

Prognostic and immune roles of synaptotagmin-4 in gastric cancer and brain lower-grade glioma

Siyuan Jiang

The First Affiliated Hospital of Xi'an Jiaotong University

Lizhe Zhu

The First Affiliated Hospital of Xi'an Jiaotong University

Chao Jiang

The First Affiliated Hospital of Xi'an Jiaotong University

Shibo Yu

The First Affiliated Hospital of Xi'an Jiaotong University

Bin Wang

The First Affiliated Hospital of Xi'an Jiaotong University

Yu Ren (✉ renyyyyy@126.com)

The First Affiliated Hospital of Xi'an Jiaotong University <https://orcid.org/0000-0003-2928-138X>

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Abstract

Background Synaptotagmins (SYTs) are a family of proteins whose primary function is serving as a calcium sensor in vesicle transport and exocytosis, playing an important role in the function of immune cells. There is also a close relationship between immune cells and tumours. SYT4 is one molecule involved in this relationship, but the relationship between SYT4 and cancer remains unclear. Therefore, we hypothesize that SYT4 can affect the prognosis of cancer, and may be related to immune cells.

Methods The following databases were used to study the immunological and prognostic role of SYT4 in cancers: OncoPrint, Kaplan-Meier plotter, The Human Protein Atlas, CCLC, GEPIA2, TIMER, and CGGA.

Results SYT4 expressions were lower in many cancers than in normal tissues. Specifically in gastric cancer and lower-grade gliomas, SYT4 played a protective and harmful role, respectively. Moreover, a difference between SYT4 expression and the levels of immune infiltration existed in stomach adenocarcinoma (STAD) and brain lower-grade glioma (LGG). In addition, we found that the relationship between markers of monocytes, M1 and M2 macrophages, tumour-associated macrophages (TAMs), Treg cells, B lymphocytes, dendritic cells (DCs) and SYT4 expression was opposite in STAD and LGG.

Conclusions The effect of SYT4 on the prognosis of patients with STAD and LGG was opposite. And SYT4 has different effects on immune infiltration in these two tumours. Therefore, SYT4 might be a potential prognostic and tumour immune-related biomarker in STAD and LGG.

Background

Calcium-mediated exocytosis is one of the methods of intercellular communication. For example, neuroendocrine cells can secrete hormones through calcium-mediated exocytosis[1]. Mast cells can release granules through exocytosis under the mediation of calcium[2]. Similarly, for T lymphocytes, calcium-mediated exocytosis is essential for maintaining normal function[3]. Synaptotagmins (SYTs) are a family of proteins whose primary function is serving as the calcium sensor in vesicle transport and exocytosis[4]. SYTs have distinct structural characteristics that determine whether they can bind to calcium and affect exocytosis[5]. According to research by Zhiping P Pang et al. [6], at least 16 SYT subtypes have been identified, which have significantly different distribution patterns and functional characteristics. SYT4 is a postsynaptic protein that does not show calcium-dependent effects[7]. Previous studies have found that SYT4 is localized on the particles of islet B cells and can affect insulin secretion[8]. SYT4 is an essential vesicle protein that determines the secretion of brain-derived neurotrophic factors[9]. In cancer-related research, some studies have found a relationship between SYTs and cancer. Qin Li et al. reported that SYT13 was helpful for monitoring the occurrence and development of colorectal cancer[10]. Wu Z et al. reported that SYT7 was beneficial for monitoring the development of osteosarcoma[11]. A recent study found that SYT4 regulates Ca²⁺ influx through TRPM1, leading to melanin production and axon elongation in alpaca melanocytes, which suggests that the growth and metastasis of melanoma are controlled by the suppression of SYT4 expression in melanoma cells[12]. In addition, the relationship between tumours and immunity has also been studied thoroughly. The tumour microenvironment includes tumour, stromal, immune, vascular and endothelial cells as well as extracellular matrix[13]. CD8⁺ and cytotoxic T

lymphocytes have a tumour-killing functions[14], while regulatory T cells attenuate effector T cell activity and promote the immunosuppression of the TME[15]. Generally, M1 macrophages secrete Th1 cytokines, which play a pro-inflammatory and antitumour role[16]. However, M2-type macrophages, which can help tumour cells complete immune escape, promote tumour angiogenesis and promote lymph node and distant metastasis[17, 18]. In recent years, immunotherapy, including programmed cell death-1 and programmed cell death-ligand 1 inhibitors, has been used in clinical treatment as an alternative to traditional anticancer therapy[19]. However, more potential therapeutic targets are still waiting to be discovered. We found that SYTs were the key proteins of vesicle transport and exocytosis. Exocytosis and vesicle transport play an important role in the function of immune cells. In addition, there was also a close relationship between immune cells and tumours. Therefore, we hypothesized that SYT4, a member of the SYT family, might affect the prognosis of cancer, and was related to immune cells.

In this study, the Oncomine, Kaplan-Meier plotter, GEPIA2, and the CGGA dataset were used to explore the expression level of SYT4 in various cancers and its association with the prognosis. Additionally, TIMER was used to study the correlation between the expression levels of SYT4 and the levels of immune infiltration. SYT4 had the opposite effects on the prognosis of patients with STAD and LGG. And SYT4 had different effects on immune infiltration in these two tumours. Therefore, SYT4 might be a potential prognostic and tumour immune-related biomarker in STAD and LGG.

Material And Methods

Oncomine database

Oncomine is a platform used to explore datasets from multiple gene expression experiments[20]. The mRNA expression level of SYT4 in human cancers was analyzed using Oncomine. The parameters used were as follows: the gene name was "SYT4", the rank was top 10%, the fold change was 2, and the *p*-value was 0.001.

The Human Protein Atlas database

The Human Protein Atlas (HPA) database provides the distributions of human proteins in tissues and cells, and utilizes data gained with immunohistochemical techniques to analyse the distribution and expression of each protein in 48 human normal tissues, 20 tumour tissues, 47 cell lines, and 12 blood cells , The results are described in least 576 immunohistochemical staining diagrams, and indexed by professionals. We used this database to explore the expression level of SYT4 determined by immunohistochemical staining of tumour tissues and normal tissues.

Cancer Cell Line Encyclopedia database

Cancer Cell Line Encyclopedia (CCLE) is a database of cancer cell lines maintained by the Broad Institute. It currently includes data on more than 1,400 cell lines, which can help researchers explore the expression levels of genes in different cancer cell lines. We used this database to investigate the expression level of SYT4 in different cancer cell lines.

Kaplan-Meier plotter database

Kaplan-Meier plotter[21] was used to assess the impact of different genes on the prognosis of multiple cancers, including breast, ovarian, lung, and gastric cancer. The data were primarily taken from Gene Expression Omnibus (GEO), [European Genome-phenome Archive](#) (EGA) and The Cancer Genome Atlas (TCGA). We used it to research the potential prognostic significance of SYT4 in different cancers. We generated survival curves via this database to show the final results.

GEPIA2 database

GEPIA2 is an updated version of Gene Expression Profiling and Interactive Analyses (GEPIA), including RNA sequencing data from 9,736 tumours and 8,587 normal samples in TCGA and Genotype-Tissue Expression (GTEx) databases[22]. We used it to explore the prognostic values of SYT4 and collected the hazard ratios (HRs) with 95% confidence intervals (CI) and the p -values. In addition, we performed a correlation analysis of SYT4 expression and immune cell markers. The correlation was estimated using Spearman's rho value.

CGGA database

Chinese Glioma Genome Atlas (CGGA) is a dataset with data from more than 2,000 brain tumour samples from China, including whole-exome sequencing, DNA methylation, mRNA sequencing, mRNA microarray, microRNA microarray and clinical data. Two mRNA datasets, mRNAseq_325 and mRNAseq_693, were used to analyse the prognostic significance of SYT4 in primary glioma patients.

