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RESEARCH

Exploring the role of TIGIT in patients with Small Cell Lung Cancer as a novel predictor of prognosis and immunotherapy response

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Abstract

Background T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) is a novel immune checkpoint playing a crucial role in immunosuppression and immune evasion. This study aims to elucidate the expression patterns, characteristics, and possible mechanisms of TIGIT in small cell lung cancer (SCLC).

Methods TIGIT expression was analyzed across various cancers and normal tissues using The Cancer Genome Atlas (TCGA). Transcriptomic data from SCLC patients, sourced from the Gene Expression Omnibus (GEO) and literature, were analyzed to assess TIGIT-related characteristics. Immunohistochemistry (IHC) was used to verify TIGIT expression in post-surgical and advanced SCLC samples, focusing on expression characteristics, prognostic value, and treatment response.

Results TIGIT was significantly overexpressed in various tumors, including SCLC ($p < 0.05$). Higher expression was associated with better overall survival (OS) ($p < 0.05$). Notably, a significant positive correlation was observed between TIGIT expression and immune-related metagenes, such as HCK, interferon, and LCK ($p < 0.05$). Immune infiltration analysis revealed a strong positive correlation between TIGIT expression and immune score in multiple cohorts. Additionally, TIGIT expression correlated positively with immune cells, including CD8 T cells, cytotoxic lymphocytes, and B cells ($p < 0.05$), and multiple immune checkpoints like BTLA, ICOS, and LAG3 ($p < 0.05$), while it had a significant negative correlation with the TIDE score ($p < 0.05$). In the validation section, patients with high TIGIT expression showed significantly prolonged disease-free survival (DFS) and OS ($p < 0.05$), and demonstrated a better response to adjuvant chemotherapy (ACT) and immunotherapy.

Conclusion TIGIT serves as a biomarker in SCLC, with its high expression indicating favorable prognosis and treatment response. These effects may be due to TIGIT's unique immune landscape and its association with other immune checkpoints.

Keywords Small cell lung cancer · TIGIT · Prognosis · Immunotherapy · PD-L1/PD-1 · Checkpoint

Introduction

Lung cancer remains the most prevalent cancer globally and in China, leading in both incidence and mortality [1, 2]. SCLC, a neuroendocrine (NE) tumor originating in the bronchial epithelium, accounts for 15% of lung cancer cases and is considered the most aggressive type [3].

While significant advancements have been made in treating non-small cell lung cancer (NSCLC) through molecular-targeted therapies and immunotherapy [4], SCLC treatment has stagnated. Standard chemotherapy and radiotherapy have remained largely unchanged for decades, with limited effectiveness. Most SCLC patients relapse or develop drug resistance after initial treatment, and second-line therapies, such as topotecan, offer poor efficacy (15%~20%) [5]. This underscores the urgent need for new therapeutic strategies. Recent progress in immunotherapy has made it a standard first-line treatment for extensive stage-SCLC (ES-SCLC) [6]. Although data on immunotherapy for limited stage-SCLC (LS-SCLC) is lacking, ongoing trials like KEYLYNK-013 are evaluating its potential [7].

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Currently, there are no formal therapies targeting genes with high mutational rates. Furthermore, the mutation rate of potentially targetable gene loci within the SCLC patient population remains notably low [6, 8, 9]. This highlights the need to identify novel biomarkers to predict survival outcomes and treatment responses, thus optimizing existing therapies.

TIGIT, a novel immune checkpoint, is highly expressed in tumor-infiltrating lymphocytes (TILs) including CD8, CD4, regulatory T cells, and natural killer (NK) cells [10, 11]. Studies suggest a correlation between TIGIT expression and factors such as tumor stage, survival rate, and TIL composition in various malignant tumors [12–14]. In NSCLC, high TIGIT levels are linked to worse prognosis [13, 15], but its role in SCLC remains underexplored. Current literature indicates no significant correlation between TIGIT expression and survival in SCLC, necessitating further research [16].

This study analyzed 223 SCLC specimens from three cohorts, including two public datasets and one independent cohort, to evaluate TIGIT's impact on prognosis, immune characteristics, clinicopathological features, and responses to chemotherapy and immunotherapy.

Materials and methods

Publicly available mRNA datasets

We collected the pan-cancer dataset from the cancer genomics browser of the University of California Santa Cruz (UCSC) Xena (https://xenabrowser.net/datapages/). This dataset includes RNA-seq data from 18,102 tumor and normal tissue samples across 33 cancer types. The RNA-seq data were uniformly processed using the Toil pipeline, with the formula $\log_2(\text{tpm}+1)$ applied for analysis. The dataset was utilized for pan-cancer analysis of TIGIT mRNA expression, excluding SCLC. Additionally, two datasets from the GEO database (http://www.ncbi.nlm.nih.gov/geo), GSE60052 (47 LS-SCLC and 7 normal controls) and GSE149507 (18 paired samples), were analyzed to assess TIGIT mRNA expression differences between SCLC and normal tissues. Further detailed analysis incorporated 68 LS-SCLC samples from the Nature cohort [8]. Supplementary Table 1 provides additional details.

Patient cohorts and tissue sampling

The National Cancer Centre (NCC) cohort included 108 formalin-fixed paraffin-embedded (FFPE) SCLC samples collected at the National Cancer Centre of China from January 2017 to August 2021. Clinical features were derived from the medical record system, and pathological specifics were extracted from pathology reports and confirmed by two pathologists (LL and JD) according to the 2021 WHO classification of lung tumors [17]. The 8th edition of the TNM classification was used to determine the stage and prognosis [18]. All patients had primary tumors and had not received preoperative radiotherapy, chemotherapy or any other tumor-related treatments. Additionally, baseline biopsy FFPE specimens from 28 SCLC patients who underwent sequential chemotherapy and anti-PD-L1 or PD-1 treatment from November 2019 to July 2022 were analyzed.

DFS was calculated from the date of surgery to the time of recurrence, metastasis, or last follow-up, while OS was defined as the time from surgery to either the date of death or the last follow-up, whichever occurred first. This study was approved by the Ethics Committee and Institutional Review Boards of Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College (CHCAMS No.22/085–3286). Detailed clinicopathological characteristics of the patients are provided in Supplementary Tables 2 and 3.

TIGIT and the tumor microenvironment (TME)

Analysis of TIGIT-related inflammatory responses

Unsupervised clustering was employed to reduce features, operating under the assumption that many genes are interdependent, which led to the formation of metagenes [19]. Correlation analysis was conducted between TIGIT mRNA levels and seven immune-system-related metagenes, identified by Rody et al. [19], to differentiate inflammatory responses associated with high and low TIGIT mRNA expression. These metagenes include: IgG, interferon, hemopoietic cell kinase (HCK), lymphocyte-specific kinase (LCK), major histocompatibility complex—I and II (MHC-I and II), and signal transducer and activator of transcription 1 (STAT1).

Analysis of TIGIT-related immune infiltration

The ESTIMATE package (version 1.0.13, https://bioinformatics.mdanderson.org/publicsoftware/estimate/) [20] was used to calculate the stromal, immune, and estimate scores. Higher immune and stromal scores indicate a greater proportion of immune or stromal cells within the TME. In addition, the MCP-counter method was used to quantify the abundance of 8 types of immune cells and 2 types of stromal cells in tissues based on gene expression matrices, including T cells, CD8 T cells, cytotoxic lymphocytes, NK cells, B lineage, monocytic lineage, myeloid dendritic cells, neutrophils, as well as endothelial cells and fibroblasts [21]. The TIMER was also used to assess the infiltration of immune cells, including the following 6 types: B cells, CD4 T cells, CD8 T cells, neutrophils, macrophages, and dendritic cells [22].

TIDE analysis for immunotherapy prediction

The TIDE computational framework was used to predict immunotherapeutic responses, specifically with checkpoint blockade strategies [23]. Transcriptome profiles from the Nature and GSE60052 cohorts were uploaded to the TIDE website (http://tide.dfci.harvard.edu), and scores for T-cell dysfunction, exclusion, and overall TIDE were downloaded for analysis [24, 25].

