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ORIGINAL ARTICLE

Immune-Related Adverse Events in Patients with Solid Tumors Treated with Nivolumab: A Retrospective Single-Center Cohort Study

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OBJECTIVE

Immune checkpoint inhibitors have substantially improved outcomes in multiple solid tumors but are associated with immune-related adverse events (irAEs). However, the incidence, risk factors, and prognostic implications of irAEs in real-world settings remain unclear.

METHODS

This retrospective single-center study included 223 patients with solid tumors who were treated with nivolumab. irAEs were identified and graded according to the Common Terminology Criteria for Adverse Events Criteria for Adverse Events, version 5.0. The baseline demographic, clinical, and laboratory parameters were also evaluated. Cox proportional hazards models were used to assess factors associated with irAE development and overall survival (OS).

RESULTS

Among the 223 nivolumab-treated patients, 56 (25.1%) developed 64 irAEs. Endocrine toxicities were predominant, with hypothyroidism being the most frequent (43.8%). The median time to irAE onset was 13 weeks, and 20.4% of events were grade 3–4. Corticosteroids were required for 14.1% of the events, and permanent treatment discontinuation occurred in 7.8%. Prior radiotherapy was independently associated with an increased risk of first irAE development (hazard ratio [HR] 2.23, 95% confidence interval [CI] 1.14–4.34, p=0.019). In the multivariable OS analysis, higher body mass index was independently associated with improved survival (HR 0.950, 95% CI 0.913–0.988, p=0.011), whereas elevated lactate dehydrogenase (LDH) was associated with increased mortality (HR 1.020 per 10 U/L increase, 95% CI 1.008–1.031, p<0.001). irAEs, modeled as a time-dependent covariate, were not independently associated with OS (HR 0.747, 95% CI 0.488–1.144, p=0.180).

CONCLUSION

In this real-world cohort study, irAEs occurred in approximately one-quarter of patients during nivolumab therapy, with endocrine toxicities representing the predominant spectrum. Prior radiotherapy was independently associated with the development of irAEs. When analyzed as a time-dependent variable, irAE occurrence was not independently associated with OS. Baseline body mass index and LDH remained independent prognostic factors for survival.

Keywords: Immune checkpoint inhibitors; immune-related adverse events; nivolumab; overall survival; solid tumors.
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INTRODUCTION

Immune checkpoint inhibitors have reshaped modern cancer treatment by counteracting inhibitory signals that restrain antitumor immunity, thus enabling more effective immune attack against tumors.[1] Immune checkpoint inhibitors disrupt inhibitory signaling mediated by the PD-1/PD-L1 and CTLA-4 pathways, thereby enhancing T-cell activation and effector function, which ultimately promotes immune-mediated tumor cell apoptosis and sustained antitumor responses.[2]

Over the past decade, immune checkpoint inhibitors have become integral to the management of multiple solid tumors and have demonstrated meaningful improvements in clinical outcomes across diverse malignancies. Evidence from large retrospective cohorts and systematic reviews indicates that immune checkpoint inhibitors (ICIs) confer significant survival and response benefits in cancers, such as non-small cell lung cancer, malignant melanoma, renal cell carcinoma, urothelial carcinoma, and head and neck squamous cell carcinoma, with reported objective response rates ranging from approximately 30% to over 40% and substantial gains in progression-free and overall survival (OS) compared with historical outcomes.[3,4] As a result, the indications for ICIs continue to expand rapidly, and these agents are increasingly being incorporated into routine clinical practice, both as monotherapy and in combination regimens.

Despite their substantial clinical efficacy, immune checkpoint inhibitors are associated with a distinct spectrum of toxicities, termed immune-related adverse events (irAEs), which arise from non-specific immune activation and breakdown of immune self-tolerance. Large-scale pharmacovigilance analyses comprising more than 50,000 reported irAE cases have shown that these toxicities can involve nearly every organ system, with the most commonly affected being the skin (approximately 22–25%), lungs (18–20%), gastrointestinal tract (14–15%), and endocrine organs, particularly the thyroid (around 12%).[5] Across different immune checkpoint inhibitor regimens, the median time to onset of irAEs has been reported to range from approximately 30 to 45 days, although onset times vary widely from as early as 1–2 weeks to beyond 6–9 months. Delayed events occurring after treatment discontinuation have also been documented.[6] While the majority of irAEs are low to moderate in severity, real-world data indicate that severe or life-threatening toxicities account for a substantial proportion of cases, with reported fatality rates of approximately 20–28% for myocarditis, 20–23% for myositis and myasthenia-like syndromes, and 20–21% for pneumonitis.[5–7]