TIMER database

TIMER (Tumor Immune Estimation Resource)[23], a web tool for exploring tumour-infiltrating immune cells, contains data from 10,897 samples in 32 cancer types, which can be used to study the levels of infiltration by B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells in cancers via a deconvolution method[24]. The web based DiffExp module was used to explore the different levels of SYT4 between tumour and normal tissues in TCGA data. We used box plots to show the results. The Wilcoxon test was used to evaluate whether the results were statistically significant. The Gene module was used to assess the association between the expression levels of SYT4 and the levels of immune infiltration in various cancers. In addition, the Correlation module was used to assess the association between SYT4 and immune cell markers. All immune cell markers were derived from the R & D Systems website. The results are expressed as scatter plots. The correlation was estimated using Spearman's rho value.

Results

The expression levels of SYT4 in cancers

First, we used the Oncomine database to explore the mRNA expression levels of SYT4 in different tumours (Figure 1A). The results suggested that the mRNA expression of SYT4 was higher in the lung tumour tissues than in normal lung tissues. In contrast, the mRNA expression of SYT4 was lower in the brain and nervous system cancer, colorectal, oesophageal, gastric, and prostate cancer, as well as in sarcoma tissues, than in

the respective normal tissues. Supplemental Table 1 explicitly presents the mRNA expression levels of SYT4 in tumours according to different studies.

Subsequently, we used the TIMER database to explore the expression levels of SYT4 in different cancers (Figure 1B). We found a significant difference in the expression levels of SYT4 between cancer tissues and normal tissues in the following cancers: bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), colon adenocarcinoma (COAD), oesophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), and uterine corpus endometrial carcinoma (UCEC).

To verify the above results at the tissue and cell levels, we analyzed SYT4 expression in HPA and CCLE. In the immunohistochemical staining data, we found that the expression level of SYT4 was not high in cancer tissues. Furthermore, compared to the levels in cell lines of neuroblastoma, small cell lung cancer and prostate cancer, the levels of SYT4 in other cancer cell lines were lower (Supplemental Figure 1A-P).

Prognostic significance of SYT4 in different cancers

We used gene chip data derived from the Kaplan-Meier plotter database to explore the association between SYT4 expression and the survival of breast, lung, gastric and ovarian cancer patients. The results are shown in Figure 2. For patients with gastric cancer, SYT4 was associated with an unfavourable prognosis [overall survival (OS): HR=1.39 (1.12-1.73), log-rank $P = 0.0025$; progression-free survival (PFS): HR=1.31 (1.03-1.67), log-rank $P = 0.025$]. For breast cancer patients, SYT4 was related to recurrence-free survival (RFS) [HR=0.76 (0.65-0.88), log-rank $P = 0.00042$] but had no significant impact on OS [HR=0.74 (0.54-1.02), log-rank $P = 0.065$]. SYT4 did not affect the OS or PFS of patients with lung cancer [OS: HR=1.02 (0.86-1.20), log-rank $P = 0.84$; PFS: HR=1.12 (0.86-1.47), log-rank $P = 0.40$] or ovarian cancer [OS: HR=1.01 (0.82-1.24), log-rank $P = 0.93$; PFS: HR=1.07(0.89-1.29), log-rank $P = 0.46$].

After the exploration of SYT4 in the Kaplan-Meier plotter database, we analysed the impact of SYT4 on prognosis of different cancers by analysing RNA sequencing data from the TCGA database through GEPIA2 (Supplemental Figure 2). The results that the impacts of SYT4 on both the OS and disease-free survival (DFS) of LGG and STAD were consistent. High expression levels of SYT4 were related to a poor prognosis in patients with STAD (OS: HR=1.60, log-rank $P = 0.006$; DFS: HR=1.80, log-rank $P = 0.0041$). In contrast, high expression levels of SYT4 were correlated with a good prognosis in LGG patients (OS: HR=0.53, log-rank $P = 0.00047$; DFS: HR=0.58, log-rank $P = 6e-04$).

To further explore the correlation between the expression levels of SYT4 and the survival of LGG patients, we verified it in the CGGA database (Supplemental Figure 3). In the mRNAseq_325 dataset, the result suggested a significant correlation between the expression level of SYT4 and survival in all primary glioma patients, including patients with WHO grade II and III tumours, but there was no correlation between SYT4 and prognosis in patients with grade IV tumours. Similarly, in the mRNAseq_693 dataset, the result indicated a

correlation between the expression level of SYT4 and the survival of all primary glioma patients, including patients with WHO grade III tumours, but there was no correlation between SYT4 and prognosis in patients with grade II and IV tumours. The above results partially verify our hypothesis, suggesting the prognostic value of SYT4 in LGG and STAD. SYT4 had a beneficial effect on the prognosis of LGG patients. In contrast, SYT4 had a detrimental effect on the survival of STAD patients.

The expression of SYT4 has an impact on the survival of gastric patients with lymphatic metastasis

To explore the mechanism by which the expression level of SYT4 affected the survival of gastric cancer patients, we used the Kaplan-Meier plotter database to explore the association between the expression levels of SYT4 and clinical factors of gastric cancer patients (Table 1). We conducted a stratified analysis of clinical factors affecting OS and PFS, such as sex, AJCC stage, T stage, N stage, and M stage. In terms of sex, high expression of SYT4 was related to an unfavourable prognosis in terms of OS in both males [HR = 1.49 (1.11-2.01), log-rank $P = 0.0082$] and females [HR = 1.89 (1.22-2.93), log-rank $P = 0.0039$] and an unfavourable prognosis in terms of PFS in female patients [HR = 1.56 (1.02-2.38), log-rank $P = 0.038$]. In addition, a significant correlation was also shown between the expression level of SYT4 and the lymphatic metastasis of patients. We did not find a significant association between the expression level of SYT4 and the survival of gastric cancer patients without lymph node metastasis [OS: HR = 1.10 (0.47-2.57), log-rank $P = 0.83$; PFS: HR = 1.16 (0.50-2.70), log-rank $P = 0.73$]. However, there was a significant correlation between the expression level of SYT4 and the survival of gastric cancer patients with N1 stage tumours [OS: HR = 1.85 (1.21-2.81), log-rank $P = 0.0036$; PFS: HR = 1.90 (1.27-2.83), log-rank $P = 0.0014$]. Moreover, those patients with gastric cancer with lymph node metastasis had correlations of SYT4 expression with OS [HR = 1.31 (1.01-1.70), log-rank $P = 0.045$] and PFS [HR = 1.32 (1.02-1.70), log-rank $P = 0.031$]. Therefore, the expression level of SYT4 might further affect the prognosis of gastric cancer patients by affecting lymph node metastasis.

SYT4 expression is related to the level of immune infiltration in gastric cancer and lower-grade brain glioma

Among the various factors affecting the survival and lymph node metastasis of cancer patients, lymphocyte infiltration is a significant independent predictor[25]. Therefore, we analysed the association between the expression levels of SYT4 and the levels of immune infiltration in 39 types of cancer in the TIMER database (Supplemental Figure 4). According to the results, we found that tumour purity and the expression levels of SYT4 had significant correlations in 12 cancer types. Similarly, the infiltration levels of B lymphocytes, CD4+ T lymphocytes, CD8+ T lymphocytes, macrophages, neutrophils, and DCs had significant correlations with the expression levels of SYT4 in 11, 14, 10, 19, 11 and 13 types of cancer, respectively.

