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Impact of irae characteristics on efficacy of consolidative immunotherapy following chemoradiotherapy in locally advanced NSCLC

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Abstract

Background Consolidative PD-L1 inhibitors after concurrent chemoradiotherapy (cCRT) have become standard care in locally advanced non-small cell lung cancer (LA-NSCLC). However, the correlation between immune-related adverse event (irAE) characteristics and patient outcomes remains unclear.

Methods This retrospective study enrolled LA-NSCLC patients who received consolidative PD-L1 inhibitors after CRT at four cancer centers. Patients who received CRT alone were also included for comparison. Associations between irAE characteristics, frequency, timing, affected systems, and severity, and progression-free survival (PFS) and overall survival (OS) were assessed. Tumor immune microenvironment (TIME) features were analyzed to identify subpopulations at higher risk of severe irAEs.

Results Among 107 patients, 59 (55.1%) developed irAEs; 89.8% were grade 1–2 and 10.2% grade 3–4. Patients with irAEs had significantly longer PFS than those without. Late-onset, single-system, endocrine, and mild irAEs predicted better PFS. In contrast, patients with severe irAEs had worse survival than those without ICI consolidation. TIME analysis revealed that severe irAEs were associated with higher $CD103^+CD8^+$ T cells infiltration. A > 1.545% cutoff for $CD103^+CD8^+$ T cells may help identify patients less likely to benefit from PD-L1 inhibitor consolidation.

Background

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. Non-small-cell lung cancer (NSCLC) represents approximately 80% of all lung cancers, and over one-third of NSCLC cases are diagnosed at the locally advanced (LA) stage III [2]. Definitive concurrent or sequential chemoradiotherapy (CRT) was the standard of care for unresectable LA-NSCLC in the pre-immunotherapy era. However, the consolidation of programmed death-ligand 1 (PD-L1) inhibitor durvalumab after CRT has demonstrated sustained survival benefits in the PACIFIC trials [3, 4], rapidly establishing a new standard

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Conclusions Occurrence of irAEs, particularly late-onset, single-system, or grade 1–2 correlated with greater benefit from consolidative PD-L1 inhibitors in LA-NSCLC. Conversely, severe irAEs predict poorer survival, even compared to no ICI consolidation. Elevated $CD103^+CD8^+$ T cell infiltration may serve as a biomarker to identify patients at risk of severe irAEs who may not benefit from immunoconsolidation therapy.

Keywords Immune-related adverse events, Locally advanced non-small cell lung cancer, Survival, Consolidative immunotherapy, Tumor immune microenvironment

of treatment for these patients. Subsequently, sugemalimab was approved in China based on similar survival benefits observed in the GEMSTONE-301 trial [5].

Immune checkpoint inhibitors (ICIs) exert anti-tumor efficacy by reactivating the immune system against cancers [6]. However, overactivation of the immune microenvironment can induce autoimmunity in specific tissues and organs, resulting in immune-related adverse event (irAE) [7–9]. Although the exact pathophysiological mechanisms remain unclear, previous studies have identified a positive correlation between irAE incidence and treatment outcomes, particularly in metastatic melanoma, NSCLC, and small cell lung cancer [10–13]. However, a meta-analysis indicated that irAEs are unsuitable as surrogate markers for immunotherapy efficacy [14] due to their complexity, including different grades, timing, affected systems, and irAE types. Additionally, some serious irAEs, such as immune-related pneumonia, myocarditis [15], hematologic irAEs [16], and cutaneous irAEs [17], can be fatal [18]. Given that irAE development after chemoradiotherapy combined with immunotherapy is more complex than with immunotherapy alone, it is crucial to clarify the predictive value of irAE characteristics for ICI efficacy in LA-NSCLC.

The characteristics of the tumor immune microenvironment (TIME) are closely associated with the efficacy of ICIs and the occurrence of irAEs [19]. Tissue-resident memory T cells (TRM), marked by CD103 expression, depend on interactions between integrin αEβ7 and epithelial E-cadherin to facilitate their infiltration and retention within tumor epithelial regions [20]. These cells undergo early expansion during ICI therapy, recognize tumor neoantigens, and are strongly correlated with clinical responses [21]. Following ICI treatment, reactivated $CD103^+CD8^+$ T cells in tumors release pro-inflammatory cytokines such as IFNγ and TNFα, which contribute to the development of irAEs in healthy tissues [22]. Severe irAEs, such as grade 3–5 events, may lead to a worse prognosis in several studies [23, 24]. Therefore, investigating TIME features in patients with severe irAEs—including the infiltration patterns of T cells, TRM, and macrophages—may help predict the occurrence of severe irAEs.

Here, we investigate the correlation between irAEs and the efficacy of PD-L1 inhibitor consolidation after CRT in LA-NSCLC. We also explored the TIME features of patients who experienced severe irAEs and sought to identify the sub-population that may not benefit from immune consolidation.

Methods

Patients selection and data collection

LA-NSCLC patients who received consolidative PD-L1 inhibitors following concurrent CRT were retrospectively enrolled from 4 cancer institutions in China (Shandong Cancer Hospital, Shandong Provincial Hospital, Qilu Hospital of Shandong University, and Affiliated Hospital of Qingdao University) between January 2019 and December 2022. Previous studies have suggested that severe irAEs may adversely affect patient prognosis. The study also included LA-NSCLC patients who did not undergo immunotherapy consolidation following concurrent CRT, ensuring balanced baseline characteristics with the previous cohort. Inclusion Criteria: (1) Histologically or cytologically confirmed NSCLC; (2) Clinically staged as unresectable stage III disease confirmed by PET-CT, EBUS/EUS, mediastinoscopy, or pathological examination; (3) Received immunotherapy consolidation as monotherapy following concurrent CRT; (4) Received only concurrent CRT; (5) Age ≥ 18 years. Exclusion Criteria: (1) Received immunotherapy combined with chemoradiotherapy or immunotherapy combined with consolidation therapy after CRT; (2) Undergone immunotherapy consolidation after disease progression following CRT; (3) Received consolidation therapy with PD-1 inhibitors; (4) Presence of other active malignancies or concurrent systemic cancers. Based on the occurrence of irAEs, patients who received PD-L1 inhibitor therapy following CRT were further divided into irAE versus no irAE groups.

