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Preliminary Exploration of the Clinical Features and Immunological Correlation between TIGIT and Esophageal Squamous Cell Carcinoma

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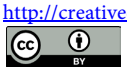


Abstract

Objective: To analyze the relationship between TIGIT and clinical features of Esophageal Squamous Cell Carcinoma, we use transcriptomic data from the TCGA database, and to investigate the relationship between TIGIT and the immune microenvironment of Esophageal Squamous Cell Carcinoma, to provide a basis for improving the treatment strategy and prognosis of patients with Esophageal Squamous Cell Carcinoma. Methods: RNA sequencing data and clinical data corresponding to cancer tissues were obtained from the TCGA database for Esophageal carcinoma, Esophageal Squamous Cell Carcinoma tissues, and paraneoplastic tissues; then we analyzed the differences in TIGIT expression in Esophageal carcinoma, Esophageal Squamous Cell Carcinoma, and normal esophageal tissues; then we analyzed the relationship between TIGIT expression levels and overall survival in Esophageal Squamous Cell Carcinoma; finally, we explored the relationship between TIGIT expression levels and overall survival in Esophageal Squamous Cell Carcinoma. We investigated the relationship between TIGIT and the tumor immune microenvironment of Esophageal Squamous Cell Carcinoma by tumor immune infiltration and functional enrichment analysis. Results: Our study revealed that TIGIT was highly expressed in Esophageal Squamous Cell Carcinoma, and patients with high TIGIT expression had worse overall survival. We also found a close relationship between TIGIT expression levels and the immune microenvironment of Esophageal Squamous Cell Carcinoma, with high TIGIT expression positively correlated with multiple immune cells. Conclusion: Our study demonstrates that TIGIT is associated with Esophageal Squamous Cell Carcinoma malignancy and is closely linked to the immune microenvironment. Furthermore, high expression of TIGIT often predicts poorer clinical features.

Keywords

Esophageal Squamous Cell Carcinoma, TIGIT, Database, Immunogene, Tumour Immune Microenvironment

1. Introduction

According to the latest global cancer statistics released in 2020, Esophageal carcinoma (ESCA) ranks 7th among global malignancies and 6th in mortality [1]. In China, the number of patients with ESCA is the first in the world. Esophageal Squamous Cell Carcinoma (ESCC) predominates, accounting for more than 90% of the total number of deaths due to ESCA each year [2] [3], and is usually at an advanced stage when first diagnosed [4] [5]. Epidemiological studies have shown that China has a high incidence of ESCA, with the highest rates found in the southern part of the Taihang Mountains, particularly in Linzhou [6]; this is probably due to dietary habits such as a preference for salty foods, eating too fast or too much, and inadequate intake of trace elements in food and water [7]. Despite the development of multidisciplinary treatments such as surgery, chemotherapy, radiotherapy, and radiotherapy [8], the prognosis for patients with ESCA remains poor, with a five-year survival rate of approximately 15% - 40% [9]. The tiny improvement in ESCC treatment outcomes with conventional therapies has prompted the search for revolutionary ESCC treatment strategies, particularly immune-targeted therapy [10].

In recent years, immunotherapy has been recognized as an exciting therapeutic strategy for treating various types of cancer [11]. It uses the patient's immune system to fight tumor cells by inhibiting the immune checkpoint pathway [12]. In particular, the development of monoclonal antibodies that inhibit programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) has produced compelling responses and clinical benefits in a variety of malignancies, including ESCC [13] [14]. The effects of immune checkpoint inhibitors are increasingly being correlated with tumor cell-intrinsic factors, such as PD-L1 expression, tumor mutational load, and high microsatellite instability state, as evidenced by recent studies [15]. Furthermore, cancer resistance to immunotherapy can be induced by external factors, including tumor-infiltrating lymphocytes (TIL), tumor-associated macrophages (TAM), and myeloid-derived suppressor cells (MDSC) [16] [17] [18] [19]. Therefore, it is increasingly important to understand better the tumor immune microenvironment (TIME), such as tumor PD-L1 expression, TILs, TAMs, and MDSCs.

