Prognostic value of TIGIT in East Asian patients with solid cancers: A systematic review, meta-analysis and pancancer analysis

Sicong Li1†, Lanxing Li2†, Tianyan Pan2, Xiaoqun Li3, Yujia Tong4 and Yongdong Jin5*

1School of Pharmacy, Peking University Health Science Centre, Beijing, China, 2School of Medicine, University of Electronic Science and Technology of China, Chengdu, China, 3Center of Disease Prevention Treatment, The Third Affiliated Hospital of Beijing University of Chinese Medicine, Beijing, China, 4Institute of Medical Information, Chinese Academy of Medical Sciences/Peking Union Medical College, Beijing, China, 5Department of Medical Oncology, Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China

Background: T-cell immunoreceptor with Ig and ITIM domains (TIGIT) participates in tumor immune escape by delivering inhibitory signals to T cells. The purpose of this article was to assess the prognostic value of TIGIT and its immunological function in solid cancers.

Methods: Three databases were searched for relevant articles. The main endpoints were overall survival (OS), progression-free survival (PFS), recurrence-free survival (RFS), and disease-free survival (DFS). Hazard ratios (HR) were pooled by using fixed-effects or random-effects models. Pancancer analysis of TIGIT was performed based on public online databases, mainly The Cancer Genome Atlas (TCGA), Genotype-Tissue Expression (GTEx), and UCSC Xena. The possible relationships between TIGIT expression and the tumor microenvironment (TME), infiltration of immune cells, immune-related genes, tumor mutation burden (TMB), and microsatellite instability (MSI) were revealed in this article.

Results: Sixteen studies met the inclusion criteria. High expression of TIGIT was associated with worse OS (HR = 1.73, 95% confidence interval [CI] 1.50, 1.99), PFS (HR = 1.53, 95% CI [1.25, 1.88]), RFS (HR = 2.40, 95% CI [1.97, 2.93]), and DFS (HR= 6.57, 95% CI [0.73, 59.16]) in East Asian patients with solid cancers. TIGIT expression was positively correlated with immune infiltration scores and infiltration of CD8 T lymphocytes in all of the cancers included. TIGIT was found to be coexpressed with the genes encoding immunostimulators, immunoinhibitors, chemokines, chemokine receptors, and major histocompatibility complex (MHC), especially in gastrointestinal cancer. TMB and MSI were also associated with TIGIT upregulation in diverse kinds of cancers.
Conclusion: High expression of TIGIT is associated with poorer prognosis in East Asian patients with solid cancers. TIGIT is a novel prognostic biomarker and immunotherapeutic target for various solid cancers because of its activity in cancer immunity and tumorigenesis.

KEYWORDS
TIGIT, solid cancer, prognosis, meta-analysis, systematic review

1 Introduction

In the tumor microenvironment (TME), T cells are the second most abundant cell type after tumor-associated macrophages (TAMs) (1–3). Several immune inhibitor receptors (IRs), such as TIGIT, are upregulated in solid cancers and take part in tumor immune escape (4–6). As an important T-cell receptor in the TME, TIGIT competes with the costimulatory receptor cluster of differentiation 226 (CD226) for its interaction with the cluster of differentiation 155 (CD155) (7, 8) and participates in inhibiting adaptive and innate immunity. Highly expressed on active Regulatory T cells (Tregs), memory cluster of differentiation 8 (CD8) and memory cluster of differentiation (CD4) T-cell (9, 10), TIGIT can inhibit the cytotoxicity mediated by natural killer (NK) cells (1), the maturation and proinflammatory response of dendritic cells (DCs) (11), the effector functions of T helper cell 17 (Th17) and T helper cell 1 (Th1) cells (12), and enhance the immunosuppressive functions of Tregs by promoting the production of interleukin-10 (IL-10) and fibrinogen-like protein 2 (Fgl2) (13).

The prognostic value of TIGIT has become a research hotspot in recent years, but the results remain controversial. Therefore, we conducted a meta- and bioinformatic analysis in this article for the following purposes: ① to evaluate the prognostic value of TIGIT in OS, DFS, PFS, and RFS and ② to determine the relationship between TIGIT expression and the tumor microenvironment and immune microenvironment.

2 Methods

2.1 Meta-analysis

2.1.1 Data sources and search strategy

This systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (14). Embase (https://www.embase.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), and the Cochrane Library (https://www.cochranelibrary.com/) were searched for articles. The retrieval time was from inception to May 28, 2022. This review was registered on the PROSPERO platform (CRD42022324498). The search strategy is described in Supplementary Materials Tables 1–3.

2.1.2 Inclusion and exclusion criteria

Inclusion criteria included ① East Asian patients diagnosed with solid cancer before enrollment, ② randomized controlled trials (RCTs) or observational studies, ③ sufficient data about TIGIT expression and clinical outcome for meta-analysis, and ④ TIGIT expression was determined by using immunohistochemistry. The exclusion criteria included ① case reports, single-cell sequencing data, animal experiments, meta-analyses, network meta-analyses, conference presentations, or study protocols.

2.1.3 Outcomes

Outcomes included ① overall survival (OS), ② progression-free survival (PFS), ③ recurrence-free survival (RFS), and ④ disease-free survival (DFS).

2.1.4 Study selection and data extraction

Two review authors (Sicong Li and Lanxing Li) independently reviewed the titles and abstracts of trials with potential eligibility. After that, we downloaded the full texts of trials eligible for inclusion. Two authors (Xiaochun Li and Tianyan Pan) independently extracted the following data: ① basic information, including first author, publication year, sample size, country, and study design; ② characteristics of patients, including sex, age, type, and stage of cancer; ③ details about TIGIT, including expression location and cutoff value to judge high expression; ④ details about clinical outcomes; ⑤ information of cancer treatment; ⑥ information of quality assessment. Any disagreement was resolved by group discussion and consensus. We excluded results reported in
only one study. In the studies that did not report HR values, we obtained the required data related to survival analysis from the survival curve by using GetData Graph Digitizer software.