Tissue microarray (TMA) construction and IHC analysis

The preparation of hematoxylin–eosin (HE) slides involved identifying and marking representative tumor regions. Tissue wax blocks corresponding to these regions were then selected, and tissue chips were constructed according to the delineated areas. A tissue core, 1.5 mm in diameter and 6 mm in depth, was extracted from each case and embedded into a 25 × 20 × 10 mm recipient wax block. To ensure slice integrity, 4-μm TMA sections were prepared by an experienced technician (WL).

For IHC, various markers were used, including traditional NE markers (CD56, chromogranin A [ChrA], and synaptophysin [Syn]), a novel NE marker (insulinoma-associated protein 1 [INSM1]), molecular typing markers (achaete-scute homologue 1 [ASCL1], neurogenic differentiation factor 1 [NEUROD1], POU class 2 homeobox 3 [POU2F3], Yes-associated protein 1 [YAP1]), and the immune microenvironment marker TIGIT. Detailed information on antibodies, dilutions, staining locations, and manufacturers is provided in Supplementary Table 4. All staining procedures were conducted using the Roche automated IHC apparatus (Roche Diagnostic Products Co., LTD., Shanghai, China) following standard protocols. Prior to formal testing, suitable tissues were selected for preliminary testing and quality control, as specified by the manufacturer.

Scoring criteria: The semi-quantitative scoring of ASCL1, NEUROD1, POU2F3, and YAP1 protein expression was performed using the Histo-score (H-score) method [26]. TIGIT expression was assessed by calculating the percentage of positive cells within the total TILs. Scoring was manually conducted, with artificial intelligence-based software, Qupath (version 0.3.2), used for supplementary analysis. The H-score ranges from 0 to 300, calculated by multiplying the percentage of positively stained cells by staining intensity (graded on a scale from 0 to 3), with the formula: H-score = (0 ~ 3)*(0 ~ 100%)*100. This score was utilized for molecular subtypes classification in SCLC.

The semi-quantitative evaluation of CD56, ChrA, Syn, and INSM1 expression was based on a four-tier scale (0 ~ 3 +): negative (0) for no staining or staining in less than 5% of cells; weakly positive (1 +) for staining in 5% ~ 25% of tumor cells; moderately positive (2 +) for 25% ~ 50% staining; and strongly positive (3 +) for staining in more than 50% of tumor cells. Low expression was defined as scores of negative and 1 +, while high expression was defined as 2 + and 3 +. Two pathologists (LL and JD) independently reviewed and diagnosed the samples, with any discrepancies resolved by consensus.

Statistical analysis

For the statistical analysis, differences between groups were assessed using the Wilcoxon rank-sum test, while continuous variables were analyzed using Pearson's correlation test. Univariate Cox proportional hazards regression was utilized to identify clinicopathological features and biomarker expressions most strongly associated with DFS and OS in SCLC patients. Variables with a *p*-value of less than 0.1 were included in the multivariate Cox regression analysis. Survival effects of factors were visualized through Kaplan–Meier curves. The optimum cutoff survival analysis was completed using the "surv_cut point" function of the "survminer" R package. The analyses were performed using Hiplot Pro in conjunction with R software (version 4.3.3), with significance levels denoted as '*' ($p < 0.05$), '**' ($p < 0.01$), '***' ($p < 0.001$), and '****' ($p < 0.0001$). Additional descriptive statistical analyses were conducted using Microsoft Office Excel 2021 and SPSS (version 23.0, IBM-SPSS, Inc., Chicago, IL, USA).

Results

Molecular characteristics of TIGIT in SCLC based on public databases

In our study, we aimed to delineate the expression profile of TIGIT across various cancer types and tissue specimens, starting with a pan-cancer analysis. Data from the TCGA indicated that TIGIT mRNA expression is significantly elevated in tumor tissues compared to normal tissues, with particularly high expression levels observed in lung adenocarcinoma (LUAD), skin cutaneous melanoma (SKCM), and diffuse large B-cell lymphoma (DLBC). The DLBC, in particular, showed markedly elevated expression levels. The detailed expression patterns of TIGIT are depicted in Fig. 1A. Further, we analyzed the relationship between TIGIT and the proportion of immune cells in pan-cancer and found that TIGIT is significantly positively correlated with various immune cells, such as T cells, NK cells (Supplementary Fig. S1). This is highly consistent with the results based on SCLC presented in the later part of our paper.

Beyond the TCGA data, we further explored TIGIT mRNA expression specifically in SCLC by utilizing datasets

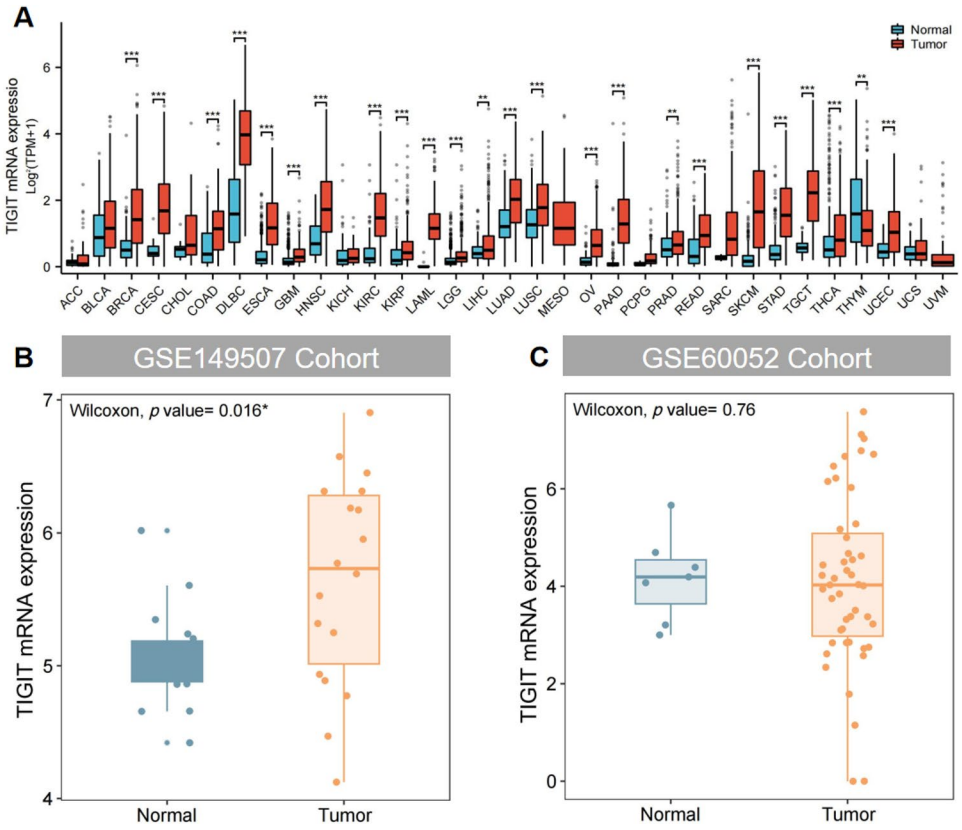


Fig. 1 Pan-cancer analysis of TIGIT expression. **A**, Differential TIGIT mRNA expression between tumor and normal tissue samples in multiple cancer types from TCGA. **B**, TIGIT expression in SCLC and normal lung tissues from GSE149507. **C**, TIGIT expression in SCLC and normal lung tissues from GSE60052

from the GEO. Analysis of the GSE149507 cohort revealed significantly higher TIGIT mRNA expression in SCLC tissues than in normal tissues (Fig. 1B). However, in the GSE60052 cohort, while TIGIT mRNA expression did not show a significant difference between SCLC and normal tissues, there was considerable variability in expression levels within tumor tissues (Fig. 1C). These findings suggest that the expression of TIGIT in SCLC tumor tissues and its potential links to critical pathways, biomarkers, and other factors deserve further in-depth investigation.

Prognostic significance of TIGIT in public databases

Given TIGIT's prominent expression in SCLC tumor tissues, its prognostic relevance was examined. We evaluated the correlation between TIGIT expression and patient survival in SCLC, utilizing data from the Nature cohort and the GSE60052 cohort. These analyses predominantly focused on patients with LS-SCLC who had undergone surgery, as detailed in Supplementary Table 1. The results indicated that higher TIGIT expression was significantly associated with improved survival rates in both cohorts (Nature cohort: 68 patients, $p = 0.04$, Fig. 2A; GSE60052 cohort: 47 patients, $p = 0.02$, Fig. 2B), suggesting that TIGIT could serve as a positive prognostic marker for SCLC.

