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Original Article

Efficacy of chemotherapy combined with immune checkpoint inhibitors for advanced non-small cell lung cancer and construction and validation of a prognostic model: a multicenter retrospective cohort study

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Abstract: The goal of this multicenter retrospective cohort study was to determine the efficacy of chemotherapy in combination with immune checkpoint inhibitors (ICIs) as compared to chemotherapy alone in patients with advanced non-small cell lung cancer (NSCLC). Further, the study will assess the efficacy between the PD-1 inhibitors, evaluate independent prognostic factors and build nomogram models for predicting progression free survival (PFS) and overall survival (OS). Clinical data were retrospectively collected from patients of two centers who received first-line treatment between January 2019 and December 2023 (training cohort n=286, external validation cohort n=124). To balance baseline characteristics, propensity score matching (PSM) was adopted. Cox regression analyses were then performed to find the independent prognostic factors. After PSM (propensity score matching), a significantly higher objective response rate and disease control rate were found in the combination therapy group as compared with a single-agent therapy group (both P<0.05). The combination therapy group also exhibited a significantly longer median PFS of 10 months as compared with 6 months of single-agent therapy group; HR=1.92, P<0.001. Similarly, the combination therapy group exhibited significantly longer median OS of 21 months as compared with 12 months of single-agent therapy group; HR=2.07, P<0.001. The effectiveness of tislelizumab was similar to sintilimab in treating multiple cancers, which was further confirmed by network meta-analysis. Based on the multivariate analysis, treatment regimen, serum albumin, age, smoking status, Charlson Comorbidity Index, ECOG performance status, organ metastasis status and number of organ metastasis were independent prognostic factors for PFS, while first six variables (except smoking status and CCI) for OS. The area under the curve (AUC) values for both nomograms in internal and external validation were greater than 0.75, and they showed good calibration, good clinical utility and good risk stratification performances or capabilities. In conclusion, chemotherapy plus ICIs significantly improves short-term efficacy and long-term survival in advanced NSCLC, tislelizumab and sintilimab showed comparable efficacy, and the constructed nomograms could provide some significance for individualized clinical decision-making.

Keywords: Non-small cell lung cancer, immune checkpoint inhibitors, chemotherapy, prognosis, nomogram, propensity score matching

Introduction

Lung cancer is one of the most common cancers and causes of cancer-related deaths in the world. It poses a serious risk to human health. As per global estimates for cancer, there were an estimated 2.48 million new lung cancer cases and 1.82 million deaths worldwide in 2022, both these figures are ranking first among all malignant tumours in terms of incidence and mortality, respectively [1]. In China, lung cancer is the most common cancer

with over 1 million new cases and about 730,000 deaths per year, putting a heavy burden of disease [2]. Non-small cell lung cancer (NSCLC) is the main pathological type, comprising about 80%-85% of all lung cancers [3]. As a result of their insidious early symptoms, most patients with non-small cell lung cancer (NSCLC) present with locally advanced or metastatic disease, thereby losing the opportunity of curative surgery [4]. Patients diagnosed with advanced NSCLC are less likely to survive, and five-year survival rates of less than 20% point to an urgent need for better treatment strategies [5].

Advanced NSCLCs (non-small lung cancers) have been subjected to platinum-based doublet chemotherapy for many years [6]. Nevertheless, chemotherapy by itself is not very effective. The objective response rate (ORR) is only 25% to 35%, while median progression-free survival (PFS) is approximately 4-6 months and median overall survival (OS) is approximately 10-12 months. Treatment is often associated with significant side effects too [7]. Advances in tumor immunology led to immune checkpoint inhibitors (ICIs), which have revolutionized the treatment of advanced non-small cell lung cancer (NSCLC) in recent years [8]. ICIs have long-lasting antitumor effects mainly by blocking the interaction of programmed cell death protein 1 (PD-1) with its ligand - programmed cell death ligand 1 (PD-L1). This alleviates tumor cells' immunosuppressive impact on T cells and stimulates the organism's antitumor immune response [9].

Multiple large randomized controlled trials have confirmed that chemotherapy combined with ICIs can significantly improve both short-term efficacy and long-term survival in patients with advanced NSCLC. The KEYNOTE-189 study demonstrated that pembrolizumab plus chemotherapy significantly prolonged PFS and OS compared to chemotherapy alone in patients with non-squamous NSCLC [10]. The KEYNOTE-407 study confirmed similar survival benefits of this combination regimen in squamous NSCLC patients [11]. Additionally, the CameL and ORIENT-11 studies conducted in China validated the efficacy and safety of camrelizumab and sintilimab combined with chemotherapy in Chinese populations, respectively [12, 13]. Based on this evidence, chemotherapy combined with ICIs has been recommended by authoritative guidelines both domestically and internationally as the standard first-line treatment for driver gene-negative advanced NSCLC [14]. Currently, several domestic PD-1 inhibitors such as tislelizumab and sintilimab have been approved for first-line combination treatment of advanced NSCLC in China, greatly expanding treatment options for patients [15].

However, existing evidence on chemotherapy combined with ICIs for advanced NSCLC mainly comes from randomized controlled trials with strict enrollment criteria and highly selected patient populations. It remains controversial whether these results can be generalized to heterogeneous patients in the context of clinical practice [16]. Nonetheless, there is currently no direct comparative evidence on whether efficacy differs among PD-1 inhibitors overall. More importantly, the independent factors affecting prognosis in patients receiving chemoimmunotherapy have not been fully elucidated. So, personalized prognostic predictive tools for this specific population are lacking in clinical practice [17]. Nomograms act as visual tools that can convert complex statistical models into easy clinical scoring systems and have been widely used for prognostic prediction in many cancers [18]. Thus, investigating the main prognostic factors and creating reliable prognostic prediction models based on real-world data has important practical significance in guiding individualized clinical treatment.

In view of this, the present study aimed to systematically compare the short-term efficacy and long-term survival of chemotherapy combined with ICIs versus chemotherapy alone for advanced NSCLC using multicenter real-world retrospective cohort data. We have further investigated whether there is a difference between the efficacy of two PD-1 inhibitors (tislelizumab vs sintilimab) in the group of combination therapy. Furthermore, we sought to identify independent prognostic factors for PFS and OS through univariate and multivariate Cox regression analyses, construct corresponding nomogram models for predicting patients' prognosis, and assess model discrimination, calibration, and clinical utility by internal and external validation. The aim of our analysis was to provide evidence-based accessibility for making clinical treatment decisions and prognostic assessment of patients with advanced NSCLC.

Materials and methods

Sample size calculation

This retrospective cohort study calculated sample size using the Schoenfeld formula [19], which is appropriate for survival analysis studies based on Cox proportional hazards models. The formula is as follows:

$$E = (Z\_\alpha/2 + Z\_\beta)^2/[P_1 \times P_2 \times (\ln HR)^2]$$

Where E represents the required number of events; Z_α/2 is the critical value of the standard normal distribution corresponding to the two-sided α level (Z_α/2=1.96 when α=0.05); Z_β is the critical value corresponding to statistical power (Z_β=0.84 when β=0.20, i.e., 80% power); P_1 and P_2 represent the proportions of patients in the two groups; and HR is the expected hazard ratio. In reference to the KEYNOTE-189 study [10], it was demonstrated that the inclusion of ICIs improved OS in patients with advanced NSCLC when coupled with chemotherapy, compared to chemotherapy alone (HR=0.49). Both groups are assumed to have the same proportions (P_1=P_2=0.5) and HR=0.50, caluclation give the minimum 65 events required. According to [20], the number of events was approximately 80% in patients suffering from advanced NSCLC, hence, the sample size was calculated as. As per the calculations, a total of 82 patients are required for the trial to arrive at a statistically significant conclusion. Given that this study required multivariate Cox regression analysis and prognostic model development, and considering the principle of at least 10 events for each predictor variable, with an estimated 20% data missingness, we determined the minimum sample size for the training cohort to be 200 patients. A total of 286 patients from the internal training cohort and 124 patients from the external validation cohort (410 patients in total) proved sufficient for statistical analysis.

Study population

In the period between January 2019 and December 2023, clinical data were collected retrospectively from patients with advanced NSCLC who received first-line treatment at 1 of 2 locations: 1) First People's Hospital of Shuangliu District and 2) Chengdu/West China (Airport) Hospital, Sichuan University (training cohort) and 3) Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital (external validation cohort). Patients were classified into either the combination (chemotherapy plus PD-1 inhibitor) or chemotherapy-alone groups according to regimen. The cohort of the training consisted of 286 patients in total where 156 patients were in the combination therapy group and 130 in the chemotherapy alone group. The external validation cohort consisted of 124 patients, 68 of whom received combination therapy and 56 received chemotherapy alone. The Medical Ethics Committees of First People's Hospital of Shuangliu District, Chengdu/West China (Airport) Hospital, Sichuan University and Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital approved this study. The study's nature was retrospective so informed consent was waived.

Inclusion and exclusion criteria

Inclusion criteria: (1) Histologically or cytologically confirmed NSCLC; (2) Clinical stage IIIB/IIIC (unresectable) or IV; (3) Age ≥18 years; (4) Received first-line chemotherapy or chemotherapy combined with PD-1 inhibitor; (5) Completed at least 2 cycles of systemic treatment; (6) Measurable lesions according to RECIST 1.1 criteria; (7) Complete clinical and follow-up data.

Exclusion criteria: (1) Concurrent other primary malignancies; (2) Harboring EGFR-sensitizing mutations or ALK fusion positivity and receiving targeted therapy; (3) Prior systemic antitumor therapy; (4) Severe cardiac, hepatic, or renal dysfunction; (5) Active autoimmune disease; (6) Missing baseline or follow-up data; (7) Lost to follow-up or follow-up duration <3 months.

Treatment regimens

Patients in the combination therapy group received chemotherapy plus PD-1 inhibitor. PD-1 inhibitors included tislelizumab (200 mg, intravenous infusion, every 3 weeks) [15] and sintilimab (200 mg, intravenous infusion, every 3 weeks) [13]. Chemotherapy regimens were selected based on histological type:

(1) Non-squamous NSCLC: Pemetrexed plus platinum regimen. Pemetrexed 500 mg/m^2, intravenous infusion, day 1; combined with cis-

platin 75 mg/m^2 or carboplatin (AUC=5) intravenous infusion, day 1; every 3 weeks for 4-6 cycles. After induction therapy, patients without disease progression continued maintenance therapy with pemetrexed (500 mg/m^2, every 3 weeks) plus PD-1 inhibitor until disease progression or intolerable toxicity [21].

(2) Squamous NSCLC: Taxane plus platinum regimen. Paclitaxel 175 mg/m^2 or nab-paclitaxel 260 mg/m^2, intravenous infusion, day 1; combined with cisplatin 75 mg/m^2 or carboplatin (AUC=5) intravenous infusion, day 1; every 3 weeks for 4-6 cycles. After induction therapy, patients without disease progression continued PD-1 inhibitor monotherapy maintenance until disease progression or intolerable toxicity [11].

Patients in the chemotherapy-alone group received platinum-based doublet chemotherapy only, with drug selection and dosing identical to the combination therapy group:

(1) Non-squamous NSCLC: Pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) or carboplatin (AUC=5), every 3 weeks for 4-6 cycles. After induction therapy, patients without disease progression continued pemetrexed (500 mg/m^2, every 3 weeks) monotherapy maintenance until disease progression or intolerable toxicity.

(2) Squamous NSCLC: Paclitaxel (175 mg/m^2) or nab-paclitaxel (260 mg/m^2) plus cisplatin (75 mg/m^2) or carboplatin (AUC=5), every 3 weeks for 4-6 cycles. After induction therapy, best supportive care or regular follow-up observation was provided.

Both groups received standard premedication and supportive care, including antiemetics, hydration, and folic acid and vitamin B12 supplementation (for pemetrexed regimens). Dose adjustments or treatment delays were permitted based on patient tolerance and adverse reactions.

Clinical data collection

The following clinical data were collected through the electronic medical record system:

Sex, age (dichotomized at 65 years as <65 and ≥65), BMI (dichotomized at 24 kg/m^2 as <24 and ≥24), smoking history (yes/no). The CCI was used to assess comorbidity burden, dichotomized at 2 points as 0-1 and ≥2 [22]. ECOG PS was used to assess functional status, dichotomized at 2 points as 0-1 and ≥2 [23]. Disease stage (according to the 8th edition TNM staging system, classified as IIIB/IIIC and IV), histological type (adenocarcinoma, squamous cell carcinoma, other), EGFR mutation status (positive, negative, not tested/unknown), ALK fusion status (positive, negative, not tested/unknown), organ metastasis status (yes/no), number of metastatic organs (dichotomized at 2 as 0-1 and ≥2). Treatment regimen (combination therapy/chemotherapy alone), PD-1 inhibitor type (tislelizumab/sintilimab, combination therapy group only), year of treatment initiation (2019-2020/2021-2023). Serum ALB, Hb, PLT, ALT, AST, and Cr, all of which were collected from fasting venous blood samples within one week before treatment initiation.

