Correlation between immune-related adverse events and treatment efficacy of anti-PD1 immunotherapy in patients with esophageal squamous cell carcinoma

RUIJIE CAO[1], CHENSI WU[2], YALEI LV[3], SHUO XU[1], CUIZHEN LI[2], FEI YIN[2] and JING LI[4]

Departments of [1]Immunology and Rheumatology, [2]Gastroenterology and Hepatology, and [3]Medical Oncology, The Fourth Hospital of Hebei Medical University; [4]College of Integrated Chinese and Western Medicine, Hebei Medical University, Shijiazhuang, Hebei 050011, P.R. China

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Abstract. Immune-related adverse events (irAEs) caused by immune checkpoint inhibitors (ICIs) are associated with improved treatment efficacy in certain types of cancer. In the present study, we assessed the association between irAEs and ICI efficacy. Patients with esophageal squamous cell carcinoma (ESCC) who received ICI treatment were stratified into irAEs and non-irAE groups. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) were used to evaluate the therapeutic efficacy of ICIs. Of the 78 ICI-treated ESCC patients, 39 developed irAEs. The median OS and PFS for all patients were 600 and 300 days, respectively. Median OS (P<0.001) and PFS (P<0.001) times of the patients with irAEs were longer than those in the non-irAE group. In addition, the DCR of the irAE group was higher than that of the non-irAE group (P=0.006). Univariate analysis indicated that the non-irAE group was associated with a relatively shorter OS [hazard ratio (HR)=3.687, 95% CI, 1.974-6.888, P<0.001] and PFS (HR=2.967, 95% CI, 1.691-5.204, P<0.001). The multifactorial analysis demonstrated that irAE status was an independent predictor of PFS (HR=3.564, 95% CI, 1.786-7.114, P<0.001) and OS (HR=3.288, 95% CI, 1.636-6.606, P=0.001). In conclusion, the present study demonstrated that irAEs could be used to predict improved treatment efficacy in patients with ESCC who received ICI therapy.

Correspondence to: Professor Fei Yin, Department of Gastroenterology and Hepatology, The Fourth Hospital of Hebei Medical University, 12 Jiankang Road, Shijiazhuang, Hebei 050011, P.R. China
E-mail: yinfei_4y@sina.com

Professor Jing Li, College of Integrated Chinese and Western Medicine, Hebei Medical University, 361 East Zhongshan Road, Shijiazhuang, Hebei 050011, P.R. China
E-mail: lijingtiger@163.com

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Introduction

Esophageal cancer (EC) is divided into two major histological subtypes, squamous cell carcinoma (SCC) and adenocarcinoma (AC), and is the eighth-most common type of tumor, and the sixth leading cause of tumor-related death worldwide (1). Esophageal squamous cell carcinoma (ESCC) is the predominant subtype of EC in developing eastern countries, including Turkey, Iran, Kazakhstan, and China. The primary treatment approaches for ESCC include surgery, radiotherapy, chemotherapy, targeted therapy, and multimodal treatments (2-5). In China, 60-70% of patients with ESCC are diagnosed with advanced-stage cancer, for whom surgery is no longer possible (6). Chemoradiotherapy with cisplatin- and 5-fluorouracil-based regimens represent the standard mode of treatment for unresectable ESCC; however, the overall survival (OS) times are <12 months (7,8).

In the tumor microenvironment, stimulation and inhibition of ligand-receptor interactions in macrophages, dendritic cells, T-cells, and tumor cells regulate the activation of T-cells as part of the immune defense against cancer (9). The ligand-receptor pairs that negatively regulate T-cell activation, including cytotoxic T-lymphocyte antigen 4 (CTLA4)-B7 and programmed death-1 (PD-1)-programmed death ligand 1 (PD-L1), are called 'immune checkpoints' (10). Immune checkpoint inhibitors (ICIs) have drastically improved the survival rate of patients with several tumor types, including melanoma, non-small cell lung cancer (NSCLC), renal cell cancer, ovarian cancer, and gastrointestinal tract cancers (11-16). Patients with high PD-L1 expression appear to benefit more from ICI treatment for certain types of cancer (11,15). The randomized phase III KEYNOTE-181 study on advanced EC demonstrated that pembrolizumab monotherapy significantly improved the objective response rate (ORR), disease control rate (DCR), and OS in patients with PD-L1-positive (combined positive score ≥10) EC as the second-line treatment (16). Clinical benefit has also been found for pembrolizumab combined with

chemotherapy as the first-line treatment in patients with ESCC subtype owing to increased PD-L1 expression (17).