The clinicopathological information of these patients, including age, gender, smoking status, Eastern Cooperative Oncology Group (ECOG) score, histological type, TNM staging, treatment duration, and response, was collected. We also recorded the irAE features of immunoconsolidation therapy patients during ICI treatment, including the timing of occurrence, types, grades, and management.

Definition and assessment of IrAEs

IrAEs were defined as adverse events with a potential immunologic basis that required close monitoring

or treatment. The irAEs were classified as early-onset (≤3 months) [25] and late-onset (>3 months) based on the onset time (duration from the first ICI administration to the first occurrence of irAEs). IrAEs involving only 1 organ were defined as "single-organ irAEs," and those involving ≥2 organs were defined as "multi-organ irAEs." The organ-specific irAEs included pneumonitis, thyroid dysfunction, hepatic toxicity, hematologic toxicity, skin toxicity, diarrhea/colitis, myocarditis, pain, and hydronephrosis. In this study, the incidence of irAEs was determined through routine assessments and physician documentation in medical records. Physicians evaluated the potential association of irAEs with ICIs using diagnostic methods, including pathological analysis, specialist consultations, and laboratory testing. The final conclusions regarding irAE causality were documented in the patients' medical charts. The grade of each irAE was evaluated using the Common Terminology Criteria for Adverse Events version 5.0, ranging from grade 1 to grade 5.

The response to ICIs was evaluated by radiography and laboratory examination every 6–8 weeks, according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Progression-free survival (PFS) was defined as the period from initiating anti-PD-L1 monotherapy to disease progression, death, or the last follow-up. Overall survival (OS) was calculated from the first anti-PD-L1 administration to death due to any cause or the last follow-up. The time of last visit for enrolled patients was October 27, 2023.

Multiplex Immunofluorescence (mIF) detection

Paraffin-embedded tissue sections were collected from patients before first-line treatment, and the percentages of immune cell subsets, including $CD4^+$, $CD8^+$, $FOXP3^+$, $CD103^+$, $CD68^+$, and $CD163^+$ cells, were detected by mIF. mIF staining was performed using a 7-color fluorescence immunohistochemistry kit (10268100010; Panovue, China). Briefly, Sect. (4 μm thick) were obtained from formalin-fixed paraffin-embedded lung cancer tissues. After deparaffinization and rehydration in a descending ethanol series, Tris-EDTA buffer (pH 9) or citrate buffer (pH 6) was used for antigen retrieval in a microwave oven. After protein blocking with 1% bovine serum albumin, mIF staining was performed sequentially using the primary antibody and the corresponding secondary horseradish peroxidase-conjugated antibody against mouse or rabbit immunoglobulins (Absin, Shanghai, China). The primary antibodies used were as follows: Pan-cytokeratin (1:500, Abcam, ab7753), CD4 (1:2000, Abcam, ab183685), Foxp3 (1:500, Abcam, ab215206), CD103 (1:200, Abcam, ab237728), CD8 (1:400, CST, 85336), CD68 (1:400, CST, 76437), CD163 (1:500, CST, 93498). The slides were then incubated with different Opal fluorophores (1:100) diluted in 1×Plus Amplification Diluent (Absin, Shanghai, China). All fluorescently labeled slides were scanned using an OLYMPUS VS200 microscope (Olympus, Tokyo, Japan) at 40 × magnification with appropriate exposure times, and 5 representative regions were randomly selected. The percentage of different cell subsets was determined as the ratio of positively stained cells to all nucleated cells. All images were independently reviewed by two professional senior pathologists before data export, and at least 20% of each visual field was reviewed.

The frequencies of the following cell subsets were calculated: $CD4^+$, $CD8^+$, $CD4^+FOXP3^+$(Tregs), $CD103^+CD8^+$ (Tissue-resident memory T cells), $GZMB^+CD8^+$ (cytotoxic $CD8^+$T cells), $CD68^+$, and $CD163^+$ (M2-like macrophages).

Statistical analysis

Median OS and PFS were calculated using the Kaplan-Meier method and the Log-rank test, respectively. For data conforming to a normal distribution, the commonly employed statistical method was the independent sample t-test. Conversely, non-parametric testing was utilized when the data did not follow a normal distribution. Statistical analysis was performed using SPSS 26.0 software. Positive cell percentage = (number of positive cells/ total number of nucleated cells) *100%. Plotting scale: 50 μm. (two-sided unpaired t-test, ns not significant, $^*p < 0.05$)

Results

Clinical characteristics

The baseline clinical characteristics of the 143 patients were detailed in Table 1. Of these, 107 patients were treated with ICI and 36 did not receive ICI therapy. Among them, the median age was 63 years (range 56–67), 90.2% were male, and 73.4% had a smoking history. The ECOG PS was 0–1 in 111 patients (77.6%) and 2 in 32 patients (22.4%). Lung squamous carcinomas accounted for 64.30% ($n = 92$), and non-squamous carcinomas accounted for 35.7% ($n = 51$). The patients who received PD-L1 inhibitor therapy following CRT were further categorized into irAEs group ($n = 59$) and no irAE group ($n = 48$). The baseline characteristics were generally balanced between the three groups (Table 1).