Laboratory testing methods

All baseline laboratory parameters were measured from fasting venous blood samples collected within one week before treatment initiation. Serum albumin was measured using the bromocresol green method with a fully automated biochemical analyzer (Beckman Coulter AU5800, USA) and matching reagent kits. Hemoglobin and platelet counts were measured using a fully automated hematology analyzer (Sysmex XN-9000, Japan) with matching reagents. ALT, AST, and serum creatinine were measured using rate/enzymatic methods with a fully automated biochemical analyzer (Beckman Coulter AU5800, USA) and matching reagent kits. All tests were performed according to instrument operating procedures and reagent kit instructions by trained professional technicians.

Efficacy evaluation and outcome measures

First of all, in PFS, PFS short for progression free survival, it will be defined as the time from the start of treatment until the occurrence of disease progression or death from any cause, whichever came first. OS - defined as the time from treatment start to death from any cause. Secondary outcomes were defined as Objective Response Rate (ORR) and were measured as the percentage of evaluable patients achieving complete response (CR) or partial response (PR). The term DCR refers to the percentage of

evaluable patients experiencing CR, PR, or SD. Efficacy was measured as per RECIST 1.1 criteria [24] of the photographs chest CT and/or whole-body PET-CT (every two cycles (6-8 weeks)). Follow-up methods included outpatient visit, telephone follow-up and medical record review with a follow-up cutoff date of 31 December 2025.

Statistical analysis

Statistical analyses were performed using R 4.5.1 software (R Foundation for Statistical Computing, Austria) and SPSS 27.0 software (IBM Corporation, USA). Normally distributed continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm s$), with intergroup comparisons using independent samples t-test; non-normally distributed continuous variables were expressed as median (interquartile range) [M (Q1, Q3)], with intergroup comparisons using Mann-Whitney U test. Categorical variables were expressed as frequency (percentage) [n (%)], with intergroup comparisons using χ^2 test or Fisher's exact test. To reduce selection bias between groups, PSM was used to balance baseline characteristics. Using treatment regimen as the dependent variable, covariates including sex, age, CCI, ECOG PS, disease stage, histological type, organ metastasis status, number of metastatic organs, and year of treatment initiation were entered into a logistic regression model to calculate propensity scores. One-to-one nearest neighbor matching was performed with a caliper of 0.2. Standardized mean difference (SMD) was used to assess covariate balance after matching, with SMD <0.1 indicating good balance [25]. Survival curves were plotted using the Kaplan-Meier method, with intergroup comparisons using log-rank test. Univariate Cox proportional hazards regression models were used to screen potential prognostic factors, and variables with P<0.1 in univariate analysis were entered into multivariate Cox regression models using forward stepwise selection to identify independent prognostic factors. Results were expressed as HR and 95% CI. Based on multivariate Cox regression results, nomograms for predicting PFS and OS were constructed using the rms package in R software. Model validation was performed using the following methods: (1) Discrimination assessment: C-index and time-dependent ROC curve AUC were used to assess model discrimination ability. (2) Calibration assessment: Calibration curves were plotted, Brier scores were calculated, and Hosmer-Lemeshow test was used to assess agreement between predicted and observed values. (3) Clinical utility assessment: DCA was used to assess net benefit at different threshold probabilities. (4) Risk stratification validation: Patients were divided into high-risk and low-risk groups based on the median risk score, and survival differences between groups were compared using the Kaplan-Meier method. The training cohort was used for model construction and internal validation, while the external validation cohort was used to assess model generalizability. All statistical tests were two-sided, with P<0.05 considered statistically significant.

Results

Baseline characteristics comparison between two groups

A total of 286 patients with advanced NSCLC were included in this study, with 130 in the chemotherapy-alone group and 156 in the chemotherapy combined with ICI group (combination therapy group). Significant differences existed between groups in several baseline characteristics. Patients in the combination therapy group had better CCI (P=0.022) and ECOG PS (P=0.004), lower rates of organ metastasis (P=0.038) and multi-organ metastasis (P=0.025), and more recent treatment initiation dates (P=0.035). Regarding laboratory parameters, patients in the combination therapy group had higher serum albumin and hemoglobin levels (both P<0.001) and lower aspartate aminotransferase levels (P=0.023). No significant differences were observed between groups in sex, age, BMI, smoking history, disease stage, histological type, EGFR and ALK gene status, platelet count, alanine aminotransferase, or creatinine levels (all P>0.05) (**Table 1**).

Baseline characteristics comparison after propensity score matching

To reduce selection bias, PSM was performed using 1:1 nearest neighbor matching. Matching variables included sex, age, CCI, ECOG PS, disease stage, histological type, organ metastasis status, number of metastatic organs, and year

Table 1. Comparison of baseline characteristics between the two groups

Factor	Total (n=286)	Chemotherapy alone (n=130)	Combination therapy (n=156)	Statistic	*P* value
Sex				0.654	0.419
Male	194 (67.83%)	85 (65.38%)	109 (69.87%)		
Female	92 (32.17%)	45 (34.62%)	47 (30.13%)		
Age (dichotomized)				2.196	0.138
<65	174 (60.84%)	73 (56.15%)	101 (64.74%)		
≥65	112 (39.16%)	57 (43.85%)	55 (35.26%)		
BMI (dichotomized)				0.262	0.609
<24	178 (62.24%)	83 (63.85%)	95 (60.90%)		
≥24	108 (37.76%)	47 (36.15%)	61 (39.10%)		
Smoking history				2.561	0.110
Yes	190 (66.43%)	80 (61.54%)	110 (70.51%)		
No	96 (33.57%)	50 (38.46%)	46 (29.49%)		
CCI (dichotomized)				5.221	0.022
0-1	206 (72.03%)	85 (65.38%)	121 (77.56%)		
≥2	80 (27.97%)	45 (34.62%)	35 (22.44%)		
ECOG PS (dichotomized)				8.231	0.004
0-1	232 (81.12%)	96 (73.85%)	136 (87.18%)		
≥2	54 (18.88%)	34 (26.15%)	20 (12.82%)		
Disease stage				0.487	0.485
IIIB/IIIC	58 (20.28%)	24 (18.46%)	34 (21.79%)		
IV	228 (79.72%)	106 (81.54%)	122 (78.21%)		
Histological type				0.265	0.876
Adenocarcinoma	180 (62.94%)	80 (61.54%)	100 (64.10%)		
Squamous cell carcinoma	88 (30.77%)	42 (32.31%)	46 (29.49%)		
Other	18 (6.29%)	8 (6.15%)	10 (6.41%)		
EGFR status				1.135	0.567
Positive	48 (16.78%)	24 (18.46%)	24 (15.38%)		
Negative	146 (51.05%)	62 (47.69%)	84 (53.85%)		
Not tested/Unknown	92 (32.17%)	44 (33.85%)	48 (30.77%)		
ALK status				0.804	0.669
Positive	10 (3.50%)	4 (3.08%)	6 (3.85%)		
Negative	152 (53.15%)	66 (50.77%)	86 (55.13%)		
Not tested/Unknown	124 (43.36%)	60 (46.15%)	64 (41.03%)		
Organ metastasis				4.288	0.038
Yes	212 (74.13%)	104 (80.00%)	108 (69.23%)		
No	74 (25.87%)	26 (20.00%)	48 (30.77%)		
Number of metastatic organs (dichotomized)				5.030	0.025
0-1	170 (59.44%)	68 (52.31%)	102 (65.38%)		
≥2	116 (40.56%)	62 (47.69%)	54 (34.62%)		
Year of treatment initiation (dichotomized)				4.424	0.035
2019-2020	96 (33.57%)	52 (40.00%)	44 (28.21%)		
2021-2023	190 (66.43%)	78 (60.00%)	112 (71.79%)		
ALB (g/L)	38.09±4.94	36.84±5.01	39.13±4.65	4.019	<0.001
Hb (g/L)	122.86±15.93	117.22±16.21	127.56±14.12	5.767	<0.001
PLT ($\times 10^9$/L)	260.50±76.15	268.68±85.29	253.68±67.13	-1.664	0.097
ALT (U/L)	26.00 [16.25, 36.00]	26.00 [16.25, 37.00]	27.00 [16.75, 36.00]	0.043	0.966
AST (U/L)	24.05±11.06	25.68±11.52	22.69±10.50	-2.290	0.023
Cr (μmol/L)	75.00 [62.00, 87.00]	73.00 [59.25, 87.00]	76.00 [63.00, 86.00]	0.904	0.366

Note: BMI: Body Mass Index, CCI: Charlson Comorbidity Index, ECOG PS: Eastern Cooperative Oncology Group Performance Status, EGFR: Epidermal Growth Factor Receptor, ALK: Anaplastic Lymphoma Kinase, ALB: Albumin, Hb: Hemoglobin, PLT: Platelet, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, Cr: Creatinine. Normally distributed continuous variables are presented as mean ± standard deviation; non-normally distributed continuous variables are presented as median [interquartile range].

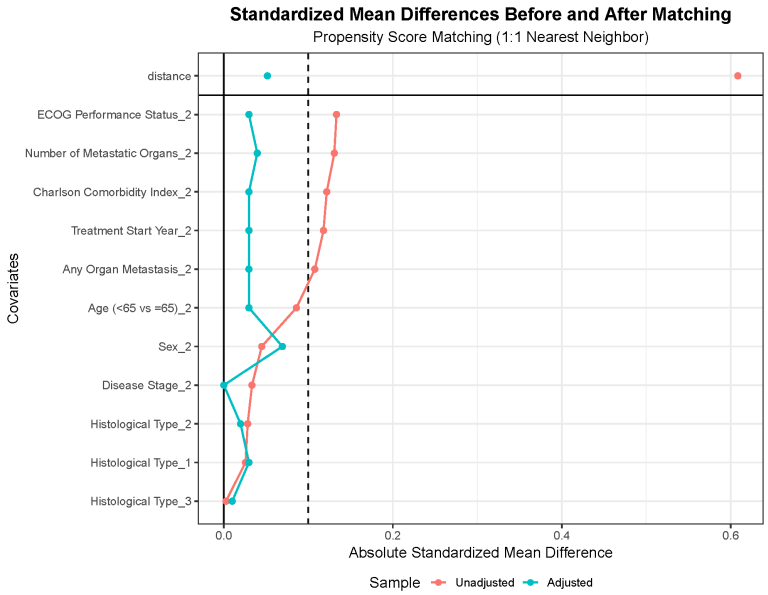

Figure 1. Love plot of standardized mean differences before and after propensity score matching. Note: PSM: Propensity Score Matching, SMD: Standardized Mean Difference, ECOG PS: Eastern Cooperative Oncology Group Performance Status, CCI: Charlson Comorbidity Index.

of treatment initiation. After matching, 101 patients were included in each group. The Love plot showed that all covariate SMD values were below 0.1 after matching, indicating well-balanced baseline characteristics between groups (**Figure 1**). After matching, no significant differences were observed between groups in sex, age, BMI, smoking history, CCI, ECOG PS, disease stage, histological type, EGFR and ALK gene status, organ metastasis status, number of metastatic organs, year of treatment initiation, platelet count, alanine aminotransferase, or creatinine levels (all P>0.05). However, differences persisted in some laboratory parameters. The chemotherapy-alone group had lower serum albumin (P=0.004) and hemoglobin (P<0.001) levels and higher aspartate aminotransferase levels (P=0.025) (**Table 2**).

Short-term efficacy comparison before and after propensity score matching

Short-term efficacy was evaluated for both groups. Before PSM, the combination therapy group had significantly higher ORR and DCR than the chemotherapy-alone group (both P< 0.001). The efficacy distribution showed higher proportions of CR and PR and lower proportion of progressive disease (PD) in the combination therapy group. After PSM, the combination therapy group still demonstrated significantly better ORR (P=0.001) and DCR (P< 0.001) than the chemotherapy-alone group, with similar efficacy distribution trends as before matching. These results indicate that chemotherapy combined with ICIs significantly improves short-term efficacy in patients with advanced NSCLC regardless of matching status (**Figure 2**).

Survival analysis before and after propensity score matching

PFS and OS were analyzed using the Kaplan-Meier method. Before PSM, the median follow-up time was 44 months. The combination therapy group had significantly longer median PFS than the chemotherapy-alone group (10 months vs 6 months, HR=1.83, 95% CI: 1.42-2.36, P<0.001) and significantly longer median OS (23 months vs 12 months, HR=1.91, 95% CI: 1.47-2.47, P<0.001). After PSM, the median follow-up time was 42 months. The survival benefit in the combination therapy group remained significant: median PFS was 10 months vs 6 months (HR=1.92, 95% CI: 1.42-2.60, P<0.001), and median OS was 21 months vs 12 months (HR=2.07, 95% CI: 1.52-2.82, P<0.001). These results indicate that chemotherapy combined with ICIs significantly improves PFS and OS in patients with advanced NSCLC regardless of matching status (**Figure 3**).

