

A Pan-Cancer Analysis Reveals the Prognostic Significance and Oncogenic Role of *LncRNA TUG1*

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Submitted: 29 February 2024 Revised: 8 April 2024 Accepted: 12 April 2024 Published: 1 June 2024

Background: *LncRNA* taurine up-regulated gene1 (*TUG1*) is a valuable *lncRNA* that is abnormally expressed in a number of tumor types. However, investigations into its expression, prognostic implications, and associations with the tumor microenvironment and immunity remain limited. In this study, we evaluated the prognostic value and oncogenic potential of *TUG1*, and its relationship with pathological parameters, immune infiltration, and cancer drug sensitivity.

Methods: Using data from The Cancer Genome Atlas (TCGA), Sangerbox, and the Cancer Cell Line Encyclopedia (CCLE), we analyzed *TUG1* expression. Kaplan-Meier and Cox regression analyses were employed to evaluate the prognostic significance of *TUG1* in pan-cancer. The association between *TUG1* expression and methylation, tumor mutational burden (TMB), microsatellite instability (MSI), immune infiltration, immune checkpoints, and drug sensitivity was examined.

Results: In adrenocortical carcinoma (ACC) and liver hepatocellular carcinoma (LIHC), *TUG1* overexpression was related to poorer overall survival (OS). In glioblastoma multiforme (GBM), lower grade glioma (LGG) and pheochromocytoma and paraganglioma (PCPG), increased *TUG1* was related to better OS. In ACC and LGG, *TUG1* may be an independent prognostic factor. Gene set enrichment analysis (GSEA) highlights the involvement of *TUG1* in various tumorigenic and signaling pathways. Additionally, *TUG1* was associated with TMB in 12 tumor types and with MSI in 11 cancer types. *TUG1* expression was positively correlated with Chelerythrine, Nelarabine, Methylprednisol, AZD-9496, and ZM-336372, while it negatively correlated with CG-806, BPTES, Vincristine, AZD-4547, CFI-400945, XR-5944, and Danusertib.

Conclusions: Our findings revealed dysregulated *TUG1* expression in the human pan-cancer dataset. Drug sensitivity analysis suggested a potential association between *TUG1* and drug resistance of specific drugs. Moreover, *TUG1* expression was correlated with immune checkpoint genes, immune cell infiltration, and the tumor microenvironment across various cancers, underscoring its potential as a promising target for tumor prognosis and treatment. Our findings highlight the fundamental impact of *TUG1* across multiple cancer types, offering insights that could pave the way for novel therapeutic strategies in cancer patients.

Keywords: *lncRNA TUG1*; pan-cancer; prognostic; tumor microenvironment; target

Introduction

Cancer is a significant global public health challenge, ranking as the second leading cause of death [1]. Projection indicating a rise in cancer incidence and mortality over the next four decades underscores the immense clinical burden, societal impacts, and substantial economic toll associated with malignancy, rendering it a primary public health concern [2]. Despite significant advancements in cancer diagnosis and treatment, the survival rates and quality of life for cancer patients remain unsatisfactory. Thus, there is an urgent need to identify diagnostic biomarkers and develop novel cancer treatment approaches.

Long non-coding RNA (*lncRNA*) represents a class of endogenous non-coding RNA molecules with transcriptional lengths exceeding 200 nucleotides, exerting crucial regulatory effects on cellular processes including development, differentiation, apoptosis, tumor invasion and metastasis, and angiogenesis [3]. Taurine up-regulated gene1

(*TUG1*), located on the human chromosome 22 autosomal long arm one region two sub-band (22q 12.2), was first identified in retinal cells of neonatal mice in 2005 [4,5]. Notably, *TUG1* can act as both a tumor suppressor gene and an oncogene in tumors, relying on the type of cancer in which it is dysregulated.

This study aimed to explore the involvement of *TUG1* across various cancer types by exploring its associations with prognosis, tumor mutational burden (TMB), microsatellite instability (MSI), clinical staging, immune checkpoint genes, and infiltrating immune cells using diverse public databases. The insights garnered from this exploration hold promise for informing future experimental and pharmaceutical endeavors in cancer research.

Methods and Materials

Data Acquisition and *TUG1* Expression

Gene expression profiles, mutation data, and clinical information from the The Cancer Genome Atlas (TCGA) pan-cancer project, including disease-specific survival (DSS), disease-free interval (DFI), overall survival (OS), and progression-free interval (PFI) across 33 malignancies, were retrieved from UCSC Xena (<http://xena.ucsc.edu/>). **Supplementary Table 1** provides full names and tumor abbreviations.

Additionally, data from TCGA for normal tissues were obtained and paired the differential expression of *TUG1* in tumor tissues (<https://www.xiantao.love/products>). Utilizing Strawberry Perl scripts software (<https://strawberryp Perl.com/>) and RStudio (<http://www.rstudio.org>, Version 3.6.1), we performed ID conversion and extracted *TUG1* expression data. Visualization of the data was conducted using the “ggpubr” R-package. *TUG1* expression in TCGA combined with genotype-tissue expression (GTEx) was integrated using the Sangerbox database (<http://sangerbox.com/>). Furthermore, *TUG1* expression in cell lines was explored using the Cancer Cell Line Encyclopedia (CCLE) (<https://portals.broadinstitute.org/ccle/>) [6].

Clinical Features and Survival Analysis Correlation with *TUG1* Expression

Patients were stratified into low- and high-expression groups based on the median level of *TUG1* expression. OS, DSS, DFI, and PFI were further analyzed using the R packages “limma” (Version 3.40.6) and “survival” (Version 3.2-11). Kaplan-Meier survival curves were generated using the “survminer” (Version 0.4.9) package. Cox regression analyses were performed for further analysis in adrenocortical carcinoma (ACC), BLCA, glioblastoma multiforme (GBM), lower grade glioma (LGG), liver hepatocellular carcinoma (LIHC), and pheochromocytoma and paraganglioma (PCPG). Forest plots were generated using the R package “forestplot” (Version 2.0.1) to illustrate hazard ratios (HR), 95% confidence interval (CI), and *p*-values. *TUG1* expression across 33 cancer types at various clinical stages was analyzed using the “limma” package, and box plots were generated with “ggpubr” (Version 0.4.0).

Methylation Analysis

The UALCAN database (<http://ualcan.path.uab.edu/>) [7], a comprehensive, interactive, and user-friendly web tool for studying cancer OMICS data, was employed to investigate the correlation between *TUG1* DNA methylation and cancer.

Correlation Analysis of *TUG1* Expression with TMB and MSI

TMB is a biomarker that can predict the response to immunotherapy [8]. MSI, characterized by alterations in short repetitive DNA sequences, reflects defects in the mismatch repair (MMR) system, a critical mechanism for maintaining DNA integrity [9]. The downloaded mutation data were calculated using Perl software to calculate the TMB for each sample. MSI values were also retrieved from the TCGA database. Subsequently, we examined the relationship between *TUG1* expression and TMB as well as MSI, and showed radar maps by R package “fmsb”.