The incidence, spectrum, and management of IrAEs

Overall, a total of 59 patients (55.1%) developed 74 irAEs, where 44 patients presented with single-organ irAEs and 15 patients presented with multi-organ irAEs involving 2 to 5 organs. Pneumonitis combined with thyroid dysfunction ($N = 6$, 40.0%), pneumonitis combined with hepatic toxicity ($N = 3$, 20.0%), and hepatic toxicity combined with thyroid dysfunction ($N = 2$, 13.3%) were the most common multisystem irAEs. In addition,

Table 1 Baseline characteristics of patients with versus without IrAEs

Variables	All patients (*n* = 143)	No irAE (*n* = 48)	irAEs (*n* = 59)	No ICIs (*n* = 36)	*P* value
Age (y), median (range)	63 (56–67)	62.5 (53–66)	64 (56–66)	64 (52–70)	0.644
Gender (% male)	129 (90.2)	44 (91.7)	52 (88.1)	33 (91.7)	0.783
Smoking (%)	105 (73.4)	32 (66.7)	45 (76.3)	28 (77.8)	0.424
ECOG PS (%)					0.352
0 ~ 1	111 (77.6)	34 (70.8)	47 (79.7)	30 (83.3)	
2	32 (22.4)	14 (29.2)	12 (20.3)	6 (16.7)	
Histology					0.997
Squamous carcinoma	92 (64.3)	31 (64.6)	38 (64.4)	23 (63.9)	
Non-Squamous carcinoma	51 (35.7)	17 (35.4)	21 (35.6)	13 (36.1)	
Stage					0.751
IIIa	60 (42.0)	20 (41.7)	25 (42.4)	15 (41.7)	
IIIb	61 (42.7)	18 (37.5)	27 (45.8)	16 (44.4)	
IIIc	22 (15.4)	10 (20.8)	7 (11.9)	5 (13.9)	
T					0.483
T1-3	93 (65.0)	28 (58.3)	40 (67.8)	25 (69.4)	
T4	50 (35.0)	20 (41.7)	19 (32.2)	11 (30.6)	
N					0.542
N0-2	97 (67.8)	34 (70.8)	37 (62.7)	26 (72.2)	
N3	46 (32.2)	14 (29.2)	22 (37.3)	10 (27.8)	
Immunotherapy start time					0.679
≤ 6week	72(56.8)	31 (64.6)	41 (69.5)	-	
> 6week	35 (24.5)	17 (35.4)	18 (30.5)	-	
Immunotherapy cycle	8 (3–14)	6 (3–9)	10 (5–18)		0.010
PD-L1expression					0.278
< 1%	8	3	5	0	
≥ 1%	16	4	9	3	
NA	119	41	45	33	

Abbreviations: Note: ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event

skin toxicity often occurred in combination with other adverse effects such as pain, hematologic toxicity, and hydroncus (see Supplementary Figure S1A in Additional file 1).

The median onset time of the first irAE was 2.3 (interquartile range 1.4–4.7) months. Of all irAEs, the earliest to occur were colitis (0.5 months) and skin toxicity (0.6 months) (see Supplementary Figure S1B in Additional file 1). No statistical difference was found in the onset time of first irAE in patients with single-system versus multisystem irAEs (2.3 vs. 3.5 months, $P = 0.74$) (see Supplementary Figure S1C in Additional file 1).

Most patients (53/59, 89.8%) exhibited irAEs of grade 1–2, and only 10.2% (6/59) had grade 3–4 irAEs. Pneumonitis was the most frequent irAE (30/74, 40.5%), followed by thyroid dysfunction (22/74, 29.7%), hepatic toxicity (12/74, 16.2%), hematologic toxicity (4/74, 5.4%), skin toxicity (3/74, 4.1%), and some other relatively uncommon irAEs. Thirty-eight (38/74, 51.4%) patients received systemic steroids due to irAEs, of whom 11 patients (9/74, 12.2%) permanently discontinued ICIs, but no patients died due to irAEs (Table 2).

Correlation of IrAEs with ICI efficacy

Association between overall IrAEs and patient survival

In the overall population, the consolidation of PD-L1 inhibitors after CRT prolonged PFS (22.57 months vs. 11.8 months, $p < 0.0001$; Fig. 1A) and OS ($p = 0.018$, Fig. 1B) compared with chemoradiotherapy alone. Patients were then divided into irAEs and no irAE groups according to the presence or absence of irAEs. Compared with patients who did not receive consolidation treatment, patients in both irAEs and no irAE groups displayed superior PFS and OS, while those with irAEs exhibited significantly prolonged median PFS (33.18 vs. 16.46 months, $p < 0.001$) and numerically longer median OS versus those without irAEs (Fig. 1C and D).

A multivariate COX regression analysis of PFS and OS was performed for all patients receiving consolidation

Table 2 IrAEs spectrum according to the involved organs

IrAEs	Median time of irAEs onset (range), months	Any grade (*N* = 59)	G 1–2 (*N* = 53)	G 3–4 (*N* = 6)	Systemic steroid (*N* = 24)
All irAEs	2.3(1.4–4.7)	74	68	6	24
Pneumonitis	2.5(1.5–7.2)	30 (40.5%)	27	3	20
Thyroi dysfunction	3.5(1.2–5.8)	22 (29.7%)	22	-	0
Hepatic toxicity	4.2(2.0-6.8)	12 (16.2%)	12	-	2
Hematologic toxicity	3.3(2.1–4.8)	4 (5.4%)	2	2	0
Skin toxicity	1.5(0.5–8.3)	3 (4.1%)	2	1	1
Diarrhea/colitis	0.5	1 (1.4%)	1	-	1
Pain	2.7	1 (1.4%)	1	-	0
Hydroncus	2.9	1 (1.4%)	1	-	0

irAEs, immune-related adverse events; G, grade. a) Skin toxicity includes pruritus, rash or both. Hepatic toxicity includes increased alanine aminotransferase or aspartate aminotransferase, bilirubin levels, and hepatitis. Hematologic toxicity included anemia, thrombocytopenia, and granulocytopenia

