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Original Article

A comparative study of the efficacy and safety of PD-1/L1 inhibitor and platinum-containing dual-agent chemotherapy in patients with advanced non-small cell lung cancer resistant to EGFR-TKIs

Chunhui Shi, Xiaochun Liu, Jing Zhao, Wenjiang Xu, Rui Zhang, Zhongqin He

Department of Oncology, Baoji Traditional Chinese Medicine Hospital, No. 43 Baofu Road, Jintai District, Baoji 721000, Shaanxi, China

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Abstract: Objective: To assess the efficacy and safety of combining Programmed Death-1/Programmed Death-Ligand 1 (PD-1/L1) inhibitors with platinum-containing chemotherapy for treating late-stage Non-Small Cell Lung Cancer (NSCLC) patients who have developed resistance to Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors (EGFR-TKIs). Methods: A retrospective analysis was conducted at Baoji Traditional Chinese Medicine Hospital involving 133 patients with advanced NSCLC who had shown resistance to EGFR-TKIs and were treated from October 2018 to May 2021. The cohort was categorized into two groups: one treated with immune checkpoint inhibitors (ICIs) plus chemotherapy and antiangiogenic agents (ICIs+BCP group), and the other treated with ICIs alone (ICIs group). Baseline data collected included demographic factors, smoking status, PD-L1 Tumor Proportion Score (TPS), EGFR mutation, Eastern Cooperative Oncology Group (ECOG) score, and routine blood markers prior to second-line therapy. Computed Tomography (CT) scans were performed every two treatment courses to evaluate the treatment efficacy. Results: The ICIs+BCP group exhibited a statistically significant improvement in Overall Survival (OS) compared to the ICIs group (P=0.001). Cox survival analysis uncovered age (P=0.012), PD-L1 TPS expression (P<0.001), treatment regimen (P=0.006), Neutrophil-to-Lymphocyte Ratio (NLR) (P=0.024), and Platelet-to-Lymphocyte Ratio (PLR) (P=0.005) as independent factors influencing OS in patients with advanced NSCLC resistant to primary-line EGFR-TKI therapy. The nomogram model, based on these prognostic factors, exhibited Area Under the Curve (AUC) values of 0.823 and 0.769, indicating its predictive accuracy for 1-year and 2-year survival, respectively. Conclusion: Combining ICIs with BCP prolongs OS in patients with NSCLC resistant to EGFR-TKIs. This study underscores the importance of personalized treatment plans and biomarker evaluations to improve outcomes in drug-resistant cases.

Keywords: Programmed death-1, programmed death-ligand 1 chemotherapy, advanced non-small cell lung cancer, epidermal growth factor receptor-tyrosine kinase inhibitors resistance, efficacy

Introduction

Malignant tumors, with lung cancer (LC) at the forefront, pose considerable challenges to health systems worldwide, impacting both economic and health outcomes [1]. According to World Health Organization data from 2018, LC is accounts for approximately 2.2 million new cases annually, constituting 11.4% of all new cancer diagnoses and leading to around 1.79 million deaths. This represents 18% of total cancer-related fatalities, making it the leading cause of cancer-related mortality [2]. In China, LC maintains its status as the most widespread and lethal cancer, with an incidence rate of 59.89 per 100,000 individuals and a mortality rate of 47.51 per 100,000 individuals [3]. LC is primarily categorized into two main forms: Non-Small Cell Lung Cancer (NSCLC) and small cell lung cancer. NSCLC constitutes approximately 85% of all cases and is characterized by its aggressive nature and propensity for metastasis [4].

