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Prognostic Impact of Immune-Related Adverse Events in Advanced Gastric Cancer Patients Treated with Immune Checkpoint Inhibitors: A Real-world Retrospective Study

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ABSTRACT

While immune checkpoint inhibitors (ICIs) are a key treatment for advanced gastric cancer (AGC), the prognostic significance of their associated immune-related adverse events (irAEs) remains unclear. This real-world study aims to evaluate irAE incidence and impact on clinical outcomes.

This retrospective study consecutively enrolled 156 patients with AGC who received ICI therapy and completed follow-up between January 2021 and June 2023. Baseline characteristics, treatment regimens, irAE occurrence, and survival data were collected. The prognostic impact of irAEs was assessed by objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).

A total of 156 patients were included, of whom 76 (48.72%) developed irAEs. The most common types were endocrine, cutaneous, and gastrointestinal toxicities, mostly of grades 1-2. Multivariate logistic regression analysis identified age≥70 years (OR=2.615), BMI ≥ 25 kg/m² (OR=5.791), prior chemotherapy (OR=4.954), prior targeted therapy (OR=5.532), ICI combined with chemotherapy (OR=5.456), ICI combined with targeted therapy (OR=2.850), and a history of smoking (OR=3.224) as independent predictors of irAEs. Compared with the non-irAEs group, the irAEs group showed superior clinical efficacy, with a significantly higher ORR (38.16% vs. 20.00%) and DCR (80.26% vs. 66.25%). Kaplan-Meier survival analysis revealed a significant association between the occurrence of irAEs and prolonged survival, with the irAEs group showing superior median PFS (8.0 vs. 5.0 months) and OS (15.0 vs. 10.0 months) compared to the non-irAEs group.

For AGC patients receiving ICI therapy, the development of irAEs correlates significantly with improved survival, serving as a potential biomarker of clinical benefit.

Keywords: Checkpoint inhibitors; Drug-related side effects and adverse reactions; Immune system; Prognosis; Stomach neoplasms

INTRODUCTION

In 2020, gastric cancer ranked fifth in global incidence and fourth in cancer deaths, with 1.08 million new cases and approximately 769,000 fatalities.[1] For

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patients with early-stage gastric cancer, timely curative surgery after diagnosis can lead to effective control or even a cure.[2] However, due to the insidious clinical presentation and rapid progression in its early stages, most patients are diagnosed at an advanced stage, missing the curative surgical opportunity.[3] Commonly used chemotherapeutic agents include fluoropyrimidines, taxanes, and platinum-based drugs, but the median overall survival (OS) for advanced gastric cancer (AGC) with conventional chemotherapy rarely exceeds 12 months.[4,5] Advances in precision medicine have yielded targeted therapies like trastuzumab, ramucirumab, and apatinib, which demonstrate clinical benefit in gastric cancer.[6] Nevertheless, due to the toxicity of chemotherapy, the difficulty in screening patient populations who would benefit from targeted therapies, and the propensity for drug resistance, the prognosis for patients with gastric cancer has not substantially improved.[7]

Recent breakthroughs in cancer immunotherapy present a promising new direction for treating AGC. Immune checkpoint inhibitors (ICIs), such as those targeting PD-1/PD-L1 or CTLA-4 pathways, work by blocking immunosuppressive signals to reactivate the anti-tumor immune response. This approach has demonstrated significant and durable clinical benefits across various solid tumors.[8] In the field of gastric cancer, a series of pivotal Phase III randomized controlled trials (RCTs), including KEYNOTE-059, KEYNOTE-061, KEYNOTE-062, ATTRACTION-2, CheckMate-649, and ORIENT-16, have established that PD-1/PD-L1 inhibitors, as monotherapy or combined with chemotherapy/targeted therapy, significantly improve the progression-free survival (PFS) and OS in AGC.[9] However, while immunotherapy brings survival benefits, it is also associated with a unique and complex spectrum of adverse events known as immune-related adverse events (irAEs) .[10] Mild cases may present as rash, pruritus, diarrhea, or hypothyroidism, while severe cases can lead to immune-mediated myocarditis, pneumonitis, hepatitis, colitis, hypophysitis, or even fatal multi-organ failure.[11]

Emerging evidence consistently links irAE occurrence to enhanced treatment efficacy.[12] In cancers such as melanoma, non-small cell lung cancer (NSCLC) , renal cell carcinoma (RCC), and urothelial carcinoma, this association is reflected in higher objective response rates and extended PFS and OS.[13-16] In particular, low-grade irAEs, such as dermatologic and endocrine toxicities, are considered predictive indicators of a favorable prognosis. However, the association between irAEs and prognosis in AGC has not been systematically investigated. The existing evidence is primarily derived from post-hoc analyses of RCTs or single-center retrospective studies with limited sample sizes, leading to considerable heterogeneity in conclusions. Several studies correlate the development of irAEs with improved OS.[17-20] However, Namikawa et al.[21] reported comparable OS between patients with and without irAEs. Patient baseline characteristics, comorbidities, treatment regimens, and follow-up patterns in real-world clinical practice differ significantly from those in clinical trials, which limits the generalizability of the research findings. Hence, a systematic real-world study to determine the incidence, identify risk factors, and evaluate the prognostic impact of irAEs in AGC is scientifically and clinically important.