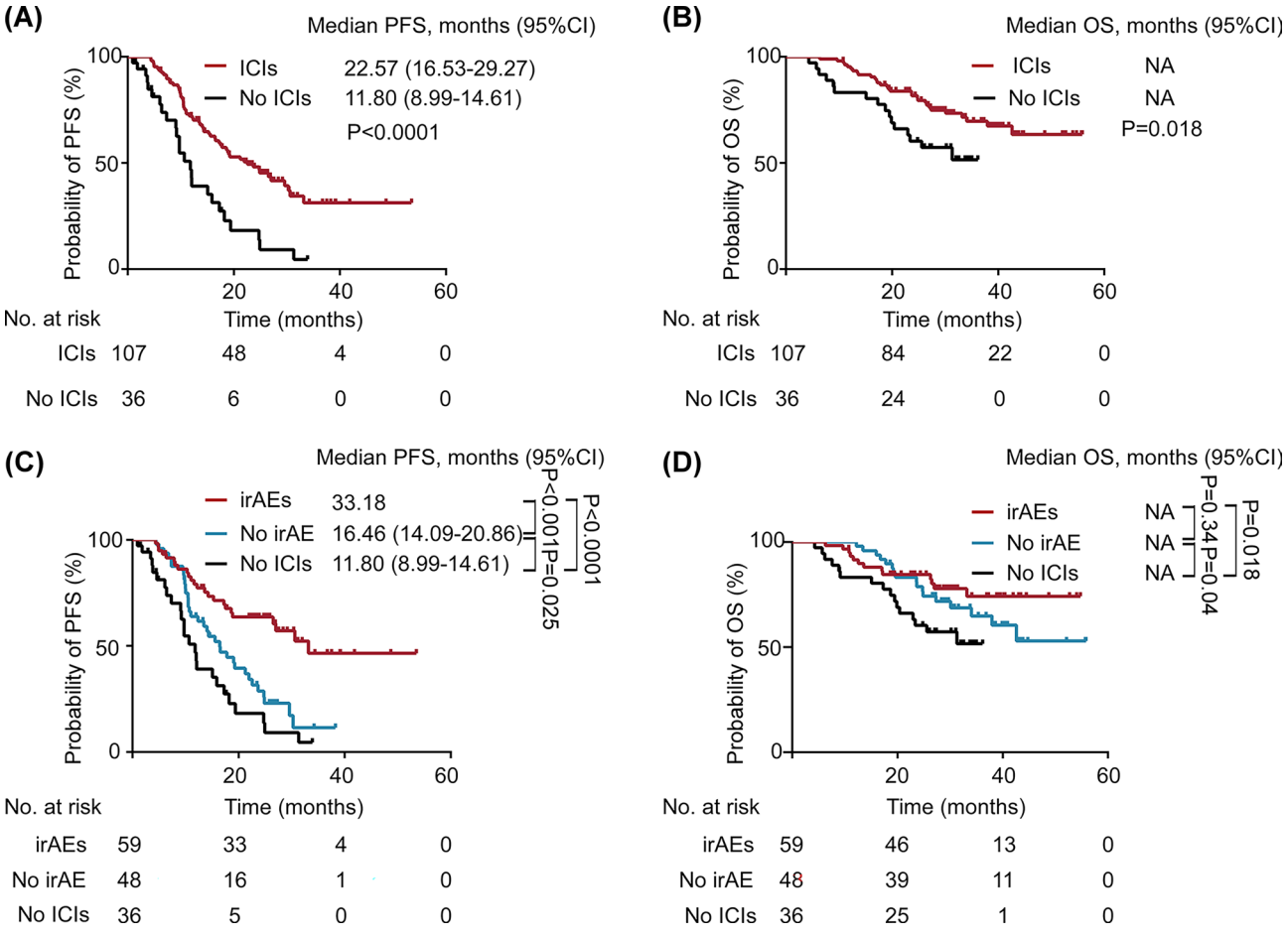

Fig. 1 The association between overall irAEs and patient survival. (**A** and **B**) PFS (**A**) and OS (**B**) in all LA-NSCLC patients treated with/ without ICIs following CRT; (**C** and **D**) PFS (**C**) and OS (**D**) in patients with/without irAEs and patients with no ICI treatment. PFS, progression-free survival. OS, overall survival. NA, not arrived

immunotherapy. The analysis incorporated indicators, including systemic steroid therapy and the number of immunotherapy cycles, to identify factors associated with patient prognosis. The results are presented in Supplementary Table S1 and Table S2 (Additional file 1). Univariate analysis revealed that the occurrence of irAEs (HR: 0.403; 95%CI: 0.237–0.683; $p < 0.001$), systemic steroid therapy (HR: 0.549; 95%CI: 0.309–0.977; $p < 0.05$), and more immunotherapy cycles (HR: 0.904; 95%CI: 0.864–0.946; $p < 0.001$) were all associated with longer PFS (see Supplementary Table S1 in Additional file 1). However, only more immunotherapy cycles was correlated with better OS (HR: 0.911; 95%CI: 0.851–0.976; $p < 0.01$) in univariate rather than in multivariate analysis (See Supplementary Table S2 in Additional file 1).

Impact of onset time of IrAEs on survival

Given that the development of irAEs predicts superior benefit from PD-L1 inhibitor consolidation, we next sought to explore how different irAE features affect ICI efficacy. We first analyzed patient outcomes based on the time of first irAE onset. We divided the irAEs into early-onset and late-onset groups. We found that patients with late-onset irAEs (30.62 vs. 16.46 months, $p = 0.001$) and early-onset irAEs ($p = 0.03$) had a longer median PFS compared to those without irAEs (Fig. 2A). The median OS for the above groups was not reached (Fig. 2B).

Impact of involved systems and organs of IrAEs on survival

Next, we analyzed patient survival based on multi-system and single-system irAE development. Compared with the no irAE group, patients with single-system irAEs (NA vs. 16.46 months, $p = 0.0006$), rather than those with multi-system irAEs, manifested a prolonged median PFS (Fig. 3A). Meanwhile, patients with single-system irAEs showed numerically better OS compared to those without irAEs (Fig. 3B). In addition to the number of involved systems, the involved organs of irAEs were also summarized and analyzed (Table 2). The development of endocrine system irAEs was significantly associated with better PFS and OS (Fig. 3C and D), while