Based on the findings in GEPIA2, Kaplan-Meier plotter and CGGA, we focused on cancer types in which the expression level of SYT4 was negatively correlated with tumour purity in TIMER and had a significant correlation with the prognosis of patients in GEPIA2 and Kaplan-Meier plotter: STAD and LGG (Figure 3). BRCA was selected as a control. It is worth noting that the expression level of SYT4 was negatively related to the prognosis of STAD but had a positive association with the infiltration of immune cells. We found that the expression level of SYT4 in STAD patients was negatively related to tumour purity (cor = -0.172, $P=7.75e-04$) but was positively associated with infiltration of the following immune cells: B cells (cor =

0.192, $P=2.09e-04$), CD4+ T cells (cor = 0.385, $P=2.38e-14$), CD8+ T cells (cor = 0.122, $P=1.82e-02$), macrophages (cor = 0.385, $P=1.72e-14$), and dendritic cells (cor = 0.207, $P=6.01e-05$). However, the expression level of SYT4 was positively related to the prognosis of LGG patients but negatively associated with infiltration of the following immune cells: B cells (cor = -0.385, $P=6.54e-12$), CD4+ T cells (cor = -0.577, $P=1.34e-43$), neutrophils (cor = -0.375, $P=2.49e-17$), macrophages (cor = -0.505, $P=6.45e-32$), and dendritic cells (cor = -0.478, $P=1.37e-28$). We did not find similar correlations in BRCA. These above results suggested that the reasons why the expression level of SYT4 impacted the prognosis of STAD and LGG patients in the different ways was probably the different relationships between the expression level of SYT4 and the level of immune infiltration in STAD and LGG.

Correlations between the expression levels of SYT4 and markers of immune cells

To further explore the potential mechanisms of interaction between SYT4 and various immune infiltrating cells, such as CD8+ T cells, T cells (general), B cells, monocytes, TAMs, M1 and M2 macrophages, neutrophils, natural killer cells, and dendritic cells, in STAD and LGG, we analysed the correlations between the expression levels of SYT4 and immune markers of multiple immune cells in STAD and LGG based on the TIMER and GEPIA databases. In addition, we also performed correlation analysis with the immune markers of the following types of functional T cells: T helper cells, follicular helper T cells, regulatory T cells, and exhausted T cells. The correlation coefficient was adjusted based on tumour purity[26] (Table 2). According to the correlation analysis between the expression levels of 56 immune cell markers and the expression levels of SYT4, we found that the purity-adjusted correlation coefficients of 35 markers were statistically significant in STAD patients, and they were all positive. The purity-adjusted correlation coefficients of 46 markers were statistically significant in LGG patients, however, most of them were negatively. Only ten markers had statistically significant purity-adjusted correlations with the expression levels of SYT4 in BRCA patients. In addition, we also found significant correlations between the expression levels of markers of monocytes, TAMs and M2 macrophages and the expression levels of SYT4 in patients with STAD and LGG but not in BRCA (Table 2, Figure 4). In detail, these markers, such as CD115, CCL2, IL10, VSIG4, and MS4A4A, had significantly positive correlations with SYT4 expression levels in STAD ($P<0.0001$, Figure 4A-D). For LGG, these markers, such as CD163 of M2 macrophages, NOS2, IRF5 and COX2 of M1 macrophages, and CD86 of monocytes, also showed a significant correlation with SYT4 expression levels but the markers that were correlated with SYT4 expression in STAD did not show a correlation in LGG ($P<0.0001$, Figure 4I-L). However, the expression of SYT4 in BRCA did not show significant correlations with the above markers (Figure 4E-H). Then, to verify the results, we analysed the correlation between monocytes, TAMs, and M1 and M2 macrophages immune markers and the expression levels of SYT4 in STAD, LGG, and BRCA with the GEPIA2 database. The results were similar to those achieved in the TIMER analysis (Table 3). Moreover, it is worth noting that the correlations between the expression level of SYT4 and the levels of immune markers were positive and negative in STAD and LGG, respectively. Hence, we concluded that SYT4 likely interacts with various immune cells in STAD and LGG in the opposite ways

Discussion

Calcium-mediated exocytosis is an integral part of the human immune system. Exocytosis of mast cells, natural killer cells, and cytotoxic lymphocytes protects humans from pathogen invasion, infected cells and malignant cells[27]. SYTs, a large class of membrane transporters, are the primary calcium sensors during exocytosis. They have significant regulatory effects in nerves, the endocrine system, and the immune system[28]. Baram D et al. confirmed that SYT1 expression was observed in mouse bone marrow-derived mast cells (BMMCs) and rat abdominal mast cells (RPM-Cs) by immunoblotting, and played a decisive regulatory role in mast cell exocytosis. SYT2 plays a negative supervisory role in lysosomal exocytosis of mast cells[29]. Lindmark IM et al. confirmed that SYT2 was expressed in human neutrophils (PMNs), while SYT1, SYT3, and SYT4 were not, and SYT2 was involved in PMN phagocytosis and exocytosis[30]. These studies reflect the effects of the SYT family members on immune cells and the diversity of their functions. In terms of the relationship between SYTs and tumours, one study found that SYT13 was helpful for predicting the occurrence and development of colorectal cancer[10]. SYT7 was beneficial for monitoring the development of osteosarcoma[11]. A recent study found that SYT4 regulates Ca²⁺ influx through TRPM1, leading to melanin production and axon elongation in alpaca melanocytes, which suggests that the growth and metastasis of melanoma are controlled by the suppression of SYT4 expression in melanoma cells[12]. Therefore, we hypothesized that SYT4 can affect the prognosis of cancer, and its mechanism may be related to tumour immunity.

This study used the following databases to explore the associations between SYT4 and cancers: Oncomine, Kaplan-Meier plotter, GEPIA2, TIMER, HPA, CCLE and CGGA. Data from Oncomine showed that SYT4 was expressed at low levels in brain and nervous system cancer, colorectal cancer, oesophageal cancer, gastric cancer, prostate cancer, and sarcoma compared to normal tissues. Only one dataset showed higher expression levels of SYT4 in lung cancer than in the respective normal tissues (Figure 1A). The results from TIMER showed that compared to those in normal adjacent tissues, the expression levels of SYT4 were significantly different in the following cancers: BLCA, BRCA, COAD, ESCA, HNSC, KICH, KIRC, KIRP, LIHC, LUAD, LUSC, PRAD, READ, STAD, THCA, and UCEC (Figure 1B). In addition, we verified the expression of SYT4 in the HAL and CCLE databases at the tissue and cell levels, and obtained similar results. Throughout these databases, we determined the consistency of SYT4 expression in cancers. In the analysis of patient prognosis, we employed the Kaplan-Meier plotter and GEPIA2 databases. The results suggested that high expression of SYT4 was related to a favourable prognosis of LGG patients. In contrast, high expression of SYT4 was correlated with an unfavourable prognosis in STAD. The CGGA database verified the above result, and similar results were obtained. In addition, immunohistochemical staining data from HPA also suggested that SYT4 was expressed at low levels in STAD and LGG tissues than in normal gastric and brain tissues, respectively (Supplemental Figure 1-Q). These findings suggested that the relationships between the expression level of SYT4 and prognosis is different in different cancers,, indicating that SYT4 might be a potential prognostic biomarker, at least in STAD and LGG.