More than half of patients with cancer receiving ICI treatment develop immune-related adverse events (irAEs), the mechanisms of which depend on the type of ICIs used (18,19). In addition to eliciting autoantibody formation by inducing a cross-reaction between anti-tumor T-cells and healthy cell antigens, CTLA-4 inhibitors can initiate the activation and proliferation of T-cells, thereby impairing the survival of regulatory T-cells (Tregs). PD-1 and PD-L1 inhibitors can reduce the number and inhibit the function of Tregs by increasing cytokine production (20). Multiple organ injuries participate in the development of irAEs, including skin reactions, hypothyroidism, pneumonitis, hepatitis, myositis, adrenal insufficiency, and myocardial damage, because the T-cell immune response is not tissue-specific (10,18).

Recently, irAEs have been shown to be positively correlated with the efficacy of ICIs in patients with NSCLC and hepatocellular carcinoma (21,22). Therefore, here, the correlation between irAEs and ICI therapeutic efficacy based on anti-PD-1 antibodies in patients with ESCC was evaluated.

Materials and methods

Patients. Patients with ESCC treated with at least one cycle of anti-PD-1 antibodies (monotherapy or combination therapy), regardless of the treatment line, between October 2018 and May 2022 in the Fourth Hospital of Hebei Medical University were included in this analysis. Patients who were alive and progression-free were censored at the last follow-up date (September 30, 2022). Patients who had previously received immunotherapy were excluded. The following clinical data were collected: sex, age, Eastern Cooperative Oncology Group performance status (ECOG PS) (23), treatment line number, stage of disease (TNM), metastasis, history of radiotherapy or surgery, and concurrent therapy.

Treatment and assessment. The patients were treated with standard anti-PD-1 antibodies (monotherapy or combined with chemotherapy, targeted medicine, or radiotherapy) in a three-week cycle until disease progression, unacceptable toxicity, clinical deterioration, or patient rejection was observed. The anti-PD-1 antibody treatment included toripalimab at a dose of 240 mg every 2 weeks as well as sintilimab, camrelizumab, and pembrolizumab at a dose of 200 mg every 3 weeks; the dose of combination chemotherapy drugs, target drugs, and radiotherapy was adjusted by the clinicians according to the guidelines of the Chinese Society of Clinical Oncology based on the age, PS score, and degree of tolerance of the patients (24). Computed tomography (CT), magnetic resonance imaging (MRI), or endoscopy assessment were repeated every 2 or 3 cycles to evaluate the objective tumor response based on the New Response Evaluation Criteria in Solid Tumours: revised RECIST guideline (version 1.1) (25). IrAEs were defined as inflammatory side effects caused by an imbalance in immunological tolerance upon ICI treatment. The National Cancer Institute Common Terminology Criteria for Adverse Events ver. 4.03 was used for evaluating the irAEs (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40). We assigned patients to irAE and non-irAE groups based on the occurrence of irAEs. Common Terminology Standard for Adverse Events with a scale from grade 1 to grade 5 (1=mild, 2=moderate, 3=severe, 4=life-threatening, and 5=death associated with toxicity) was used to grade irAEs.

Statistical analysis. A χ^2 test was used to compare the difference between the two groups of classified variables. Continuous data presented as medians (ranges) were analyzed using a Mann-Whitney U test. Progression-free survival (PFS) was defined as the time from the start of immunotherapy to disease progression or death from any cause. OS was defined as the time from the start of immunotherapy to death or censoring at the latest follow-up in surviving patients. Survival probability was estimated using the Kaplan-Meier approach using a log-rank test. The Cox proportional hazards regression model was used for univariate and multivariate analyses. All statistical data were analyzed using SPSS (SPSS 21.0; IBM Corp.). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. In total, 82 patients with ESCC were included in this analysis, out of which four patients were lost to follow-up and 46 (59.0%) of the remaining 78 patients died during the follow-up period. The clinical characteristics of patients in the irAE and non-irAE groups showed no significant differences (Table I). The median OS and PFS for all patients were 600 days [95% confidence interval (CI), 518-682 days] and 300 days (95% CI, 191-409 days), respectively. Partial response (PR) was achieved in eight patients, whereas stable disease (SD) was observed in 15 patients, which led to an ORR of 10.3% (95% CI, 5.7-17.8%) and a DCR of 29.5% (95% CI, 21.5-39.1%) (Table II).

