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Different associations between organ-specific immune-related adverse event and survival in non-small cell lung cancer patients treated with programmed death-1 inhibitors-based combination therapy

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Yuzhong Chen*, **Yuanjian Shi***, **Hanlin Ding***, **Yipeng Feng**, **Te Zhang**, **Yingkuan Liang**, **Hui Wang**, **Xuming Song**, **Bing Chen**, **Wenjie Xia**, **Qixing Mao**, **Bo Shen**, **Lin Xu**, **Gaochao Dong** and **Feng Jiang**

Abstract

Background: The profile of immune-related adverse events (irAEs) due to programmed death-1 (PD-1) inhibitors-based combination therapy in advanced non-small cell lung cancer (NSCLC) and its relationship with survival have not been fully described.

Objective: Designed to capture the spectrum of irAEs and explore the association between irAEs and clinical outcomes in patients with NSCLC.

Design: This retrospective single-center study included patients with advanced NSCLC treated with PD-1 inhibitors (mainly in combination with chemotherapy) at Jiangsu Cancer Hospital.

Methods: The relationship between irAEs and survival was explored using landmark analysis and time-dependent Cox regression. The subgroup analyses focused on investigating the effects of organ-specific irAE, irAE grade, and steroid dose used to treat irAE.

Results: This study included 301 patients, 199 of whom received PD-1 inhibitors plus chemotherapy. The most common irAEs were skin toxicity (19.3%), endocrinopathy (21.3%), and pneumonitis (17.6%). In the entire cohort, the median progression-free survival (PFS) for patients developing and not developing irAE was 12.3 and 10.7 months ($p < 0.001$), and the median overall survival (OS) was 23.5 months and 20.1 months ($p = 0.137$), respectively. Subgroup analyses indicated that grade 3 or higher irAE, high steroid dose, and immune-related pneumonitis were detrimental to OS, whereas skin toxicity was beneficial to survival. These findings were further corroborated by both landmark analyses and Cox regression models conducted over four time points (1, 3, 6, and 12 months).

Conclusion: In the real world, NSCLC patients receiving PD-1 inhibitor-based combination therapy (particularly combined with chemotherapy) experience longer PFS with irAE, though not necessarily OS. Immune-related skin toxicity is associated with a better prognosis, whereas pneumonitis grade ⩾3 irAE and high steroid dose compromise survival. Clinicians should remain cognizant of the organ-specific manifestations of irAE and take proactive measures to mitigate the progression of irAE.

Keywords: combination therapy, immune-related adverse event, non-small cell lung cancer, organ-specific, PD-1 inhibitors, time bias

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Correspondence to:
Feng Jiang
Gaochao Dong
Department of Thoracic Surgery, Affiliated Cancer Hospital of Nanjing Medical University & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, 42 Baiziting Road, Xuanwu District, Nanjing 210009, China

Jiangsu Key Laboratory of Molecular and Translational Cancer Research, Nanjing, China

The Fourth Clinical College of Nanjing Medical University, Nanjing, China
fengjiang_nj@njmu.edu.cn
gaochao_dong@njmu.edu.cn

Yuzhong Chen
Yuanjian Shi
Hanlin Ding
Yipeng Feng
Te Zhang
Hui Wang
Xuming Song
Department of Thoracic Surgery, Affiliated Cancer Hospital of Nanjing Medical University & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, China

Jiangsu Key Laboratory of Molecular and Translational Cancer Research, Nanjing, China

The Fourth Clinical College of Nanjing Medical University, Nanjing, China

Yingkuan Liang
Department of Thoracic Surgery, Affiliated Cancer Hospital of Nanjing Medical University & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, China

Jiangsu Key Laboratory of Molecular and Translational Cancer Research, Nanjing, China

Department of Thoracic Surgery, The First Affiliated Hospital of Soochow University, Suzhou, China

Bing Chen
Wenjie Xia
Qixing Mao
Department of Thoracic Surgery, Affiliated Cancer Hospital of Nanjing Medical University & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, China

Jiangsu Key Laboratory of Molecular and Translational Cancer Research, Nanjing, China

Bo Shen
The Fourth Clinical College of Nanjing Medical University, Nanjing, China

Department of Oncology, Affiliated Cancer Hospital of Nanjing Medical University & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, China

Lin Xu
Department of Thoracic Surgery, Affiliated Cancer Hospital of Nanjing Medical University & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, China

Jiangsu Key Laboratory of Molecular and Translational Cancer Research, Nanjing, China

The Fourth Clinical College of Nanjing Medical University, Nanjing, China

Collaborative Innovation Center for Cancer Personalized Medicine, Nanjing Medical University, Nanjing, China

*These authors contributed equally.

Introduction

Nowadays, immune checkpoint inhibitors (ICIs) alone or in combination are very effective against advanced non-small cell lung cancer (NSCLC), and programmed death-1 (PD-1) inhibitor combined with chemotherapy is the standard first-line therapy for this disease.[1,2] Although ICIs offer impressive clinical benefits, the occurrence of immune-related adverse events (irAEs), a distinct group of organ-specific inflammatory toxicities that differ from those associated with chemotherapy and targeted therapies, is concerning.[3] IrAEs can lead to treatment discontinuation, irreversible tissue damage, and even fatal consequences.[4] For instance, pneumonitis is the most common fatal irAE among patients receiving ICIs, accounting for 35% of all deaths related with irAE.[5] Furthermore, while less common, myocarditis has a particularly high fatality rate of approximately 50%.[6] More astonishingly, over 40% of patients continue to suffer from chronic toxicity even after discontinuation of ICI treatment.[7]

The relationship between irAEs and efficacy has been a debatable issue over the past decade. Although the mechanism underlying irAEs is uncertain, it is generally acknowledged that irAE is associated with T-cell immunologic enhancement, which may mean greater effectiveness.[8] Numerous studies have suggested that irAEs may be an external manifestation of the long-term benefit of ICI, particularly in NSCLC and melanoma.[9] Two meta-analyses comprising 30 and 51 studies, respectively, revealed that patients who experienced irAEs tended to have higher response rates and longer PFS and OS.[10,11] Several multicenter studies indicated that irAE was associated with better clinical outcomes in NSCLC patients treated with PD-1 inhibitors.[12–15] However, irAE is highly heterogeneous, leading to inconsistent subgroup results in existing studies. Ricciuti *et al.* and Haratani *et al.* came to the opposite conclusion in exploring whether skin toxicity and longer survival were related.[12,13] Zhou *et al.*[11] found that endocrinal, dermatological, and low-grade toxicity were associated with longer survival, whereas gastrointestinal, pulmonary, and hepatic toxicity were not. Some irAEs even impair survival, such as grade 3 or higher irAEs[10] and pneumonitis.[16]