To continue to investigate how the expression level of SYT4 affects the prognosis of cancer patients, we conducted a stratified analysis of the clinical characteristics of STAD patients and found that the expression of SYT4 had an impact on the survival of gastric patients with lymphatic metastasis (Table 1), which suggested that SYT4 might be related to the level of tumour immune infiltration. Therefore, we explored the associations between the expression level of SYT4 and the levels of immune infiltration in STAD and LGG

with in TIMER database. Moreover, the associations were also analysed in BRCA as a control, because the prognosis of BRCA patients was not related to the expression of SYT4. First, there was no correlation between SYT4 expression and tumour purity in LGG, but a negative correlation with tumour purity was found in STAD. We speculated that the difference might be due to the different expression patterns of SYT4 in the TME. Genes that had a high expression in cells of the TME compared with tumour cells were negatively related to the level of tumour purity, while genes with a high expression in tumour cells had a positive correlation with tumour purity[26]. The expression of SYT4 had different associations with tumour purity under different circumstances, indicating that SYT4 might have different functions in various tumours. Second our findings indicated that the expression of SYT4 was related to the infiltration levels of B cells, CD4+ T cells, macrophages, and DCs in STAD and LGG, but this correlation was not present in BRCA (Figure 3). Interestingly, there was a positive correlation coefficient between the levels of immune cell infiltration and SYT4 expression levels in STAD, while a negative correlation coefficient existed in LGG. Although causality cannot be established through the current research, we did find different correlations between the expression levels of SYT4 and the levels of immune cell infiltration and different correlations between the expression of SYT4 and prognosis in STAD and LGG.

In addition, the correlation between the expression of SYT4 and immune cell marker genes suggested that SYT4 had a role in regulating tumour immunity in LGG and STAD. We first focused on monocytes, M1 and M2 macrophages, and TAMs (Figure 4). Some studies found that TAMs aid tumour cell migration in a mechanism that involves secretion of epidermal growth factor family ligands by the macrophages and secretion of colony-stimulating factor-1 by tumour cells[31], and M2 macrophages were detrimental to the prognosis of cancer patients because they stimulated lymphangiogenesis and angiogenesis[32]. While, M1 macrophages have significant antitumour effects[16]. Our results showed that the expression level of SYT4 was positively related to the molecular markers of TAMs (CCL2 and IL10) and M2 macrophages (CD163, VSIG4 and MS4A4A) in STAD, while the expression of SYT4 showed a negative relationship with these markers in LGG. In addition, the markers of M1 macrophages had a strong correlation with the expression of SYT4 in LGG. However, the correlation was weak in STAD. These results reveal the potential regulatory role of SYT4 in TAM polarization. Therefore, we speculated that SYT4 might affect the prognosis of cancer patients through TAMs.

In addition, we also examined the correlation between SYT4 expression and Treg cell markers. Treg cells have been shown to be associated with poor prognosis[33]. Activated TGF- β existed widely in the TME, and inhibited the activity of NK cells and CTLs, the proliferation of Teff cells and the production of cytokines, as well as inhibited the differentiation of Teff cells into Th1 and Th17 cells, aiding the migration and metastasis of tumour cells[34]. Moreover, current research has determined that CCR8+ regulatory T cells are drivers of immunosuppression, which can help the immune escape of tumours[35]. In our study, we found that the Treg cell marker TGFB1 had the highest correlation coefficient (cor = 0.38) with SYT4 expression levels, and other Treg cells markers, such as CCR8, FOXP3 and STAT5B, also had significantly positive correlations with SYT4 expression in STAD. However, the Treg cells markers CCR8 and TGFB1 showed a negative association with the expression level of SYT4 in LGG. These findings suggested that the molecular markers of Treg cells are positively correlated with the expression of SYT4 in STAD and that high expression of SYT4 is related to the poor prognosis of STAD patients. It is worth noting that the research by Yiftah

Barshesheta et al.[35] showed that certain ligands of CCL1 could induce Ca²⁺ flux by binding to CCR8 and enhance the inhibitory activity of Treg cells. CCR8 could also induce melanoma cells to enter the lymph nodes by binding to CCL1 secreted by the lymph node sinusoidal endothelial cells, causing lymphatic metastasis[36]. A recent study found that SYT4 regulates Ca²⁺ influx through TRPM1, leading to melanin production and axon elongation in alpaca melanocytes, which suggests that the growth and metastasis of melanoma is controlled by the suppression of SYT4 expression in melanoma cells[12]. As a membrane protein that can regulate calcium flux, whether SYT4 plays an important role in the binding of CCR8 and CCL1 and whether this role is related to Treg cells require further research.

In addition, we also considered the relationship between the markers of DCs and SYT4 expression in STAD and LGG. DCs in promote tumour metastasis by increasing Treg cells and reducing the cytotoxicity of CD8⁺ T cells[37]. We found that the relationship between DC markers, including HLA-DPB1, HLA-DQB1, HLA-DRA, HLA-DPA1, BDCA-1, BDCA-4 and CD11c, and SYT4 expression levels showed a negative correlation in LGG. However, the expression levels of HLA-DPB1, HLA-DQB1, HLA-DRA and HLA-DPA1 did not show a significant correlation with SYT4 in STAD,, while the expression levels of BDCA-1, BDCA-4 and CD11c showed a significantly positive correlation with SYT4. The results suggest that SYT4 might be a potential factor affecting tumour metastasis through DCs.

In addition, we also found that SYT4 was associated with B lymphocyte infiltration in STAD and LGG. B cell receptors on the surface of B lymphocytes bind to the tumour antigen, resulting in the processing and presentation the tumour antigen; The response of T lymphocytes to the tumour can then be activated, which plays a very important role in the tumour immunity[38]. We found that the relationship between the surface markers (CD19 and CD79a) and the expression level of SYT4 showed a significant positive correlation in STAD. However, in LGG, it opposite correlation was observed. These findings together indicate that SYT4 plays an important role in the recruitment and regulation of infiltrating immune cells in LGG and STAD.

However, our study had some limitations. First, we explored multiple databases, and biases might exist in their data. Second, due to the different sources of data, some results were contradictory. Third, our study was a bioinformatics analysis of SYT4, and the results were not verified in vivo or in vitro. Fourth, causal inferences cannot be made from our current research results, and follow-up prospective studies are needed.

Conclusions

In general, SYT4 had the opposite effect on the prognosis of patients with STAD and LGG. And SYT4 has different effects on immune infiltration in these two tumours. Therefore, SYT4 might be a potential prognostic and tumour immune-related biomarker in STAD and LGG.

List Of Abbreviations

Synaptotagmins (SYTs), synaptotagmin-4 (SYT4), Gene Expression Omnibus (GEO), [European Genome-phenome Archive](#) (EGA), The Cancer Genome Atlas (TCGA), TIMER (Tumor Immune Estimation Resource), Gene Expression Profiling and Interactive Analyses (GEPIA), Genotype-Tissue Expression (GTEx), Chinese Glioma Genome Atlas (CGGA), hazard ratios (HRs), confidence intervals (CI), bladder urothelial carcinoma

(BLCA), breast invasive carcinoma (BRCA), colon adenocarcinoma (COAD), oesophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), brain lower-grade glioma (LGG), uterine corpus endometrial carcinoma (UCEC), overall survival (OS), progression-free survival (PFS), recurrence free survival (RFS), disease-free survival (DFS), tumour-associated macrophages (TAMs), Breast cancer(BC), tumour-associated macrophage(TAM), T helper cell(Th), Follicular helper T cell (Tfh), regulatory T cell(Treg).

Declarations

Ethics approval and consent to participate

The human data in this study were all from the online databases, and thus, their use did not require ethical approval.

Consent for publication

Not applicable

Availability of data and materials

Our study analysed data from publicly available datasets. All these data can be found on the following websites: <https://www.oncomine.org>, <https://kmplot.com/analysis/>, <http://gepia2.cancer-pku.cn/#index>, <https://cistrome.shinyapps.io/timer/>, <http://cgga.org.cn/>, <https://www.proteinatlas.org/>, and <https://portals.broadinstitute.org/ccle>.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SY-J: Collection and/or assembly of data, data analysis and interpretation, manuscript writing, methodology and software. LZ-Z: Data analysis and interpretation, manuscript editing. SB-Y: Data analysis, and interpretation. C-J: Manuscript writing and project administration. B-W: Conception/design. Y-R: Conception/design, supervision and editing.

