Original Article

Immune-related adverse events as independent prognostic factors for camrelizumab in patients with esophageal squamous cell carcinoma: a retrospective cohort study

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Background: While programmed cell death protein 1 (PD-1) blockade has demonstrated varying effectiveness in treating advanced esophageal squamous cell carcinoma (ESCC), no validated prognostic factors have been identified. Immune-related adverse events (irAEs) have been shown to predict immunotherapy outcomes in multiple cancers, but their relationship with ESCC remains unclear. This study aims to evaluate the prognostic value of irAEs in patients with advanced ESCC treated with camrelizumab.

Methods: We conducted a retrospective chart review of patients with recurrent or metastatic ESCC who were treated with single-agent camrelizumab at the Department of Oncology and Hematology in China-Japan Union Hospital of Jilin University between 2019 and 2022. The study's primary endpoint was objective response rate (ORR), while secondary endpoints included disease control rate (DCR), overall survival (OS), and safety. We used the chi-squared test and odds ratio (OR) to evaluate any relationships between the occurrence of irAEs and ORR. Prognostic factors for OS were identified through survival analysis using the Kaplan-Meier method and multivariate Cox regression.

Results: The study included 136 patients with a median age of 60 years, of whom 81.6% were male and 89.7% received platinum-based chemotherapy as their first-line therapy. Among these patients, 128 irAEs were observed in 81 patients (59.6%). Patients who experienced irAEs achieved a significantly better ORR [39.5% *vs.* 14.5%; OR =3.84; 95% confidence interval (CI): 1.60–9.18; P=0.003] and longer OS [13.5 *vs.* 5.6 months; adjusted hazard ratio (HR) =0.56, 95% CI: 0.41–0.76; P=0.0013] than those who did not experience irAEs. Multivariate analysis identified the presence of irAEs as an independent prognostic factor for OS (HR =0.57, 95% CI: 0.42–0.77; P=0.0002).

Conclusions: The presence of irAEs in ESCC patients treated with anti-PD-1 therapy (camrelizumab) may serve as a clinical prognostic factor, indicating improved therapeutic effectiveness. These findings suggest that irAEs could be used as a potential marker to predict outcomes in this patient population.

Keywords: Immune-related adverse events (irAEs); camrelizumab; esophageal squamous cell carcinoma (ESCC); prognostic factor; tumor response

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Introduction

In 2020, esophageal carcinoma (EC) ranked as the sixth most fatal malignancy and the seventh most frequently diagnosed cancer (1). The most frequent histologic subtype of EC is esophageal squamous cell carcinoma (ESCC), which accounts for more than 90% of EC cases (2). Despite improvements in surgical techniques and treatment strategies, such as the use of platinum-based doublet systemic chemotherapy as the standard of care (3,4), the mortality associated with advanced ESCC remains severe, with a 5-year overall survival (OS) rate of less than 20% (5).

Immune checkpoint inhibitors (ICIs) that target programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) have completely changed the landscape in which patients with ESCC have been treated over the past decade. Trials studying the PD-1/PD-L1 pathway have demonstrated prolonged survival and safety benefits with anti-PD-1 antibodies compared with chemotherapy in patients with advanced ESCC. In the KEYNOTE-181 study, pembrolizumab increased the OS in the PD-L1 combined positive score (CPS) ≥10 subgroups as compared to chemotherapy (6). In the ATTRACTION-3 trial, regardless of PD-L1 expression, nivolumab demonstrated a statistically significant and clinically meaningful improvement in OS compared to chemotherapy in patients with advanced ESCC (7). In the ESCORT study, camrelizumab significantly increased OS in patients with advanced or metastatic ESCC compared to chemotherapy (8). Overall, PD-1 monotherapy has become the standard of care for second-line advanced ESCC.