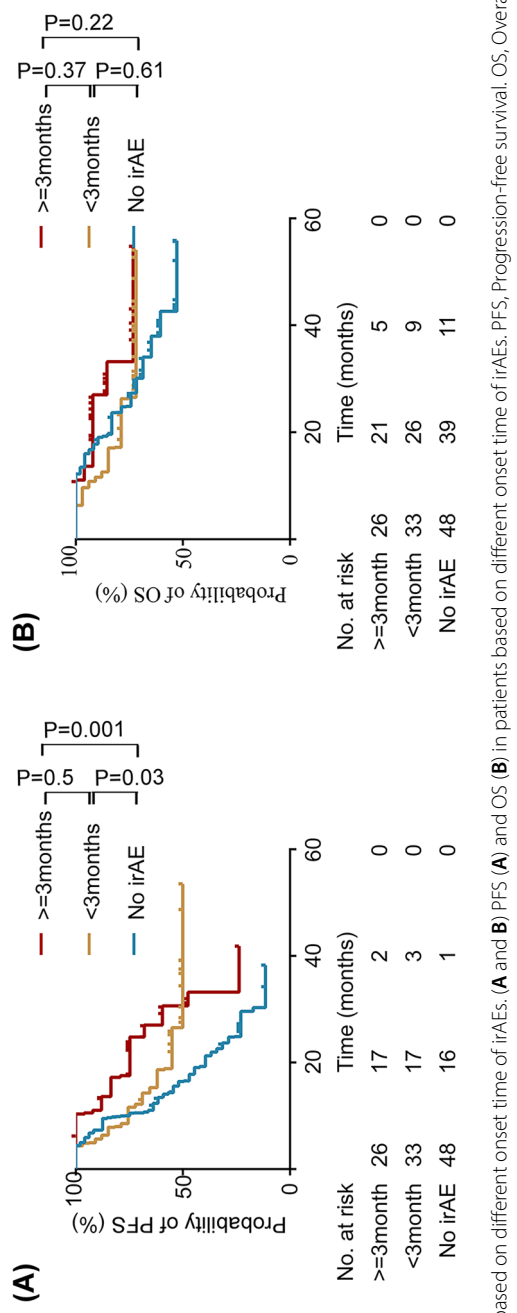

Fig. 2 Patients survival based on different onset time of irAEs. (**A** and **B**) PFS (**A**) and OS (**B**) in patients based on different onset time of irAEs. PFS, Progression-free survival. OS, Overall survival

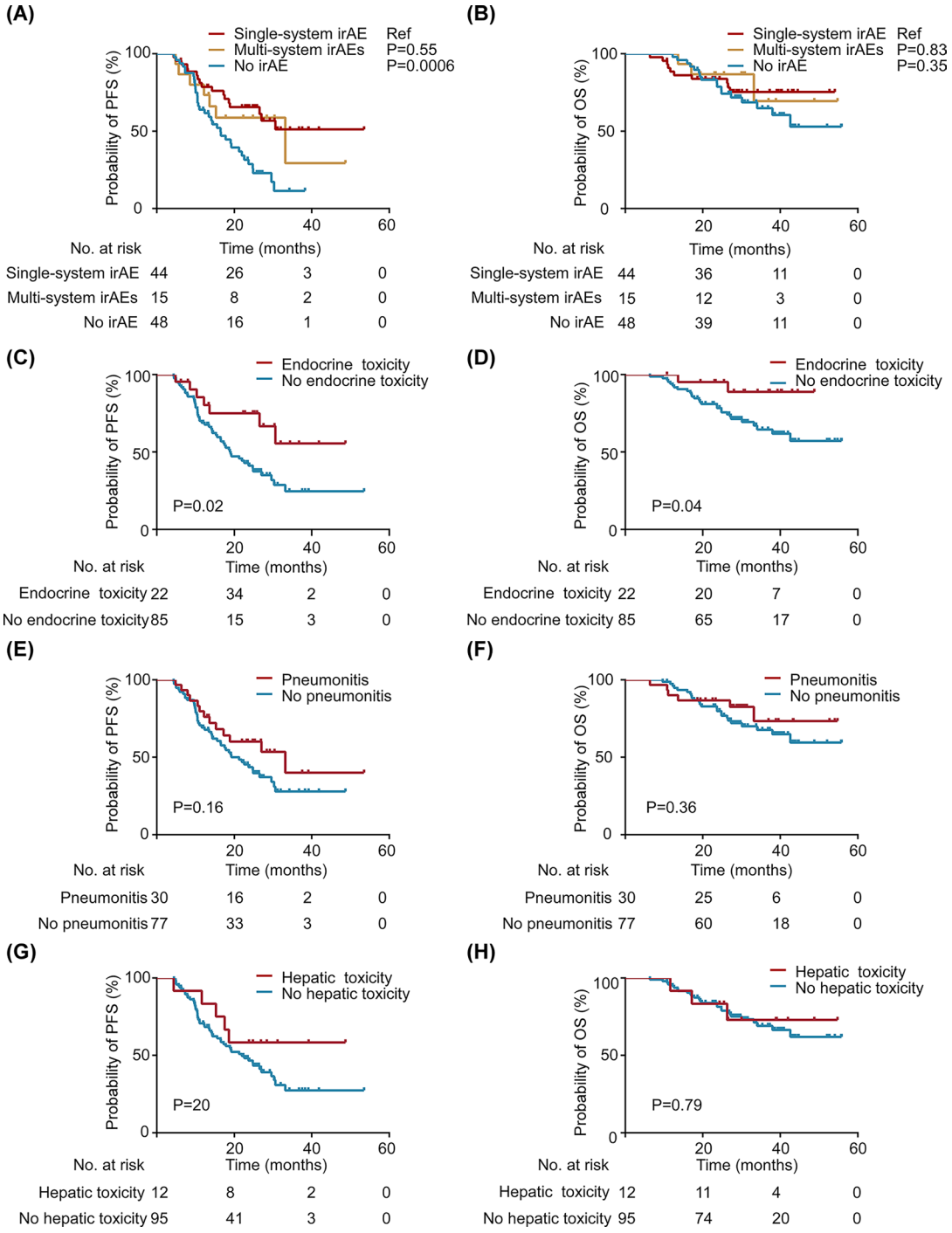

Fig. 3 Patient survival based on different system irAEs. (**A** and **B**) PFS (**A**) and OS (**B**) in patients with multi-system irAEs, single-system irAEs, and without irAEs; PFS and OS in patients with/without endocrine toxicity (**C** and **D**), pneumonitis (**E** and **F**), and hepatic toxicity (**G** and **H**). PFS, Progression-free survival. OS, Overall survival

pneumonitis and hepatitis had no significant impact on survival (Fig. 3E-H).