2.1.5 Strategy for meta-analysis

This meta-analysis was performed by using R (version 4.0.3). The chi-square test and I² value were used to measure statistical heterogeneity. I²<50% and P value>0.05 indicated no substantial heterogeneity, and a fixed-effects model was used to pool the value of HR and 95% confidence interval. Otherwise, the random-effects model was used because of significant heterogeneity. Subgroup analysis was conducted to analyze sources of heterogeneity, while sensitivity analysis was conducted by excluding one study each time. Beggs’s and Egger’s tests were used to assess publication bias. Statistical significance was set as α=0.05 in this study.

2.1.6 Quality assessment

Two reviewers (Yongdong Jin, Yujia Tong) assessed the quality of eligible studies independently by using the Newcastle–Ottawa Quality Assessment Scale (NOS) (15). The NOS assessed the quality of studies from the aspects of selection, comparability, and exposure, with a total score ranging from 0 to 9 points. More than 6 points was defined as high-quality.

2.2 Pan-cancer analysis

2.2.1 Data extraction and preprocessing

We downloaded the standardized pancancer data set from the UCSC (https://xenabrowser.net/) database: TCGA TARGET GTEx (PANCAN, N=19131, G=60499). Then, we extracted the expression data of the ENSG00000181847 (TIGIT) gene and 150 immune-related genes, including chemokines (n = 41), receptors (n = 18), major histocompatibility complexes (n = 21), immunoinhibitors (n = 24) and immunostimulators (n = 46), in normal solid tissues, primary solid tumors, normal tissues, primary blood-derived cancer-bone marrow, and peripheral blood. After excluding the cancer species with less than 3 samples in a single cancer species, the expression data of cancer species mentioned in the meta-analysis were finally obtained, including bladder urothelial carcinoma (BLCA), colon adenocarcinoma (COAD), colon adenocarcinoma/Rectum adenocarcinoma esophageal carcinoma (COADREAD), esophageal carcinoma (ESCA), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma(LUAD), lung squamous cell carcinoma (LUSC), rectum adenocarcinoma (READ), stomach adenocarcinoma (STAD), skin cutaneous melanoma (SKCM), stomach and esophageal carcinoma(STES), thyroid carcinoma (THCA). We also extracted the gene expression profile of each tumor and converted the Tag names into gene symbols.

2.2.2 Differential expression of TIGIT among tumor and normal samples

We used the unpaired Wilcoxon-rank sum and signed-rank tests to compare the difference in TIGIT expression between normal samples and tumor samples in each tumor. A violin plot was used to visualize the results.

2.2.3 Differential expression of TIGIT among simple nucleotide variation (SNV) and copy number variation (CNV) data

From the GDC (https://portal.gdc.cancer.gov/) database, we downloaded the simple nucleoside variation (SNV) data set (level 4) and the copy number variation (CNV) data set (level 4) of all TCGA samples processed by MuTect2 (16) and GISTIC software (17), respectively. After removing samples of synonymous mutations, we obtained the expression data of 9 and 6 cancer species for CNV and SNV, respectively. Moreover, the domain information of TIGIT was obtained from the maftools package (version 2.2.10) of R software. A lollipop plot was used to depict the protein mutational distribution and domains.

2.2.4 Relevance between TIGIT expression and the tumor microenvironment

We used the ESTIMATE package (version 1.0.13, https://bioinformatics.mdanderson.org/public software/estimate/) (18) to calculate the stromal, immune, and estimate scores for the cancers included in this article. The increased stromal and immune scores indicated an increased proportion of immune cells or stromal cells in the TME. Furthermore, the corr.test function of the psych package in R software (version 2.1.6) was used to conduct Pearson’s correlation test.

2.2.5 Correlation between TIGIT expression and immune cell infiltration

We used the deconvo.CIBERSOR (19) and TIMER methods (20) in iOBDR (version 0.99.9) (21) of R software to calculate the infiltration score of the 22 tumor-infiltrating immune cells, including naive B cells, memory B cells, plasma cells, CD8 T cells, naive CD4 T cells, resting and activated memory T cells, follicular helper T cells (Tfh), regulatory T cells (Treg), gamma delta T cells, resting and activated NK cells, monocytes, resting M0, M1 and M2 macrophages, resting and activated dendritic cells (DCs), resting and activated mast cells, eosinophils, and neutrophils. The results are displayed in the form of heatmap plots.

2.2.6 Associations of TIGIT expression with immune-related genes, tumor mutation burden (TMB) level and microsatellite instability (MSI) status

First, we calculated the Spearman correlation between TIGIT and the 150 immunomodulators. The results were
visualized in heatmap plots. Then, we used the TMB function of the maftools package (version 2.8.05) in R software to calculate the TMB score for each tumor and obtained the MSI score of each tumor from a previous study reported by Russell Bonneville (22). We integrated the MSI and gene expression data of the samples and further performed log2 (x+0.001) transformation on each expression value. The correlation between TIGIT expression and TMB or MSI was analyzed by means of the Spearman correlation coefficient, and the results are displayed in the form of lollipop plots (23).

2.2.7 Protein–protein interaction network construction

GeneMANIA (http://www.genemania.org) was used to build a protein–protein interaction (PPI) network. Physical interaction, coexpression, and gene enrichment analyses were performed by using the network integration algorithm. The results were visualized by using the bioinformatic website (http://www.bioinformatics.com.cn/).

2.2.8 Construction of competing endogenous RNA (ceRNA) networks

First, we used miRwalk (http://mirwalk.umm.uni-heidelberg.de/ accessed on 30 May 2022) to predict target miRNAs of TIGIT that can bind to the TIGIT 3’-UTR. Next, miRNA–lncRNA interactions were obtained from RNAInter v4.0 (http://www.rnainter.org/search/) with the species set as Homo sapiens. Finally, the ceRNA network was visualized by using Cytoscape 3.8.2 (24) software.