However, only a small percentage of people can benefit from ICIs, and the effectiveness of anti-PD-1 treatment differs among individuals (9). The rate of response to PD-1 inhibitors in patients previously treated for ESCC is relatively low compared to other cancer types (10). Despite the emerging evidence indicating that anti-PD-1 therapies may be beneficial for patients with positive PD-L1 expression, high tumor mutation burden (TMB), and high microsatellite instability (MSI-H) (11-13), the optimum prognostic biomarkers for ESCC are lacking. PD-L1 is well-known for predicting the efficacy of immunotherapy, it directly reflects the immune status of tumors and has predictive value in many types of cancer, with simple detection methods. However, PD-L1 expression is influenced by multiple factors, such as detection methods, tissue source, sampling time and method, and the determination of PD-L1 expression threshold is controversial. In addition, some PD-L1-negative patients may also benefit from immunotherapy, so PD-L1 cannot be used as a single predictive indicator. Tumors with high TMB usually have more neoantigens, which can induce stronger immune responses. However, TMB detection methods vary and different methods may yield different results. The assessment of TMB is expensive and time-consuming, making it difficult to meet clinical needs. MSI-H is rare in patients with ESCC, so routine testing for MSI alone is not realistic, despite the potential value to those rare patients. Establishing easily accessible, cost-effective predictive factors to recognize patients with ESCC who might benefit from PD-1 inhibition is therefore urgently needed.

Recent research has shown some correlations between the effects of ICIs and immune-related adverse events (irAEs) (14). IrAEs are defined as inflammatory adverse effects of immune system activation that affect the skin, liver, lungs, and endocrine glands (15,16). The presence of irAEs was associated with positive responses and prolonged survival in patients with upper gastrointestinal cancer receiving ICIs therapies in a retrospective study (17), but the solid proof in ESCC is lacking.

Highlight box

Key findings

- irAEs are the prognostic indicators of outcome for camrelizumab (anti-PD-1 antibody) treatment in patients with ESCC.

What is known and what is new?

- The effectiveness of immunotherapy in advanced ESCC is heterogeneous, and there is currently a lack of reliable and practical biomarkers for identifying and evaluating treatment outcomes. There is controversy surrounding the predictive value of biomarkers such as PD-L1 expression and TMB, and they are inconvenient and costly to obtain. Recent studies have demonstrated a positive correlation between the efficacy of ICIs and the occurrence of irAEs in patients with other types of solid tumors.
- IrAEs may serve as a promising and ideal marker for assessing the efficacy of immunotherapy in patients with advanced ESCC.

What is the implication, and what should change now?

- There is a strong correlation between the prevalence of irAEs and better clinical outcomes in patients with ESCC treated with camrelizumab, indicating that recognizing and monitoring irAEs throughout anti-PD-1 therapy is vitally important. When irAEs occur, effective intervention should be given immediately to prevent severe adverse reactions and improve outcomes.

We thus conducted a retrospective study to establish whether there is an association between irAEs and the treatment efficacy of camrelizumab [a humanized immunoglobin G4 (IgG4) monoclonal antibody against the PD-1 receptor] in patients with advanced ESCC in terms of antitumor response and survival. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-75/rc).

Methods

Study design and patients

We conducted a single-center, retrospective cohort study from January 13, 2019, to February 5, 2022, at the China-Japan Union Hospital of Jilin University. The inclusion criteria were ICI-naive patients who had recurrent or metastatic ESCC and who were treated with single-agent camrelizumab for at least 1 dose; those treated previously with targeted therapy or chemotherapy were also deemed eligible. No patients were excluded. The sample size was determined by the number of cases that fulfilled the inclusion criteria over the study period. All patients were followed up until May 28, 2022. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of China-Japan Union Hospital of Jilin University (No. 20220418). Individual consent for this retrospective analysis was waived.

Data collection

The clinical data collected were as follows: sex, age, previous therapy, site of metastases, number of prior therapies, Eastern Cooperative Oncology Group (ECOG) performance status, number of prior therapies, the PD-L1 CPS [defined as the number of PD-L1-positive cells (tumor cells, macrophages, and lymphocytes) divided by the total number of tumor cells], and smoking status (current, former, or never).