Immunological events associated with TIGIT expression in SCLC

Inflammatory responses linked to TIGIT expression

In our exploration of TIGIT as a potential prognostic marker, we analyzed its relationship with inflammatory responses. We utilized 7 metagenes (HCK, interferon, LCK, MHC-I, MHC-II, STAT1, and IgG) to investigate the associations between inflammatory responses and TIGIT mRNA expression. These metagenes broadly reflect pathways related to inflammation and immune regulation. The analysis revealed significant correlations ($p < 0.05$), with TIGIT showing a negative association with the IgG metagene and positive associations with the other 6 metagenes (Fig. 3A-B). This indicates a strong link between TIGIT expression and immune responses in SCLC.

Immune infiltration and TIGIT expression

To further understand TIGIT's role in the TME, we employed the ESTIMATE method to calculate immune and stromal scores, which are critical for prognostic assessment and therapeutic development. We observed significant positive correlations between TIGIT expression and both stromal score (Coefficients 0.724 and 0.503, both $p < 0.001$) and immune score

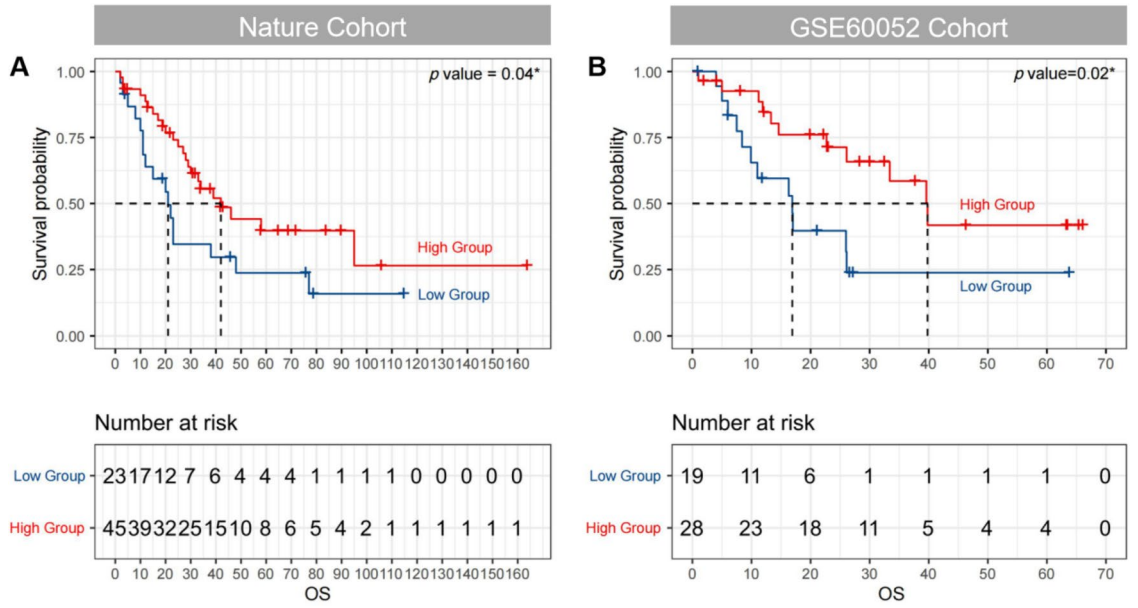


Fig. 2 TIGIT expression significantly impacted OS in SCLC patients. **A**, Kaplan–Meier curve of OS in 68 SCLC patients, stratified by TIGIT expression. **B**, Kaplan–Meier curve of OS in 47 SCLC patients stratified by TIGIT expression

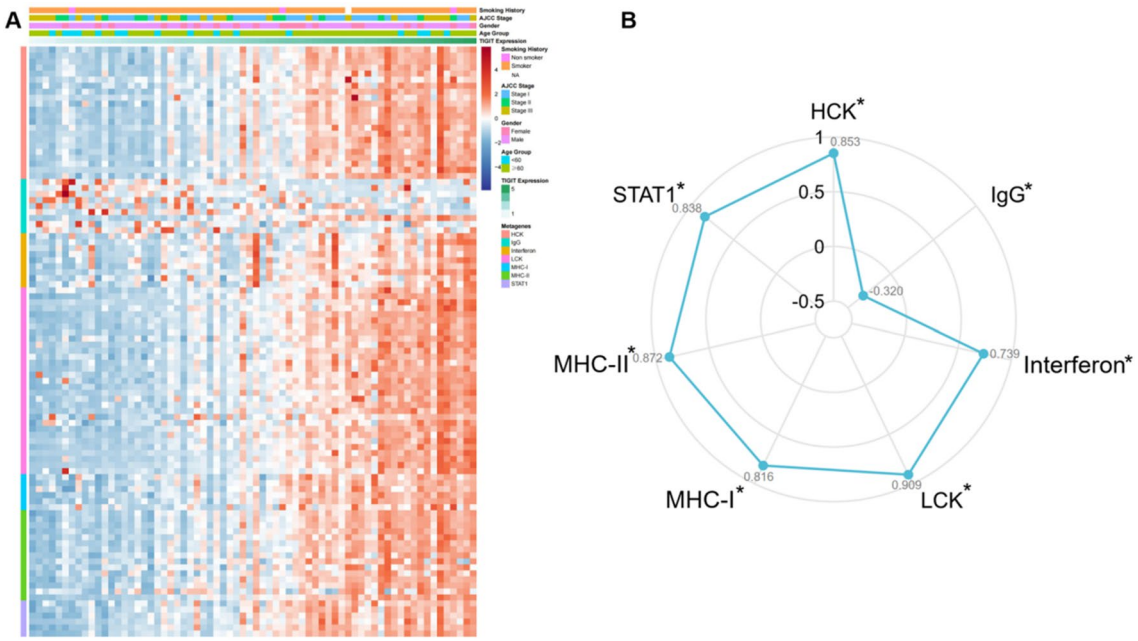


Fig. 3 TIGIT expression is correlated with inflammatory gene expression in SCLC patients. **A**, The expression of inflammatory metagenes and TIGIT mRNA expression in patients from the Nature cohort. **B**, The correlation between TIGIT mRNA expression and seven inflammatory metagenes in the Nature cohort

(Coefficients 0.921 and 0.404, $p<0.001$ and $p=0.005$), in both Nature cohort and GSE60052 cohort (Fig. 4A-B), indicating that higher TIGIT levels are associated with greater immune and stromal cell infiltration in the TME. The heatmaps and radar charts based on MCP-counter revealed strong positive relationships between TIGIT expression and various immune cells, such as T cells, B lineage, NK cells, monocytic lineage, myeloid dendritic cells, endothelial cells, and fibroblasts ($p<0.05$, Fig. 4C-F), reinforcing the role of TIGIT in immune

