Analysis of Predictive Factors for Immunotherapy-Related Adverse Events and Their Correlation with Treatment Efficacy in Esophageal Squamous Cell Carcinoma: A Postprint

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Abstract

Background: Immunotherapy has become the standard regimen for advanced esophageal squamous cell carcinoma (ESCC), but there is currently a lack of clear biomarkers for predicting immune-related adverse events (irAEs), and the relationship between irAEs and efficacy remains unclear. Objective: To investigate the predictive factors for irAEs in patients with advanced ESCC and the correlation between irAEs and treatment efficacy. Methods: A total of 118 patients with advanced ESCC who received programmed death protein-1 (PD-1) inhibitor therapy at Nanjing Drum Tower Hospital from January 2020 to December 2023 were retrospectively enrolled as the study subjects. Follow-up of the enrolled patients was conducted through medical record review, outpatient visits, readmissions, telephone calls, and other means. Clinical data and irAEs information of the two groups were collected. Based on whether irAEs occurred during treatment, patients were divided into an irAEs-positive group and an irAEs-negative group. Univariate and multivariate Logistic regression analyses were employed to explore factors associated with the occurrence of irAEs. Efficacy was evaluated as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR) and disease control rate (DCR) were compared between the two groups. Kaplan-Meier survival analysis was used to compare differences in progression-free survival (PFS) and overall survival (OS) between the two groups. Results: Among the 118 patients, 47 (39.83%) developed one or more irAEs. The most common irAEs were skin toxicity (21 cases, 17.80%), endocrine toxicity (16 cases, 13.56%), and lung toxicity (16 cases, 13.56%). Comparisons of autoantibody profiles and ANA between the irAEs-positive and irAEs-negative groups showed statistically significant differences ($P<0.05$). Univariate Logistic analysis revealed that positive autoantibody profile (OR=3.375, 95%CI=1.527~7.456, P=0.003)

and positive ANA (OR=3.072, 95%CI=1.404~6.722, P=0.005) were risk factors for irAEs occurrence (P<0.05). Multivariate Logistic analysis results showed that positive autoantibody profile (OR=2.367, 95%CI=0.841~6.663, P=0.103) and positive ANA (OR=1.733, 95%CI=0.621~4.837, P=0.293) were not significantly associated with irAEs occurrence. However, patients with positive autoantibody profiles had a higher incidence of endocrine toxicity than those with negative profiles, and ANA-positive patients had higher incidences of endocrine toxicity and myotoxicity than ANA-negative patients (P<0.05). Moreover, the DCR in the irAEs-positive group was higher than that in the irAEs-negative group (2=6.690, P=0.01). There was no statistically significant difference in ORR between the two groups (2=2.628, P=0.105). Kaplan-Meier survival analysis results showed that median PFS and median OS in the irAEs-positive group were higher than those in the irAEs-negative group, with statistically significant differences (PFS: 2=9.521, P=0.002; OS: 2=4.254, P=0.039). Conclusion: ESCC patients with positive autoantibody profiles or ANA may be more prone to irAEs after receiving immunotherapy, and the occurrence of irAEs is associated with better treatment efficacy.

Full Text

Analysis of Predictors for Immune-Related Adverse Events and Their Correlation with Efficacy in Esophageal Squamous Cell Carcinoma Immunotherapy

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Abstract

Background Immunotherapy has become the standard regimen for advanced esophageal squamous cell carcinoma (ESCC). However, clear biomarkers for predicting immune-related adverse events (irAEs) are lacking, and the relationship between irAEs and treatment efficacy remains unclear.

Objective To investigate the predictive factors for irAEs in patients with advanced ESCC and the correlation between irAEs and treatment efficacy.

Methods We retrospectively enrolled 118 patients with advanced ESCC who received programmed death protein-1 (PD-1) inhibitor therapy at Nanjing Drum

Tower Hospital between January 2020 and December 2023. Patients were followed up through medical record review, outpatient visits, readmissions, and telephone calls. Clinical data and irAEs information were collected. Based on the occurrence of irAEs during treatment, patients were divided into an irAEs-positive group and an irAEs-negative group. Univariate and multivariate logistic regression analyses were performed to explore factors associated with irAEs occurrence. Treatment efficacy was evaluated as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response rate (ORR) and disease control rate (DCR) were compared between groups. Kaplan-Meier survival analysis was used to compare progression-free survival (PFS) and overall survival (OS) between groups.