End points and follow-up

Patients were treated with camrelizumab at a fixed dose of 200 mg every 21 days. The primary end point was objective response rate (ORR) as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and was defined as the percentage of patients who achieved a complete response (CR) or a partial response (PR) as the best overall response assessed by investigators. The secondary end points included disease control rate (DCR), which was defined as the proportion of patients who had a CR, PR, or stable disease (SD); OS, which was defined as the duration from the initiation of anti-PD-1 treatment to death from any cause; and safety profile. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Clinical and analytical evaluations were performed every 3 weeks after the start of treatment. Every 8 to 12 weeks, or as often as clinically necessary, patients underwent enhanced computed tomography (CT) scans. Patients were contacted every 12 weeks to assess survival during follow-up. During these visits, physical examinations, routine laboratory tests, and imaging studies were performed. For patients who could not be contacted, we supplemented their information by reviewing their electronic medical records and contacting their family members. We also conducted multiple confirmations and verifications for any missing data. Throughout the entire follow-up process, we adhered to the same follow-up procedures to ensure accuracy and completeness of the data.

Statistical analysis

Continuous variables are summarized using medians and ranges (minimum and maximum). Categorical variables are summarized using frequencies and proportions and were compared using Fisher exact test or chi-squared test. Odds ratio (OR) and chi-squared test were used to identify any relationships between the occurrence of irAEs and ORR. OS was calculated using the Kaplan-Meier curves and was compared with log-rank (Mantel-Cox) test. We utilized Cox regression analysis adjusted for age and sex (in order to reduce potential bias) to investigate the correlation between the occurrence of immune-related adverse events (irAEs) and OS. Results are expressed as hazard ratios (HRs) with a 95% confidence interval (CI). Univariate and multivariate analyses were conducted to identify prognostic factors for OS. Factors with a univariate P value less than 0.1 were included in multivariate analysis. Statistical analysis was performed with R software version 4.1.1 (R Foundation for Statistical Computing). $P<0.05$ (two-sided) was considered statistically significant.

Results

Patient characteristics

From January 13, 2019, to February 5, 2022, 136 consecutive patients were included. As of May 28, 2022, the median follow-up was 26 months (range, 3–32 months). *Table 1* shows the characteristics of all study participants. The median age was 60 years (range, 32–84 years). Males accounted for 81.6% of the sample population, 89.7% of patients received platinum-based chemotherapy as first-line therapy, and 106 patients (77.9%) had lymph node metastases at the time of diagnosis. The ECOG score was 0 in 24 patients (17.6%), 1 in 102 patients (75.0%), and 2 in 10 (7.4%). Baseline characteristics were well balanced between the 2 groups with or without irAEs.

irAEs

A total of 128 irAEs were observed in 81 out of 136 patients (59.6%). The details are shown in *Table 2*. The most frequent irAE was reactive cutaneous capillary endothelial proliferation (RCCEP) solely caused by camrelizumab (n=48 events; 45 cases in grade 1–2, 3 cases in grade 3), followed by aspartate aminotransferase (AST) increase (n=12; all in grade 1), diarrhea (n=10), hypothyroidism (n=10), and fatigue (n=10). Of the 136 patients, 22 (16.2%) had interrupted treatment, and 9 (6.6%) of them discontinued anti-PD-1 treatment owing to irAEs. No treatment-related deaths occurred during the follow-up.

Treatment efficacy

Of the 136 patients, objective response was observed in 40 patients (29.4%): CR in 10 cases (7.4%) and PR in 30 (22.1%). SD was detected in 44 cases (32.4%), progressive disease was detected in 52 cases (38.2%), and 84 patients (61.8%) achieved disease control (*Table 3*). The median OS for all patients was 8.4 (95% CI: 6.1–12.9) months.

Correlation of irAEs with treatment efficacy

Patients who presented irAEs showed an increase in the probability of achieving an objective response (OR =3.84; 95% CI: 1.60–9.18; P=0.003). As shown in *Table 3*, 32 of the 81 (39.5%) patients who experienced toxicity demonstrated an objective response, while this occurred in only 8 of the 55 (14.5%) patients who did not experience toxicity (P=0.003).