The T cell immunoreceptor with Ig and ITIM domains (TIGIT) is a T cell and NK cell co-suppressor receptor known as WUCAM, Vstm3, or VSIG9 [20]. It was first identified by bioinformatics in 2009 by Yu *et al.* [21], and its ligands include CD112, CD113, and the polio virus receptor (PVR), which is a high-affinity homologous receptor for TIGIT, also known as CD155, Necl-5, and Tage4 [22]. TIGIT is mainly expressed in various immune cells, including CD8+ CTL, CD4+

follicular helper T (Th) cells, FOXP3+ regulatory T (Treg) cells, and NK cells [23]. According to studies, TIGIT plays a crucial role in limiting adaptive and innate immunity by inhibiting the anti-tumor response of T and NK cells through binding to the ligand CD155, leading to immune escape of tumor cells. This suggests that TIGIT's role in tumor immunosurveillance is similar to that of the PD-1/PD-L1 axis in tumor immunosuppression [21] [24] [25] [26].

The study of TIME in EC is now well established [27], but screening ESCC-related immune checkpoint genes and their relationship with TIME still holds great promise. We selected the TIGIT gene in this study, as previous studies have shown its immunological role in cancer and the potential for immunotherapy [28] [29] [30] [31]. Still, few studies have explored the relationship between TIGIT and ESCC. The significance of this study is to systematically demonstrate that the immune checkpoint gene TIGIT has the potential to develop into a new effective molecular marker for the clinical diagnosis and early warning of ESCC and to provide a corresponding theoretical basis for the immunotherapeutic aspects of ESCC.

2. Materials & Methods

2.1. Data Collection and Collation

We downloaded whole transcriptome sequencing data (11 standard samples, 184 tumor samples for ESCA RNA sequencing data, and 82 tumor samples for ESCC RNA sequencing data) and clinical data related to ESCC from the TCGA database (https://portal.gdc.cancer.gov/) in this study. Tumour samples containing complete survival data and gene expression data (82 ESCC cases) were used for survival analysis.

2.2. Statistical Analysis Methods for Results

We performed the Wilcoxon rank sum test to detect differences in TIGIT expression between ESCA, ESCC, and normal tissues. We utilized the "survival ROC" package to perform a receiver operating characteristic (ROC) curve analysis to evaluate prognostic accuracy and plotted Kaplan-Meier curves to investigate the relationship between TIGIT expression levels and the overall survival (OS) of patients. Gene expression datasets were obtained from the online database GEO to analyse the differential co-expression of TIGIT in the ESCC and its functional enrichment analysis. The R package "Limma" was used to study the differential expression of TIGIT with an "Adjusted $P < 0.05$ and$|$ log2 fold change$|> 1.5$ threshold to screen for TIGIT differentially co-expressed genes. The R package "clusterProfiler" was used to perform the Gene Ontology GO, Kyoto Encyclopedia of Genes and Genomes, and to analyze the differential expression of TIGIT genes and their functional enrichment. Encyclopedia of Genes and Genomes KEGG) for enrichment analysis. We divided TIGIT expression into high and low groups using the median and used the best cut-off value of the ROC curve for survival analysis. All statistical studies and plots were conducted using the R language.

3. Results

3.1. Expression of TIGIT in Different Tumor Types

Analysis of TIGIT expression in different cancer types using the TIMER 2.0 database revealed that TIGIT expression was upregulated in breast, oesophageal, head and neck squamous cell (HNSC), gastric, Kidney renal clear cell carcinoma (KIRC), Skin Cutaneous Melanoma (SKCM)and Stomach adenocarcinoma (STAD), while downregulated in Colon adenocarcinoma (COAD), Pancreatic adenocarcinoma (PAAD) and Rectum adenocarcinoma (READ), predicting that TIGIT may be associated with a variety of cancers (Figure 1).

3.2. Transcript Expression Levels of TIGIT in ESCA and ESCC

To further investigate the role of TIGIT in ESCC, we analyzed the expression levels of TIGIT using ESCA, ESCC and normal esophagus data obtained from the TCGA database, and the expression profiles were analyzed using the Wilcoxon rank sum test statistical method. As shown in Figure 2, TIGIT expression was upregulated in ESCA and ESCC ($P < 0.01$; $P < 0.001$).

