisputable survival benefit. Despite receiving second-line standard treatment, this advantage is sufficient for patients with poor survival. Therefore, it is important to screen the benefit population of anlotinib treatment by methods. Recently, three retrospective studies about SCLC treatment with anlotinib had tried to select some ways to identify those benefit patients, which indicated that the response to first-line treatment,\textsuperscript{22} prognostic nutritional indexes,\textsuperscript{11} and tumor cavitation\textsuperscript{9} could predict survival independently, yet all through relatively simple means. Our team once established a system of risk scores by different combinations of multiple inflammatory indicators in NSCLC, which

\begin{table}[h]
\centering
\caption{Multivariable analysis of factors associated with progression-free survival and overall survival.}
\begin{tabular}{|l|l|l|l|l|l|l|}
\hline
Prognostic factors & Progression-free survival & & Overall survival & & \\
 & HR & 95\% CI & \textit{p}-Value & HR & 95\% CI & \textit{p}-Value \\
\hline
Post-NLR variation (≤3.62 vs >3.62) & 2.995 & 1.366–6.565 & 0.006 & 1.705 & 0.819–3.549 & 0.154 \\
Pre-PLR (≤240.56 vs >240.56) & 3.977 & 1.771–8.932 & 0.001 & 1.660 & 0.733–3.761 & 0.225 \\
Pre-LMR (decrease vs rise) & 0.462 & 0.218–0.979 & 0.044 & 0.773 & 0.342–1.744 & 0.534 \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Treatment response and prognosis for different patient scores stratified according to independent prognostic factors (post-NLR variation, pre-PLR, and pre-LMR).}
\begin{tabular}{|l|l|l|l|l|l|l|}
\hline
Treatment response and prognosis & Score & \\
 & 0 & 1 & 2 & 3 & \\
\hline
DCR & 13 (81.3\%) & 16 (88.9\%) & 6 (50.0\%) & 0 (0.0\%) & 0.001\textsuperscript{a} \\
PD & 3 (18.7\%) & 2 (11.1\%) & 6 (50.0\%) & 7 (100.0\%) & \\
mPFS (months) & 8.0 & 3.5 & 2.0 & 0.8 & 0.001 \\
mOS (months) & 11.4 & 7.8 & 3.4 & 2.5 & \\
\hline
\end{tabular}
\end{table}

\textit{Note:} 0: patients negative for all the risk factors (post-NLR variation, pre-PLR, and pre-LMR). 1: patients with 1 of the above mentioned prognostic factors. 2: patients with two of the three prognostic factors. 3: patients with all the three risk factors. aAnalyzed with Fisher.
was capable of predicting the best population for anlotinib treatment. Therefore, this study was focused on developing a prognostic scoring system in SCLC that included NLR, PLR, and LMR and successfully selecting the dominant population, which was bound to be more comprehensive than a single prognostic factor as previously described. The inflammation-based prognostic scoring system revealed favorable predictive ability from the ROC curve (AUC: 0.791) (Figure 7).

At the time, researchers believed that there was a link between pre-treatment inflammatory marker status and cancer prognosis, and inflammatory markers would change as tumors developed. The most frequently used and easily available inflammatory markers in clinical were NLR, PLR, and LMR. They could be used as prognostic factors in SCLC patients treated in various ways, including surgery, radiochemotherapy, and immunotherapy. However, only NLR had been discussed as a prognostic inflammatory marker in SCLC patients who received anlotinib, an anti-vascular targeting drug. For the first time, this research focused on the variation of the three inflammatory factors called NLR, PLR, and LMR before and after the anlotinib treatment in SCLC so that we could evaluate their prognostic values entirely and systematically. The result indicated a significant correlation between the change of those factors and the DCR in anlotinib treatment. Furthermore, the outcomes revealed that the post-NLR elevation, pre-PLR > 240.56, and pre-LMR < 1.61 were independent prognostic factors of PFS but not OS. It could be due to the various follow-up treatments or other unknown factors. Our study found that post-NLR elevation was an independent prognostic factor of PFS but not for OS, as Cuicui Zhang et al. described. Although we found similar results in this study but did not share the same cut-off value, which is 240.56 in SCLC and 205.63 in NSCLC, the conclusion from our previous study about NSCLC patients receiving anlotinib indicated that high pre-PLR was related to poor outcome. This phenomenon revealed the existence of different tumors with different cutoff values and the possibility of the difference being caused by insufficient sample capacity. In order to improve the predictive ability of the anlotinib drug, we set up an inflammatory-based prognostic score system according to the independent prognostic factors from our research (post-NLR elevation, pre-PLR > 240.56, and pre-LMR < 1.61). The four grades from 0 to 3 could distinguish PFS and OS. The mPFS of patients scored 0–3 points was 8.5 months, 3.5 months, 2.0 months, and 0.8 months, respectively. The mOS was 11.4 months, 7.8 months, 3.4 months, and 2.5 months.