Subgroup survival analysis of different PD-1 inhibitors in the combination therapy group

To investigate the impact of different PD-1 inhibitors on patient prognosis within the combination therapy group, subgroup survival analysis was performed comparing patients receiving tislelizumab versus sintilimab. Before PSM, the median follow-up time was 42 months. No statistically significant differences were observed between the tislelizumab and sintilimab groups in median PFS (10 months vs 13 months, HR=0.87, 95% CI: 0.59-1.27, P=0.468) or median OS (22 months vs 25 months,

Table 2. Comparison of baseline characteristics between the two groups after propensity score matching

Factor	Total (n=202)	Chemotherapy alone (n=101)	Combination therapy (n=101)	Statistic	*P* value
Sex				1.112	0.292
Male	137 (67.82%)	65 (64.36%)	72 (71.29%)		
Female	65 (32.18%)	36 (35.64%)	29 (28.71%)		
Age (dichotomized)				0.189	0.664
<65	125 (61.88%)	64 (63.37%)	61 (60.40%)		
≥65	77 (38.12%)	37 (36.63%)	40 (39.60%)		
BMI (dichotomized)				0.000	1.000
<24	128 (63.37%)	64 (63.37%)	64 (63.37%)		
≥24	74 (36.63%)	37 (36.63%)	37 (36.63%)		
Smoking history				1.112	0.292
Yes	137 (67.82%)	65 (64.36%)	72 (71.29%)		
No	65 (32.18%)	36 (35.64%)	29 (28.71%)		
CCI (dichotomized)				0.242	0.622
0-1	153 (75.74%)	75 (74.26%)	78 (77.23%)		
≥2	49 (24.26%)	26 (25.74%)	23 (22.77%)		
ECOG PS (dichotomized)				0.266	0.606
0-1	159 (78.71%)	78 (77.23%)	81 (80.20%)		
≥2	43 (21.29%)	23 (22.77%)	20 (19.80%)		
Disease stage				0.000	1.000
IIIB/IIIC	44 (21.78%)	22 (21.78%)	22 (21.78%)		
IV	158 (78.22%)	79 (78.22%)	79 (78.22%)		
Histological type				0.224	0.894
Adenocarcinoma	127 (62.87%)	62 (61.39%)	65 (64.36%)		
Squamous cell carcinoma	64 (31.68%)	33 (32.67%)	31 (30.69%)		
Other	11 (5.45%)	6 (5.94%)	5 (4.95%)		
EGFR status				0.615	0.735
Positive	34 (16.83%)	15 (14.85%)	19 (18.81%)		
Negative	101 (50.00%)	51 (50.50%)	50 (49.50%)		
Not tested/Unknown	67 (33.17%)	35 (34.65%)	32 (31.68%)		
ALK status				0.000	1.000
Positive	6 (2.97%)	3 (2.97%)	3 (2.97%)		
Negative	106 (52.48%)	53 (52.48%)	53 (52.48%)		
Not tested/Unknown	90 (44.55%)	45 (44.55%)	45 (44.55%)		
Organ metastasis				0.275	0.600
Yes	161 (79.70%)	79 (78.22%)	82 (81.19%)		
No	41 (20.30%)	22 (21.78%)	19 (18.81%)		
Number of metastatic organs (dichotomized)				0.322	0.570
0-1	114 (56.44%)	55 (54.46%)	59 (58.42%)		
≥2	88 (43.56%)	46 (45.54%)	42 (41.58%)		
Year of treatment initiation (dichotomized)				0.204	0.651
2019-2020	65 (32.18%)	31 (30.69%)	34 (33.66%)		
2021-2023	137 (67.82%)	70 (69.31%)	67 (66.34%)		
ALB (g/L)	37.79±5.19	36.75±5.18	38.83±5.01	2.890	0.004
Hb (g/L)	122.32±16.70	116.87±16.78	127.77±14.81	4.896	<0.001
PLT ($\times 10^9$/L)	262.62±73.08	267.50±82.38	257.74±62.46	-0.948	0.344
ALT (U/L)	26.00 [15.00, 38.00]	26.00 [15.00, 38.00]	26.00 [15.00, 38.00]	0.164	0.870
AST (U/L)	24.42±11.68	26.26±11.69	22.58±11.44	-2.258	0.025
Cr (μmol/L)	75.00 [61.00, 87.00]	72.00 [58.00, 87.00]	75.00 [62.00, 87.00]	0.848	0.397

Note: PSM: Propensity Score Matching, BMI: Body Mass Index, CCI: Charlson Comorbidity Index, ECOG PS: Eastern Cooperative Oncology Group Performance Status, EGFR: Epidermal Growth Factor Receptor, ALK: Anaplastic Lymphoma Kinase, ALB: Albumin, Hb: Hemoglobin, PLT: Platelet, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, Cr: Creatinine.

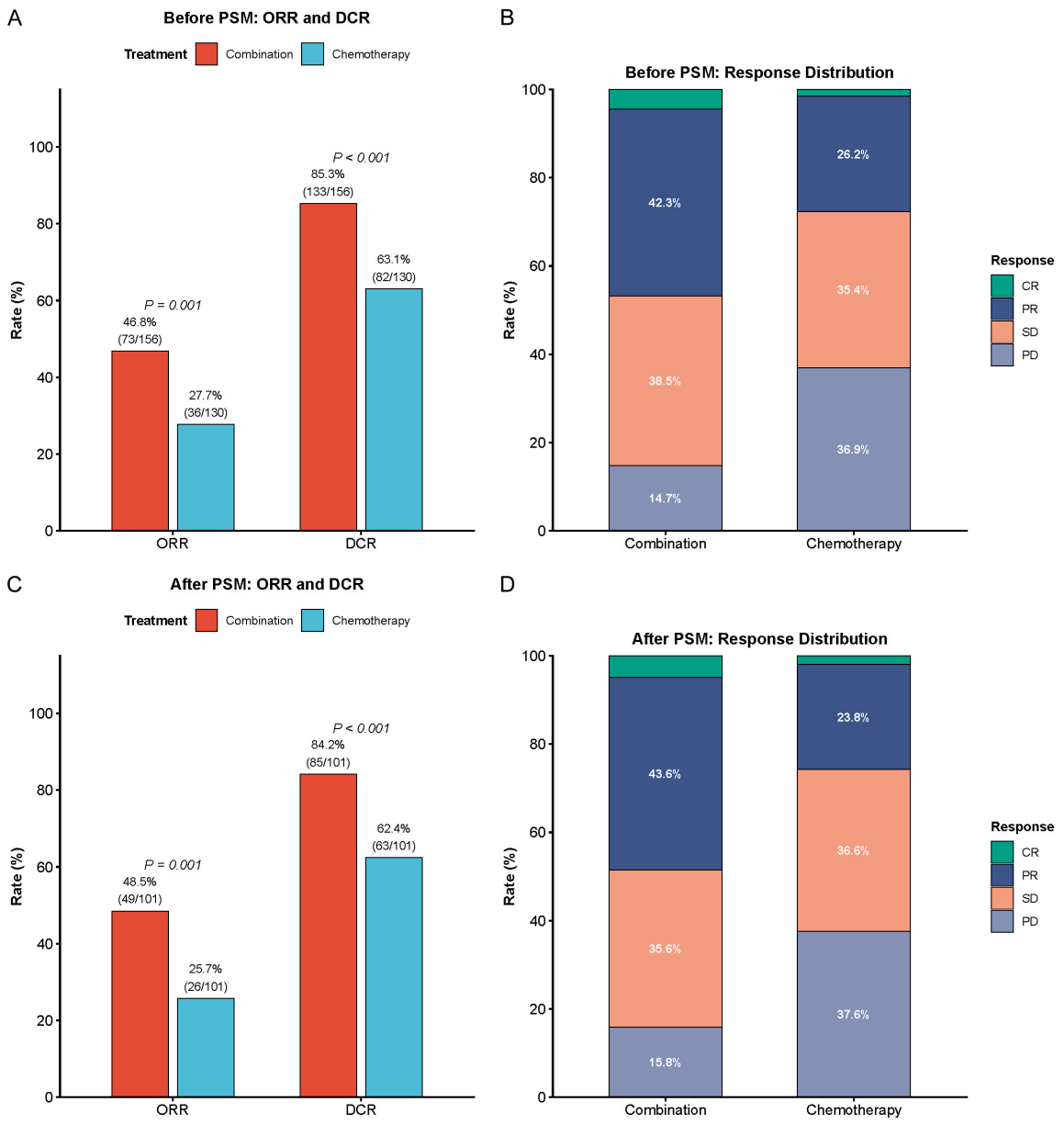

Figure 2. Short-term efficacy comparison between the combination therapy and chemotherapy alone groups before and after propensity score matching. A. Comparison of objective response rate (ORR) and disease control rate (DCR) between the combination therapy group and chemotherapy alone group before propensity score matching. B. Distribution of tumor response (CR, PR, SD, PD) between the two groups before matching. C. Comparison of ORR and DCR between the two groups after propensity score matching. D. Distribution of tumor response between the two groups after matching. Note: PSM: Propensity Score Matching, ORR: Objective Response Rate, DCR: Disease Control Rate, CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease.

HR=0.84, 95% CI: 0.56-1.27, P=0.407). After PSM, the median follow-up time was 42 months. No significant differences remained between groups in median PFS (10 months vs 11 months, HR=0.83, 95% CI: 0.51-1.37, P=0.475) or median OS (20.5 months vs 23 months, HR=0.79, 95% CI: 0.46-1.37, P=0.390). These results indicate comparable efficacy between tislelizumab and sintilimab in patients receiving chemotherapy combined with ICIs (**Figure 4**).

Univariate and multivariate cox regression analysis of prognostic factors

To identify independent risk factors affecting prognosis in patients with advanced NSCLC, univariate and multivariate Cox proportional

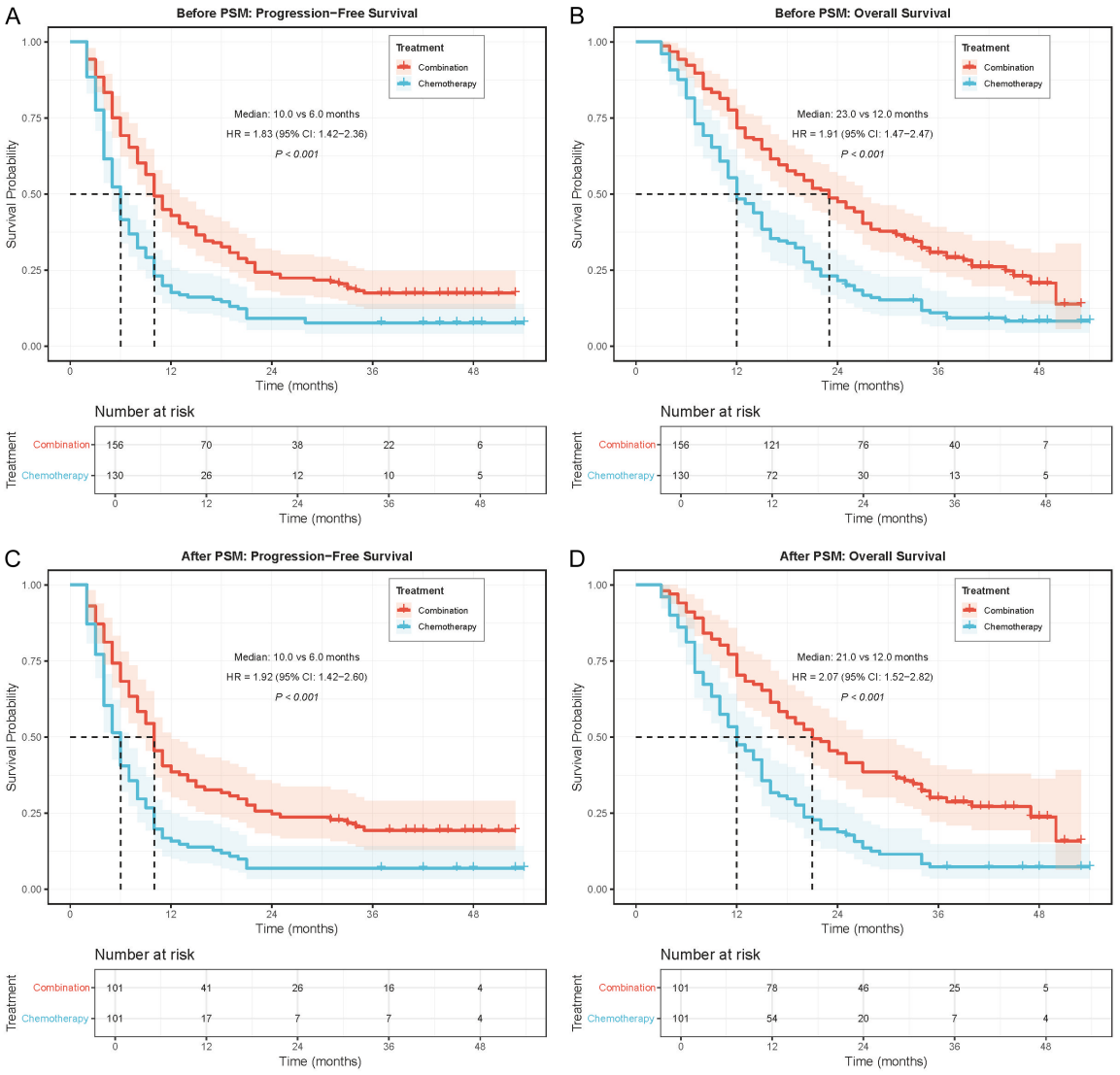

Figure 3. Kaplan-Meier survival curves for progression-free survival and overall survival before and after propensity score matching. A. Kaplan-Meier curves for progression-free survival (PFS) before propensity score matching. B. Kaplan-Meier curves for overall survival (OS) before propensity score matching. C. Kaplan-Meier curves for PFS after propensity score matching. D. Kaplan-Meier curves for OS after propensity score matching. The shaded areas represent 95% confidence intervals. The dashed lines indicate median survival time. The number at risk is shown below each plot. Note: PSM: Propensity Score Matching, PFS: Progression-Free Survival, OS: Overall Survival, HR: Hazard Ratio, CI: Confidence Interval.

hazards regression analyses were performed on the pre-PSM cohort.