Impact of irAE grade on survival

We then stratified different severity of irAEs according to CTCAE 5.0 and analyzed their impact on survival. We defined all irAEs < grade 3 as mild irAEs (m-irAEs), and at least one irAE ≥ grade 3 as severe irAEs (s-irAEs). The results revealed that compared to patients without irAEs, those developing mild irAEs had superior median PFS and OS, while those developing s-irAEs had shorter median PFS and OS (Fig. 4A and B). These results

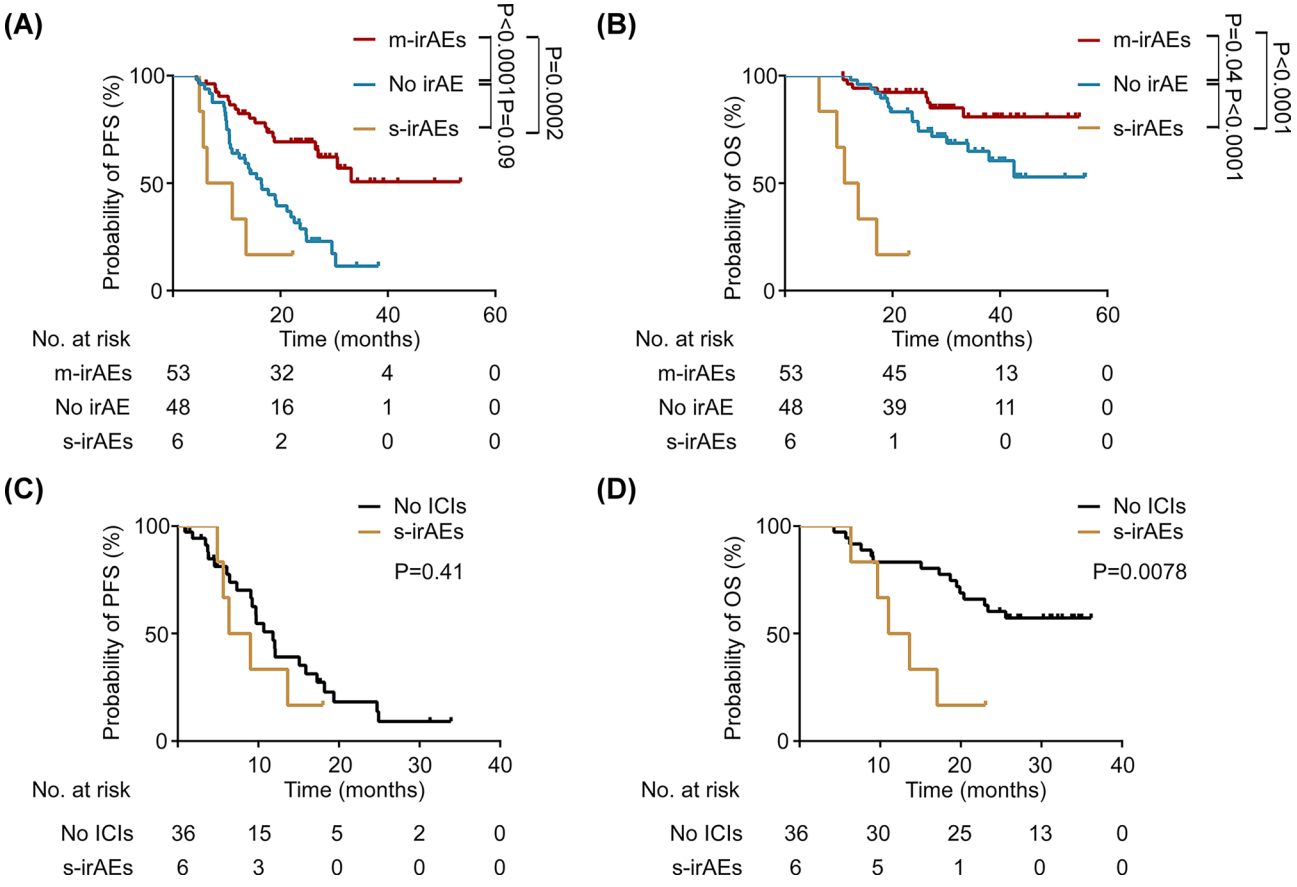

Fig. 4 Patient survival based on the different grades irAEs. (**A** and **B**) PFS (**A**) and OS (**B**) in patients based on different grade irAEs; (**C** and **D**) PFS (**C**) and OS (**D**) in patients with s-irAEs and patients with no ICIs teatment. PFS, Progression-free survival. OS, Overall survival

suggest that the development of s-irAEs may partly offset the benefit of ICI consolidation. To explore whether patients with s-irAEs should be exempted from ICIs, we further compared PFS and OS in patients experiencing s-irAEs versus those without PD-L1 inhibitor consolidation (balancing baseline characteristics of s-irAEs and no ICI groups) (see Supplementary Table S3 in Additional file 1). Unexpectedly, although these 2 sub-populations displayed comparable PFS, patients developing s-irAEs showed significantly worse OS than those who did not receive immunoconsolidation (Fig. 4C and D). These findings could imply that immunoconsolidation might not be routinely required for patients prone to s-irAEs.