This study consecutively enrolled 156 patients with AGC treated with PD-1/PD-L1 inhibitors. Using electronic medical records and the picture archiving and communication system, we collected comprehensive baseline characteristics, treatment details, irAE occurrences, and survival follow-up data. Our objectives were to systematically evaluate the real-world incidence of irAEs in this population, analyze associated risk factors, and investigate the relationship between irAEs and clinical outcomes. This will provide evidence-based guidance for the development of management strategies for irAEs and for patient prognostic assessment in clinical practice.

MATERIALS AND METHODS

Subjects

This real-world, retrospective observational study included 156 patients with AGC and was approved by the hospital ethics review committee. All patients received PD-1/PD-L1 inhibitor therapy and completed follow-up at our institution between January 2021 and June 2023. Clinical data were collected via electronic medical record review. See Figure 1.

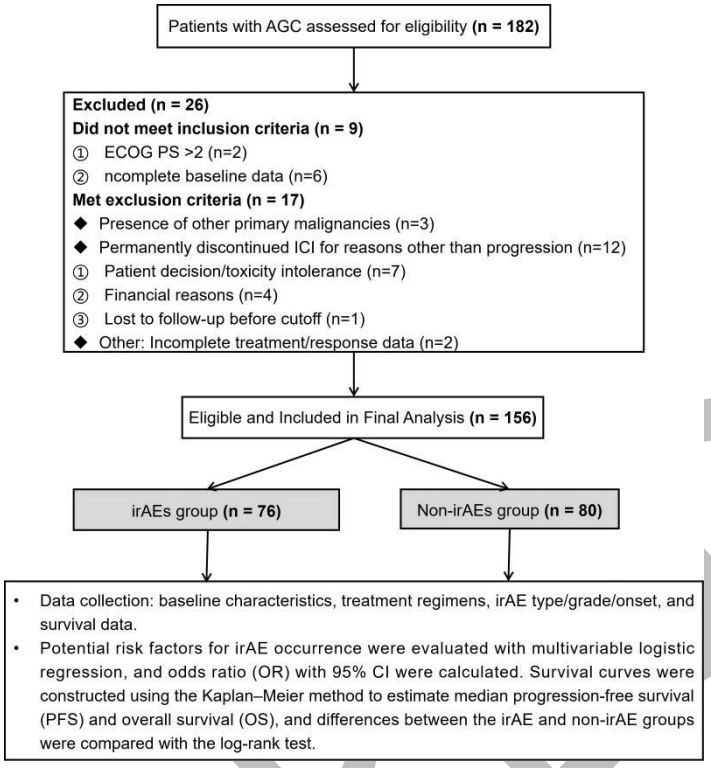

Figure 1. Research process.

Inclusion Criteria

(1) Age ≥ 18 years;

(2) Patients with AGC confirmed by histopathological or cytological examination;

(3) Eastern Cooperative Oncology Group performance status (ECOG) score of 0-2;

(4) Received PD-1/PD-L1 inhibitor therapy for the first time;

(5) Availability of complete baseline clinical data, treatment records, and follow-up records for efficacy and safety assessment.

Exclusion Criteria

(1) Presence of other primary malignant tumors prior to receiving immunotherapy;

(2) Totally incomplete clinical data, precluding efficacy or safety assessment;

(3) Presence of active pre-existing autoimmune diseases requiring systemic immunosuppressive therapy prior to immunotherapy initiation;

(4) Premature permanent discontinuation of immunotherapy, where the cause was not disease progression;

(5) Lost to follow-up before the data collection cut-off date.

Sample Size Calculation

This is a retrospective study. The sample size consisted of all consecutive patients who were enrolled and met the inclusion criteria during the study period, totaling 156 cases. To evaluate the statistical power, we performed a post-hoc power analysis on the primary endpoint, OS. Based on the median survival observed in this study (15 months for the irAEs group vs. 10 months for the non-irAEs group), with a two-sided significance level (α) set at 0.05, the calculated statistical power of the study was greater than 90%. This result indicates that the current sample size was sufficient to effectively detect a statistically significant difference in survival between the two groups, ensuring the high reliability of the study conclusions.

Treatment Regimens and irAE Management

All patients received a PD-1/PD-L1 inhibitor-based treatment regimen, which was determined by the attending physician according to clinical guidelines and the patient's condition. These regimens included: (1) immunotherapy monotherapy; (2) immunotherapy combined with chemotherapy; and (3) immunotherapy

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combined with anti-angiogenic targeted drugs.

The diagnosis and grading of irAEs followed Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). To distinguish irAEs from chemotherapy-related toxicities in combination regimens, we considered: (1) onset timing relative to ICI initiation; (2) clinical/laboratory features characteristic of immune-mediated injury (e.g., colitis vs. mucositis); (3) response to immunosuppressive management; and (4) exclusion of alternative causes (e.g., infection). All irAEs were adjudicated by the treating team with specialist consultation as needed. Management details, including corticosteroid use (agent, dose, duration), were documented. The time of onset, type, grade, management measures, and outcome of irAEs were recorded.