Figure 1 demonstrates that the OS of patients with and without irAEs was 13.5 (95% CI: 7.9–24.3) and 5.6 (95% CI: 3.0–8.5) months, respectively (adjusted HR =0.56, 95% CI: 0.41–0.76; P=0.0013). The 12- and 24-month survival rates for the patients with and without irAEs were 54.0% *vs.* 25.6% and 38.1% *vs.* 15.0%, respectively. In the subgroup of patients with PD-L1 CPS <10, patients who developed irAEs had a remarkably increased median OS when compared with patients without irAEs (13.5 *vs.* 2.3 months; adjusted HR =0.36, 95% CI: 0.19–0.68; P=0.0009), while in the subgroup of patients with PD-L1 CPS ≥10, patients who developed irAEs had a longer median OS over patients without irAEs (15.4 *vs.* 9.7 months), but this difference was not statistically significant (P=0.24). Details are shown in *Figure 2* and *Figure 3*.

The correlation between irAEs and OS was significant (HR =0.57, 95% CI: 0.42–0.77; P=0.0002) in the multivariate analysis of OS and was unaffected by age, sex, ECOG, smoking status, prior lines of treatment, or any other demographic or clinical characteristic examined (*Table 4*). Moreover, the OS benefit with patients who developed irAEs was observed across almost all the subgroups (*Figure 4*).

Discussion

To the best of our knowledge, this is the first study to examine the presence of irAEs as a prognostic factor in patients with advanced ESCC receiving anti-PD-1 monotherapy. The development of irAEs was directly and significantly correlated with improved objective response and prolonged OS in the current study, regardless of sex and age, suggesting that irAEs may serve as prognostic indicators of immunotherapy effectiveness in patients with ESCC.

In addition to being effective against the tumor cells, PD-1 blockade may also cause autoimmunity, which might lead to mild or severe adverse reactions irAEs (18,19). Although the exact pathophysiology underlying the start of irAE is yet to be known, potential explanations include the stimulation of autoantibodies, overactivation of T cells, and an increase in cytokine levels (15,20). It has been discovered that irAEs that occur with particular malignancies are associated with better clinical outcomes. For instance, it has been demonstrated that vitiligo is strongly associated with successful outcomes in patients with melanoma (21-23), but other real-world research has fallen short of establishing clear relationships between irAEs and the efficacy of ICIs

Table 1 Patient demographics and pathological characteristics

Characteristic	All patients (n=136)	Non-irAEs (n=55)	irAEs (n=81)	P value
Sex				0.103
Female	25 (18.4)	6 (10.9)	19 (23.5)	
Male	111 (81.6)	49 (89.1)	62 (76.5)	
Age (years)				0.912
<65	77 (56.6)	31 (56.4)	46 (56.8)	
≥65	59 (43.4)	24 (43.6)	35 (43.2)	
Previous therapy				
Surgery	50 (36.8)	16 (29.1)	34 (42.0)	0.178
Radiotherapy	87 (64.0)	33 (60.0)	54 (66.7)	0.540
First-line platinum-based chemotherapy	122 (89.7)	53 (96.4)	69 (85.2)	0.069
Site of metastases				
Liver	31 (22.8)	17 (30.9)	14 (17.3)	0.099
Lung	58 (42.6)	24 (43.6)	34 (42.0)	0.988
Bone	18 (13.2)	5 (9.1)	13 (16.0)	0.359
Lymph node	106 (77.9)	42 (76.4)	64 (79.0)	0.877
Other	33 (24.3)	13 (23.6)	20 (24.7)	0.937
ECOG performance status				0.829
0	24 (17.6)	9 (16.4)	15 (18.5)	
1	102 (75.0)	41 (74.5)	61 (75.3)	
2	10 (7.4)	5 (9.1)	5 (6.2)	
Number of prior therapies				0.272
1	83 (61.0)	30 (54.5)	53 (65.4)	
≥2	53 (39.0)	25 (45.5)	28 (34.6)	
PD-L1 combined positive score				0.965
<10	56 (41.2)	22 (40.0)	34 (42.0)	
≥10	66 (48.5)	27 (49.1)	39 (48.1)	
Not evaluable	14 (10.3)	6 (10.9)	8 (9.9)	
Smoking status				0.982
Former	41 (30.1)	17 (30.9)	24 (29.6)	
Current	77 (56.6)	31 (56.4)	46 (56.8)	
Never	18 (13.2)	7 (12.7)	11 (13.6)	