Analysis of TIME characteristics predicting s-irAEs

We have demonstrated that s-irAEs may shorten patient survival, therefore we aimed to identify patients who might develop s-irAEs and avoid immunotherapy. It is reported that the response of T cell clones to self-antigens is a major driving mechanism underlying the development of irAEs [26], suggesting that TIME profiles might be useful in predicting irAE development. Therefore, we analyzed the densities of different T-cell and tumor-associated macrophage (TAM) subsets, 2 major immunocyte components in the TME [27], in patients with s-irAEs, m-irAEs, and no irAE. We found that the percentage of $CD103^+CD8^+$ T cells, rather than other T-cell or TAM subsets, was higher in s-irAEs than in no irAE ($p = 0.012$) and m-irAE groups ($p = 0.042$) (Fig. 5A and B). We also used ROC curve analysis to determine the optimal cut-off values of $CD103^+CD8^+$T cell density in predicting s-irAEs. We found a $CD103^+CD8^+$ expression threshold of 1.545% displayed the optimal specificity (81.8%) and sensitivity(100%) with an AUC value of 0.939 (Fig. 5C). Next, we categorized patients into high and low $CD103^+CD8^+$ T cells groups based on the cut-off value. We observed that patients with low $CD103^+CD8^+$ T cells density exhibited longer PFS (Fig. 5D) and OS (Fig. 5E) compared to those with high $CD103^+CD8^+$ T cells densities. These results indicate that high $CD103^+CD8^+$ T cell infiltration may predict the development of s-irAEs and worse prognosis.

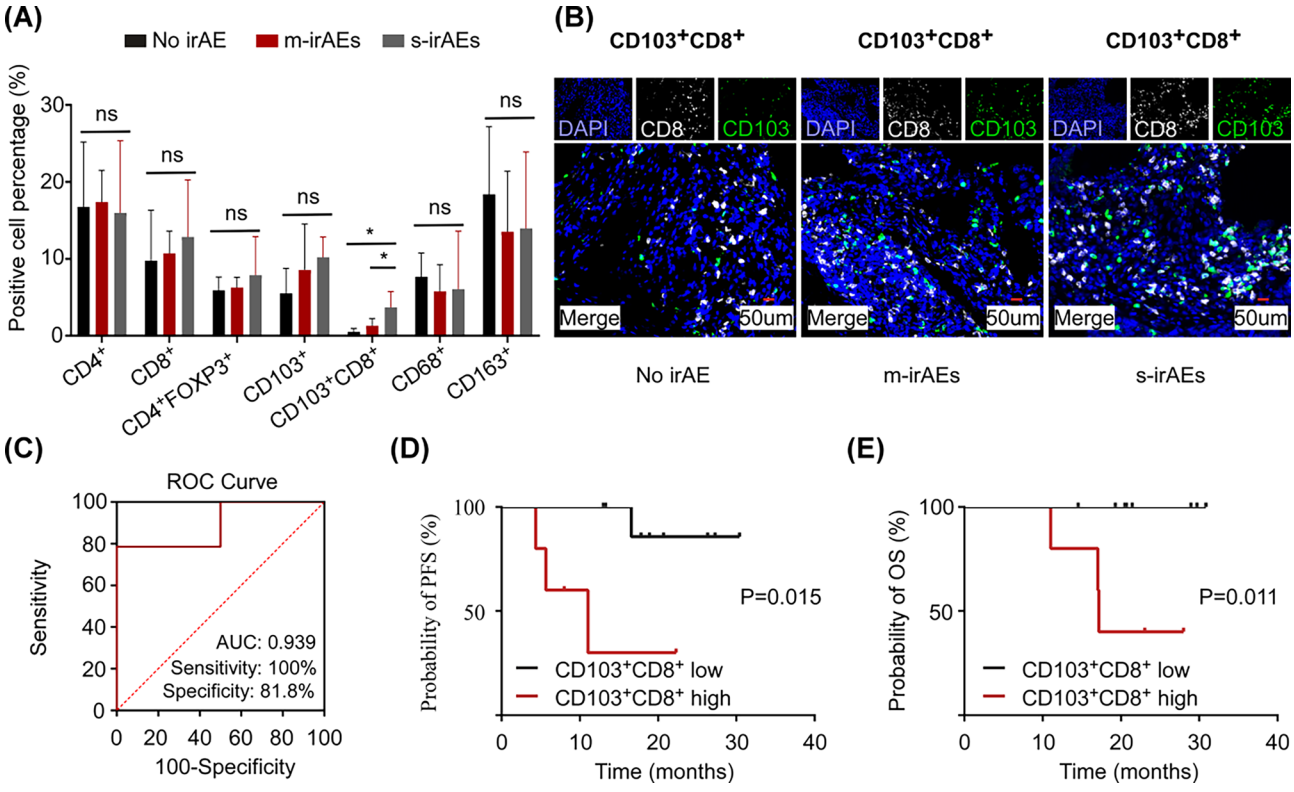

Fig. 5 The correlations between the TIME characteristics and different grade irAEs. (**A**) Correlations between the TIME characteristics and different grade irAEs. (**B**) Comparison of representative mIF images of $CD103^+CD8^+$ T cells infiltration in no irAE, m-irAEs and s-irAEs; (**C**) ROC curve of $CD103^+CD8^+$ T cells infiltration; (**D** and **E**) PFS (**D**) and OS (**E**) in patient with high and low $CD103^+CD8^+$ T cells infiltration. PFS, Progression-free survival. OS, Overall survival. Positive cell percentage =(number of positive cells/ total number of nucleated cells) *100%. Plotting scale: 50 μm. (two-sided unpaired t-test, ns, not significant, $*p < 0.05$)

Discussion

The PACIFIC trial has established PD-L1 inhibitor consolidation as the standard of care for LA-NSCLC [3, 4]. However, whether irAEs occurring after chemoimmunotherapy affect clinical outcomes remains unclear. Additionally, biomarkers predictive of s-irAEs require further exploration. In this retrospective study, we found that irAE development predicted prolonged PFS in patients with LA-NSCLC. Detailed analysis revealed that late-onset irAEs, single -system involvement, endocrine system involvement, and mild -grade irAEs were significantly associated with longer PFS, whereas s-irAEs indicated worse PFS and OS. TIME analysis showed patients experiencing s-irAEs had a higher proportion of $CD103^+CD8^+$ T cells infiltration. Emerging data suggest a cutoff value of > 1.545% $CD103^+CD8^+$ T cells may be useful as a reference parameter to identify patients less likely to benefit from PD-L1 inhibitor consolidation therapy.