In addition to the heterogeneity of irAE, the issue of time bias is also critical. Simply explained, compared to patients with rapid progression or shorter survival, patients with long survival receive larger treatment doses and are more likely to develop irAEs.[17] Studies considering time bias may yield conflicting results. Sato *et al.*[18] found no significant correlation between irAEs and PFS using a 60-day landmark analysis, and Owen *et al.*[19] revealed that irAE was not associated with OS using a 3-month landmark analysis. Interestingly, Kfoury *et al.*[20] applied landmark analysis and time-dependent Cox regression model to address time bias, but reached inconsistent conclusions. Therefore, it is inconclusive whether irAE represents better prognosis. More importantly, most of the current studies were conducted in the ICI monotherapy setting, whereas in the real world, the use of ICI-based combination therapy is gradually increasing. So the spectrum of irAEs due to combination therapy and its correlation with clinical outcomes has not been comprehensively characterized.

Here, we performed a retrospective observational real-world study, taking into account immortal-time bias, to explore the relationship between irAEs and clinical outcomes in NSCLC patients treated with PD-1 inhibitor-based combination therapy, primarily in combination with chemotherapy. We further investigated whether irAE grade, irAEs involving different organs, and steroid dose had different impacts on survival. We also described the occurrence of irAEs in patients who were rechallenged with ICI after discontinuation due to irAEs.

Methods

This was a retrospective, observational, and single-center study conducted at the Affiliated Cancer Hospital of Nanjing Medical University, following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study population

This study included patients with NSCLC who received anti-PD-1 antibodies with or without chemotherapy or anti-angiogenesis therapy between June 2018 and June 2021. Chemotherapy regimens comprised platinum in combination with other drugs, such as pemetrexed, docetaxel, gemcitabine, or paclitaxel/nab-paclitaxel. The anti-angiogenesis drug used was bevacizumab. Patients continued treatment until experiencing disease progression, intolerable toxicity, or physician decision to discontinue. Inclusion criteria were patients ⩾18 years old with histologically

confirmed locally advanced or metastatic NSCLC; treatment lines ⩽3; follow-up over 1 year. Exclusion criteria were receiving radiotherapy during immunotherapy; previously treated with anti-PD-L1 antibodies; with autoimmune diseases; lost to follow-up with unexplained discontinuation of treatment.

The study followed good clinical practice guidelines and the principles outlined in the Declaration of Helsinki. As this is a retrospective study, patients' informed consent was not required.

Data collection and evaluation of irAEs

We collected patient baseline clinical data through electronic medical records or telephone inquiries, including age, sex, cancer stage, histology, differentiation, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status, presence of distant metastases (i.e. bone, liver, and brain), line of therapy, treatment type, driver mutation status, PD-L1 tumor proportion score (TPS), and irAEs. Once patients discontinued treatment due to irAEs, we monitored whether they opted for ICI rechallenge and assessed the occurrence of the second irAEs. The date of progression or death and the status of last follow-up were also collected. The data collection ended on 31 March 2023.

Patients' irAEs were defined based on (in rank order) pathological proof, multidisciplinary committee judgment, or clinical improvement in treatment for irAEs, after excluding other causes. Apart from these, we distinguished between PD-1 inhibitor-related and chemotherapy-related adverse events based on the following aspects: differences in the toxicity spectrum (incidence) of the treatments, variations in the time of toxicity onset, and identification of the treatment that effectively alleviate the toxicity. We monitored irAEs from the start of treatment until 1 year after cessation to prevent missed delayed events.[7] The ESMO Clinical Practice Guideline[21] was utilized to gather information on irAEs, which encompasses details such as the time of irAEs onset, the organs affected by irAEs, the grade of irAEs, and the steroid dosage administered (topical administration was excluded). The time of irAE onset was defined as the time from the start of treatment to the first irAE. The type of irAEs depended on the organs affected, such as skin toxicity, endocrinopathies, pneumonitis, gastrointestinal toxicity, etc. IrAEs have five grades: 1–2 are mild and moderate, 3–4 are severe and life-threatening, and 5 is lethal. The steroid doses were classified into three categories: 0, low, and high. High doses were defined as an initial methylprednisolone dose >1 mg/kg/day or equivalent doses of other hormones. In addition, to ensure the quality of irAEs data, two doctors independently reviewed the medical records, and conflicting information was adjudicated through discussion with a third senior doctor.

Study endpoints

Tumors were assessed using computed tomography and cranial magnetic resonance imaging (in the case of brain metastases) scans every 6 weeks approximately after the start of treatment, and efficacy was measured according to Response Evaluation Criteria in Solid Tumors (version 1.1). The primary endpoints were PFS and OS. PFS was defined as the time from initial immunotherapy to radiographic/clinical progression or death. OS was defined as the time from initial treatment to death from any cause. The secondary clinical endpoint was 'responders rate'. Responders were defined as those whose best response was complete response, partial response, or 'disease stable responders'.[22]

Statistical analysis

Continuous variables were expressed as medians, categorical variables as percentages. We conducted chi-square test to determine if 'responders' rate' differed between patients with and without irAE. Median follow-up time was calculated using the reverse Kaplan–Meier method. We plotted survival curves for PFS and OS using the Kaplan–Meier method and used Log-rank test to identify differences between groups. We also carried out sensitivity analyses for irAEs grade (0, 1–2, ⩾3) and each irAE type. Since irAE was a time-varying factor, we used two approaches to control the immortal-time bias: landmark analysis and time-dependent Cox regression model. In the landmark study design, patients who had an event before the preset time point and those who experienced irAEs after the time were excluded. Taking into account previous studies and our own data, we set four time points: 1-month, 3-month, 6-month, and 12-month. Multivariable Cox proportional hazards regression models were utilized to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for PFS and OS. The proportional

hazards assumption was evaluated by calculating the Schoenfeld residuals. The variables included in the models were: age, sex, smoking, ECOG performance status, histology, distant metastasis, EGFR mutation, treatment line, PD-L1 expression, and the presence of irAE. These analyses were conducted in all patients, as well as in the subset of patients who received combination chemotherapy.

The study was not designed to test specific hypotheses; therefore, the calculation of the sample size was not required. Statistical analysis and graphical representation were conducted using GraphPad Prism 9.0.0 and R software with the 'survival, survminer, and forestplot' packages. All p values were two-sided, and $p < 0.05$ was considered significant. In case of more than two groups, significance is only attributed to p values lower than 0.05 divided by the number of groups.