Data are presented as n (%), unless otherwise specified. ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death ligand-1; irAE, immune-related adverse event.

combined with chemotherapy or targeted therapy (24,25). We restricted our analysis to patients with advanced ESCC receiving single-agent camrelizumab in order to avoid this heterogeneity and enhance the study comparability.

Our study revealed a strong correlation between the incidence of irAEs and better clinical outcomes, including ORR, DCR, and OS, in patients with ESCC treated with camrelizumab. The odds of obtaining a CR or PR were nearly 4 times higher for those who experienced irAEs. Patients who experienced irAEs of any kind were 44% less likely to die than those who did not. In particular, in the subgroup of PD-L1 CPS <10, the risk of death was reduced by 51%. For those with PD-L1 CPS ≥10, a tendency for a longer median OS was observed but not statistically significant, perhaps due to the small sample size. In most subgroups, the risk of death was lower in patients who developed adverse reactions than in those who did not, especially in patients who had received prior platinum-based chemotherapy, were younger than 65 years of age, had lymph node metastases, or were former or current smokers. These findings suggest that irAEs are crucial in predicting the effectiveness of PD-1 treatment in patients with ESCC.

Interestingly, we found that patients with RCCEP had a remarkably better prognosis. The possible reason for

Table 2 Summary of immune-related adverse events

Immune-related adverse event	Grade 1–2	Grade 3–5
RCCEP	45 (33.1)	3 (2.2)
AST increased	12 (8.8)	0 (0.0)
Diarrhea	10 (7.4)	3 (2.2)
Hypothyroidism	10 (7.4)	2 (1.5)
Fatigue	10 (7.4)	3 (2.2)
Decreased appetite	7 (5.1)	2 (1.5)
Nausea	7 (5.1)	1 (0.7)
Vomiting	3 (2.2)	1 (0.7)
Stomatitis	2 (1.5)	0 (0.0)
Constipation	2 (1.5)	0 (0.0)
Weight decreased	1 (0.7)	0 (0.0)
WBC count decreased	1 (0.7)	0 (0.0)
Neutrophil count decreased	1 (0.7)	0 (0.0)

Data are presented as n (%). Listed are immune-related adverse events that occurred during the study period or within 30 days thereafter (within 90 days for events higher than grade 3). RCCEP, reactive cutaneous capillary endothelial proliferation; AST, aspartate aminotransferase; WBC, white blood cell.

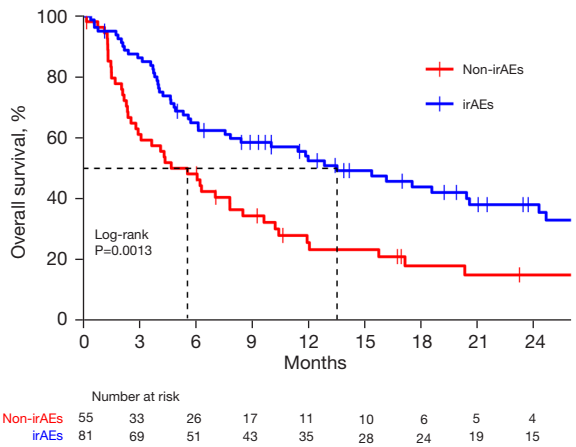

Figure 1 Kaplan-Meier curve of the overall survival for all patients. irAE, immune-related adverse event.