Clinical Data

In this real-world study, clinical data were collected through retrospective analysis of patient records.

(1) Demographic characteristics: including age, sex, body mass index (BMI), comorbidities, history of smoking, history of alcohol consumption, and ECOG performance status score.

(2) Tumor characteristics: including tumor differentiation, pathological type, and Lauren classification. Additionally, we collected data on the site and number of metastases, including liver and bone metastases.

(3) Treatment information: including whether the patient had undergone gastric surgery, prior treatments, types of prior treatments, specific immunotherapy drugs used, immunotherapy combination regimens, and line of immunotherapy.

Clinical Outcome Measures

(1) Primary endpoints: OS: Time from first ICI administration to death from any cause. PFS: Time from first ICI administration to the first occurrence of disease progression or death from any cause. Assessed monthly [per response evaluation criteria in solid tumors (RECIST) version 1.1].

(2) Secondary endpoints: Objective response rate (ORR): The proportion of patients achieving a complete response (CR) or partial response (PR). Disease control rate (DCR): The proportion achieving CR, PR, or stable disease (SD). Incidence, types, and timing of irAEs were analyzed. Patients were then stratified into irAE and non-irAE groups based on the occurrence of any irAE during treatment and follow-up for comparative analysis.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics (version 26.0; IBM Corp., Armonk, NY, USA).. Continuous data are presented as mean ± SD (t-test for normal distribution) or median (IQR) [Mann-Whitney U test for non-normal distribution]. Categorical data are expressed as n (%) and compared by χ^2 or Fisher's exact test. Risk factors for irAEs were analyzed by multivariate logistic regression, reported as OR (95% CI). Kaplan-Meier curves estimated median PFS and OS, with between-group comparisons performed using the log-rank test. Statistical significance was set at $p<0.05$.

RESULTS

Types of irAEs in Patients

Among the 156 patients with AGC receiving ICI therapy included in this study, a total of 76 (48.72%) experienced at least one irAE during the treatment period (Figure 2). A total of 87 separate irAE events were recorded among all patients, and their specific types and severity distribution are shown in Table 2. The majority of irAEs were mild to moderate (Grades 1-2); severe (Grades 3-4) events were uncommon. Among all irAEs, the most common type was endocrine toxicity, occurring in 24 cases, followed by dermatologic toxicity (23 cases) and gastrointestinal toxicity (18 cases). Other less frequent irAEs included hepatic toxicity (10 cases), pneumonitis (6 cases), musculoskeletal toxicity (3 cases), cardiotoxicity (2 cases), and neurotoxicity (1 case).

Furthermore, 14 out of 156 patients (8.97%) temporarily discontinued treatment due to more severe irAEs but resumed medication after management, with no treatment-related deaths. Additionally, we conducted an in-depth analysis of all immune-related adverse reaction data that occurred from the initiation of immunotherapy until the study cut-off date. The median time to irAE onset was approximately 8 (range, 1-28) weeks. Onset occurred at a median of 4 (1-14), 9 (1-28), and 6 (1-12) weeks for dermatologic, endocrine, and gastrointestinal toxicities, respectively.

Comparison of Baseline Data of Patients

Baseline characteristics differed significantly (Table 1), particularly in age, BMI, smoking history, prior chemotherapy or targeted therapy, and the use of

combination chemotherapy or targeted therapy. (p<0.05). The proportion of patients in the irAEs group was significantly higher than in the non-irAEs group for those aged≥70 years (47.37% vs 28.75%), those with a BMI≥25 kg/m² (34.21% vs 18.75%), those with a history of prior chemotherapy (46.05% vs 28.75%), those with a history of prior targeted therapy (23.68% vs 10.00%), those receiving combination chemotherapy (86.84% vs 72.50%), those receiving combination targeted therapy (32.89% vs 16.25%), and those with a smoking history (35.53% vs 20.00%) (p<0.05 for all). Other baseline characteristics, including sex, pathological type, tumor location, ECOG performance status, Lauren classification, differentiation, metastatic status, and choice of immunotherapy drug, showed no significant differences (p>0.05).

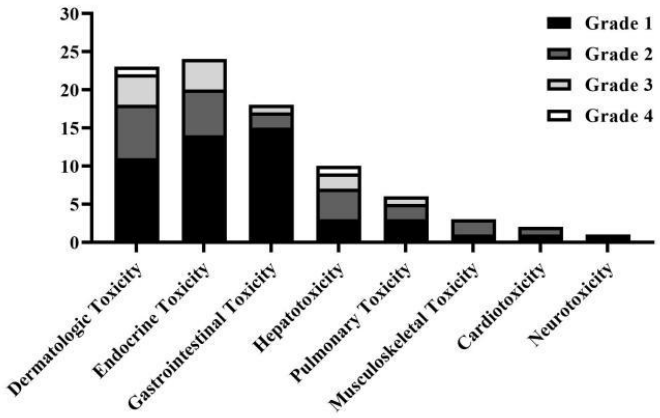

Figure 2. Classification of immune-related adverse reactions

Table 1. Baseline data (n,%)