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Additional Files

Supplemental Figure 1. SYT4 expression in different cancer tissues and cancer cell lines. A: Colorectal cancer, B: Lung cancer, C: Cervical cancer, D: Melanoma, E: Thyroid cancer, F: Liver cancer, G: Testicular cancer, H: Glioma, I: Ovarian cancer, J: Breast cancer, K: Kidney cancer, L: Head and neck cancer, M: Gastric cancer, N: Pancreatic cancer, O: Endometrial cancer. P: SYT4 expression in different cancer cell lines. Q: Differences in SYT4 expression levels between tumour and normal tissues in LGG and STAD.

Supplemental Figure 2. Survival analysis of SYT4 in different cancers via GEPIA2 database. A, B: The impact of SYT4 on the prognosis of patients with STAD. C, D: The impact of SYT4 on the prognosis of patients with LGG. E: Survival analysis of SYT4 in 33 types of cancer via GEPIA2 database. ACC: Adrenocortical carcinoma; BLCA: Bladder urothelial carcinoma; BRCA: Breast invasive carcinoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: Cholangiocarcinoma; COAD: Colon adenocarcinoma; DLBC: Diffuse large B cell lymphoma; ESCA: Oesophageal carcinoma; GBM: Glioblastoma multiforme; HNSC: Head and neck squamous cell carcinoma; KICH: Kidney chromophobe;

KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute myeloid leukemia; LGG: Brain lower-grade glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; MESO: Mesothelioma; OV: Ovarian serous cystadenocarcinoma; PAAD: Pancreatic adenocarcinoma; PCPG: Pheochromocytoma and paraganglioma; PRAD: Prostate adenocarcinoma; READ: Rectum adenocarcinoma; SARC: Sarcoma; SKCM: Skin cutaneous melanoma; STAD: Stomach adenocarcinoma; TGCT: Testicular Germ Cell Tumors; THCA: Thyroid carcinoma ; THYM: Thymoma; UCEC: Uterine corpus endometrial carcinoma; UCS: Uterine carcinosarcoma; UVM: Uveal melanoma.

Supplemental Figure 3. Survival analysis of SYT4 in primary glioma via CGGA database. A-D: Survival analysis of SYT4 in primary glioma in the mRNAseq_325 dataset. E-H: Survival analysis of SYT4 in primary glioma in the mRNAseq_693 dataset.

Supplemental Figure 4. Correlation between the expression level of SYT4 and the level of immune infiltration in 39 types of cancer based with TIMER. ACC, Adrenocortical carcinoma; BLCA, Bladder urothelial carcinoma; BRCA, Breast invasive carcinoma; BRCA-Basal, Breast invasive carcinoma-basal; BRCA-Luminal, Breast invasive carcinoma-luminal; BRCA-Her2, Breast invasive carcinoma-her2; CESC, Cervical and endocervical cancer; CHOL, Cholangiocarcinoma; COAD, Colon adenocarcinoma; DLBC, Diffuse large B-cell lymphoma; ESCA, Oesophageal carcinoma; GBM, Glioblastoma multiforme; HNSC, Head and neck cancer; HNSC-HPVpos, Head and neck cancer-HPV positive; HNSC-HPVneg, Head and neck cancer-HPV negative; KICH, Kidney chromophobe; KIRC, Kidney renal clear cell carcinoma; KIRP, Kidney renal papillary cell carcinoma; LGG, Brain lower-grade glioma; LIHC, Liver hepatocellular carcinoma; LUAD, Lung adenocarcinoma; LUSC, Lung squamous cell carcinoma; MESO, Mesothelioma; OV, Ovarian serous cystadenocarcinoma; PAAD, Pancreatic adenocarcinoma; PCPG, Pheochromocytoma and paraganglioma; PRAD, Prostate adenocarcinoma; READ, Rectum adenocarcinoma; SARC, Sarcoma; SKCM, Skin cutaneous melanoma; SKCM-Primary, Skin cutaneous melanoma-primary; SKCM-Metastasis, Skin cutaneous melanoma-metastasis; STAD, Stomach adenocarcinoma; TGCT, Testicular germ cell tumors; THCA, Thyroid carcinoma; THYM, Thymoma; UCEC, Uterine corpus endometrial carcinoma; UCS, Uterine carcinosarcoma; UVM, Uveal melanoma.

Supplemental Table 1. SYT4 expression in cancers versus normal tissues in Oncomine.

Tables

Table 1. Correlation of SYT4 mRNA expression and clinical factors in gastric cancer.

	Overall survival (n=881)			Progression-free survival (n=645)		
	N	HR	<i>P</i> -value	N	HR	<i>P</i> -value
Sex						
Female	187	1.89 (1.22-2.93)	0.0039	179	1.56 (1.02-2.38)	0.038
Male	349	1.49 (1.11-2.01)	0.0082	341	1.30 (0.97-1.74)	0.073
Stage						
1	62	0.66 (0.22-2.01)	0.46	60	0.69 (0.23-2.11)	0.52
2	135	1.77 (0.93-3.38)	0.077	131	1.79 (0.97-3.31)	0.061
3	197	1.26 (0.87-1.84)	0.22	186	1.21 (0.84-1.78)	0.29
4	140	1.20 (0.81-1.78)	0.46	141	1.03 (0.70-1.51)	0.89
T stage						
2	241	1.45 (0.94-2.21)	0.088	239	1.26 (0.83-1.90)	0.27
3	204	1.01 (0.71-1.42)	0.97	204	1.11 (0.80-1.55)	0.54
4	38	1.59 (0.70-3.65)	0.27	39	0.92 (0.43-1.98)	0.84
N stage						
0	74	1.10 (0.47-2.57)	0.83	72	1.16 (0.50-2.70)	0.73
1	225	1.85 (1.21-2.81)	0.0036	222	1.90 (1.27-2.83)	0.0014
2	121	0.86 (0.55-1.35)	0.52	125	0.82 (0.53-1.25)	0.35
3	76	1.26 (0.74-2.13)	0.4	76	1.04 (0.62-1.76)	0.88
1+2+3	422	1.31 (1.01-1.70)	0.045	423	1.32 (1.02-1.70)	0.031
M stage						
0	444	1.32 (1.00-1.74)	0.052	443	1.33 (1.02-1.73)	0.038
1	56	1.44 (0.81-2.56)	0.21	56	1.10 (0.61-1.96)	0.76

Table 2. Correlation analysis between the expression level of SYT4 and markers of immune cells in TIMER.