irAEs are most commonly graded using the Common Terminology Criteria for Adverse Events (CTCAE); however, complementary consensus-based frameworks, such as those proposed by the Society for Immunotherapy of Cancer, have been developed to better capture the unique clinical features of immune-mediated toxicities.[8,9] Management of irAEs is guided by toxicity grade and organ involvement, and may involve treatment interruption, systemic corticosteroids, additional immunosuppressive therapy, or permanent discontinuation of immune checkpoint inhibitors. Early recognition and appropriate management are essential, as inadequately controlled irAEs may lead to significant morbidity, treatment non-adherence, and, in rare cases, mortality, whereas timely intervention often allows safe continuation or reintroduction of immunotherapy.

Moreover, the identification of patients at an increased risk of developing irAEs remains an unresolved clinical challenge. Although previous studies have explored demographic, clinical, and laboratory parameters as potential predictors of irAE susceptibility, the results have been heterogeneous, and no reliable predictive model has been universally adopted. Importantly, variations in genetic background, environmental factors, comorbidity profiles, and treatment practices across populations may contribute to differences in the incidence and presentation of irAEs, underscoring the need for real-world data from diverse clinical settings. Although several studies have evaluated irAEs across heterogeneous immune checkpoint inhibitor regimens, real-world data focusing specifically on nivolumab-treated populations remain comparatively limited, particularly in routine clinical practice settings.

In this context, we conducted a single-center retrospective cohort study to characterize the incidence, spectrum, and timing of irAEs in adult patients with solid tumors treated with nivolumab. We further aimed to identify clinical and laboratory factors associated with the development of irAEs and evaluate the relationship between irAE occurrence and OS using time-to-event analyses. We hypothesized that specific baseline clinical and laboratory characteristics would be associated with an increased risk of irAE development, and sought to determine whether irAE occurrence was associated with survival outcomes in routine clinical practice.

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MATERIALS AND METHODS

Data Curation and Study Cohort

Patients initiating nivolumab between January 2014 and March 2025 were included. Follow-up data were censored on March 31, 2025. Between 2014 and 2025, 233 adult patients with solid malignancies who initiated nivolumab therapy were identified. Three patients who received nivolumab for hematologic malignancies were excluded. Seven patients were excluded because of incomplete baseline or follow-up data. The remaining 223 patients constituted the final study cohort. Patients were included irrespective of treatment duration; therefore, individuals who discontinued nivolumab early because of death, treatment discontinuation, or loss to follow-up remained in the analysis until the time of censoring or event occurrence.

Follow-up started on the date of nivolumab initiation. During the observation period, 56 patients developed a total of 64 irAEs. Multiple adverse events occurred in a subset of patients. Follow-up time was calculated from nivolumab initiation until death or the last clinical contact. Total person-time was calculated as the sum of individual follow-up times, and the incidence rate of first irAEs was expressed per 1,000 patient-weeks with 95% confidence intervals based on the Poisson distribution.

irAEs were identified through retrospective review of electronic medical records, laboratory results, imaging findings, and oncology clinic documentation. Potential irAEs were assessed by review of the treating oncologists' clinical records. When uncertainty regarding causality existed, classification was based on the documented multidisciplinary clinical assessment and available diagnostic work-up recorded in the medical records. The diagnosis of endocrine, hepatic, gastrointestinal, neurological, pulmonary, and dermatological irAEs was based on the treating oncologist's clinical assessment together with laboratory, imaging, and specialist consultation findings, after exclusion of alternative etiologies whenever appropriate. irAEs were identified and graded according to the CTCAE, version 5.0.[8,9]

Patients with previously documented endocrine disorders were not classified as having endocrine irAEs unless a new immune-related event was clinically diagnosed after nivolumab initiation.

History of radiotherapy was defined as any radiotherapy administered before initiation of nivolumab treatment. Radiotherapy delivered after nivolumab initiation was not considered in the analyses.

Ethics

Ethics committee approval was obtained from the Izmir Katip Çelebi University Institutional Review Board on April 9, 2026 (approval no: 0280). The requirement for informed consent was waived by the ethics committee because of the retrospective design of the study. This study was conducted in accordance with the principles of the Declaration of Helsinki and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational cohort studies.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences version 27.0 (IBM Corp., Armonk, NY). Continuous variables are summarized as means with standard deviations or medians with interquartile ranges, whereas categorical variables are presented as frequencies and percentages. The incidence of irAEs has been described overall and by organ-specific subtypes. For patients who experienced more than one irAE, only the time to the first irAE was used in time-to-event analyses.