Comparison between irAE and non-irAE groups. An ORR of 15.4% (95% CI, 9.6-23.7%) and a DCR of 43.6% (95% CI, 34.3-53.4%) was found for all 39 irAEs patients (6 PR, 11 SD), whereas the 39 patients in the non-irAE group (2 PR, 4 SD) achieved an ORR of 5.1% (95% CI, 2.2-11.3%) and a DCR of 15.4% (95% CI, 9.6-23.7%). The DCR in the irAE group was higher than that in the non-irAE group (P=0.006; Table II).

The median OS and PFS of the irAE and non-irAE groups were calculated using the Kaplan-Meier method. The median OS ($P<0.001$) and PFS ($P<0.001$) in the irAE group were higher than those in the non-irAE group (Fig. 1). In the univariate analysis for OS and PFS with ECOG score, treatment line number, TNM stage, therapy plan, postoperative recurrence status, metastasis status, and irAE status as covariates, only the irAE status displayed its association with OS [hazard ratio (HR)=3.687, 95% CI, 1.974-6.888, $P<0.001$] and PFS (HR=2.967, 95% CI, 1.691-5.204, $P<0.001$) at a significant level, and irAEs were linked to relatively longer PFS and OS. TNM stage also showed a trend for association with OS (HR=1.718, 95% CI, 0.918-3.214, P=0.090). There were no Stage I patients, although there were eight Stage II patients; therefore Stage I, II, and III patients were included in one group and Stage IV patients in a separate group for comparison. Subsequent multivariate analysis showed that

Table I. Characteristics of patients in the irAEs and non-irAE groups.

Factor	Total, n (%)	non-irAE, n (%)	irAE, n (%)	P-value
Total patients	78	39	39	
Sex				
Female	28 (35.9)	17 (43.6)	22 (56.4)	0.157[a]
Male	50 (64.1)	22 (56.4)	28 (71.8)	
Age, years				
<65	32 (41.0)	16 (41.0)	16 (41.0)	1.000[a]
≥65	46 (59.0)	23 (59.0)	23 (59.0)	
ECOG PS				
≤1	66 (84.6)	36 (92.3)	30 (76.9)	0.060[a]
>1	12 (15.4)	3 (7.7)	9 (23.1)	
Treatment line				
≤1	37 (47.4)	16 (41.0)	21 (53.8)	0.257[a]
≥2	41 (52.6)	23 (59.0)	16 (41.0)	
TNM				
≤III	28 (36.4)	11 (28.2)	17 (44.7)	0.132[a]
IV	49 (63.6)	28 (71.8)	21 (55.3)	
Combined chemotherapy or targeted therapy				
No	7 (9.0)	2 (5.1)	5 (12.8)	0.428[b]
Yes	71 (91.0)	37 (94.9)	34 (87.2)	
Combined radiotherapy				
No	40 (51.3)	16 (41.0)	24 (61.5)	0.070[a]
Yes	38 (48.7)	23 (59.0)	15 (38.5)	
Postoperative recurrence				
No	62 (79.5)	33 (84.6)	29 (74.4)	0.262[a]
Yes	16 (20.5)	6 (15.4)	10 (25.6)	
Metastasis				
No	17 (21.8)	8 (20.5)	9 (23.1)	0.784[a]
Yes	61 (78.2)	31 (79.5)	30 (76.9)	

[a]Pearson's χ^2 test. [b]χ^2 with continuous corrections. irAE, immune-related adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table II. Response to immunotherapy.

Response	Total	irAE group	Non-irAE group	P-value
Progressive disease, n	55	22	33	-
Stable disease, n	15	11	4	-
Partial response, n	8	6	2	-
Complete response, n	0	0	0	-
Objective response rate	10.3% (95% CI, 5.7-17.8)	15.4% (95% CI, 9.6-23.7)	5.1% (95% CI, 2.2-11.3)	0.263[b]
Disease control rate	29.5% (95% CI, 21.5-39.1)	43.6% (95% CI, 34.3-53.4)	15.4% (95% CI, 9.6-23.7)	0.006[a,c]

[a]P<0.01. [b]Pearson's χ^2 test. [c]χ^2 with continuous corrections. irAE, immune-related adverse event; CI, confidence interval.