Correlation Analysis of *TUG1* and the Tumor Microenvironment

The tumor microenvironment can be quantitatively assessed through stromal and immune scores, representing stromal and immune cell infiltration in tumor tissues. These scores were calculated using the R packages “limma” and “estimate” (Version 1.0.13) [10]. We analyzed and plotted the correlations between *TUG1* expression and both stromal and immune scores using the R packages “ggplot2” (Version 3.3.6), “ggpubr”, and “ggextra”. Finally, 22 immune cell types [11] were used to analyze the correlation with *TUG1* expression. The “CIBERSORT” package (Version 4.10.1) [12] was used to calculate immune cell infiltration score. Results with *p* < 0.001 were visualized. Furthermore, we explored the co-expression relationship between *TUG1* and common immune checkpoint genes as well as immune marker genes using the “limma” package. A heat map illustrating *TUG1* co-expression with associated genes was generated using the R packages “reshape2” (Version 1.4.4) and “RColorBrewer” (Version 1.1-3).

Kyoto Encyclopedia of Genes and Genomes (KEGG) Analysis

The “KEGG gene sets as Gene Symbols” was downloaded from gene set enrichment analysis (GSEA) (<http://www.gsea-msigdb.org/gsea/index.jsp>). The R package “clusterProfiler” (Version 3.12.10) [13] was utilized to examine the biological and molecular functions associated with *TUG1*. Plots displaying the top five pathways with the highest normalized enrichment scores and *p*-values less than 0.05 were considered.

Drug Sensitivity of *TUG1* in Cancers

Utilizing the CellMiner database (<https://discover.nci.nih.gov/cellminer/home.do>) [14], we retrieved the NCI-60 compound activity data and RNA-seq expression profiles. Only FDA-approved drugs or clinical trials could be analyzed. The R packages “impute” (Version 1.58.0), “limma”, “ggplot2”, and “ggpubr” were employed to examine the drug sensitivity of *TUG1*.

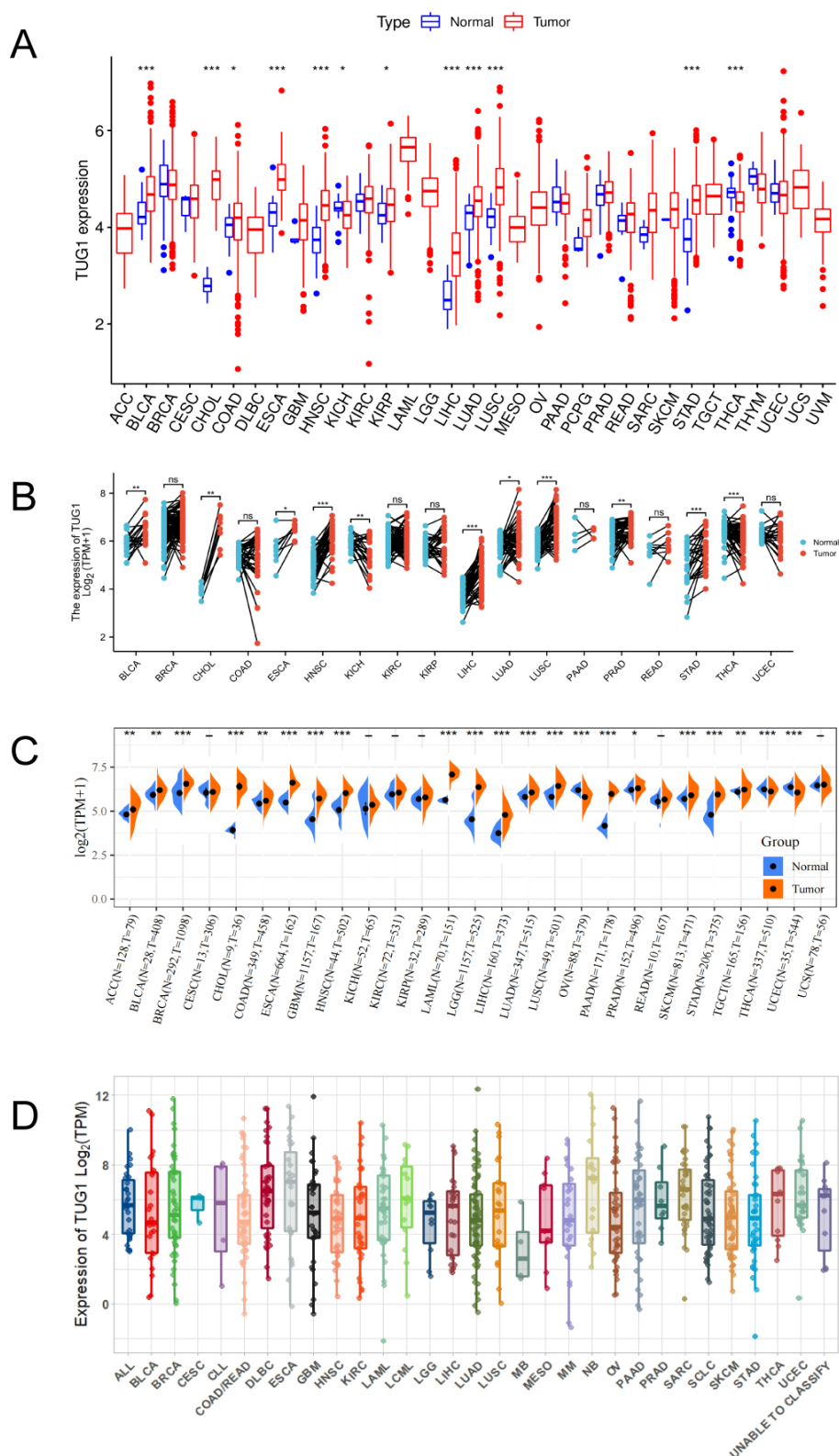


Fig. 1. Taurine up-regulated gene1 (*TUG1*) expression across 33 cancer types. (A) *TUG1* expression in various cancers from The Cancer Genome Atlas (TCGA). (B) *TUG1* expression between adjacent tissues and matched cancer tissues from TCGA. (C) *TUG1* expression in cancers from TCGA and genotype-tissue expression (GTEx). (D) *TUG1* expression in various cancer cell lines from the Cancer Cell Line Encyclopedia (CCLE) database. ns, $p \geq 0.05$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

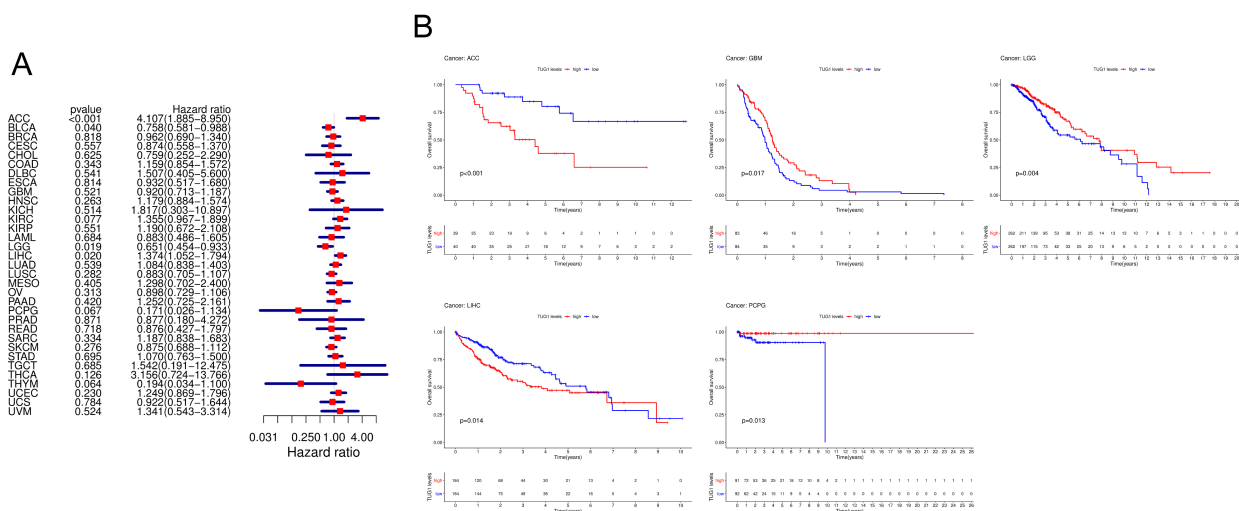


Fig. 2. Correlation between *TUG1* expression and overall survival (OS) in cancers. (A) Cox model analysis demonstrating the association between *TUG1* and OS across different cancers. (B) Kaplan-Meier survival curves illustrating the impact of *TUG1* expression on OS in adrenocortical carcinoma (ACC), liver hepatocellular carcinoma (LIHC), glioblastoma multiforme (GBM), lower grade glioma (LGG), and pheochromocytoma and paraganglioma (PCPG).