2.2.9 Statistical analysis

Statistical data analysis was conducted by using R software (version 4.0.3) (https://www.r-project.org/). The unpaired Wilcoxon-rank sum and signed-rank tests were used to analyze the significance of the difference between two groups, and the Kruskal test was used to test the difference among multiple groups of samples. The correlation between TIGIT expression and the other variable was assessed utilizing the Spearman correlation coefficient. P values of less than 0.05, 0.01 and 0.001 are presented as “*”, “**”, and “***”, respectively.

3 Results

3.1 Results of the meta-analysis

3.1.1 Search results

In total, 16 studies involving 2488 patients with solid cancers were found to meet the inclusion criteria. All of them were retrospective cohort studies. Although Pooja Ghatalia (25) and Pankaj Ahluwalia (26) reported the prognostic value of TIGIT in cancer patients, they did not report the hazard ratio or odds ratio value of TIGIT. Therefore, the patients included were from the East Asian population. The flow chart of the study selection process is presented in Figure 1.

3.1.2 Study characteristics

The basic characteristics of the included studies are shown in Table 1. Studies were published between 2018 and 2022. Zhao JJ (27), Peipei Wang (28) and Zhao K (29) reported survival outcomes of esophageal squamous cell carcinoma (ESCC) or primary small cell carcinoma of esophagus (PSCCE), Tang W (30) and Liu HF (31) reported gastric cancer (GC), Xu Y (32) reported small cell lung cancer (SCLC), Sun Y (33) and Jiang C (34) reported non-small cell...
| Author          | Sample size | Country | Age               | Treatment other than surgery | TIGIT+ expression | Expression location | Cutoff value of TIGIT | Outcome Method       | Method to estimate HR |
|-----------------|-------------|---------|-------------------|-----------------------------|-------------------|---------------------|----------------------|----------------------|----------------------|
| Zhao JJ (2018)  | 154         | China   | 55 (37–48)        | ESCC                         | Not available     | TIL                 | Median level         | OS                   | Multivariate          |
| Tang W (2019)   | 441         | China   | (<62.159, ≥62.282) | GC                           | Adjuvant chemotherapy | 343 (77.8%) Tumor cell | ≥5% positivity cell | OS                   | Multivariate          |
| Xu Y (2020)     | 60          | China   | (<60.34, >60.26)  | SCLC                         | Adjuvant chemotherapy | 21 (35%) Tumor cell | Median level         | OS                   | Univariate            |
| Lee WJ (2020)   | 124         | Korea   | 61.8 (25–89)      | Melanoma                     | Not available     | 52 (41.9%) Tumor cell | ≥20% positivity cell | OS/PFS               | Univariate            |
| Sun Y (2020)    | 334         | China   | 56 (28–81)        | NSCLC                        | Not available     | 204 (61.1%) TIL    | ≥5% positivity cell | OS/PFS               | Multivariate          |
| Zhao K (2020)   | 114         | China   | ≤60 76, >60 38    | PSCCE                        | Adjuvant chemotherapy/chemoradiotherapy | 74 (64.9%) Tumor cell | ≥5% positivity cell | OS/PFS               | Multivariate          |
| Zhou X (2020)   | 60          | China   | ≤60 34, >60 26    | CRC                          | Not available     | 21 (35%) Tumor cell | CPS≥1                | OS/DFS               | Multivariate          |
| Liang R (2021)  | 139         | China   | ≤45.25, >45 114   | CRC                          | Not available     | 40 (28.8%) Tumor cell | Median level         | OS/DFS               | Univariate            |
| Liu HF (2022)   | 194         | China   | 56 ± 12.66        | GC                           | Adjuvant chemotherapy | 97(50%) TIL        | Median level         | OS                   | Multivariate          |
| Peipei Wang (2021) | 95         | China   | 58 ± 10           | ESCC                         | Not available     | 68(72%) Tumor cell | Median level         | OS                   | Multivariate          |
| Daisuke Murakami (2022) | 100        | Japan   | >70 53 (53%); <70 years 47 (47%) | CRC                          | Not available     | 79(79%) TIL         | ≥10% positivity cell | OS                   | Multivariate          |
| Jiang C (2022)  | 81          | China   | 63 (29–81)        | NSCLC                        | Not available     | 33 (40.7%) TIL     | CPS≥1                | OS                   | Multivariate          |
| Yu LH (2021)    | 133         | China   | 58.3 ± 11.4       | HBV-HCC                       | Adjuvant immunotherapy + adjuvant chemotherapy | 65(48.87%) TIL | Median level         | PFS                  | Multivariate          |
| Shi X (2021)    | 200         | China   | 49 (12–80)        | MTC                          | Not available     | 6 (3.0%) Tumor cell | CPS≥1                | OS/DFS               | Univariate            |
| Liu ZP (2020)   | 141         | China   | ZSHC cohort 62 (56-71); FUSCC cohort 62 (56-68) | MIBC                        | Adjuvant chemotherapy | ZSHC cohort46 (32.62%); FUSCC cohort 68 (57.63%) | TIL | Median level | OS/DFS | Multivariate          |
| Luo Y (2022)    | 234         | China   | 55.50 (41.25, 66.50) | TC                          | Not available     | 37 (15.81%) Tumor cell and TIL | CPS≥1                | OS/DFS               | Multivariate          |