Table 3 Best responses to anti-PD-1 treatment

Variables	All patients (n=136)	Non-irAEs (n=55)	irAEs (n=81)	P value
Best overall response				0.001
Complete response	10 (7.4)	4 (7.3)	6 (7.4)	
Partial response	30 (22.1)	4 (7.3)	26 (32.1)	
Stable disease	44 (32.4)	18 (32.7)	26 (32.1)	
Progressive disease	52 (38.2)	29 (52.7)	23 (28.4)	
Objective response rate	40 (29.4; 21.9–37.8)	8 (14.5; 6.50–26.7)	32 (39.5; 28.8–51.0)	0.003
Disease control	84 (61.8; 53.0–70.0)	26 (47.3; 33.7–61.2)	58 (71.6; 60.5–81.1)	0.007

Data are n (%; 95% CI) or n (%), unless stated otherwise. Percentages might not add up to 100% due to rounding. CI, confidence interval; irAE, immune-related adverse event; PD-1, programmed cell death-1.

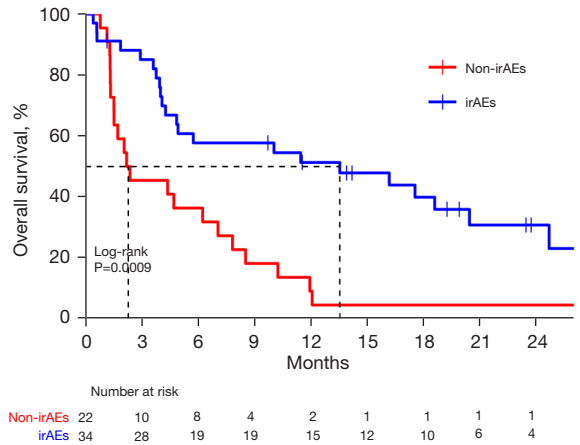

Figure 2 Kaplan-Meier curve of the overall survival for patients with PD-L1 CPS <10. irAE, immune-related adverse event; PD-L1, programmed death ligand-1; CPS, combined positive score.

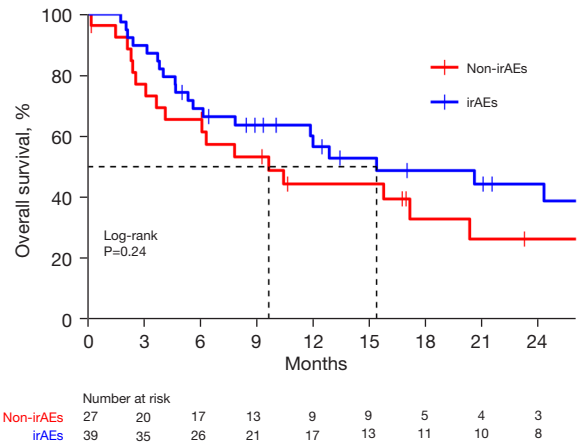

Figure 3 Kaplan-Meier curve of the overall survival for patients with PD-L1 CPS ≥10. irAE, immune-related adverse event; PD-L1, programmed death ligand-1; CPS, combined positive score.

this is the high incidence of RCCEP in patients treated with camrelizumab and the better-than-average prognosis in this group of patients. The appearance of RCCEP has been reported to be associated with good outcome in hepatocellular carcinoma (26). More studies are warranted to determine whether this particular irAE is associated with a better treatment effect.

Our study found that 59.6% of the patients experienced at least 1 irAE, which is comparable to findings from other trials using anti-PD-1 antibodies as the sole treatment for advanced ESCC (6-8). Furthermore, with timely and effective interventions, the majority of patients' symptoms were mild and manageable. Only 22 (16.2%) of 136 patients experienced interrupted treatment, and 9 (6.6%) of these discontinued anti-PD-1 treatment due to irAEs. Neither unanticipated severe adverse events nor deaths associated with the treatment occurred. Our study featured a longer follow-up time and a higher percentage of patients with an ECOG performance score of 2, which more closely approximates actual clinical practice compared to other randomized controlled trials.