Variables	Total (n=156)	irAEs group (n=76)	Non-irAEs group (n=80)	χ^2	p
Age (years)				5.745	0.017
< 70	97 (62.18)	40 (52.63)	57 (71.25)		
≥ 70	59 (37.82)	36 (47.37)	23 (28.75)		
Gender				0.305	0.581
male	93 (59.62)	47 (61.84)	46 (57.50)		
female	63 (40.38)	29 (38.16)	34 (42.50)		
BMI (kg/m²)				4.808	0.028
< 25	115 (73.72)	50 (65.79)	65 (81.25)		
≥ 25	41 (26.28)	26 (34.21)	15 (18.75)		
Pathological Type				0.187	0.911
Adenocarcinoma	132 (84.62)	64 (84.21)	68 (85.00)		
Signet ring cell carcinoma	13 (8.33)	6 (7.89)	7 (8.75)		
Mixed	11 (7.05)	6 (7.89)	5 (6.25)		
Primary Tumor Site				0.822	0.365
Gastric body	102 (65.38)	47 (61.84)	55 (68.75)		
Gastroesophageal junction	54 (34.62)	29 (38.16)	25 (31.25)		
ECOG Score				0.149	0.700
0-1	138 (88.46)	68 (89.47)	70 (87.50)		
2	18 (11.54)	8 (10.53)	10 (12.50)		

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Table 1. Continued...

Variables	Total (n=156)	irAEs group (n=76)	Non-irAEs group (n=80)	χ^2	*p*
Lauren Classification				2.607	0.272
Intestinal type	68 (43.59)	36 (47.37)	32 (40.00)		
Diffuse type	55 (35.26)	22 (28.95)	33 (41.25)		
Mixed type	33 (21.15)	18 (23.68)	15 (18.75)		
Degree of Differentiation				0.309	0.578
Poorly differentiated	120 (76.92)	57 (75.00)	63 (78.75)		
Moderately differentiated	36 (23.08)	19 (25.00)	17 (21.25)		
Peritoneal Metastasis				0.568	0.451
No	93 (59.62)	43 (56.58)	50 (62.50)		
Yes	63 (40.38)	33 (43.42)	30 (37.50)		
Liver Metastasis				0.329	0.566
No	100 (64.10)	47 (61.84)	53 (66.25)		
Yes	56 (35.90)	29 (38.16)	27 (33.75)		
Bone Metastasis				0.142	0.707
No	141 (90.38)	68 (89.47)	73 (91.25)		
Yes	15 (9.62)	8 (10.53)	7 (8.75)		
Lung Metastasis				0.133	0.716
No	137 (87.82)	66 (86.84)	71 (88.75)		
Yes	19 (12.18)	10 (13.16)	9 (11.25)		
Retroperitoneal Lymph Node Metastasis				0.142	0.707
No	141 (90.38)	68 (89.47)	73 (91.25)		
Yes	15 (9.62)	8 (10.53)	7 (8.75)		
Number of Metastatic Sites				0.161	0.688
< 3	145 (92.95)	70 (92.11)	75 (93.75)		
≥ 3	11 (7.05)	6 (7.89)	5 (6.25)		
Line of Immunotherapy				0.176	0.675
First-line	140 (89.74)	69 (90.79)	71 (88.75)		
Second-line or later	16 (10.26)	7 (9.21)	9 (11.25)		
Prior Gastric Surgery				1.173	0.279
No	91 (58.33)	41 (53.95)	50 (62.50)		
Yes	65 (41.67)	35 (46.05)	30 (37.50)		
Prior Chemotherapy				4.996	0.025
No	98 (62.82)	41 (53.95)	57 (71.25)		
Yes	58 (37.18)	35 (46.05)	23 (28.75)		
Prior Targeted Therapy				5.255	0.022
No	130 (83.33)	58 (76.32)	72 (90.00)		
Yes	26 (16.67)	18 (23.68)	8 (10.00)		
History of Liver Radiotherapy				0.003	0.954
No	151 (96.79)	73 (96.05)	78 (97.50)		
Yes	5 (3.21)	3 (3.95)	2 (2.50)		
Immunotherapy Drug				0.238	0.993
Camrelizumab	41 (26.28)	19 (25.00)	22 (27.50)		
Tislelizumab	34 (21.79)	17 (22.37)	17 (21.25)		
Sintilimab	31 (19.87)	15 (19.74)	16 (20.00)		

Table 1. Continued...