In univariate analysis for PFS, treatment regimen (P<0.001), albumin (P<0.001), age (P< 0.001), smoking history (P=0.018), CCI (P< 0.001), ECOG PS (P<0.001), organ metastasis status (P<0.001), and number of metastatic organs (P<0.001) were significantly associated with PFS. Sex, BMI, hemoglobin, platelet count, ALT, AST, creatinine, disease stage, histological type, EGFR status, ALK status, and year of treatment initiation showed no significant association with PFS (all P>0.05). Variables with P<0.1 in univariate analysis were entered into multivariate analysis. Results showed that chemotherapy alone (P=0.036), low albumin level (P<0.001), age ≥65 years (P<0.001), smoking history (P=0.018), CCI ≥2 (P=0.045), ECOG PS ≥2 (P<0.001), presence of organ metastasis (P<0.001), and ≥2 metastatic organs (P=0.035) were independent risk factors for PFS.

In univariate analysis for OS, treatment regimen (P<0.001), albumin (P<0.001), age (P= 0.003), smoking history (P=0.012), CCI (P=

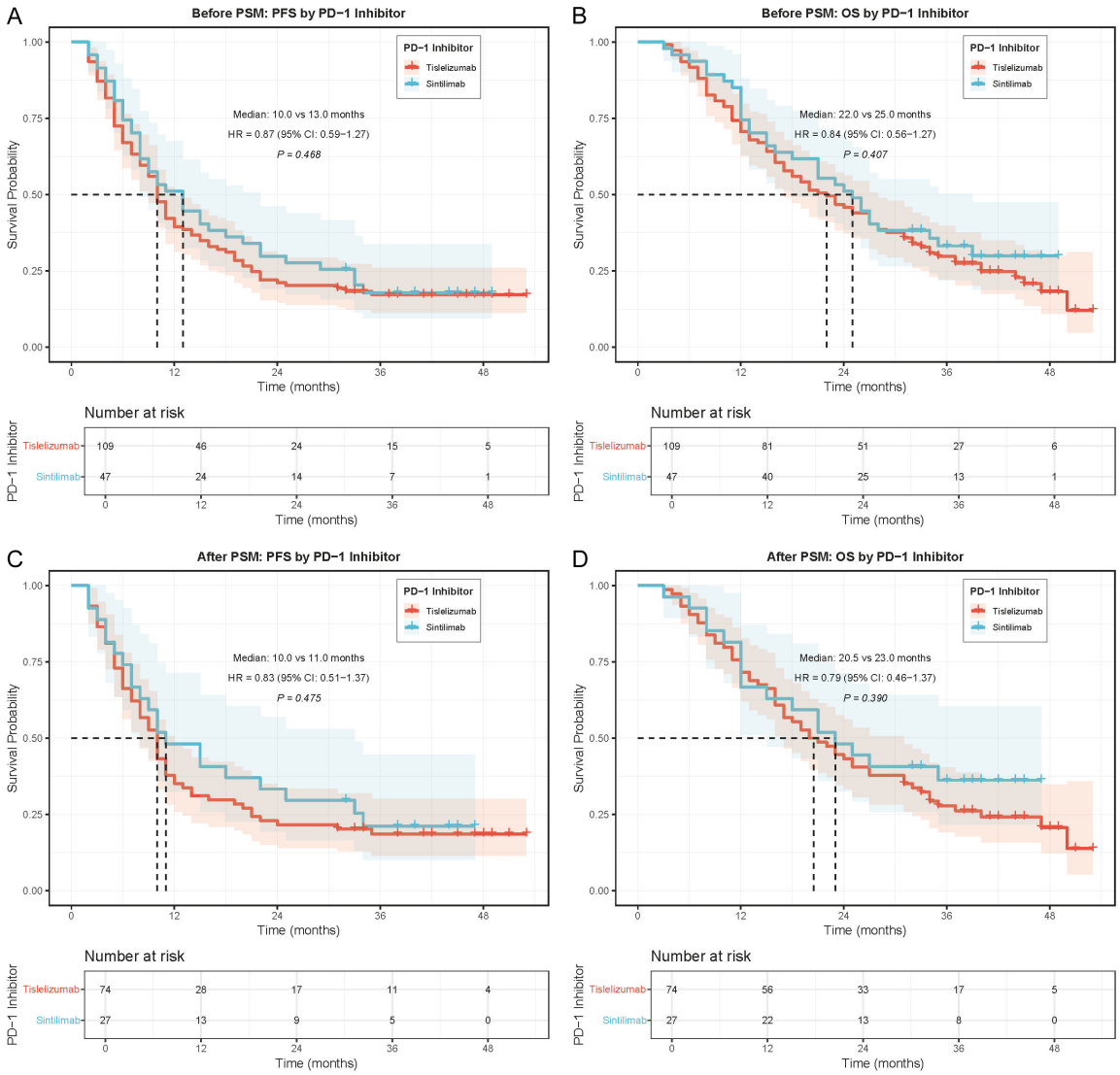

Figure 4. Kaplan-Meier survival curves for progression-free survival and overall survival by PD-1 inhibitor type before and after propensity score matching. A. Kaplan-Meier curves for progression-free survival (PFS) comparing tislelizumab and sintilimab before propensity score matching. B. Kaplan-Meier curves for overall survival (OS) comparing the two PD-1 inhibitors before matching. C. Kaplan-Meier curves for PFS after propensity score matching. D. Kaplan-Meier curves for OS after matching. The shaded areas represent 95% confidence intervals. The dashed lines indicate median survival time. The number at risk is shown below each plot. Note: PSM: Propensity Score Matching, PFS: Progression-Free Survival, OS: Overall Survival, PD-1: Programmed Cell Death Protein 1, HR: Hazard Ratio, CI: Confidence Interval.

0.001), ECOG PS (P<0.001), EGFR status (P=0.033), organ metastasis status (P<0.001), and number of metastatic organs (P<0.001) were significantly associated with OS. Sex, BMI, hemoglobin, platelet count, ALT, AST, creatinine, disease stage, histological type, ALK status, and year of treatment initiation showed no significant association with OS (all P>0.05). Multivariate analysis showed that chemotherapy alone (P=0.027), low albumin level (P< 0.001), age ≥65 years (P=0.012), ECOG PS ≥2 (P=0.008), presence of organ metastasis (P< 0.001), and ≥2 metastatic organs (P=0.024) were independent risk factors for OS. Smoking history (P=0.065), CCI (P=0.150), and EGFR status (P=0.054) did not demonstrate independent prognostic value in multivariate analysis (**Tables 3**, **4** and S1).

Univariate and multivariate cox regression analysis after propensity score matching

To further validate independent risk factors affecting prognosis in patients with advanced

Table 3. Univariate and multivariate Cox regression analysis for progression-free survival before propensity score matching

Variable	Univariate			Multivariate		
	β	*P* value	HR (95% CI)	β	*P* value	HR (95% CI)
Treatment regimen						
Combination therapy (Ref)			1.000 (Ref)			
Chemotherapy alone	0.605	<0.001	1.831 (1.424-2.356)	0.291	0.036	1.338 (1.019-1.756)
Albumin (g/L)	-0.075	<0.001	0.927 (0.906-0.950)	-0.056	<0.001	0.945 (0.921-0.971)
Hemoglobin (g/L)	-0.006	0.173	0.994 (0.986-1.002)			
Platelet ($\times 10^9$/L)	0.002	0.063	1.002 (1.000-1.003)	0.000	0.626	1.000 (0.999-1.002)
ALT (U/L)	0.000	0.961	1.000 (0.991-1.009)			
AST (U/L)	0.006	0.355	1.006 (0.994-1.018)			
Creatinine (μmol/L)	-0.006	0.118	0.994 (0.987-1.001)			
Sex						
Female (Ref)			1.000 (Ref)			
Male	-0.206	0.126	0.814 (0.626-1.059)			
Age						
<65 years (Ref)			1.000 (Ref)			
≥65 years	0.430	<0.001	1.537 (1.191-1.983)	0.453	<0.001	1.573 (1.212-2.042)
BMI						
<24 (Ref)			1.000 (Ref)			
≥24	0.046	0.722	1.047 (0.811-1.353)			
Smoking history						
No (Ref)			1.000 (Ref)			
Yes	0.315	0.018	1.370 (1.055-1.779)	0.334	0.018	1.396 (1.058-1.842)
CCI						
0-1 (Ref)			1.000 (Ref)			
≥2	0.470	<0.001	1.601 (1.219-2.102)	0.287	0.045	1.333 (1.007-1.765)
ECOG PS						
0-1 (Ref)			1.000 (Ref)			
≥2	0.785	<0.001	2.192 (1.608-2.989)	0.608	<0.001	1.837 (1.332-2.533)
Disease stage						
IIIB/IIIC (Ref)			1.000 (Ref)			
IV	0.246	0.129	1.279 (0.931-1.758)			
Histological type						
Adenocarcinoma (Ref)			1.000 (Ref)			
Squamous cell carcinoma	-0.054	0.700	0.947 (0.720-1.247)			
Other	-0.153	0.572	0.858 (0.505-1.458)			
EGFR status						
Positive (Ref)			1.000 (Ref)			
Negative	-0.269	0.132	0.764 (0.538-1.085)			
Unknown	0.012	0.950	1.012 (0.698-1.467)			
ALK status						
Positive (Ref)			1.000 (Ref)			
Negative	-0.390	0.236	0.677 (0.355-1.291)			
Unknown	-0.265	0.425	0.767 (0.401-1.470)			
Organ metastasis						
No metastasis (Ref)			1.000 (Ref)			
Metastasis	0.642	<0.001	1.901 (1.409-2.565)	0.619	<0.001	1.856 (1.365-2.524)

Number of metastatic organs						
0-1 (Ref)			1.000 (Ref)			
≥2	0.478	<0.001	1.613 (1.252-2.078)	0.281	0.035	1.324 (1.020-1.718)
Year of treatment initiation						
2021-2023 (Ref)			1.000 (Ref)			
2019-2020	-0.148	0.280	0.863 (0.660-1.127)			

Note: PFS: Progression-Free Survival, OS: Overall Survival, HR: Hazard Ratio, CI: Confidence Interval, BMI: Body Mass Index, CCI: Charlson Comorbidity Index, ECOG PS: Eastern Cooperative Oncology Group Performance Status, EGFR: Epidermal Growth Factor Receptor, ALK: Anaplastic Lymphoma Kinase, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, Ref: Reference.

Table 4. Univariate and multivariate Cox regression analysis for overall survival before propensity score matching

Variable	Univariate			Multivariate		
	β	*P* value	HR (95% CI)	β	*P* value	HR (95% CI)
Treatment regimen						
Combination therapy (Ref)			1.000 (Ref)			
Chemotherapy alone	0.647	<0.001	1.910 (1.474-2.475)	0.317	0.027	1.373 (1.036-1.819)
Albumin (g/L)	-0.076	<0.001	0.927 (0.904-0.950)	-0.049	<0.001	0.952 (0.926-0.978)
Hemoglobin (g/L)	-0.004	0.309	0.996 (0.987-1.004)			
Platelet ($\times 10^9$/L)	0.001	0.097	1.001 (1.000-1.003)	0.001	0.381	1.001 (0.999-1.003)
ALT (U/L)	0.001	0.876	1.001 (0.992-1.010)			
AST (U/L)	0.006	0.348	1.006 (0.994-1.018)			
Creatinine (μmol/L)	-0.007	0.073	0.993 (0.986-1.001)	-0.001	0.832	0.999 (0.991-1.007)
Sex						
Female (Ref)			1.000 (Ref)			
Male	-0.219	0.110	0.803 (0.614-1.051)			
Age						
<65 years (Ref)			1.000 (Ref)			
≥65 years	0.395	0.003	1.485 (1.143-1.929)	0.349	0.012	1.418 (1.080-1.861)
BMI						
<24 (Ref)			1.000 (Ref)			
≥24	0.101	0.452	1.106 (0.850-1.439)			
Smoking history						
No (Ref)			1.000 (Ref)			
Yes	0.340	0.012	1.406 (1.076-1.836)	0.273	0.065	1.314 (0.983-1.755)
CCI						
0-1 (Ref)			1.000 (Ref)			
≥2	0.455	0.001	1.577 (1.194-2.082)	0.217	0.150	1.242 (0.925-1.669)
ECOG PS						
0-1 (Ref)			1.000 (Ref)			
≥2	0.652	<0.001	1.919 (1.392-2.646)	0.476	0.008	1.609 (1.135-2.283)
Disease stage						
IIIB/IIIC (Ref)			1.000 (Ref)			
IV	0.291	0.086	1.338 (0.960-1.865)	0.115	0.517	1.121 (0.793-1.586)
Histological type						
Adenocarcinoma (Ref)			1.000 (Ref)			
Squamous cell carcinoma	-0.072	0.618	0.931 (0.702-1.234)			
Other	-0.138	0.623	0.871 (0.504-1.508)			

EGFR status						
Positive (Ref)			1.000 (Ref)			
Negative	-0.389	0.033	0.678 (0.474-0.970)	-0.359	0.054	0.698 (0.484-1.007)
Unknown	-0.078	0.684	0.925 (0.635-1.347)	-0.072	0.713	0.931 (0.634-1.366)
ALK status						
Positive (Ref)			1.000 (Ref)			
Negative	-0.620	0.060	0.538 (0.282-1.027)	-0.391	0.262	0.676 (0.341-1.340)
Unknown	-0.468	0.159	0.626 (0.327-1.201)	-0.411	0.242	0.663 (0.334-1.319)
Organ metastasis						
No metastasis (Ref)			1.000 (Ref)			
Metastasis	0.689	<0.001	1.991 (1.451-2.732)	0.627	<0.001	1.872 (1.351-2.595)
Number of metastatic organs						
0-1 (Ref)			1.000 (Ref)			
≥2	0.541	<0.001	1.717 (1.322-2.229)	0.314	0.024	1.368 (1.043-1.796)
Year of treatment initiation						
2021-2023 (Ref)			1.000 (Ref)			
2019-2020	-0.079	0.572	0.924 (0.702-1.216)			

Note: PFS: Progression-Free Survival, OS: Overall Survival, HR: Hazard Ratio, CI: Confidence Interval, BMI: Body Mass Index, CCI: Charlson Comorbidity Index, ECOG PS: Eastern Cooperative Oncology Group Performance Status, EGFR: Epidermal Growth Factor Receptor, ALK: Anaplastic Lymphoma Kinase, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, Ref: Reference.