Statistical Analysis

Statistical analysis was performed using R Studio (R Version 3.6.1). Differences and correlations between groups were analyzed using the Wilcoxon rank-sum and Spearman tests. The log-rank test and Cox hazard regression model were adopted to examine the survival results by Kaplan-Meier survival curves and calculate the hazard ratio (HR), respectively. Statistical significance was set at $p < 0.05$.

Results

The Expression of *TUG1* in Pan-Cancer

We collected a total of 11,057 samples, comprising 10,327 tumor samples and 730 normal samples, from UCSC Xena for analysis. Analysis of the TCGA data revealed that *TUG1* exhibited elevated expression level in bladder urothelial carcinoma (BLCA), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), esophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), kidney renal papillary cell carcinoma (KIRP), LIHC, lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and stomach adenocarcinoma (STAD), while it displayed low expression in kidney chromophobe (KICH) and thyroid carcinoma (THCA) compared to adjacent normal tissues (Fig. 1A). Furthermore, a comparison between tumor tissues and adjacent normal tissues revealed significantly higher *TUG1* expression in BLCA, CHOL, ESCA, HNSC, LIHC, LUAD, LUSC, prostate adenocarcinoma (PRAD), STAD, and THCA, with a decrease in KICH (Fig. 1B). Notably, the differences in *TUG1* expression reached statistical significance in 21 out of 33 cancer types.

Moreover, we assessed *TUG1* expression in ACC, BLCA, breast invasive carcinoma (BRCA), CHOL, COAD, ESCA, GBM, HNSC, acute myeloid leukemia (LAML), LGG, LIHC, LUAD, LUSC, ovarian serous cystadenocarcinoma (OV), pancreatic adenocarcinoma (PAAD), PRAD, Skin Cutaneous Melanoma (SKCM), STAD, testicular germ cell tumors (TGCT), THCA, and uterine corpus endometrial carcinoma (UCEC) (Fig. 1C). Additionally, we examined *TUG1* expression across various cancer cell lines using data from the CCLE database (Fig. 1D). Additionally, elevated *TUG1* was observed in neuroblastoma (NB), diffuse large b-cell lymphoma (DLBC), ESCA, sarcoma (SARC), and THCA.

Prognostic Values of *TUG1* in Different Cancers

We investigated the association between *TUG1* expression and the prognosis of patients with pan-cancer, including OS, DSS, DFI, and PFI. Notably, *TUG1* exhibited associations with OS in ACC, BLCA, LGG, and LIHC (Fig. 2A). Kaplan-Meier survival curves revealed that higher *TUG1* expression levels were associated with poorer OS in ACC and LIHC, while in GBM, LGG, and PCPG, elevated *TUG1* expression correlated with better OS (Fig. 2B).

Moreover, we examined the association between *TUG1* expression and DSS. Cox regression analysis revealed a correlation between *TUG1* expression and DSS in ACC, BLCA, LGG, THCA, and THYM (Fig. 3A). Kaplan-Meier results demonstrated that elevated *TUG1* expression in ACC and Mesothelioma (MESO) indicated worse DSS, while in GBM, LGG, and PCPG, higher *TUG1* expression correlated with improved DSS (Fig. 3B).

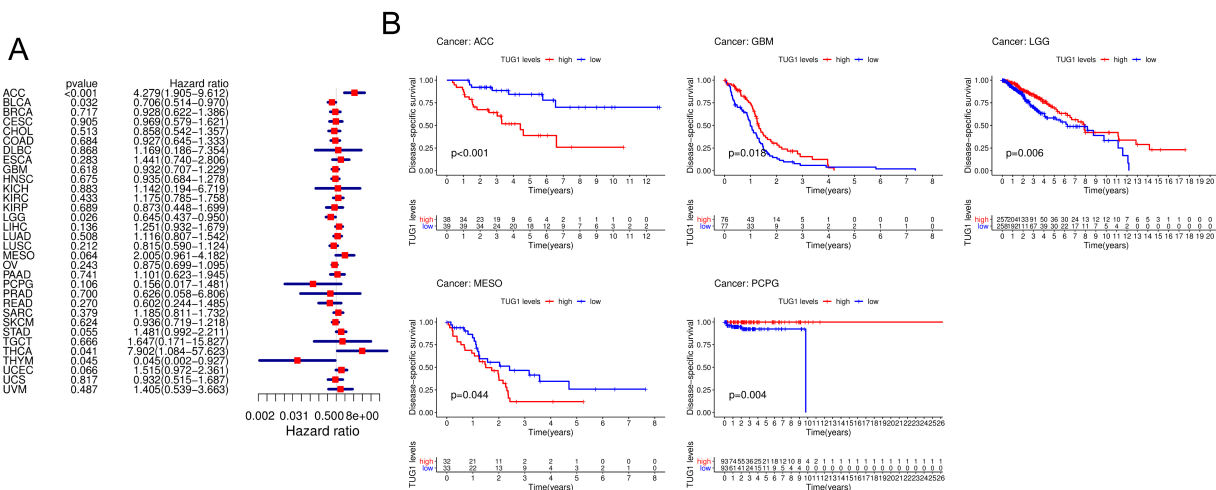


Fig. 3. Relationship between *TUG1* expression and disease-specific survival (DSS) in pan-cancer. (A) Cox regression analysis demonstrating the correlation of *TUG1* expression with DSS across various cancers. (B) DSS curves comparing high and low expression of *TUG1* in ACC, GBM, LGG, Mesothelioma (MESO), and PCPG.