According to the study, we supplemented the predictive efficacy value of NLR, PLR, and LMR and their changes in SCLC patients treated with anlotinib. Furthermore, we established an inflammatory-based prognostic scoring system that could be used more simply and comprehensively. This system deserves further research and promotion as another new-built inflammatory factor prediction model. However, our study was limited because it was a single-center study with small sample size. Only seven people got 3 points in it. Our study cohort was relatively limited representing in mostly males, the lack of race, and so on. These factors contributed to varying degrees of bias. As a result of the moderate accuracy of pre-NLR, pre-PLR, and pre-LMR AUCs in the cutoff value determined by ROC analysis (0.692, 0.683, and 0.697, respectively) in the present data, there was some uncertainty in these data. In addition, these specific cutoff values were analyzed through this retrospective small sample data, which was insufficient to represent all SCLC populations. Finally, the different treatment factors before and after anlotinib were excluded from this prognostic scoring system, which might lead to a decline in the predictive value of OS. As a result, prospective studies with large sample sizes and strict inclusion criteria are needed to back up and strengthen the findings of this study.

5 | CONCLUSIONS

Inflammation-based prognostic scoring systems are generally inexpensive and easy to use with some relationship to treatment response. They can also accurately predict the PFS and OS for advanced SCLC patients treated with anlotinib monotherapy. Furthermore, this stratified risk evaluation system can be used to judge whether the patients can get benefit and the degree of it on anlotinib monotherapy stratified risk evaluation. Patients who scored less than 1 point on the inflammation-based prognostic scoring system had superior effectiveness and survival, as measured by a higher DCR, longer mPFS, and mOS.
FIGURE 8  Progression-free survival according to the inflammation-based prognostic scoring system (A, \( p = 0.001 \), (B, \( p < 0.001 \), (C, \( p < 0.001 \)) based on post-NLR elevation (+1), pre-PLR > 240.56 (+1), and pre-LMR ≤1.61 (+1).
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AUTHOR CONTRIBUTIONS
Tian Chen and Weiyu Shen contributed to the conception and design of the study. Tian Chen and Mengqiu Tang wrote the article together. Xiaoyu Xu, Gaofeng Liang, and Chen Wang contributed to the acquisition and analysis of the data. Zhenfei Xiang and Yi Lu participated in revising of the article.

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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES
1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33.
2. Yang S, Zhang Z, Wang Q. Emerging therapies for small cell lung cancer. J Hematol Oncol. 2019;12(1):47.
3. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2021;22(1):51-65.

4. Sun Y, Niu W, Du F, et al. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. J Hematol Oncol. 2016;9(1):105.

5. Cheng Y, Wang Q, Li K, et al. Anlotinib vs placebo as third- or further-line treatment for patients with small cell lung cancer: a randomised, double-blind, placebo-controlled phase 2 study. Br J Cancer. 2021;125(3):366-371.

6. Han B, Li K, Wang Q, et al. Effect of Anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: the ALTER 0303 phase 3 randomized clinical trial. JAMA Oncol. 2018;4(11):1569-1575.

7. Chen T, Song C, Liang G, et al. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and their variations as a basis for a prediction model in advanced NSCLC patients receiving anlotinib. Dis Markers. 2022;2022:5879137.