Lung cancer (NSCLC), Zhou X (35), Liang R (36) and Daisuke Murakami (37) reported colorectal cancer (CRC), Lee WJ (38) reported melanoma, Yu LH (39) reported hepatitis B virus hepatocellular carcinoma (HBV-HCC), and Liu ZP et al. reported the ZSHS cohort and the FUSCC cohort that reported survival outcomes of patients with muscle-invasive bladder cancer (MIBC) (40). Luo Y reported (41) 3 cohorts of patients with advanced thyroid carcinoma (ATC), including anaplastic thyroid carcinoma (ATC), poorly differentiated thyroid carcinoma (PDTC), and locally advanced papillary thyroid carcinoma (PTC). HR values in the studies reported by Xu Y (2019), Liang R (2021), Lee WJ (2020), Sun Y (2020),
A Overall survival

| Study      | TE  | seTE | Hazard Ratio | HR   | 95%-CI (common) | Weight (random) |
|------------|-----|------|--------------|------|-----------------|-----------------|
| Zhao JJ, 2018 | 0.59 | 0.2445 | 1.81 | [1.12; 2.92] | 8.3% | 8.6% |
| Tang W, 2019  | 0.58 | 0.1748 | 1.79 | [1.27; 2.52] | 16.3% | 13.4% |
| Xu Y, 2019    | 0.32 | 0.5181 | 1.38 | [0.50; 3.81] | 1.9% | 2.4% |
| Lee W, 2020   | 0.73 | 0.2937 | 2.08 | [1.17; 3.70] | 5.8% | 6.5% |
| Sun Y, 2020   | 0.25 | 0.1571 | 1.28 | [0.94; 1.74] | 20.2% | 15.1% |
| Zhao K, 2020  | 0.46 | 0.2525 | 1.59 | [0.97; 2.61] | 7.8% | 8.2% |
| Zhou X, 2020  | -0.39| 0.4494 | 0.68 | [0.28; 1.64] | 2.5% | 3.1% |
| Liang R, 2021 | 1.44 | 0.3654 | 4.22 | [2.06; 8.64] | 3.7% | 4.5% |
| Liu HF, 2022  | 0.50 | 0.2377 | 1.64 | [1.03; 2.62] | 8.8% | 8.9% |
| Wang PP, 2021 | 1.56 | 0.5479 | 4.78 | [1.63; 13.90] | 1.7% | 1.7% |
| Daisuke Murakami, 2022 | 1.19 | 0.5485 | 3.27 | [1.12; 9.59] | 1.7% | 2.2% |
| Jiang C, 2022 | 0.43 | 0.3023 | 1.53 | [0.85; 2.77] | 5.4% | 6.2% |
| Shi X, 2021   | 0.56 | 0.7238 | 1.73 | [0.47; 7.15] | 1.0% | 1.3% |
| Liu GP a, 2020 | 0.68 | 0.2608 | 1.97 | [1.18; 3.28] | 7.3% | 7.8% |
| Liu GP b, 2020 | 0.97 | 0.3659 | 2.63 | [1.28; 5.36] | 3.7% | 4.5% |
| Luo Y a, 2022  | 0.25 | 0.5347 | 1.29 | [0.45; 3.68] | 1.7% | 2.3% |
| Luo Y b, 2022  | 0.57 | 0.5995 | 1.76 | [0.65; 4.78] | 1.9% | 2.5% |
| Luo Y c, 2022  | 2.18 | 1.1592 | 8.81 | [0.91; 86.45] | 0.4% | 0.5% |

Common effect model: 1.73 [1.51; 1.99] 100.0% --
Random effects model: 1.78 [1.51; 2.09] -- 100.0%

B Progression free survival

| Study      | TE  | seTE | Hazard Ratio | HR   | 95%-CI (common) | Weight (random) |
|------------|-----|------|--------------|------|-----------------|-----------------|
| Sun Y, 2020   | 0.41 | 0.1347 | 1.50 | [1.15; 1.95] | 61.1% | 61.1% |
| Zhao K, 2020   | 0.26 | 0.2238 | 1.30 | [0.84; 2.02] | 22.1% | 22.1% |
| Yu LH, 2021   | 0.72 | 0.2573 | 2.06 | [1.24; 3.39] | 16.8% | 16.8% |

Common effect model: 1.63 [1.26; 1.88] 100.0% --
Random effects model: 1.63 [1.26; 1.88] -- 100.0%

C Recurrence free survival

| Study      | TE  | seTE | Hazard Ratio | HR   | 95%-CI (common) | Weight (random) |
|------------|-----|------|--------------|------|-----------------|-----------------|
| Liang R, 2021 | 1.03 | 0.1296 | 2.80 | [2.17; 3.61] | 61.5% | 45.4% |
| Shi X, 2021  | 0.55 | 0.7238 | 1.73 | [0.42; 7.15] | 2.0% | 4.1% |
| Liu GP a, 2020 | 0.76 | 0.2644 | 2.13 | [1.27; 3.58] | 14.8% | 22.1% |
| Liu GP b, 2020 | 0.66 | 0.2176 | 1.74 | [1.14; 2.67] | 21.8% | 28.3% |

Common effect model: 2.40 [1.97; 2.93] 100.0% --
Random effects model: 2.26 [1.68; 3.04] -- 100.0%

D Disease free survival

| Study      | TE  | seTE | Hazard Ratio | HR   | 95%-CI (common) | Weight (random) |
|------------|-----|------|--------------|------|-----------------|-----------------|
| Zhou XB, 2020 | 1.38 | 0.5526 | 3.96 | [1.34; 11.70] | 80.5% | 80.5% |
| Luo Y, 2022  | 1.88 | 1.1213 | 6.57 | [0.73; 59.16] | 19.5% | 19.5% |

Common effect model: 4.37 [1.65; 11.55] 100.0% --
Random effects model: 4.37 [1.65; 11.55] -- 100.0%

FIGURE 2
Forest plot for all outcomes. (A. Overall survival B. Progression free survival C. Recurrence free survival D. Disease free survival).
and Zhao K (2020) were obtained by calculating the data extracted from the survival curve.

The HR values in the studies reported by Xu Y (2019), Liang R (2021), Lee WJ (2020), and Shi X (2021) were estimated by only univariate analysis, while the others were estimated by both multivariate analyses. Regarding the quality of the included studies, NOS scores ranged from 6 to 8.