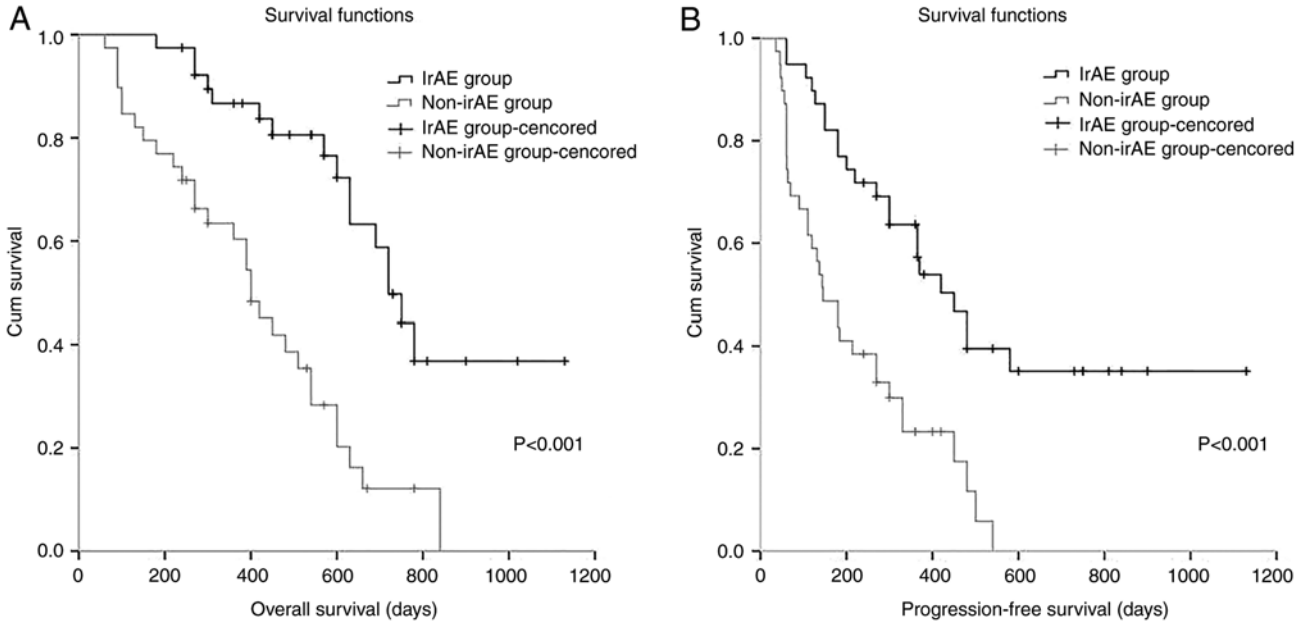

Figure 1. Association between irAEs and prognosis of patients with ESCC. (A) The Kaplan-Meier survival curve of OS for patients with and without irAEs. (B) The Kaplan-Meier survival curve of PFS for patients with and without irAEs. irAEs, immune-related adverse events; ESCC, esophageal squamous cell carcinoma; OS, overall survival; PFS, progression free survival.

the irAE status was an independent predictor of OS and PFS (OS: HR=3.288, 95% CI, 1.636-6.606, P=0.001; PFS: HR=3.564, 95% CI, 1.786-7.114, P<0.001) (Table III). These data indicate that irAEs could extend the PFS and OS of patients with ESCC.

Toxicity. The median time to irAE onset was 76 days (range: 5-570 days). Grade 3 irAEs were observed in eight patients and grade 4 irAEs were observed in one patient (Table IV). Three patients discontinued ICI treatment owing to the development of a grade 3 rash, grade 4 cutaneous capillary hyperplasia, and grade 3 myocardial damage. Cutaneous capillary hyperplasia (n=15) was the most frequent adverse event reported followed by hypothyroidism (n=12).

Patients with irAEs were stratified into an irAE-A group (patients with endocrine and cutaneous irAEs) and an irAE-B group (patients with other irAEs) for survival analysis. The median OS and PFS times in the irAE-A group were longer than those in the non-irAE group (median OS: 720 vs. 400 days, P<0.001; median PFS: 480 vs. 145 days, P<0.001), while no significant differences were found in the median OS (P=0.080) and PFS (P=0.085) between the irAE-B and the non-irAE groups (Table V). In addition, eight of the 39 patients with irAEs developed grade 3 irAEs, one developed grade 4 irAEs, and none had grade 5 irAEs. The 9 patients with grade 3 and higher irAEs were assigned to group irAE-C, and the other 30 patients with grade 1 and 2 irAEs were assigned to group irAE-D. There was no significant difference in the median OS and PFS between these two groups (Fig. S1). Of the 39 patients with irAEs, six developed ≥1 type of irAE, and these were stratified into 'single-site' and 'multiple-site' groups; there was also no significant difference in their median OS and PFS (Fig. S2). No significant differences were found in the median OS and PFS between patients whose irAE onset was within 90 days and those with an onset >90 days (Table SI).

