Initiation of immune checkpoint inhibitor therapy in winter is associated with improved overall survival in patients with advanced non-small cell lung cancer

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Abstract. Immune checkpoint inhibitors (ICIs), targeting programmed cell death protein 1, programmed death-ligand 1 and cytotoxic T-lymphocyte-associated protein 4, have become a standard treatment resulting in improved outcomes in advanced non-small cell lung cancer (NSCLC); however, the influence of seasonal variations on treatment efficacy and toxicity remains underexplored. In the present single-center retrospective study, 310 patients with advanced NSCLC who initiated first-line ICI therapy between January 2018, and December 2023 were analyzed. Patients were categorized by season of treatment initiation: Winter (December-February), spring (March-May), summer (June-August) and autumn (September-November). Primary endpoints were overall survival (OS) and progression-free survival (PFS), assessed via Kaplan-Meier and Cox regression analyses. Immune-related adverse events (irAEs) were evaluated using χ^2 tests. Winter initiation of ICI was associated with the most favorable OS (P=0.02) but no significant difference in PFS was observed across seasonal groups (P=0.74). After multivariable adjustment, winter initiation remained an independent prognostic factor for OS, with adjusted hazard ratios of 1.82 (95% CI: 0.88-3.77; P=0.105) for summer and 2.59 (95% CI: 1.37-4.87; P=0.003) for spring/autumn, using winter as reference. The overall incidence of irAEs did not differ by season; however, respiratory irAEs, predominantly immune-mediated pneumonitis, were significantly more frequent in patients initiating ICI in winter (17.1%) compared with summer (5.9%; adjusted P=0.026). In conclusion, initiation of ICI therapy during winter is associated with improved overall survival in advanced NSCLC but may also confer a higher risk of immune-mediated pneumonitis. These findings highlight the potential role of seasonal factors in optimizing immunotherapy timing and monitoring.

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Introduction

Lung cancer remains one of the most common types of cancer worldwide, with an estimated 2.64 million new cases and 1.86 million associated deaths in 2024, accounting for 12.8% of total cancer incidence and 19.1% of total cancer mortality (1-3). The widespread implementation of immune checkpoint inhibitors (ICIs) has markedly transformed the treatment landscape of advanced non-small cell lung cancer (NSCLC). The KEYNOTE-407 study demonstrated that in patients with squamous NSCLC, pembrolizumab combined with chemotherapy could notably improve progression-free survival (PFS) and overall survival (OS) compared with chemotherapy alone, regardless of programmed death-ligand 1 (PD-L1) expression profile (4). However, a marked proportion of patients exhibit primary resistance to immunotherapy and fail to derive notable clinical benefit. Therefore, identifying reliable biomarkers capable of predicting treatment efficacy and toxicity is required for optimizing individualized therapeutic strategies (5,6).

Emerging evidence has suggested that the efficacy of immunotherapy is determined not only by tumor cell-intrinsic features but also by the functional status of the host's immune system. Notably, human immune function is regulated by biological rhythms at multiple levels, including circadian rhythms and macroscopic seasonal variations (7). Both innate and adaptive immune responses have been reported to exhibit

cyclical fluctuations, which may affect the timing of immunotherapy administration. Several studies have explored the association between the time of day of drug administration and immunotherapeutic outcomes. For example, in patients with melanoma, administration of ICIs later in the afternoon (after 4:30 pm) was associated with shorter PFS and OS (8). Similarly, in NSCLC, although the timing of the first ICI administration did not significantly affect outcomes, a higher proportion of afternoon dosing was associated with poorer survival outcomes (9). Collectively, these findings support the presence of time-dependent characteristics in immune responses.

In addition to circadian rhythms, macroscopic seasonal variations can also affect immune status through numerous environmental and physiological mechanisms, including daylight duration, ambient temperature and vitamin D metabolism (10). Serum vitamin D levels exhibit notable seasonal fluctuations and positively associate with sunlight exposure. Studies have indicated that sufficient vitamin D levels are associated with reduced cancer incidence and mortality (11,12). Furthermore, variations in melatonin levels during winter have been proposed to affect tumor progression through antioxidant, antiproliferative and immunomodulatory mechanisms, particularly in breast cancer (13). A large population-based epidemiological study conducted in Switzerland revealed that patients diagnosed with cancer during summer or autumn, particularly those with colorectal or breast cancer, experienced improved survival outcomes, suggesting that seasonal factors could play a key role in cancer biology (12).

However, evidence regarding the influence of the season of treatment initiation on treatment efficacy and toxicity in patients with advanced NSCLC remains limited and inconsistent. Therefore, the present study aimed to investigate the association between the season of immunotherapy initiation and clinical outcomes, including survival and the risk of immune-related adverse events (irAEs), in patients with advanced NSCLC through a single-center retrospective analysis.