Our study highlights the need for recognizing and monitoring irAEs throughout anti-PD-1 therapies by showing the correlations between irAEs and improved immunological responses to anti-PD-1 antibodies. Patients with ESCC who develop moderate irAEs may fare better than those who do not. Severe irAEs, such as myocarditis and pneumonia, can occasionally be fatal (15,17,27,28), and patients who experience them may have to discontinue anti-PD-1 therapy. As a result, careful observation and early identification of irAEs might lead to less severe side effects (29,30), as would classifying patients with efficient immune response to PD-1 inhibitors (30) and preventing the development of irAEs into more serious adverse events (30). When irAEs are found in a patient, effective intervention should be given immediately to prevent adverse reactions from becoming more severe and to enhance patient outcomes (31). Our study provides insight into on the nuanced but significant role that irAEs play in the utilization of anti-PD-1 therapy in patients with ESCC, which may help to modernize ESCC treatment. Furthermore, with appropriate monitoring and the application of standardized treatment to recognize and address toxic effects, ICI rechallenge would be safe (32). A rechallenge of ICI therapy may be an option for those patients with ESCC who experience ≥ grade 2 irAEs (33).

The study has several limitations. First, it was a retrospective study. In order to reduce the heterogeneity, we conducted Cox regression adjusted by sex and age. Second, the sample size was limited. The results of subgroup analysis should be cautiously interpreted. Third, our analysis demonstrates correlations rather than causal results. More research is warranted to clarify the underlying mechanisms through which irAEs can predict the results of ICIs and to determine whether other biomarkers are related to the occurrence of irAEs.

Conclusions

This study found a statistically significant and clinically

Table 4 Univariate and multivariate analysis of prognostic factors for overall survival

Factors	Cases (n=136)	Overall survival			
		Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Sex (male/female)	111/25	1.22 (0.72–2.07)	0.465	–	–
Age (≥65/<65 years)	59/77	1.12 (0.74–1.71)	0.588	–	–
Previous therapy					
Surgery (yes/no)	50/86	0.97 (0.64–1.48)	0.883	–	–
Radiotherapy (yes/no)	87/49	0.79 (0.52–1.21)	0.283	–	–
First-line platinum-based chemotherapy (yes/no)	122/14	0.99 (0.50–1.97)	0.972	–	–
Site of metastases					
Liver (yes/no)	31/105	1.12 (0.69–1.82)	0.652	–	–
Lung (yes/no)	58/78	0.79 (0.52–1.19)	0.258	–	–
Bone (yes/no)	18/118	1.34 (0.75–2.37)	0.322	–	–
Lymph node (yes/no)	106/30	1.25 (0.74–2.12)	0.409	–	–
Other (yes/no)	33/103	0.76 (0.46–1.24)	0.272	–	–
ECOG performance score					
0	24	Ref	–	Ref	–
1	102	2.04 (1.1–3.76)	0.023	2.01 (1.07–3.77)	0.031
2	10	2.44 (0.96–6.21)	0.061	2.25 (0.88–5.78)	0.091
Number of prior therapies (≥2/1)	53/83	1.36 (0.90–2.06)	0.145	–	–
PD-L1 combined positive score					
<10	56	Ref	–	Ref	–
≥10	66	1.55 (1.06–2.26)	0.023	1.5 (1.02–2.22)	0.041
Not evaluable	14	1.00 (0.63–1.6)	0.995	0.95 (0.59–1.52)	0.833
Smoking status					
Former	41	Ref	–	–	–
Current	77	0.96 (0.62–1.51)	0.870	–	–
Never	18	0.73 (0.35–1.54)	0.413	–	–
Group (irAEs/non-irAEs)	81/55	0.62 (0.46–0.83)	0.002	0.57 (0.42–0.77)	0.0002

CI, confidence interval; irAE, immune-related adverse event; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death ligand-1; Ref, reference.

meaningful association between the presence of irAEs and a favorable prognosis for patients with advanced ESCC treated with anti-PD-1 antibodies, suggesting that irAEs might serve as clinical prognostic indicators for the therapeutic efficacy of anti-PD-1 antibodies in patients with ESCC.