Patients with incomplete baseline or follow-up data were excluded before analysis. Therefore, all analyses were performed using complete-case data without further imputation.

The association between baseline clinical and laboratory parameters and the risk of developing irAEs was evaluated using Cox proportional hazards regression models. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. Candidate variables were selected a priori based on clinical relevance and univariate associations. To minimize overfitting, only a limited number of covariates were entered into the final multivariable model, considering the number of observed first irAE events. Age and sex were retained as clinically relevant adjustment variables irrespective of statistical significance, whereas prior radiotherapy and lactate dehydrogenase (LDH) were included because of their potential biological relevance and univariate associations.

LDH values were scaled per 10-U/L increment before inclusion in Cox regression models to improve the interpretability of hazard ratios. To avoid model overfitting, the number of covariates included was restricted based on the number of observed events. Multicollinearity was assessed using variance inflation factors (VIFs) and condition indices. Variables demonstrating substantial collinearity (VIF >3 or condition index >10) or conceptual redundancy were

excluded from the final models. The proportional hazards assumption was assessed by visual inspection of log-minus-log survival plots for categorical variables and by testing time-dependent interactions between selected continuous covariates and log(time). No meaningful violation of the proportional hazards assumption was identified. Because of substantial conceptual overlap and shared components among laboratory-derived inflammatory indices (neutrophil-to-lymphocyte ratio [NLR], derived neutrophil-to-lymphocyte ratio [dNLR], platelet-to-lymphocyte ratio [PLR], and systemic immune-inflammation index [SII]), only one representative inflammatory marker was included in the multivariable model to minimize multicollinearity. SII was selected a priori based on its broader representation of systemic inflammatory status and previous literature.

OS was defined as the interval from nivolumab initiation to death from any cause or the past follow-up. Cox proportional hazards regression was used to evaluate factors associated with OS. To minimize immortal time bias, the occurrence of irAEs was modeled as a time-dependent covariate such that patients contributed person-time to the non-irAE group until the first irAE occurred and to the irAE group thereafter.

The multivariable model evaluating first irAE included 56 first irAE events, whereas the OS model included 153 deaths. The number of covariates was restricted according to the number of observed events to reduce the risk of model overfitting.

All statistical tests were two-sided, and a $p<0.05$ was considered statistically significant.

RESULTS

Clinical and Laboratory Characteristics of the Study Cohort According to Adverse Event Development

Among the 223 patients treated with nivolumab, 56 (25.1%) developed irAEs (Table 1). The median observation time was 92 weeks (interquartile range [IQR], 56–184), corresponding to a total follow-up of 32,136 patient-weeks. The incidence rate of first irAEs was 1.74 per 1,000 patient-weeks (95% CI, 1.31–2.26). Baseline characteristics were largely comparable between patients with and without irAEs, including age (65.3±8.5 vs. 64.8±9.5 years), sex distribution (male: 78.6% vs. 78.4%), Eastern Cooperative Oncology Group (ECOG) performance status, body mass index, Charlson comorbidity index, tumor histology, and number of prior systemic therapies.

Connective tissue disorders were more frequent among patients who developed irAEs (8.9% vs. 1.2%), while the rates of diabetes mellitus and chronic obstructive pulmonary disease were comparable. Mortality occurred in 60.7% and 71.3% of the patients with irAEs and without irAEs, respectively.

irAEs

Five patients experienced multiple irAEs (three patients had three irAEs each and two patients had two irAEs each). These patients accounted for 13 irAEs in total, including eight additional events beyond the first event (Table 2).

Endocrine toxicities were predominant, with hypothyroidism being the most common (43.8%), followed by hyperthyroidism (14.1%), adrenal insufficiency (12.5%), and hypophysitis (9.4%). Non-endocrine irAEs included dermatitis or rash (10.9%), neurological toxicity (optic neuritis, 3.1%), immune-related hepatitis (3.1%), colitis (1.6%), and myositis (1.6%).

The median time to irAE onset was 13 weeks (range, 1–182 weeks), with an earlier onset of hyperthyroidism (10 weeks) and later onset of adrenal insufficiency (44 weeks). Most events were grade 2 (56.3%), and grades 3 and 4 events accounted for 14.1% and 6.3%, respectively. Systemic corticosteroids were used in nine events (14.1%), and permanent nivolumab discontinuation occurred in five patients (7.8%).