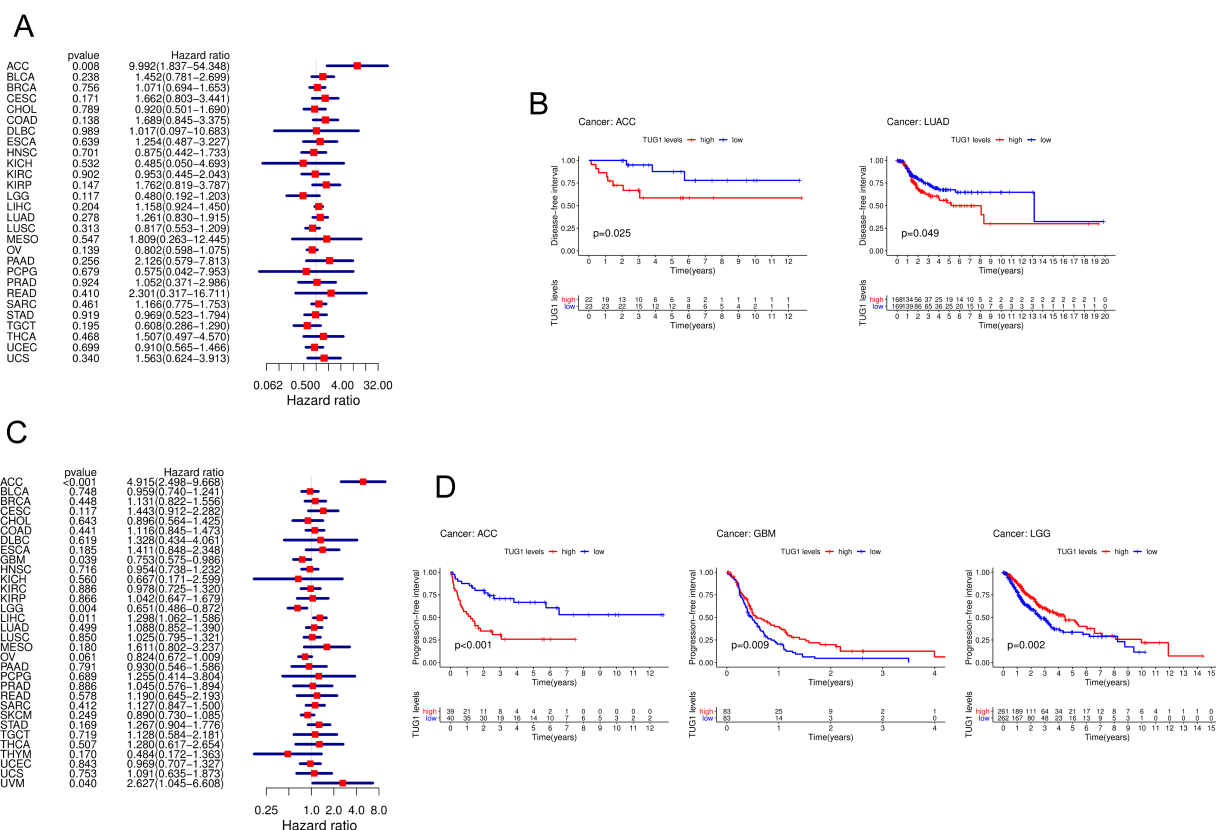


Fig. 4. Correlation of *TUG1* expression with disease-free interval (DFI) and progression-free interval (PFI) in pan-cancer. (A) Cox regression analysis demonstrating the relationship between *TUG1* expression and DFI across various cancers. (B) DFI curves comparing high and low expression of *TUG1* in ACC and lung adenocarcinoma (LUAD). (C) Cox regression analysis revealing the correlation of *TUG1* expression with PFI across various cancers. (D) PFI curves comparing high and low expression of *TUG1* in ACC, GBM, and LGG.

Additionally, in line with the Cox analysis findings, *TUG1* overexpression was linked to worse DFI in ACC (Fig. 4A). Kaplan-Meier analysis of DFI results indicated

that *TUG1* overexpression was associated with poor DFI in ACC and LUAD (Fig. 4B). Similarly, the expression of *TUG1* correlated with the PFI in ACC, GBM, LGG, LIHC,

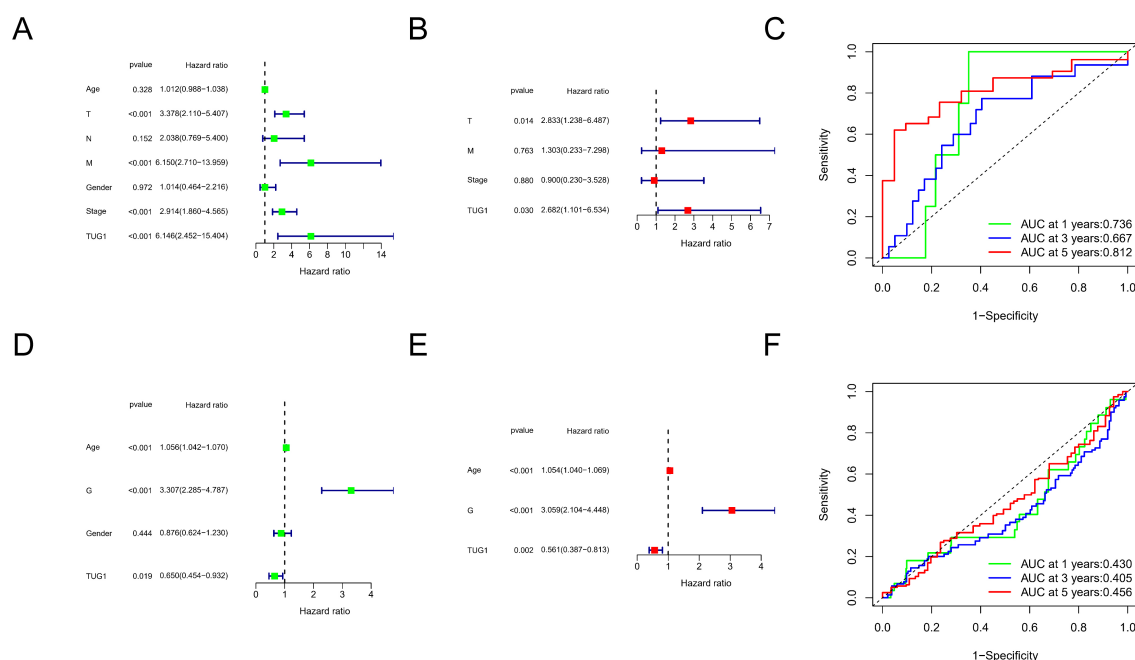


Fig. 5. *TUG1* is an independent prognostic factor in ACC and LGG patients. (A,B) *TUG1* overexpression associated with poor OS in ACC. (C) Receiver operating characteristic curve (ROC) analysis for ACC. 1 year (area under the curve (AUC) = 0.736, 95% confidence interval (CI) 0.6225–0.8505, cutoff = 3.6173); 3 years (AUC = 0.667, 95% CI 0.5202–0.8295, cutoff = 4.2393); 5 years (AUC = 0.812, 95% CI 0.6786–0.9435, cutoff = 3.7106). (D,E) *TUG1* overexpression linked to improved OS in LGG. (F) ROC analysis for LGG. 1 year (AUC = 0.429, 95% CI 0.3111–0.5461, cutoff = 4.3752); 3 years (AUC = 0.399, 95% CI 0.3203–0.4779, cutoff = 4.0685); 5 years (AUC = 0.442, 95% CI 0.3528–0.5304, cutoff = 5.3717).

and UVM (Fig. 4C). Kaplan-Meier analysis of PFI revealed that high expression of *TUG1* was associated with shorter PFI in ACC, while in GBM and LGG, high expression of *TUG1* indicated longer PFI (Fig. 4D).

TUG1 Emerges as an Independent Prognostic Factor for ACC and LGG

Univariate and multivariate Cox regression analyses were conducted for ACC, BLCA, GBM, LGG, LIHC, and PCPG, considering various clinicopathological features, including age, gender, T stage, N stage, M stage, and grading, to verify the independent prognostic significance of *TUG1* for pan-cancer (Supplementary Table 2).