3.1.3 Results of OS, PFS, RFS, and DFS

The I² value was less than 50%, and the p value was above 0.05, so the fixed-effect model was used in the comparison of OS, PFS, RFS, and DFS. The pooled results of the meta-analysis showed that high expression of TIGIT was associated with shorter OS (HR = 1.73, 95% CI [1.50, 1.99]), PFS (HR = 1.53, 95% CI [1.25, 1.88]), RFS (HR = 2.40, 95% CI [1.97, 2.93]) and
DFS (HR = 4.37, 95% CI [1.65, 11.55]) in patients with solid cancers than low expression of TIGIT (see Figure 2).

In the 2 studies about DFS, TIGIT was expressed on tumor cells, and CPS≥1 was set as the cutoff value of TIGIT expression. Moreover, multivariate analysis was used to estimate the HR value in the comparison of DFS and PFS, so we did not conduct subgroup analysis in these aspects. No significant prognostic value of TIGIT was found in the OS of cancers, including SCLC, CRC, MTC, ATC, PDTC and PTC. Studies with sample sizes <100 did not support the prognostic value of TIGIT and OS (HR = 1.55, 95% CI [0.76, 3.19]). PSCCE and TIGIT expressed on tumor cells did not support the prognostic value of TIGIT in PFS, while medullary thyroid carcinoma and papillary thyroid carcinoma did not support the prognostic value of TIGIT in RFS and DFS, respectively. Postoperative treatments were not found to be a source of heterogeneity in OS and RFS, probably because nearly half of the studies did not describe them. In terms of PFS, adjuvant chemotherapy/chemoradiotherapy did not support the prognostic value of TIGIT, and this result should be discussed with care because of limited study numbers and sample sizes (see Figures 3–6).

The p values of Begg’s test and Egger’s test for OS and RFS were above 0.05, which indicated no significant publication bias. In the sensitivity analysis, the DFS results would change if Zhou XB (2020) was omitted. (Liang R, 2021), (Yu LH, 2021), (Liu ZP, 2020), and (Luo YC, 2022) contributed the most to the overall heterogeneity in OS, PFS, RFS, and DFS, respectively.

### 3.2 Pancancer analysis

The design flow and implementation approaches of this study are illustrated in Figure 7. This study integrally revealed the role of TIGIT in the tumor immune microenvironment.
3.2.1 Differential expression of TIGIT among cancer and normal samples

The expression of TIGIT was significantly upregulated in the 9 cancers involved in this study, including LUAD (tumor:1.44 ± 1.33, normal:0.49 ± 0.99, P=2.6e^{-32}<0.05), ESCA (tumor: 0.29 ± 1.59, normal:-2.58 ± 1.72,P=2.5e^{-57}<0.05), STES (tumor: 0.71 ± 1.57, normal: -2.35 ± 1.73, P=1.3e^{-151}<0.05), COAD (tumor:0.01 ± 1.62,normal:-1.81 ± 2.07, P=1.4e^{-26}<0.05), COADREAD (tumor:-0.03 ± 1.60,normal:-1.75 ± 2.08,P=1.9e^{-27}<0.05), STAD (tumor:0.89 ± 1.53,normal:-1.66± 1.58,P=7.8e^{-54}<0.05),LUSC (tumor:1.25 ± 1.36,normal:0.49 ± 0.99,P=1.8e^{-32}<0.05),

LIHC (tumor:-1.18 ± 1.86,normal:-1.71 ± 1.23,P=3.4e^{-3}<0.05), SKCM (tumor:-0.10 ± 2.07,normal:-2.40 ± 1.31,P=1.6e^{-26}<0.05), THCA (tumor:-0.51 ± 2.01,normal:-0.89 ± 1.92,P=1.6e^{-4}<0.05). However, no significant difference was observed between cancer and normal samples in BLCA (P=0.09>0.05) and READ (P=0.11>0.05) (Figure 8). The TIGIT expression values in different cancers are shown in Supplementary Table 5.

3.2.2 Impact of CNV and SNV on TIGIT expression

TIGIT expression was higher in CNV neutrals than in CNV gains in STAD and LUSC. Moreover, TIGIT expression was
higher in CNV neutral samples than in samples with CNV losses in LIHC and SKCM. This result indicated that CNV influenced TIGIT expression. No significant difference was found in TIGIT expression among patients with wild type and TIGIT mutation in terms of SNV.

Missense mutation was the most common type of mutation in the cancers included. Missense mutations in V-seIg were found in STES, COAD, COADREAD, LUAD, STAD, SKCM and READ. Among them, LUAD was found to have the most missense mutations. In-frame deletion occurred in COAD and COADREAD. A splice site was found in STAD and STES (see Figure 9). READ presented a relatively high mutation frequency (2.2%). TIGIT expression values in patients with wild-type, SNV or CNV are presented in Supplementary Tables 6, 7.

3.2.3 Correlation between TIGIT expression and the tumor microenvironment

Stromal and immune cells are two main types of nontumor components in the TME. The ESTIMATE algorithm can help to predict the tumor purity in tumor samples. We calculated the Spearman correlation coefficient between TIGIT expression and immune infiltration scores by using corr.test psych (version 2.1.6) in R software. Finally, a significant positive correlation was observed between TIGIT expression and immune infiltration scores (Stromals score, Immunes score and ESTIMATE score) in 12 kinds of cancers involved in these studies (see Supplementary Figures 5–7).

3.2.4 Correlation between TIGIT expression and the infiltration score of immune cells (CIBERSORT AND TIMER)

Tumor-infiltrating immunocytes could affect the survival prognosis of patients. TIGIT expression showed a positive correlation with the infiltration scores of CD8 T cells (especially in SKCM), M1 macrophages in 12 kinds of cancers, naive B cells in 10 kinds of cancers, activated memory CD4 T cells, Tregs in LUAD, LUSC, LIHC, SKCM, THCA, COADREAD and activated NK cells in LUAD, LUSC, SKCM, STES, BLCA. TIGIT expression was also negatively correlated with activated dendritic cells and mast cells in most of the cancers included. The correlation coefficient between TIGIT expression and immune cell infiltration (CIBERSORT) is presented in Supplementary Table 8. Moreover, TIGIT expression was found to be positively related to B cell, CD4, CD8 T cell, neutrophil, macrophage and DC infiltration in most cancers based upon the TIMER algorithm (Figure 10).