NSCLC, univariate and multivariate Cox proportional hazards regression analyses were performed on the post-PSM cohort.

In univariate analysis for PFS, treatment regimen (P<0.001), albumin (P<0.001), age (P= 0.041), CCI (P<0.001), ECOG PS (P<0.001), organ metastasis status (P=0.001), and number of metastatic organs (P=0.008) were significantly associated with PFS. Sex, BMI, hemoglobin, platelet count, ALT, AST, creatinine, smoking history, disease stage, histological type, EGFR status, ALK status, and year of treatment initiation showed no significant association with PFS (all P>0.05). Multivariate analysis showed that chemotherapy alone (P< 0.001), low albumin level (P=0.002), age ≥65 years (P=0.041), CCI ≥2 (P=0.008), ECOG PS ≥2 (P<0.001), and presence of organ metastasis (P<0.001) were independent risk factors for PFS, while treatment initiation in 2019-2020 was an independent protective factor for PFS (P=0.038).

In univariate analysis for OS, treatment regimen (P<0.001), albumin (P<0.001), CCI (P< 0.001), ECOG PS (P=0.007), organ metastasis status (P=0.002), and number of metastatic organs (P=0.005) were significantly associated with OS. Sex, age, BMI, hemoglobin, platelet count, ALT, AST, creatinine, smoking history, disease stage, histological type, EGFR status, ALK status, and year of treatment initiation showed no significant association with OS (all P>0.05). Multivariate analysis showed that chemotherapy alone (P<0.001), low albumin level (P=0.009), CCI ≥2 (P=0.024), ECOG PS ≥2 (P=0.004), and presence of organ metastasis (P<0.001) were independent risk factors for OS. Age (P=0.219), ALK status (P=0.073), and number of metastatic organs (P=0.121) did not demonstrate independent prognostic value in multivariate analysis (**Tables 5** and **6**).

Construction of nomograms for predicting prognosis in advanced NSCLC patients

Nomograms for predicting PFS and OS were constructed based on independent prognostic factors identified through multivariate Cox regression analysis of the pre-PSM cohort. The PFS prediction model incorporated 8 predictors: treatment regimen, serum albumin, age, smoking history, CCI, ECOG PS, organ metastasis status, and number of metastatic organs. The linear predictor formula was:

PFS risk score = 0.291 × treatment regimen - 0.056 × albumin + 0.453 × age + 0.334 × smoking history + 0.287 × CCI + 0.608 × ECOG PS + 0.619 × organ metastasis status + 0.281 × number of metastatic organs.

Table 5. Univariate and multivariate Cox regression analysis for progression-free survival after propensity score matching

Variable	Univariate			Multivariate		
	β	*P* value	HR (95% CI)	β	*P* value	HR (95% CI)
Treatment regimen						
Combination therapy (Ref)			1.000 (Ref)			
Chemotherapy alone	0.654	<0.001	1.923 (1.422-2.600)	0.641	<0.001	1.899 (1.378-2.616)
Albumin (g/L)	-0.067	<0.001	0.935 (0.910-0.961)	-0.047	0.002	0.954 (0.926-0.984)
Hemoglobin (g/L)	-0.006	0.202	0.994 (0.985-1.003)			
Platelet ($\times 10^9$/L)	0.001	0.305	1.001 (0.999-1.003)			
ALT (U/L)	-0.001	0.917	0.999 (0.989-1.010)			
AST (U/L)	0.005	0.464	1.005 (0.991-1.019)			
Creatinine (μmol/L)	0.000	0.950	1.000 (0.991-1.009)			
Sex						
Female (Ref)			1.000 (Ref)			
Male	-0.277	0.083	0.758 (0.554-1.037)	-0.100	0.548	0.905 (0.652-1.255)
Age						
<65 years (Ref)			1.000 (Ref)			
≥65 years	0.316	0.041	1.372 (1.013-1.857)	0.320	0.041	1.378 (1.013-1.874)
BMI						
<24 (Ref)			1.000 (Ref)			
≥24	0.093	0.553	1.097 (0.808-1.490)			
Smoking history						
No (Ref)			1.000 (Ref)			
Yes	0.188	0.240	1.207 (0.882-1.653)			
CCI						
0-1 (Ref)			1.000 (Ref)			
≥2	0.596	<0.001	1.815 (1.309-2.517)	0.470	0.008	1.600 (1.133-2.262)
ECOG PS						
0-1 (Ref)			1.000 (Ref)			
≥2	0.664	<0.001	1.943 (1.358-2.780)	0.649	<0.001	1.914 (1.313-2.790)
Disease stage						
IIIB/IIIC (Ref)			1.000 (Ref)			
IV	0.271	0.157	1.311 (0.901-1.907)			
Histological type						
Adenocarcinoma (Ref)			1.000 (Ref)			
Squamous cell carcinoma	-0.168	0.309	0.846 (0.612-1.168)			
Other	-0.401	0.274	0.670 (0.327-1.373)			
EGFR status						
Positive (Ref)			1.000 (Ref)			
Negative	-0.086	0.689	0.917 (0.602-1.399)			
Unknown	0.305	0.179	1.356 (0.870-2.114)			
ALK status						
Positive (Ref)			1.000 (Ref)			
Negative	-0.363	0.392	0.696 (0.303-1.597)			
Unknown	-0.302	0.479	0.739 (0.321-1.705)			
Organ metastasis						
No metastasis (Ref)			1.000 (Ref)			
Metastasis	0.635	0.001	1.887 (1.283-2.774)	0.780	<0.001	2.181 (1.461-3.254)

Number of metastatic organs						
0-1 (Ref)			1.000 (Ref)			
≥2	0.404	0.008	1.498 (1.110-2.022)	0.269	0.092	1.309 (0.957-1.791)
Year of treatment initiation						
2021-2023 (Ref)			1.000 (Ref)			
2019-2020	-0.275	0.095	0.759 (0.550-1.049)	-0.361	0.038	0.697 (0.495-0.981)

Note: PSM: Propensity Score Matching, PFS: Progression-Free Survival, OS: Overall Survival, HR: Hazard Ratio, CI: Confidence Interval, BMI: Body Mass Index, CCI: Charlson Comorbidity Index, ECOG PS: Eastern Cooperative Oncology Group Performance Status, EGFR: Epidermal Growth Factor Receptor, ALK: Anaplastic Lymphoma Kinase, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, Ref: Reference.

Table 6. Univariate and multivariate Cox regression analysis for overall survival after propensity score matching

Variable	Univariate			Multivariate		
	β	*P* value	HR (95% CI)	β	*P* value	HR (95% CI)
Treatment regimen						
Combination therapy (Ref)			1.000 (Ref)			
Chemotherapy alone	0.726	<0.001	2.067 (1.516-2.818)	0.674	<0.001	1.962 (1.424-2.704)
Albumin (g/L)	-0.066	<0.001	0.936 (0.910-0.963)	-0.041	0.009	0.960 (0.932-0.990)
Hemoglobin (g/L)	-0.004	0.364	0.996 (0.986-1.005)			
Platelet ($\times 10^9$/L)	0.001	0.442	1.001 (0.999-1.003)			
ALT (U/L)	0.000	0.969	1.000 (0.990-1.011)			
AST (U/L)	0.006	0.423	1.006 (0.992-1.020)			
Creatinine (μmol/L)	-0.001	0.748	0.999 (0.989-1.008)			
Sex						
Female (Ref)			1.000 (Ref)			
Male	-0.249	0.129	0.780 (0.566-1.075)			
Age						
<65 years (Ref)			1.000 (Ref)			
≥65 years	0.260	0.100	1.297 (0.951-1.769)	0.197	0.219	1.218 (0.889-1.668)
BMI						
<24 (Ref)			1.000 (Ref)			
≥24	0.153	0.338	1.166 (0.852-1.595)			
Smoking history						
No (Ref)			1.000 (Ref)			
Yes	0.222	0.173	1.249 (0.907-1.719)			
CCI						
0-1 (Ref)			1.000 (Ref)			
≥2	0.571	<0.001	1.770 (1.267-2.472)	0.409	0.024	1.505 (1.056-2.146)
ECOG PS						
0-1 (Ref)			1.000 (Ref)			
≥2	0.513	0.007	1.670 (1.149-2.427)	0.565	0.004	1.760 (1.198-2.586)
Disease stage						
IIIB/IIIC (Ref)			1.000 (Ref)			
IV	0.304	0.127	1.356 (0.917-2.004)			

Histological type						
Adenocarcinoma (Ref)			1.000 (Ref)			
Squamous cell carcinoma	-0.161	0.337	0.851 (0.612-1.183)			
Other	-0.348	0.343	0.706 (0.344-1.450)			
EGFR status						
Positive (Ref)			1.000 (Ref)			
Negative	-0.171	0.438	0.843 (0.548-1.298)			
Unknown	0.247	0.281	1.281 (0.817-2.008)			
ALK status						
Positive (Ref)			1.000 (Ref)			
Negative	-0.718	0.092	0.487 (0.211-1.124)	-0.795	0.073	0.451 (0.189-1.077)
Unknown	-0.601	0.160	0.548 (0.237-1.268)	-0.707	0.113	0.493 (0.206-1.182)
Organ metastasis						
No metastasis (Ref)			1.000 (Ref)			
Metastasis	0.634	0.002	1.885 (1.264-2.811)	0.736	<0.001	2.087 (1.385-3.147)
Number of metastatic organs						
0-1 (Ref)			1.000 (Ref)			
≥2	0.435	0.005	1.545 (1.137-2.101)	0.254	0.121	1.290 (0.935-1.779)
Year of treatment initiation						
2021-2023 (Ref)			1.000 (Ref)			
2019-2020	-0.192	0.254	0.826 (0.594-1.148)			

Note: PSM: Propensity Score Matching, PFS: Progression-Free Survival, OS: Overall Survival, HR: Hazard Ratio, CI: Confidence Interval, BMI: Body Mass Index, CCI: Charlson Comorbidity Index, ECOG PS: Eastern Cooperative Oncology Group Performance Status, EGFR: Epidermal Growth Factor Receptor, ALK: Anaplastic Lymphoma Kinase, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, Ref: Reference.

Where treatment regimen (combination therapy=0, chemotherapy alone=1), age (<65 years =0, ≥65 years =1), smoking history (no=0, yes=1), CCI (0-1=0, ≥2=1), ECOG PS (0-1=0, ≥2=1), organ metastasis status (no =0, yes =1), number of metastatic organs (0-1=0, ≥2=1), and albumin entered the model as original values (g/L). This model can predict 6-month, 12-month, and 24-month progression-free survival probability.

The OS prediction model incorporated 6 predictors: treatment regimen, serum albumin, age, ECOG PS, organ metastasis status, and number of metastatic organs. The linear predictor formula was:

OS risk score = 0.317 × treatment regimen - 0.049 × albumin + 0.349 × age + 0.476 × ECOG PS + 0.627 × organ metastasis status + 0.314 × number of metastatic organs.

Variable coding was the same as the PFS model. This model can predict 12-month, 24-month, and 36-month overall survival probability (**Figure 5**).