Results

Overall, a total of 1238 potentially eligible patients were screened between June 2018 and June 2021, out of which only 301 patients were eventually included, based on the inclusion criteria. Flowchart of the screening is presented in Supplemental Figure 1, and Supplemental Table 1 shows the detailed reasons for exclusion.

Patients' characteristics and irAEs profiles

In the whole cohort, the median age was 63 years (range 54–69), 75.7% ($n = 228$) of patients were male, 42.2% ($n = 127$) of patients were never smokers, 34.2% ($n = 101$) of patients had squamous cell carcinoma, and 13.0% ($n = 39$) of patients with EGFR mutation detected by next-generation sequencing. Only 8.6% ($n = 26$) of patients received anti-PD-1 monotherapy, whereas 66.1% ($n = 199$) of patients received anti-PD-1 combination chemotherapy, and 38.5% ($n = 116$) of patients responded to treatment. First-line treatment was administered to 41.9% ($n = 126$) of all patients, whereas 9.3% ($n = 28$) of patients were identified as PD-L1 negative. Furthermore, 29.6% ($n = 89$) of patients had PD-L1 TPS $\geqslant$50%. As of March 2023, 38 patients were still on treatment and 263 patients had discontinued due to progression ($n = 166$), irAEs ($n = 67$), AE not related to immunotherapy ($n = 16$) or others ($n = 14$). Detailed baseline clinical characteristics of all patients and those with and without irAE are shown in Table 1 and Supplemental Table 2. The median follow-up for

Table 1. Characteristics of patients with NSCLC treated with PD-1 inhibitors.

Characteristics	No. (%) or median (IQR)		
	All patients ($N = 301$)	Patients with irAE ($n = 176$)	Patients without irAE ($n = 125$)
Age, years	63 (54–69)	64 (54–68)	63 (55–69)
Sex			
Female	73 (24.3)	51 (29.0)	22 (17.6)
Male	228 (75.7)	125 (71.0)	103 (82.4)
Stage			
IIIB	16 (5.3)	10 (5.7)	6 (4.8)
IIIC	17 (5.6)	8 (4.5)	9 (7.2)
IVA	160 (53.2)	92 (52.3)	68 (54.4)
IVB	103 (35.9)	66 (37.5)	42 (33.6)
Histology			
Adenocarcinoma	189 (63.8)	124 (70.5)	68 (54.4)

(Continued)

Table 1. (Continued)

Characteristics	No. (%) or median (IQR)		
	All patients (*N* = 301)	**Patients with irAE (*n* = 176)**	**Patients without irAE (*n* = 125)**
Squamous carcinoma	101 (34.2)	47 (26.7)	56 (44.8)
Others	6 (2.0)*	5 (2.8)	1 (0.8)[$]
Smoking			
Never	127 (42.2)	75 (42.6)	52 (41.6)
Current or former	174 (57.8)	101 (57.4)	73 (58.4)
ECOG			
0	48 (15.9)	28 (15.9)	20 (16.0)
1	249 (82.7)	146 (83.0)	103 (82.4)
⩾2	4 (1.3)	2 (1.1)	2 (1.6)
Bone metastasis			
No	191 (63.5)	111 (63.1)	80 (64.0)
Yes	110 (36.5)	65 (36.9)	45 (63.0)
Liver metastasis			
No	233 (77.4)	139 (79.0)	94 (75.2)
Yes	68 (22.6)	37 (21.0)	31 (24.8)
Brain metastasis			
No	243 (80.7)	140 (79.5)	103 (82.4)
Yes	58 (19.3)	36 (20.5)	22 (17.6)
Line of therapy			
First	126 (41.9)	82 (46.6)	44 (35.2)
Second/third	175 (58.1)	94 (53.4)	81 (64.8)
Type of treatment			
Anti-PD-1 monotherapy	26 (8.6)	16 (9.1)	10 (8.0)
Anti-PD-1 + chemotherapy	199 (66.1)	111 (63.1)	88 (70.4)
Anti-PD-1 + anti-angiogenesis	23 (7.6)	17 (9.7)	6 (4.8)
Anti-PD-1 + chemotherapy + anti-angiogenesis	53 (17.6)	32 (18.2)	21 (16.8)
EGFR mutation			
No	262 (87.0)	157 (89.2)	105 (84.0)
Yes	39 (13.0)	19 (10.8)	20 (16.0)

(Continued)

Table 1. (Continued)

Characteristics	No. (%) or median (IQR)		
	All patients (*N* = 301)	Patients with irAE (*n* = 176)	Patients without irAE (*n* = 125)
PD-L1 TPS			
<1%	28 (9.3)	15 (8.5)	13 (10.4)
1%–50%	115 (38.2)	63 (35.8)	52 (41.6)
>50%	89 (29.6)	60 (34.1)	29 (23.2)
Unknown	69 (22.9)	38 (21.6)	31 (24.8)
No. of irAE			
0	125 (41.5)	0	125 (100)
1	155 (51.5)	154 (87.5)	0
2	18 (6.0)	19 (10.8)‡	0
>2	3 (1.0)	3 (1.7)§	0

No Anaplastic Lymphoma Kinase mutation.
*Adenosquamous carcinoma (*n* = 4), sarcomatoid carcinoma (*n* = 2).
$Adenosquamous carcinoma (*n* = 1).
‡Pneumonitis and endocrinopathy (*n* = 1), pneumonitis and skin toxicity (*n* = 5), pneumonitis and gastrointestinal toxicity (*n* = 2), pneumonitis and cardiovascular toxicity (*n* = 1), skin toxicity and endocrinopathy (*n* = 5), endocrinopathy and hematological toxicity (*n* = 1), endocrinopathy and hepatotoxicity (*n* = 3).
§endocrinopathy, gastrointestinal toxicity and hepatotoxicity (*n* = 1); skin toxicity, endocrinopathy, gastrointestinal toxicity and hepatotoxicity (*n* = 1); endocrinopathy, hepatotoxicity, pancreatic toxicity, and cardiovascular toxicity (*n* = 1).
IQR, interquartile range; irAE, immune-related adverse events; PD-L1 TPS, programmed cell death 1-ligand 1 tumor proportion score.

the whole cohort was 28.6 months (95% CI, 25.9–31.2) and 29.4 months (95% CI, 26.0–32.7) for combination chemotherapy.