Description	Gene markers	STAD				LGG				BC			
		None		Purity		None		Purity		None		Purity	
		Cor	p-value	Cor	p-value	Cor	p-value	Cor	p-value	Cor	p-value	Cor	p-value
CD8+ T cell	CD8A	0.24	***	0.25	***	0.23	***	0.27	***	0.03	3.58E-01	-0.02	4.37E-01
	CD8B	0.21	***	0.23	***	0.02	6.44E-01	-0.03	4.57E-01	-0.01	7.51E-01	-0.01	7.50E-01
T cell (general)	CD3D	0.19	***	0.18	**	-0.22	***	-0.21	***	-0.01	7.72E-01	-0.02	5.78E-01
	CD3E	0.22	***	0.21	***	-0.25	***	-0.25	***	0.00	9.64E-01	-0.01	8.00E-01
	CD2	0.21	***	0.20	***	-0.25	***	-0.24	***	-0.01	8.24E-01	-0.01	7.07E-01
B cell	CD19	0.28	***	0.27	***	-0.33	***	-0.30	***	-0.02	4.88E-01	-0.04	2.68E-01
	CD79A	0.30	***	0.28	***	-0.40	***	-0.40	***	-0.02	4.84E-01	-0.04	1.87E-01
Monocyte	CD86	0.16	**	0.14	*	-0.51	***	-0.52	***	0.01	6.83E-01	-0.01	8.73E-01
	CD115 (CSF1R)	0.26	***	0.24	***	-0.48	***	-0.50	***	0.03	3.99E-01	-0.01	7.55E-01
TAM	CCL2	0.27	***	0.27	***	-0.34	***	-0.32	***	0.07	2.27E-02	-0.06	4.41E-02
	IL10	0.23	***	0.23	***	-0.41	***	-0.38	***	0.07	1.92E-02	-0.06	5.34E-02
M1 macrophage	INOS (NOS2)	-0.09	6.59E-02	-0.10	6.29E-02	0.29	***	0.29	***	0.08	*	0.07	2.63E-02
	IRF5	0.12	1.24E-02	-0.10	4.23E-02	-0.50	***	-0.52	***	0.08	1.26E-02	-0.06	5.88E-02
	COX2 (PTGS2)	0.13	*	0.13	*	0.14	*	0.18	***	0.13	***	0.14	***
M2 macrophage	CD163	0.20	***	0.18	**	-0.39	***	-0.36	***	0.07	1.67E-02	-0.06	6.48E-02
	VSIG4	0.20	***	0.20	***	-0.54	***	-0.53	***	0.04	1.63E-01	-0.03	3.01E-01
	MS4A4A	0.24	***	0.24	***	-0.54	***	-0.53	***	0.08	*	0.07	2.67E-02
Neutrophil	CD66b (CEACAM8)	0.07	1.73E-01	-0.07	1.91E-01	-0.10	2.37E-02	-0.09	6.09E-02	0.10	**	0.10	*
	CD11b (ITGAM)	0.18	**	0.16	*	-0.46	***	-0.47	***	-0.07	3.03E-02	-0.08	1.27E-02
	CCR7	0.33	***	0.33	***	-0.11	1.25E-02	-0.10	2.65E-02	0.02	5.72E-01	-0.01	7.41E-01
Natural killer cell	KIR2DL1	0.06	2.39E-01	-0.06	2.33E-01	-0.02	6.77E-01	-0.04	4.35E-01	0.05	1.05E-01	-0.04	1.88E-01
	KIR2DL3	0.07	1.40E-01	-0.05	3.58E-01	-0.12	*	-0.13	*	0.03	3.56E-01	-0.03	4.22E-01
	KIR2DL4	-0.04	3.61E-01	-0.05	2.95E-01	-0.33	***	-0.33	***	0.00	9.55E-01	-0.02	5.96E-01
	KIR3DL1	0.13	*	0.10	6.29E-02	-0.02	5.72E-01	-0.03	5.12E-01	-0.03	4.06E-01	-0.00	9.65E-01
	KIR3DL2	0.10	3.82E-02	-0.08	1.16E-01	-0.14	*	-0.15	**	0.02	4.97E-01	-0.02	4.99E-01
	KIR3DL3	-0.03	5.53E-01	-0.01	8.78E-01	-0.03	4.44E-01	-0.03	5.45E-01	-0.02	5.72E-01	-0.01	7.47E-01

		01	01	01	01	01	01	01	01	01	01	01	
	KIR2DS4	-0.02	6.94E-01	-0.04	4.12E-01	-0.10	2.07E-01	-0.10	2.75E-01	0.02	4.91E-01	0.01	6.99E-01
Dendritic cell	HLA-DPB1	0.06	2.09E-01	-0.07	1.55E-01	-0.34	***	-0.35	***	0.12	***	0.01	8.51E-01
	HLA-DQB1	0.00	9.76E-01	-0.02	7.23E-01	-0.26	***	-0.28	***	0.11	**	0.03	3.65E-01
	HLA-DRA	-0.01	8.03E-01	-0.00	9.89E-01	-0.32	***	-0.34	***	0.10	*	-0.01	6.59E-01
	HLA-DPA1	0.01	8.99E-01	-0.01	7.75E-01	-0.31	***	-0.32	***	0.08	1.00E-02	-0.04	2.66E-01
	BDCA-1 (CD1C)	0.20	***	0.21	***	-0.19	***	-0.19	***	0.13	***	0.03	2.86E-01
	BDCA-4 (NRP1)	0.38	***	0.40	***	-0.13	*	-0.10	2.62E-02	0.19	***	0.13	***
	CD11c (ITGAX)	0.17	**	0.18	**	-0.23	***	-0.27	***	0.08	*	-0.02	6.12E-01
Th1 cell	T-bet (TBX21)	0.09	7.70E-02	-0.10	5.91E-02	-0.22	***	-0.20	***	0.11	**	0.00	9.71E-01
	STAT4	0.17	**	0.18	**	0.47	***	0.45	***	0.17	***	0.07	3.55E-02
	STAT1	-0.04	3.74E-01	-0.02	6.56E-01	-0.08	7.37E-02	-0.08	8.91E-02	0.03	3.50E-01	-0.02	5.51E-01
	IFNG (INF- γ)	-0.14	*	-0.12	2.02E-02	-0.13	*	-0.15	*	0.05	6.90E-02	-0.03	3.79E-01
	TNF (TNF- α)	0.08	1.20E-01	-0.10	4.92E-02	-0.10	2.19E-02	-0.11	2.09E-02	0.02	4.81E-01	-0.01	7.89E-01
Th2 cell	GATA3	0.19	***	0.21	***	-0.21	***	-0.22	***	-0.17	***	-0.13	***
	STAT6	0.09	6.78E-02	-0.11	3.74E-02	-0.15	**	0.10	2.35E-02	0.07	2.97E-02	-0.05	1.32E-01
	STAT5A	0.16	**	0.20	**	-0.28	***	-0.33	***	0.07	1.30E-02	-0.00	9.57E-01
	IL13	0.12	1.30E-02	-0.13	1.11E-02	-0.15	**	0.14	*	0.08	*	0.04	2.03E-01
Tfh cell	BCL6	0.32	***	0.34	***	-0.09	4.38E-02	-0.04	3.53E-01	0.07	2.16E-02	-0.05	1.54E-01
	IL21	-0.03	5.42E-01	-0.01	7.90E-01	-0.13	*	-0.15	**	0.00	9.35E-01	-0.05	9.30E-02
Th17 cell	STAT3	0.23	***	0.25	***	-0.24	***	-0.22	***	0.02	4.62E-01	-0.00	9.84E-01
	IL17A	-0.05	3.23E-01	-0.05	3.06E-01	-0.05	2.38E-01	-0.04	4.41E-01	0.01	6.91E-01	-0.02	4.56E-01
Treg cell	FOXP3	0.10	4.81E-02	-0.12	2.09E-02	-0.15	**	0.14	*	0.13	***	0.04	1.66E-01
	CCR8	0.14	*	0.17	*	-0.19	***	-0.20	***	0.04	1.56E-01	-0.02	4.40E-01
	STAT5B	0.33	***	0.34	***	0.00	9.21E-01	-0.07	1.06E-01	0.00	9.58E-01	-0.03	3.03E-01
	TGFB1 (TGF β)	0.38	***	0.38	***	-0.22	***	-0.26	***	0.19	***	0.10	*
T cell exhaustion	PDCD1 (PD-L1)	0.06	2.34E-01	-0.09	7.94E-02	-0.27	***	-0.27	***	0.12	***	0.02	4.86E-01
	CTLA4	0.01	8.88E-01	-0.04	4.23E-01	-0.11	*	-0.11	1.79E-02	0.07	1.71E-02	-0.02	5.58E-01
	LAG3	-0.01	9.13E-01	-0.03	6.23E-01	-0.14	*	-0.13	*	0.04	1.66E-01	-0.01	8.03E-01

TIM-3 (HAVCR2)	0.13	1.07E-02	0.14	*	-0.29	***	-0.35	***	0.06	4.89E-02	-0.03	4.30E-01
GZMB	-0.07	1.64E-01	-0.05	3.09E-01	-0.02	5.89E-01	-0.03	4.85E-01	0.08	*	-0.01	7.38E-01

STAD: Stomach adenocarcinoma; LGG: Brain lower-grade glioma; BC: Breast cancer; TAM: Tumour-associated macrophage; Th: T helper; Tfh: Follicular helper T; Treg: Regulatory T; Cor: R value of Spearman's correlation; None: Correlation without adjustment; Purity: Correlation adjusted by purity. *p < .01; **p < .001; ***p < .0001.