Variables	Total (n=156)	irAEs group (n=76)	Non-irAEs group (n=80)	χ^2	*p*
Nivolumab	17 (10.90)	8 (10.53)	9 (11.25)		
Toripalimab	33 (21.15)	17 (22.37)	16 (20.00)		
Immunotherapy + Chemotherapy				4.917	0.027
No	32 (20.51)	10 (13.16)	22 (27.50)		
Yes	124 (79.49)	66 (86.84)	58 (72.50)		
Immunotherapy + Radiotherapy				0.381	0.537
No	138 (88.46)	66 (86.84)	72 (90.00)		
Yes	18 (11.54)	10 (13.16)	8 (10.00)		
Immunotherapy Combined with Targeted Therapy				5.860	0.015
No	118 (75.64)	51 (67.11)	67 (83.75)		
Yes	38 (24.36)	25 (32.89)	13 (16.25)		
History of Hypertension				1.693	0.193
No	118 (75.64)	54 (71.05)	64 (80.00)		
Yes	38 (24.36)	22 (28.95)	16 (20.00)		
History of Hepatitis				0.050	0.822
No	145 (92.95)	71 (93.42)	74 (92.50)		
Yes	11 (7.05)	5 (6.58)	6 (7.50)		
History of Diabetes				2.282	0.131
No	134 (85.90)	62 (81.58)	72 (90.00)		
Yes	22 (14.10)	14 (18.42)	8 (10.00)		
Smoking History				4.706	0.030
No	113 (72.44)	49 (64.47)	64 (80.00)		
Yes	43 (27.56)	27 (35.53)	16 (20.00)		
Alcohol History				0.541	0.462
No	113 (72.44)	53 (69.74)	60 (75.00)		
Yes	43 (27.56)	23 (30.26)	20 (25.00)		

Logistic regression analysis of irAEs related factors of patients

Univariate logistic regression indicated that age≥70 years (OR=2.230, *p*=0.017), BMI≥25 kg/m² (OR=2.253, *p*=0.030), prior chemotherapy (OR=2.116, *p*=0.026), prior targeted therapy (OR=2.793, *p*=0.026), the current treatment regimen being immunotherapy combined with chemotherapy (OR=2.503, *p*=0.030), immunotherapy combined with targeted therapy (OR=2.526, *p*=0.017), and a history of smoking (OR=2.204, *p*=0.032) were all potential risk factors for the occurrence of irAEs. See Table 2.

Multivariate logistic regression confirmed that age≥70 years (OR=2.615, *p*=0.022), BMI≥25 kg/m² (OR=5.791, *p*<0.001), prior chemotherapy (OR=4.954, *p*<0.001), prior targeted therapy (OR=5.532, *p*=0.003), immunotherapy combined with chemotherapy (OR=5.456, *p*=0.002), immunotherapy combined with targeted therapy (OR=2.850, *p*=0.031), and a history of smoking (OR=3.224, *p*=0.008) were all independent risk factors for the development of irAEs in patients with AGC. See Table 3.

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Table 2. Univariate Logistic Regression

Variables	*β*	*S.E*	*Z*	*p*	OR (95% CI)
Age (≥ 70 years)	0.802	0.337	2.378	0.017	2.230 (1.151-4.321)
BMI (≥ 25 kg/m²)	0.812	0.375	2.167	0.030	2.253 (1.081-4.698)
Prior chemotherapy	0.749	0.338	2.219	0.026	2.116 (1.092-4.100)
Prior targeted therapy	1.027	0.460	2.232	0.026	2.793 (1.134-6.882)
Immunotherapy + chemotherapy	0.918	0.422	2.176	0.030	2.503 (1.095-5.721)
Immunotherapy + targeted therapy	0.927	0.389	2.381	0.017	2.526 (1.178-5.417)
Smoking history	0.790	0.368	2.146	0.032	2.204 (1.071-4.536)

Table 3. Multivariate Logistic Regression

Variables	*β*	*S.E*	*Z*	*p*	OR (95% CI)
Age (≥ 70 years)	0.961	0.419	2.292	0.022	2.615 (1.149-5.948)
BMI (≥ 25 kg/m²)	1.756	0.479	3.666	< 0.001	5.791 (2.265-14.809)
Prior chemotherapy	1.600	0.446	3.585	< 0.001	4.954 (2.065-11.881)
Prior targeted therapy	1.710	0.584	2.927	0.003	5.532 (1.759-17.391)
Immunotherapy + chemotherapy	1.697	0.544	3.121	0.002	5.456 (1.880-15.832)
Immunotherapy + targeted therapy	1.047	0.484	2.161	0.031	2.850 (1.102-7.365)
Smoking history	1.171	0.441	2.655	0.008	3.224 (1.358-7.653)

Evaluation of Therapeutic Effect and Prognosis of patients

Compared to the non-irAEs group, the irAEs group demonstrated superior ORR (38.16% vs. 20.00%; p=0.012) and DCR (80.26% vs. 66.25%; p=0.049). A detailed breakdown revealed a significantly higher proportion of patients achieving a PR (34.21% vs. 18.75%; p=0.028) and a lower proportion with PD (19.74% vs. 33.75%; p=0.049) in the irAEs group. No significant differences were observed for CR or SD (p>0.05). See Table 4.

PFS Comparison

The Kaplan-Meier survival curve (Figure 3) visually demonstrates the superior PFS benefit for patients in the irAEs group. According to the log-rank test, the difference in PFS was statistically significant (χ^2=8.538, p=0.004). As shown in Table 5, the irAEs group exhibited a superior median PFS of 8.0 months (95% CI: 6-10) versus 5.0 months (95% CI: 4-7) in the non-irAEs group, with a HR of 0.635 (95% CI: 0.452-0.891), indicating a 36.5% lower risk of progression.