Factors Associated with irAEs

Factors associated with the development of irAEs were evaluated using Cox proportional hazards models, considering the time to the first irAE (Table 3). In univariate analyses, a history of radiotherapy was associated with an increased risk of adverse events (HR 1.877, 95% CI, 1.012–3.478; p=0.046), whereas age, sex, body mass index, ECOG performance status, Charlson comorbidity index, and most baseline laboratory parameters showed no clear association with irAE occurrence.

In the multivariable analysis, prior radiotherapy remained independently associated with an increased risk of first irAE (HR 2.23, 95% CI 1.14–4.34; p=0.019). Baseline LDH showed a borderline association with irAE risk (HR 1.012/10 U/L increase, 95% CI 0.999–1.024; p=0.055). No other evaluated baseline characteristics were independently associated with first irAE occurrence.

Factors Associated with OS

OS was evaluated using Cox proportional hazards models, with irAEs entered as a time-dependent covariate (Table 4).

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Table 1 Study cohort characteristics

Variables	Adverse event (n=56)	No adverse event (n=167)	Total (n=223)	p
Age, mean±SD	65.3±8.5	64.8±9.5	65.0±9.2	0.724
Sex, n (%)				0.984
Male	44 (78.6)	131 (78.4)	175 (78.5)	
Female	12 (21.4)	36 (21.6)	48 (21.5)	
BMI, mean±SD	25.2±4.2	24.2±4.8	24.4±4.7	0.159
ECOG-PS scale, n (%)				0.400
0	46 (82.1)	124 (74.3)	170 (76.2)	
1	10 (17.9)	41 (24.6)	51 (22.9)	
2	0 (0)	2 (1.2)	2 (0.9)	
CCI, mean±SD	9.5±1.6	9.2±1.7	9.3±1.7	0.409
Histopathological types, n (%)				0.187
Lung adenocarcinoma	16 (28.6)	58 (34.7)	74 (33.2)	
Lung SSC	14 (25.0)	43 (25.7)	57 (25.6)	
Malign melanoma	10 (17.9)	33 (19.8)	43 (19.3)	
Renal cell carcinoma	15 (26.8)	26 (15.6)	41 (18.4)	
Other	1 (1.7)	7 (4.2)	8 (3.5)	
Comorbidities, n (%)				
Hypertension	32 (57.1)	66 (39.5)	98 (43.9)	**0.021**
Diabetes mellitus	15 (26.8)	41 (24.6)	56 (25.1)	0.739
COPD	14 (25.0)	43 (25.7)	57 (25.6)	0.912
Connective tissue disorder	5 (8.9)	2 (1.2)	7 (3.1)	**0.004**
Observation duration, weeks, median (IQR)	150 (81-250)	84 (48-164)	92 (56-184)	**<0.001**
Number of treatment regimens before nivolumab, n (%)				0.766
1	37 (66.1)	118 (70.6)	155 (69.5)	
2	13 (23.2)	34 (20.4)	47 (21.1)	
3	6 (10.7)	11 (6.6)	17 (7.6)	
>3	0 (0)	4 (2.4)	4 (1.8)	
History of radiotherapy, n (%)	14 (25.0)	34 (20.4)	48 (21.5)	0.465
Nivolumab duration, weeks, median (IQR)	34 (13–83)	14 (8–31)	16 (10–42)	**<0.001**
Creatinine, mg/dL, median (IQR)	0.99 (0.83–1.14)	0.90 (0.80–1.11)	0.92 (0.80–1.11)	0.371
FBG, mg/dL, mean±SD	112±35	116±41	116±40	0.885
ALT, U/L, median (IQR)	16 (11–21)	14 (9–20)	14 (10–20)	0.235
AST, U/L, median (IQR)	19 (15–24)	16 (13–21)	17 (14–21)	**0.023**
GGT, U/L, median (IQR)	28 (18–52)	27 (19–45)	27 (19–46)	0.823
ALP, U/L, median (IQR)	77 (66–101)	88 (69–111)	85 (67–109)	0.101
LDH, U/L, median (IQR)	188 (158–243)	183 (152–232)	185 (154–235)	0.420
Albumin, g/dL, mean±SD	4.0±0.4	3.9±0.5	3.9±0.5	0.300
WBC, 109/L, mean±SD	7.2±3.0	8.0±3.5	7.9±3.6	0.123
NEU, 109/L, median (IQR)	3.6 (2.7–5.0)	5.0 (3.6–6.5)	4.7 (3.3–6.3)	0.001
LYM, 109/L, median (IQR)	1.7 (1.2–2.3)	1.4 (1.0–2.0)	1.5 (1.0–2.1)	0.064
Hemoglobin, g/dL, mean±SD	12.5±1.9	12.1±2.0	12.2±2.0	0.272
Platelets, 109/L, mean±SD	260±101	293±117	286±115	0.111
TSH, mU/L, median (IQR)	1.72 (0.81–2.63)	1.38 (0.89–2.50)	1.41 (0.87–2.52)	0.765
fT4, ng/dL, median (IQR)	0.95 (0.81–1.17)	0.99 (0.84–1.20)	0.97 (0.83–1.18)	0.403
Mortality, n (%)	34 (60.7)	119 (71.3)	153 (68.6)	0.141

ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; CCI: Charlson comorbidity index; COPD: Chronic obstructive pulmonary disease; ECOG: Eastern Cooperative Oncology Group; eGFR: Estimated glomerular filtration rate; FBG: Fasting blood glucose; fT4: Free thyroxine; GGT: Gamma-glutamyl transferase; LDH: Lactate dehydrogenase; LYM: Lymphocytes; NEU: Neutrophil; N/A: Not applicable; IQR: Interquartile range; SD: Standard deviation; TSH: Thyroid stimulating hormone; WBC: White blood cells.

Table 2 Immune-related adverse events (event-based analysis) (n=64)

Adverse event category	n (%)	Time to onset, weeks, median (min -max)	CTCAE Grade, n	Steroid use, n (%)	Permanent nivolumab discontinuation, n (%)
Hypophysitis	6 (9.4)	27 (4–76)	G1: 0; G2: 5; G3: 1; G4: 0	1 (1.6)	0 (0)
Hypothyroidism	28 (43.8)	13 (4–90)	G1: 14; G2: 12; G3: 1; G4: 1	2 (3.1)	0 (0)
Hyperthyroidism	9 (14.1)	10 (5–24)	G1: 1; G2: 8; G3: 0; G4: 0	0 (0)	0 (0)
Adrenal insufficiency	8 (12.5)	44 (9–136)	G1: 0; G2: 4; G3: 2; G4: 2	3 (4.7)	1 (1.6)
Hepatitis (immune-related)	2 (3.1)	41 (11–70)	G1: 0; G2: 0; G3: 1; G4: 1	1 (1.6)	1 (1.6)
Dermatitis/rash	7 (10.9)	13 (3–182)	G1: 0; G2: 5; G3: 2; G4: 0	0 (0)	1 (1.6)
Neurologic (optic neuritis)	2 (3.1)	26 (1–51)	G1: 0; G2: 0; G3: 2; G4: 0	2 (3.1)	2 (3.1)
Colitis	1 (1.6)	10 (10–10)	G1: 0; G2: 1; G3: 0; G4: 0	0 (0)	0 (0)
Myositis	1 (1.6)	7 (7–7)	G1: 0; G2: 1; G3: 0; G4: 0	0 (0)	0 (0)
Total*	64 (100)	13 (1–182)	G1: 15; G2: 36; G3: 9; G4: 4	9 (14.1)	5 (7.8)

A single patient may have experienced more than one immune-related adverse event; therefore, counts represent the total number of events, not patients. Grade, steroid use, and treatment discontinuation are reported per event. *: Five patients experienced multiple irAEs (three patients had three irAEs each and two patients had two irAEs each), accounting for a total of 13 irAEs. Because five of these were first events, the remaining eight represented additional irAEs beyond the first event. Overall, 64 irAEs occurred in 56 patients. AE: Adverse effect; CTCAE: Common Terminology Criteria for Adverse Events; IQR: İnterquartile range; SD: Standard deviation.

Table 3 Cox proportional hazards model evaluating associated factors for the first irAE