Results Among 118 patients, 47 (39.83%) developed one or more irAEs. The most common irAEs were cutaneous toxicity (21 cases, 17.80%), endocrine toxicity (16 cases, 13.56%), and pulmonary toxicity (16 cases, 13.56%). There were statistically significant differences in autoantibody profiles and antinuclear antibody (ANA) status between the irAEs-positive and irAEs-negative groups ($P<0.05$). Univariate logistic analysis showed that positive autoantibody profile (OR=3.375, 95%CI=1.527-7.456, P=0.003) and ANA positivity (OR=3.072, 95%CI=1.404-6.722, P=0.005) were risk factors for irAEs ($P<0.05$). Multivariate logistic analysis revealed no significant association between autoantibody profile positivity (OR=2.367, 95%CI=0.841-6.663, P=0.103) or ANA positivity (OR=1.733, 95%CI=0.621-4.837, P=0.293) and irAEs occurrence. However, patients with positive autoantibody profiles had higher incidence of endocrine toxicity than those with negative profiles, and ANA-positive patients had higher incidence of endocrine and muscular toxicity than ANA-negative patients ($P<0.05$). The irAEs-positive group showed higher DCR than the irAEs-negative group (^{2}=6.690, P=0.01), while no significant difference was observed in ORR between groups (^{2}=2.628, P=0.105). Kaplan-Meier survival analysis demonstrated that median PFS and median OS were significantly higher in the irAEs-positive group than in the irAEs-negative group (PFS: ^{2}=9.521, P=0.002; OS: ^{2}=4.254, P=0.039).

Conclusion ESCC patients with positive autoantibody profiles or ANA may be more prone to developing irAEs after immunotherapy, and the occurrence of irAEs is associated with better treatment efficacy.

Keywords Esophageal squamous cell carcinoma; Immunotherapy; Immune-related adverse events; Autoantibody profiles; ANA; Efficacy

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Introduction

Esophageal cancer is one of the most common digestive system malignancies in China, accounting for more than half of global cases. Over 90% of esophageal cancers in China are squamous cell carcinomas [1]. Due to the lack of typical clinical symptoms in early stages, more than half of patients are diagnosed

at advanced stages, with a 5-year survival rate of only approximately 5% for advanced esophageal cancer treated with dual-agent chemotherapy [2-3]. In recent years, multiple randomized clinical trials have demonstrated that programmed death protein-1 (PD-1) inhibitors combined with chemotherapy exhibit significant therapeutic efficacy in advanced esophageal squamous cell carcinoma (ESCC), providing long-term survival benefits and establishing a new standard first-line treatment regimen [4-6]. While immune checkpoint inhibitors (ICIs) can activate the immune system and induce anti-tumor immune responses, activated T cells may also cause damage to multiple organ systems throughout the body, leading to immune-related adverse events (irAEs) [7]. Statistics indicate that approximately half of cancer patients develop varying degrees of irAEs during PD-1 inhibitor immunotherapy [8].

Previous studies have found that irAEs correlate with immunotherapy efficacy in various malignancies including lung cancer, renal cell carcinoma, cholangiocarcinoma, urothelial carcinoma, and melanoma [9-13]. However, research on the correlation between irAEs and immunotherapy efficacy in ESCC remains limited, and no clear biomarkers exist for predicting irAEs. This study retrospectively analyzed clinical data from advanced ESCC patients receiving immunotherapy to investigate the occurrence patterns and influencing factors of irAEs in real-world settings, and to further clarify the correlation between irAEs and immunotherapy efficacy, thereby enabling effective prediction of irAEs and treatment outcomes in ESCC patients.

Methods

1.1 Study Population We retrospectively analyzed clinical data from advanced ESCC patients who received chemotherapy combined with immunotherapy at Nanjing Drum Tower Hospital between January 2020 and December 2023. Inclusion criteria were: (1) patients with pathologically and radiologically confirmed advanced ESCC, deemed inoperable or refusing surgery and unsuitable for radical radiotherapy, with TNM stage III-IV according to the 8th edition of the AJCC Cancer Staging Manual [14]; (2) patients who received $ $2 cycles of PD-1 inhibitors; and (3) presence of measurable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [15]. Exclusion criteria were: (1) patients without autoantibody testing; (2) those with other concurrent malignancies; and (3) patients lost to follow-up. This study complied with the principles of the Helsinki Declaration and was approved by the Ethics Committee of Nanjing Drum Tower Hospital (approval number: 2025-0226-01). All enrolled patients provided informed consent.