Materials and methods

Study design and participants. The present single-center, retrospective study enrolled 310 patients with advanced NSCLC who initiated first-line ICI treatment, either as monotherapy or in combination with platinum-based chemotherapy, between January 2018 and December 2023 at Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University (Nanjing, China). Clinical data were retrospectively extracted from the electronic medical record system between June 2024 and December 2024. The inclusion criteria were as follows: i) Age between 18 and 90 years; ii) histologically confirmed stage III or IV NSCLC according to the 9th edition of the IASLC TNM staging system (14), without indication for curative surgical therapy (patients were retrospectively restaged according to the 9th edition criteria if needed); and iii) receipt of first-line ICI-based therapy. The main exclusion criteria included: i) Diagnosis of SCLC; ii) previous radical lung resection or surgery involving mediastinal lymph node dissection; iii) presence of sensitizing mutations in *EGFR*, anaplastic lymphoma kinase or ROS proto-oncogene 1; and iv) incomplete clinical records regarding baseline characteristics or treatment regimens. All treatment strategies were reviewed and approved by a multidisciplinary team. The present study was approved by the Jinling Hospital Research Ethics Committee (Nanjing, China; approval no. 2024DZKY-049-01).

Seasonal grouping and definitions. Patients were categorized into four groups according to the season in which they received the first dose of ICI therapy, namely the winter (December to February), spring (March to May), summer (June to August) and autumn (September to November). Nanjing has a subtropical monsoon climate, characterized by marked seasonal variation in temperature and sunshine duration. Spring and autumn exhibit comparable climatic features, with moderate temperatures and intermediate sunshine hours that lie between the extremes of summer and winter. Therefore, to enhance statistical power for comparing the two climatically distinct seasons (summer and winter), and to reduce the risk of overfitting in multivariable models, spring and autumn were combined into a single group ('spring/autumn'). The differential diagnosis of irAEs was performed by two experienced oncologists. The primary endpoints were OS, defined as the interval from treatment initiation to death from any cause, and PFS, defined as the time from treatment initiation to radiographic or clinical disease progression, or death from any cause. IrAEs were identified and graded according to the Common Terminology Criteria for Adverse Events, version 5.0 (15).

Statistical analysis. Baseline characteristics were summarized using descriptive statistics. Continuous variables are expressed as the mean ± standard deviation or median with interquartile range, depending on data distribution assessed using the Shapiro-Wilk test. Categorical variables are expressed as frequencies and percentages. Survival curves for OS and PFS were constructed using the Kaplan-Meier method and compared among groups with the log-rank test. Pairwise comparisons among seasonal groups were performed using the Renyi weighted test with Bonferroni correction. Univariate and multivariate Cox proportional hazards regression models were employed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) and to identify independent prognostic factors. The multivariate models were adjusted for age, sex, histologic type, smoking history, treatment modality, primary tumor size, N stage, M stage, Eastern Cooperative Oncology Group (ECOG) performance status and baseline pulmonary comorbidities. The proportional hazards assumption was assessed using Schoenfeld residuals. A formal interaction analysis between season and histologic subtype (squamous vs. non-squamous) was performed using the likelihood ratio test. As a sensitivity analysis, the four individual seasons (winter, spring, summer, autumn) were also analyzed separately using the same Cox regression framework, and the corresponding results are provided as supplementary material. Associations between the season of treatment initiation and the incidence of irAEs were evaluated using the χ^2 test or Fisher's exact test, as appropriate. For respiratory irAEs, pairwise comparisons among the three seasonal groups were performed using the Fisher-Freeman-Halton exact test with Holm correction for multiple testing. All statistical tests were two-sided, and $P<0.05$ was considered to indicate a statistically significant