Discussion

In the present study, it was confirmed that irAEs are concordantly correlated with a higher DCR, longer PFS, and longer OS in patients with ESCC undergoing immunotherapy, which was comparable with the treatment efficiency for irAEs in other types of cancer including melanoma, head and neck squamous cell carcinoma, NSCLC, renal cell carcinoma, and urothelial carcinoma (26-28). The sample size was small in the present study; however, cases where irAEs are associated with better treatment efficacy of ICIs still exist even after adjustment for other prognostic factors by multiple analyses. The KEYNOTE-590 clinical trial enrolled patients with unresectable locally advanced (TNM stage III) or metastatic EC who were treated with a first-line treatment. The results showed that pembrolizumab combined with chemotherapy was significantly superior to chemotherapy alone regarding OS, PFS, ORR, and DOR (29). The patients with TNM stage III in the present study included a subset of patients with first-line unresectable locally advanced disease as well as a subset of older patients or patients with stage II ESCC who could not tolerate surgery.

IrAEs are induced by a non-specifically activated immune system involving almost any organ system. Cutaneous, gastrointestinal, pulmonary, endocrine, and musculoskeletal irAEs are common, whereas renal, hematological, neurological, cardiovascular, and ophthalmological irAEs occur less frequently (30,31). Dermatological, endocrine, and gastrointestinal irAEs are associated with a favorable prognosis, whereas other irAEs are not (32). Here, it was similarly found that endocrine and dermatological irAEs were associated with a favorable prognosis in patients with ESCC. Previous reports on NSCLC indicated that 'single-site' irAEs are associated with relatively better clinical results (ORR, PFS, and OS) when compared with 'multi-site' irAEs (19); however,

Table III. Univariate and multivariate analyses of OS and PFS with Cox regression models.

	OS								PFS							
	Univariate analysis (n=54)				Multivariate analysis (n=54)				Univariate analysis (n=54)				Multivariate analysis (n=54)			
Covariate	HR	95% CI		P-value	HR	95% CI		P-value	HR	95% CI		P-value	HR	95% CI		P-value
Group																
irAE	Reference				Reference				Reference				Reference			
Non-irAE	3.687	1.974	6.888	<0.001	3.288	1.636	6.606	0.001	2.967	1.691	5.204	<0.001	3.564	1.786	7.114	<0.001[a]
ECOG PS																
≤1	Reference				Reference				Reference				Reference			
1	0.689	0.291	1.629	0.396	0.565	0.206	1.549	0.267	0.939	0.460	1.920	0.864	0.976	0.394	2.421	0.959
Treatment line																
≤1	Reference				Reference				Reference				Reference			
≥2	1.646	0.882	3.072	0.117	2.127	1.032	4.382	0.041	1.352	0.791	2.310	0.270	1.763	0.928	3.350	0.083
TNM																
≤III	Reference				Reference				Reference				Reference			
IV	1.718	0.918	3.214	0.090	2.372	1.121	5.019	0.024	1.510	0.883	2.583	0.132	1.541	0.811	2.927	0.187
Combine chemotherapy or targeted therapy																
No	Reference				Reference				Reference				Reference			
Yes	1.557	0.554	4.376	0.401	1.286	0.418	3.954	0.661	1.931	0.694	5.373	0.207	1.263	0.429	3.719	0.671
Combine radiotherapy																
No	Reference				Reference				Reference				Reference			
Yes	1.303	0.727	2.337	0.374	1.101	0.566	2.142	0.777	0.893	0.526	1.518	0.676	0.667	0.360	1.236	0.198
Postoperative recurrence																
No	Reference				Reference				Reference				Reference			
Yes	1.079	0.547	2.126	0.827	0.973	0.451	2.100	0.945	1.096	0.577	2.081	0.781	1.304	0.642	2.650	0.463
Metastasis																
No	Reference				Reference				Reference				Reference			
Yes	1.348	0.649	2.800	0.423	0.958	0.431	2.129	0.916	1.813	0.885	3.712	0.104	1.334	0.620	2.870	0.461

[a]P<0.001. irAE, immune-related adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; OS overall survival; PFS, progression free survival; HR, hazard ratio; CI, confidence interval; TNM, Tumor-Node-Metastasis.