During the follow-up period, 176 (58.5%) patients experienced 298 irAEs of all grades and 67 (22.3%) patients discontinued therapy due to irAEs. In the whole cohort, 155 patients developed only one irAE, whereas 21 patients presented with two or more irAEs. Grade 1–2 and grade ⩾ 3 irAEs occurred in 45.8% (*n* = 138) and 12.6% (*n* = 38) of patients, respectively. A total of 91 patients who developed irAEs received steroid treatment, including 32 who received high doses. irAEs were more commonly observed in skin [19.3%, e.g. pruritus, rash, and reactive cutaneous capillary endothelial proliferation (RCCEP)], thyroid (21.3%, e.g. primary hypothyroidism, hyperthyroidism, and diabetes), and lungs (17.6%; Table 2). Skin toxicity and endocrine disorders were mainly grade 1–2, but one patient developed grade 4 diabetes and required a lifelong insulin pump. In contrast, pneumonitis was more severe, leading to most discontinuation and three deaths. Notably, all RCCEPs were associated with camrelizumab. Only six cases of gastrointestinal toxicity occurred, but two were severe; one case of grade 3 hepatitis and two cases of severe cardiovascular toxicity. The median time for the onset of all irAEs in the entire cohort was 12.9 weeks. The incidence of irAEs in patients receiving anti-PD-1 combined with chemotherapy was similar to the overall population (Supplemental Table 3). The median time for the onset of each type of irAE is illustrated in Figure 1.

Impact of irAEs on therapeutic response

In the entire cohort, patients with irAEs had a more significant treatment response rate than those without irAEs (43.8% *versus* 31.2%; Supplemental Figure 2A). Moreover, the response

rate was found to be higher among patients who experienced grade 1–2 irAEs (51.4%) compared to those who either did not experience any irAEs (31.2%) or those who experienced grade 3 or higher irAEs (15.8%; Supplemental Figure 2B). In patients receiving anti-PD-1 combination chemotherapy, the response rate was slightly higher in patients who developed irAE, although the difference did not reach statistical significance (Supplemental Figure 2C). Additionally, the response rate was significantly higher in patients who developed grade 1–2 irAEs than in those who developed grade 3 and above (Supplemental Figure 2D). Therefore, patients who develop mild or moderate irAE have a higher response rate to treatment.

Results of no landmark survival analyses

The median PFS and OS for the entire population were 11.2 months (95% CI: 10.5–12.2) and 22.3 months (95% CI: 20.1–24.3), whereas in the combination chemotherapy population these were 10.9 months (95% CI: 10.1–11.7) and 21.1 months (95% CI: 18.8–23.4), respectively. In the entire cohort, no landmark survival analysis showed the median PFS was 12.3 months (95% CI: 11.1–14.6) for patients with irAE and 10.7 months (95% CI: 8.8–11.3) for patients without irAE ($p < 0.001$), and the median OS was 23.5 months (95% CI: 21.3–28.3) and 20.1 months (95% CI: 17.8–23.4; $p = 0.137$), respectively [Figure 2(a), 3(a)]. The median PFS for patients with no irAE, grade 1–2 irAE, and grade 3–5 irAE was 10.7, 13.8, and 9.5 months, and the median OS was 20.1, 25.7, and 14.1 months [Figures 2(b) and 3(b)]. Similarly, the median PFS for patients using steroid doses of 0, low and high was 11.2, 12.2, and 8.0 months, and the median OS was 23.2, 23.6, and 12.0 months, respectively [Figures 2(c) and 3(c)]. In patients receiving anti-PD-1 combined with chemotherapy, the median PFS was also significantly longer in patients with irAE (12.0 months, 95% CI: 10.5–14.1) than in those without irAE (9.4 months, 95% CI: 7.9–11.2; $p < 0.001$), as well as the median OS [22.9 months (95% CI: 19.1–27.6), 18.7 months (95% CI: 16.7–22.0), $p = 0.129$; Supplemental Figure 3A, 4A). Additionally, survival analyses based on irAE grade and steroid dose are shown in Supplemental Figures 3B and C, 4B and C. More details are presented in Supplemental Table 4. In general, patients with irAE had a significantly longer PFS and only a numerical increase in OS. Patients who experienced grade 3 or higher irAE or were on high-dose steroids had notably shorter survival, particularly OS.

We further performed sensitivity analyses based on the types of irAEs, including skin toxicity, endocrinopathies, and pneumonitis. In the entire cohort, the presence of skin toxicity

Table 2. IrAEs according to category and grade in all patients ($N = 301$).

Category of irAE	All grades No. (%)	Grade 3–5 No. (%)
Skin toxicity	58 (19.3)	9 (3.0)
Pruritus	12 (4.0)	1 (0.3)
Rash	38 (12.6)	6 (2.0)
RCCEP*	8 (2.7)	2 (0.7)
Psoriasis	1 (0.3)	1 (0.3)
Endocrinopathy	64 (21.3)	9 (3.0)
Primary hypothyroidism	49 (16.3)	6 (2.0)
Hyperthyroidism	14 (4.7)	2 (0.7)
Diabetes	1 (0.3)	1 (0.3)
Pneumonitis	53 (17.6)	14 (4.7)
Gastrointestinal toxicity	6 (2.0)	2 (0.7)
Diarrhea	5 (1.7)	2 (0.7)
Colitis	4 (1.3)	2 (0.7)
Gastritis/esophagitis	1 (0.3)	0
Hepatotoxicity	9 (3.0)	1 (0.3)
Liver enzyme elevation	7 (2.4)	0
Hepatitis	3 (1.0)	1 (0.3)
Pancreatic toxicity	2 (0.7)	1 (0.3)
Lipase elevation	2 (0.7)	1 (0.3)
Pancreatitis	1 (0.3)	1 (0.3)
Renal toxicity	1 (0.3)	1 (0.3)
Hematological toxicity	2 (0.7)	1 (0.3)
Neurological toxicity	2 (0.7)	0
Cardiovascular toxicity	5 (1.7)	2 (0.7)

*Both camrelizumab.
irAE, immune-related adverse events; RCCEP, reactive cutaneous capillary endothelial proliferation.