Univariate Cox regression analysis revealed significant correlations between OS and T stage, M stage, TNM stage, and *TUG1* expression in ACC, as well as age, grade, and *TUG1* expression in LGG. Multivariate analysis demonstrated that T stage and *TUG1* expression were independently associated with OS in ACC, while age, grade, and *TUG1* expression were independent predictors of OS in LGG. These findings underscore *TUG1* as an independent prognostic factor in ACC and LGG (Fig. 5). However, it is noteworthy that in LGG, the area under the curve (AUC) value was less than 0.5, suggesting low sensitivity. This observation may be attributed to a smaller univariate prognostic difference and warrants further validation in clinical settings.

Association between TUG1 and Clinical Staging

We explored the association between *TUG1* expression and clinical staging across 33 cancers. Our findings revealed significant associations between *TUG1* and tumor staging in 12 cancers (Fig. 6). Specifically, high expression of *TUG1* was positively correlated with tumor stage in ACC, while a negative correlation was observed in BLCA. In BRCA, *TUG1* expression was lower in stage IV compared to stage II, while in HNSC, stage IV exhibited higher *TUG1* expression than stage II.

In ESCA, *TUG1* expression was higher in stages II and III compared to stage I. Similarly, in LIHC, *TUG1* expression in stage III was higher than in stages I and II. Conversely, in LUAD, *TUG1* expression in stage III was lower than in stage I. In LUSC, patients with stage II exhibited higher *TUG1* expression than in stages I and III, while in SKCM, *TUG1* expression in stage II was lower than in stages I and III. Moreover, in STAD, *TUG1* expression in stage III was higher than in stage II. TGCT exhibited higher *TUG1* expression in stage I compared to stage II, and THCA exhibited higher *TUG1* expression in stage I compared to stages II and III. These findings underscore the diverse tumor-promoting or tumor-suppressing effects of *TUG1* across cancer types.

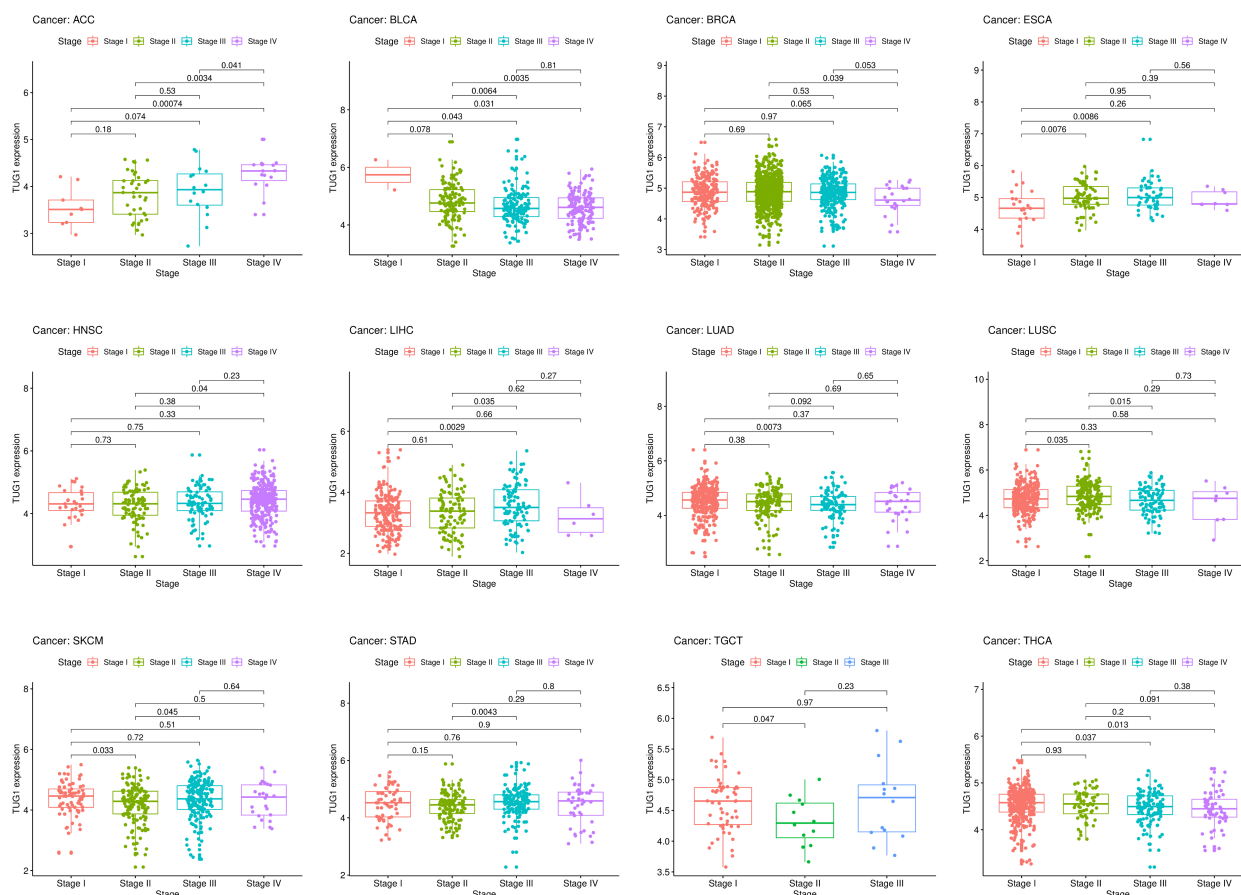


Fig. 6. The association between *TUG1* expression and clinical staging.

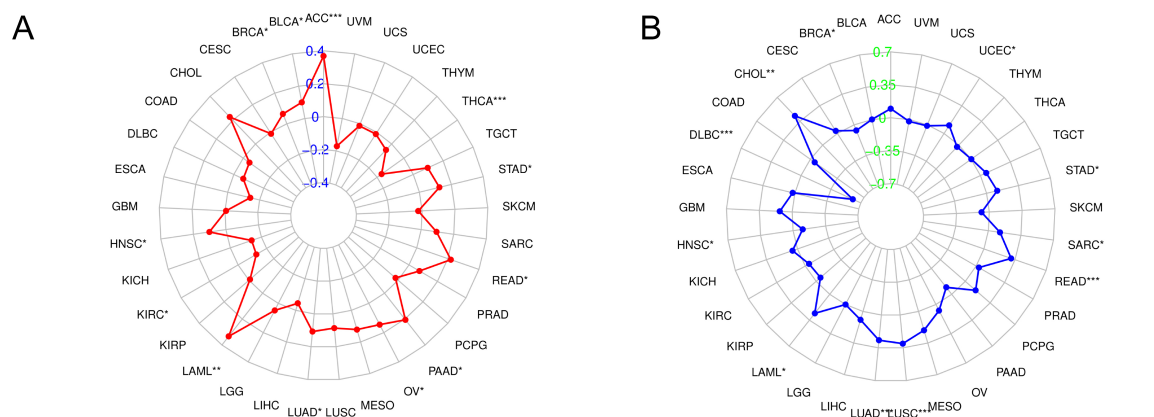


Fig. 7. Relationship between *TUG1* expression and tumor mutational burden (TMB), microsatellite instability (MSI) in TCGA pan-cancer. (A) Radar chart illustrating the relationship between *TUG1* expression and TMB. The red curve represents the correlation parameter, while blue values indicate the range. (B) Radar chart illustrating the association between *TUG1* expression and MSI in pan-cancer. The blue curve represents the relationship coefficient, while green values denote the range. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