Variables	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age (per a year increase)	1.012	0.981–1.045	0.438	1.013	0.980–1.046	0.449
Female sex (vs male)	1.114	0.585–2.120	0.742	1.213	0.624–2.357	0.569
BMI (per one-point increase)	0.992	0.939–1.048	0.785	—	—	—
ECOG-PS (per one-point increase)	0.928	0.482–1.787	0.823	—	—	—
CCI (per one-point increase)	1.080	0.919–1.270	0.351	—	—	—
History of radiotherapy (yes)	1.877	1.012–3.478	**0.046**	2.225	1.140–4.342	**0.019**
Connective tissue disorder (yes)	1.932	0.760–4.914	0.167	—	—	—
DM (yes)	0.890	0.483–1.638	0.707	—	—	—
HT (yes)	1.527	0.895–2.604	0.120	—	—	—
WBC (per 1×10^9/L increase)	0.970	0.882–1.066	0.526	—	—	—
NEU (per 1×10^9/L increase)	0.944	0.836–1.067	0.351	—	—	—
LYM (per 1×10^9/L increase)	1.107	0.790–1.553	0.554	—	—	—
Hemoglobin (per 1 g/dL increase)	0.996	0.878–1.130	0.949	—	—	—
Platelets (per 1×10^9/L increase)	0.998	0.996–1.001	0.239	—	—	—
LDH (per 10 U/L increase)	1.010	0.998–1.023	0.099	1.012	0.999–1.024	0.055
AST (per 1 U/L increase)	1.010	0.998–1.022	0.112	—	—	—
ALT (per 1 U/L increase)	1.005	0.998–1.013	0.182	—	—	—
TSH (per 1 mU/L increase)	0.980	0.914–1.051	0.572	—	—	—
NLR (per one-point increase)	0.983	0.893–1.082	0.730	—	—	—
dNLR (per one-point increase)	0.956	0.789–1.158	0.646	—	—	—
PLR (per one-point increase)	0.988	0.966–1.011	0.306	—	—	—
SII (per 100-point increase)	1.301	0.913–1.856	0.146	—	—	—
HALP (per one-point increase)	1.001	0.990–1.013	0.816	—	—	—

For patients who developed more than one irAE, only the time to the first irAE was used in the survival analyses. irAE: Immunotherapy-related adverse event ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; CCI: Charlson comorbidity index; CI: Confidence interval; DM: Diabetes mellitus; dNLR: Derived neutrophil-to-lymphocyte ratio; ECOG: Eastern Cooperative Oncology Group; HALP: Hemoglobin–albumin–lymphocyte–platelet; HR: Hazard ratio; HT: Hypertension; LDH: Lactate dehydrogenase; LYM: Lymphocyte ; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; TSH: Thyroid stimulating hormone; SII: Systemic immune-inflammation index; WBC: White blood cell.

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Table 4 Cox proportional hazards model evaluating associated factors for overall survival

Variables	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age (per a year increase)	1.004	0.986–1.022	0.695	1.024	0.994–1.055	0.117
Male sex (vs. female)	1.131	0.758–1.689	0.541	1.213	0.755–1.949	0.425
BMI (per one-point increase)	0.943	0.909–0.978	**0.001**	0.950	0.913–0.988	**0.011**
ECOG-PS (per one-point increase)	1.281	0.940–1.746	0.128	1.088	0.741–1.596	0.667
CCI (per one-point increase)	1.029	0.932–1.137	0.567	0.858	0.725–1.015	0.075
Histopathological type						
Lung cancer		Reference			Reference	
RCC	0.757	0.507–1.130	0.757	0.648	0.399–1.054	0.081
Melanoma	0.308	0.187–0.509	**<0.001**	0.306	0.178–0.526	**<0.001**
irAE, (yes)*	0.693	0.469–1.025	0.066	0.747	0.488–1.144	0.180
DM, (yes)	1.133	0.795–1.614	0.489	—	—	—
HT, (yes)	0.819	0.594–1.128	0.222	—	—	—
COPD, (yes)	1.232	0.855–1.776	0.263	—	—	—
LDH (per 10 U/L increase)	1.018	1.009–1.028	**<0.001**	1.020	1.008–1.031	**<0.001**
NLR (per one-point increase)	1.053	1.020–1.087	**0.002**	—	—	—
dNLR (per one-point increase)	1.087	1.018–1.161	**0.012**	—	—	—
PLR (per one-point increase)	1.009	1.003–1.015	**0.004**	—	—	—
SII (per 100-point increase)	1.647	1.250–2.189	**0.002**	—	—	—
HALP (per one-point increase)	0.988	0.980–0.996	**0.005**	0.993	0.985–1.001	0.087

*: irAE is evaluated as a time-dependent variable. İrAE: Immunotherapy-related adverse event; ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; CCI: Charlson comorbidity index; CI: Confidence interval; DM: Diabetes mellitus; dNLR: Derived neutrophil-to-lymphocyte ratio; ECOG: Eastern Cooperative Oncology Group; HALP: Hemoglobin–albumin–lymphocyte–platelet; HR: Hazard ratio; HT: Hypertension; LDH: Lactate dehydrogenase; LYM: Lymphocyte ; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; WBC: White blood cell.