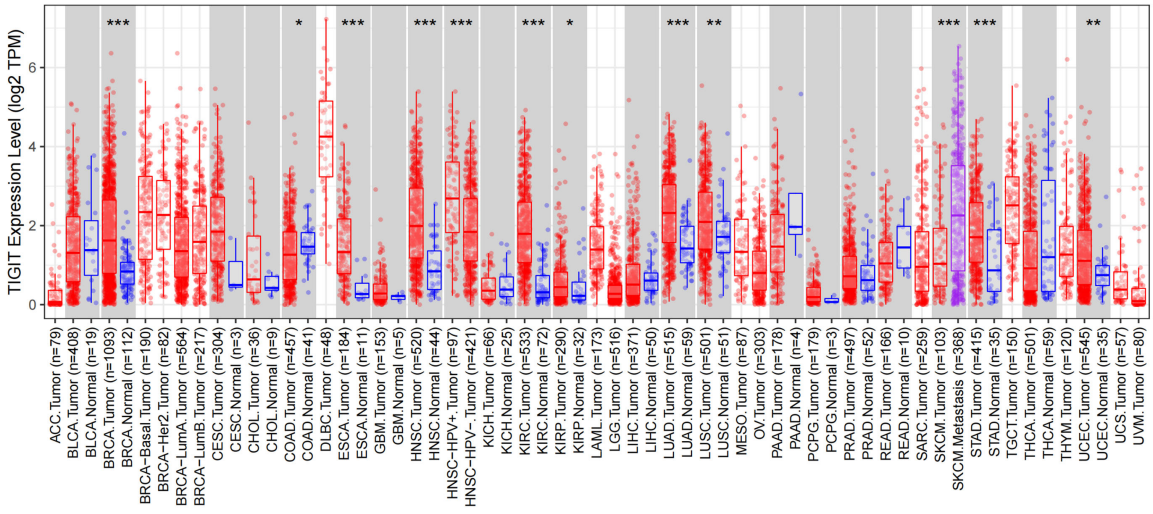


Figure 1. Expression of TIGIT in different cancer types.

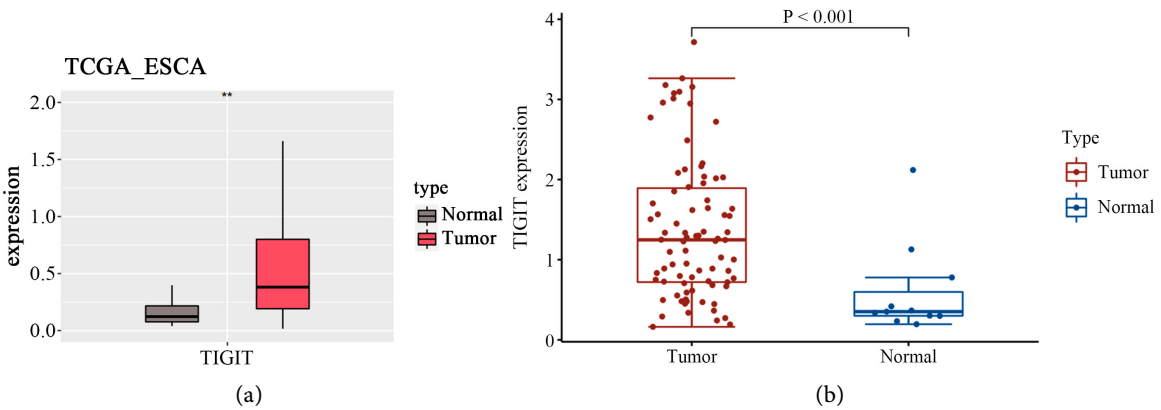


Figure 2. Transcript expression levels of TIGIT in ESCA and ESCC: (a) ESCA, (b) ESCC.

3.3. TIGIT Survival Analysis in the ESCC

To gain insight into the relationship between TIGIT expression and prognosis in ESCC patients and to explore possible prognostic indicators, we performed receiver operating characteristic (ROC) curve analysis using the survival ROC package. The area under the ROC curve represents the predictive accuracy. The 1-year area under the curve (AUC) for ESCC was 0.561, indicating that the risk prediction model was a good predictor (**Figure 3(a)**). Kaplan-Meier curves and log-rank tests were performed to investigate further the relationship between TIGIT expression levels and overall patient survival. The results showed that TIGIT expression affected the overall survival of ESCC patients, and the overall survival of the high TIGIT expression group was lower than that of the low TIGIT expression group, indicating a correlation between high TIGIT expression and the prognosis of ESCC patients (**Figure 3(b)**).