Table 4. Therapeutic effect

Therapeutic effect	Total (n=156)	irAEs group (n=76)	Non-irAEs group (n=80)	χ^2	*P*
CR	4 (2.56)	3 (3.95)	1 (1.25)	0.312	0.576
PR	41 (26.28)	26 (34.21)	15 (18.75)	4.808	0.028
SD	69 (44.23)	32 (42.11)	37 (46.25)	0.271	0.602
PD	42 (26.92)	15 (19.74)	27 (33.75)	3.89	0.049
ORR	45 (28.85)	29 (38.16)	16 (20.00)	6.261	0.012
DCR	114 (73.08)	61 (80.26)	53 (66.25)	3.890	0.049

Table 5. PFS Comparison

PFS	irAEs group (n=76)	Non-irAEs group (n=80)
n (%)	14 (18.42)	6 (7.50)
Mean (95%CI)	9.75 (8.06-11.44)	6.65 (5.34-7.96)
Median (95%CI)	8 (6-10)	5 (4-7)
HR (95%CI)	0.635 (0.452-0.891)	1.576 (1.122-2.213)
Log-rank χ^2	8.538	
p	0.004	

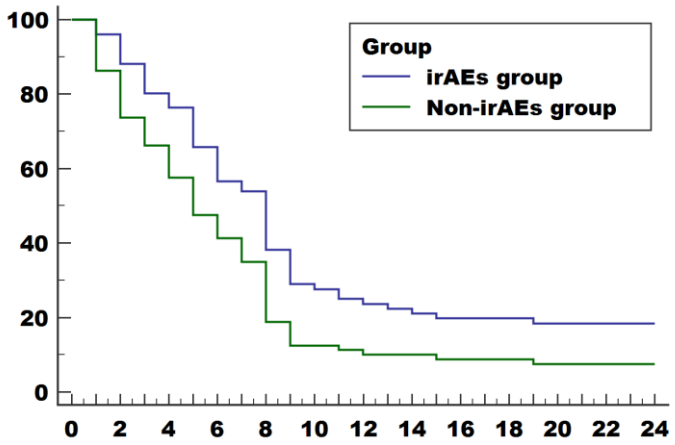

Figure 3. Kaplan-Meier curve of PFS for the patient

OS Comparison

The Kaplan-Meier curve (Figure 6) showed a clear separation between the irAEs and non-irAEs groups, with markedly superior OS in patients who experienced irAEs (log-rank test: χ^2=12.630, p<0.001). In the irAEs group, median OS was 15.0 months (95% CI: 15-20) compared with only 10.0 months in the non-irAEs group (95% CI: 8-11) (Table 7). HR analysis further indicated a 47.5% reduction in the risk of death among patients with irAEs (HR = 0.525, 95% CI: 0.357-0.772).

3.7 Landmark Analysis for Immortal Time Bias

To mitigate immortal time bias, a landmark analysis at 3 months was conducted. After excluding 12 patients who died, experienced disease progression or were lost before landmark, 114 patients were included (irAE group: n=61, non-irAE group: n=53). Consistent with the primary analysis, the irAE group showed significantly longer PFS (HR=0.680, 95% CI: 0.450-1.026; p=0.036) and OS (HR=0.598, 95% CI: 0.363-0.986; p=0.031) compared to the non-irAE group. These results suggest that the survival advantage associated with irAEs is not solely attributable to immortal time bias.

3.8 Corticosteroid Use for irAE Management

Among the 76 irAE patients, 31 (40.79%) received systemic corticosteroids. Their outcomes (ORR, PFS, OS) were comparable to irAE patients not requiring corticosteroids (all p>0.05), suggesting the survival benefit linked to irAEs was not negated by this immunosuppression.

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Table 6. OS Comparison

OS	irAEs group (n=76)	Non-irAEs group (n=80)
n (%)	31 (40.79)	19 (23.75)
Mean (95%CI)	16.80 (15.28-18.32)	12.25 (10.73-13.77)
Median (95%CI)	15 (15-20)	10 (8-11)
HR (95%CI)	0.525 (0.357-0.772)	1.907 (1.296-2.805)
Log-rank χ^2	12.630	
P	< 0.001	