In the univariate analysis, a higher body mass index was associated with lower mortality (HR 0.943, 95% CI, 0.909–0.978; p=0.001). Melanoma histology was associated with improved survival compared with lung cancer (HR 0.308, 95% CI, 0.187–0.509; p<0.001). Higher baseline LDH levels and inflammatory indices (NLR, dNLR, PLR, and SII) were associated with an increased mortality risk, whereas higher hemoglobin–albumin–lymphocyte–platelet (HALP) scores were associated with reduced mortality. The occurrence of irAEs, modeled as a time-dependent variable, was associated with a numerically lower hazard of death, but did not reach statistical significance (HR 0.693, 95% CI, 0.469–1.025; p=0.066).

In the multivariable analysis, a higher body mass index remained independently associated with improved OS (HR 0.950, 95% CI 0.913–0.988, p=0.011), whereas higher baseline LDH levels were independently associated with an increased risk of mortality (HR 1.020 per 10 U/L increase, 95% CI 1.008–1.031, p<0.001). Melanoma histology was also independently associated with improved survival compared with lung cancer (HR 0.306, 95% CI 0.178–0.526, p<0.001), while renal cell carcinoma was not significantly associated with survival (HR 0.648, 95% CI 0.399–1.054, p=0.081). Higher HALP scores showed a trend toward improved survival after multivariable adjustment, although the association did not reach statistical significance (HR 0.993, 95% CI 0.985–1.001, p=0.087). irAEs, modeled as a time-dependent covariate, were not independently associated with OS (HR 0.747, 95% CI 0.488–1.144, p=0.180).

DISCUSSION

In this real-world cohort of patients with solid tumors treated with nivolumab, irAEs were observed in approximately one-quarter of the patients and were predominantly endocrine in nature, with thyroid dysfunction representing the most frequent toxicity. The development of irAEs was associated with distinct baseline clinical and laboratory features, including prior exposure to radiotherapy. Although patients who developed irAEs demonstrated a numerically lower mortality risk, this association was not statistically significant when the irAE occurrence was modeled as a time-dependent covariate. Baseline LDH levels, body

mass index, and melanoma histology remained independently associated with OS, whereas HALP showed a non-significant trend toward improved survival.

In our cohort, irAEs developed in 25.6% of patients receiving nivolumab, a rate comparable to that of previous retrospective studies reporting irAE frequencies of approximately 20–35% with PD-1 inhibitors and other immune checkpoint inhibitors.[8,9] Baseline demographic and clinical characteristics were largely similar between patients with and without irAEs, including age, performance status, comorbidity burden, tumor histology, prior treatment exposure, and nivolumab duration, in line with previous reports indicating that routine baseline features have limited value in anticipating irAE development.[10,11] The pronounced male predominance in our cohort (approximately 79%) is attributable to the high proportion of lung cancer cases and reflects the established epidemiologic patterns in thoracic malignancies.[12] Overall, the consistency of irAE prevalence and demographic distribution with the existing literature supports the representativeness of our real-world population.

Endocrine toxicities were predominant in our cohort, with hypothyroidism (43.8%), hyperthyroidism (14.1%), adrenal insufficiency (12.5%), and hypophysitis (9.4%) being the most frequent irAEs. These findings are broadly consistent with those of previous studies, which reported that thyroid dysfunction is the most common endocrine toxicity associated with PD-1 inhibition.[13] The median time to irAE onset was 13 weeks, with earlier thyroid dysfunction and later adrenal insufficiency, paralleling the previously described temporal patterns.[13–15] Most irAEs were low to moderate in severity, and permanent nivolumab discontinuation was required in only 7.8% of the events, supporting the generally manageable nature of endocrine-predominant toxicity profiles observed during PD-1 inhibitor therapy.