The Role of DNA Methylation of *TUG1* in Pan-Cancer

As an epigenetic molecular mechanism, DNA hypermethylation leads to widespread inactivation of tumor suppressor genes. In this study, we examined the methyla-

tion levels of *TUG1* across various cancers. Analysis of the UALCAN database revealed varying DNA methylation levels of *TUG1*, with increased methylation observed in BRCA, HNSC, KIRP, LIHC, LUSC, PRAD, PAAD, READ, THCA, and UCEC, and decreased methylation ob-

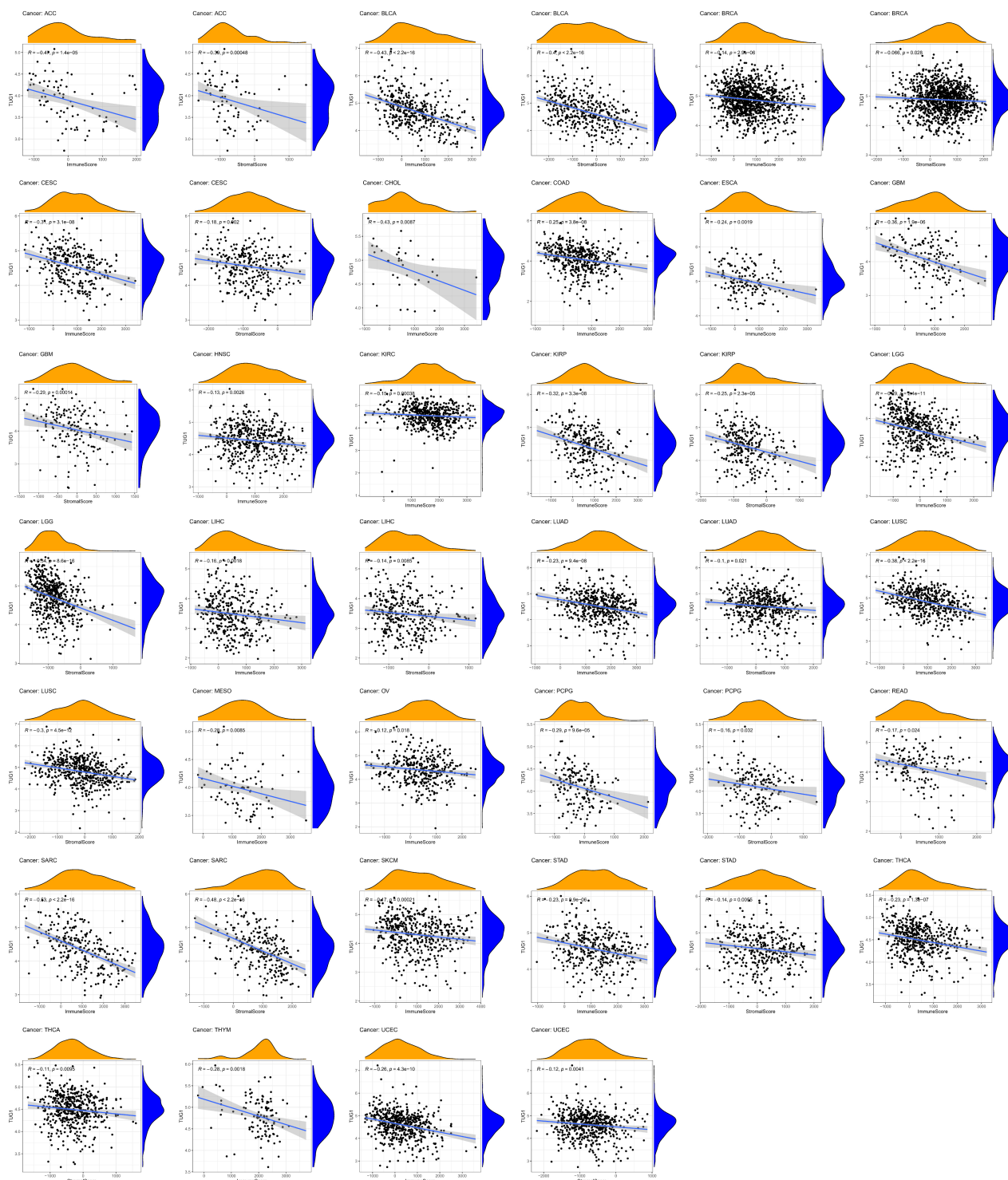


Fig. 8. Correlation of *TUG1* expression with stromal score and immune score.

served in BLCA, CHOL, COAD, ESCA, kidney renal clear cell carcinoma (KIRC), LUAD, TGCT (**Supplementary Fig. 1**).

*Correlation of *TUG1* with TMB and MSI*

Subsequently, we investigated the relationship between *TUG1* expression and TMB by calculating the TMB

of each tumor sample. Our results demonstrated a positive correlation between *TUG1* expression and TMB in ACC, STAD, READ, PAAD, OV, LUAD, LAML, HNSC, BRCA, and BLCA, while a negative correlation was observed in THCA and KIRC (Fig. 7A).

MSI is closely associated with tumorigenesis. In our study, we explored the correlation between *TUG1* expres-