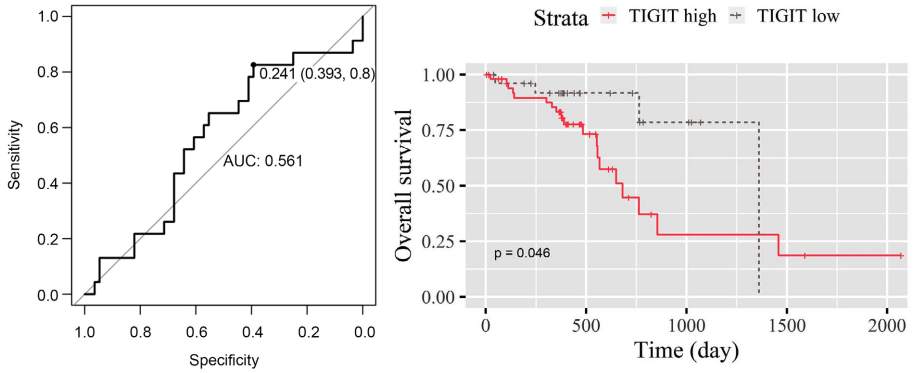
3.4. Correlation between TIGIT Expression and the Level of Immune Cell Infiltration in ESCC

To investigate the relationship between TIGIT and the tumor immune microenvironment of ESCC, we analyzed the ratio of ESCC data to the content of 22 immune cells in the TCGA database (**Figure 4(a)**). Also, we divided TIGIT into two groups of high and low expression by the median word of TIGIT in ESCC. The difference in immune infiltration was higher in the increased expression group compared to the low expression group, with higher scores for tumour stromal cells and infiltrating immune cells (**Figure 4(b)**); As immune infiltration is associated with altered immune cells in the tumour immune microenvironment and immune cells infiltrating the TME are usually considered to be tumour cells, we further performed the StromalScore, ImmuneScore and ESTIMATESScore as shown in **Figure 4(c)**, All scores in the TIGIT high expression group were higher than those in the low expression group, and the difference between the Immune score and the Estimated score was more pronounced, and since the Estimated score was the sum of the Stromal score and the Immune score, we concluded that TIGIT was significantly correlated with immune cell infiltration; In addition, we further assessed the difference in immune infiltration between the high and low TIGIT expression groups, as shown in **Figure 4(d)**, TIGIT expression significantly affected CD8+ T cells, activated CD4+ T cells and M1 macrophages, and we also assessed the possible correlation between TIGIT expression and 22 immune cells, and **Figure 4(e)** shows the relationship between the 22 immune cell abundances.

3.5. TIGIT Expression Correlates with Immune Genes

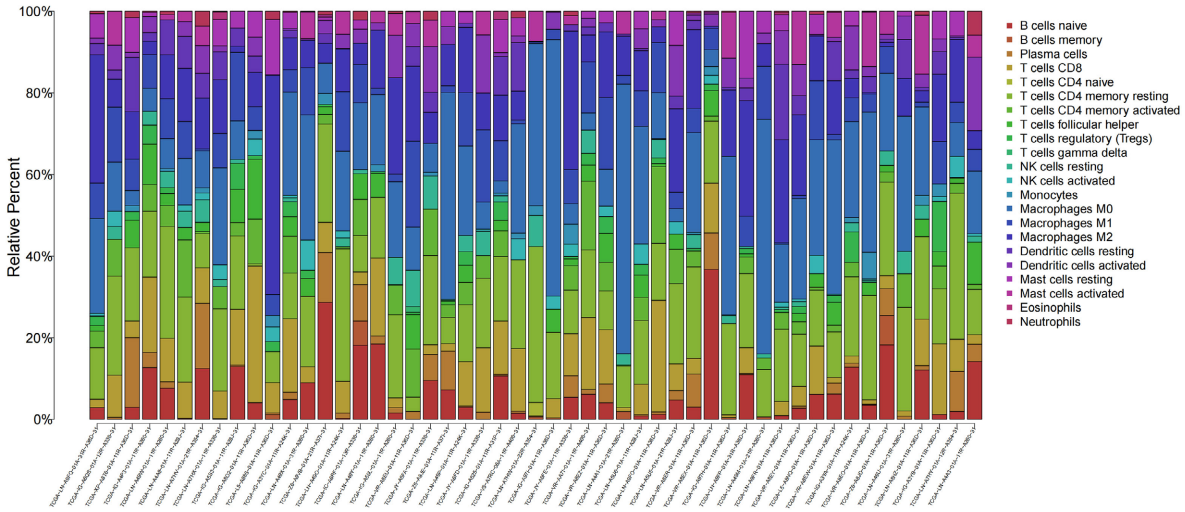
More than one immune gene may be involved in the development of a tumor. To determine the correlation between TIGIT expression and other immune genes, we analyzed the expression of TIGIT with the expression of 14 common immune genes, as shown in **Figure 5**. TIGIT expression was significantly correlated and positively correlated with PDCD1, CD274, IDO1, LAG3, TNSFS14,

HAVCR2, and CTLA4, suggesting that TIGIT may act in conjunction with these genes to promote ESCC development.