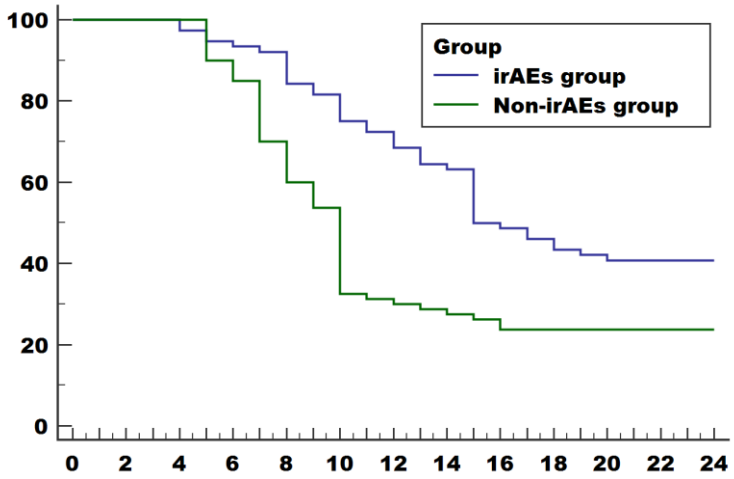

Figure 4 Kaplan-Meier curve of OS for the patient

DISCUSSION

ICIs have revolutionized the treatment of AGC, now representing a cornerstone of therapy for specific patient populations.[22] However, with their increasingly widespread clinical application, the irAEs they trigger have also garnered growing attention.[23] Mechanistically, the development of irAEs is a direct consequence of therapeutic-induced immune system activation, which has prompted in-depth investigation into the potential association between their occurrence and anti-tumor efficacy.[24] Immunologically, ICIs work by blocking inhibitory signals that normally maintain peripheral tolerance, thereby reinvigorating tumor-specific T cells. This same loss of immune regulation can also unleash self-reactive T cells that recognize antigens expressed in normal tissues, leading to irAEs. Emerging evidence suggests shared pathways between tumor rejection and autoimmunity, such as molecular mimicry, epitope spreading, and bystander activation of pre-existing autoreactive lymphocytes. These mechanisms may explain why a robust anti-tumor response often coincides with irAEs, reflecting a state of generalized immune activation. Whether the emergence of irAEs can predict better treatment outcomes has become one of the core scientific questions in the field of cancer

immunotherapy.[25-27] Therefore, this study, grounded in real-world data, aims to conduct a more in-depth and systematic investigation of this critical scientific question.

The overall incidence of irAEs was 48.72% in this study. The most common types were endocrine toxicity, dermatologic toxicity, and gastrointestinal toxicity, and the vast majority were mild (Grade 1-2) adverse events. Patients who developed irAEs experienced significantly better efficacy outcomes, including higher ORR and DCR, as well as longer PFS and OS. This correlation in AGC aligns with established trends in other malignancies such as melanoma and renal cell carcinoma, lending further credence to a shared underlying immunological mechanism.[28] This hypothesis posits that the occurrence of irAEs is not an isolated drug-induced toxicity but rather a clinical manifestation of the successful reactivation of the body's immune system.[29] This systemic immune activation, while effectively attacking tumor cells, may concurrently exert off-target or bystander effects on normal host tissues. This is essentially caused by a breach of immune tolerance to self-antigens, which in turn leads to inflammatory tissue damage.[30-32] Therefore, the emergence of irAEs indicates that the patient has mounted an effective immune response to ICI therapy. The generalized nature of this response means that it can not only eliminate tumor cells but may also inadvertently damage healthy tissues. This association suggests that clinicians, particularly when encountering low-grade irAEs, should consider them as a positive signal of treatment efficacy rather than merely a therapeutic obstacle. Consequently, under the condition of close monitoring and proactive management, maintaining effective immunotherapy should be prioritized to maximize the potential for survival benefit for the patient.

This study found that endocrine, dermatologic, and gastrointestinal toxicities were the most common, which is broadly similar to reports in other tumor types, although the ranking and proportions of specific toxicities may differ.[33, 34] This variation may be attributable to differences in the genetic background, tumor microenvironment, and immune status associated with different tumor types. Notably, the vast majority of irAEs in this study were mild-to-moderate events, with a low incidence of severe irAEs and no treatment-related deaths. In a real-world setting, standardized management strategies help make ICI therapy safety generally manageable. For the patient population with AGC, which has a poor prognosis, this suggests that most patients can derive continued benefit from immunotherapy within a tolerable range of toxicity.

Our multivariate analysis identified patients over 70 as more prone to irAEs. This aligns with findings from Baldini et al.[35]. The association is biologically plausible due to age-related immunosenescence, which fosters a state of chronic low-grade inflammation and cellular dysfunction.[36] When treated with ICIs, the drugs may disrupt this pre-existing immune balance, further activating T cells and enhancing the inflammatory response, leading to an excessive immune reaction and an increased risk of irAEs. BMI $\geq$ 25 kg/m² was associated with an increased risk of irAEs, potentially due to obesity-induced chronic low-grade inflammation and immune microenvironment remodeling. A meta-analysis confirmed a high BMI as a significant risk factor for irAEs, associated with an OR of 2.62.[37] Based on this, Cortellini et al.[38] hypothesized that obese patients, due to their inherent pro-inflammatory state, are more susceptible to immune dysregulation after receiving immunotherapy, leading to irAEs. The notably high odds ratio for BMI $\geq$25 kg/m² (OR=5.791) in the multivariate logistic regression model should be interpreted with caution. While obesity is biologically plausible as a risk factor for irAEs due to chronic inflammation and immune dysregulation, the magnitude of the effect may be influenced by model overfitting or collinearity with other included variables, such as prior therapies or combination regimens. The sample size, though sufficient for overall analysis, may be limited for robust multivariable modeling when numerous predictors are considered. Future studies with larger cohorts are needed to validate this association and to adjust for potential confounding through more comprehensive modeling approaches.