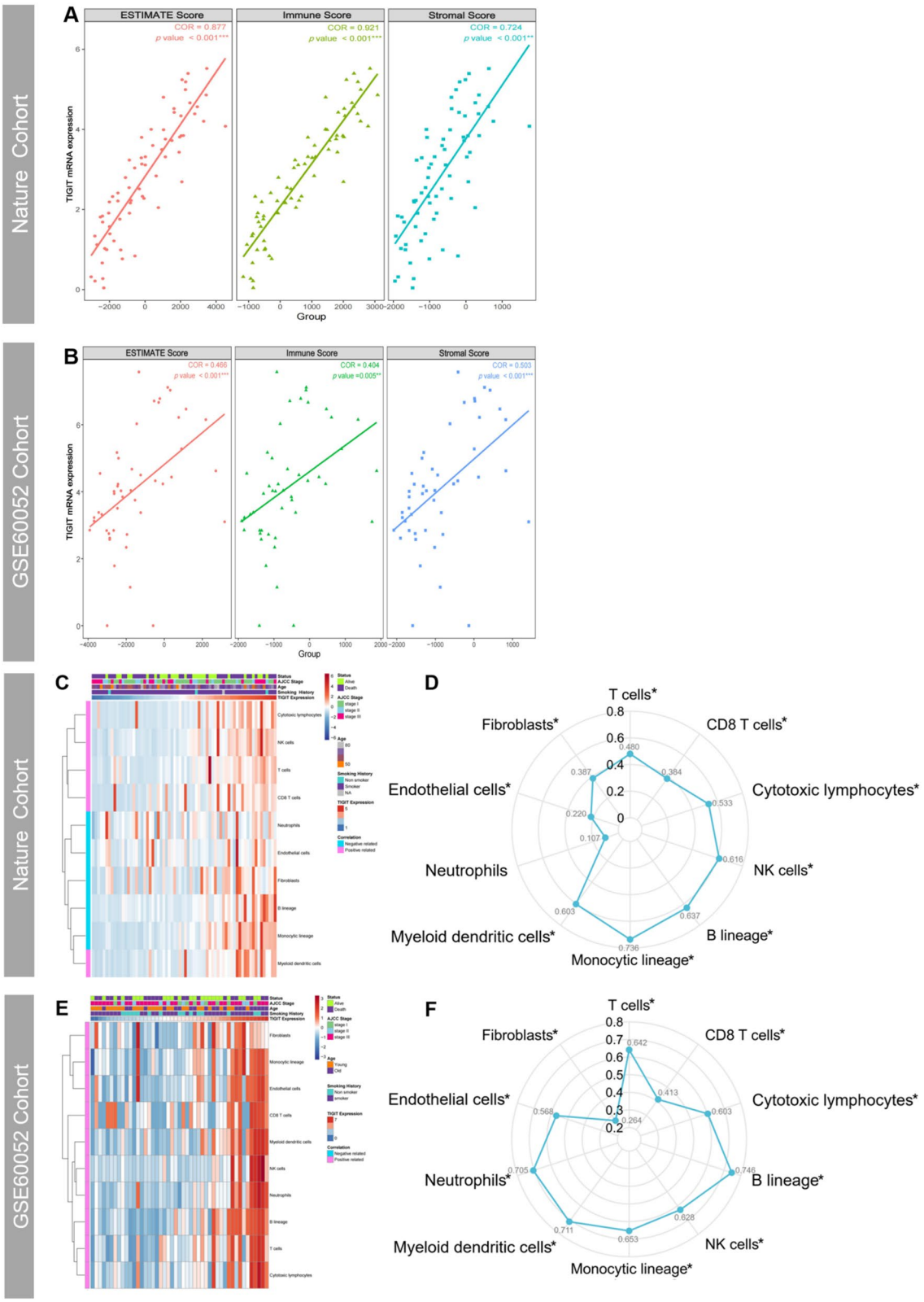


Fig. 4 TIGIT expression and its relation to immune cell infiltration. **A-B**, Association between TIGIT expression and immune cell infiltration status, including immune score and stromal score. **C-F**, Heatmaps of immune cell infiltration in SCLC patients with TIGIT expression. The radar charts on the right illustrate the correlation between TIGIT expression and various immune cells

cell dynamics within the TME. Additionally, the above results were further validated by TIMER (Supplementary Fig. S2).

TIGIT expression and immune checkpoints

With immunotherapy becoming a cornerstone in treating ES-SCLC [6], we examined the relationship between TIGIT and other immune checkpoints. The correlation analysis (Fig. 5B, D) was an extension of the differential analysis (Fig. 5A, C). They demonstrated from two perspectives that TIGIT expression has a significant positive correlation with various immune checkpoints, such as BTLA, ICOS, LAG3, PDCD1, CD48, and IDO1 in both Nature and GSE60052 cohorts ($p < 0.05$, Fig. 5A-D). This suggests that targeting TIGIT, alongside other immune checkpoints, could enhance the effectiveness of immunotherapy in SCLC. Furthermore, patients with high TIGIT expression exhibited higher CD8 T cell infiltration, coupled with lowered TIDE and T cell exclusion scores (Fig. 5E-L), suggesting these patients might benefit more from immunotherapeutic approaches. These findings highlight the potential of TIGIT as a critical biomarker and therapeutic target in SCLC.

Enrichment trend of TIGIT + TILs in SCLC patients with high ASCL1 expression

In this study, we analyzed 108 patients from the NCC cohort to investigate specific characteristics of TIGIT + TILs in SCLC. The patient demographics revealed a median age of 62 years (range: 40~79), with a male predominance (88.0%). Among the cohort, 80 patients were smokers, and 101 were in clinical stages I-III, while 7 patients lacked Node and AJCC staging due to the absence of lymph node dissection.

TIGIT expression in TILs was assessed using IHC, with 53.7% (58/108) of SCLC patients showing high TIGIT expression in tumor tissues, while the remaining 46.3% (50/108) exhibited low expression (Fig. 6A-D). We examined the association between TIGIT expression and molecular subtypes of SCLC, particularly focusing on ASCL1, NEUROD1, POU2F3, and YAP1 as typing markers [27]. A weak correlation was found between high TIGIT expression and elevated ASCL1 H-score ($p = 0.046$, Fig. 6E). Further, molecular subtypes of SCLC were distinguished by the highest H-score of the typing markers. Although the analysis showed no significant difference in TIGIT + TILs across the four molecular subtypes, there was a trend towards higher TIGIT expression in the SCLC-A subtype (Supplementary Fig. S3).

TIGIT + TILs predicted the prognosis of SCLC patients

High TIGIT + TILs infiltration correlates with favorable prognosis

To evaluate TIGIT's potential as an independent prognostic marker in SCLC patients, both univariate and multivariate Cox regression analyses were performed on the NCC cohort (Supplementary Fig. S4A-S4C and Fig. 7A). The cohort's median DFS was 17.95 months, with 45.4% (49/108) of patients experiencing recurrence or metastasis. The median OS was 30.89 months, with a mortality rate of 29.6%.

Univariate analysis identified several factors significantly associated with DFS, including Veterans Administration Lung Study Group (VALSG) Stage ($p < 0.001$, HR = 5.18, 95% CI 2.36–11.40), AJCC^{8th} Stage ($p = 0.005$, HR = 2.31, 95% CI 1.29–4.31), Primary Tumor Stage ($p = 0.044$, HR = 1.96, 95% CI 1.02–3.76), Tumor Thrombosis ($p = 0.001$, HR = 3.41, 95% CI 1.70–6.84), Nerve Invasion ($p = 0.001$, HR = 2.62, 95% CI 1.46–4.71), Pleura Invasion ($p = 0.026$, HR = 1.91, 95% CI 1.08–3.37), and TIGIT Group ($p = 0.015$, HR = 0.49, 95% CI 0.28–0.87). For OS, predictive factors included AJCC^{8th} Stage ($p = 0.046$, HR = 2.05, 95% CI 1.01–4.14), Regional Lymph node Metastasis ($p = 0.026$, HR = 2.25, 95% CI 1.10–4.60), Tumor Thrombosis ($p = 0.005$, HR = 3.96, 95% CI 1.52–10.29), and TIGIT Group ($p = 0.045$, HR = 0.47, 95% CI 0.23–0.98) (Supplementary Fig. S4A-S4C). It is noteworthy that despite employing identical statistical approaches to TIGIT for TILs prognostic cutoff exploration, none of the potential thresholds reached statistical significance ($p > 0.05$). Consequently, a literature-based and somewhat meaningful cutoff (30%) for our cohort was adopted for survival grouping [28]. Kaplan–Meier survival curves demonstrated that patients with higher TIGIT + TILs infiltration had significantly improved DFS ($p = 0.015$) and OS ($p = 0.045$) (Fig. 7B-C).

In the multivariate analysis, VALSG Stage (ES-Stage vs. LS-Stage, $p = 0.009$, HR = 6.49, 95% CI 1.60–26.33), Tumor Thrombosis (Yes vs. No, $p = 0.011$, HR = 2.65, 95% CI 1.25–5.59), Nerve Invasion (Yes vs. No, $p = 0.001$, HR = 3.00, 95% CI 1.59–5.65), and TIGIT Group (≥ 1% vs. < 1%, $p = 0.037$, HR = 0.51, 95% CI 0.27–0.96) were significant independent factors for DFS. Additionally, Tumor Thrombosis (Yes vs. No, $p = 0.049$, HR = 2.77, 95% CI 1.00–7.64), TIGIT Group (≥ 1% vs. < 1%, $p = 0.031$, HR = 0.41, 95% CI 0.18–0.92) were independent predictors of OS. These results are visualized in the forest plot in Fig. 7A. Collectively, high infiltration of TIGIT + TILs is associated with better survival outcomes in SCLC, marking it as a significant prognostic indicator.