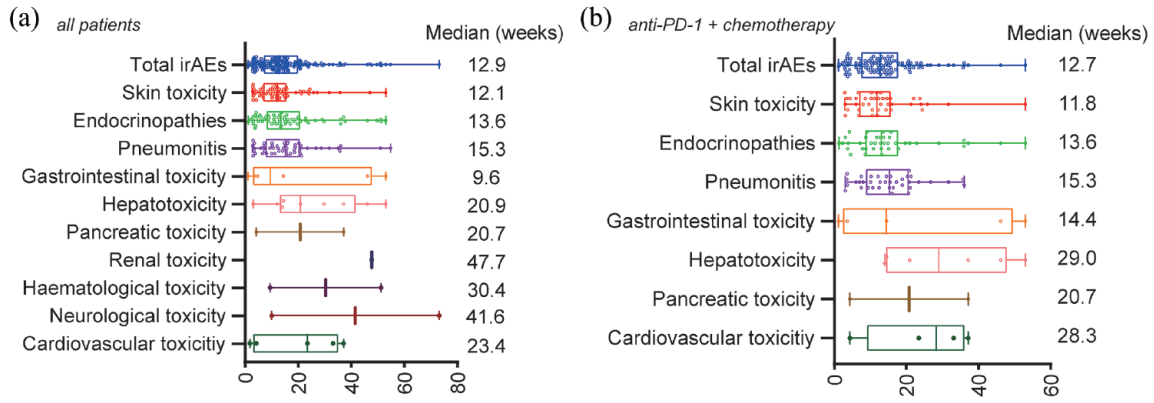

Figure 1. Time of irAE onset. (a) All patients and (b) patients receiving PD-1 inhibitors plus chemotherapy.
irAE, immune-related adverse event.

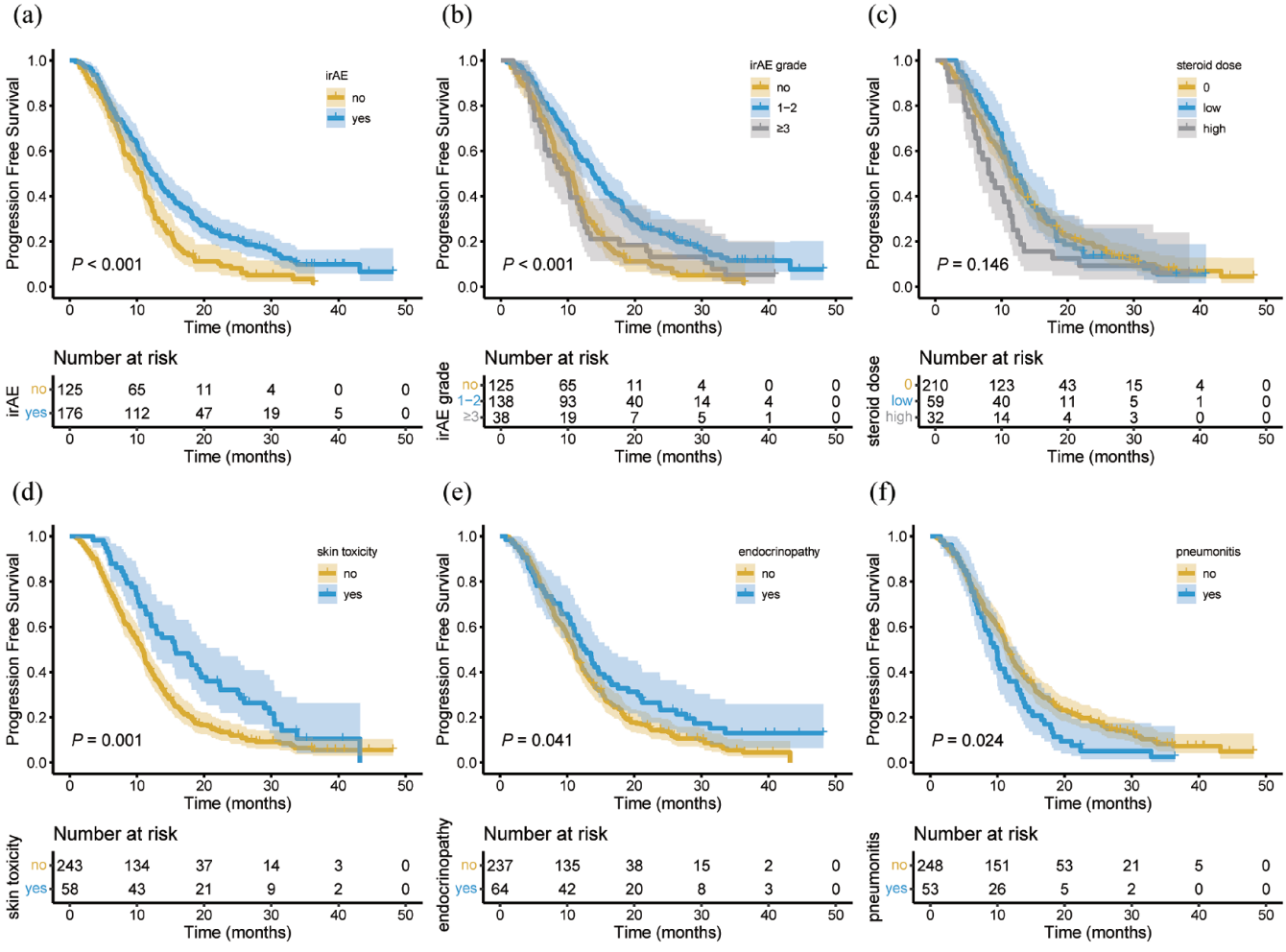

Figure 2. Progression-free survival curves for all patients according to: (a) irAE, (b) irAE grade, (c) steroid dose, (d) skin toxicity, (e) endocrinopathy, and (f) pneumonitis.
Survival was estimated using the Kaplan–Meier method, and comparisons between groups were made using the log-rank test.
irAE, immune-related adverse event.