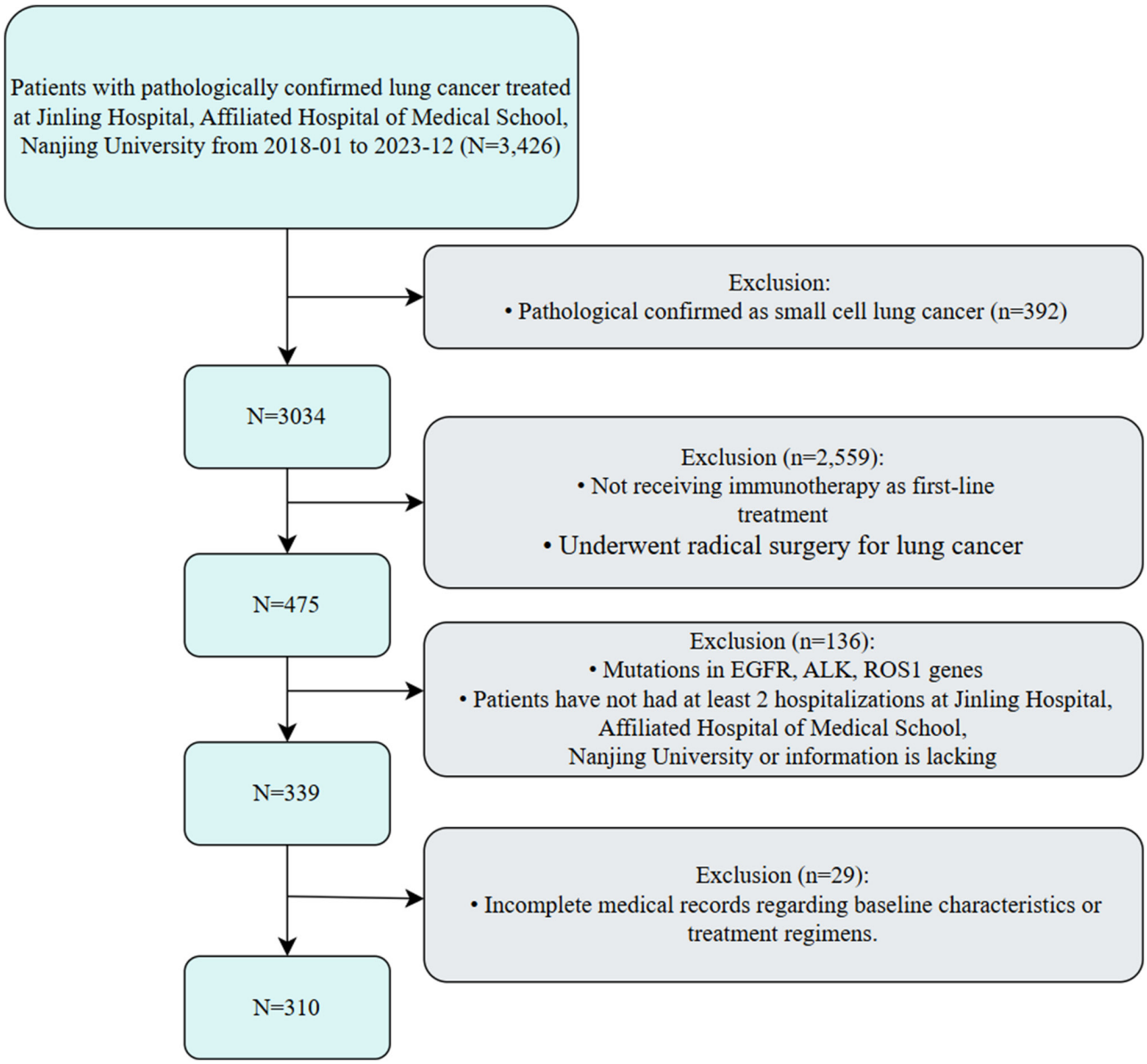

Figure 1. Flow chart. A total of 3,426 patients with lung cancer were screened, of whom 3,116 were excluded based on the exclusion criteria. Ultimately, 310 patients with advanced non-small cell lung cancer were included in the final analysis.

difference. All analyses were performed using R software (version 4.5.0; RStudio, Inc.).

Results

Baseline patient characteristics. A total of 310 eligible patients were enrolled in the current study (Fig. 1). Among them, 166 patients (53.5%) had squamous cell carcinoma (SCC), while 144 patients (46.5%) suffered from non-squamous cell carcinoma (non-SCC), predominantly adenocarcinoma and adenosquamous carcinoma. Regarding the season of ICI initiation, 70 patients (22.6%) started treatment during winter, 85 (27.4%) during summer and 155 (50.0%) during spring/autumn. All patients received ICI as first-line therapy. Among the 310 patients, 282 (91.0%) received ICIs in combination with platinum-based chemotherapy. Of these, 270 patients received ICI plus chemotherapy alone, while the remaining 12 patients received ICI plus chemotherapy plus bevacizumab (an anti-angiogenic agent). During follow-up, irAEs of any grade occurred in 63 patients (20.3%). Respiratory irAEs were the most common category, affecting 31 patients (10.0% of the total cohort), all of which were immune-mediated pneumonitis. Baseline characteristics stratified by season of ICI initiation are summarized in Tables I and SI. The distribution of key prognostic factors, including performance status (P=0.526), ICI regimen (P=0.531) and baseline pulmonary comorbidities (P=0.061), was generally well balanced across the three seasonal groups.

Local climate context. The present study was conducted in Nanjing, Jiangsu Province, China, a region characterized by a humid subtropical climate with four distinct seasons (16). Meteorological data indicate that summers are typically hot and humid (mean temperature in July, 28.1˚C; relative humidity, >80%), whereas winters are cold and damp (mean temperature in January, 2.7˚C).

Table I. Baseline demographic and clinical characteristics.

Characteristic	Overall (n=310)	Non-SCC (n=144)	SCC (n=166)	P-value
Patient age, years				0.056
<60	81 (26)	45 (31)	36 (22)	
≥60	229 (74)	99 (69)	130 (78)	
Sex				<0.001
Female	41 (13)	29 (20)	12 (7.2)	
Male	269 (87)	115 (80)	154 (93)	
Tumor size, cm				0.531
<5.0	78 (25)	32 (22)	46 (28)	
>7.0	167 (54)	80 (56)	87 (52)	
5.0-7.0	65 (21)	32 (22)	33 (20)	
N stage				0.467
N1	46 (15)	22 (15)	24 (14)	
N2	121 (39)	51 (35)	70 (42)	
N3	143 (46)	71 (49)	72 (43)	
Metastasis				<0.001
Absent	110 (35)	26 (18)	84 (51)	
Present	200 (65)	118 (82)	82 (49)	
Smoking history				0.005
Yes	232 (75)	97 (67)	135 (81)	
No	78 (25)	47 (33)	31 (19)	
Season				0.602
Spring/Autumn	155 (50)	71 (49)	84 (51)	
Summer	85 (27)	37 (26)	48 (29)	
Winter	70 (23)	36 (25)	34 (20)	
irAEs				0.356
Absent	247 (80)	118 (82)	129 (78)	
Present	63 (20)	26 (18)	37 (22)	
Immunotherapy modality				0.425
Combination therapy	282 (91)	133 (92)	149 (90)	
Monotherapy	28 (9.0)	11 (7.6)	17 (10)	
ECOG, n (%)				0.009
0	247 (79.7)	125 (86.8)	122 (73.5)	
1	61 (19.7)	19 (13.2)	42 (25.3)	
2	2 (0.6)	0 (0.0)	2 (1.2)	
Lung comorbidity, n (%)				0.027
Absent	254 (81.9)	125 (86.8)	129 (77.7)	
Present	56 (18.1)	19 (13.2)	37 (22.3)	

Data are present as n (%). Non-SCC mainly included adenocarcinoma and adenosquamous carcinoma. Combination therapy refers to immunotherapy combined with chemotherapy or anti-angiogenic agents. Monotherapy refers to single-agent immunotherapy. irAEs were identified and graded according to the Common Terminology Criteria for Adverse Events version 5.0. SCC, squamous cell carcinoma; Non-SCC, non-squamous cell carcinoma; irAEs, Immune-related adverse events.