Internal validation of PFS prediction model in training cohort

The PFS prediction model was internally validated in the training cohort using time-dependent ROC curves, calibration curves, DCA, and risk stratification survival analysis. Time-dependent ROC curves showed AUC values of 0.804, 0.789, and 0.766 for predicting 6-month, 12-month, and 24-month PFS, indicating good model discrimination. Calibration curves showed good agreement between predicted and observed survival probabilities for 12-month PFS, with a Brier score of 0.1664 and Hosmer-Lemeshow test P>0.05, suggesting good model calibration. DCA results showed that the model's net benefit exceeded both "treat all" and "treat none" strategies across a wide range of threshold probabilities, indicating good clinical utility. Based on the median

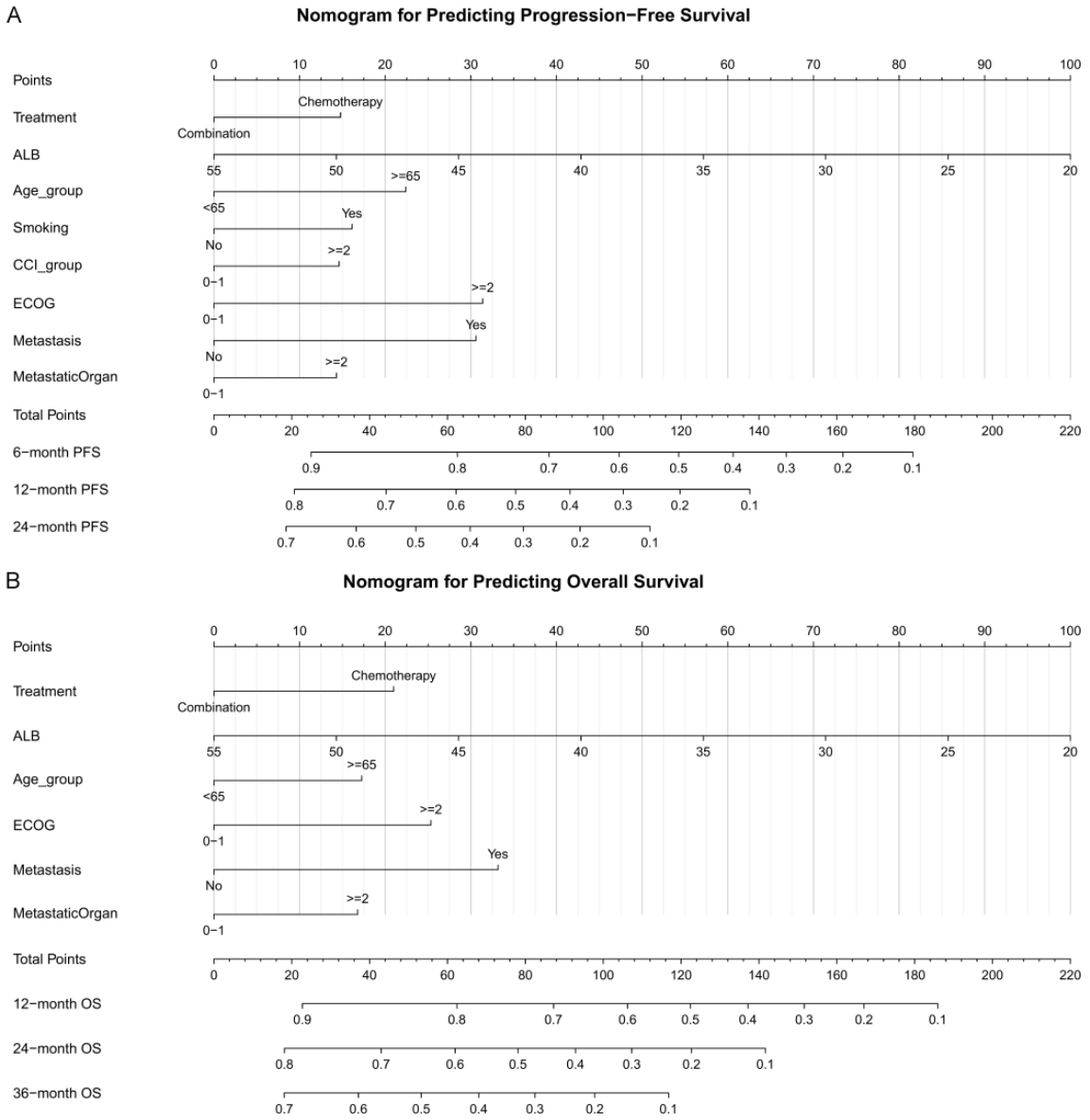

Figure 5. Nomograms for predicting progression-free survival and overall survival in patients with advanced non-small cell lung cancer. A. Nomogram for predicting 6-month, 12-month, and 24-month progression-free survival (PFS). The model incorporates treatment regimen, serum albumin, age, smoking history, Charlson Comorbidity Index, ECOG performance status, organ metastasis, and number of metastatic organs. B. Nomogram for predicting 12-month, 24-month, and 36-month overall survival (OS). The model incorporates treatment regimen, serum albumin, age, ECOG performance status, organ metastasis, and number of metastatic organs. To use the nomogram, the value of each variable is located on the corresponding axis, and a vertical line is drawn upward to the "Points" axis to determine the points for each variable. The total points are calculated by summing all individual points, and the predicted survival probability is obtained by drawing a vertical line from the "Total Points" axis to the survival probability axis. Note: PFS: Progression-Free Survival, OS: Overall Survival, ALB: Albumin, ECOG PS: Eastern Cooperative Oncology Group Performance Status, CCI: Charlson Comorbidity Index.

model risk score, patients were divided into high-risk and low-risk groups. Kaplan-Meier survival curves showed significant differences in PFS between the two groups (P<0.001), with worse prognosis in the high-risk group, indicating good risk stratification capability (**Figure 6**).

Internal validation of OS prediction model in training cohort

The OS prediction model was internally validated in the training cohort using time-dependent ROC curves, calibration curves, DCA, and risk

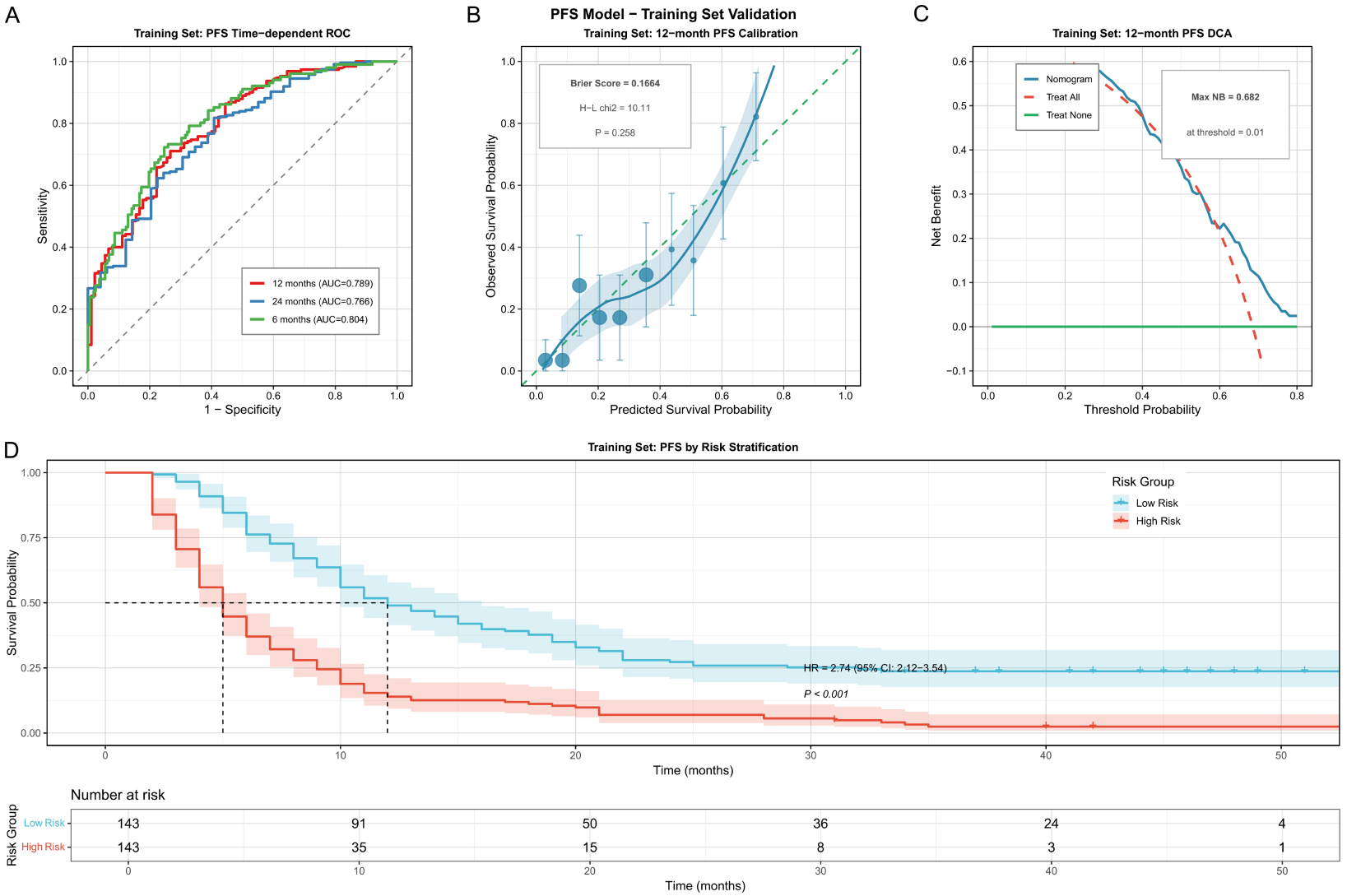

Figure 6. Internal validation of the PFS prediction model in the training set. A. Time-dependent receiver operating characteristic (ROC) curves for predicting 6-month, 12-month, and 24-month progression-free survival (PFS). B. Calibration curve for 12-month PFS prediction; the dashed line represents ideal calibration. C. Decision curve analysis (DCA) for 12-month PFS prediction; the blue line represents the nomogram model, the red dashed line represents the “treat all” strategy, and the green line represents the “treat none” strategy. D. Kaplan-Meier survival curves for PFS stratified by risk score; patients were divided into high-risk and low-risk groups based on the median risk score. Note: PFS: Progression-Free Survival, ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, DCA: Decision Curve Analysis, HR: Hazard Ratio, CI: Confidence Interval.

stratification survival analysis. Time-dependent ROC curves showed AUC values of 0.784, 0.756, and 0.797 for predicting 12-month, 24-month, and 36-month OS, indicating good model discrimination. Calibration curves showed good agreement between predicted and observed survival probabilities for 24-month OS, with a Brier score of 0.1867 and Hosmer-Lemeshow test P>0.05, suggesting good model calibration. DCA results showed that the model's net benefit exceeded both "treat all" and "treat none" strategies across a wide range of threshold probabilities, indicating good clinical utility. Based on the median model risk score, patients were divided into high-risk and low-risk groups. Kaplan-Meier survival curves showed significant differences in OS between the two groups (HR=2.26, 95% CI: 1.81-3.35, P<0.001), with worse prognosis in the high-risk group, indicating good risk stratification capability (**Figure 7**).

Baseline characteristics comparison between training and external validation cohorts

To validate the extrapolation performance of the prognostic prediction models, this study included 124 patients in the external validation cohort. No significant differences were observed between the training cohort (n=286) and external validation cohort (n=124) in treatment regimen, sex, age, BMI, smoking history, CCI, ECOG PS, disease stage, histological type, EGFR status, ALK status, organ metastasis status, number of metastatic organs, year of treatment initiation, or laboratory parameters including albumin, hemoglobin, platelet count, alanine aminotransferase, aspartate aminotransferase, and creatinine (all P>0.05). This indicates good comparability of baseline characteristics between the two cohorts, and the external validation cohort can be used to assess model generalizability (**Table 7**).

External validation of PFS prediction model

The PFS prediction model was independently validated using the external validation cohort. Time-dependent ROC curves showed AUC values of 0.830, 0.797, and 0.806 for predicting 6-month, 12-month, and 24-month PFS, indicating that the model maintained good discrimination in the external validation cohort. Calibration curves showed good agreement between predicted and observed survival probabilities for 12-month PFS, with a Brier score of 0.1714 and Hosmer-Lemeshow test P>0.05, suggesting good model calibration. DCA results showed that the model's net benefit exceeded both "treat all" and "treat none" strategies across a wide range of threshold probabilities, indicating good clinical utility in the external population. Based on the median model risk score, patients were divided into high-risk and low-risk groups. Kaplan-Meier survival curves showed significant differences in PFS between the two groups (HR=2.01, 95% CI: 1.75-3.86, P=0.001), with worse prognosis in the high-risk group, further validating the model's risk stratification capability (**Figure 8**).

External validation of OS prediction model

The OS prediction model was independently validated using the external validation cohort. Time-dependent ROC curves showed AUC values of 0.836, 0.783, and 0.817 for predicting 12-month, 24-month, and 36-month OS, indicating that the model maintained good discrimination in the external validation cohort. Calibration curves showed good agreement between predicted and observed survival probabilities for 24-month OS, with a Brier score of 0.1813 and Hosmer-Lemeshow test P>0.05, suggesting good model calibration. DCA results showed that the model's net benefit exceeded both "treat all" and "treat none" strategies across a wide range of threshold probabilities, indicating good clinical utility in the external population. Based on the median model risk score, patients were divided into high-risk and low-risk groups. Kaplan-Meier survival curves showed significant differences in OS between the two groups (HR=2.38, 95% CI: 1.70-3.81, P<0.001), with worse prognosis in the high-risk group, further validating the model's risk stratification capability (**Table 7**; **Figure 9**).