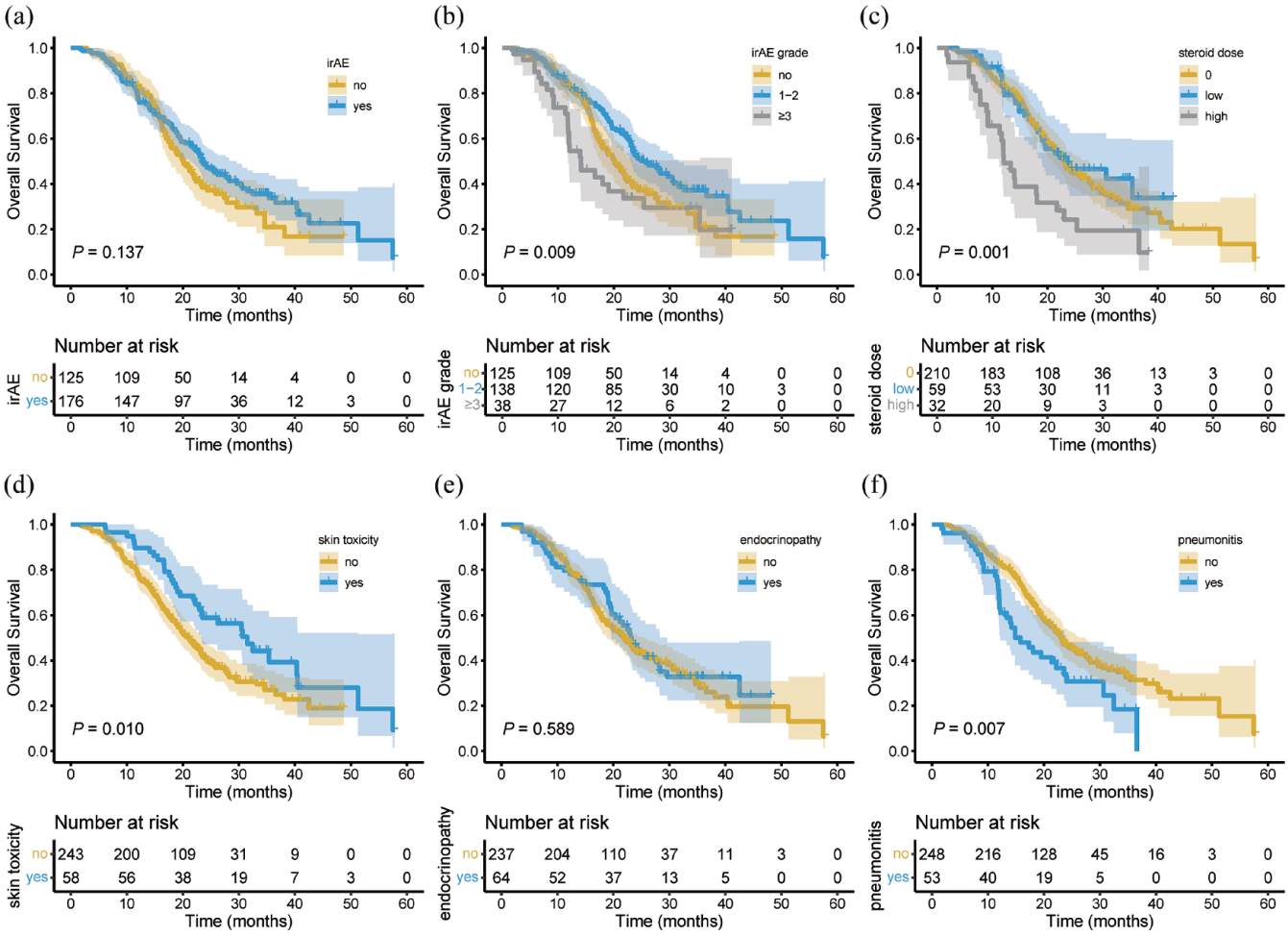

Figure 3. Overall survival curves for all patients according to: (a) irAE, (b) irAE grade, (c) steroid dose, (d) skin toxicity, (e) endocrinopathy, and (f) pneumonitis.
Survival was estimated using the Kaplan–Meier method, and comparisons between groups were made using the log-rank test.
irAE, immune-related adverse event.

was significantly associated with longer survival [PFS: 15.7 months (95% CI: 12.2–22.3), 10.8 months (95% CI: 9.7–11.6), $p = 0.001$; OS: 31.5 months (95% CI: 23.3–Not reached), 21.1 months (95% CI: 18.9–23.4, $p = 0.010$; Figure 2(d), 3(d)], whereas endocrinopathies were related to longer PFS, but not OS [PFS: 12.7 months (95% CI: 10.9–16.3), 11.1 months (95% CI: 10.0–12.1), $p = 0.041$; OS: 23.2 months (95% CI: 19.7–29.6), 21.9 months (95% CI: 18.9–25.3, $p = 0.589$; Figure 2(e), 3(e)]. However, pneumonitis impaired survival [PFS: 9.9 months (95% CI: 8.0–12.9), 11.6 months (95% CI: 10.9–12.7, $p = 0.024$; OS: 15.8 months (95% CI: 12.2–24.0), 23.2 months (95% CI: 21.2–27.4, $p = 0.007$; Figures 2(f) and 3(f)]. Similar findings were observed in patients who received anti-PD-1 combination chemotherapy (Supplemental Figures 3D–F, 4D–F). Supplemental Table 4 shows more detailed results.

Results of landmark survival analyses and time-dependent Cox regression models

Considering immortal-time bias, we performed landmark analysis (1, 3, 6, and 12-month) to analyze the relationship between irAEs and survival. In the 1-month landmark analysis with PFS as the endpoint, patients who progressed within 1 month and experienced irAEs after 1 month were excluded in the entire cohort. Therefore, 125 patients without irAE and 24 patients with irAE were included in this analysis, of whom 117 and 19 had events. With OS as the endpoint, 125 patients without irAE and 28 patients with irAE, of whom 78 and

28 had events, remained. The numbers of patients and events in other landmarks analyses are listed in Supplemental Tables 5 and Table 6.

Survival data by irAE status in the landmark subgroups are shown in Supplemental Table 7 and Supplemental Figures 5 and 6. In the entire cohort, Patients who experienced irAEs had significantly longer PFS than those who did not, except for the 1-month subgroup. Conversely, OS variations were observed only in the 12-month subgroup. Survival data by each type of irAE in the landmark subgroups are shown in Supplemental Figures 7–9, and Supplemental Tables 8–10. An interesting finding was that the results consistent with the non-landmark analysis were only observed in the 6-month subgroup. In this subgroup, patients experiencing skin toxicity had significantly longer PFS and OS than those who did not. Conversely, patients with pneumonitis had significantly shorter PFS and OS. The landmark analyses results showed consistent findings across patients receiving anti-PD-1 combination chemotherapy (Supplemental Tables 7–10).

The covariates included in the Cox regression model were: age, sex, smoking, ECOG performance status, histology, bone metastasis, liver metastasis, brain metastasis, EGFR mutation, treatment line, PD-L1 expression, and irAE. Schoenfeld residuals >0.05 suggested that models met the proportional hazards assumption (data not shown). Table 3 shows the PFS and OS HRs for patients with irAEs in the adjusted time-dependent Cox regression models. In the entire cohort, the PFS HRs (95% CI) in patients with irAEs (compared with patients without irAEs) were 0.64 (0.38–1.08) in the 1-month subgroup, 0.81 (0.58–1.12) in the 3-month subgroup, 0.68 (0.50–0.93) in the 6-month subgroup, and 0.57 (0.37–0.87) in the 12-month subgroup; the OS HRs (95% CI) were 0.87 (0.49–1.54), 1.00 (0.69–1.45), 0.94 (0.67–1.32), and 0.70 (0.48–1.02), respectively. HRs of other covariates are shown in Supplemental Figure 10–13. The PFS and OS HRs in patients with skin toxicity or endocrinopathy were both less than 1.00, whereas HRs were all greater than 1.00 in patients experiencing pneumonitis compared with patients without it. The results of the adjusted Cox regression models were largely similar amongst patients who received anti-PD-1 combined with chemotherapy (Table 3).