Survival outcomes according to season of treatment initiation. Kaplan-Meier analysis showed a significant association between the season of ICI initiation and OS (Renyi test; spring/autumn vs. winter, unadjusted P=0.007, Bonferroni-corrected P=0.020; other pairwise comparisons, Bonferroni-corrected P>0.05; Fig. 2). Patients who initiated treatment during winter exhibited the most favorable survival outcomes, with a median OS of 58 months. By contrast, the median OS was not reached in the summer group and was 38 months in the spring/autumn group. Using winter as the reference category, univariate Cox regression analysis revealed a HR for death of 1.63 (95% CI, 0.80-3.29; P=0.176) for summer and 2.28 (95% CI, 1.22-4.25; P=0.009) for spring/autumn. In contrast to the OS findings,

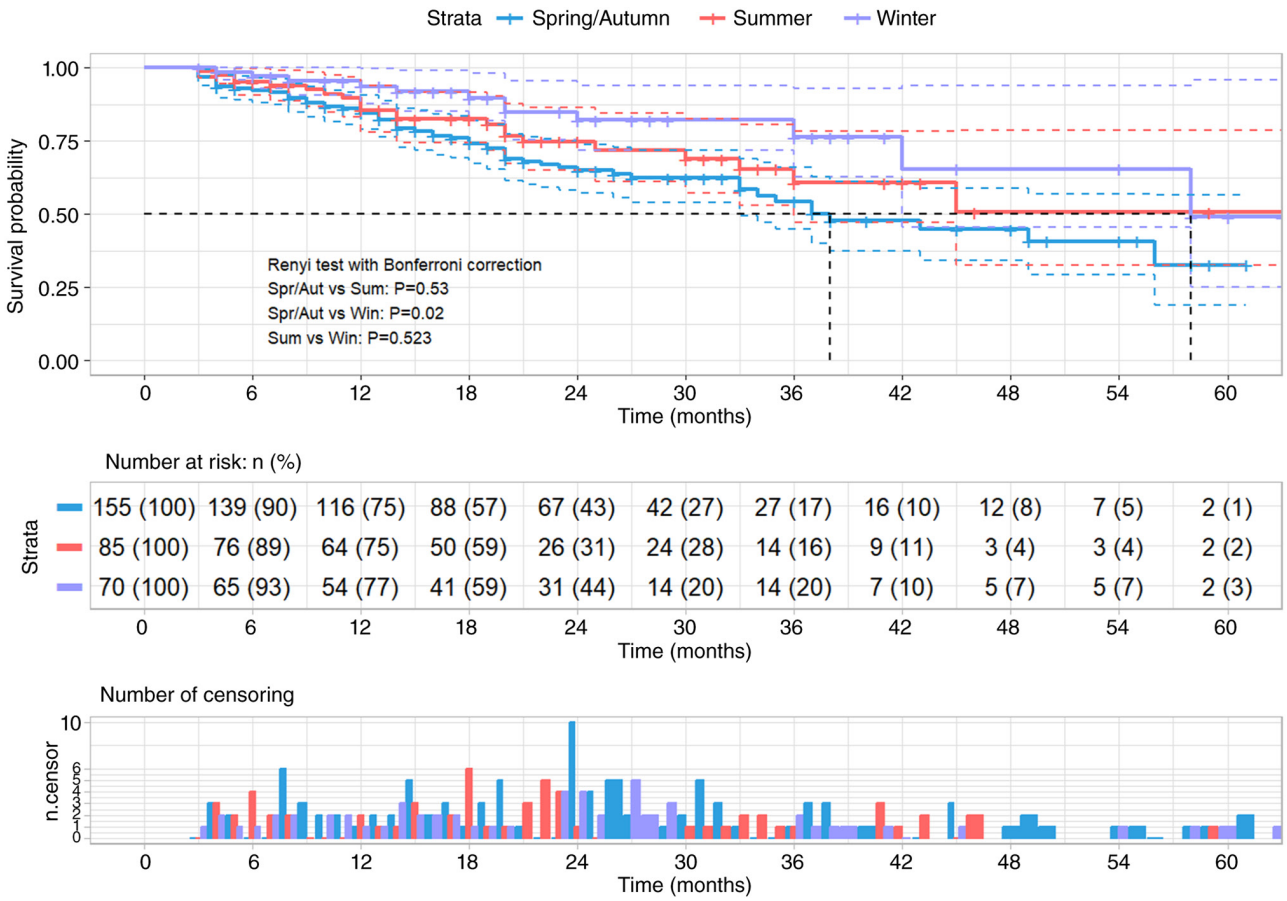

Figure 2. Kaplan-Meier survival analysis curve. Kaplan-Meier survival curves for overall survival based on the season (three-category classification) of immune checkpoint inhibition initiation; n=310. P-values were calculated using the Renyi weighted test with Bonferroni correction for pairwise comparisons.