Discussion

Non-small cell lung cancer (NSCLC) causes a lot of death. Utilizing multicenter real-world cohort data, the study illustrates that the addition of PD-1 inhibitors to chemotherapy was substantially linked with a higher ORR, higher DCR, longer PFS and OS than chemotherapy alone. Even after applying PSM and multivariate adjustment, this association persisted. The efficacy of tislelizumab and sintilimab is similar. Several independent prognostic factors were

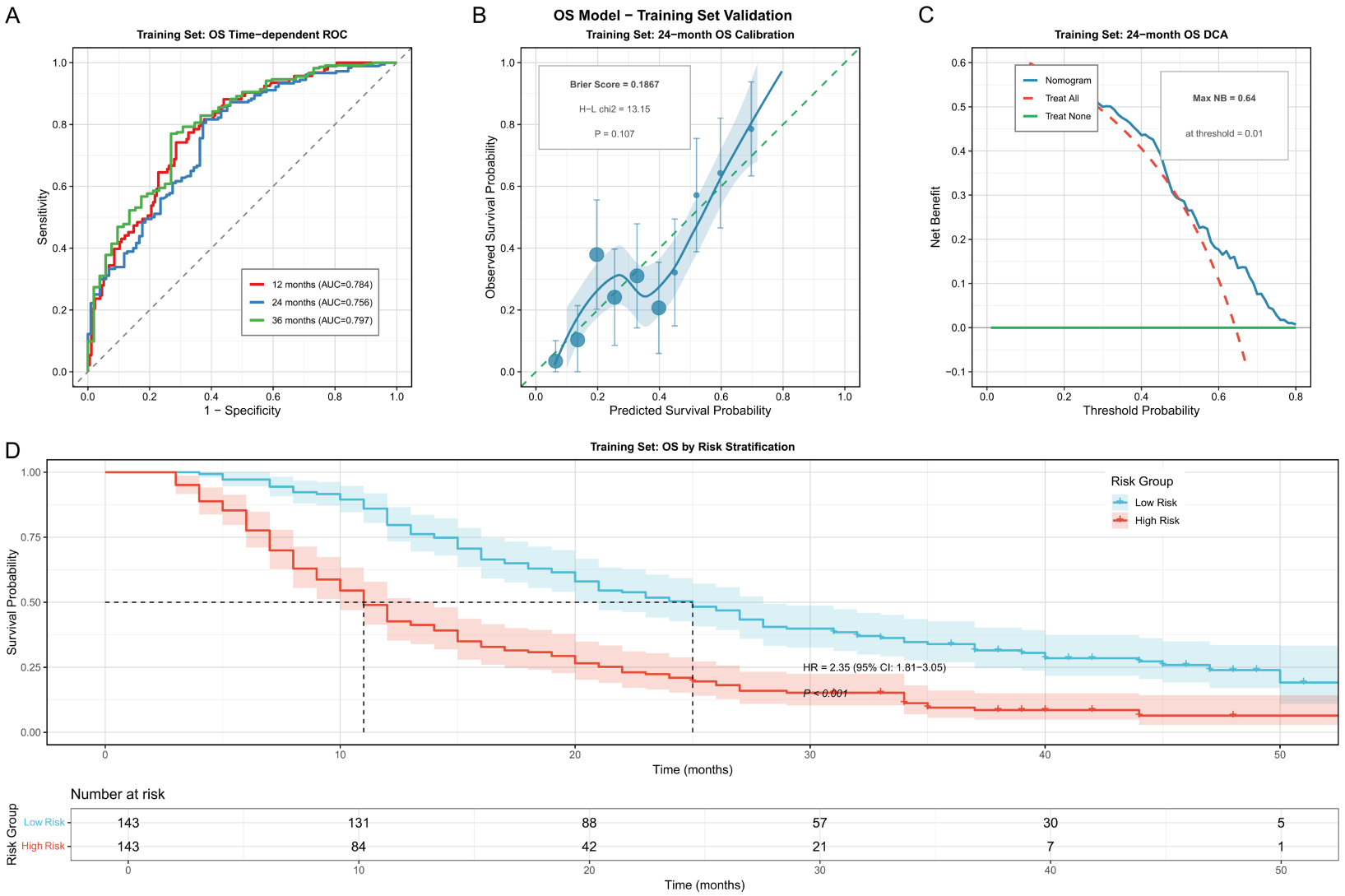

Figure 7. Internal validation of the OS prediction model in the training set. A. Time-dependent receiver operating characteristic (ROC) curves for predicting 12-month, 24-month, and 36-month overall survival (OS). B. Calibration curve for 24-month OS prediction; the dashed line represents ideal calibration. C. Decision curve analysis (DCA) for 24-month OS prediction; the blue line represents the nomogram model, the red dashed line represents the “treat all” strategy, and the green line represents the “treat none” strategy. D. Kaplan-Meier survival curves for OS stratified by risk score; patients were divided into high-risk and low-risk groups based on the median risk score. Note: OS: Overall Survival, ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, DCA: Decision Curve Analysis, HR: Hazard Ratio, CI: Confidence Interval.

Table 7. Comparison of baseline characteristics between the training and external validation cohorts

Factor	Total (n=410)	Chemotherapy alone (n=286)	Combination therapy (n=124)	Statistic	*P* value
Treatment regimen				0.003	0.956
Combination therapy (Ref)	186 (45.37%)	130 (45.45%)	56 (45.16%)		
Chemotherapy alone	224 (54.63%)	156 (54.55%)	68 (54.84%)		
Sex				0.000	0.986
Female (Ref)	278 (67.80%)	194 (67.83%)	84 (67.74%)		
Male	132 (32.20%)	92 (32.17%)	40 (32.26%)		
Age				0.140	0.708
<65 years (Ref)	247 (60.24%)	174 (60.84%)	73 (58.87%)		
≥65 years	163 (39.76%)	112 (39.16%)	51 (41.13%)		
BMI				0.080	0.777
<24 (Ref)	257 (62.68%)	178 (62.24%)	79 (63.71%)		
≥24	153 (37.32%)	108 (37.76%)	45 (36.29%)		
Smoking history				0.048	0.827
No (Ref)	271 (66.10%)	190 (66.43%)	81 (65.32%)		
Yes	139 (33.90%)	96 (33.57%)	43 (34.68%)		
CCI				0.148	0.701
0-1 (Ref)	293 (71.46%)	206 (72.03%)	87 (70.16%)		
≥2	117 (28.54%)	80 (27.97%)	37 (29.84%)		
ECOG PS				0.974	0.324
0-1 (Ref)	339 (82.68%)	233 (81.47%)	106 (85.48%)		
≥2	71 (17.32%)	53 (18.53%)	18 (14.52%)		
Disease stage				0.500	0.480
IIIB/IIIC (Ref)	87 (21.22%)	58 (20.28%)	29 (23.39%)		
IV	323 (78.78%)	228 (79.72%)	95 (76.61%)		
Histological type				1.613	0.446
Adenocarcinoma (Ref)	260 (63.41%)	180 (62.94%)	80 (64.52%)		
Squamous cell carcinoma	128 (31.22%)	88 (30.77%)	40 (32.26%)		
Other	22 (5.37%)	18 (6.29%)	4 (3.23%)		
EGFR status				0.438	0.803
Positive (Ref)	66 (16.10%)	48 (16.78%)	18 (14.52%)		
Negative	213 (51.95%)	146 (51.05%)	67 (54.03%)		
Unknown	131 (31.95%)	92 (32.17%)	39 (31.45%)		
ALK status				1.009	0.604
Positive (Ref)	17 (4.15%)	10 (3.50%)	7 (5.65%)		
Negative	216 (52.68%)	152 (53.15%)	64 (51.61%)		
Unknown	177 (43.17%)	124 (43.36%)	53 (42.74%)		
Organ metastasis				0.035	0.852
No metastasis (Ref)	305 (74.39%)	212 (74.13%)	93 (75.00%)		
Metastasis	105 (25.61%)	74 (25.87%)	31 (25.00%)		
Number of metastatic organs				0.255	0.614
0-1 (Ref)	247 (60.24%)	170 (59.44%)	77 (62.10%)		
≥2	163 (39.76%)	116 (40.56%)	47 (37.90%)		
Year of treatment initiation				1.509	0.219
2021-2023 (Ref)	130 (31.71%)	96 (33.57%)	34 (27.42%)		
2019-2020	280 (68.29%)	190 (66.43%)	90 (72.58%)		
Albumin (g/L)	38.27±5.02	38.09±4.94	38.69±5.20	-1.110	0.268
Hemoglobin (g/L)	122.93±16.05	122.86±15.93	123.09±16.39	-0.134	0.893
Platelet ($\times 10^9$/L)	258.56±75.61	260.50±76.15	254.07±74.45	0.790	0.430
ALT (U/L)	26.00 [17.00, 36.00]	26.00 [16.25, 36.00]	25.50 [17.00, 36.00]	0.113	0.910
AST (U/L)	24.00 [17.00, 31.00]	24.00 [17.00, 32.00]	23.50 [16.75, 29.25]	0.368	0.713
Creatinine (μmol/L)	75.16±17.70	74.68±17.52	76.27±18.13	-0.838	0.402

Note: BMI: Body Mass Index, CCI: Charlson Comorbidity Index, ECOG PS: Eastern Cooperative Oncology Group Performance Status, EGFR: Epidermal Growth Factor Receptor, ALK: Anaplastic Lymphoma Kinase, ALB: Albumin, Hb: Hemoglobin, PLT: Platelet, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, Cr: Creatinine.

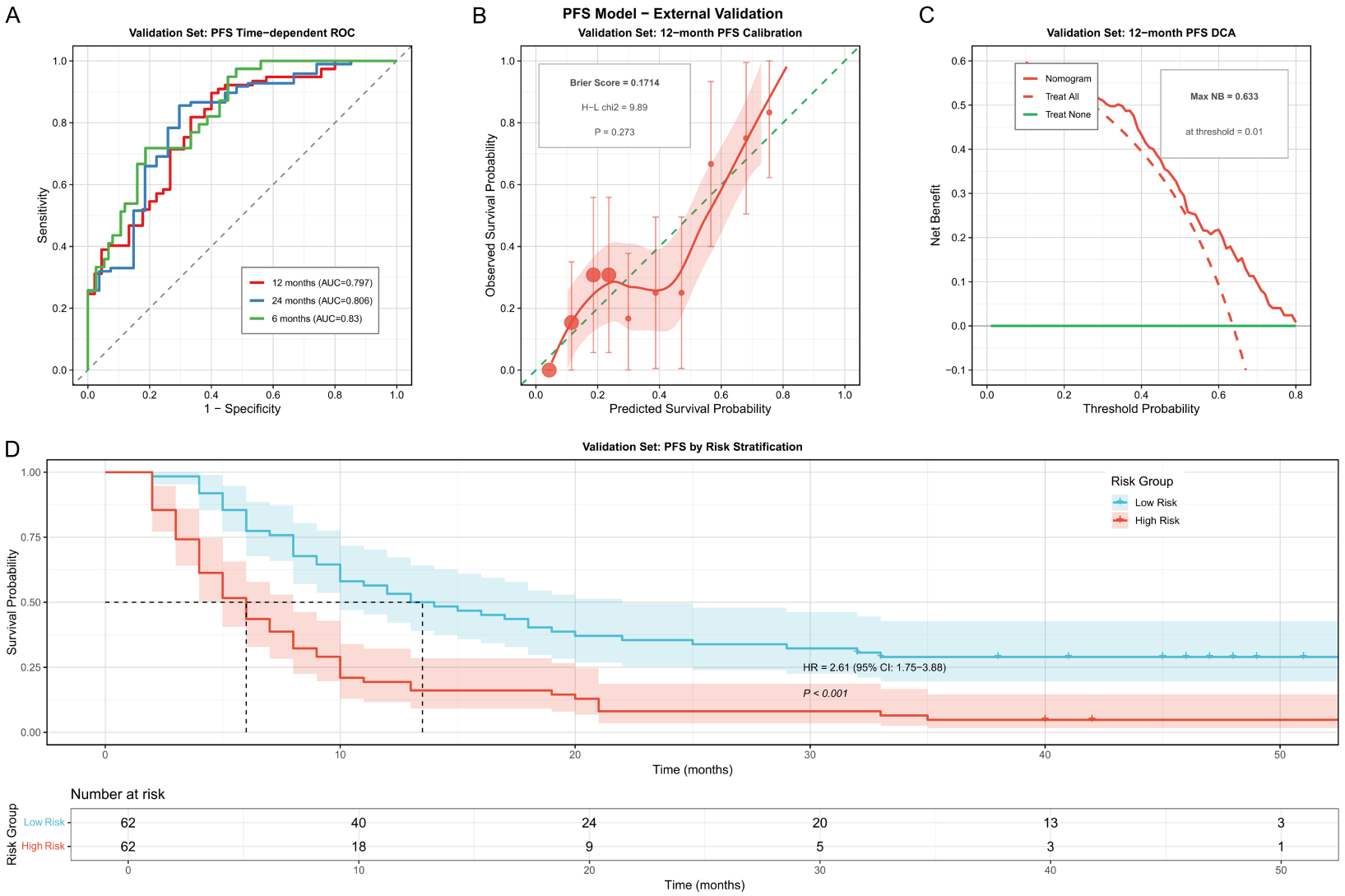

Figure 8. External validation of the PFS prediction model in the validation cohort. A. Time-dependent receiver operating characteristic (ROC) curves for predicting 6-month, 12-month, and 24-month progression-free survival (PFS) in the external validation cohort. B. Calibration curve for 12-month PFS prediction; the dashed line represents ideal calibration. C. Decision curve analysis (DCA) for 12-month PFS prediction; the red line represents the nomogram model, the red dashed line represents the “treat all” strategy, and the green line represents the “treat none” strategy. D. Kaplan-Meier survival curves for PFS stratified by risk score; patients were divided into high-risk and low-risk groups based on the median risk score. Note: PFS: Progression-Free Survival, ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, DCA: Decision Curve Analysis, HR: Hazard Ratio, CI: Confidence Interval.