Table 3. Correlation analysis between the expression level of SYT4 and markers of monocytes, TAMs, and M1 and M2 macrophages in GEPIA.

Description	Gene markers	STAD		BRCA		LGG	
		Tumour		Tumour		Tumour	
		Cor	p-value	Cor	p-value	Cor	p-value
Monocyte	CD86	0.16	*	0.01	0.74	-0.48	***
	CD115 (CSF1R)	0.25	***	0.027	0.37	-0.45	***
TAM	CCL2	0.25	***	0.055	0.07	-0.32	***
	IL10	0.20	***	0.099	*	-0.36	***
M1 macrophage	NOS2	-0.07	0.16	0.073	0.016	0.31	***
	IRF5	0.11	0.027	0.10	**	-0.48	***
	COX2 (PTGS2)	0.16	*	0.12	***	0.14	*
M2 macrophage	CD163	0.15	*	0.056	0.064	-0.39	***
	VSIG4	0.18	**	0.045	0.14	-0.51	***
	MS4A4A	0.22	***	0.09	*	-0.52	***

STAD: Stomach adenocarcinoma; BRCA: Breast invasive carcinoma; LGG: Brain lower-grade glioma; TAM: tumour-associated macrophage; Cor: R value of Spearman's correlation; *p < 0.01; **p < 0.001; ***p < 0.0001.

Figures

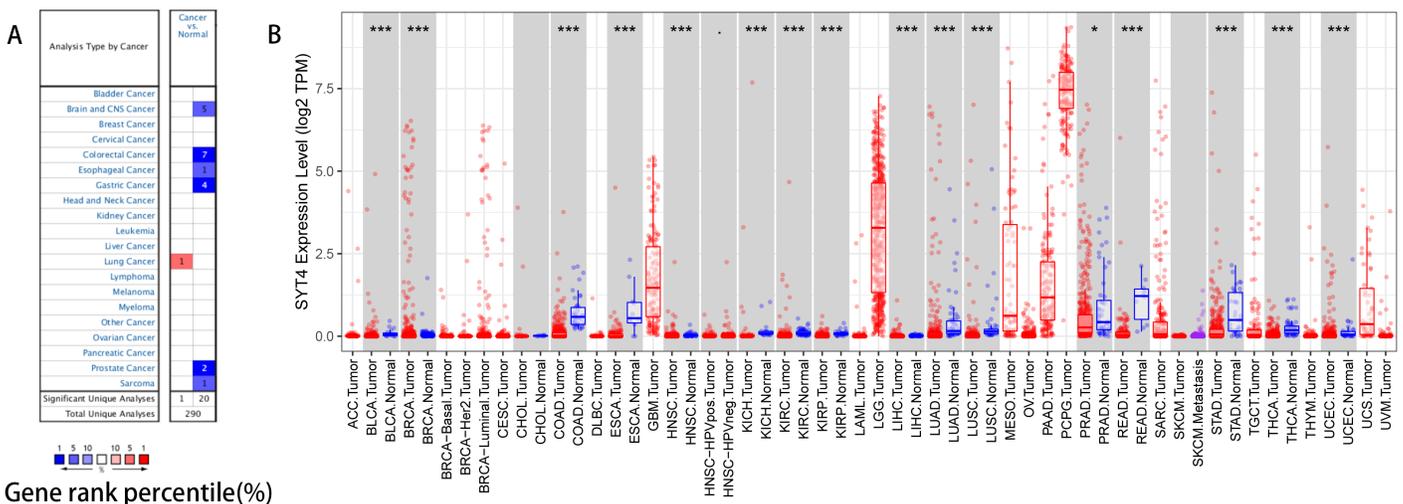


Figure 1

The expression levels of SYT4 in cancers. A. The data from Oncomine show the differences between the expression levels of SYT4 in tumours and normal tissues. B. The data from TIMIER show the expression level of SYT4 in different cancers.

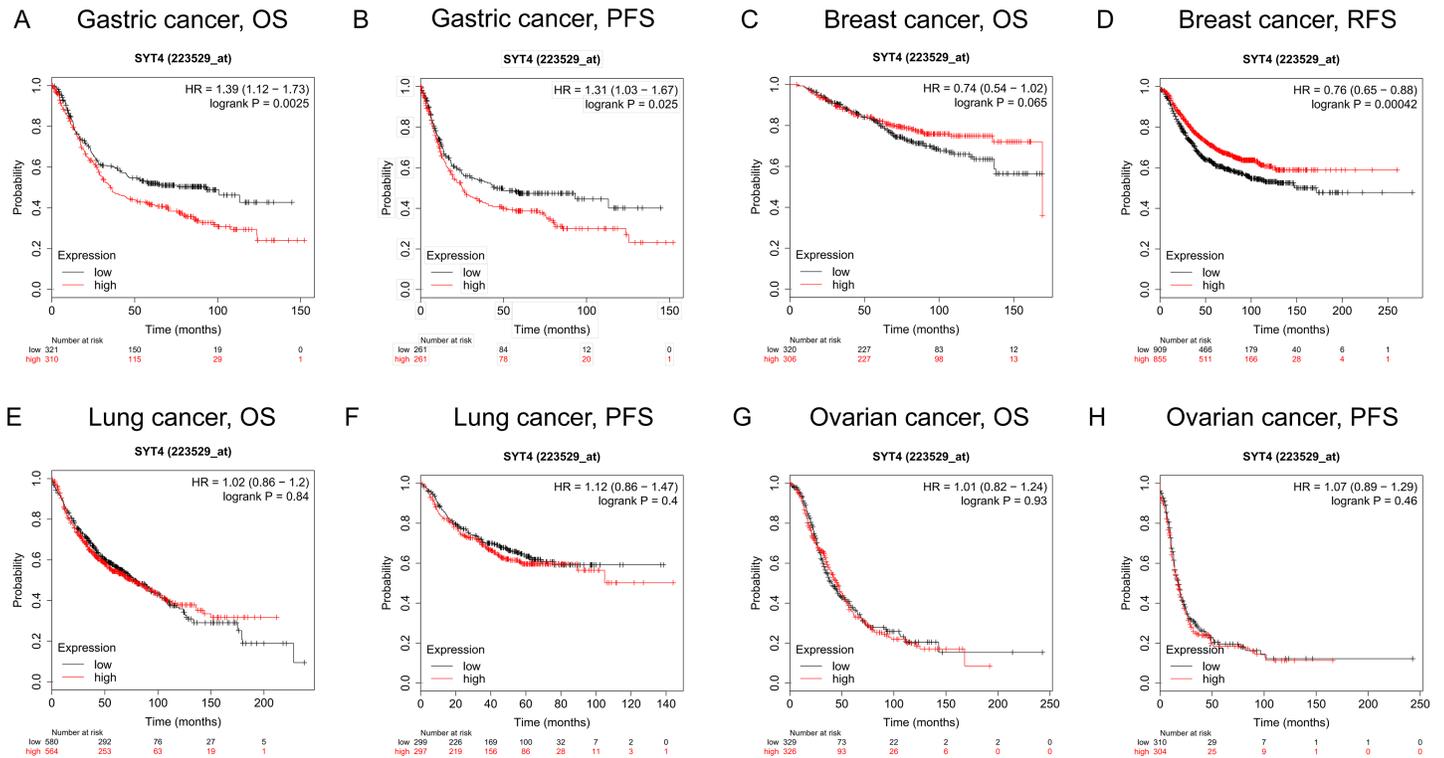


Figure 2

Survival analysis of SYT4 in different cancers with Kaplan-Meier plotter database. A, B: The impact of SYT4 on the prognosis of patients with gastric cancer. C, D: The impact of SYT4 on the prognosis of patients with breast cancer. E, F: The impact of SYT4 on the prognosis of patients with lung cancer. G, H: The impact of SYT4 on the prognosis of patients with ovarian cancer. (OS: Overall survival; PFS: Progression-free survival; RFS: Recurrence-free survival)