no significant differences in PFS were observed among the three seasonal groups (Renyi test; all pairwise comparisons, unadjusted P>0.05, Bonferroni-corrected P>0.05; Fig. 3). After multivariable adjustment for tumor size, N stage, M stage, sex, smoking history, treatment modality, age, baseline pulmonary comorbidity, and ECOG performance status, the season of ICI initiation remained an independent prognostic factor for OS. Compared with winter, the adjusted HR for death was 1.82 (95% CI, 0.88-3.77; P=0.105) for summer and 2.59 (95% CI, 1.37-4.87; P=0.003) for spring/autumn (Table II). The proportional hazards assumption was formally tested and was satisfied for all variables included in the model, including season (Schoenfeld residual test, P=0.719; Fig. S1). Additional independent prognostic factors significantly associated with OS included primary tumor size >7.0 cm (adjusted HR=2.19; 95% CI, 1.23-3.89; P=0.008), the presence of distant metastasis (adjusted HR=1.90; 95% CI, 1.19-3.07; P=0.009) and ECOG performance status of 2 (adjusted HR=8.84; 95% CI, 1.03-76.0; P=0.047). In a sensitivity analysis using the original four-season classification (winter, spring, summer, autumn), the association between season of treatment initiation and OS remained significant. Renyi test showed that patients initiating treatment in winter had significantly greater OS compared with those initiating in spring (unadjusted P=0.001, Bonferroni-corrected P=0.007), while all other pairwise comparisons were not significant (Bonferroni-corrected P>0.05; Fig. S2). A consistent pattern favoring treatment initiation during winter was observed in multivariable analysis (Table SII).

To determine whether the prognostic effect of season varied according to histologic subtype, a formal interaction test between season and histologic subtype (SCC vs. non-SCC) was performed. No statistically significant interaction was observed (likelihood ratio test, P=0.960), indicating that the association between season and OS was comparable between the SCC and non-SCC subgroups. To further visually illustrate the direction and magnitude of the effect in the two subgroups, we performed multivariable Cox regression analyses were performed separately in patients with SCC and those with non-SCC (Tables II and SII). Subgroup-specific adjusted HRs are presented in Table SII and should be interpreted as exploratory.

Association between season of treatment initiation and irAEs. The overall incidence of irAEs of any grade was 20.3% (63/310 patients), with no significant differences among the three seasonal groups [winter, 20.0%; (n=14/70); summer, 20.0% (n=17/85); spring/autumn, 20.6%; (n=32/155); P=0.99]. The distribution of irAE categories according to season of treatment initiation is presented in Fig. 4. The most common category was immune-mediated pneumonitis, which occurred in 31 patients (10.0% of the total cohort). All 31 cases of respiratory irAEs were confirmed as immune-mediated pneumonitis. The incidence of immune-mediated pneumonitis differed significantly according

Table II. Univariate and multivariate Cox regression analysis for overall survival in patients with advanced non-small cell lung cancer, stratified by three-season classification of immune checkpoint inhibitor initiation (Winter, Summer, Spring/Autumn).

Variable	Level	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
		Overall		SCC		Non-SCC	
Age, years	<60	(Reference)		(Reference)		(Reference)	
	≥60	1.09 (0.69-1.72)	1.13 (0.70-1.83)	0.87 (0.45-1.69)	1.00 (0.49-2.04)	1.37 (0.72-2.60)	1.22 (0.62-2.40)
Comorbidity	Absent	(Reference)		(Reference)		(Reference)	
	Present	0.82 (0.48-1.41)	0.56 (0.22-1.47)	0.39[a] (0.17-0.89)	0.14[b] (0.04-0.50)	2.29[a] (1.09-4.79)	3.90 (0.65-23.24)
ECOG	0	(Reference)		(Reference)		(Reference)	
	1	0.96 (0.58-1.59)	1.75 (0.73-4.17)	0.66 (0.33-1.33)	2.74 (0.97-7.77)	1.81 (0.83-3.90)	0.59 (0.09-3.89)
	2	2.69 (0.37->19.46)	8.84[a] (1.03->75.96)	2.42 (0.33-17.77)	15.54[a] (1.65-146.07)		
Sex	Female	(Reference)		(Reference)		(Reference)	
	Male	1.30 (0.71-2.39)	1.93 (0.89-4.15)	2.52 (0.61-10.44)	7.18[a] (1.40-36.73)	1.11 (0.55-2.24)	1.14 (0.41-3.18)
M stage	M0	(Reference)		(Reference)		(Reference)	
	M1	1.70[a] (1.08-2.68)	1.90[b] (1.17-3.07)	2.04[a] (1.12-3.72)	2.37[a] (1.21-4.62)	1.38 (0.65-2.97)	1.88 (0.79-4.50)
N stage	N1	(Reference)		(Reference)		(Reference)	
	N2	0.99 (0.52-1.88)	1.18 (0.60-2.30)	1.23 (0.46-3.29)	1.78 (0.60-5.28)	0.84 (0.35-2.01)	0.79 (0.32-1.95)
	N3	1.10 (0.59-2.03)	1.31 (0.69-2.48)	1.37 (0.52-3.65)	2.28 (0.79-6.56)	0.94 (0.42-2.09)	0.93 (0.40-2.17)
Season	Winter	(Reference)		(Reference)		(Reference)	
	Spring/Autumn	2.28[b] (1.22-4.25)	2.59[b] (1.37-4.87)	1.99 (0.77-5.18)	2.40 (0.89-6.46)	2.51[a] (1.10-5.73)	2.98[a] (1.23-7.22)
	Summer	1.63 (0.80-3.29)	1.82 (0.88-3.77)	1.48 (0.52-4.22)	2.28 (0.74-7.02)	1.74 (0.66-4.59)	1.72 (0.62-4.78)
Smoking	No	(Reference)		(Reference)		(Reference)	
	Yes	0.93 (0.58-1.48)	0.77 (0.43-1.37)	0.91 (0.42-1.95)	0.83 (0.35-1.96)	0.98 (0.54-1.80)	0.84 (0.34-2.12)
Treatment	Monotherapy	(Reference)		(Reference)		(Reference)	
	Combination therapy	1.01 (0.49-2.10)	0.94 (0.45-1.97)	1.39 (0.50-3.90)	0.98 (0.33-2.90)	0.59 (0.21-1.66)	0.96 (0.30-3.01)
Tumor size, cm	<5.0	(Reference)		(Reference)		(Reference)	
	5.0-7.0	2.17[a] (1.15-4.12)	2.40[b] (1.25-4.62)	1.44 (0.62-3.36)	1.08 (0.44-2.64)	4.27[a] (1.39-13.11)	4.91[b] (1.55-15.54)
	>7.0	1.92[a] (1.10-3.36)	2.19[b] (1.23-3.89)	1.19 (0.59-2.40)	1.43 (0.66-3.05)	3.95[a] (1.39-11.23)	4.26[b] (1.47-12.32)