Patient screening process: A total of 152 patients with advanced ESCC were initially identified. Based on inclusion and exclusion criteria, 20 patients without autoantibody profile testing and 14 patients who received only one cycle of immunotherapy were excluded, resulting in a final cohort of 118 patients. Accord-

ing to whether they developed one or more irAEs during treatment, patients were divided into an irAEs-positive group (47 cases) and an irAEs-negative group (71 cases).

1.2 Data Collection and Assessment 1.2.1 Clinical Data Collection: We collected comprehensive clinical data including age, gender, tumor TNM stage, Eastern Cooperative Oncology Group (ECOG) performance status, combined positive score (CPS), tumor differentiation, tumor location, liver metastasis, lung metastasis, number of metastatic sites, treatment line, PD-1 inhibitor usage, and irAEs occurrence. ECOG performance status was defined as: 0 = fully active, no performance restrictions; 1 = ambulatory, capable of light work; 2 = ambulatory, capable of self-care but unable to work, active >50% of waking hours; 3 = limited self-care, confined to bed/chair >50% of waking hours; 4 = completely disabled, unable to perform self-care; 5 = deceased. CPS was defined as the percentage of PD-L1-positive tumor cells and tumor-associated immune cells among all viable tumor cells. Based on previous meta-analysis results [16] and the KEYNOTE-181 study [17], CPS $ $10 was defined as the positive threshold.

1.2.2 Sample Collection and Processing: Blood samples were collected from all patients before initiating immunotherapy. Autoantibody profiles were measured using line immunoassay analysis of serum samples. Testing kits were purchased from EUROIMMUN AG (Germany) and included 19 items such as antinuclear antibody (ANA) and anti-Ro-52 antibody. Positivity for any single item was defined as a positive autoantibody profile. This study primarily analyzed autoantibody profiles, ANA, and anti-Ro-52 antibody.

1.2.3 Assessment Indicators: Treatment efficacy and irAEs were the primary endpoints.

(1) **Treatment Efficacy:** Imaging evaluations were performed every two cycles after initiating chemotherapy combined with immunotherapy. Efficacy was assessed using RECIST version 1.1 and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response rate (ORR) was calculated as (CR+PR)/total cases $×$100%, and disease control rate (DCR) as (CR+PR+SD)/total cases $×$100%.

(2) **irAEs:** irAEs occurring during immunotherapy were evaluated and recorded according to the Chinese Society of Clinical Oncology (CSCO) "Guidelines for the Management of Toxicities Associated with Immune Checkpoint Inhibitors-2021" [18], including cutaneous, endocrine, cardiac, pulmonary, gastrointestinal, hepatic, muscular, renal, and neurological toxicities.

1.2.4 Treatment Regimen and Follow-up

(1) **Treatment Regimen:** All patients received PD-1 inhibitors combined

with chemotherapy, administered intravenously once every 3 weeks, with imaging re-evaluation every 6 weeks. PD-1 inhibitors included camrelizumab, sintilimab, and tislelizumab (200 mg each), and toripalimab (240 mg). Chemotherapy regimens consisted of either albumin-bound paclitaxel plus carboplatin (albumin-bound paclitaxel: 175-260 mg/m^2; carboplatin: AUC=4-5) or albumin-bound paclitaxel plus cisplatin (albumin-bound paclitaxel: 175-260 mg/m^2; cisplatin: 60-75 mg/m^2). Treatment continued until disease progression or intolerable toxicity.

(2) **Follow-up:** All patients were followed up through medical record review, outpatient visits, readmissions, and telephone calls. Follow-up began at the time of first ICI treatment and continued until December 31, 2024. Follow-up indicators included general condition, tumor progression, and survival status. Progression-free survival (PFS) was defined as the time from first ICI treatment to tumor progression. Overall survival (OS) was defined as the time from first ICI treatment to death, loss to follow-up, or last follow-up.

1.3 Statistical Analysis Statistical analysis was performed using SPSS version 22.0. Normally distributed continuous variables were expressed as mean ± standard deviation and compared between groups using independent samples t-test. Categorical variables were expressed as proportions and compared using ^{2} test. Kaplan-Meier analysis was used to compare PFS and OS between groups. Univariate and multivariate logistic regression analyses were performed to identify factors associated with irAEs. P<0.05 was considered statistically significant.