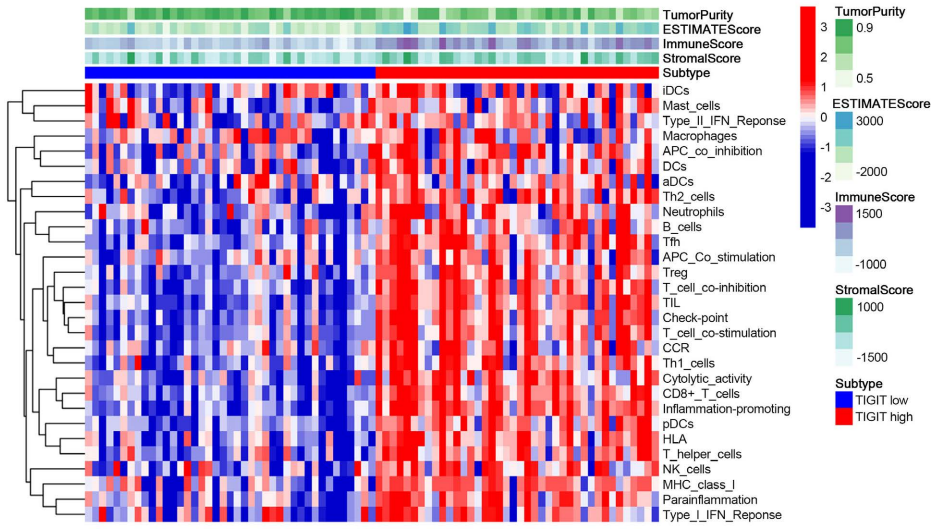


(a) (b)

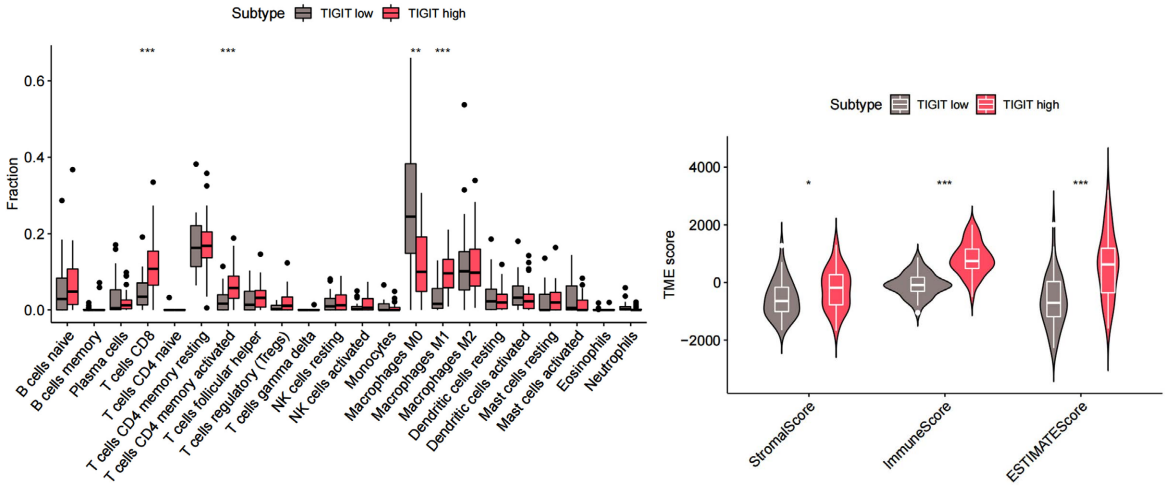
Figure 3. TIGIT survival analysis in ESCC.