Overall, patients with irAEs had significantly longer PFS than those without irAE, whereas those with grade 3–5 irAE or those treated with high doses of steroids had significantly shorter OS. Interestingly, different types of irAE had inconsistent effects on survival – skin toxicity had a positive impact, whereas pneumonitis had a negative impact.

Outcomes of ICI rechallenge in patients discontinued for irAE

In our study, 67 patients discontinued treatment due to irAE, including 14 with multisystem irAE. Among them, 29 patients underwent ICI rechallenge, with 7 experiencing multisystem irAE. Out of these 29 patients, 25 patients continued with the same PD-1 inhibitor, whereas 3 patients switched to a PD-L1 inhibitor, and 1 patient switched from pembrolizumab to sintilimab. Details of ICI rechallenge in patients with different initial irAE are presented in Supplemental Figure 14. During the rechallenge, 13 patients experienced the second irAEs, but there were no cases of grade 4 or fatal irAE and four patients had to discontinue treatment again. Although the median OS was prolonged in patients who underwent ICI rechallenge compared to those who did not, the difference was not statistically significant (Supplemental Figure 15).

Discussion

During ICIs treatment, irAEs occur unpredictably and can be life-threatening.[5,23] It is essential to have a deeper understanding of irAEs in order to effectively manage the benefit-to-risk ratio of ICIs. In this observational study, we evaluated the association between irAEs and response rate and survival in NSCLC patients treated with PD-1 inhibitors-based combination therapy, especially in combination with chemotherapy. Patients with irAEs were more likely to respond to treatment, although the response rate was comparatively less in those patients with grade $\geqslant$3 irAE. In survival analysis, we found a strong positive correlation between overall irAE and PFS, but no relationship with OS. Subgroup analysis revealed that grade $\geqslant$3 irAE, high-dose steroid use and pneumonitis substantially compromised survival, but patients who experienced skin toxicity had significantly extended survival. Our landmark study design was more rigorous and patients who developed irAE after the preset time point were also excluded. So patients who developed irAE later would not have been classified as non-irAE, and the sample size was also

Table 3. Hazard ratio (95% confidence intervals) of the association between irAEs and survival.

Subgroup		1-month	3-month	6-month	12-month
All patients					
irAE	PFS	0.64 (0.38–1.08)	0.81 (0.58–1.12)	0.68 (0.50–0.93)	0.57 (0.37–0.87)
	OS	0.87 (0.49–1.54)	1.00 (0.69–1.45)	0.94 (0.67–1.31)	0.70 (0.48–1.02)
Skin toxicity	PFS	0.56 (0.21–1.45)	0.71 (0.46–1.12)	0.62 (0.43–0.90)	0.62 (0.38–0.99)
	OS	0.84 (0.33–2.14)	0.75 (0.45–1.29)	0.66 (0.43–1.00)	0.66 (0.42–1.03)
Endocrinopathy	PFS	0.34 (0.14–0.81)	0.59 (0.35–1.00)	0.74 (0.49–1.14)	0.73 (0.44–1.21)
	OS	0.37 (0.13–1.07)	0.94 (0.54–1.70)	0.96 (0.62–1.50)	0.99 (0.63–1.58)
Pneumonitis	PFS	1.32 (0.56–3.12)	1.80 (1.09–3.00)	1.78 (1.19–2.71)	2.22 (1.25–3.98)
	OS	1.86 (0.65–5.31)	1.84 (1.00–3.42)	1.72 (1.12–2.65)	1.33 (0.78–2.26)
Patients treated with combination chemotherapy					
irAE	PFS	0.42 (0.21–0.82)	0.68 (0.44–1.04)	0.55 (0.37–0.82)	0.48 (0.26–0.89)
	OS	0.53 (0.26–1.09)	0.82 (0.51–1.33)	0.81 (0.54–1.23)	0.65 (0.40–1.05)
Skin toxicity	PFS	0.33 (0.10–1.12)	0.61 (0.34–1.14)	0.42 (0.26–0.69)	0.35 (0.18–0.67)
	OS	0.34 (0.09–1.28)	0.78 (0.40–1.51)	0.52 (0.31–0.89)	0.55 (0.31–0.97)
Endocrinopathy	PFS	0.23 (0.07–0.75)	0.64 (0.34–1.20)	0.92 (0.54–1.53)	1.36 (0.67–2.76)
	OS	0.33 (0.11–1.04)	0.79 (0.40–1.53)	0.92 (0.55–1.55)	0.94 (0.54–1.64)
Pneumonitis	PFS	0.95 (0.31–2.89)	1.33 (0.73–2.45)	1.81 (1.10–2.98)	3.86 (1.76–8.51)
	OS	0.77 (0.17–3.49)	1.20 (0.55–2.61)	1.84 (1.09–3.11)	1.96 (1.05–3.68)

irAE, immune-related adverse event; OS, overall survival; PFS, progression-free survival.

reduced. Even so, both the landmark analyses and the adjusted time-dependent Cox regression models produced findings that generally supported the aforementioned observations.

Our study population was mainly NSCLC patients treated with PD-1 inhibitors in combination with chemotherapy, which was rare in previous studies. The incidence of irAE has increased after the introduction of chemotherapy in the real world, particularly pneumonitis (all grade 18.6%, grade ⩾3 5.5%). Two studies reporting PD-1 inhibitors in combination with chemotherapy found that overall irAE was associated with a PFS benefit.[24,25] Nonetheless, due to their small sample sizes and short follow-up periods, these studies failed to analyze OS or investigate organ-specific irAE. In a recent meta-analysis that included 62 randomized clinical studies, the investigators concluded that irAE should not be seen as a proxy for OS of anti-PD-1 treatment,[26] which is in agreement with our findings. Dall'Olio *et al.*[27] demonstrated the confounding effect of immortal-time bias, which has been properly addressed in our study. Kfoury *et al.*[20] discussed the differences between landmark analysis and time-dependent Cox regression, with contradictory results, the latter appearing to be the more accurate.[28] However, this study did not include grade 1 irAE and time-dependent Cox regression was performed in all patients, whereas our study population was consistent across the two methods, as was done by Haratani *et al.*[13]