3.2.5 Correlation between TIGIT expression and 150 immune-related genes

The results showed that TIGIT exhibited a significant coexpression relationship with most chemokines, receptors, major histocompatibility complex (MHC), immunoinhibitors and immunostimulators. Notably, TIGIT expression was positively correlated with the expression of programmed cell death 1 (PDCD1), programmed cell death 1 ligand 2 (PDCD1LG2), cytotoxic T-lymphocyte associated protein 4 (CTLA4), lymphocyte activating 3 (LAG3), indoleamine 2,3-dioxygenase 1 (IDO1), interleukin 10 (IL-10), and transforming growth factor beta 1 (TGFBI), especially in gastroesophageal tumors and melanoma (Figure 11).

The correlation coefficients are presented in detail in Supplementary Table 9.

3.2.6 Associations of TIGIT expression with tumor mutational burden (TMB) and microsatellite instability (MSI)

Because of the essential roles of TMB and MSI in the prediction of the response to immune therapy, Spearman
Correlation analysis was conducted to assess the relationship between TIGIT expression, TMB, and MSI. The results showed that TIGIT expression was positively related to TMB in BLCA, COADREAD, COAD, and SKCM but negatively related to TMB in THCA. Moreover, TIGIT expression was positively correlated with MSI in COAD, COADREAD, and LUAD, while it was negatively correlated with MSI in ESCA and STES (see Figure 12). The correlation coefficients and P values are presented in Supplementary Tables 10, 11.

The results strongly indicated that TIGIT was well associated with tumor immunity. Therefore, TIGIT might be considered a promising biomarker for predicting the immunotherapy response.
3.2.7 Construction of the protein protein interaction (PPI) network, gene ontology (GO) and Kyoto encyclopedia of gene and genomes (KEGG) enrichment analysis

As presented in Figure 13A, we utilized the GeneMANIA online program to create a PPI network for 21 genes that interacted with TIGIT. TIGIT was found to interact with PDCD1, which indicated that patients with resistance to PD-1 inhibitors might benefit from the combination of TIGIT inhibitors. The biological processes (BP) enriched in this gene set were primarily those related to cell adhesion, heterophilic cell–cell adhesion via plasma membrane cell adhesion molecules and homophilic cell adhesion via plasma membrane adhesion molecules, while the cellular components (CC) enriched were plasma membrane AND integral component of membrane. The enriched molecular functions (MF) were linked to identical protein binding and receptor binding. The KEGG results showed that they were mainly enriched in the cell adhesion molecules, adherens junction and T-cell receptor signaling pathways (Figures 13B, C).

3.2.8 Construction of the ceRNA regulatory network

As shown in Figure 14, a ceRNA coexpression network consisting of 70 lncRNAs, 34 miRNAs, and 1 mRNA was visualized by Cytoscape after merging these predicted results. By using the CytoHubba plug-in in Cytoscape, we screened out the top 10 node degrees to represent the central genes of the PPI network, including TIGIT, hsa-miR-4516, hsa-miR-1255a, hsa-miR-1255b-5p, hsa-miR-1306-5p, hsa-miR-514a-3p, hsa-miR-6849-3p, hsa-miR-514b-3p, SNHG16, and hsa-miR-4534.

4 Discussion

The results of the meta-analysis showed that high expression of TIGIT was associated with poorer OS, PFS, RFS and DFS in East Asian patients with solid cancers. In contrast to the study reported by Kunmin Xiao et al (42), we also discussed the relationship between TIGIT and DFS and RFS. DFS and RFS are important clinical outcomes for cancers with relatively good clinical prognosis. Most importantly, we discussed the heterogeneity caused by postoperative treatments, which might have a very important impact on the prognosis of cancer patients. It was found in our study that the cancer type, sample sizes, and different cutoff values might be the source of heterogeneity. The high expression of TIGIT was not significantly correlated with poor PFS of PSCCE, RFS of MTC, DFS of PTC or OS of SCLC, CRC, MTC, ATC, PDTC and PTC. Studies with sample sizes <100 did not support the relationship between high expression of TIGIT and OS or DFS, while studies taking CPS≥1 as the cutoff value did not support the relationship.
FIGURE 11 (Continued)
between high expression of TIGIT and OS or RFS. Whether postoperative treatments result in heterogeneity still needs further study.

SCLC is a classical neuroendocrine tumor with low immunogenicity and low MHC I expression levels, which makes it difficult to recognize by CD8 T-cell receptors. Its immune regulation is more complex than that of other solid tumors due to the existence of autocrine or paracrine molecules. In ATC, TIGIT expression is not found to have prognostic value (38). The reason may be that ATC patients suffer from extremely short survival, and the sample size may be too small to distinguish the prognosis.

In our meta-analysis, a relationship between high expression of TIGIT and poorer OS was not found in the studies taking CPS \( \geq 1 \) as the cutoff value. The tumor proportion score (TPS) and the combined positive score (CPS) have been widely used in clinical research. TPS calculates the ratio of TIGIT-stained tumor cells to the total number of viable tumor cells, while CPS calculates the ratio of potential TIGIT expression, including tumor cells and immune cells, to the

![Figure 12](https://example.com/figure12.png)

**FIGURE 12**
Spearman correlation between TMB, MSI and TIGIT gene expression were presented in (A, B) respectively. The correlation coefficient is presented by using the length of the lollipop. The redder the color, the more statistically significant it is.
total number of viable tumor cells. However, it remains unclear which is more suitable for assessing TIGIT expression as a prognostic biomarker (43).

Vascular endothelial cells, nonmalignant cells, immunocytes, tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs), natural killer (NK) cells, dendritic cells (DCs) and tumor-associated neutrophils (TANs) make up the tumor microenvironment (TME) (44, 45). TIGIT was highly positively correlated with the ESTIMATE score in all of the cancers included, which indicated an advanced cancer stage with a poor prognosis.

Tumor-infiltrating immunocytes can promote or antagonize tumorigenesis and progression (46). TIGIT expressed on TILs responded to the TME. TIGIT marks the most dysfunctional subset of CD8+ T cells and Tregs with a highly suppressive function (47). In this study, high TIGIT expression promoted the infiltration levels of CD8 T cells, M1 macrophages, naive B cells, activated memory CD4 T cells, Tregs and activated NK cells while inhibiting the infiltration levels of activated dendritic cells and mast cells in most of the cancers included. Among them, M1 macrophages, activated memory CD4 T cells, activated dendritic cells, mast cells and activated NK cells play antitumor roles in the TME and are related to better outcomes, while Tregs play immune suppression roles and are related to worse survival prognosis (48). A positive correlation was discovered between the expression of TIGIT and most of the other immune checkpoints, especially in ESCA, STAD, STES and SKCM (12, 47, 49, 50). This result suggested that TIGIT might be involved in different immune responses and immunocyte infiltration. The combined blockade of TIGIT and other new immune checkpoints may be a possible option for immunotherapy, especially in patients with gastroesophageal tumors and melanoma.

MSI and TMB are two valuable indexes suggesting the sensitivity of immune checkpoint inhibitors. TMB can induce
new antigens to facilitate immune recognition. MSI caused by hypermutability (gain or loss) of nucleotides from DNA elements is associated with increased expression of neoantigens, higher PD-L1 expression and TMB-H (51). In this study, TIGIT expression was positively related to TMB and MSI in COAD and COADREAD, which indicated that patients with COAD or COADREAD might benefit from TIGIT inhibitors.

Regarding the possible regulatory mechanisms, the results of the GO and KEGG enrichment analyses indicated that TIGIT was closely related to the functions of cell adhesion, adherens junction and the T-cell receptor signaling pathway, which supported the oncogenic role and immunological function of TIGIT in the tumor immune microenvironment.

Currently, it is urgent to find new immune checkpoints to compensate for drug resistance and severe adverse reactions caused by PD-1/PD-L1 and CTLA4 inhibitors. Studies on TIGIT expression provided more encouraging results than those on LAG-3 and TIM-3 (52). TIGIT inhibitors, such as tibolumab, vibostolimab, ocperlimab, M-6223, ASP-8374, COM-902 and IBI-939, have been under clinical trials in patients with non-small cell lung cancer (NSCLC), esophageal squamous cell carcinoma (ESCC) and gastric adenocarcinoma (GAC). TIGIT expression paralleled that of PD-1 (2). Most TIGIT inhibitors are used in combination with PD-L1/PD-1 inhibitors, such as zimberelimab and atezolizumab (53, 54). We will continue to follow up the results of relevant clinical reports.

There were some limitations in our meta-analysis. Over half of the studies did not report postoperative therapy, which led to some bias in our analysis. Second, all of the subjects were Asian, and whether the conclusion could be applied to other populations remained uncertain. Third, the scale of the included studies was limited. Some parts of the subgroup analysis only included one kind of cancer. Large sample size studies are still needed to determine the relationship between TIGIT expression and survival prognosis, especially PFS, RFS and DFS.

5 Conclusion

TIGIT is valuable in predicting the survival prognosis of patients with solid cancers. TIGIT is correlated with the TME, infiltration of immune cells, immune-related genes, MSI and TMB. The results indicate the role of TIGIT in tumor f classogenesis and progression. TIGIT inhibitors may be promising choices for solid cancers in the future.
Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

SL and LL contributed equally to manuscript writing and revisions for intellectual content. TP and XL were responsible for data extraction and English translation. YT was responsible for data extraction, English translation and quality assessment. YJ was the corresponding author and was responsible for data extraction, English translation and quality assessment. All authors contributed to the article and approved the submitted version.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2022.977016/full#supplementary-material
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| Glossary | Abbreviation |
|----------|--------------|
| Bladder Urothelial Carcinoma | BLCA |
| Colon adenocarcinoma | COAD |
| Colon adenocarcinoma/Rectum adenocarcinoma | COADREAD |
| Esophageal carcinoma | ESCA |
| Liver hepatocellular carcinoma | LIHC |
| Lung squamous cell carcinoma | LUSC |
| Rectum adenocarcinoma | READ |
| Skin Cutaneous Melanoma | SKCM |
| Stomach adenocarcinoma | STAD |
| Stomach and Esophageal carcinoma | STES |
| Activated dendritic cells | DCs |
| Advanced thyroid carcinoma | ATC |
| Anaplastic thyroid carcinoma | ATC |
| Bladder urothelial carcinoma | BLCA |
| Cancer-associated fibroblasts | CAFs |
| Cancer-associated fibroblasts | CAFs |
| China national knowledge infrastructure | CNKI |
| Colon adenocarcinoma | COAD |
| Colon adenocarcinoma/Rectum adenocarcinoma esophageal carcinoma | COADREAD |
| Colorectal cancer | CRC |
| Combined positive score | CPS |
| Cytotoxic T-lymphocyte associated protein 4 | CTLA4 |
| Defective DNA mismatch repair | dMMR |
| Dendritic cells | DCs |
| Disease free survival | DFS |
| Disease-free survival | DFS |
| Esophageal carcinoma | ESCA |
| Esophageal squamous cell carcinoma | ESCC |
| Follicular helper T cells | Tfh |
| Gastric adenocarcinoma | GC |
| Gastric cancer | GC |
| Hepatitis B virus hepatocellular carcinoma | HBV-HCC |
| Indoleamine 2 3-dioxygenase 1 | IDO1 |
| Interleukin 10 | IL-10 |
| Liver hepatocellular carcinoma | LIHC |
| Locally advanced papillary thyroid carcinoma | PTC |
| Lung adenocarcinoma | LUAD |
| Lung squamous cell carcinoma | LUSC |
| Lymphocyte activating 3 | LAG3 |
| Microsatellite instability | MSI |
| Muscle-invasive bladder cancer | MBRC |
| Muscle-invasive bladder cancer | MBRC |
| Myeloid-derived suppressor cells | MDSCs |
| Myeloid-derived suppressor cells | MDSCs |