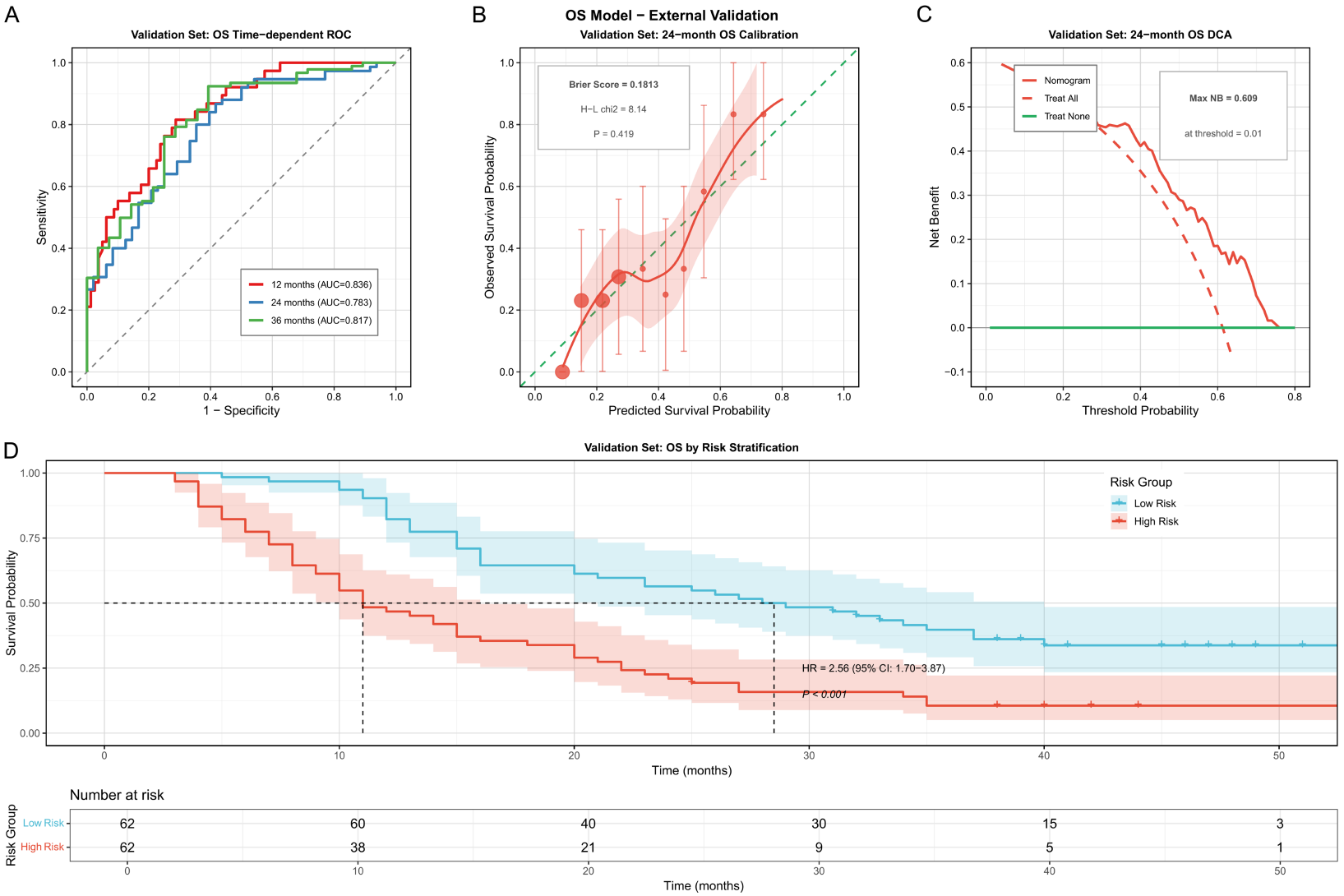

Figure 9. External validation of the OS prediction model in the validation cohort. A. Time-dependent receiver operating characteristic (ROC) curves for predicting 12-month, 24-month, and 36-month overall survival (OS) in the external validation cohort. B. Calibration curve for 24-month OS prediction; the dashed line represents ideal calibration. C. Decision curve analysis (DCA) for 24-month OS prediction; the red line represents the nomogram model, the red dashed line represents the "treat all" strategy, and the green line represents the "treat none" strategy. D. Kaplan-Meier survival curves for OS stratified by risk score; patients were divided into high-risk and low-risk groups based on the median risk score. Note: OS: Overall Survival, ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, DCA: Decision Curve Analysis, HR: Hazard Ratio, CI: Confidence Interval.

also identified and nomogram models for predicting PFS and OS were constructed with both predictive performances verified in internal and external validation.

Our efficacy findings are largely consistent with prior large RCTs. According to the KEYNOTE-189 study [10], the pembrolizumab plus chemotherapy regimen has been associated with an ORR of 47.6% and a median PFS of 8.8 months in patients with non-squamous NSCLC. According to the findings of the KEYNOTE-407 study [11] on squamous NSCLC, the ORR was 57.9%, the median PFS was 6.4 months, and the median OS was 15.9 months. The efficacy and safety of camrelizumab were illustrated in the CameL study [12], with an ORR for the 1L treatment of Chinese patients with advanced NSCLC. Also, the ORIENT-11 study ()13) provides evidence of sintilimab combined with chemotherapy has an ORR of 51.9% in this population. Our combination therapy's overall response rate (ORR) was 48.5% with a median progression-free survival (PFS) of 10 months and a median overall survival (OS) of 21 months, consistent with these findings. These data confirm the real-world applicability of these results. As previously mentioned [16], the longer PFS that we observed as compared to KEYNOTE-189 study can be attributed to the longer imaging evaluation intervals and less stringent progression assessment timepoints in real-world practice. Notably, real-world studies often enroll older patients and patients with more comorbidities that are excluded from RCT, which may improve the external validity of our results. Prior systematic reviews and network meta-analyses suggest that there may be limited overall efficacy differences among PD-1 and PD-L1 inhibitors with chemotherapy [26]. Our direct comparison showed that there was no significant difference in PFS or OS between tislelizumab and sintilimab, either before PSM or after PSM. This suggests that drug of choice in clinical practice may be guided by be guided by availability and economic factors.

The treatment regimen turned out to be an independent prognostic factor for PFS and OS. A possible synergistic mechanism involving chemotherapy-induced immunogenic cell death and release of tumor-associated antigens, together with the modulation and reprogramming of immunosuppressive cell types within the tumor microenvironment, may underlie the survival benefit of combination therapy with PD-1 inhibitors [27]. This mechanistic basis sheds light on the persistence of survival advantage, even when baseline characteristics were balanced by PSM. There was an independent correlation of serum albumin with both PFS and OS. A low level of the protein albumin indicates poor nutrition and inflammation throughout the body; both of these lead to immune dysfunction and reduced immunotherapy responsiveness [28]. Similarly, we recognized Peng et al. [29] who showed that baseline albumin is an independent prognostic predictor in NSCLC patient receiving ICIs. Older age (at least 65) and poor performance status (ECOG PS 2 or more) are independent poor prognostic factors. Often elderly patients may have poorer immune function plus more illness, so less tolerance Patients with low performance status have increased risk of treatment-related toxicity and dose reductions [30]. Pooled analyses of KEYNOTE-010, KEYNOTE-024 and KEYNOTE-042 [31] show elderly patients can gain meaningful benefit from immunotherapy, so age alone should not rule out combination treatment.

CCI equal or more than 2 was an independent risk factor for PFS. This is consistent with real-world evidence showing that heavier comorbidity burden was associated with reduced treatment intensity and increased risk of adverse event in patients receiving immunotherapy [32]. In the pre-PSM cohort, history of smoking was an independent risk factor for PFS. This seems counterintuitive considering that smoking is associated with increased tumor mutational burden, which is advantageous for immunotherapy [33]. However, in the real world, smokers often have a higher burden of comorbidity, such as COPD and cardiovascular disease. Our investigation also did not include pulmonary function and systemic inflammation markers, such as neutrophil-to-lymphocyte ratio, which may have allowed the detrimental influences on smoking to prevail. The effect of smoking on immunotherapy efficacy in patients requires further investigation with stratification or interaction analyses. The existence of metastasis to organs and at least 2 other organs were independent risk factors for PFS and OS, a finding consistent with the established correlation between greater tumor burden and poor prog-

nosis [34]. These findings highlight the significance of metastatic status in risk assessment.

Following the independent prognostic factors suggested in the study, nomograms prediction PFS and OS were constructed. The PFS model used eight predictors which were treatment regimen, serum albumin, age, smoking history, CCI, ECOG PS, organ metastasis status, and number of metastatic organs. A total of 6 predictors were used in the OS model, omitting those for smoking history and the CCI. All internal and external validation had AUC values were more than 0.75. This indicates a good discrimination. The calibration curves indicated close agreement between predicted and observed values with Brier scores and non-significant Hosmer-Lemeshow tests. DCA has verified net clinical benefit across a spectrum of threshold probabilities. Both cohorts showed well-separated survival curves when risk stratification was based on median risk scores. In comparison to the EPSILoN score that Prelaj et al. [17] developed, which included only ECOG PS, metastatic sites, and smoking history, our models include more comprehensive predictors that have been independently externally validated. All variables in our model are routinely collected clinical variables that can be implemented more easily without extra testing.

There are numerous strengths of this current study. The multicenter real-world design highly improves generalizability compared to highly selective populations. PSM successfully balanced important baseline characteristics between the two groups, and all matched covariates had SMD <0.1. Both PFS and OS validated by using a complementary approach of multiple methods. A major evidence gap was filled by the direct head-to-head comparison of tislelizumab and sintilimab in a real-world cohort.

There are Limitations which must be admitted Despite PSM adjustment, it is not possible to totally exclude unmeasured confounding as the study was retrospective. The laboratory parameters which are imbalanced post matching indicate some selection bias may remain. In post-PSM analysis, participants who initiated treatment in 2019-2020 appeared to be protected. However, this is likely due to differences in follow-up duration and censoring. This should not be interpreted as cause or effect. The absence of biomarker inclusion like PD-L1 expression and TMB may reduce prediction accuracy. Due to the significant data quality issues, including duplications and missing values, the adverse reaction data were collected but ultimately excluded from the final data set. The omission of subsequent treatment information may influence OS estimates. The cohort for external validation was relatively small (n= 124), and our findings were based on Chinese populations, limiting ethnic generalizability.

In conclusion, the combination of chemotherapy and ICIs is significantly associated with better short-term efficacy and long-term survival in patients with advanced NSCLC in this real-world multicenter cohort. Tislelizumab and sintilimab had similar effectiveness. The nomogram models constructed here have demonstrated good discrimination, calibration, and clinical usefulness, effectively providing practical tools for individual prognostic assessment. Future studies should prioritize validation in a prospective setting, incorporation of biomarkers such as PD-L1, TMB and ctDNA and evaluation of optimal sequence.

Disclosure of conflict of interest

None.

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Table S1. Variable assignment for Cox regression analysis

Variable	Assignment/Grouping
Treatment regimen	0 = Combination therapy (chemotherapy plus PD-1 inhibitor); 1 = Chemotherapy alone
Sex	0 = Female; 1 = Male
Age	0 = <65 years; 1 = ≥65 years
BMI	0 = <24; 1 = ≥24
Smoking history	0 = No; 1 = Yes
CCI	0 = 0-1; 1 = ≥2
ECOG PS	0 = 0-1; 1 = ≥2
Disease stage	0 = IIIB/IIIC; 1 = IV
Histological type	1 = Adenocarcinoma; 2 = Squamous cell carcinoma; 3 = Other
EGFR status	1 = Positive; 2 = Negative; 3 = Unknown
ALK status	1 = Positive; 2 = Negative; 3 = Unknown
Organ metastasis	0 = No metastasis; 1 = Metastasis
Number of metastatic organs	0 = 0-1; 1 = ≥2
Year of treatment initiation	0 = 2021-2023; 1 = 2019-2020
Albumin (g/L)	Continuous variable (entered as original value)
Hemoglobin (g/L)	Continuous variable (entered as original value)
Platelet ($\times 10^9$/L)	Continuous variable (entered as original value)
ALT (U/L)	Continuous variable (entered as original value)
AST (U/L)	Continuous variable (entered as original value)
Creatinine (μmol/L)	Continuous variable (entered as original value)

Note: BMI: Body Mass Index, CCI: Charlson Comorbidity Index, ECOG PS: Eastern Cooperative Oncology Group Performance Status, EGFR: Epidermal Growth Factor Receptor, ALK: Anaplastic Lymphoma Kinase, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase.