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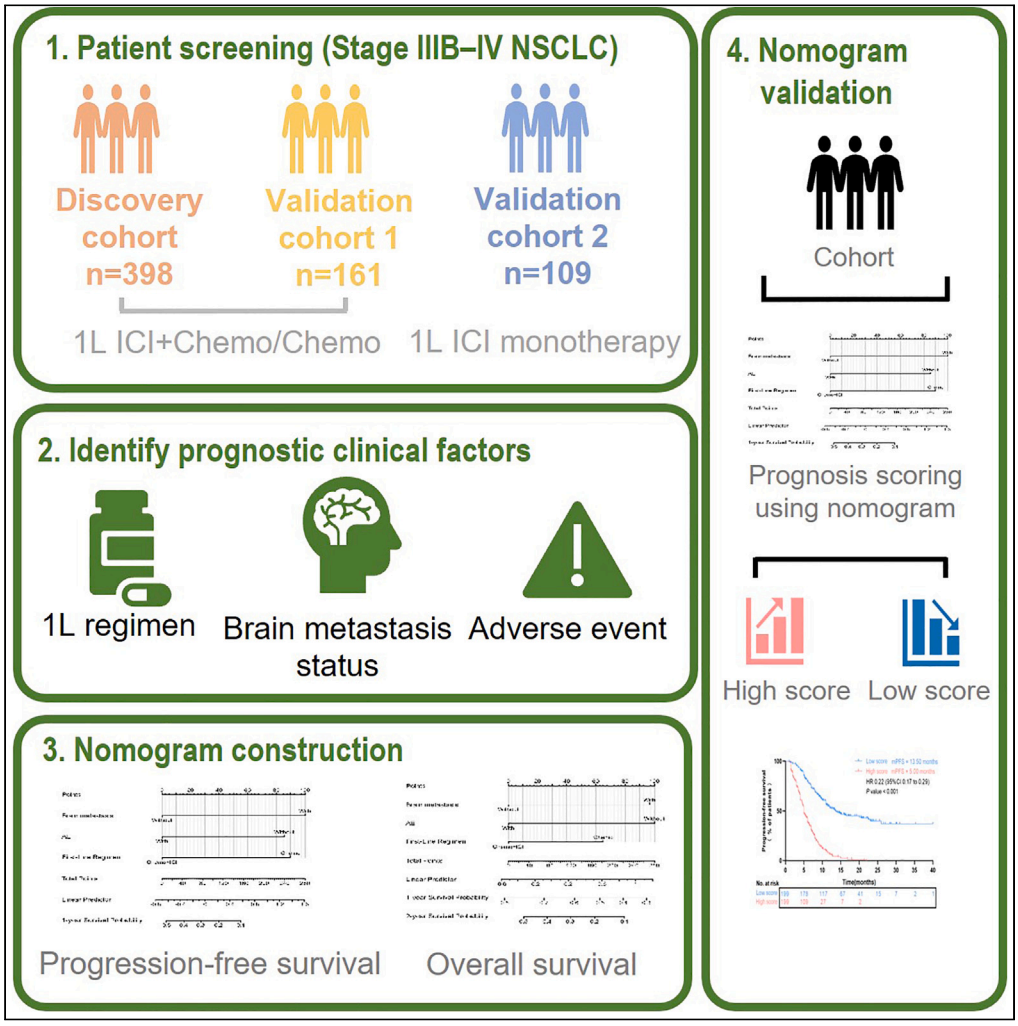

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Highlights

Immune-related adverse events (irAEs) with immunotherapy have survival implications

Mild irAEs were associated with longer progression-free and overall survival

Nomogram is useful in prognosticating patients receiving immune checkpoint inhibitors

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Development of a prognostic nomogram for advanced non-small cell lung cancer using clinical characteristics

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SUMMARY

This retrospective study demonstrated that patients with advanced non-small cell lung cancer who experienced any-grade or grade 1–2 immune-related adverse events (irAEs) with immune checkpoint inhibitor plus chemotherapy (ICI+Chemo) as first-line treatment regimen had significantly longer progression-free survival (PFS; $p < 0.001$) and overall survival (OS; $p < 0.05$) compared with patients without any irAE. Three variables were identified as predictors of favorable PFS and OS: absence of baseline brain metastasis ($p < 0.05$), receiving first-line ICI+Chemo ($p < 0.01$), and occurrence of any grade adverse events ($p < 0.001$). Using these three variables, two nomograms were generated to predict PFS and OS, which were validated using two independent cohorts treated with Chemo or ICI+Chemo ($n = 161$) or ICI monotherapy ($n = 109$). Patients with low scores in discovery and validation cohorts consistently had significantly longer PFS ($p < 0.001$) and OS ($p < 0.05$) than those with high scores. Our findings provide preliminary evidence of the clinical utility of a nomogram in prognosticating ICI-treated patients.

INTRODUCTION

The prognosis of patients diagnosed with unresectable non-small cell lung cancer (NSCLC) harboring targetable molecular alterations has remarkably improved due to the rapid advances in the field of precision medicine over the last decade. On the other hand, the prognosis remains unfavorable for about half of patients diagnosed with NSCLCs that lacked these targetable mutations and were being managed with platinum-based doublet chemotherapy as the standard first-line regimen. The discovery of immune checkpoint inhibitors (ICIs), such as programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors, has led to a paradigm shift in the management of non-oncogene-addicted advanced NSCLC by extending survival benefits over conventional standard chemotherapy alone.[1] ICIs exert their anti-tumor response through the activation of T cell response, which could also cause a spectrum of adverse events related to the mechanism of action and thus are collectively referred to as immune-related adverse events (irAEs).[2–4] These adverse events can involve various organs, most frequently affecting the skin, gastrointestinal system, liver, lung, and endocrine system, with varying incidence and onset based on the type and dose of ICI administered, the cancer type, and other patient-related factors.[4]

Adverse drug reactions could impact healthcare decision-making as they are a major cause of morbidity and mortality, particularly among hospitalized cancer patients.[5] A growing amount of real-world evidence has shown the association between the development of irAEs during ICI treatment and favorable survival outcomes in patients with advanced NSCLC and other solid tumors.[6–14] A pooled analysis of the IMpower 130/132/150 showed that patients who experienced grade 1 or 2 irAEs during ICI therapy had better survival outcomes.[12] In contrast, overall survival was shorter for patients who experienced more severe irAEs (grade 3 or higher).[14] Despite providing evidence on the survival implications of irAEs, most of these studies lacked cross-validation either from larger sample size cohorts to accurately represent real-world

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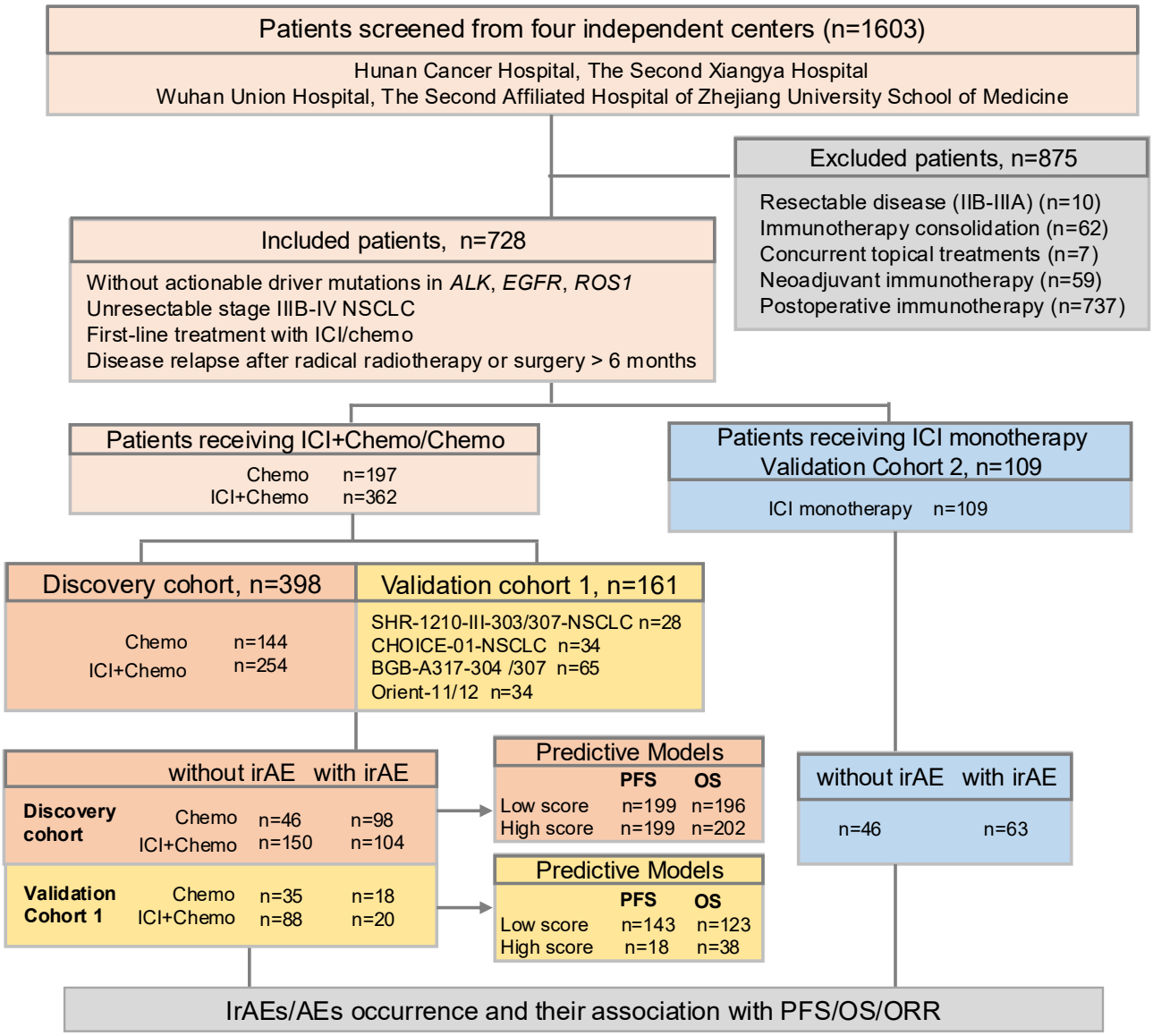

Figure 1. Patient populations screened and included in this retrospective study

Abbreviations: NSCLC, non-small cell lung cancer; AEs, adverse events; irAEs, immune-related adverse events. Chemo, chemotherapy; ICI, immune checkpoint inhibitor.

treatment scenarios or from prospective clinical studies. Moreover, there remains a knowledge gap regarding the impact of irAEs on the efficacy of ICI monotherapy, as well as the significance of irAEs of varying severity on the efficacy of ICI treatment.

Our multicenter retrospective study explored the impact of irAEs on treatment efficacy in patients with advanced NSCLC treated with ICIs as the first-line regimen in real-world clinical practice. The findings from the discovery cohort were then independently validated using data gathered from patients enrolled in randomized controlled clinical studies on ICIs (validation cohort 1) as well as patients who received ICI monotherapy in the real world (validation cohort 2). Furthermore, we developed predictive nomogram models based on three non-invasive, clinically accessible parameters associated with survival outcomes and validated their utility using independent cohorts to explore their utility in predicting survival outcomes in patients receiving ICI treatment.

RESULTS

Baseline characteristics of the three study cohorts

Figure 1 summarizes the patient population screened and included in this retrospective study. Our study screened a total of 1,603 patients from four independent cancer centers. A total of 398 patients with advanced NSCLC who received either chemotherapy or ICI-containing

regimens from Hunan Cancer Hospital between October 25, 2017 and April 24, 2022 were included in the discovery cohort. The median follow-up of this cohort was 21.0 months (range: 19.4–22.6 months). The discovery cohort was stratified into four groups according to their treatment regimen and the presence or absence of treatment-related irAE/AE as follows: chemotherapy (Chemo) group with AE (n = 46), Chemo group without AE (n = 98), ICI combined with chemotherapy (ICI+Chemo) with irAE (n = 150), and ICI+Chemo without irAE (n = 104).

An independent cohort of 161 patients with advanced NSCLC who were enrolled in seven different phase III clinical trials investigating various PD-1 inhibitors vs. chemotherapy as first-line therapy were included as the validation cohort 1. The validation cohort 1 had an overall median follow-up time of 22.3 months (21.2–23.4 months) with the following distribution: 28 patients from Wuhan Union Hospital with a median follow-up time of 30.4 months (22.6–38.2 months); 65 and 34 patients from two clinical trial conducted in Hunan Cancer Hospital with a median follow-up time of 21.5 months (18.5–24.5 months) and 37.0 months (32.8–41.2 months), respectively; and 34 patients from the Second Affiliated Hospital of Zhejiang University School of Medicine with a median follow-up time of 21.5 months (20.6–22.4 months). Similar to the discovery cohort, the validation cohort 1 was stratified into four subgroups as follows: Chemo group with AE (n = 35), Chemo group without AE (n = 18), ICI+Chemo with irAE (n = 88), and ICI+Chemo without irAE (n = 20).

Another independent cohort of 109 patients with advanced NSCLC who received ICI monotherapy served as validation cohort 2. This cohort was included to understand the impact of irAEs on survival outcomes. The overall median follow-up was 26.8 months (24.1–29.5 months); 97 patients were from Hunan Cancer Hospital with a median follow-up of 27.4 months (23.7–31.1 months) and 12 patients from the Second Xiangya Hospital of Central South University with a median follow-up of 20.3 months (15.0–25.6 months). Validation cohort 2 was stratified into two groups based on the occurrence of irAE into with irAE (n = 63) and without irAE (n = 46).

The baseline characteristics of patients in the discovery and the two validation cohorts are presented in Table 1. All patients had stage IIIB–IV NSCLCs that lacked targetable mutations. Clinical features with significant differences are marked in bold font. Males account for the majority of the study cohort across the discovery and validation cohorts. A majority of patients included in the Chemo group from the discovery cohort had lung squamous cell carcinoma (134/144; 93.1%). This could be attributed to the fact that patients diagnosed with lung squamous cell carcinoma are not required to submit samples for genetic testing due to the lack of an effective targeted treatment option. Hence, chemotherapy was the only accessible standard first-line treatment for this cancer subtype, particularly in China.

In the ICI+Chemo group of the validation cohort 1, 78.4% (69/88) of patients with irAE had a history of tobacco smoking, whereas only 15.0% (3/20) of patients without irAE had a smoking history. It should be noted that the patients included in the validation cohort 1 were participants of any of the seven phase 3 randomized-controlled clinical trials (all have been unblinded), which were inherently patient selective. It remains inconclusive whether smoking history affects the occurrence of AEs during treatment.

Clinical response and adverse events observed in the study cohort

Table 2 and Figures S1 and S2 summarize the irAEs/AEs observed in the discovery and validation cohorts. Hepatitis was the most frequent any grade and grade 3–4 treatment-related AEs across the cohorts. Tables S1 and S2 list the treatment management strategies implemented to address and resolve the toxicities observed in patients who received ICI-containing regimens and chemotherapy, respectively.

The objective response rate (ORR) of each group for the three cohorts was also analyzed and compared (Figure S3). In the Chemo group of the discovery cohort, ORR was higher in patients who experienced AE with first-line Chemo than those without AE (54.4% vs. 40.8%, p = 0.152). In the ICI+Chemo group of the discovery cohort, ORR was also higher in patients who experienced irAE with first-line ICI+Chemo (68.0% vs. 51.9%, p = 0.013). Similarly, ORR was higher in patients who experienced irAEs with ICI+Chemo (61.4% vs. 30.0%, p = 0.013; Figure S3) or ICI monotherapy (52.4% vs. 26.1%, p = 0.010; Figure S3) as compared with patients who did not experience irAEs in the validations cohorts 1 and 2. ORR was statistically comparable between patients with or without AEs during Chemo treatment (45.7% vs. 38.9%, p = 0.772; Figure S3).

Table S3 lists the distribution of the subsequent treatment received by the discovery cohort and validation cohorts 1 and 2.

Patients who experienced irAEs/AEs have significantly longer survival outcome

Survival analysis was initially performed on the patients in the discovery cohort who did and did not develop irAE/AE (Figures 2A and 2B). In the Chemo group, patients who experienced AE had significantly longer progression-free survival (PFS, 7.2 months vs. 5.0 months; hazard ratio (HR): 0.60, 95% confidence intervals (CI): [0.41–0.86], p = 0.005) and OS (17.8 months vs. 13.6 months; HR: 0.58, 95% CI: [0.38–0.90], p = 0.013) as compared to patients without AE. In the ICI+Chemo group, patients with irAE also had significantly longer PFS (12.0 months vs. 6.0 months; HR: 0.47, 95% CI: [0.35–0.64], $p < 0.001$) and OS (26.0 months vs. 15.5 months; HR: 0.54, 95% CI: [0.37–0.77], $p < 0.001$) as compared to patients without irAE.

These results were validated using the data from the independent validation cohort. Consistent with the discovery cohort, significantly longer survival outcomes were also observed in patients who experienced AEs with Chemo (PFS: 6.3 months vs. 4.2 months; HR: 0.36, 95% CI: [0.18–0.69], p = 0.001), patients who experienced irAEs with ICI+Chemo (PFS: 13.8 months vs. 6.7 months; HR: 0.39, 95% CI: [0.23–0.66], $p < 0.001$; OS: 26.0 months vs. 16.0 months; HR: 0.51, 95% CI: [0.27–0.97], p = 0.036) (Figure S4) and patients who experienced irAE with ICI monotherapy (PFS: 14.5 months vs. 4.0 months; HR: 0.41, 95% CI: [0.27–0.64], $p < 0.001$; OS: 24.0 months vs. 8.7 months; HR: 0.46, 95% CI: [0.28–0.77], p = 0.002) (Figure S5).

Previous studies have shown that severe irAE/AEs affect survival, wherein poorer survival outcomes were observed among patients who experienced greater than or equal to grade (G) 3 irAE/AE than those who experienced G1-2 irAE/AE.[15] We then re-analyzed our data to exclude patients with ≥G3 irAE/AE to better understand the association between irAE/AE occurrence and survival outcomes in our cohorts. In the discovery cohort, patients with G1-2 AE/irAE in both Chemo group and ICI+Chemo group had significantly longer PFS and OS than the

Table 1. Clinical characteristics

Characteristics	Discovery Cohort (*n* = 398)						Validation Cohort 1 (*n* = 161)						Validation Cohort 2 (*n* = 109)		
	Chemo		ICI+Chemo				Chemo		ICI+Chemo				ICI monotherapy		
	With AE (*n* = 46)	Without AE (*n* = 98)	With irAE (*n* = 150)	Without irAE (*n* = 104)	p[a] value	p[b] value	With AE (*n* = 35)	Without AE (*n* = 18)	With irAE (*n* = 88)	Without irAE (*n* = 20)	p[c] value	p[d] value	With irAE (*n* = 63)	Without irAE (*n* = 46)	p[e] value
Age, years; median (range)	62.5 (48–77)	62.5 (42–83)	57 (35–79)	54.5 (33–76)			57 (44–70)	62 (55–69)	56 (37–75)	59.5 (36–73)			67 (28–84)	65 (39–87)	
Sex, No. (%)					1.000	1.000					0.397	0.296			0.462
Female	3 (6.5)	7 (7.1)	24 (16.0)	16 (15.4)			3 (8.6)	3 (16.7)	15 (17.0)	1 (5.0)		**< 0.001**	10 (15.9)	10 (21.7)	
Male	43 (93.5)	91 (92.9)	126 (84.0)	88 (84.6)			32 (91.4)	15 (83.3)	73 (83.0)	19 (95.0)			53 (84.1)	36 (78.3)	
Smoking history, No. (%)					0.582	0.121					1.000	**< 0.001**			0.379
Former smoker	42 (91.3)	85 (86.7)	113 (75.3)	87 (83.7)			8 (22.9)	4 (22.2)	69 (78.4)	3 (15.0)			49 (77.8)	32 (69.6)	
Never smoker	4 (8.7)	13 (13.3)	37 (24.7)	17 (16.3)			27 (77.1)	14 (77.8)	19 (21.6)	17 (85.0)			14 (22.2)	14 (30.4)	
Drinking history, No. (%)					1.000	0.797					1.000	1.000			0.686
Yes	24 (52.2)	50 (51.0)	61 (40.7)	44 (42.3)			16 (45.7)	8 (44.4)	40 (45.5)	9 (45.0)			24 (38.1)	15 (32.6)	
No	22 (47.8)	48 (49.0)	89 (59.3)	60 (57.7)			19 (54.3)	10 (55.6)	48 (54.5)	11 (55.0)			39 (61.9)	31 (67.4)	
ECOG PS, No. (%)					0.777	1.000					0.464	0.534			1.000
0	6 (13.0)	10 (10.2)	21 (14.0)	14 (13.5)			8 (22.9)	2 (11.1)	16 (18.2)	5 (25.0)			8 (12.7)	5 (10.9)	
1	40 (87.0)	88 (89.8)	129 (86.0)	90 (86.5)			27 (77.1)	16 (88.9)	72 (81.8)	15 (75.0)			55 (87.3)	41 (89.1)	
Stage of disease, No. (%)					0.592	0.366					1.000	**0.009**			1.000
IIIB/IIIC	21 (45.7)	51 (52.0)	19 (12.7)	18 (17.3)			5 (14.3)	2 (11.1)	6 (6.8)	6 (30.0)			9 (14.3)	6 (13.0)	
IV	25 (54.3)	47 (48.0)	131 (87.3)	86 (82.7)			30 (85.7)	16 (88.9)	82 (93.2)	14 (70.0)			54 (85.7)	40 (87.0)	
Histology type, No. (%)					0.169	0.097					1.000	0.306			0.120
Non-squamous NSCLC	1 (2.2)	9 (9.2)	82 (54.7)	45 (43.3)			12 (34.3)	6 (33.3)	35 (40.0)	5 (25.0)			38 (60.3)	20 (43.5)	

(*Continued on next page*)

Table 1. *Continued*

Characteristics	Discovery Cohort (*n* = 398)						Validation Cohort 1 (*n* = 161)						Validation Cohort 2 (*n* = 109)		
	Chemo		ICI+Chemo				Chemo		ICI+Chemo				ICI monotherapy		
	With AE (*n* = 46)	Without AE (*n* = 98)	With irAE (*n* = 150)	Without irAE (*n* = 104)	p[a] value	p[b] value	With AE (*n* = 35)	Without AE (*n* = 18)	With irAE (*n* = 88)	Without irAE (*n* = 20)	p[c] value	p[d] value	With irAE (*n* = 63)	Without irAE (*n* = 46)	p[e] value
Squamous NSCLC	45 (97.8)	89 (90.8)	68 (45.3)	59 (56.7)			23 (65.7)	12 (66.7)	53 (60.0)	15 (75.0)			25 (39.7)	26 (56.5)	
PD-L1 TPS, No. (%)					0.275	0.179					0.595	0.570			0.794
≥50%	1 (2.2)	1 (1.0)	32 (21.3)	15 (14.4)			2 (5.7)	0	9 (10.2)	1 (5.0)			44 (69.8)	35 (76.1)	
1-49%	2 (4.3)	5 (5.1)	36 (24.0)	34 (32.7)			2 (5.7)	3 (16.7)	10 (11.4)	2 (10.0)			9 (14.3)	6 (13.0)	
< 1%	9 (19.6)	9 (9.2)	31 (20.7)	15 (14.4)			3 (8.6)	2 (11.1)	14 (15.9)	1 (5.0)			6 (9.5)	2 (4.3)	
Unknown	34 (73.9)	83 (84.7)	51 (34.0)	40 (38.5)			28 (80.0)	13 (72.2)	55 (62.5)	16 (80.0)			4 (6.3)	3 (6.5)	
Baseline brain metastasis status, No. (%)					0.177	**0.005**					0.111	1.000			0.405
Yes	0	6 (6.1)	25 (16.7)	5 (4.8)			0	2 (11.1)	3 (3.4)	0			7 (11.1)	8 (17.4)	
No	46 (100.0)	92 (93.9)	125 (83.3)	99 (95.2)			35 (100.0)	16 (88.9)	85 (96.6)	20 (100.0)			56 (88.9)	38 (82.6)	
Baseline liver metastasis status, No. (%)					1.000	0.256					0.245	0.459			0.386
Yes	3 (7.0)	8 (8.2)	15 (10.0)	6 (5.8)			4 (11.4)	5 (27.8)	11 (12.5)	1 (5.0)			6 (9.5)	7 (15.2)	
No	43 (93.0)	90 (91.8)	135 (90.0)	98 (94.2)			31 (88.6)	13 (72.2)	77 (87.5)	19 (95.0)			57 (90.5)	39 (84.8)	
Relapsed					0.680	1.000									
Yes	3 (6.5)	4 (4.1)	6 (4.0)	4 (3.8)			0	0	0	0			0	0	
No	43 (93.5)	94 (95.9)	144 (96.0)	100 (96.2)			36 (100.0)	18 (100.0)	88 (100.0)	20 (100.0)			63 (100.0)	46 (100.0)	
HBV infection, No. (%)					0.393	0.225					0.165	0.064			0.641
Past	18 (39.1)	45 (45.9)	73 (48.7)	62 (59.6)			24 (68.6)	10 (55.6)	58 (65.9)	8 (40.0)			16 (25.4)	11 (23.9)	
Current	9 (19.6)	11 (11.2)	19 (12.7)	10 (9.6)			3 (8.6)	0	6 (6.8)	3 (15.0)			19 (30.2)	18 (39.1)	
None	19 (41.3)	42 (42.9)	58 (38.6)	32 (30.8)			8 (22.8)	8 (44.4)	24 (27.3)	9 (45.0)			28 (44.4)	17 (37.0)	
ICI regimen received, No. (%)						0.063						0.820			0.379

(*Continued on next page*)

Table 1. *Continued*

	Discovery Cohort (*n* = 398)						Validation Cohort 1 (*n* = 161)						Validation Cohort 2 (*n* = 109)		
	Chemo		ICI+Chemo				Chemo		ICI+Chemo				ICI monotherapy		
Characteristics	With AE (*n* = 46)	Without AE (*n* = 98)	With irAE (*n* = 150)	Without irAE (*n* = 104)	p[a] value	p[b] value	With AE (*n* = 35)	Without AE (*n* = 18)	With irAE (*n* = 88)	Without irAE (*n* = 20)	p[c] value	p[d] value	With irAE (*n* = 63)	Without irAE (*n* = 46)	p[e] value
Pembrolizumab	0	0	94 (62.7)	57 (54.8)			0	0	0	0			49 (77.8)	32 (69.6)	
Sintilimab	0	0	19 (12.7)	22 (21.2)			0	0	18 (20.5)	3 (15.0)			14 (22.2)	14 (30.4)	
Camrelizumab	0	0	13 (8.7)	3 (2.9)			0	0	12 (13.6)	3 (15.0)			0	0	
Toripalimab	0	0	17 (11.3)	12 (11.5)			0	0	19 (21.6)	3 (15.0)			0	0	
Tislelizumab	0	0	7 (4.7)	10 (9.6)			0	0	39 (44.3)	11 (55.0)			0	0	

NOTE: Statistical analysis was performed to compare the features of subgroups with irAE and without irAE for each cohort. Features found to be statistically different ($p < 0.05$) are denoted in bold.

Abbreviations: Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; NSCLC, non-small cell lung cancer; PD-L1 TPS, programmed death-ligand 1 tumor proportion score.

[a]Chemo subgroup of Discovery cohort.

[b]ICI+Chemo subgroup of Discovery cohort.

[c]Chemo subgroup in Validation cohort 1.

[d]ICI+Chemo subgroup in Validation cohort 1.

[e]Validation cohort 2 (ICI monotherapy).

Table 2. Distribution of adverse events in each cohort

	Discovery Cohort (*n* = 398)				Validation Cohort 1 (*n* = 161)				Validation Cohort 2 (*n* = 63)	
	Chemo (*n* = 144)		ICI+Chemo (*n* = 254)		Chemo (*n* = 53)		ICI+Chemo (*n* = 108)		ICI monotherapy (*n* = 63)	
Adverse events, n (%)	G1-2	G3-5	G1-2	G3-5	G1-2	G3-5	G1-2	G3-5	G1-2	G3-5
Hepatitis										
Elevated transaminase	30 (20.8)	1 (0.7)	64 (25.2)	14 (5.5)	23 (43.4)	1 (1.9)	57 (52.8)	4 (3.7)	18 (28.6)	8 (12.7)
Elevated bilirubin	6 (4.2)	0	13 (5.1)	0	7 (13.2)	0	18 (16.7)	0	6 (9.5)	1 (1.6)
Thyroid dysfunction										
Hypothyroidism	0	0	26 (10.2)	0	3 (5.7)	0	15 (13.9)	0	18 (28.6)	0
Hyperthyroidism	0	0	38 (15.0)	1 (0.4)	1 (1.9)	0	20 (18.5)	0	6 (9.5)	0
Pneumonia	0	0	13 (5.1)	10 (3.9)	2 (3.8)	0	3 (2.8)	4 (3.7)	7 (11.1)	3 (4.8)
Rash	0	0	7 (2.8)	3 (1.2)	3 (5.7)	0	9 (8.3)	2 (1.9)	10 (15.9)	2 (3.2)
Encephalitis	0	0	1 (0.4)	1 (0.4)	0	0	0	0	0	0
Myocarditis	0	0	1 (0.4)	4 (1.6)	0	0	3 (2.8)	1 (0.9)	0	0
Enteritis	1 (0.7)	0	2 (0.8)	2 (0.8)	0	0	1 (0.9)	0	1 (1.6)	0
Renal insufficiency	10 (6.9)	0	15 (6.0)	0	5 (9.4)	0	13 (12.0)	1 (0.9)	4 (6.3)	1 (1.6)
Fatigue	7 (4.9)	0	18 (7.1)	0	10 (18.9)	1 (1.9)	10 (9.3)	1 (0.9)	2 (3.1)	0
Others	0	0	6 (2.4)	1 (0.4)	0	0	6 (5.6)	3 (2.8)	8 (12.7)	0

The grading of the AEs was based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
Abbreviations: Chemo, chemotherapy; G1-2, grade 1–2 (mild); G3-5, grade 3–5 (severe); ICI, immune checkpoint inhibitor.

patients without AE/irAE (Chemo group PFS: 7.3 months vs. 5.0 months; HR: 0.59, 95% CI: [0.41–0.85], $p = 0.005$; OS:17.6 months vs. 13.6 months; HR: 0.59, 95% CI: [0.39–0.92], $p = 0.017$; ICI+Chemo group PFS: 13.0 months vs. 6.0 months; HR: 0.45, 95% CI: [0.33–0.62], $p < 0.001$; OS: not reached vs. 15.5 months; HR: 0.49, 95% CI: [0.33–0.73], $p < 0.001$) (Figures 2C and 2D). Consistently, the patients in the validation cohort 1 who experienced G1-2 irAE with ICI+Chemo had significantly longer PFS (13.8 months vs. 6.7 months; HR: 0.40, 95% CI: [0.24–0.69], $p < 0.001$) and OS (26.0 months vs. 16.0 months, HR: 0.51, 95% CI: [0.27–0.97], $p = 0.036$). The median PFS was significantly longer in patients with G1-2 AE in the Chemo group of the validation cohort 1 (6.9 months vs. 4.2 months; HR: 0.36, 95% CI: [0.18–0.69], $p = 0.001$). However, no significant difference was observed in OS between patients with G1-2 AE and those without AE in the Chemo group of the validation cohort 1 (21.0 months vs. 14.4 months; HR: 0.69, 95% CI: [0.34–1.40], $p = 0.300$) (Figure S6). Moreover, the patients in the validation cohort 2 who experienced G1-2 irAE with ICI monotherapy had significantly longer PFS (14.5 months vs. 4.0 months; HR: 0.43, 95% CI: [0.27–0.69], $p < 0.001$) and OS (28.0 months vs. 8.7 months; HR: 0.42, 95% CI: [0.24–0.73], $p = 0.002$) (Figure S7).

To further understand the survival implications of irAE severity, we stratified the discovery cohort into G1-2 irAE and G3-5 irAE subgroups. The analysis found no statistical difference between the two subgroups in terms of PFS and OS (Figures 2E and 2F). We further analyzed the subgroup of 34 patients from the discovery cohort who developed G3-5 irAEs. Based on Figure S8, 13 patients did not change their treatment strategies after the occurrence of G3-5 irAE. Of these 13 patients, five patients resumed the original treatment plan, while eight patients resumed the original treatment plan after appropriate clinical intervention. All the 13 patients continued to achieve considerable clinical benefits. Another 21 patients terminated the original treatment plan after the occurrence of G3-5 irAE based on shared decision-making. Among them, the disease of six patients remained stable after treatment termination; however, most patients experience disease progression within three months. Subsequently, we compared the survival outcomes of these 21 patients with the group of patients who had G1-2 irAEs. As compared with patients who had G1-2 irAEs, those with G3-5 irAE who had treatment termination had significantly shorter PFS (7.0 months vs. 13.0 months, $p = 0.017$) and OS (9.0 months vs. not reached, $p < 0.001$) (Figures 2G and 2H).

Figures S8–S10 show the PFS outcome, time points of onset of toxicity, and AE management strategy implemented in patients who experienced G3-5 irAE in the discovery cohort (G3, $n = 31$; G4, $n = 3$; G5, $n = 0$) (Figure S8), patients who experienced G3-5 irAE in the validation cohort 1 (G3, $n = 8$; G4, $n = 2$; G5, $n = 2$) and G3-5 AE in the discovery (G3, $n = 1$; G4-5, $n = 0$) and validation cohorts (G3, $n = 2$; G4-5, $n = 0$) (Figure S9), and patients who experienced G3-5 irAE in the validation cohort 2 (G3, $n = 11$; G4, $n = 2$; G5, $n = 0$) (Figure S10). From our study cohort, only two patients experienced G5 irAE—P106, a participant of the Orient 12 study who received sintilimab plus platinum and gemcitabine as first-line therapy and experienced pneumonia after 121 days of treatment and P109, a participant of the CHOICE-01 study who received toripalimab plus pemetrexed and carboplatin as first-line therapy and experienced pneumonia after 22 days of treatment (Figure S9). More than half of the patients who experienced G3-5 toxicities discontinued treatment at irAE onset (discovery cohort, 64.7% [22/34]; validation cohort 1, 75.0% [9/12]; validation cohort 2, 38.5% [5/13]). Of the patients who experienced G3-5 toxicities, 20 survived at least a year after

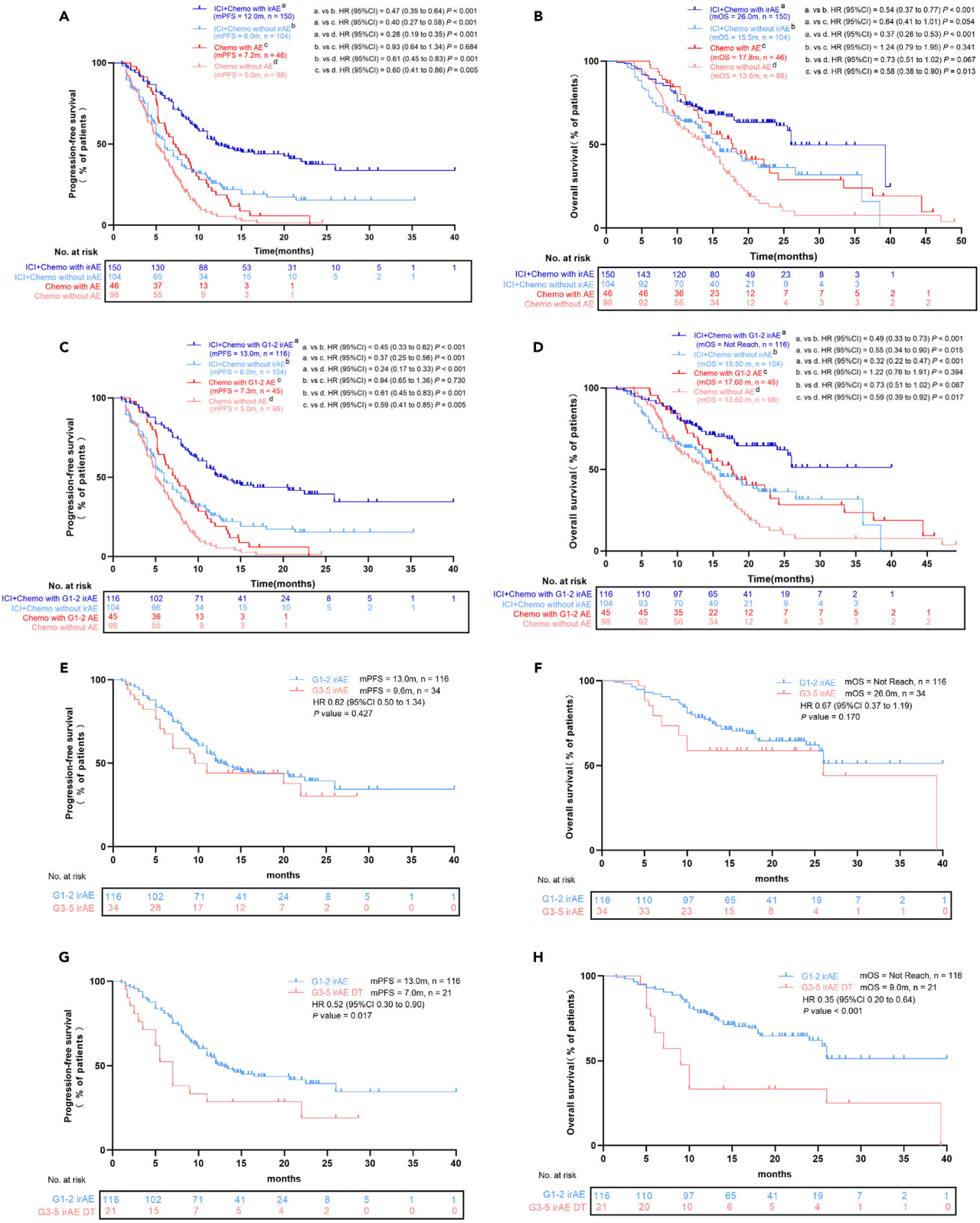
A
ICI+Chemo with irAE[a] (mPFS = 12.0m, n = 150)
ICI+Chemo without irAE[b] (mPFS = 6.0m, n = 104)
Chemo with AE[c] (mPFS = 7.2m, n = 46)
Chemo without AE[d] (mPFS = 5.0m, n = 98)
a. vs b. HR (95%CI) = 0.47 (0.35 to 0.64) P < 0.001
a. vs c. HR (95%CI) = 0.40 (0.27 to 0.58) P < 0.001
a. vs d. HR (95%CI) = 0.26 (0.19 to 0.35) P < 0.001
b. vs c. HR (95%CI) = 0.93 (0.64 to 1.34) P = 0.684
b. vs d. HR (95%CI) = 0.61 (0.45 to 0.83) P = 0.001
c. vs d. HR (95%CI) = 0.60 (0.41 to 0.86) P = 0.005
Progression-free survival (% of patients)
Time(months)
No. at risk
ICI+Chemo with irAE 150 130 88 53 31 10 5 1 1
ICI+Chemo without irAE 104 65 34 15 10 5 2 1
Chemo with AE 46 37 13 3 1
Chemo without AE 98 55 9 3 1
B
ICI+Chemo with irAE[a] (mOS = 26.0m, n = 150)
ICI+Chemo without irAE[b] (mOS = 15.5m, n = 104)
Chemo with AE[c] (mOS = 17.8m, n = 46)
Chemo without AE[d] (mOS = 13.6m, n = 98)
a. vs b. HR (95%CI) = 0.54 (0.37 to 0.77) P < 0.001
a. vs c. HR (95%CI) = 0.64 (0.41 to 1.01) P = 0.054
a. vs d. HR (95%CI) = 0.37 (0.26 to 0.53) P < 0.001
b. vs c. HR (95%CI) = 1.24 (0.79 to 1.95) P = 0.341
b. vs d. HR (95%CI) = 0.73 (0.51 to 1.02) P = 0.067
c. vs d. HR (95%CI) = 0.58 (0.38 to 0.90) P = 0.013
Overall survival (% of patients)
Time(months)
No. at risk
ICI+Chemo with irAE 150 143 120 80 49 23 8 3 1
ICI+Chemo without irAE 104 92 70 40 21 9 4 3
Chemo with AE 46 36 23 12 7 7 5 2 1
Chemo without AE 98 92 56 34 12 4 3 3 2 2
C
ICI+Chemo with G1-2 irAE[a] (mPFS = 13.0m, n = 116)
ICI+Chemo without irAE[b] (mPFS = 6.0m, n = 104)
Chemo with G1-2 AE[c] (mPFS = 7.3m, n = 45)
Chemo without AE[d] (mPFS = 5.0m, n = 98)
a. vs b. HR (95%CI) = 0.45 (0.33 to 0.62) P < 0.001
a. vs c. HR (95%CI) = 0.37 (0.25 to 0.56) P < 0.001
a. vs d. HR (95%CI) = 0.24 (0.17 to 0.33) P < 0.001
b. vs c. HR (95%CI) = 0.94 (0.65 to 1.36) P = 0.730
b. vs d. HR (95%CI) = 0.61 (0.45 to 0.83) P = 0.001
c. vs d. HR (95%CI) = 0.59 (0.41 to 0.85) P = 0.005
Progression-free survival (% of patients)
Time(months)
No. at risk
ICI+Chemo with G1-2 irAE 116 102 71 41 24 8 5 1 1
ICI+Chemo without irAE 104 66 34 15 10 5 2 1
Chemo with G1-2 AE 45 36 13 3 1
Chemo without AE 98 55 9 3 1
D
ICI+Chemo with G1-2 irAE[a] (mOS = Not Reach, n = 116)
ICI+Chemo without irAE[b] (mOS = 15.50 m, n = 104)
Chemo with G1-2 AE[c] (mOS = 17.60 m, n = 45)
Chemo without AE[d] (mOS = 13.60 m, n = 98)
a. vs b. HR (95%CI) = 0.49 (0.33 to 0.73) P < 0.001
a. vs c. HR (95%CI) = 0.55 (0.34 to 0.90) P = 0.015
a. vs d. HR (95%CI) = 0.32 (0.22 to 0.47) P < 0.001
b. vs c. HR (95%CI) = 1.22 (0.76 to 1.91) P = 0.394
b. vs d. HR (95%CI) = 0.73 (0.51 to 1.02) P = 0.067
c. vs d. HR (95%CI) = 0.59 (0.39 to 0.92) P = 0.017
Overall survival (% of patients)
Time(months)
No. at risk
ICI+Chemo with G1-2 irAE 116 110 97 65 41 19 7 2 1
ICI+Chemo without irAE 104 93 70 40 21 9 4 3
Chemo with G1-2 AE 45 45 35 22 12 7 7 5 2 1
Chemo without AE 98 92 56 34 12 4 3 3 2 2
E
G1-2 irAE mPFS = 13.0m, n = 116
G3-5 irAE mPFS = 9.6m, n = 34
HR 0.82 (95%CI 0.50 to 1.34)
P value = 0.427
Progression-free survival (% of patients)
months
No. at risk
G1-2 irAE 116 102 71 41 24 8 5 1 1
G3-5 irAE 34 28 17 12 7 2 0 0 0
F
G1-2 irAE mOS = Not Reach, n = 116
G3-5 irAE mOS = 26.0m, n = 34
HR 0.67 (95%CI 0.37 to 1.19)
P value = 0.170
Overall survival (% of patients)
months
No. at risk
G1-2 irAE 116 110 97 65 41 19 7 2 1
G3-5 irAE 34 33 23 15 8 4 1 1 0
G
G1-2 irAE mPFS = 13.0m, n = 116
G3-5 irAE DT mPFS = 7.0m, n = 21
HR 0.52 (95%CI 0.30 to 0.90)
P value = 0.017
Progression-free survival (% of patients)
months
No. at risk
G1-2 irAE 116 102 71 41 24 8 5 1 1
G3-5 irAE DT 21 15 7 5 4 2 0 0 0
H
G1-2 irAE mOS = Not Reach, n = 116
G3-5 irAE DT mOS = 9.0m, n = 21
HR 0.35 (95%CI 0.20 to 0.64)
P value < 0.001
Overall survival (% of patients)
months
No. at risk
G1-2 irAE 116 110 97 65 41 19 7 2 1
G3-5 irAE DT 21 20 10 6 5 4 1 1 0

Figure 2. Patients who experienced toxicity had better survival outcomes than those who did not experience adverse events (AE)

(A and B) Kaplan-Meier curves comparing the progression-free survival (PFS) (A) and overall survival (OS) (B) of patients in the discovery cohort who did or did not experience any grade AE with chemotherapy or immune-related AE (irAE) with ICI plus chemotherapy (ICI+Chemo).

(C and D) In this analysis, the patients with grade 3–5 toxicities were excluded from the cohort. Kaplan-Meier curves comparing the PFS (C) and OS (D) of patients in the discovery cohort who did or did not experience grade 1–2 AE with chemotherapy or immune-related AE (irAE) with ICI+Chemo.

(E–H) Kaplan-Meier curves comparing the PFS and OS between patients in the discovery cohort who experienced grade 1–2 irAE (n = 116) and grade 3–5 irAE with ICI+Chemo (n = 34) (E and F) and patients with grade 3–5 irAE with ICI+Chemo who terminated the treatment (n = 21) (G and H). The tick marks indicate censored patients. Risk table below indicates the number of patients included in the analysis per timeline. Statistical comparison between groups was performed using log rank test. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were computed using SPSS Statistics (version 27, IBM Corp., Armonk, NY, USA). Abbreviations: AE, adverse event; Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; mOS, median overall survival; mPFS, median progression-free survival. DT, discontinued treatment.

irAE onset, wherein five patients had persistent stable disease during treatment discontinuation (P23, P89, and P92 from Figure S8, P20 from Figure S9, and P9 from Figure S10), seven patients continued to benefit from the regimen for more than one year (P48, P71, P137, and P169 from Figure S8, P39 from Figure S9, P18 and P14 from Figure S10), and five patients had disease progression following treatment interruption (P4 and P41 from Figure S8 and P18, P35, and P44 from Figure S9).

Landmark analyses

Based on a pooled analysis report from the IMpower-130/132/150,[12,14] we stratified the patients into four subgroups according to the time of occurrence of irAE/AE after treatment (in the first month, third month, sixth month, and twelfth month and beyond). Survival analysis was then conducted for all subgroups for the discovery cohort and validation cohort, as shown in Figures S11–S14, respectively. We observed that in the discovery cohort, patients with irAE/AEs that occurred in the first month, third month, and sixth month tended to have longer PFS and OS. The median PFS and OS were the longest in patients who experienced any grade irAE within the first six months of ICI+Chemo treatment, while the median PFS and OS were the shortest in patients who did not experience any grade AE with chemotherapy alone. However, this phenomenon was not observed in the 12-month subgroup, mainly considering the sample size limitation (Figures S11 and S12). Consistently, findings from the validation cohort were similar to the discovery cohort (Figures S13 and 14).

Identifying predictors of PFS and OS probability

We performed univariate and multivariate Cox regression analysis of clinical characteristics, treatment options, and clinical outcomes of the discovery cohort (n = 398). The results consistently indicated that the absence of brain metastasis at baseline (HR: 2.28, 95% CI: [1.54–3.38]; $p < 0.001$), occurrence of any grade treatment-related irAE/AE (HR: 0.46, 95% CI: [0.36–0.59]; $p < 0.001$), and receiving ICI+Chemo as first-line therapy (HR: 0.42, 95% CI: [0.32–0.55]; $p < 0.001$) were three independent factors that could predict favorable PFS (Figure 3A). In terms of OS, multivariate analyses also identified the same three variables for predicting favorable OS—the absence of brain metastasis at baseline (HR: 1.90, 95% CI: [1.20–3.00]; $p = 0.006$), occurrence of any grade treatment-related irAE/AE (HR: 0.53, 95% CI: [0.40–0.71]; $p < 0.001$), and receiving ICI+Chemo as first-line therapy (HR: 0.63, 95% CI: [0.47–0.85]; $p = 0.002$) (Figure 3B). Consistently, occurrence of irAE during ICI monotherapy was associated with favorable PFS (HR: 0.42, 95% CI: [0.27–0.67], $p < 0.001$; Figure S15) and OS (HR: 0.43, 95% CI: [0.25–0.74], $p < 0.01$; Figure S16) in multivariate analysis.

Moreover, we generated two nomograms using the three variables identified from the discovery cohort to predict PFS and OS (Figures 4A and 4B). The nomogram assigned scores to patients based on their baseline brain metastasis status, presence or absence of treatment-related irAE/AE, and the first-line treatment regimen they received (Chemo or ICI+Chemo). The cohort was then stratified into two subgroups based on the selected cut-off that could divide the group into two equal parts as possible. Given that the three independent factors used for the model were all dichotomous categorical variables and not continuous quantitative values; there is a possibility of having multiple duplicate scores across the cohort.

In the discovery cohort, patients in the low-score group had significantly longer PFS (13.5 months vs. 5.0 months, HR: 0.22, 95% CI: [0.17–0.29], $p < 0.001$) and OS (26.0 months vs. 15.0 months, HR: 0.51, 95% CI: [0.39–0.67], $p < 0.001$) as compared with the high-score group (Figures 4C and 4D).

Using the same cut-off as the discovery cohort, the validation cohort was stratified into two groups into low and high scores. Consistent with the findings from the discovery cohort, the patients with low scores from the validation cohort 1 also had significantly longer PFS (10.0 months vs. 4.2 months, HR: 0.25, 95% CI: [0.14–0.42], $p < 0.001$) and OS (24.0 months vs. 16.0 months, HR: 0.58, 95% CI: [0.37–0.92], $p = 0.020$) as compared with the high-score group (Figures 4E and 4F).

DISCUSSION

In this retrospective study, we initially investigated the relationship between AEs and clinical outcomes. Data from the discovery and independent validation cohorts consistently showed that patients with advanced NSCLC who experienced any grade irAE/AE had better ORR, longer PFS, and OS than the patients who did not experience any irAEs/AEs with chemotherapy without or with ICI. This finding suggests the association between the occurrence of any grade irAEs/AEs and clinical efficacy regardless of treatment modality. We then constructed a nomogram model using three clinical characteristics identified as predictors of favorable survival outcomes: absence of baseline brain metastasis, receiving first-line ICI+Chemo, and occurrence of any grade irAE/AE. Across the discovery and validation cohorts, patients

A

Characteristics	Total(N)	HR(95% CI)	Univariate analysis	P value	HR(95% CI)	Multivariate analysis	P value
Gender	398						
Male	348	Reference			Reference		
Female	50	0.879 (0.624 - 1.240)		0.464	1.050 (0.634 - 1.738)		0.849
Age	398						
≤58	154	Reference			Reference		
>58	244	0.939 (0.747 - 1.180)		0.589	0.836 (0.654 - 1.070)		0.155
Smoking	398						
Smoker	327	Reference			Reference		
Never smoker	71	0.880 (0.653 - 1.187)		0.403	1.156 (0.753 - 1.777)		0.507
Drinking	398						
Never drinking	219	Reference			Reference		
Drinking	179	1.177 (0.940 - 1.474)		0.155	1.188 (0.927 - 1.522)		0.173
ECOG PS	398						
1	347	Reference			Reference		
0	51	0.799 (0.564 - 1.132)		0.207	0.809 (0.569 - 1.151)		0.239
Stage	398						
IIIB-C	109	Reference			Reference		
IV	289	0.898 (0.701 - 1.148)		0.39	1.257 (0.940 - 1.680)		0.123
Relapsed	398						
No	381	Reference			Reference		
Yes	17	0.861 (0.483 - 1.533)		0.611	0.831 (0.460 - 1.503)		0.541
Brain metastasis	398						
Without	362	Reference			Reference		
With	36	1.523 (1.050 - 2.209)		0.027	2.252 (1.517 - 3.344)		< 0.001
Hepatitis	398						
Without	151	Reference			Reference		
Previous infection	198	1.233 (0.969 - 1.569)		0.089	1.397 (1.086 - 1.798)		0.009
Current hepatitis	49	0.924 (0.627 - 1.363)		0.69	1.003 (0.674 - 1.494)		0.988
Liver metastasis	398						
Without	366	Reference			Reference		
With	32	1.312 (0.884 - 1.949)		0.178	1.388 (0.914 - 2.107)		0.125
AE	398						
Without	202	Reference			Reference		
With	196	0.446 (0.355 - 0.561)		< 0.001	0.462 (0.362 - 0.591)		< 0.001
First-line regimen	398						
Chemo	144	Reference			Reference		
Chemo+ICI	254	0.436 (0.345 - 0.550)		< 0.001	0.417 (0.319 - 0.546)		< 0.001

B

Characteristics	Total(N)	HR(95% CI)	Univariate analysis	P value	HR(95% CI)	Multivariate analysis	P value
Gender	398						
Male	348	Reference			Reference		
Female	50	0.639 (0.407 - 1.003)		0.051	0.648 (0.343 - 1.223)		0.181
Age	398						
≤58	154	Reference			Reference		
>58	244	1.300 (0.985 - 1.716)		0.064	1.173 (0.867 - 1.586)		0.301
Smoking	398						
Smoker	327	Reference			Reference		
Never smoker	71	0.801 (0.555 - 1.156)		0.236	1.279 (0.766 - 2.136)		0.346
Drinking	398						
Never drinking	219	Reference			Reference		
Drinking	179	1.336 (1.025 - 1.742)		0.032	1.253 (0.940 - 1.670)		0.124
ECOG PS	398						
1	347	Reference			Reference		
0	51	0.793 (0.519 - 1.212)		0.285	0.833 (0.541 - 1.283)		0.406
Stage	398						
IIIB-C	109	Reference			Reference		
IV	289	1.052 (0.778 - 1.422)		0.744	1.268 (0.904 - 1.780)		0.17
Relapsed	398						
No	381	Reference			Reference		
Yes	17	1.051 (0.538 - 2.050)		0.885	1.116 (0.563 - 2.210)		0.754
Brain metastasis	398						
Without	362	Reference			Reference		
With	36	1.420 (0.921 - 2.189)		0.113	1.912 (1.209 - 3.025)		0.006
Hepatitis	398						
Without	151	Reference			Reference		
Previous infection	198	1.244 (0.933 - 1.658)		0.136	1.190 (0.883 - 1.604)		0.253
Current hepatitis	49	0.982 (0.615 - 1.567)		0.938	0.949 (0.591 - 1.524)		0.829
Liver metastasis	398						
Without	366	Reference			Reference		
With	32	1.321 (0.842 - 2.073)		0.226	1.478 (0.912 - 2.396)		0.112
AE	398						
Without	202	Reference			Reference		
With	196	0.511 (0.389 - 0.671)		< 0.001	0.529 (0.396 - 0.706)		< 0.001
First-line regimen	398						
Chemo	144	Reference			Reference		
Chemo+ICI	254	0.606 (0.463 - 0.792)		< 0.001	0.633 (0.469 - 0.853)		0.003

Figure 3. Brain metastasis status, first-line treatment regimen, and treatment-related adverse event are independent predictors of survival outcomes
Forest plots summarizing the results of the univariate (left) and multivariate (right) Cox regression analysis for predicting the progression-free survival (A) and overall survival (B) of patients in the discovery cohort (n = 398). Abbreviations: AE, adverse events; CI, confidence intervals; HR, hazard ratio; ICI, immune checkpoint inhibitor.

with low scores from the nomogram consistently had significantly longer PFS and OS than those with high scores. This finding suggests that the nomogram model can serve as a biomarker for prognosticating patients who will receive ICI+Chemo.

Numerous studies have reported the association between the occurrence of any grade irAEs and longer PFS for ICI monotherapy and ICI+Chemo.[6–14] Our data contributes to the growing body of evidence regarding the relationship between irAEs and favorable clinical outcomes. The association between favorable clinical outcomes and irAEs affecting various organ systems has been reported individually, including skin reactions,[8] immune-associated pneumonia,[10] and thyroid dysfunction.[11] However, there is still a lack of a reliable and practical method to predict the clinical outcomes with ICI+Chemo or the occurrence of irAEs and guide clinical decision-making.

ICIs activate immune cells, decrease T cell tolerance, and disrupt the body's immune homeostasis, leading to a series of irAEs in the body. Currently, there are four possible mechanisms to explain the occurrence of irAE: (i) an increase in the antigenic activity of T cells against healthy tissues; (ii) an increase in the level of pre-existing autoantibodies; (iii) an increase in the level of inflammatory cytokines; and (iv) the direct binding of anti-CTLA-4 antibodies to normal CTLA-4 expressed on tissues binds directly, causing enhanced complement-mediated inflammation.[16] These underlying mechanisms suggest that the patient's immune system is highly active under the action of ICIs, especially in activated T cells, which have a strong response to tumor antigens. This strong T cell response, in addition to the possible attack on normal cells, is often associated with more effective tumor control and a better prognosis. Moreover, the effect of ICIs may also lead to an increase in the activity of inflammatory cells in the tumor microenvironment, changing the tumor microenvironment and making it more unfavorable for the survival and spread of tumor cells. IrAEs may serve as a manifestation of this environmental change. In addition, it has been suggested that the induction of the differentiation of tissue-resident memory T cells into cytotoxic effectors can persist long after ICIs are cleared *in vivo*. Some irAEs linger or emerge after ICIs are discontinued, which is considered a manifestation of incessant cytotoxicity after ICI discontinuation.[17] Therefore, we speculate that the occurrence of irAEs may also be related to long-term immune memory formation. Long-lasting immune memory can help the body respond quickly when tumors recur or metastasize, leading to improved survival rates.

To account for the bias contributed by the longer survival of patients that may heighten the likelihood of experiencing irAEs/AEs, we performed a time-dependent landmark survival analysis based on the time at which irAEs/AEs occurred in the study cohort. Our observation suggests that experiencing irAE/AE within six months of treatment was associated with longer PFS and OS outcomes. This finding is generally consistent with the observations reported by Socinski and colleagues.[14] However, the findings showed a trend of separation in the survival curve for some of the subgroups but had no statistical difference. We speculate that the limited sample size may present as one of the key challenges for this analysis. Another potential confounder might be inherent to the retrospective nature of our study where gaps may exist in the collection and sorting of irAE/AE information. It is worth noting that, as shown in Table S3, all patients in validation cohort 1 who received first-line chemotherapy alone have continued to receive second-line treatment, where 83.3% of patients received ICI-based regimens with good clinical outcomes. The favorable outcomes with subsequent treatment may have implications on the OS analysis.

In the KEYNOTE-010 study, the three most common any-grade irAEs in the two pembrolizumab dose arms (2 mg/kg and 10 mg/kg) were gastrointestinal reactions (31.6% and 25.1%), fatigue (13.6% and 14.3%), and rash (8.6% and 12.8%).[18] In a study by Ono et al., the two most frequent irAEs with ICI treatment were skin reaction (29.0%) and pneumonitis (14.0%).[10] Fatigue (32.5%, 38/117) was the most common irAE with nivolumab treatment reported in the CheckMate-063 study.[19] A retrospective study conducted by Haratani et al. reported a 3.7% (5/134; G3–4, 5/5) incidence of immune-related hepatitis with nivolumab treatment of NSCLC, with rash as the most frequently reported type of irAE (24.6%, 43/134).[20] In our present study, hepatic irAEs were the most common any-grade and severe adverse drug reaction observed across the cohorts. We speculate that the difference in treatment regimens administered and overall baseline characteristics of our cohort contributed to the difference in the incidence of irAEs between our cohort and other reported data. Despite the fact that alcohol consumption and hepatitis B virus infection contribute to increasing the patients' susceptibility to hepatic AEs, these variables were found to be not associated with survival outcomes with treatment using univariate and multivariate survival analyses. As ICI therapy becomes easily accessible to more patients with NSCLC, irAEs are rapidly becoming a global concern. To address this concern and ensure optimal care of patients who experience irAEs, clinical practice guidelines and recommendations have been developed and published by oncology societies, including the American Society of Clinical Oncology (ASCO),[4,21] the Society for Immunotherapy of Cancer (SITC),[22] and the European Society of Medical Oncology (ESMO).[23] To contribute to a deeper understanding of their mechanism, we believe that it is essential to consider the role of various biomarkers and other potential predictors in predicting the occurrence of irAEs, which can contribute to maximizing the clinical utility of ICI therapy, and a more precise and timely therapeutic strategy for resolving these irAEs.

Clinical outcomes may be impacted by the difference in severity of irAE/AE. A previous study by Hussaini et al. indicated that the development of irAEs was significantly associated with ORR, PFS, and OS in patients treated with ICIs, wherein G3 or higher toxicities resulted in better ORR but worse OS.[15] In our study, shorter OS was observed among the 19 patients who discontinued treatment or developed disease progression due to severe toxicity (OS < 300 days). Of them, 15 patients experienced G3 irAEs/AEs, two patients had G4 irAE (P204 and P218, Figure S8) and the other two patients developed G5 irAE (P106 and P109, Figure S9). Interestingly, survival outcomes were encouraging for a subset of patients who continued treatment after G3 irAEs/AEs occurred, including patients who continued treatment after temporary suspension of treatment for a few cycles (marked by green triangles in Figures S8–S10). Similar to our findings, long-term follow-up of the CA209-003 study also observed long-term clinical and survival benefits despite ICI discontinuation after severe irAEs.[24] We speculate that treatment

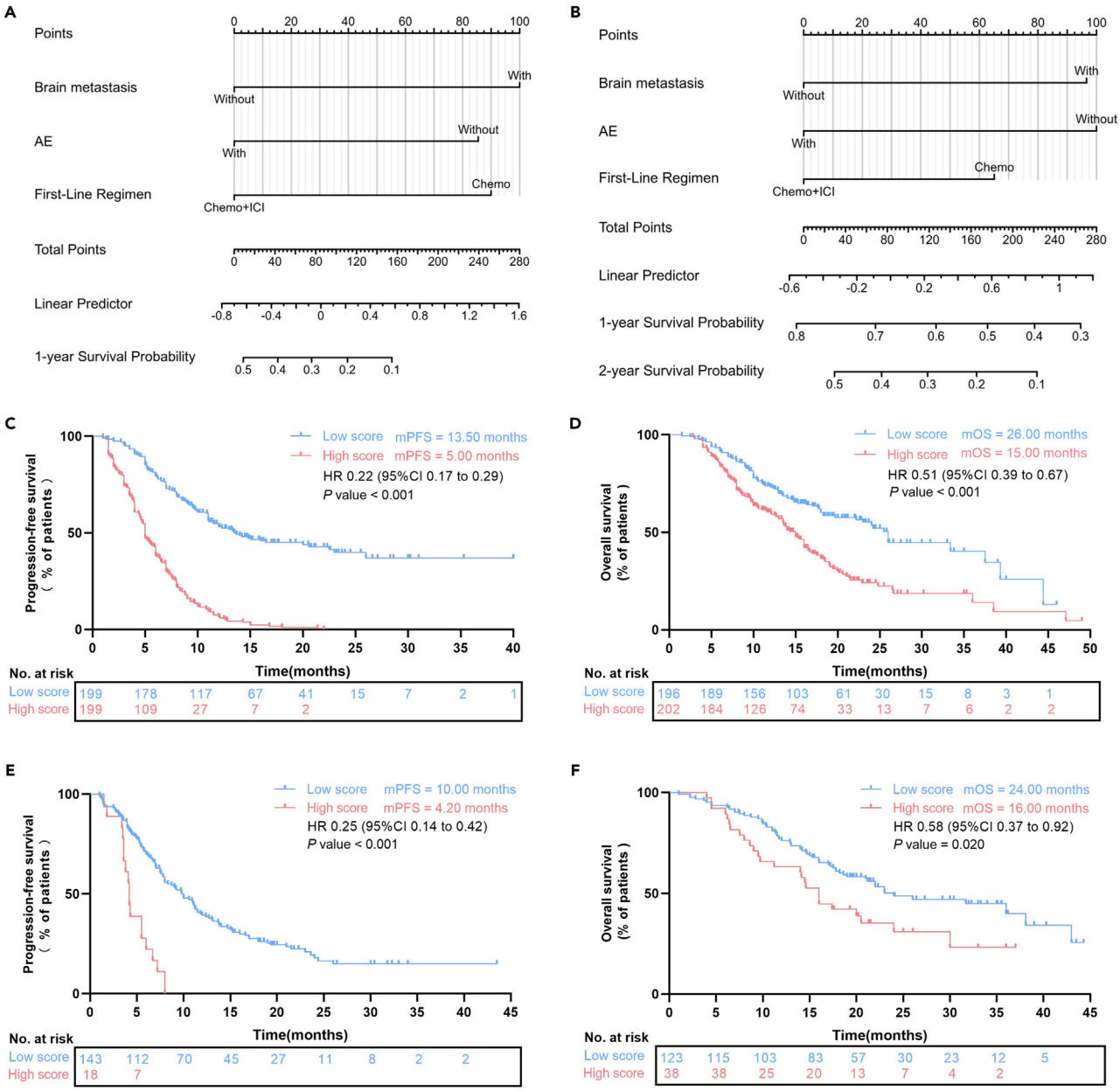

Figure 4. Nomogram predicts the survival outcomes of patients who experienced adverse events (AEs)/immune-related adverse events (irAEs) during treatment

(A and B) Nomograms illustrating the calculation of 1-year progression-free survival (PFS) probability (A) or 1-year and 2-year overall survival (OS) probability (B) using the three clinical variables found to be statistically significant from the multivariate analysis, including brain metastasis status, treatment regimen received in the first-line setting, and occurrence of adverse event with first-line treatment.