Genetic alterations in the Epidermal Growth Factor Receptor (EGFR) are common in NSCLC,

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seen in 18.9%-51.4% of cases. Tyrosine Kinase Inhibitors (TKIs) targeting EGFR effectively impede tumor growth by inhibiting downstream signaling pathways [5]. High-frequency EGFR genetic alterations, including exon 19 deletions and exon 21 L858R point mutations, have been identified as prime targets for EGFR-TKI therapies [6]. The U.S. Food and Drug Administration approved the initial EGFR-TKIs, such as erlotinib and gefitinib, in 2013 for the first-line treatment of metastatic NSCLC patients with EGFR 19DEL or 21L858R mutations [7]. Although first- and second-generation EGFR-TKIs have demonstrated significant advantages in terms of Progression-Free Survival (PFS), safety, and tolerability, approximately half of the treated patients eventually acquire resistance to these therapies [8]. The third-generation EGFR-TKI, osimertinib, acts by irreversibly binding to the EGFR receptor to suppress kinase activation and downstream signaling, showing notable efficacy and prolonged survival in patients with the T790M mutation [9, 10].

The optimal treatment plan for patients with drug-resistant NSCLC who lack the T790M mutation remains controversial. The National Comprehensive Cancer Network advocates for a tailored approach based on individual patient factors, such as continuing osimertinib and offering localized treatments for oligometastases [11]. In contrast, the European Society for Medical Oncology recommends platinum-containing dual-agent chemotherapy following disease progression. However, the effectiveness of this strategy remains uncertain [12-14]. Immune checkpoint inhibitors targeting the Programmed Death-1 (PD-1) and Programmed Death-Ligand 1 (PD-L1) pathway have introduced new treatment options in NSCLC [15, 16]. Although results for PD-1/PD-L1 inhibitors in patients with EGFR mutation-positive NSCLC have been mixed, their application in specific patient groups shows encouraging efficacy. This suggests that PD-1/PD-L1 inhibitors, especially in combination with chemotherapy or antiangiogenic therapy, could serve as a viable second-line therapy option after EGFR-TKI resistance.

Focusing on NSCLC patients who have developed resistance to EGFR-TKIs, this study explores the potential of immune checkpoint inhibitors, aiming to address the controversies and challenges currently facing clinical practice. Examining the combination of immunotherapy with other therapeutic modalities seeks to delineate a more precise and efficacious treatment strategy for patients with NSCLC.

Methods and data

Case sources

This retrospective analysis focused on 133 participants with advanced NSCLC who developed resistance to EGFR-TKIs. These participants received treatment at Baoji Traditional Chinese Medicine Hospital from October 2018 to May 2021. This study was approved by the Ethic Committee of Baoji Traditional Chinese Medicine Hospital.

Requirements for inclusion and exclusion

Criteria for participant inclusion: 1) Age above 18 years old; 2) NSCLC diagnosis confirmed via histological or cytological analysis, following the 8th edition AJCC diagnostic criteria for LC and TNM classification for stage IV disease [17]; 3) At least one measurable lesion based on RECIST 1.1 guidelines [18]; 4) Presence of an EGFR driver mutation confirmed through next-generation sequencing, possibly accompanied by other driver mutations; 5) Previous administration of first- or second-generation EGFR-TKIs as primary-line therapy; 6) Disease deterioration after primary-line therapy with EGFR-TKIs; and 7) EGFR T790M mutation found to be negative using next-generation sequencing following resistance to primary-line therapy [19].

Criteria for participant exclusion: 1) EGFR driver gene test results negative at initial diagnosis; 2) Simultaneous use of other treatments, such as chemotherapy or radiotherapy, with first-line EGFR-TKI therapy; 3) Positive T790M mutation detected through next-generation sequencing after resistance to primary-line therapy with EGFR-TKIs; 4) Difficulty in managing subsequent treatments due to severe toxic reactions; 5) Incomplete clinical data, limiting comprehensive analysis.