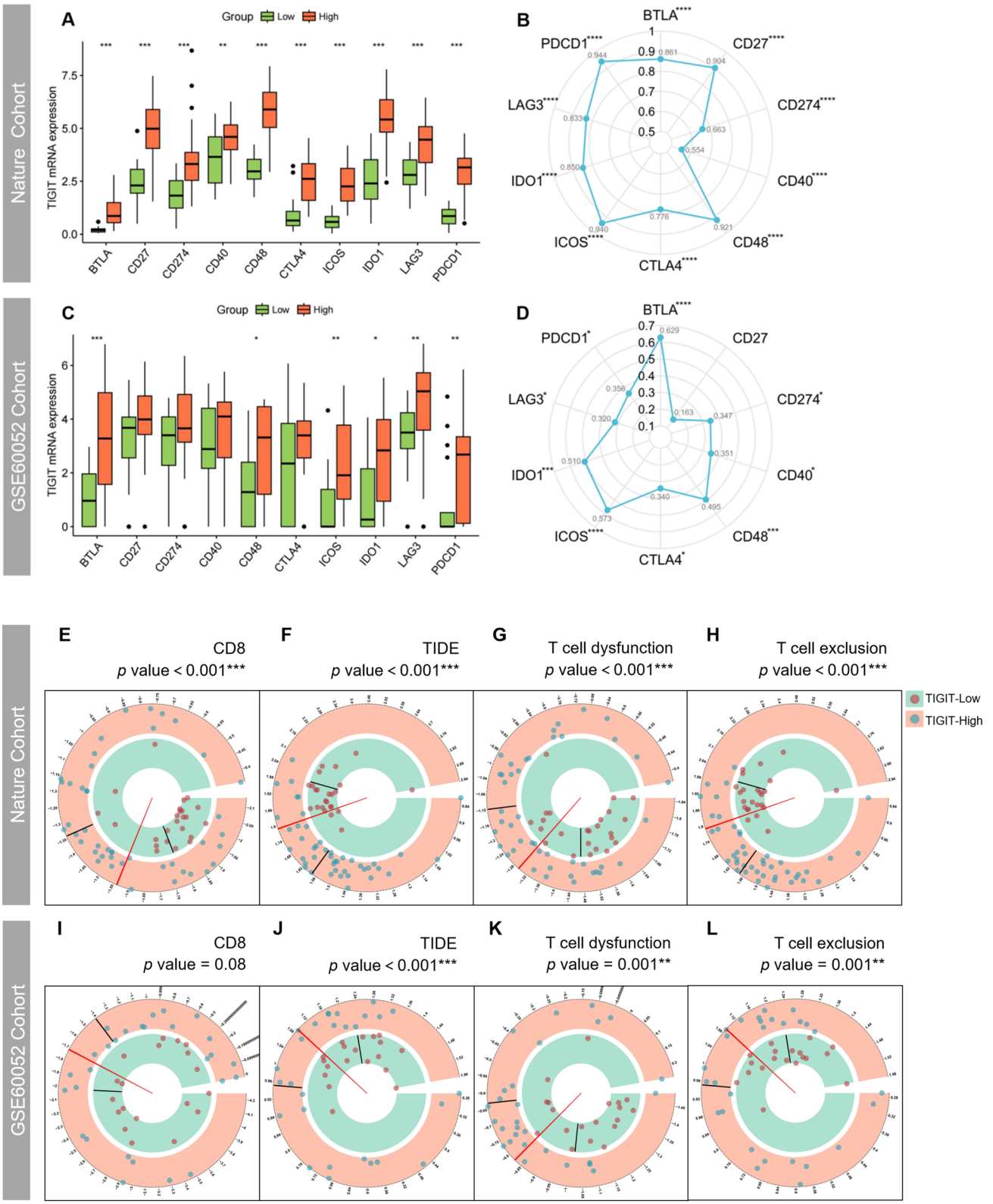


Fig. 5 Distribution of immunotherapy response markers stratified by TIGIT expression. **A-D**, The correlation between TIGIT expression and several novel immune checkpoints. **E** and **I**, The distribution of CD8 expression stratified by TIGIT expression levels. **F–H** and **J-L**, The distribution of TIDE, T cell dysfunction, and T cell exclusion scores stratified by TIGIT expression

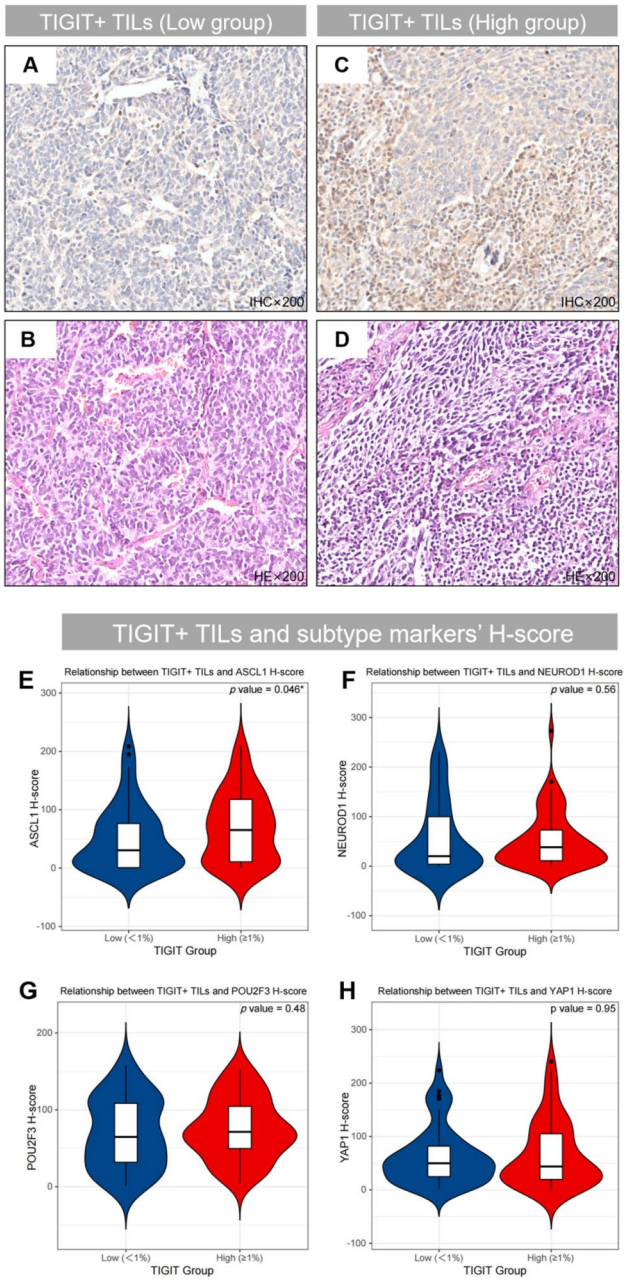


Fig. 6 Analysis of TIGIT + TILs in SCLC tissue samples and the correlation of typing markers. **A** shows staining for TIGIT in a sample with lower density and **B** shows corresponding HE staining. **C** shows staining for TIGIT in a sample with higher density, and **D** shows corresponding HE staining. **E–H**, Comparative analysis of TIGIT expression stratified by the H-score of different typing markers in SCLC

Prognostic impact of TIGIT + TILs across clinical subsets

In alignment with analysis of the public databases, survival analysis was also conducted after excluding 9 ES-SCLC cases (8.3%). Among the remaining 99 LS-SCLC patients, those with high TIGIT + TILs continued to show significantly better DFS and OS, consistent with the overall cohort findings (DFS: $p = 0.017$, OS: $p = 0.032$, Supplementary Fig. S5A-S5B).

Next, we explored the prognostic value of TIGIT + TILs across various clinical stages. In early-stage (stage I and II) patients, those with higher TIGIT + TILs exhibited better DFS and OS, although these differences were not statistically significant ($p = 0.148$ and 0.192, Supplementary Fig. S6A-S6B). However, in advanced-stage (stage III) patients, high TIGIT + TILs were associated with significantly prolonged DFS and a trend toward improved OS ($p = 0.005$ and 0.080, Supplementary Fig. S6C-S6D).