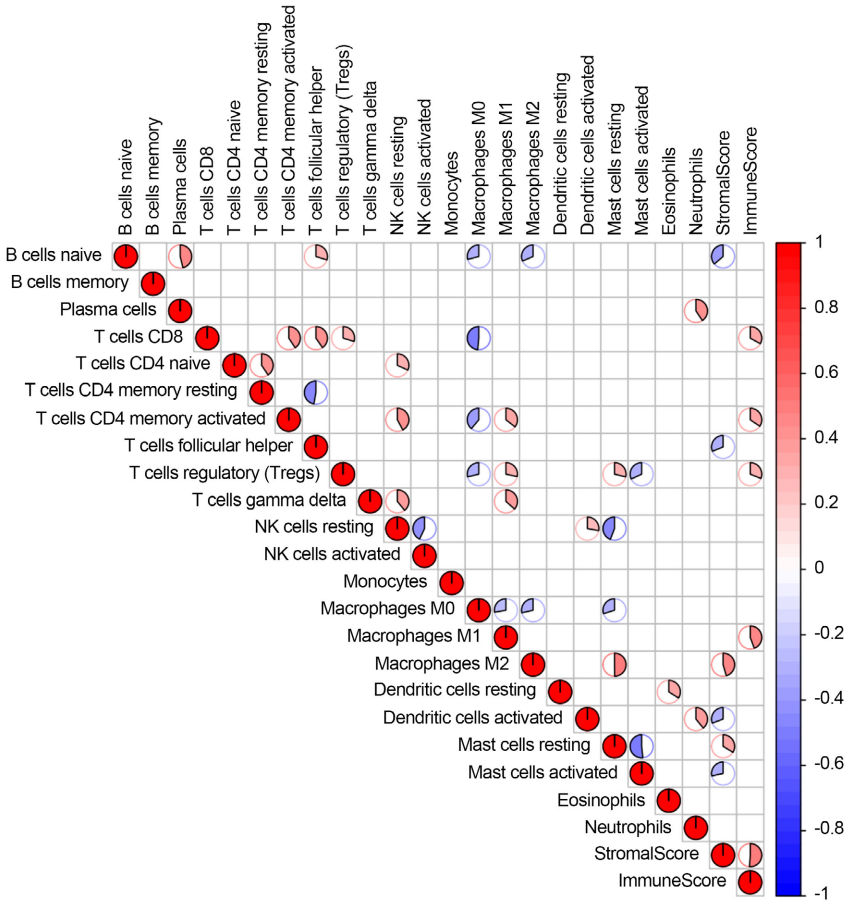
(a)



(b)



(c) (d)



(e)

Figure 4. Correlation of TIGIT expression with the level of immune cell infiltration in ESCC (e: The value indicates the correlation value. Red represents positive correlations, blue represents negative correlations.).

3.6. KEGG and GO Analysis

To gain a deeper understanding of the biological functions of TIGIT in ESCC and the possible pathways involved, we performed GO, and KEGG enrichment

analyses, which showed that TIGIT was significantly involved in T cell receptor signaling pathways, cytokine-cytokine interactions, and GO functional analysis showed that TIGIT was involved in T cell activation, natural killer cell-mediated immunity (**Figure 6(a)**, **Figure 6(b)**) HALLMARK enrichment analysis showed that TIGIT is closely associated with interferon-gamma effector genes (**Figure 6(c)**). GSEA showed that TIGIT is highly enriched in the signature genome and also indicated that TIGIT is substantially involved in the GO gene set, including mediation of immunity, cytokine binding and T cell activation. Finally, the KEGG genome showed that TIGIT is associated with T cell receptor signaling pathways.