In the present study, prior radiotherapy was the only independent factor associated with irAE development. Demographic characteristics, performance status, comorbidity burden, and routinely proposed hematologic or inflammatory indices did not demonstrate a significant predictive value. These findings are consistent with contemporary reviews emphasizing the absence of robust and universally applicable biomarkers for irAE prediction, despite extensive investigation of blood counts, inflammatory ratios, and composite immune indices.[16] Although several studies have suggested associations between irAEs and markers, such as NLR, PLR, sex, or nutritional status, these findings have not been consistently replicated across different populations and tumor types.[10,16]

Although baseline LDH showed a borderline association with first irAE development, this association did not remain statistically significant after multivariable adjustment. Elevated LDH may nevertheless reflect greater tumor burden, enhanced immune activation, or increased systemic inflammation. Previous studies have linked elevated LDH levels to adverse oncologic outcomes and, in some settings, to the severity of immune-mediated toxicities.[17,18] Furthermore, prior radiotherapy was independently associated with a more than two-fold increase in the irAE risk. While some pooled analyses have not demonstrated a clear increase in toxicity among patients previously exposed to radiotherapy,[19,20] other real-world investigations have reported similar findings.[21,22] Radiation-induced tissue injury, persistent inflammatory signaling, and immune priming within irradiated tissues may contribute to the enhanced susceptibility to subsequent immune-mediated toxicity during checkpoint blockade.[23]

The relationship between irAEs and survival remains a subject of debate. Numerous retrospective studies have reported improved survival in patients who develop irAEs during immune checkpoint inhibitor therapy.[24,25] However, conventional analyses comparing patients with and without irAEs are susceptible to immortal time bias because patients must survive long enough to experience adverse events. To address this issue, we modeled irAE occurrence as a time-dependent covariate in the survival analysis. Although the hazard ratio remained below 1 (HR 0.747), irAE occurrence was not independently associated with OS after accounting for event timing, suggesting a possible trend toward improved survival. This finding suggests that at least part of the apparent survival advantage observed in previous studies may be attributable to methodological bias, rather than a direct biological effect. Nevertheless, the direction of the observed association remains consistent with the hypothesis that irAEs may reflect enhanced immune activation. Larger prospective studies are needed to clarify whether a true causal relationship exists.

In contrast, several baseline characteristics remained independently associated with OS. Melanoma histology was associated with significantly better survival than lung cancer, consistent with the well-established long-term efficacy of PD-1 inhibition in advanced melanoma.[3,4] Elevated baseline LDH was independently associated with increased mortality, supporting its role as a surrogate marker of tumor burden and aggressive disease biology. Conversely, a higher body mass index was independently associated with improved survival, in line with previous reports suggesting that nutritional

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status and the so-called obesity paradox may influence outcomes during immunotherapy. Although HALP score showed a favorable trend, it did not retain statistical significance after multivariable adjustment.

Limitations of the Study

This study had several limitations. First, its retrospective single-center design may limit generalizability and introduce the possibility of selection and information bias. Second, low-grade or subclinical irAEs may have been under-recognized, resulting in an underestimation of the true incidence of immune-mediated toxicity. Third, although management strategies, such as corticosteroid use and treatment discontinuation, were recorded, detailed information regarding treatment intensity and duration was not consistently available. Fourth, the modest sample size and limited number of adverse events restricted the statistical power for subgroup analyses and the evaluation of individual toxicity categories. In addition, prior radiotherapy may also reflect underlying disease characteristics, such as tumor type, metastatic burden, or previous treatment strategies, rather than representing a direct causal determinant of irAE development. Moreover, detailed radiotherapy characteristics (dose, fractionation, treatment intent, and irradiated site) were not consistently available because of the retrospective design and therefore were not analyzed. The relatively high proportion of endocrine irAEs may partly reflect routine thyroid function monitoring in patients receiving nivolumab, potentially increasing detection of asymptomatic endocrine abnormalities compared with other organ toxicities. Finally, multiple candidate clinical and laboratory variables were evaluated without formal adjustment for multiple comparisons. Accordingly, borderline associations, particularly those involving baseline biomarkers, should be interpreted cautiously and considered exploratory.

CONCLUSION

In this real-world cohort of patients with solid tumors treated with nivolumab, irAEs occurred in approximately one-quarter of patients and were predominantly endocrine. Prior radiotherapy exposure was independently associated with an increased risk of irAEs. When the timing of adverse events was appropriately accounted for using time-dependent survival analysis, irAE occurrence was not independently associated with OS, although a non-significant trend toward improved outcomes was observed. Baseline LDH level and body mass index were independently associated with OS, whereas HALP showed a non-significant trend toward improved survival. These findings highlight the importance of rigorous methodological approaches when evaluating the prognostic significance of irAEs and support further prospective studies incorporating clinical, laboratory, and immunological biomarkers to better characterize the toxicity risk and treatment outcomes during immune checkpoint inhibitor therapy.

Ethics Committee Approval: The study was approved by the Izmir Katip Çelebi University Ethics Committee (no: 0280, date: 09/04/2026).

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