TIGIT as a predictor of therapeutic response in SCLC

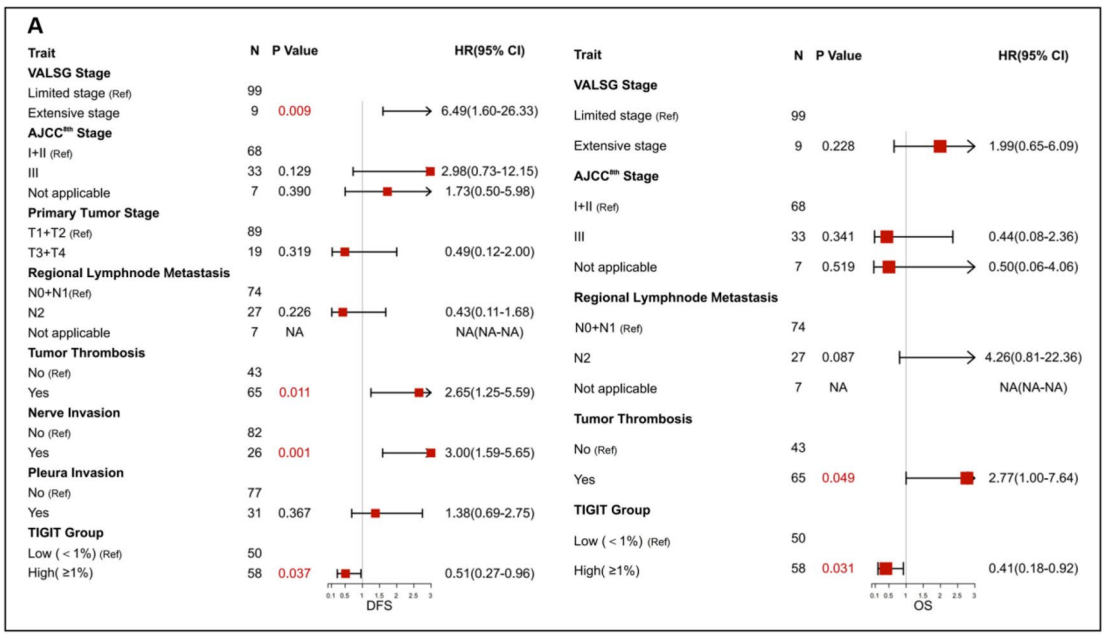
High TIGIT expression predicts better response to ACT

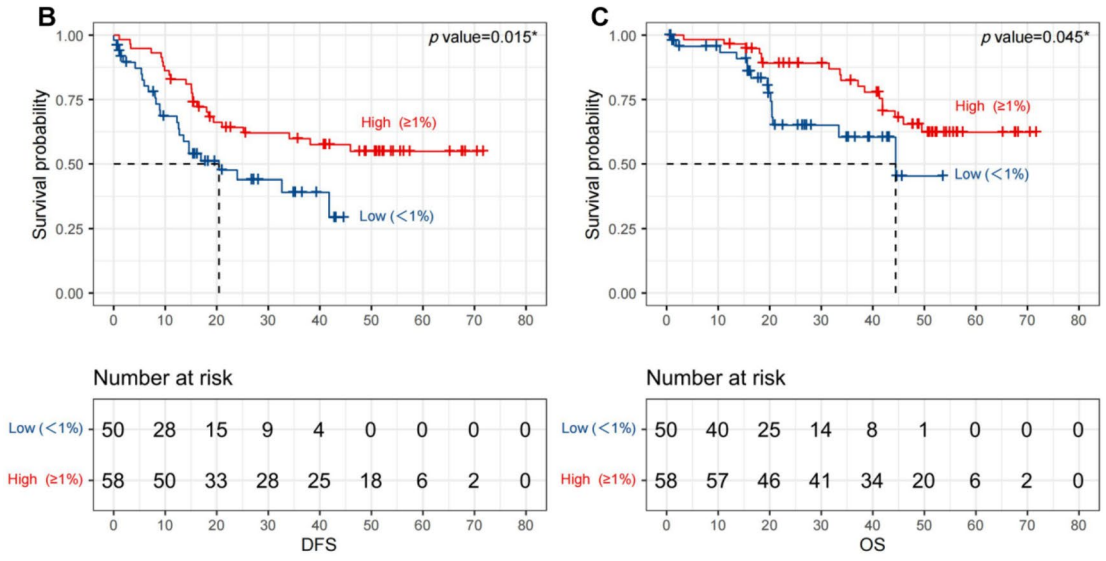
ACT is a well-established treatment for SCLC following surgical resection [6]. However, many patients experience drug resistance and poor clinical outcomes [5], highlighting the need for predictive biomarkers to guide treatment decisions. In this study, we explored the association between TIGIT expression and the efficacy of ACT in SCLC patients. Due to limitations such as incomplete treatment records and missing post-operative details, our analysis was restricted to the subset of patients with complete ACT histories. Among the 77 patients in the NCC cohort who underwent ACT, those with high TIGIT expression showed significantly better DFS ($p = 0.036$, Fig. 7D). While OS did not differ significantly between the high and low TIGIT expression groups, patients with high TIGIT expression had a lower relative risk of death compared to those with low expression ($p = 0.119$, Fig. 7E).

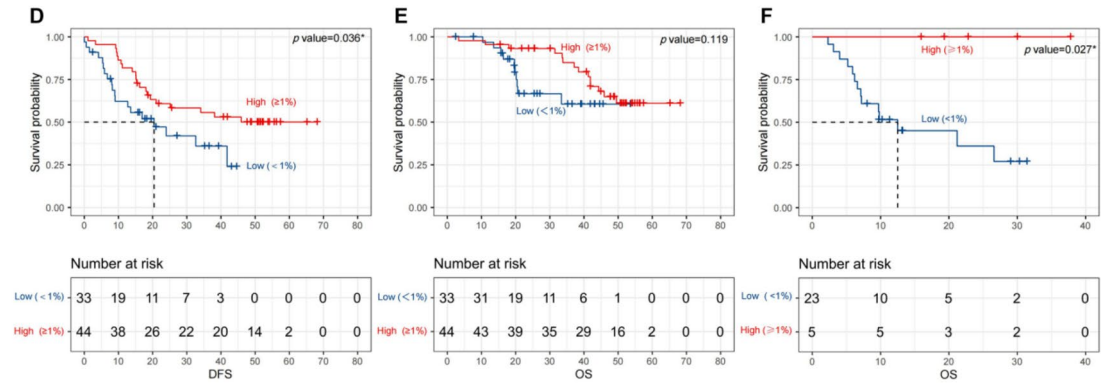
High TIGIT expression tends to be a predictor of immunotherapy efficacy

To further explore the relationship between TIGIT expression and response to immunotherapy, we collected and analyzed additional clinical data, including treatment details, prognoses, and biopsy samples from 28 advanced-stage patients.