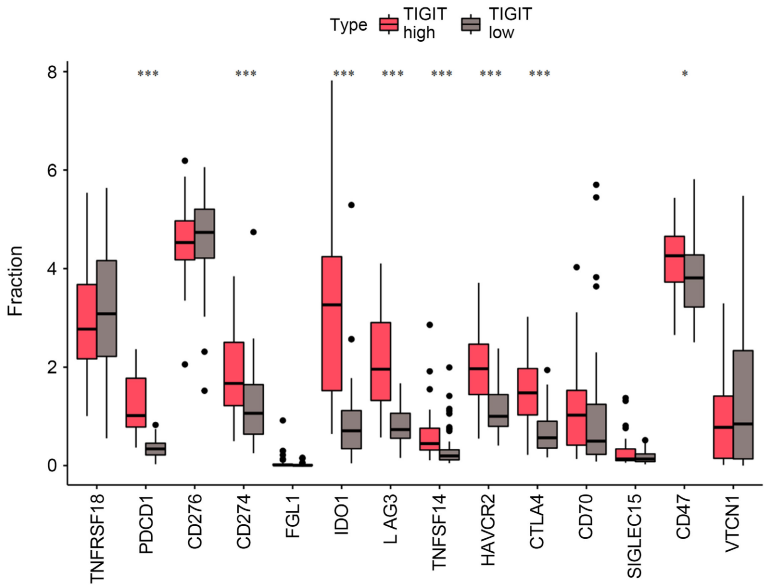
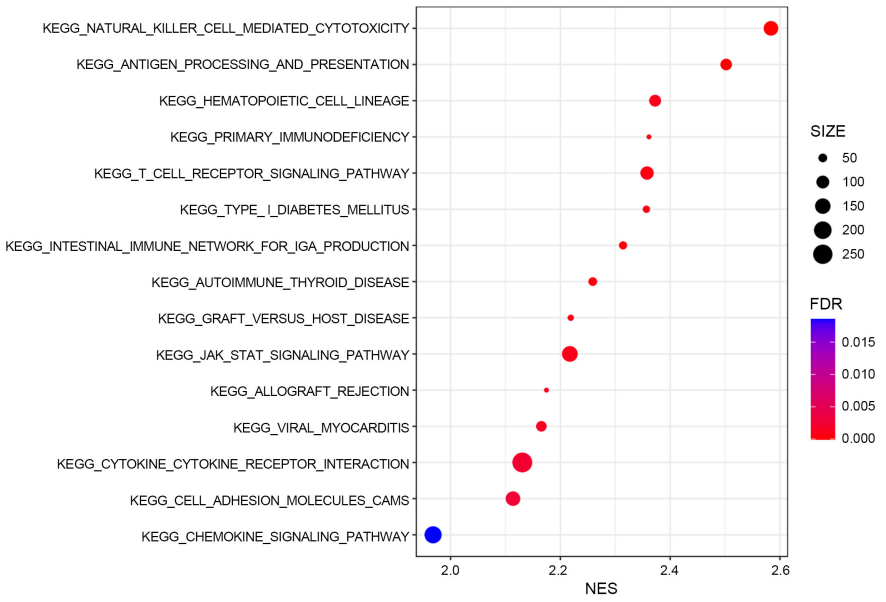
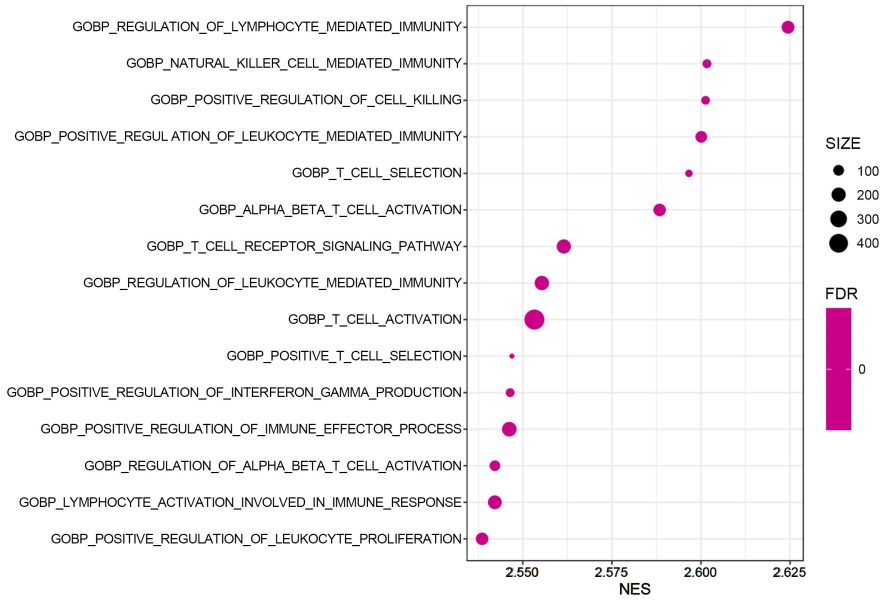


Figure 5. Correlation of TIGIT expression with immune genes.



(a)