Sample grouping

Patients meeting the inclusion criteria were divided based on the second-line treatment received: the immune checkpoint inhibitors plus chemotherapy and antiangiogenic drugs group (ICIs+BCP group, n=59) and the ICIs

Table 1. ICIs Specifications and use methods of chemotherapy drugs

Drug Name	Specification	Usage
Teraplizumab (Topic), S20202002, Suzhou Zhonghe Biomedical Technology Co.	3 mg/kg	Intravenous every 2 weeks
Duvarizumab (Infinavir), S20190039, Catalent Indiana	10 mg/kg	Intravenous every 2 weeks
Bevacizumab, S20210020, Suzhou Shengdia Biopharmaceutical Co.	15 mg/kg	IV every 3 weeks
Pemetrexed, SDA H20143380, Yangzijiang Pharmaceutical Group Co.	500 mg/m^2	IV every 3 weeks
Cisplatin, H21020212, Jinzhou Jutai Pharmaceutical Co.	75 mg/m^2	IV every 3 weeks
Paclitaxel, H20065071, Hainan General Kangli Pharmaceutical Co.	135-175 mg/m^2	IV every 3 weeks
Docetaxel, H20198003, Guangdong Xinghao Pharmaceutical Co.	70 mg/m^2	IV every 3 weeks
Albumin Paclitaxel, China Drug License H20193309, Qilu Pharmaceutical (Hainan) Co.	260 mg/m^2	IV every 3 weeks
Pembrolizumab (Koraida), SJ20180019, MSD Ireland	200 mg	IV every 3 weeks
Karelizumab (Elitol), S20190027, Suzhou Shengdia Bio-pharmaceutical Co.	200 mg	IV every 3 weeks
Tirilizumab (Bazedan), S20190045, Guangzhou Baiji Shenzhou Biopharmaceutical Co.	200 mg	IV every 3 weeks
Sindilizumab (Darbepoetin), S20180016, Cinda Biopharmaceutical (Suzhou) Co.	200 mg	IV every 3 weeks
Atilizumab (Taishengqi), S20200004, Roche Diagnostics GmbH	1200 mg	IV every 3 weeks
Gemcitabine, H20113371, Tatsunobu Pharmaceutical Co.	1000-1250 mg/m^2	IV every 3 weeks (Day 1, Day 8)
Anrotinib, China National Drug License H20180004, Zhengda Tianqing Pharmaceutical Group Co.	12 mg	2 weeks of continuous dosing, 1 week off, 3-week course of treatment

Note: IV: Intravenous, ICIs+BCP: immune checkpoint inhibitors plus chemotherapy and antiangiogenic agents.

monotherapy group (ICIs group, n=74). ICIs used included pembrolizumab, nivolumab, and others, while the chemotherapeutic agents were pemetrexed and cisplatin. Bevacizumab and erlotinib were the antiangiogenic drugs utilized (**Table 1**).

Clinical data retrieval

Clinical data were comprehensively gathered from electronic health records, outpatient reports, and in-hospital follow-up logs. Key details included gender, patient age, Body Mass Index (BMI), smoking history, and Eastern Cooperative Oncology Group (ECOG) Performance Status Score [19], as well as smoking prevalence. Additional data included Epidermal Growth Factor Receptor (EGFR) mutation types, PD-L1 Tumor Proportion Score (TPS), Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Lymphocyte-to-Monocyte Ratio (LMR). ECOG scores, EGFR mutation types, and PD-L1 TPS were assessed during patient intake, while NLR, PLR, and LMR were evaluated at initial admission.

Follow up

The follow-up period ended in January 2022. Throughout this time, essential outcome indicators like Overall Survival (OS), Overall Response Rate (ORR), and Disease Control Rate (DCR) were carefully calculated for all study participants.

Outcome measures

Primary outcome measures included comparing the treatment outcomes and OS of the ICIs+BCP and ICIs groups and using Cox survival analysis to reveal prognostic factors for EGFR-TKIs resistance. Secondary outcome measures involved evaluating baseline data, constructing a nomogram to predict 1- and 2-year survival probabilities, and assessing the model's clinical utility through time-dependent Receiver Operating Characteristic (ROC) curves, survival calibration curves, and Decision Curve Analysis (DCA) (**Figure 1**).