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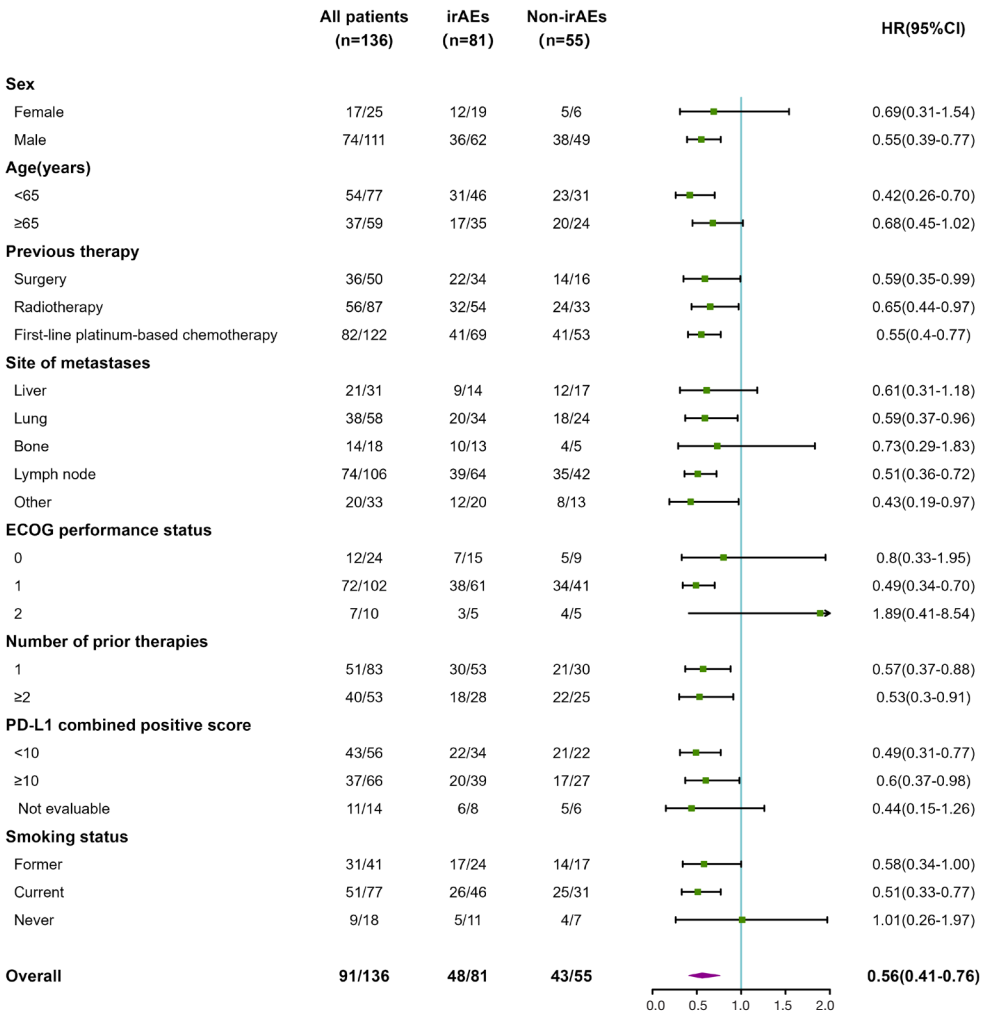

Figure 4 Forest plot for subgroup analyses of overall survival. Data are the number of deaths/number of patients. Cox regression was performed for each subgroup adjusted for sex and age. HR <1 favors the irAE group. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; irAE, immune-related adverse event; PD-L1, programmed death ligand-1.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-75/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-75/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-75/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of China-Japan Union Hospital of Jilin University (No. 20220418). Individual consent for this retrospective analysis was waived.

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