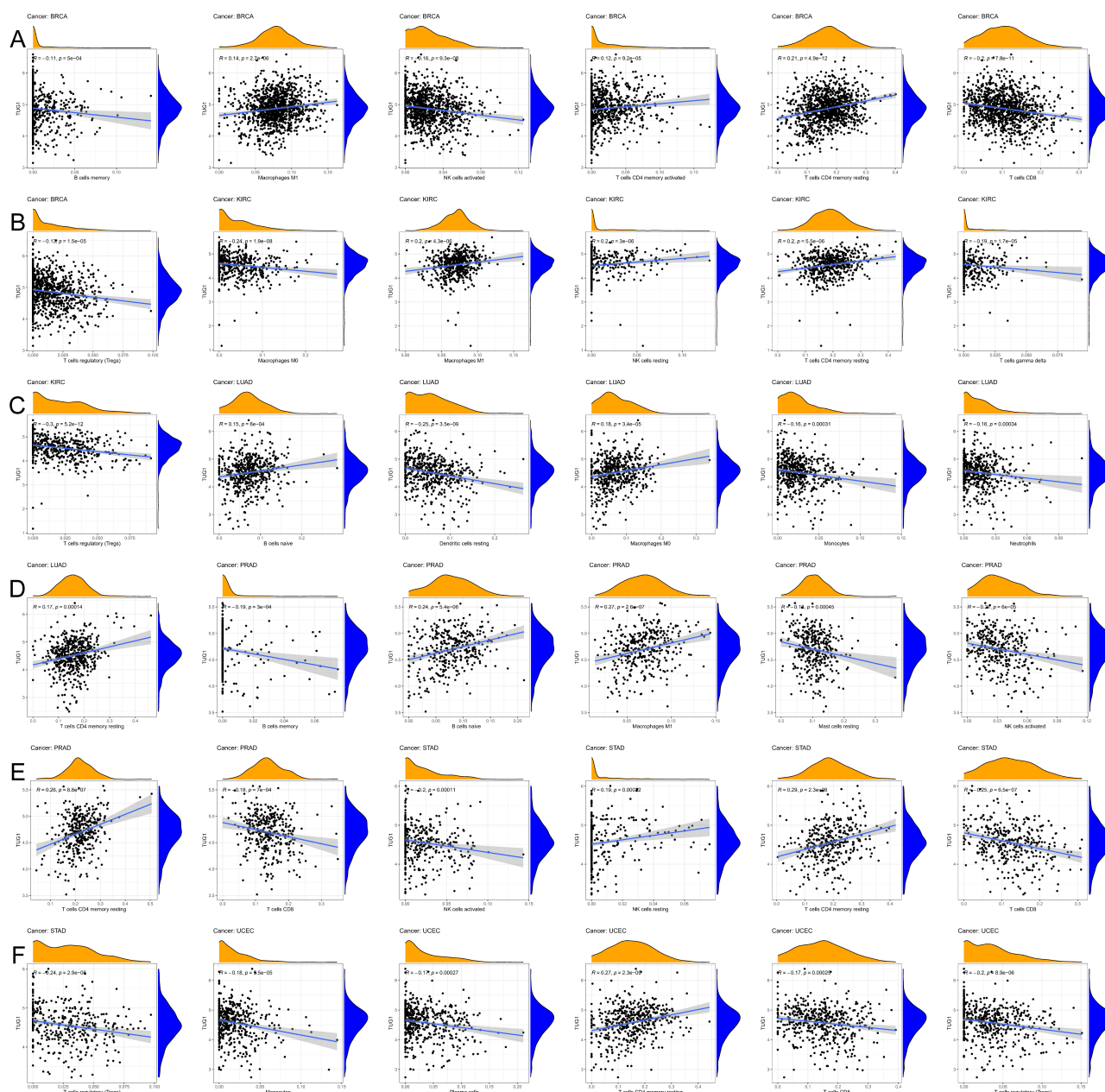


Fig. 9. Association between *TUG1* expression and immune-related cell infiltration in breast invasive carcinoma (BRCA) (A,B), kidney renal clear cell carcinoma (KIRC) (B,C), LUAD (C,D), prostate adenocarcinoma (PRAD) (D,E), stomach adenocarcinoma (STAD) (E,F), and uterine corpus endometrial carcinoma (UCEC) (F).

sion and MSI. Our analysis revealed a positive association between *TUG1* expression and MSI in UCEC, STAD, SARC, READ, LUSC, LUAD, LAML, and CHOL, while a negative correlation was observed in HNSC, DLBC, and BRCA (Fig. 7B).

Correlation Analysis of *TUG1* with Tumor Microenvironment

We assessed the relationship between *TUG1* expression and stromal, and immune scores (Supplementary Table 3). The visualized results are shown in Fig. 8. Among 33 cancers, *TUG1* expression exhibited significant correla-

tions with stromal scores in 15 and immune scores in 25. Across all tumor types, immune markers exhibited a negative correlation with *TUG1* expression, with the strongest correlation observed in SARC. Similarly, stromal markers exhibited a negative association with *TUG1* expression, indicating that higher *TUG1* expression was associated with increased tumor cell purity across various cancers.

Moreover, we investigated the association between *TUG1* expression and immune-related cell infiltration in pan-cancer. Our observations revealed that the expression level of *TUG1* was associated with seven immune-related cells in BRCA and PRAD (Fig. 9A,B,D,E). Additionally,

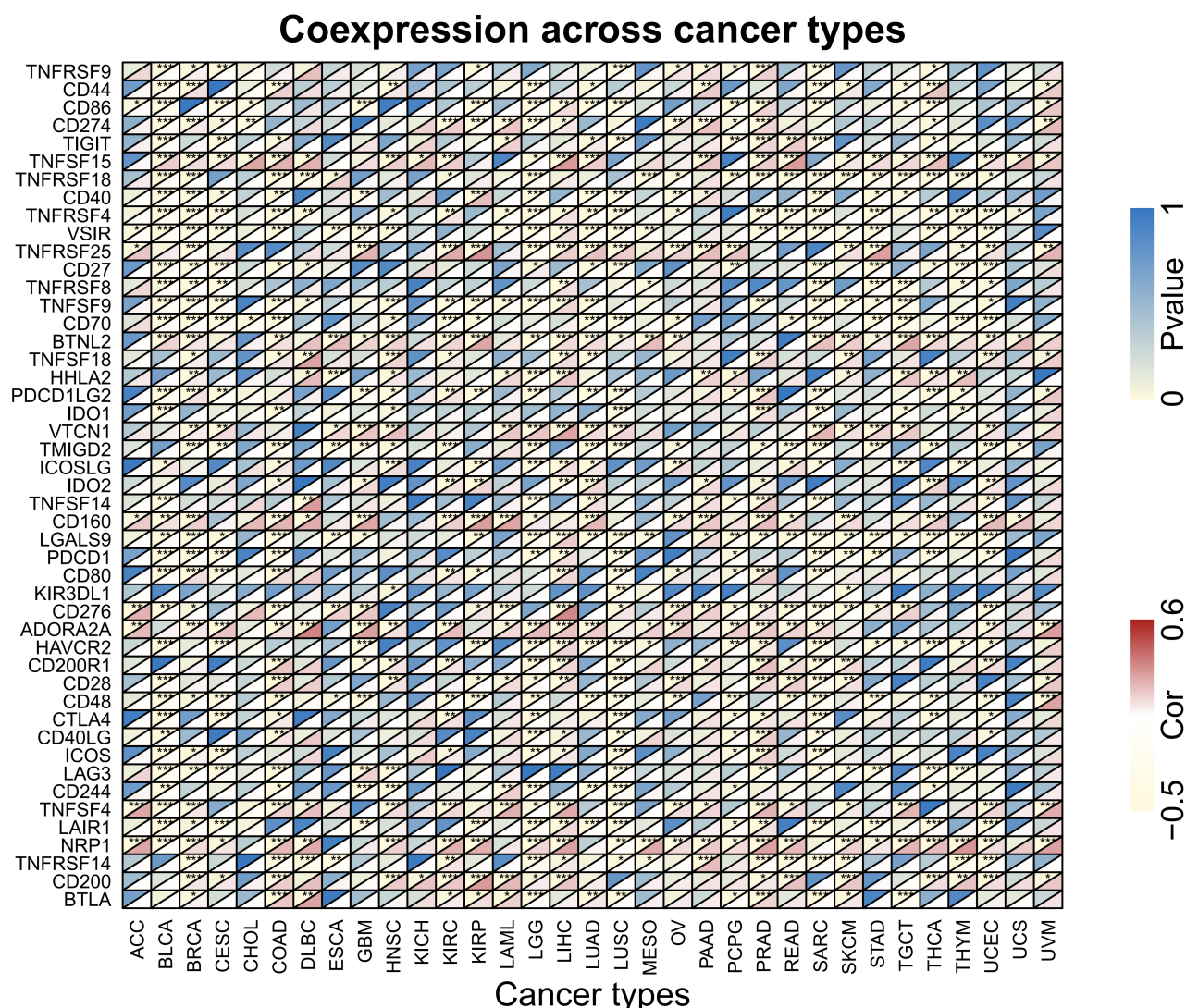


Fig. 10. Association between *TUG1* expression and immune checkpoint genes in pan-cancer from TCGA. Each cancer is represented horizontally, while immune genes are displayed vertically. Co-expression of immune genes and *TUG1* in cancer is shown in individual rectangular module. The asterisk and color in the upper left corner of the rectangles represent the *p*-value, and the color in the lower right corner represents the correlation coefficient (Cor). **p* < 0.05, ***p* < 0.01, ****p* < 0.001.