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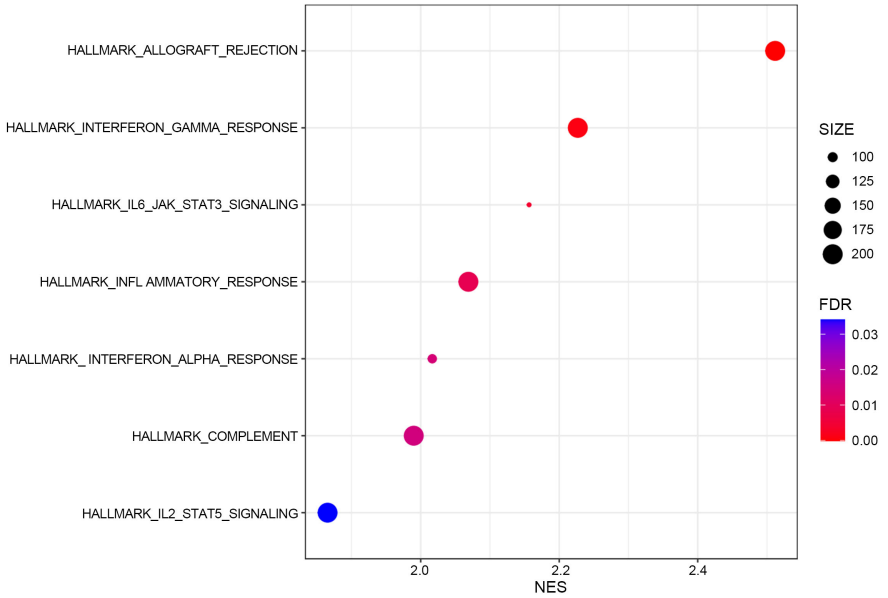

(c)

Figure 6. GSEA analysis of the role of TIGIT expression and the immune microenvironment of ESCC tumors.

4. Discussion

In recent years, research into the mechanisms of malignant tumours and therapeutic strategies has also evolved with the continuous development of malignant tumors. Traditional therapeutic means are no longer sufficient to treat malignant tumors. The emergence of immune checkpoint gene inhibitors marks a new era in tumor therapy, achieving unprecedented therapeutic effects in several malignant tumors [32]. 2002 Schreiber *et al.* first proposed the theory of immune editing, which was first proposed by Schreiber *et al.* in 2002, divided it in-

to three stages: immune clearance, homeostasis, and escape [33]. In contrast, tumor cells can alter the immune microenvironment of the tumor by recruiting immunosuppressive cells and molecules, thereby evading the body's immune recognition and attack. This makes immunosuppressive cells and molecules particularly important [34]. TIGIT, one of the emerging immune checkpoint genes, inhibits the anti-tumor response of T cells and NK cells by binding to the ligand CD155, leading to immune escape of tumor cells and thus promoting tumor progression.

In this paper, we used a bioinformatics approach to analyze the relationship between TIGIT and the clinical features of ESCC. We used the TCGA database to analyze that TIGIT was highly expressed in a variety of tumors; we further verified that TIGIT expression was significantly upregulated in oesophageal cancer by analyzing the EC data in the TCGA database; we then performed ROC curve analysis and plotted Kaplan We then performed ROC curve analysis and plotted Kaplan-Meier curves to use survival analysis further and found that ESCC cancer patients with high TIGIT expression had significantly worse OS. These results suggest that TIGIT is a relevant biomarker for survival prognosis in ESCC.

The tumor immune microenvironment plays a vital role in the development of tumourigenesis [35]. In this study, we examined the differences in immune infiltration between the high and low TIGIT expression groups by analyzing the ESCC data in the TCGA database. Compared with the low expression group, the high expression group had higher TIGIT immune cell expression and higher scores than the low expression group. The differences in immune scores and estimated scores were more pronounced, indicating that there was a significant correlation between TIGIT and immune cell infiltration. The TIGIT expression levels were significantly and positively correlated with the immune infiltration levels of CD8+ T cells, CD4+ T cells, and M1 macrophages, indicating that TIGIT is likely to be involved in the immune infiltration process of ESCC cells. We also performed GSEA to analyze the relationship between TIGIT and TME. GSEA showed that TIGIT was highly enriched in the signature genome and that TIGIT was mainly involved in mediating immunity, cytokine binding, and T cell activation, while TIGIT was also associated with the T cell receptor signaling pathway, suggesting that TIGIT is intimately involved in the alteration of TIME.

5. Conclusion

In conclusion, this study showed that TIGIT was highly expressed in ESCC by bioinformatics, and its high expression was closely associated with poor patient prognosis. TIGIT may influence the progression of ESCC by participating in the immune infiltration of TIME and thus in the remodeling of TIME. These findings provide potential prognostic indicators and therapeutic targets for diagnosing and managing ESCC. Although this study illustrates the relationship between TIGIT and clinical features of ESCC and the relationship between TIMEs, this study has certain limitations. Firstly, the sample size needs to be further expanded to cope with the wide heterogeneity of tumours, and also the lack of sys-

tematic *in vitro* cellular and corresponding molecular mechanism studies and *in vivo* animal studies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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