Results

2.1 irAEs in Enrolled Patients Among the 118 enrolled patients, 47 (39.83%) developed one or more irAEs, including 40 cases (85.11%) with grade 1-2 irAEs and 7 cases (14.89%) with grade 3-4 irAEs. The specific irAEs included cutaneous toxicity (21 cases, 17.8%), endocrine toxicity (16 cases, 13.56%), pulmonary toxicity (16 cases, 13.56%), hepatic toxicity (4 cases, 3.39%), cardiac toxicity (3 cases, 2.54%), gastrointestinal toxicity (3 cases, 2.54%), muscular toxicity (2 cases, 1.69%), and renal toxicity (1 case, 0.85%).

2.2 Comparison of Baseline Characteristics Between Groups A total of 118 advanced ESCC patients receiving immunotherapy combined with chemotherapy were enrolled, including 97 males (82.20%) and 21 females (17.80%), with a mean age of 67.5$±$8.1 years. There were statistically significant differences in autoantibody profiles and ANA status between the irAEs-positive and irAEs-negative groups (P<0.05). No significant differences were observed between groups in age, gender, tumor TNM stage, ECOG performance status, CPS score, tumor differentiation, tumor location, liver

metastasis, lung metastasis, number of recurrent sites, anti-Ro-52 antibody status, treatment line, or PD-1 inhibitor usage (P>0.05) .

2.3 Logistic Regression Analysis of Factors Influencing irAEs Occurrence Using the occurrence of irAEs (yes=1, no=0) as the dependent variable, univariate logistic regression analysis was performed with age, gender, TNM stage, ECOG performance status, CPS, tumor differentiation, tumor location, liver metastasis, lung metastasis, number of recurrent sites, autoantibody profile, ANA, anti-Ro-52 antibody, treatment line, and PD-1 inhibitor as independent variables. The results showed that positive autoantibody profile (OR=3.375, 95%CI=1.527-7.456, P=0.003) and ANA positivity (OR=3.072, 95%CI=1.404-6.722, P=0.005) were risk factors for irAEs occurrence (P<0.05) .

Variables showing significance in univariate analysis were further included in multivariate logistic regression analysis. The results indicated that positive autoantibody profile (OR=2.367, 95%CI=0.841-6.663, P=0.103) and ANA positivity (OR=1.733, 95%CI=0.621-4.837, P=0.293) were not significantly associated with irAEs occurrence .

2.4 Comparison of irAEs Incidence by Autoantibody Profile and ANA Status Comparison of irAEs incidence among patients with different autoantibody profiles and ANA status revealed that patients with positive autoantibody profiles had higher incidence of endocrine toxicity than those with negative profiles, and ANA-positive patients had higher incidence of endocrine and muscular toxicity than ANA-negative patients, with statistically significant differences (P<0.05) .

2.5 Comparison of Treatment Efficacy Between Groups Treatment efficacy evaluation showed that 62 patients (52.54%) achieved CR/PR, 44 (37.29%) had SD, and 12 (10.17%) experienced PD. The overall ORR was 52.54% and DCR was 89.83%. The irAEs-positive group demonstrated significantly higher DCR than the irAEs-negative group (^{2}=6.690, P=0.01), while no significant difference was observed in ORR between groups (^{2}=2.628, P=0.105) .

Kaplan-Meier survival analysis revealed that median PFS in the irAEs-positive group [9.1 (6.9, 11.4) months] was significantly higher than in the irAEs-negative group [5.7 (2.9, 8.6) months], and median OS in the irAEs-positive group [20.2 (16.5, 23.9) months] was significantly higher than in the irAEs-negative group [16.3 (11.2, 21.3) months], with statistically significant differences (PFS: ^{2}=9.521, P=0.002; OS: ^{2}=4.254, P=0.039) [Figure 1: see original paper].

Discussion

With breakthrough advances in immunotherapy, ICIs have demonstrated significant anti-tumor activity and excellent clinical efficacy in advanced ESCC

patients [19]. ICIs enhance T cell function by blocking PD-1/PD-L1 binding, thereby improving patients' intrinsic immunity, enhancing tumor cell killing capacity, prolonging survival, and improving prognosis [20]. However, over 50% of patients develop irAEs during ICI treatment [8]. Several pre-existing serum biomarkers (including blood cell analysis, chemokines, cytokines, and genetic susceptibility markers) may be associated with increased risk of irAEs [21-22]. Additionally, some studies have explored the correlation between serum autoantibodies and irAEs development [23-25], while others suggest no significant association [26]. The relationship between autoantibodies and irAEs in ESCC immunotherapy remains unclear. This study enrolled ESCC patients receiving immunotherapy to analyze the relationship between autoantibody profiles or ANA positivity and irAEs occurrence, exploring their potential clinical application value.