In this cohort of 28 patients, the median age was 62 years (range: 47–74). The majority were male (85.7%, 24/28), with a smaller proportion being female (14.3%, 4/28). The cohort consisted primarily of smokers (75%, 21/28), with the remaining being non-smokers (25%, 7/28). All patients were in clinical stages III-IV, and the current survival rate was 50%, with a median OS of 10.85 months. Notably, most patients exhibited low TIGIT expression (82.1%, 23/28), while a smaller fraction had high TIGIT expression (17.9%, 5/28). Survival analysis revealed that the predictive capacity of total TILs for OS is not significant ($p = 0.92$,


A
Trait N P Value HR(95% CI)
VALSG Stage
Limited stage (Ref) 99
Extensive stage 9 0.009 6.49(1.60-26.33)
AJCC8th Stage
I+II (Ref) 68
III 33 0.129 2.98(0.73-12.15)
Not applicable 7 0.390 1.73(0.50-5.98)
Primary Tumor Stage
T1+T2 (Ref) 89
T3+T4 19 0.319 0.49(0.12-2.00)
Regional Lymphnode Metastasis
N0+N1(Ref) 74
N2 27 0.226 0.43(0.11-1.68)
Not applicable 7 NA NA(NA-NA)
Tumor Thrombosis
No (Ref) 43
Yes 65 0.011 2.65(1.25-5.59)
Nerve Invasion
No (Ref) 82
Yes 26 0.001 3.00(1.59-5.65)
Pleura Invasion
No (Ref) 77
Yes 31 0.367 1.38(0.69-2.75)
TIGIT Group
Low (< 1%) (Ref) 50
High(≥1%) 58 0.037 0.51(0.27-0.96)
DFS
Trait N P Value HR(95% CI)
VALSG Stage
Limited stage (Ref) 99
Extensive stage 9 0.228 1.99(0.65-6.09)
AJCC8th Stage
I+II (Ref) 68
III 33 0.341 0.44(0.08-2.36)
Not applicable 7 0.519 0.50(0.06-4.06)
Regional Lymphnode Metastasis
N0+N1 (Ref) 74
N2 27 0.087 4.26(0.81-22.36)
Not applicable 7 NA NA(NA-NA)
Tumor Thrombosis
No (Ref) 43
Yes 65 0.049 2.77(1.00-7.64)
TIGIT Group
Low (< 1%) (Ref) 50
High(≥1%) 58 0.031 0.41(0.18-0.92)
OS


B
p value=0.015*
High (≥1%)
Low (<1%)
Survival probability
Number at risk
Low (<1%) 50 28 15 9 4 0 0 0 0
High (≥1%) 58 50 33 28 25 18 6 2 0
DFS
C
p value=0.045*
High (≥1%)
Low (<1%)
Survival probability
Number at risk
Low (<1%) 50 40 25 14 8 1 0 0 0
High (≥1%) 58 57 46 41 34 20 6 2 0
OS


D
p value=0.036*
High (≥1%)
Low (< 1%)
Survival probability
Number at risk
Low (< 1%) 33 19 11 7 3 0 0 0 0
High (≥1%) 44 38 26 22 20 14 2 0 0
DFS
E
p value=0.119
High (≥1%)
Low (<1%)
Survival probability
Number at risk
Low (<1%) 33 31 19 11 6 1 0 0 0
High (≥1%) 44 43 39 35 29 16 2 0 0
OS
F
p value=0.027*
High (≥1%)
Low (<1%)
Survival probability
Number at risk
Low (<1%) 23 10 5 2 0
High (≥1%) 5 5 3 2 0
OS

◂**Fig. 7** The infiltration of TIGIT + TILs predicts the prognosis and response to treatment of SCLC patients. **A**, Multivariate Cox regression analyses of clinicopathological factors and prognosis (DFS and OS) in 108 SCLC patients from the NCC cohort. **B-C**, Kaplan–Meier curves display DFS and OS in 108 SCLC patients from the NCC cohort stratified by TIGIT expression. **D-E**, Kaplan–Meier curves of DFS and OS in 77 ACT patients from the NCC cohort stratified by TIGIT expression. **F**, Kaplan–Meier curve of OS in 28 patients from the NCC-advanced cohort who received anti-PD-L1/PD-1 immunotherapy, stratified by TIGIT expression

Supplementary Fig. S7). However, patients with high TIGIT expression had significantly better OS ($p = 0.027$, Fig. 7F). These findings suggest that TIGIT may serve as a valuable predictive biomarker not only for ACT but also for immune checkpoint blockade therapies, particularly anti-PD-L1/PD-1 treatments.

Discussion

TIGIT, a recently identified immune checkpoint receptor, belongs to the immunoglobulin superfamily and is crucial in modulating both adaptive and innate immune responses [29]. As a co-suppressor receptor [30], TIGIT has gained considerable attention in research and clinical trials due to its pivotal role in immune regulation [11, 31–33]. TIGIT is primarily expressed in NK cells and T cells [10, 11, 29, 30], where it plays a critical role in maintaining immune homeostasis by interacting with various ligands. Various subtypes of innate immune cells have also been shown to express TIGIT, including innate lymphoid cells, invariant natural killer T cells, mucosa-associated invariant T cells, and macrophages [34]. More work is required to elucidate the complex regulatory mechanisms mediated by TIGIT.

In this study, we conducted an extensive analysis using two independent public databases (115 cases) and 108 SCLC samples to determine the clinicopathological and molecular significance of TIGIT. Notably, this research is among the first to establish TIGIT as a valuable prognostic marker in SCLC. We found that high TIGIT expression is associated with specific immune microenvironments and other immune checkpoints. Moreover, we demonstrated that TIGIT has predictive value for responses to ACT and immunotherapy. These findings highlight the importance of TIGIT as a feasible biomarker for patient stratification and a strong candidate for immunotherapy in SCLC.

The comprehensive pan-cancer analysis conducted in this study revealed a significant upregulation of TIGIT in about 70% (23/33) of tumor samples compared to normal tissue samples. Notably, elevated TIGIT expression was observed in tumor tissues such as LUAD, esophageal carcinoma, stomach adenocarcinoma, and liver hepatocellular carcinoma, among others. These findings are consistent with previous pan-cancer analyses by Li et al. and Xia et al. [35, 36], which also identified TIGIT as being highly expressed in several tumor types. Further analysis of TIGIT expression in SCLC compared to normal tissues demonstrated significant fluctuations in expression within the GSE60052 cohort, with most values ranging from medium to high levels. In the GSE149507 cohort, a marked increase in TIGIT expression in tumor tissues was observed, mirroring the trends seen in the broader pan-cancer analysis. Additionally, high TIGIT expression has been previously reported in surgically resected SCLC tissues [16], indicating the need for further investigation into TIGIT's role in SCLC.

TIGIT has been recognized as being upregulated in a variety of neoplasms, both solid and hematologic, and its expression is closely linked to patient prognosis. A systematic review, meta-analysis, and pan-cancer analysis involving 2,488 East Asian patients with solid tumors revealed that elevated TIGIT expression is associated with poorer OS, progression-free survival (PFS), recurrence-free survival (RFS), and DFS [35]. Specifically, in LUAD, higher TIGIT expression has been correlated with advanced TNM stage, lymph node metastasis, distant metastasis, and worse OS and PFS [37]. In hematologic malignancies, Yang et al. demonstrated that high TIGIT levels in both CD4 and CD8 T cells from follicular lymphoma biopsies were associated with poorer outcomes and reduced survival [38].

Interestingly, the impact of TIGIT appears to vary across different cancer types. In gastric cancer, for instance, high TIGIT expression has been linked to an active immune environment and better prognosis, including improved response to immunotherapy [39]. A pan-cancer analysis also revealed that TIGIT's prognostic value is dual-faceted. High TIGIT expression was associated with poorer OS and disease-specific survival (DSS) in kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, thymoma, and uveal melanoma. Conversely, in cancers such as breast cancer, cervical squamous cell carcinoma and endocervical adenocarcinoma, head and neck squamous cell carcinoma, ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, and SKCM, high TIGIT expression correlated with better OS and DSS [36]. Despite these findings, the impact of TIGIT on SCLC patients remains less clear, with current evidence suggesting no significant correlation between TIGIT expression and survival [16].

In our study, analysis revealed that patients in the high expression group had significantly better OS in both the Nature and GSE60052 cohorts. These findings suggest that TIGIT may serve as a prognostic marker in SCLC, with higher expression levels potentially indicating a more favorable prognosis.

The prognostic role of TIGIT in SCLC may seem paradoxical, given its established function as an inhibitory immune checkpoint. This complexity likely arises from the

interplay of various factors, including tumor type, histological grade, and molecular subtype. To explore the mechanisms underlying TIGIT's prognostic significance in SCLC, we analyzed TIGIT-related immune events. Research has demonstrated that the tumor-intrinsic interferon response and replication stress can create new therapeutic opportunities for patients with SCLC [40]. Repression of the MHC-I is a pivotal mechanism underlying resistance to T cell-based immunotherapies. Epigenetic silencing of MHC-I in SCLC significantly impairs the disease's response to ICB. Scholars have confirmed in vitro models that upregulation of MHC-I can bring rich and lasting ICB benefits [41, 42]. In addition, MHC-II is also associated with TME and immunotherapy for SCLC [43]. Metagenes identified by Rody et al. [19], including the above features, are widely utilized to characterize inflammatory features in various malignancies [44–46]. In this section, we applied the seven metagenes and discovered that high TIGIT expression was negatively correlated with the IgG cluster, implying a reduced presence of immunoglobulin gamma, typically associated with B cells. Conversely, TIGIT expression was positively associated with MHC-I, MHC-II, LCK, HCK, interferon, and STAT1, indicating enhanced immunogenicity, superior antigen presentation, and a more robust interferon response [19]. In general, our data showed that patients with high TIGIT expression showed high inflammatory and immune activity. This may, at least in part, explain their better prognosis.