(Continued)
| Name                                           | Gene Symbol | Description                                              |
|------------------------------------------------|-------------|-----------------------------------------------------------|
| C-X-C Motif Chemokine Ligand 16               | CXCL16      | Major Histocompatibility Complex Class II DR Beta 1       |
| C-C Motif Chemokine Ligand 2                  | CCL2        | Major Histocompatibility Complex II DQ Alpha 1            |
| C-X-C Motif Chemokine Ligand 12               | CXCL12      | Major Histocompatibility Complex II DO Alpha              |
| C-C Motif Chemokine Ligand 17                 | CCL17       | Major Histocompatibility Complex II DP Alpha 1            |
| C-C Motif Chemokine Ligand 1                  | CCL1        | Major Histocompatibility Complex II DP Beta 1             |
| C-C Motif Chemokine Ligand 7                  | CCL7        | Major Histocompatibility Complex II DR Alpha              |
| C-C Motif Chemokine Ligand 11                 | CCL11       | Major Histocompatibility Complex Class I G                |
| C-C Motif Chemokine Ligand 27                 | CCL27       | Major Histocompatibility Complex II DQ Alpha 2            |
| C-X-C Motif Chemokine Ligand 17               | CXCL17      | Major Histocompatibility Complex II DO Beta 1             |
| C-C Motif Chemokine Ligand 25                 | CCL25       | Transporter 2 ATP Binding Cassette Subfamily B Member     |
| C-X3-C Motif Chemokine Ligand 1               | CX3CL1      | TAP Binding Protein                                       |
| C-C Motif Chemokine Ligand 14                 | CCL14       | Major Histocompatibility Complex Class I A                |
| C-C Motif Chemokine Ligand 16                 | CCL16       | Major Histocompatibility Complex Class I C                |
| C-X-C Motif Chemokine Ligand 5                | CXCL5       | T-Cell Immunoreceptor With Ig And ITIM Domains            |
| C-X-C Motif Chemokine Ligand 2                | CXCL2       | CD96 Molecule                                             |
| C-X-C Motif Chemokine Ligand 3                | CXCL3       | Programmed Cell Death 1                                   |
| C-C Motif Chemokine Ligand 26                 | CCL26       | Cytotoxic T-Lymphocyte Associated Protein 4               |
| C-X-C Motif Chemokine Ligand 8                | CXCL8       | B And T Lymphocyte Associated                             |
| C-X-C Motif Chemokine Ligand 1                | CXCL1       | CD244 Molecule                                            |
| C-X-C Motif Chemokine Ligand 6                | CXCL6       | Programmed Cell Death 1 Ligand 2                         |
| C-C Motif Chemokine Ligand 15                 | CCL15       | Hepatitis A Virus Cellular Receptor 2                     |
| C-C Motif Chemokine Ligand 28                 | CCL28       | Lymphocyte Activating 3                                   |
| C-X-C Motif Chemokine Ligand 14               | CXCL14      | Adenosine A2a Receptor                                     |
| X-C Motif Chemokine Receptor 1                | XCR1        | Colony Stimulating Factor 1 Receptor                      |
| C-C Motif Chemokine Receptor 11               | CCR1        | Interleukin 10                                            |
| C-C Motif Chemokine Receptor 12               | CCR2        | CD274 Molecule                                            |
| C-C Motif Chemokine Receptor 8                | CCR8        | Indoleamine 2, 3-Dioxygenase 1                            |
| C-C Motif Chemokine Receptor 4                | CCR4        | Galectin 9                                                |
| C-C Motif Chemokine Receptor 7                | CCR7        | CD160 Molecule                                            |
| C-X-C Motif Chemokine Receptor 3              | CXCR3       | Killer Cell Immunoglobulin                                |
| C-C Motif Chemokine Receptor 5                | CCR5        | HLA-E                                                     |
| C-X-C Motif Chemokine Receptor 6              | CXCR6       | HLA-F                                                     |
| C-C Motif Chemokine Receptor 6                | CCR6        | HLA-DMA                                                   |
| C-C Motif Chemokine Receptor 4                | CXCR4       | HLA-DMB                                                   |
| C-X-C Motif Chemokine Receptor 2              | CXCR2       | Major Histocompatibility Complex Class II DM Beta         |
| C-C Motif Chemokine Receptor 10               | CCR10       | Major Histocompatibility Complex Class II DO Beta         |
| C-X-C Motif Chemokine Receptor 5              | CXCR5       | Major Histocompatibility Complex Class II DM Alpha        |
| C-C Motif Chemokine Receptor 9                | CCR9        |                                                           |
| C-C Motif Chemokine Receptor 3                | CCR3        |                                                           |
| C-X-C Motif Chemokine Receptor 1              | CX3CR1      |                                                           |
| Major Histocompatibility Complex Class I E    | HLA-E       |                                                           |
| Major Histocompatibility Complex Class I B    | HLA-B       |                                                           |
| Beta-2-Microglobulin                          | B2 M        |                                                           |
| Major Histocompatibility Complex Class I F    | HLA-F       |                                                           |
| Major Histocompatibility Complex II DM Beta   | HLA-DMA     |                                                           |
| Major Histocompatibility Complex II DO Beta   | HLA-DMA     |                                                           |

(Continued)