Prior or concurrent chemotherapy or targeted therapy increased the risk of irAEs. The mechanism is primarily related to treatment-induced tissue damage, exposure of self-antigens, and remodeling of the immune microenvironment. While killing tumor cells, chemotherapy and targeted drugs can cause damage to normal tissues and release cryptic self-antigens, providing an antigenic basis for subsequent autoimmune-like reactions during immunotherapy. The immunomodulatory effects of chemotherapy and the improvement of the tumor microenvironment by anti-angiogenic drugs, while enhancing efficacy, also

amplify the intensity of immune system activation, thereby increasing the probability of irAE occurrence.[39] A history of smoking is a risk factor for irAEs, primarily associated with systemic chronic inflammation and immune system disruption induced by tobacco exposure. Nicotine and other tobacco constituents adversely affect immune function. These substances elevate the risk of systemic inflammation and infection and can trigger inflammatory over-activation during ICI therapy, thereby increasing irAE incidence.[40] The identification of these risk factors enables clinicians to perform a preliminary assessment of a patient's risk for developing irAEs before treatment. This allows for closer monitoring and preventive education for high-risk individuals, which is crucial for implementing personalized irAE management strategies. Patients receiving combination therapy had a higher incidence of irAEs in our study. This raises the question of whether the observed survival benefit is attributable to irAEs per se, or to the greater efficacy of combined treatments. While our analysis cannot fully disentangle these factors, the consistent association between irAEs and improved outcomes across malignancies, including in ICI monotherapy studies, suggests that irAEs reflect an immune-active state conducive to antitumor response. Future studies should stratify by treatment regimen to clarify this relationship.

The findings of this study offer several implications for the clinical practice of immunotherapy in AGC. On one hand, the occurrence of an irAE can serve as a potential marker of treatment efficacy. Particularly when mild-to-moderate irAEs arise, effective immunotherapy should not be hastily discontinued. Instead, treatment should be continued under close monitoring with appropriate management of the adverse event. In clinical decision-making, when a patient develops manageable irAEs, physicians should feel more confident in maintaining immunotherapy. They should also engage in thorough communication with the patient, explaining the possibility that the irAE is a positive reflection of treatment efficacy, in order to improve patient adherence. On the other hand, identifying high-risk populations for irAEs helps in the proactive development of preventive and monitoring strategies, thereby optimizing patient management. For patients with multiple risk factors, consideration should be given to enhancing pre-treatment patient education, increasing the frequency of monitoring during treatment, and strengthening post-treatment follow-up.

First, as a single-center, retrospective study, our results may be subject to selection and information bias. For instance, the diagnosis and grading of irAEs might have a degree of subjective variability depending on the judgment of individual attending physicians. Additionally, the generalizability of our findings may be limited by ethnic, geographic, and healthcare system factors. Our cohort consisted exclusively of Chinese patients, whose genetic background, lifestyle, and tumor biology may differ from those of other populations. Regional variations in immunotherapy accessibility, standard treatment protocols, and irAE management practices could further influence the incidence and outcomes of irAEs. Therefore, our results should be validated in multiethnic and multinational cohorts to confirm their broader applicability. Second, although the sample size is moderate for this field and the post-hoc power analysis indicated sufficient statistical power, it remains limited for analyzing certain less common irAE subtypes or for conducting more complex subgroup analyses. Third, there was diversity in the types of ICI drugs and combination regimens received by patients in the cohort. While this heterogeneity accurately reflects real-world clinical practice, it may also introduce confounding effects on the results. Specifically, the sample size was insufficient to conduct meaningful subgroup analyses based on individual ICI agents to assess potential outcome differences. A key limitation is the lack of systematic data on important predictive biomarkers such as PD-L1 CPS, MSI status, and HER2 status. Their absence limits our ability to assess potential confounding effects on the observed relationship between irAEs and survival. The follow-up period of this study was relatively limited, which may be insufficient for assessing very late-onset irAEs or their impact on the long-term survival of patients. Therefore, future research should be conducted in more rigorously designed prospective, multi-center, large-sample cohorts with standardized data collection and should integrate molecular biomarker analysis to more precisely elucidate the complete role and underlying mechanisms of irAEs in the immunotherapy of AGC. Furthermore, while we identified baseline factors associated with irAE development, the sample size limited our ability to perform a robust multivariable Cox regression analysis to adjust for all these factors simultaneously when assessing the survival impact of irAEs. Future studies with larger cohorts are warranted to confirm the independent prognostic value of irAEs using such

comprehensive adjusted models. The small number of patients who received second-line or later immunotherapy precluded meaningful stratified survival analysis by treatment line. Additionally, the low frequency of high-grade irAEs precluded a meaningful analysis of survival stratified by irAE severity, which represents an important area for future larger-scale studies.

This real-world study confirms that, in AGC patients receiving ICI therapy, the occurrence of irAEs correlates with improved therapeutic response and survival. It also identifies clinical factors associated with irAE development, thereby supporting their utility as an efficacy biomarker and offering clinical guidance for patient management and prognostic assessment. However, management of irAEs, including decisions to continue or hold immunotherapy, should follow current clinical guidelines and be tailored to individual patient circumstances.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of Gansu Provincial Cancer Hospital (Approval No.: A202510280143).

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

AI ASSISTANCE DISCLOSURE

No AI tools were used in any part of this study or manuscript preparation.

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