Hazard ratios and 95% confidence intervals are presented for the overall population and by histological subtype (SCC and non-SCC). [a]P<0.05 and [b]P<0.01 compared with the reference category. SCC, squamous cell carcinoma; non-SCC, non-squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group.

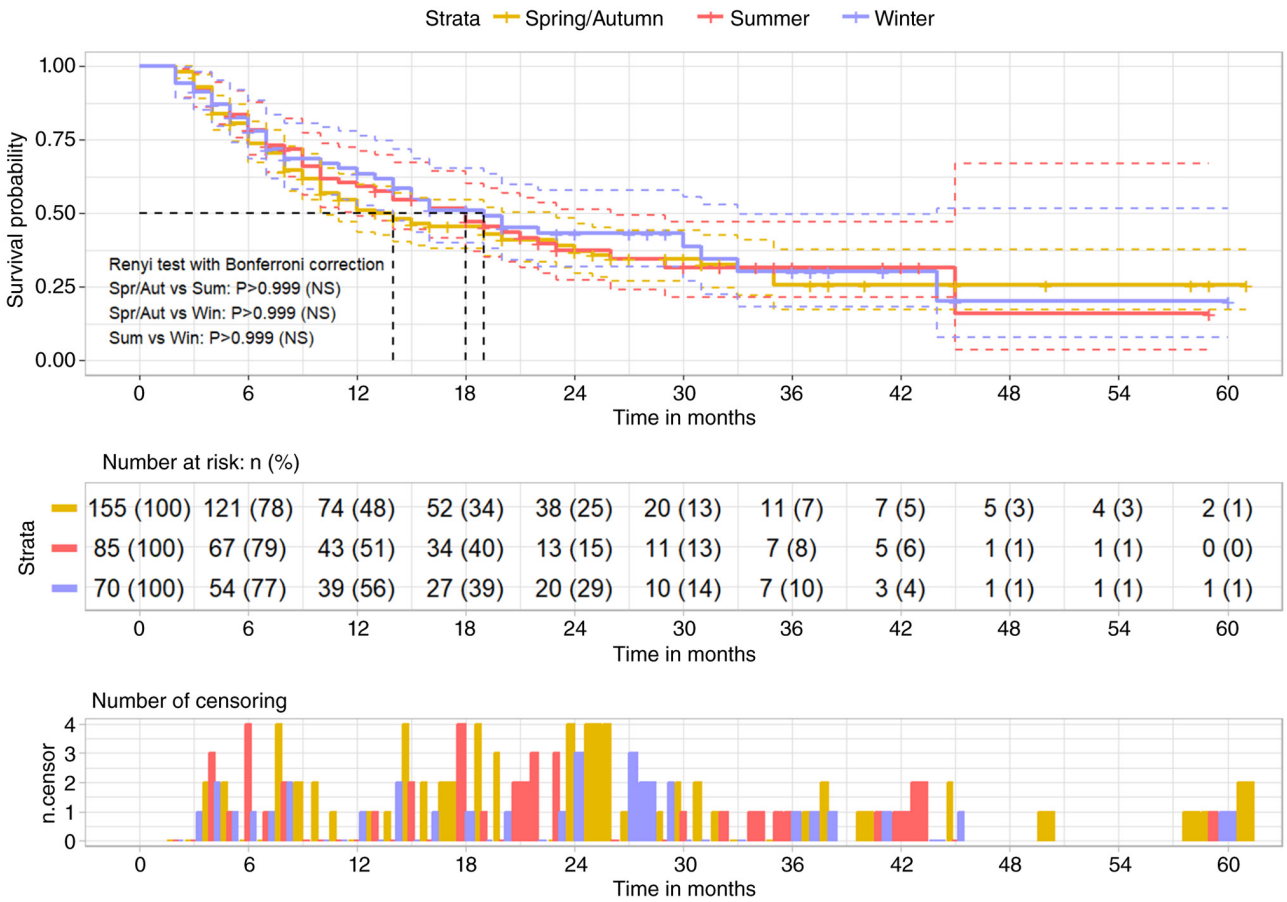

Figure 3. Kaplan-Meier survival analysis curve. Kaplan-Meier survival curves for progression-free survival based on the season of immune checkpoint inhibition initiation; n=310. P-values were calculated using the Renyi weighted test with Bonferroni correction for pairwise comparisons.

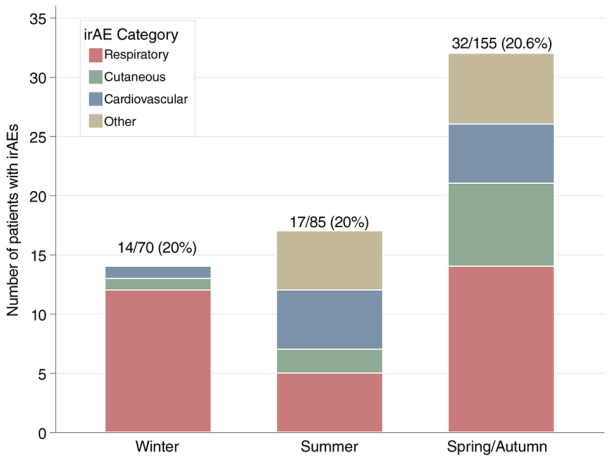

Figure 4. Stacked bar chart of the distribution of irAEs by organ system, stratified by season of immune checkpoint inhibitor initiation. irAE, immune-related adverse event.

to season of treatment initiation [winter, 17.1% (n=12/70); summer, 5.9% (n=5/85); spring/autumn, 9.0% (n=14/155); Fisher-Freeman-Halton exact test, P=0.045; Table SIII]. Post hoc pairwise comparisons showed that patients who initiated ICI therapy during winter exhibited a significantly higher incidence of immune-mediated pneumonitis compared with those who initiated during summer (Holm adjusted P=0.026).

Discussion

The present study from a Chinese single-center cohort, residing in a subtropical monsoon climate, provided additional evidence regarding the association between the season of immunotherapy initiation and clinical outcomes, including prognosis and irAEs, in patients with advanced NSCLC. The present analysis extended previous observations by also evaluating the association between treatment season and irAEs. The primary results showed that initiating ICIs during winter (December-February) was associated with significantly prolonged OS, while no significant seasonal differences were observed for PFS. Additionally, although the overall incidence of irAEs of any grade did not differ according to season, patients who initiated treatment during winter exhibited a significantly higher risk of developing immune-mediated pneumonitis compared with other seasons.

Emerging evidence has suggested that the incidence and progression of several solid tumors exhibit distinct seasonal patterns, supporting a potential role for intrinsic biological rhythms in cancer biology (17). For example, a population-based study from Norway demonstrated that young male patients with lung cancer diagnosed during autumn had ~15% lower mortality compared with those diagnosed during winter, with an even greater reduction in mortality observed among individuals residing in areas with higher ultraviolet