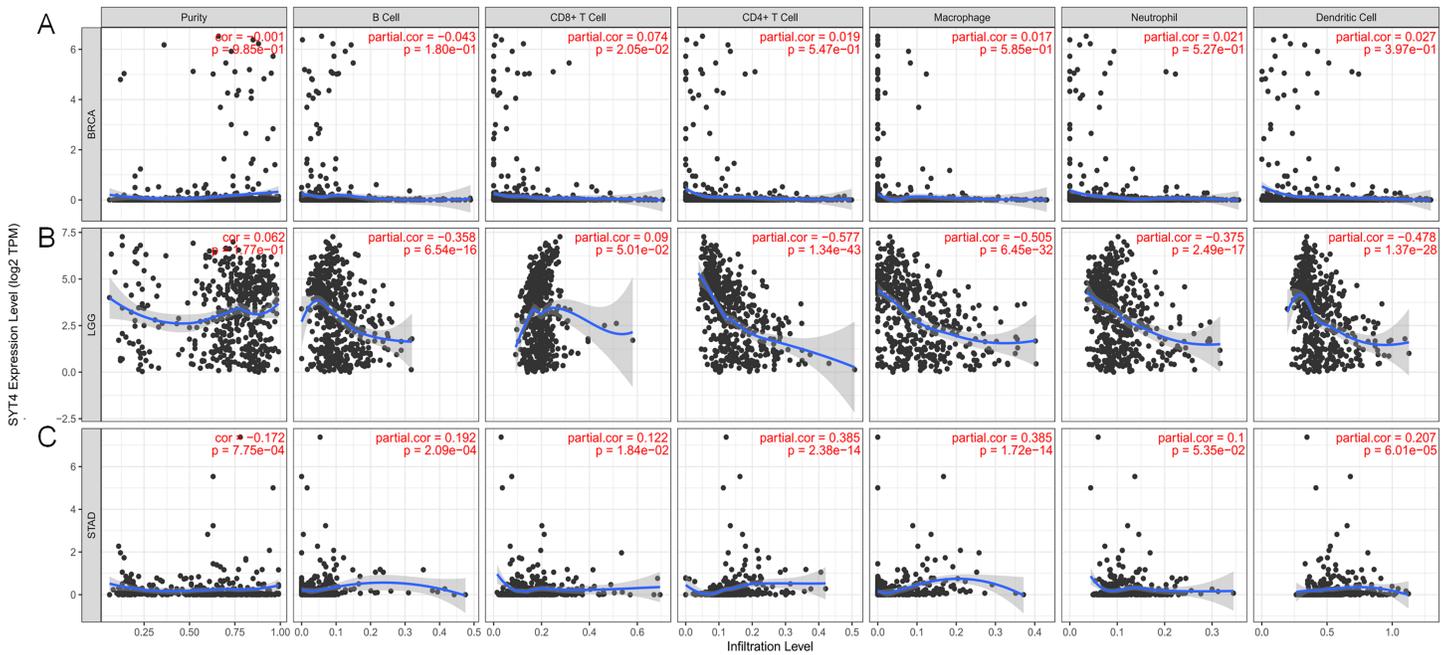


Figure 3

Correlation analysis of the expression level of SYT4 and the level of immune infiltration in STAD, LGG and BRCA. A. No correlation existed between the expression level of SYT4 and tumour purity and the infiltration of 5 immune cells types in BRCA, but there was a positive correlation between SYT4 and CD8+ T cells. B. The expression level of SYT4 had no association with tumour purity in LGG but had a negative correlation with the level of infiltration of 5 immune cells types, (not including CD8+ T cells. C. The expression level of SYT4 had a negative association with tumour purity in STAD, but had a positive correlation with the level of infiltration of 5 immune cells types, (not including neutrophils).

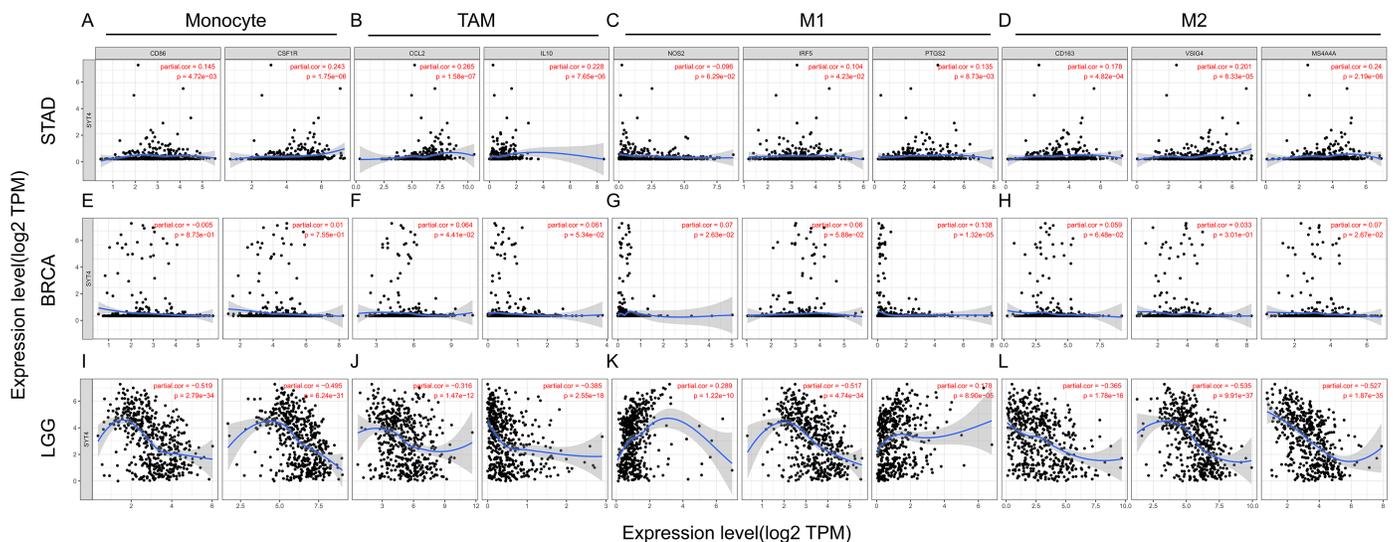


Figure 4

Correlation between the expression level of SYT4 and markers of immune cells, such as monocytes (CD86 and CSF1R), tumour-associated macrophages (CCL2 and IL10), M1 macrophages (NOS2, IRF5, and PTGS2) and M2 macrophages (CD163, VSIG4, and MS4A4A), in STAD (A-D), BRCA (E-H), and LGG (I-L).

Supplementary Files

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