Table IV. Categorization of irAEs.

irAE	No. (%)	Median days to onset	Grade of irAEs, n, 1/2/3/4/5
Hypothyroidism	12 (30.8)	155	3/9/0/0/0
Cutaneous capillary hyperplasia	15 (38.5)	60	3/10/1/1/0
Rash	8 (20.5)	52	2/4/2/0/0
Pneumonia	1 (2.6)	100	0/1/0/0/0
Adrenal insufficiency	2 (5.1)	70	0/0/2/0/0
Myositis/myocarditis	3 (7.7)	23	0/2/1/0/0
AST/ALT/Bilirubin increased	2 (5.1)	37	0/1/1/0/0
Colitis	1 (2.6)	76	0/1/0/0/0
Hypophysitis	1 (2.6)	156	0/1/0/0/0
Type 1 Diabetes	1 (2.6)	50	0/0/1/0/0

irAE, immune-related adverse event.

Table V. Kaplan-Meier survival curve of OS and PFS.

Comparison	Median OS, days	P-value	Median PFS, days	P-value
irAE group vs. non-irAE group				
irAE group	720 (95% CI: 639-801)	<0.001[a]	450 (95% CI: 340-560)	<0.001[a]
Non-irAE group	400 (95% CI: 320-480)		145 (95% CI: 86-204)	
irAE-A group vs. non-irAE group				
irAE-A group	720 (95% CI: 637-803)	<0.001[a]	480 (95% CI: 351-609)	<0.001[a]
Non-irAE group	400 (95% CI: 320-480)		145 (95% CI: 86-204)	
irAE-B group vs. non-irAE group				
irAE-B group	-	0.080	300 (95% CI: 161-439)	0.085
Non-irAE group	400 (95% CI: 320-480)		145 (95% CI: 86-204)	

[a]P<0.001. irAE, immune-related adverse event; irAE-A group, the group with endocrine, cutaneous irAEs; irAE-B group, the group with other irAEs; HR, hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression free survival.

there was no significant difference in the data of patients with ESCC in the present study. The incidence of grade 3 and 4 irAEs in the present study was lower than that reported in other studies, which may be attributed to our comprehensive baseline examination, close monitoring, and early treatment of irAEs (18,33). Since irAEs predicted better ECSS treatment efficiency, the prevention of fatal irAEs should be prioritized over all irAEs, thereby making ICI therapy efficient and uninterrupted.

The mutual effect of PD-1 with its ligands PD-L1 and PD-L2, which generates negative costimulatory signals, can weaken T-cell activation via tyrosine phosphatase 2, thereby facilitating the immune escape of tumor cells. ICIs can block the binding of PD-1 and PD-L1 to enhance T-cell activation and kill tumors in the tumor microenvironment (9). IrAEs develop owing to the destruction of autoimmune tolerance, which is at least partly mediated by antigen-specific T-cell responses. Activated T-cells can initiate a series of inflammatory reactions in multiple organs to induce irAEs when they recognize and kill tumor cells. Despite the unclear pathogenesis of immune toxicity, the inflammatory toxicity induced by activated CD8 T-cells overlaps with the immunotherapeutic effects induced by activated CD8 T-cells (30,34). This may explain the enhanced treatment efficiency for irAEs in patients with ESCC to a certain extent.

The present study has several limitations. First, the study was conducted in only one center with a small sample size. Second, this study had a short follow-up period, and several patients did not reach the point of death; therefore, these patients will continue to be followed up. Third, we could not exclude the effects of combination therapy, such as radiotherapy, chemotherapy, and target therapy. However, this is the first study to indicate a relationship between irAEs and efficacy in treating patients with ESCC, to the best of our knowledge. Thus, the findings of this pilot study provide a foundation for future studies with larger sample sizes.

In conclusion, the present study demonstrated that the occurrence of irAEs is concordantly correlated with a relatively higher DCR, longer PFS, and longer OS in patients with ESCC undergoing ICI treatment, and that irAEs may serve as

biomarkers for predicting improved treatment efficacy for ICIs in patients with ECSS.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

FY and JL designed the study. YLL, SX, and CZL were responsible for collecting the clinical data of the patients. RJC and CSW analyzed the data and wrote the manuscript. RJC, JL and FY confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of the Fourth Hospital of Hebei Medical University (Shijiazhuang, China) reviewed and approved the research protocol (approval no. 2021136).

Patient consent for publication

All patients provided informed consent prior to inclusion.

Competing interests

The authors declare that they have no competing interests.

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