radiation exposure (18). Consistently, a large-scale statistical analysis by Lim *et al* (10) showed that patients with breast and lung cancer diagnosed during summer or autumn showed notably improved survival compared with those diagnosed during winter. Collectively, these findings suggested that macro-environmental factors could affect tumor biology via modulating the physiological and immunological states of the host.

Over the years, the potential effect of seasonal immune fluctuations on immunotherapy efficacy has attracted increasing attention. Notably, the results of the present study were inconsistent with those of a study conducted in the United Kingdom, a region characterized by a temperate maritime climate with relatively mild seasonal temperature and climate variations. In the aforementioned study, no significant seasonal differences in immunotherapy outcomes were reported (10,19). However, the present results aligned with those reported in the study by Cho *et al* (20), which demonstrated that patients with advanced NSCLC initiating anti-PD-L1 therapy in winter had significantly longer PFS (HR=0.77; P=0.018) and OS (HR=0.77; P=0.032) times compared with those starting in other seasons. Therefore, it was hypothesized that similarities in climatic features, including pronounced seasonal temperature variation, could partly explain the concordant conclusions between the two studies. Lower temperatures during winter could increase the prevalence of respiratory viral infections, thereby enhancing systemic immune surveillance and potentially providing a more favorable immune microenvironment for ICIs. This hypothesis was also supported by molecular evidence showing that transcriptomic analysis of peripheral blood mononuclear cells from patients treated during winter exhibited marked enrichment of multiple immune activation pathways, including the tumor necrosis factor superfamily signaling pathway (20). Conversely, increased temperatures during summer could induce heat stress responses, suppress B-cell differentiation and cytokine production, thereby indirectly contributing to an immunosuppressive state (21,22). Such effects could be considered as a potential mechanism underlying the relatively poorer survival outcomes in the non-winter groups, particularly the summer group. However, these proposed biological mechanisms, including seasonal variation in vitamin D levels, melatonin levels, immune activation and infection-related immune priming, were not directly assessed in the present study and should therefore be interpreted as speculative hypotheses rather than mechanistic conclusions.