8. Song PF, Xu N, Li Q. Efficacy and safety of anlotinib for elderly patients with previously treated extensive-stage SCLC and the prognostic significance of common adverse reactions. Cancer Manag Res. 2020;12:11133-11143.

9. Chen D, Xu J, Zhao Y, et al. Prognostic value of tumor cavitation in extensive-stage small-cell lung cancer patients treated with anlotinib. J Cancer Res Clin Oncol. 2020;146(2):401-406.

10. Zhang C, Wang J, Wang X, et al. Peripheral blood indices to predict PFS/OS with anlotinib as a subsequent treatment in advanced small-cell lung cancer. Cancer Biol Med. 2021;19(8):1249-1258.

11. Liu J, Li S, Zhang S, et al. Pretreatment prognostic nutritional index is a prognostic marker for extensive-stage small cell lung cancer patients treated with anlotinib. J Thorac Dis. 2020;12(10):5765-5773.

12. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454(7203):436-444.

13. Guthrie GJ, Charles KA, Roxburgh CS, et al. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013;88(1):218-230.

14. Stotz M, Gerger A, Eisner F, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Br J Cancer. 2013;109(2):416-421.

15. Yodying H, Matsuda A, Miyashita M, et al. Prognostic significance of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: a systematic review and meta-analysis. Ann Surg Oncol. 2016;23(2):646-654.

16. Pinato DJ, Shiner RJ, Seckl MJ, Stebbing J, Sharma R, Mauri FA. Prognostic performance of inflammation-based prognostic indices in primary operable non-small cell lung cancer. Br J Cancer. 2014;110(8):1930-1935.

17. Templeton AJ, Age O, McNamara MG, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2014;23(7):1204-1212.

18. Tada T, Kumada T, Hiraoka A, et al. Neutrophil-to-lymphocyte ratio is associated with survival in patients with unresectable hepatocellular carcinoma treated with lenvatinib. Liver Int. 2020;40(4):968-976.

19. Fukuda N, Toda K, Fujiwara YU, et al. Neutrophil-to-lymphocyte ratio as a prognostic marker for anaplastic thyroid cancer treated with lenvatinib. In Vivo. 2020;34(5):2859-2864.

20. del Prete M, Giampieri R, Loupakis F, et al. Prognostic clinical factors in pretreated colorectal cancer patients receiving regorafenib: implications for clinical management. Oncotarget. 2015;6(32):33982-33992.

21. Lang C, Egger F, Alireza Hoda M, et al. Lymphocyte-to-monocyte ratio is an independent prognostic factor in surgically treated small cell lung cancer: an international multicenter analysis. Lung Cancer. 2022;169:40-46.

22. Qin B, Xin L, Hou Q, et al. Response to first-line treatment predicts progression-free survival benefit of small-cell lung cancer patients treated with anlotinib. Cancer Med. 2021;10(12):3896-3904.

23. Chen C, Yang H, Cai D, Xiang L, Fang W, Wang R. Preoperative peripheral blood neutrophil-to-lymphocyte ratios (NLR) and platelet-to-lymphocyte ratio (PLR) related nomograms predict the survival of patients with limited-stage small-cell lung cancer. Transl Lung Cancer Res. 2021;10(2):866-877.

24. Drpa G, Sutic M, Baranasic J, et al. Neutrophil-to-lymphocyte ratio can predict outcome in extensive-stage small cell lung cancer. Radiol Oncol. 2020;54(4):437-446.

25. Qi J, Zhang J, Ge X, et al. The addition of peripheral blood inflammatory indexes to nomogram improves the predictive accuracy of survival in limited-stage small cell lung cancer patients. Front Oncol. 2021;11:713014.

26. Xiong Q, Huang Z, Xin L, et al. Post-treatment neutrophil-to-lymphocyte ratio (NLR) predicts response to anti-PD-1/PD-L1 antibody in SCLC patients at early phase. Cancer Immunol Immunother. 2021;70(3):713-720.

SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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