Our results indicate that ESCC patients with positive autoantibody profiles or ANA are more likely to develop irAEs after immunotherapy. Univariate analysis identified positive autoantibody profile and ANA positivity as risk factors for irAEs, though multivariate analysis showed no significant association. We further analyzed the correlation between autoantibody profile/ANA positivity and different types of irAEs, finding higher incidence of endocrine-related adverse events in patients with positive autoantibody profiles or ANA positivity. Autoantibodies are antibodies directed against self-tissues, organs, cells, and intracellular components that can cause tissue damage through antibody-dependent cell-mediated cytotoxicity or by activating the complement system to form membrane attack complexes that directly lyse target cells [27]. Previous studies have shown that patients with positive anti-thyroid antibodies are more prone to thyroiditis [28], those with anti-acetylcholine receptor antibodies have increased myositis risk [29], anti-GNAL or anti-ITM2B antibody positivity is associated with increased pituitary inflammation risk [30], and anti-CD74 antibody positivity correlates with pneumonitis development [30]. Additionally, ANA-positive cancer patients have higher probability of developing immune colitis [31]. A cohort study of 137 non-small cell lung cancer patients found that baseline levels of rheumatoid factor, ANA, and thyroid-related antibodies were positively correlated with irAEs risk, and autoantibody-positive patients had better survival outcomes [32]. De Moel et al. [33] reported that positivity for a 23-autoantibody panel correlated with ipilimumab-related irAEs in 133 melanoma patients, with anti-thyroid antibodies showing significant association with irAEs risk. Our study is the first to explore the relationship between autoantibodies/ANA and irAEs in ESCC, with results consistent with previous studies, though the lack of statistical significance in multivariate analysis may be attributed to small sample size and selection bias, requiring further validation with larger cohorts.

Multiple clinical studies have reported that patients developing irAEs after PD-1 inhibitor therapy demonstrate significantly better immunotherapy efficacy than those without irAEs [34-36]. Suo et al. [12] studied irAEs in 186 advanced melanoma patients receiving PD-1 monoclonal antibodies, finding that patients

with grade $ $3 irAEs had significantly prolonged OS (HR=0.29, 95%CI=0.1-0.85). A study of 176 urothelial carcinoma patients treated with pembrolizumab showed that 77 patients (43.8%) developed irAEs, with those experiencing grade 1-2 irAEs having better OS prognosis (HR=0.49, 95%CI=0.30-0.78) [35]. A retrospective study of 803 non-small cell lung cancer patients confirmed that irAEs reduced disease progression risk by 47% (HR=0.53, 95%CI=0.40-0.70) and were significantly associated with longer survival benefits [37]. However, some studies suggest that irAEs may not be positively correlated with ICI efficacy [38]. The relationship between irAEs and immunotherapy efficacy in ESCC patients remains undefined.

Our study demonstrates that ESCC patients with irAEs after PD-1 inhibitor therapy achieve higher DCR and longer PFS and OS, indicating that irAEs correlate with ESCC prognosis. This suggests that irAEs development may be associated with more robust activation of host immune responses, leading to greater benefit from immunotherapy. The regulatory mechanisms linking immune toxicity and therapeutic efficacy remain incompletely elucidated. Current research suggests that inflammatory response mechanisms mediated by CD8+ T cells partially overlap with anti-tumor immune mechanisms, indicating that irAEs development may be associated with better clinical outcomes [42].

This study has several limitations. First, although univariate analysis suggested associations between autoantibody profile/ANA positivity and irAEs in ESCC patients, multivariate analysis showed no significant associations, possibly due to small sample size requiring further validation. Additionally, this was a single-center retrospective study with potential selection bias; future multi-center, large-sample prospective cohort studies are needed. Second, 61 of 118 patients did not undergo PD-L1 testing; given the importance of PD-L1 in predicting immunotherapy efficacy [17], future studies should include PD-L1 assessment. Finally, this study only explored correlations with autoantibodies and ANA without investigating specific regulatory mechanisms, warranting further mechanistic research.

In conclusion, ESCC patients with positive autoantibody profiles or ANA tend to be more susceptible to irAEs after immunotherapy, particularly endocrine-related adverse events. Advanced ESCC patients who develop irAEs after PD-1 inhibitor therapy tend to achieve higher DCR and longer PFS and OS, suggesting that irAEs development may be associated with more robust immune activation and greater benefit from immunotherapy. Our findings suggest that autoantibody expression profiles may serve as a convenient, cost-effective tool for monitoring irAEs in advanced ESCC patients, though further validation in larger clinical cohorts is warranted.

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