The discordance between OS and PFS observed in the present study warrants careful interpretation. ICIs do not directly kill tumor cells but instead exert their antitumor effects by activating the immune system of the host. Due to their unique mechanisms of action, including delayed therapeutic responses and altered tumor growth kinetics, PFS could represent a suboptimal surrogate endpoint for evaluating immunotherapy efficacy. Unlike conventional cytotoxic agents, immunotherapy can induce durable disease control and eventual OS benefits once effective immune system activation is achieved, even in the absence of marked radiographic prolongation of PFS (23). Furthermore, seasonal immune modulation could affect long-term antitumor immune surveillance and responsiveness to subsequent therapies, rather than the initial tumor control reflected by PFS. The lack of a significant difference in PFS could also be associated with the limited sample size and retrospective nature of the present study, which could lack sufficient statistical power to detect modest differences in PFS. In addition, the potential effect of post-progression treatments, which were not systematically assessed in the current study, cannot be excluded. Overall, these findings suggested that seasonal factors could exert a more pronounced impact on long-term immune memory function or the ability to counteract drug resistance; however, this hypothesis remains speculative and requires prospective validation.

Regarding toxicity, initiation of ICIs during winter was associated with a higher incidence of immune-mediated pneumonitis in the present study. This finding was inconsistent with those described by Rogiers *et al* (24) in patients with melanoma, where pneumonitis was more common during autumn. However, this observation should be interpreted with caution, as the diagnosis of immune-mediated pneumonitis during winter poses particular clinical challenges. The increased prevalence of community-acquired respiratory infections during winter could complicate the radiological and clinical differential diagnosis. In the current study, the diagnosis of immune-mediated pneumonitis was established through comprehensive clinical evaluation, including radiographic assessment, exclusion of active infection through microbiological testing when available, and evaluation of response to corticosteroid therapy. Nevertheless, given the retrospective design of the present study, the absence of centralized radiological review, and the lack of systematic bronchoscopic or microbiological confirmation in all cases, the possibility of misclassification between infectious pneumonia and immune-mediated pneumonitis cannot be entirely excluded. Future prospective studies should incorporate standardized diagnostic algorithms, including mandatory infection workup and independent adjudication of irAE events, to minimize this potential source of bias. Although no significant seasonality was recorded for other irAEs, such as colitis or thyroid dysfunction, the season-dependent risk of immune-mediated pneumonitis suggested that seasonal factors could specifically affect pulmonary immune responses. This phenomenon warrants further investigation. Furthermore, the occurrence of irAEs is known to be affected by multiple factors, including drug type, dosage and underlying patient comorbidities (25-27). Therefore, whether seasonal factors contribute to irAE susceptibility still requires further validation through larger studies.

The current study has several limitations. First, as a single-center retrospective analysis, it is inevitably subject to selection bias and unmeasured confounding. Although multiple clinically relevant covariates were adjusted for in the multivariate analysis, several potentially notable variables, including PD-L1 expression profile, specific ICI agent, exposure to antibiotics or corticosteroids and post-progression therapies, could not be included due to incomplete data availability. Therefore, residual confounding could persist. Second, the sample size was relatively small, and the imbalance in subgroup sizes across seasons could affect statistical power. Notably, the formal interaction test between season and histologic subtype was not statistically significant, thus indicating that the subgroup-specific findings should be regarded as exploratory. Third, the lack of potentially relevant mechanistic

variables, such as vitamin D levels, daily light exposure, and history of prior pathogen exposure, limited the mechanistic interpretation of the findings. Future prospective, multi-center studies with larger sample sizes across different climate zones are warranted to validate these results. Furthermore, mechanistic investigations are needed to further elucidate the intrinsic biological pathways through which seasons could affect immunotherapy efficacy.

In conclusion, the current study suggested that the season of ICI initiation could be associated with OS and the risk of immune-mediated pneumonitis in patients with advanced NSCLC treated with first-line ICI therapy, with winter initiation potentially conferring a survival benefit. However, these observations should be considered hypothesis-generating and warrant further prospective validation before any clinical recommendations regarding the timing of immunotherapy can be established.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HL conceived and designed the present study, acquired the funding and provided supervision. JC, YY, BW and JS curated the data, including collection and assembly of clinical data; BW, JS and XL also contributed to the data analysis and interpretation. ZC performed the formal statistical analysis. ZC, JC and YY conducted the investigation, including patient screening, data extraction and follow-up. ZC and RW developed the study methodology, including the analytical framework and statistical approach. ZC and XL provided project administration and coordination. HL and ZC provided resources, including access to the clinical database. ZC was responsible for software implementation (R statistical programming), validation of the analytical results and visualization (generation of all figures and tables). ZC, JC and YY drafted the original manuscript, and HL and ZC critically reviewed and edited the manuscript. All authors read and approved the final version of the manuscript, and agree to be accountable for all aspects of the work. HL and ZC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present retrospective study was approved by the Jinling Hospital Research Ethics Committee (approval no. 2024DZKY-049-01). The committee waived the requirement for informed consent as the research used anonymized historical data without compromising patient privacy, in compliance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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