Several studies have demonstrated a close correlation between irAE occurrence and ICI efficacy in solid tumors including melanoma, small-cell lung cancer, and metastatic NSCLC [10–13]. However, chemotherapy and radiotherapy combinations may alter irAE development, creating more complex irAE features in LA-NSCLC. Thus, the relationship between irAEs and ICI consolidation efficacy in LA-NSCLC requires further exploration. In this multicenter real-world study, we demonstrated that irAE development predicted superior immunotherapy efficacy in LA-NSCLC, consistent with findings in other solid tumors. However, detailed analysis regarding onset time, spectrum, and organ involvement revealed that later-onset, endocrine, single-system, and mild irAEs predicted longer PFS compared to pneumonia/hepatic, multi-system, and s-irAEs, respectively. Importantly, we observed that s-irAEs even shortened patient survival. It is reported that irAEs result from antigens shared between tumors and inflamed organs [28]. T cells attack normal tissues while exerting anti-tumor effects, thereby generating inflammatory [29–32] responses within affected organs. These results imply that T cell immune activation by ICIs must be appropriately balanced, as excessive immune activation might negatively impact ICI benefits. For patients at risk of s-irAEs, caution is advised in applying ICI consolidation therapy, and treatment decisions should involve individualized risk-benefit assessments with close multidisciplinary monitoring. Consequently, there is an urgent need to identify patient subgroups likely to develop severe AEs during ICI

consolidation. In our exploration of TIME factors potentially influencing irAE severity, we observed that high $CD103^+CD8^+$ T cells infiltration might serve as a promising biomarker associated with s-irAE development. This finding indicates that immunoconsolidation following radiotherapy should be cautiously considered for patients exhibiting high TIME infiltration of $CD103^+CD8^+$ T cells. Previous reports indicate that $CD103^+$ T infiltration predicts enhanced anti-tumor immune responses [33, 34] and improved patient outcomes across various tumors, including NSCLC, breast cancer, and colorectal cancer [35–38]. $CD8^+$ T lymphocytes constitute major anti-tumor effector cells, among which tissue-resident memory $CD8^+$T cells (TRM, characterized by high $CD103^+$ expression) exhibit superior tumor-killing efficacy [39–41]. $CD103^+CD8^+$ T cells bind to E-cadherin on tumor cells, facilitating residence and interaction with tumors, thereby enhancing tumor eradication [20] efficacy. Furthermore, $CD103^+$ TRMs secrete abundant tumoricidal cytokines, including IFN-γ, TNF-α, perforin-1, and granzyme B, to suppress tumor progression [35, 42]. Additionally, $CD103^+CD8^+$TRMs amplify ICI efficacy by inducing PD-1 expression within tumor tissues [43]. Emerging evidence indicates that overactivation of $CD103^+CD8^+$ T cells in barrier tissues, such as colonic mucosa and skin, significantly contributes to irAE development [44–46]. However, the correlation between $CD103^+CD8^+$ T cells infiltration in the TME and irAE occurrence in patients remains uncertain. Here, we first report that $CD103^+CD8^+$T cell density within the TIME serves as a potential biomarker predicting s-irAE development. Importantly, we identified an optimal cut-off value for $CD103^+CD8^+$T cell infiltration that distinguishes patients unlikely to benefit from overall populations. Our findings propose a novel and promising biomarker for identifying patients requiring cautious selection for ICI consolidation in LA-NSCLC, although further validation is necessary to confirm its clinical utility.

Certain limitations should be noted. First, although these retrospective analyses provide valuable insights into the association between irAE characteristics and the efficacy of consolidative immunotherapy after CRT in LA-NSCLC, their retrospective nature warrants cautious interpretation. Retrospective designs are inherently limited in directly informing guidelines or clinical practice due to potential selection bias and unmeasured confounders. Therefore, multicenter prospective trials with subgroup analyses are urgently required to rigorously validate these observations. Second, the observed lack of prognostic significance of PD-L1 expression in our study may reflect bias stemming from the limited availability of PD-L1 data. PD-L1 is a validated biomarker predictive of ICI response and is implicated in irAE development in prior studies. The absence of PD-L1-stratified analyses limits the generalizability of our conclusions. Hence, improved collection and standardization of PD-L1 expression data remain critical priorities.

Additionally, a significant limitation of this study is the scarcity of s-irAE data, primarily due to proactive clinical prevention and management strategies. Although our findings indicate a possible association between severe irAEs and poorer prognosis, the limited sample size prevents drawing definitive conclusions concerning clinical guideline implications or risk-benefit assessments. Future multicenter studies should prospectively evaluate severe irAEs in larger cohorts (target $n > 500$) utilizing standardized CTCAE v6.0 criteria to validate these preliminary findings and improve risk stratification models.

Conclusion

Occurrence of irAEs, particularly late-onset, single-system, or grade 1–2 correlated with greater benefit from consolidative PD-L1 inhibitors in LA-NSCLC. Conversely, severe irAEs predict poorer survival, even compared to no ICI consolidation. Elevated $CD103^+CD8^+$ T cells infiltration may serve as a biomarker to identify patients at risk of severe irAEs who may not benefit from immunoconsolidation therapy.

Abbreviations

CRT	Chemoradiotherapy
ECOG	Eastern cooperative oncology group
ICIs	Immune checkpoint inhibitors
IQR	Interquartile range
irAEs	Immune-related adverse events
LA-NSCLC	Locally advanced non-small cell lung cancer
m-irAEs	Mild irAEs
OS	Overall survival
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
s-irAEs	Severe irAEs
TIME	Tumor immune microenvironment

Supplementary Information

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Supplementary Material 1

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Author contributions

AG and YS conceived and designed this study. ZW guided the revision approach for the research project. XW, XF, QL, JL, YG, JZ, SW, LW, Dg, YS, YG, and HS enrolled patients and collected the data. XW, XF, QL, JL, YG, and JZ were responsible for statistical analysis, and all authors participated in data interpretation. The final version was approved for submission by all authors. The authors and corresponding authors are responsible for all aspects of this work, including data presentation and accuracy.

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Data availability
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. The contact details of corresponding author has been displayed in full on the title page.

Declarations

Ethics approval and consent to participate
This study was approved by the review board of Shandong Cancer Hospital and Institute (202502218), and the requirement for informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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