(C–F) Kaplan-Meier curves for comparing the PFS (C and E) and OS (D and F) of the patients in the discovery cohort (C and D) and validation cohort 1 (E and F) who were stratified into two groups as high and low based on the probability scores generated by the nomogram. Abbreviations: AE, adverse event; CI, confidence intervals; HR, hazard ratio; ICI, immune checkpoint inhibitor; mOS, median overall survival; mPFS, median progression-free survival.

discontinuation is one of the important factors for survival for patients who have poorer tolerance to treatment and experience adverse reactions. In one of our previous studies, we explored a variety of inflammatory signaling pathways and identified IL-1B as a potential factor that is closely related to an increased susceptibility to developing immune-related hepatitis.[25] The immune score and Euclidean distance of chemokines/cytokines may have potential value in predicting survival outcomes in patients who experience G3/4 immune-related hepatitis during ICI treatment.[25] At the same time, this also reflects the importance of timely identification and assessment of irAEs, especially irAE severity

of G3 and above. The management decisions for severe irAEs are more likely to greatly affect the clinical efficacy and overall prognosis of the patients. To further improve the prognosis of patients who experience severe irAEs, individualized patient management and intervention measures still need to be continuously explored. This conclusion is limited by the small sample size of the G3-5 subgroups in validation cohorts 1 and 2. No further analysis was conducted to verify the results of the discovery cohort. However, we can still see that the survival pattern in Figure S8 is similar to those in Figures S9 and S10.

Despite the existing clinical practice guidelines to optimize the management of irAEs,[4,21–23] various factors, such as immunological status, that might differ between patients might contribute to the occurrence of irAEs and distinct clinical outcomes from irAEs. Currently, most irAEs are diagnosed based on routine biochemical methods and physical examination.[4,21–23] In order to provide personalized treatment options to patients who experience irAEs during ICI therapy, it would also be advantageous to explore personalized diagnosis and management of irAEs using a model that integrates various clinical parameters, such as clinical, biochemical, genetic, and immunological parameters.

In this study, we constructed a prognostic scoring model based on the three independent prognostic clinical variables—baseline brain metastasis status, treatment regimen received as first-line regimen, and the occurrence of irAE/AE with first-line treatment. In contrast to biomarkers being investigated by other groups, the three clinical variables used in our nomogram model are practical and easily obtained in clinical practice. Moreover, these clinical variables, individually, are also shown to be associated with clinical benefits by other groups,[7,9,18,26–28] suggesting the potential utility of using all three clinical variables as a reliable and robust prognostic biomarker. In our future work, we plan to investigate the addition of other variables into the model, including Eastern Cooperative Oncology Group (ECOG) performance status and other laboratory parameters such as lymphocyte subsets, neutrophil/lymphocyte ratio, and lactate dehydrogenase (LDH) levels in order to achieve better sensitivity and specificity of the predictive model.

In conclusion, our study provided clinical evidence that the occurrence of grade 3 or higher irAE/AE, particularly with first-line ICI plus chemotherapy regimen, is associated with clinical benefit and favorable survival outcomes. Our findings also provided preliminary evidence supporting the utility of a nomogram in predicting the prognosis of patients who experience irAE during treatment with first-line ICI plus chemotherapy. Given that the three clinical parameters included in our nomogram model were all significantly associated with prognosis and are easily accessible in clinical practice, we believe our model is practical and easy to implement.

Limitations of the study

Our study is limited by the selection bias of the patient cohort and may not be representative of the whole population due to the retrospective nature of our study.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Yongchang Zhang (zhangyongchang@csu.edu.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

All somatic mutation status analyzed in this study was based on the electronic medical records of the patients. This study did not analyze DNA sequencing data or generate original code. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

Y.Z. and N.Y.: responsible for conceptualization, organization, data collection, auditing, supervision, project management, funding acquisition, writing, review, and editing. L.Z. and L.S.: responsible for data curation, methodology, formal analysis, original draft preparation, writing, review, and editing. Z.H., F.T., Z.L., and Q.X.: responsible for software operation, data validation, writing, review, and editing. L.S., H.Q., H.Y., X.Z., Z.H., Z.W., L.Z., and L.D.: responsible for formal analysis and visualization, writing, review, and editing. N.Y., W.G., S.L., and X.D.: responsible for critical comments and suggestions, writing, review, and editing.

DECLARATION OF INTERESTS

All authors declare no competing interest.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
Pembrolizumab	Merck Sharp and Dohme	N/A
Sintilimab	Eli Lilly and Co/Innovent Biologics	N/A
Camrelizumab	Jiangsu Hengrui Pharmaceuticals	N/A
Toripalimab	Coherus BioSciences	N/A
Tislelizumab	BeiGene	N/A
Durvalumab	Medimmune/AstraZeneca	N/A
Pemetrexed	Eli Lilly/Qilu Pharmaceuticals	N/A
Paclitaxel	Qilu Pharmaceuticals	N/A
Carboplatin	Qilu Pharmaceuticals	N/A
Biological samples		
Human archived tissue specimen	This study	N/A
Human blood samples	This study	N/A
Software and algorithms		
SPSS Statistical software (version 27.0)	IBM Corp.	RRID: SCR_002865

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Patient population

This multicenter retrospective study screened the medical records of patients treated with chemotherapy, ICI combined with chemotherapy, or ICI monotherapy between October 25, 2017 and April 24, 2022 at four different cancer centers in Hubei and Hunan provinces of China, namely Hunan Cancer Hospital, The Second Xiangya Hospital, Wuhan Union Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, and The Second Affiliated Hospital of Zhejiang University School of Medicine. Patients with stage IIIB-IV NSCLC without actionable genomic alterations in *EGFR*, *ALK* or *ROS1*, who received chemotherapy, ICI combined with chemotherapy, or ICI monotherapy as the first-line regimen were included as the study cohort. Patients with relapsed NSCLC after radical radiotherapy or surgery more than 6 months prior were included. Participant information on sex, age, and ethnicity was self-reported and recorded in the electronic medical records. Information on gender and socioeconomic status was not collected. The approval for the study protocol was obtained from the Hunan Cancer Hospital Institutional Review Board (2020YYQ-SSB-121).

METHOD DETAILS

Recording criteria for irAE/AE

In this study, we refer to toxicities observed in patients who received chemotherapy regimen as AE, whereas toxicities observed in patients who received ICI-containing regimen (whether monotherapy or combined with chemotherapy) as irAEs. All toxicities were assessed and graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 from US National Cancer Institute. All events were retrieved from medical records, including notes during ward visits and patient follow-up visits. Referring to the 2021 ASCO meeting report, the four time ranges used for assessing the onset of irAE/AEs are as follows: (i) from the start of treatment until about the first to second month, (ii) between the third and fifth month, (iii) between the sixth and eleventh month, and (iv) at or beyond the twelfth month.

QUANTIFICATION AND STATISTICAL ANALYSIS

Clinical outcome measures

Progression-free survival (PFS) was assessed as the time interval from the day of initiating treatment with either chemotherapy or ICI-containing regimen until the day of disease progression from the treatment, death, or last follow-up. Overall survival (OS) was assessed as the time interval from the day of initiating treatment with either chemotherapy or ICI-containing regimen until the day of death or last follow-up. The data cut-off date was 16 November 2022.

Statistical analysis

The difference in PFS and OS curves estimated with the Kaplan-Meier method according to the absence or presence of any irAEs/AEs was evaluated using the log-rank test. Univariate and multivariate Cox proportional hazard regression models were used to determine hazard ratios. All P values were based on a 2-sided hypothesis, and those less than 0.05 were considered statistically significant.

Clinical predictive models

The association between each clinical factor and survival outcome (ie, PFS and OS) was assessed using univariate Cox proportional hazards models. Factors with statistically significant hazard ratios were those with a significance level of 0.05. A multivariate Cox proportional hazards model was then incorporated. A nomogram plot was generated, and scores were assigned to the screened predictors. Cutoff values were selected to stratify the cohort into two groups. The survival outcomes of the two groups were compared. The predictive model was then validated using an independent cohort of patients who were also stratified into two groups.