Statistical analysis

GraphPad Prism 9 was used to manipulate and visualize the collected data for graphical analysis. The data were analyzed using SPSS 26.0 (SPSS Inc., USA). Statistical analysis was conducted on count data, expressed as percentages (%), using the chi-squared test. Cox survival analysis was utilized to analyze the prognostic factors influencing OS in patients with advanced EGFR-TKI resistance. Kaplan-Meier curves were used to analyze the effectiveness of different treatment regimens on patients' OS. The "rmda" package was used for DCA plotting, the "rocr" package for time-dependent ROC curve plotting, and the "rms" package for calibration curve plotting and C-index calculation. A p-value <0.05 indicated statistical significance.

Figure 1. Flow chart of sample acquisition and screening.

Results

Assessment of baseline patient characteristics

Both groups exhibited similarities in age, sex, BMI, ECOG score, EGFR mutation sites, smoking history, PD-L1 TPS expression, NLR, PLR, and LMR (all P>0.05, **Table 2**).

Assessment of clinical efficacy

When comparing the clinical outcomes of patients, the two groups exhibited similarities in ORR (P=0.455) and DCR (P=0.260) between patients (**Table 3**).

Assessment of patient survival

OS was evaluated in both groups. The results showed that the mean OS in the ICIs+BCP group was 450 d, while that in the ICIs group was 160 d, which was statistically different (P=0.001, **Figure 2**).

Analysis of survival outcomes in patients with resistance to EGFR TKIs

The prognostic factors affecting survival in EGFR-TKI-resistant patients were analyzed by Cox regression. Data were clustered using NLR, PLR, and LMR, and grouped using X-tile software (**Table 4**). Univariate analysis revealed that age (P=0.037), PD-L1 TPS expression (P<0.001), treatment regimen (P=0.002), NLR (P<0.001), and PLR (P=0.003) were associated with patient OS (**Table 5**). Subsequently, multivariate analysis further identified that age (P=0.012), PD-L1 TPS expression (P<0.001), treatment regimen (P=0.006), NLR (P=0.024), and PLR (P=0.005) independently influenced OS in EGFR TKIs-resistant patients (**Table 6**).

Table 2. Comparison of patients' baseline data

Considerations	ICIs+BCP group (n=59)	ICIs group (n=74)	χ^2/t/Z value	*P*-value
Age				
≥65 years	37	42	0.483	0.487
<65 years	22	32		
Gender				
Male	39	54	0.737	0.391
Female	20	20		
BMI				
≥25 kg/m^2	17	15	1.311	0.252
<25 kg/m^2	42	59		
Smoking history				
Yes	45	47	2.506	0.113
No	14	27		
ECOG score				
<1	38	56	1.66	0.198
≥1	21	19		
EGFR mutation type				
19del	41	58	1.362	0.243
21L858R	18	16		
PD-L1 TPS expression				
<1%	41	59	1.844	0.174
≥1%	18	15	0.483	0.487
NLR	2.86 [2.22, 3.32]	3.00 [2.08, 3.88]	-0.79	0.431
PLR	113.91±32.90	123.03±29.23	-1.668	0.098
LMR	4.52±1.42	4.39±1.44	0.491	0.625

Note: BMI: Body mass index, ICIs+BCP: immune checkpoint inhibitors plus chemotherapy and antiangiogenic agents, ECOG: Eastern Cooperative Oncology Group, EGFR: Epidermal Growth Factor Receptor, TPS: Tumor Proportion Score, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PD-L1: Programmed Death-Ligand 1.

Table 3. Assessment of efficacy

Clusters	CR	PR	SD	PD	ORR	DCR
ICIs+BCP group (n=59)	0	9	46	4	9	55
ICIs group (n=74)	0	15	57	2	15	72
χ^2-value					0.559	1.267
P-value					0.455	0.260

Note: CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, ORR: Overall Response Rate, DCR: Disease Control Rate.

Nomogram modeling in EGFR TKIs-resistant patients

We developed a nomogram model based on Cox regression analysis of five prognostic factors to predict 1- and 2-year survival for patients with EGFR-TKI resistance. The model highlighted strong associations with PD-L1 TPS expression, age, treatment regimen, NLR, and PLR (**Figure 3**). The calculation formula of the model is age * -0.552 + PD-L1 TPS expression * -1.011 + treatment regimen * 0.612 + NLR0 * -0.605 + PLR * -0.851. We assessed the accuracy, stability, and clinical value of the model using time-dependent ROC, survival calibration curves, and DCA. Time-dependent ROC curve analysis showed that the nomogram model had excellent accuracy in predicting 1-year survival, with an area under the curve (AUC) of 0.823. It also performed strongly in predicting 2-year

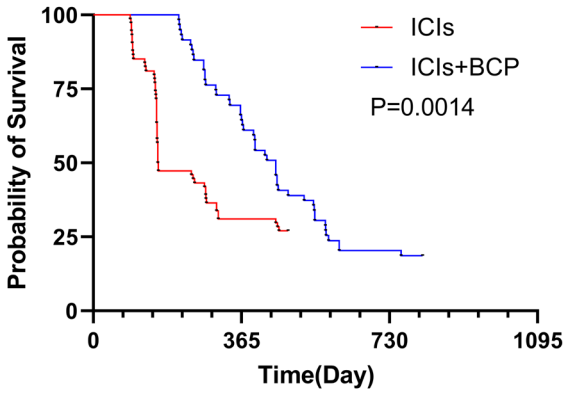

Figure 2. Effect of different treatment regimens on patient OS. ICIs+BCP: immune checkpoint inhibitors plus chemotherapy and antiangiogenic agents, OS: Overall Survival.

Table 4. Assignment table

Factor	Assign a value to something
Age	≥65 years =1, <65 years =0
Gender	Male =1, Female =0
BMI	≥25 kg/m^2 =1, <25 kg/m^2 =0
Smoking history	Yes =1, No =0
ECOG score	<1 =1, ≥1 =0
EGFR mutation type	19del =1, 21L858R =0
PD-L1 TPS expression	<1% =1, ≥1% =0
Treatment plan	ICIs+BCP =1, ICIs =0
NLR	≥4.16 =1, <4.16 =0
PLR	≥89.74 =1, <89.74 =0
LMR	≥6.21 =1, <6.21 =0

Note: BMI: Body mass index, ICIs+BCP: immune checkpoint inhibitors plus chemotherapy and antiangiogenic agents, ECOG: Eastern Cooperative Oncology Group, EGFR: Epidermal Growth Factor Receptor, TPS: Tumor Proportion Score, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PD-L1: Programmed Death-Ligand 1.

survival, evidenced by an AUC of 0.769 (**Figure 4A**). Survival calibration curve analysis confirmed the predictive accuracy of the model, demonstrating good agreement between the model predictions and actual survival data (**Figure 4B**). The survival DCA curves indicated that the C-index across different models ranged from 0.555 to 0.622, showing variable predictive ability but overall some degree of predictive accuracy (**Figure 4C**).

To illustrate the practical application of the model, we randomly selected a patient who had survived 606 d by the end of the follow-up. Using the model, we calculated this patient's 1- and 2-year survival probabilities based on their specific clinical information, resulting in estimated survival probabilities of 70% at one year and 27% at two years (**Table 7**).

Discussion

Advancements in molecularly targeted therapies have significantly improved survival outcomes for patients with late-stage NSCLC harboring EGFR mutations [20]. Studies have underscored the advantages of EGFR-TKIs over traditional chemotherapy, marking a pivotal shift in treatment paradigms [21]. As a member of the ErbB tyrosine kinase receptor family, EGFR plays a crucial role in tumor proliferation and metastasis by binding to its ligands and activating downstream signaling pathways [22]. Despite their initial effectiveness, resistance to first-, second-, and third-generation EGFR-TKIs typically develops within 7 to 14 months of treatment, which limits options after resistance emerges [23].

Recent studies have explored the efficacy of PD-1/L1 inhibitors in NSCLC patients resistant to EGFR-TKIs. Research by Lisberg [24] and Gettinger [25] indicated that PD-1 inhibitors did not significantly improve outcomes for patients with EGFR mutations. Conversely, a study by Borghaei et al. [26] demonstrated that natalizumab was more effective than second-line cytotoxic therapy in patients with PD-L1-positive lung adenocarcinoma, suggesting that PD-L1 expression may increase in patients without the T790M mutation following EGFR-TKI resistance. Contrary to expectations, our study found that the ICIs+BCP regimen did not yield higher ORR and DCR than the ICIs group alone. Similarly, research by Cai et al. [27] showed no significant difference in ORR and DCR between patients receiving ICIs combined with chemotherapy and those receiving additional antiangiogenic therapy. However, an improvement in OS was observed in patients treated with the ICIs+BCP regimen, highlighting the importance of selecting the appropriate treatment strategy for EGFR-TKI-resistant NSCLC to maximize survival benefits. This emphasizes the potential value of integrating various treatment modalities to enhance patient outcomes in future clinical practice.

Identifying reliable biomarkers to evaluate the efficacy of immunotherapy in late-stage NSCLC

Table 5. Univariate analysis of OS in patients with resistance to EGFR-TKIs

Factor	Beta coefficient	Std Err	*P* Value	HR value	Lower 95% CI	Upper 95% CI
Age	0.435	0.208	0.037	1.545	1.027	2.324
Gender	0.188	0.222	0.396	1.207	0.782	1.865
BMI	0.016	0.243	0.947	1.016	0.632	1.635
Smoking history	0.127	0.220	0.565	1.135	0.738	1.747
ECOG score	0.081	0.216	0.708	1.084	0.710	1.655
EGFR mutation type	0.093	0.228	0.681	1.098	0.703	1.715
PD-L1 TPS expression	1.092	0.273	<0.001	2.982	1.747	5.089
Treatment plan	-0.683	0.216	0.002	0.505	0.330	0.772
NLR	0.968	0.261	<0.001	2.632	1.577	4.392
PLR	0.842	0.286	0.003	2.322	1.325	4.069
LMR	0.393	0.251	0.118	1.481	0.906	2.422

Note: BMI: Body mass index, ICIs+BCP: immune checkpoint inhibitors plus chemotherapy and antiangiogenic agents, ECOG: Eastern Cooperative Oncology Group, EGFR: Epidermal Growth Factor Receptor, TPS: Tumor Proportion Score, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PD-L1: Programmed Death-Ligand 1, TKIs: Tyrosine Kinase Inhibitors, OS: Overall Survival, HR: Hazard Ratio.

Table 6. Multifactorial analysis of OS in patients with resistance to EGFR-TKIs

Factor	Beta coefficient	Std Err	*P* Value	HR value	Lower 95% CI	Upper 95% CI
Age	0.553	0.220	0.012	1.738	1.128	2.678
PD-L1 TPS expression	1.012	0.277	<0.001	2.750	1.599	4.730
Treatment plan	-0.612	0.222	0.006	0.542	0.351	0.839
NLR	0.605	0.268	0.024	1.832	1.084	3.094
PLR	0.852	0.305	0.005	2.343	1.290	4.258

Note: EGFR: Epidermal Growth Factor Receptor, TPS: Tumor Proportion Score, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, PD-L1: Programmed Death-Ligand 1, TKIs: Tyrosine Kinase Inhibitors, OS: Overall Survival, HR: Hazard Ratio.

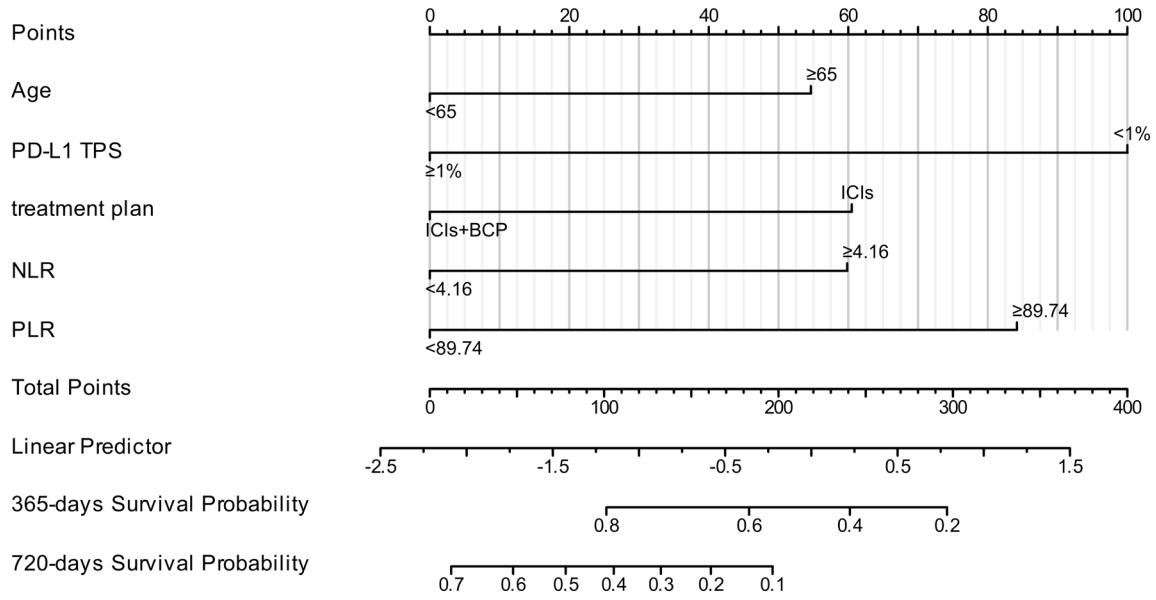

Figure 3. Nomogram model for predicting 1- and 2-year patient survival. NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, PD-L1: Programmed Death-Ligand 1.

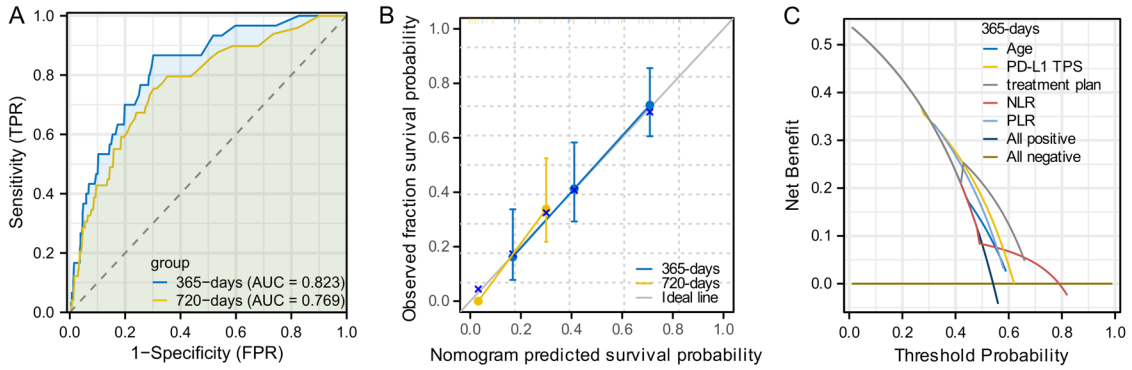

Figure 4. Internal validation of the Nomogram model. A. Time-dependent ROC curve analysis model for predicting patient survival at 1, 2 years. B. Stability of the survival calibration curve analysis model for predicting patient survival at 1 and 2 years. C. Analysis of the clinical benefits of the survival calibration curve analysis model for predicting patient survival at 1 and 2 years.

Table 7. Randomized sample of patient information and probability of survival prediction

Considerations	Patient situation	Score
Age	≥65 years	55
PD-L1 TPS expression	≥1%	0
Treatment plan	ICIs+BCP	0
NLR	<4.16	0
PLR	≥89.74	84
Totals		139
1-year survival rate		70%
2-year survival rate		27%

Note: ICIs+BCP: immune checkpoint inhibitors plus chemotherapy and antiangiogenic agents, TPS: Tumor Proportion Score, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, PD-L1: Programmed Death-Ligand 1, TKIs: Tyrosine Kinase Inhibitors.

patients who have developed resistance to first-line EGFR-TKI treatment remains a key area of research [28]. The decision to opt for immunotherapy or continue with chemotherapy as a second-line treatment hinges on these insights. High PD-L1 expression is recognized as a predictor of successful immunotherapy [29]. In our study, Cox regression analysis identified age, PD-L1 TPS expression, treatment regimen, NLR, and PLR as independent prognostic factors in patients resistant to EGFR-TKIs. Older patients generally have a poorer prognosis due to diminished physiological function, concurrent diseases, and overall health, which impact their treatment tolerance [27]. PD-L1, an immune checkpoint, shows expression levels that strongly correlate with the outcomes of immunotherapy. Therefore, high PD-L1 TPS expression is a robust predictor of favorable responses to immune checkpoint inhibitors [30]. Additional evidence suggests that NSCLC patients, especially those without the T790M mutation and resistant to EGFR-TKIs, benefit significantly from combination therapies over conventional chemotherapy in terms of ORR, median PFS, and median OS [31]. Our study concludes that combining ICIs with BCP markedly improves prognosis compared to immunotherapy alone.

The connection between inflammation, cancer progression, and the immune system's role in tumor control underscores the prognostic value of inflammatory markers [32, 33]. Elevated NLR and PLR levels suggest a strong inflammatory response and diminished immunosurveillance, indicating a less favorable prognosis [34]. Platelets and lymphocytes play critical roles in tumor dynamics and anti-tumor immunity, respectively [35]. Previous research by Chen et al. [36] highlighted that late-stage NSCLC patients with lower NLR values (≤4), including those with EGFR-sensitive mutations, might derive potential benefits from anti-PD-1 inhibitors. He et al. [37] also identified PLR as an independent prognostic factor for EGFR-mutated lung adenocarcinoma patients undergoing EGFR-TKI therapy. In summary, age, PD-L1 TPS expression, treatment regimen, NLR, and PLR are effective predictors of survival outcomes in NSCLC patients who have developed resistance to EGFR-TKIs, offering insights into physiological and immune status as well as treatment response.

Although these findings provide meaningful insights into the management of EGFR-TKI-resistant NSCLC, several limitations must be acknowledged. The retrospective nature of the study introduces risks of selection and information biases, potentially affecting the precision and reliability of the findings. Additionally, the relatively small and homogeneous sample size limits the generalizability of the results, making it difficult to apply the conclusions to a broader patient population. While specific biomarkers like PD-L1 expression, NLR, and PLR were examined, our study only captured a portion of tumor biology, possibly overlooking other key factors influencing treatment outcomes. The lack of long-term follow-up data further constrains our ability to assess the enduring impacts of these treatment modalities on survival and patient well-being. Future studies would benefit from a prospective design, larger sample size, more diverse population, and comprehensive biomarker investigation to enhance the accuracy, reliability, and relevance of the research.

In summary, our findings support the effectiveness of combining ICIs with platinum-containing chemotherapy and antiangiogenic agents to improve overall survival in patients with NSCLC who have developed resistance to EGFR-TKIs. This study underscores the importance of personalized treatment strategies and the vital role of biomarker evaluation in enhancing the prognosis of patients dealing with drug resistance.

Disclosure of conflict of interest

None.

Address correspondence to: Zhongqin He, Department of Oncology, Baoji Traditional Chinese Medicine Hospital, No. 43 Baofu Road, Jintai District, Baoji 721000, Shaanxi, China. E-mail: xythzq@163.com

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