Despite associations between overall irAE and higher response rates, sensitivity analyses demonstrated decreased response rates among patients experiencing grade ⩾3 irAE. These findings should be interpreted cautiously and may be

spurious. Ascertaining a causal relationship between irAEs and responses is difficult given the variable timing of their occurrences. Subgroup analyses conducted according to irAE grade and steroid dose indicated that grade ⩾3 irAEs and high steroid dose exhibited decreased survival. In fact, grade 3 or higher irAE often necessitate high-dose steroid therapy, making it difficult to ascertain which factor is responsible for the observed differences in survival. High-grade irAE frequently lead to drug discontinuation, which can result in shorter durations of immunotherapy in these patients. However, even with drug discontinuation, immunotherapy may achieve long-term tumor control.[29] On the other hand, steroids upregulate immune checkpoints on T cells and downregulate co-stimulatory molecules, pro-inflammatory cytokines, etc., creating an immunosuppressive tumor microenvironment that ultimately impacts immunotherapy efficacy.[30] Bai *et al.*[31] found that the use of high-dose corticosteroids to manage irAE was strongly associated with inferior survival. Therefore, the survival difference should be attributed to immunosuppression from high-dose steroid therapy for high-grade irAE rather than the irAE itself. A larger sample size is necessary to validate this observation. Subgroup analyses based on organ-specific irAE found that skin toxicity was significantly associated with longer survival, whereas pneumonitis appeared to be associated with decreased survival. Prolonged survival in patients experiencing skin toxicity may be attributed to the presence of shared antigens that can stimulate T cells in tumor tissue and skin.[32] Suresh *et al.*[16] found a 1.7-fold increased risk of death following the development of pneumonitis, which was also confirmed in our study. Moreover, OS was longer in patients with overall irAE than in those without it; however, this difference did not reach statistical significance in our study. This lack of significance was partially due to our limited sample size, but more plausibly due to the organ-specific nature of irAE.

Our study established four time points (1, 3, 6, and 12-month) for landmark analysis. Interestingly, the results differed at each point; however, the effects of organ-specific irAE on survival paralleled trends observed in non-landmark analyses. Hsiehchen *et al.*[33] identified the 3-month cut-off point as distinguishing early/late-onset irAE based on whether survival was beneficial. However, no survival difference was observed when Nigro *et al.*[34] used 12 months as cutoff, suggesting a strong heterogeneity in the time of irAE onset. There is no unambiguous optimal temporal cutoff point for landmark analysis, which requires determination through prospective studies. A recent study found that different immune subsets were associated with efficacy and toxicity in immunotherapy, implying that their mechanisms may cross but never merge.[35] Perhaps not all irAEs need to occur to derive benefit from PD-1 inhibitors, and possibly some irAEs are more directly related to anti-tumor efficacy than others. More researches are needed to explore the mechanisms behind the occurrence of different irAEs and timing of onset.

Most irAEs typically resolve or recede after discontinuing ICI and receiving steroid therapy or hormone replacement therapy. Permanent discontinuation is recommended only for grade ⩾4 irAE.[36] In some patients, it is feasible to consider ICI rechallenge after irAE remission, even if same or new toxicities occur, as most secondary irAEs are not more severe than the initial irAEs and could be manageable.[37,38] In our study, we found that the incidence of the second irAE in patients who underwent ICI rechallenge was 44.8% (13/29), which aligns with the incidence reported in previous studies.[39] Patients with initial irAEs of gastrointestinal toxicity (2/2), cardiovascular toxicity (1/1), and pneumonitis (5/10) were more prone to developing secondary irAEs. Specifically, patients with an initial irAE of pneumonitis had a higher likelihood of experiencing new irAEs (3/5). Surprisingly, the incidence of second irAEs in patients with initial multisystem irAEs (2/7) was not as high as anticipated, possibly due to the lower initial grade. Rechallenge of such patients is feasible but should be conducted with close monitoring.

The advantages of this study are the long follow-up period (median 29.60 months), the consideration of the heterogeneity of 'disease stable' patients and the rigorous irAEs data collection process. Conventional chemotherapy can stimulate anticancer immune response, an effect that can lead to the overestimation of irAEs,[40] and it is difficult to distinguish irAEs from the side effects of chemotherapy in clinical practice. It is therefore reliable for irAEs data to be collected independently by two doctors and decided by a senior physician. Our study has some weaknesses. This is a retrospective single center study and irAE is only available from medical records. Gastrointestinal toxicity was more difficult to determine and only severe ones were monitored with biopsies and

glucocorticoids; low-grade irAE may not even be documented in the medical records or available from laboratory tests and as a consequence was underestimated. The patients included in the study were heterogeneous, and even though we analyzed patients who received ICI combined with chemotherapy separately, the results of the subgroup analyses need to be interpreted with caution. The aggressive study design, while attenuating the effect of time-bias, reduces the sample size and may bring extra confounding factors. Finally, the effects of multiple irAEs were not excluded in the subgroup analysis.

Conclusion

Briefly, this real-world study shows that in NSCLC patients treated with PD-1 inhibitors-based combination therapy, particularly in combination with chemotherapy, overall irAE is linked with good clinical outcomes, but grade ⩾3 irAE and high-dose steroid use can impair survival. We also find that skin toxicity is associated with superior survival, whereas pneumonitis is associated with inferior survival, indicating the organ specificity of irAE. While larger prospective clinical studies are required to confirm our findings, our study suggests that clinicians should offer supportive care to manage irAEs and prevent the escalation of toxicities, especially pneumonitis.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of Jiangsu Cancer Hospital approved this study (No. 2022-035). We express our gratitude to all the patients who were involved in this study.

Consent for publication

Not applicable.

Author contributions

Yuzhong Chen: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Yuanjian Shi: Data curation; Investigation; Writing – original draft; Writing – review & editing.

Hanlin Ding: Formal analysis; Investigation; Visualization; Writing – original draft; Writing – review & editing.

Yipeng Feng: Investigation; Visualization; Writing – review & editing.

Te Zhang: Methodology; Writing – review & editing.

Yingkuan Liang: Writing – review & editing.

Hui Wang: Writing – review & editing.

Xuming Song: Conceptualization.

Bing Chen: Data curation; Writing – review & editing.

Wenjie Xia: Data curation; Writing – review & editing.

Qixing Mao: Data curation; Writing – review & editing.

Bo Shen: Investigation; Resources; Writing – review & editing.

Lin Xu: Methodology; Writing – review & editing.

Gaochao Dong: Conceptualization; Funding acquisition; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing.

Feng Jiang: Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Raw data are not publicly available and can be available upon reasonable request.

ORCID iDs
Yuzhong Chen https://orcid.org/0000-0002-0471-7178

Gaochao Dong https://orcid.org/0000-0002-7026-6280

Feng Jiang https://orcid.org/0000-0001-6569-5956

Supplemental material
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