Further analysis revealed that TIGIT expression correlated positively with immune scores and various immune cell populations, including T cells, NK cells, and myeloid dendritic cells. This suggests that higher TIGIT expression is linked to a more active immune microenvironment. Similar findings were reported in studies of gastric cancer, where TIGIT expression correlated positively with immune scores and diverse immune cells, such as CD8 T cells, memory CD4 T cells, and M1 macrophages [39]. Recent research has revealed an intriguing relationship between TIGIT and plasma cells, showing that TIGIT-deficient plasma cells exhibit reduced proliferation and antibody secretion, suggesting that TIGIT plays a role in enhancing the plasma cell response. These observations imply that TIGIT, traditionally known as a receptor molecule that inhibits T cell activation responses, intrinsically facilitates the plasma cell response [47]. This highlights the complex and multifaceted role of TIGIT in tumor immunity. TILs, which can either promote or inhibit tumor progression, may be influenced by varying cell types and proportions [48]. This is particularly relevant in SCLC, a NE tumor with more intricate immune regulation compared to other solid tumors, likely due to autocrine or paracrine signaling molecules [35].

Our investigation also explored the potential of TIGIT as a biomarker for immunotherapy effectiveness, especially in patients who have not responded to or have developed resistance to chemotherapy. TIGIT expression was positively correlated with several immune checkpoints, including BTLA, ICOS, LAG3, PDCD1, CD48, and IDO1, across multiple cohorts. Additionally, patients with high TIGIT expression showed decreased TIDE scores, suggesting a greater likelihood of benefiting from immunotherapy [24, 49]. Monitoring TIGIT expression along with other immune checkpoints could thus enhance personalized treatment strategies in SCLC.

Significantly, a NCC cohort of 108 patients with in-depth annotations of clinicopathological data and biomarker expression was assembled to investigate the role of TIGIT in SCLC. The dataset revealed variability in TIGIT protein expression in tumor tissues, with higher expression levels particularly noted in patients with high ASCL1 expression. ASCL1, a key regulator in NE differentiation and SCLC carcinogenesis [27], has emerged as a critical therapeutic target. Pathways regulated by ASCL1, such as delta-like ligand 3 (DLL3), have become promising avenues for treatments like the antibody–drug conjugate and chimeric antigen receptor [50, 51]. TIGIT could therefore function as an additional biomarker of patients likely to respond to these therapies. The prognostic significance of TIGIT was also evaluated through multivariate Cox regression analysis, revealing that high TIGIT + infiltration independently correlated with better DFS and OS. Conversely, low TIGIT + infiltration was associated with early recurrence, metastasis, and mortality. We performed a stratified analysis that included important clinical subsets to examine the correlation of TIGIT with prognosis. After the exclusion of 9 ES-SCLC cases, the relationship was still present. Stratifying our analysis based on stage revealed TIGIT to be a highly predictive factor, particularly in advanced stage SCLC. Overall, TIGIT was highly predictive of SCLC prognosis, including different SCLC stratified subgroups, observations found to be in line with our findings in the public databases and research direction by Ma et al. in the context of gastric cancer [39].

An available research showed that there was no distinct correlation between TIGIT expression and survival of patients with SCLC [16], while our study found that patients with high TIGIT expression tend to have better prognoses. Possible reasons for the differences include variations in the clinicopathological characteristics of the patients, discrepancies in sample sizes and differences in antibody selection, staining protocols, and evaluation criteria. These varying details may lead to discrepancies between studies. Currently, there is still limited research on TIGIT expression in patients with SCLC, and both our study and that of Xu et al. aim to provide some references for future investigations. As the research cohort expands and methodologies improve, the relationship between TIGIT and SCLC will become increasingly clear. It is also noteworthy that the lack of a statistically significant TILs cutoff in our cohort may

require further testing in SCLC. This may be related to the heterogeneity of TILs in tumors [52]. To establish robust clinical applicability, this biological phenomenon necessitates rigorous validation through multicenter studies and larger cohorts.

TIGIT further emerged as a key biomarker in predicting clinical responses to chemotherapy in SCLC. The NCC cohort study demonstrated that patients with higher TIGIT expression showed notably better clinical outcomes than those with lower expression, indicating that these patients may derive more significant benefits from chemotherapy. This suggests the potential for TIGIT to be used as a stratification marker, helping to identify which patient subsets could benefit most from specific treatments. TIGIT plays a critical role in regulating the TME and influences how a patient's immune system responds to antigen-specific tumor challenges. Its modulation significantly affects the therapeutic efficacy of treatments, particularly immunotherapies [29, 53]. Our examination of 28 advanced-stage SCLC patients further highlighted that individuals with high TIGIT expression benefited more from anti-PD-L1/PD-1 immunotherapy. Conversely, TIGIT downregulation could help identify subsets of PD-L1/PD-1 positive patients who are unlikely to respond to the treatment. Therefore, our results highlight TIGIT's potential as a valuable immunotherapy marker to improve treatment outcomes and precision in patient categorization in SCLC. In terms of predicting the efficacy of immunotherapy, Liu et al. analyzed a cohort of 348 patients with metastatic urothelial carcinoma after PD-L1 blockade (IMvigor210) and found that the high subgroup of TIGIT exhibited significantly improved responses [54]. Based on the current data set, our findings are preliminary due to the limited number of patients with immunotherapy, and we emphasize that this finding needs to be further validated, especially in a cohort of patients treated with immune checkpoint inhibitors.

TIGIT has the potential to predict prognosis and treatment efficacy, as it demonstrates distinct immune profiles across various expression subgroups in patients [35, 37–39]. Functioning as an immune checkpoint, TIGIT holds significant promise as a therapeutic target [11, 32, 34]. Moreover, the inhibition of TIGIT, particularly when combined with PD-1/PD-L1 inhibitors, has shown antitumor potential [55–58]. While initial trials, such as the Phase III SKYSCRAPER-02 trial with Tiragolumab, indicated promise for combining anti-TIGIT therapies with PD-L1 inhibitors, the trial ultimately failed to meet its endpoint in treating ES-SCLC. However, we still need to pay attention to the fact that for patient subgroups with a tumor cell score of $\geq 5\%$ or an immune cell score of $\geq 5\%$, OS remains beneficial [59]. Given that our study suggested a positive correlation between high TIGIT expression and immune cells, it naturally raises considerations regarding the rationale for using TIGIT inhibitors. A recent study has shown that simultaneous inhibition of TIGIT and PD-L1 promotes the expansion of tumor-reactive CD8 T cells in draining lymph nodes under the influence of CD226, allowing them to enter the bloodstream. Subsequently, this dual inhibition creates co-stimulatory conditions that drive these T cells to differentiate into effector phenotypes rather than exhausted phenotypes, thereby enhancing the anti-cancer effect of the CD8 T cells that infiltrate the tumor [60]. Therefore, we speculate that patients with high TIGIT expression alongside enriched immune cells may benefit more from this mechanism. Future research should continue to investigate the mechanisms behind TIGIT-associated tumorigenesis.

The small sample size and the lack of diverse detection methods are limitations of this study. Expanding research efforts with larger, more diverse cohorts and employing varied analytical methods will provide deeper insights into TIGIT's role in SCLC.

Conclusions

Our study emphasizes that TIGIT serves as an independent prognostic marker and a predictive biomarker for both ACT and anti-PD-L1/PD-1 immunotherapy in SCLC. Tumors with high infiltration of TIGIT + TILs exhibit a distinct immune landscape, highlighting the potential of TIGIT as a promising biomarker for personalized prognosis and treatment strategies in SCLC.

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Declarations

Conflict of interest The authors declare no competing interests.

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