TUG1 expression was significantly correlated with T cell CD4 memory quiescence in 13 cancer types, T cell CD8 in 9 cancer types, NK cell activation in 6 cancer types, T cell regulation in 5 cancer types, and immune-related cell infiltration levels in macrophage M0 (Fig. 9, **Supplementary Fig. 2**).

*Correlation between *TUG1* Expression Levels and Immune Checkpoint Genes*

We examined the relationship between *TUG1* and common immune checkpoint genes across 33 cancers (Fig. 10). The findings revealed that while *TUG1* was not strongly correlated with the expression of immune checkpoints in CHOL, KICH, and Uterine Carcinosarcoma (UCS), it exhibited significant associations with the expres-

sion of immune checkpoints in most tumors. This observation was observed in common targets of checkpoint inhibitors and in molecular targets that activate checkpoints.

*Biological Functions of *TUG1* in Tumors*

We examined the KEGG data to elucidate the main biological processes influenced by *TUG1* expression in tumors using GSEA. The results revealed that *TUG1* positively regulated signaling pathways in GBM, HNSC, and UCS while negatively regulated signaling pathways in CHOL, LGG, LUSC, MESO, PCPG, and SARC (Fig. 11). Furthermore, *TUG1* was observed to participate in various biological functions, including cytochrome p450 metabolism, RIG-I-like receptor signaling pathway, olfactory transduction, cytokine, and transduction receptor inter-

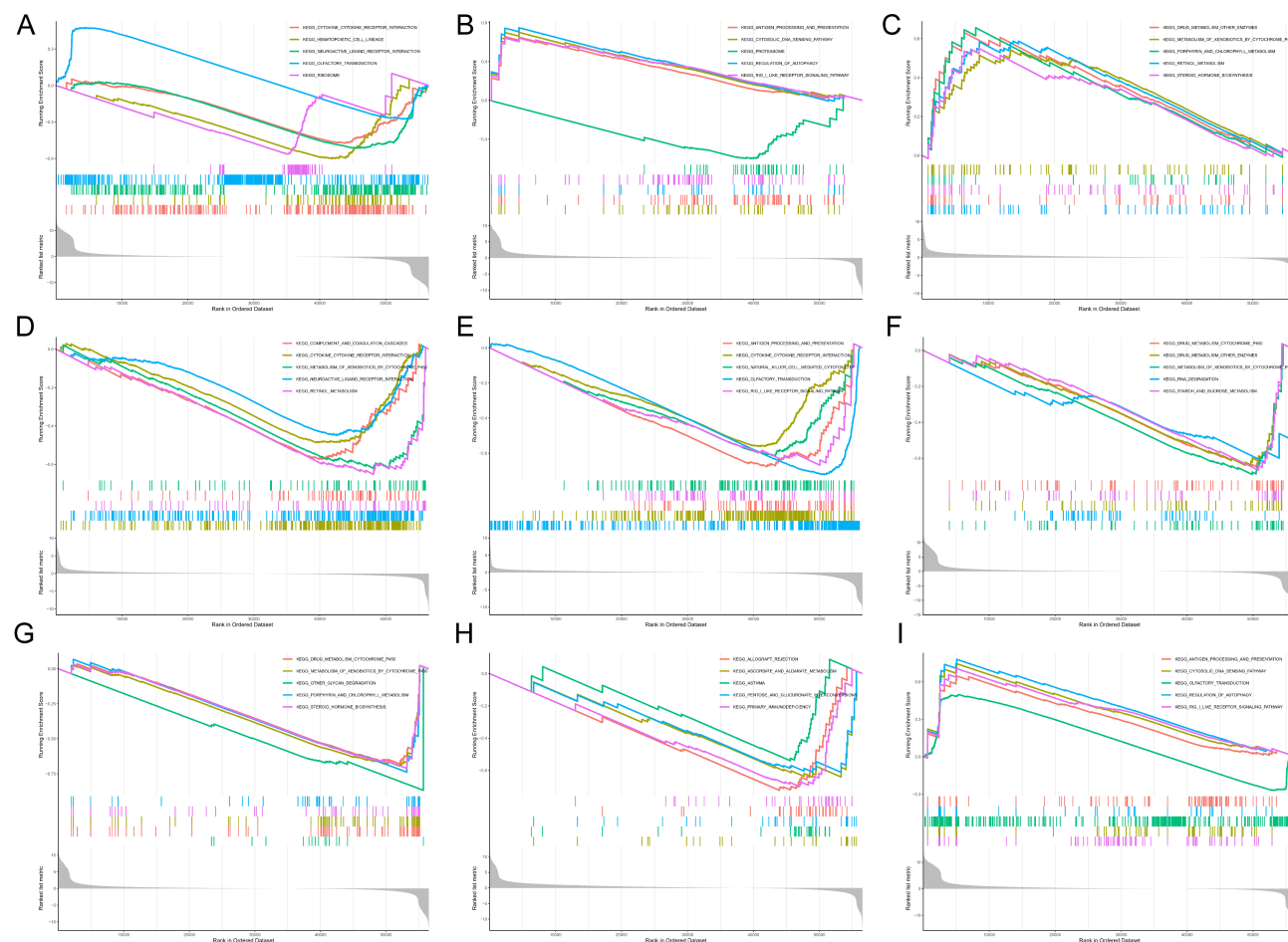


Fig. 11. Gene set enrichment analysis (GSEA) enrichment analysis of *TUG1* with signaling pathways from the Kyoto Encyclopedia of Genes and Genomes (KEGG) database in cholangiocarcinoma (CHOL) (A), GBM (B), head and neck squamous cell carcinoma (HNSC) (C), LGG (D), lung squamous cell carcinoma (LUSC) (E), MESO (F), PCPG (G), sarcoma (SARC) (H), and Uterine Carcinosarcoma (UCS) (I). Curves of different colors represent various functions or pathways. The peaks of the upward and downward curves indicate the positive and negative control of *TUG1*, respectively.

action, and antigen presentation. The Normalized Enrichment Score (NES) and *p*-values are highlighted in **Supplementary Table 4**.

Drug Sensitivity Analysis of *TUG1*

We conducted an analysis to explore the potential association between drug sensitivity and *TUG1* expression. As shown in Fig. 12, *TUG1* expression was positively correlated with Chelerythrine, Nelarabine, Methylprednisol, AZD-9496, and ZM-336372, while it negatively correlated with CG-806, BPTES, Vincristine, AZD-4547, CFI-400945, XR-5944, and Danusertib. These findings suggest that increased *TUG1* expression may be linked to resistance to some commonly used chemotherapeutic agents.

Discussion

Given the escalating global health burden posed by cancer, early detection and effective treatment are imperative for improving prognosis. Currently, the primary approaches for tumor management include surgical resection, radiotherapy, chemotherapy, targeted therapy, and immunotherapy [15]. However, the efficiency of cancer treatment remains limited. Therefore, identifying novel biological targets and elucidating their molecular mechanisms in tumor development could positively contribute to tumor diagnosis and treatment. It has been reported that *lncRNA TUG1* is dysregulated in various tumors and involved in tumor cell progression, metastasis, recurrence, and drug resistance [16]. However, a comprehensive pan-cancer analysis of *TUG1* has not yet been conducted.

Our study systematically analyzed *TUG1* expression in pan-cancer. The findings indicated dysregulation of *TUG1* in most tumors. Expression profiles of *TUG1* in var-

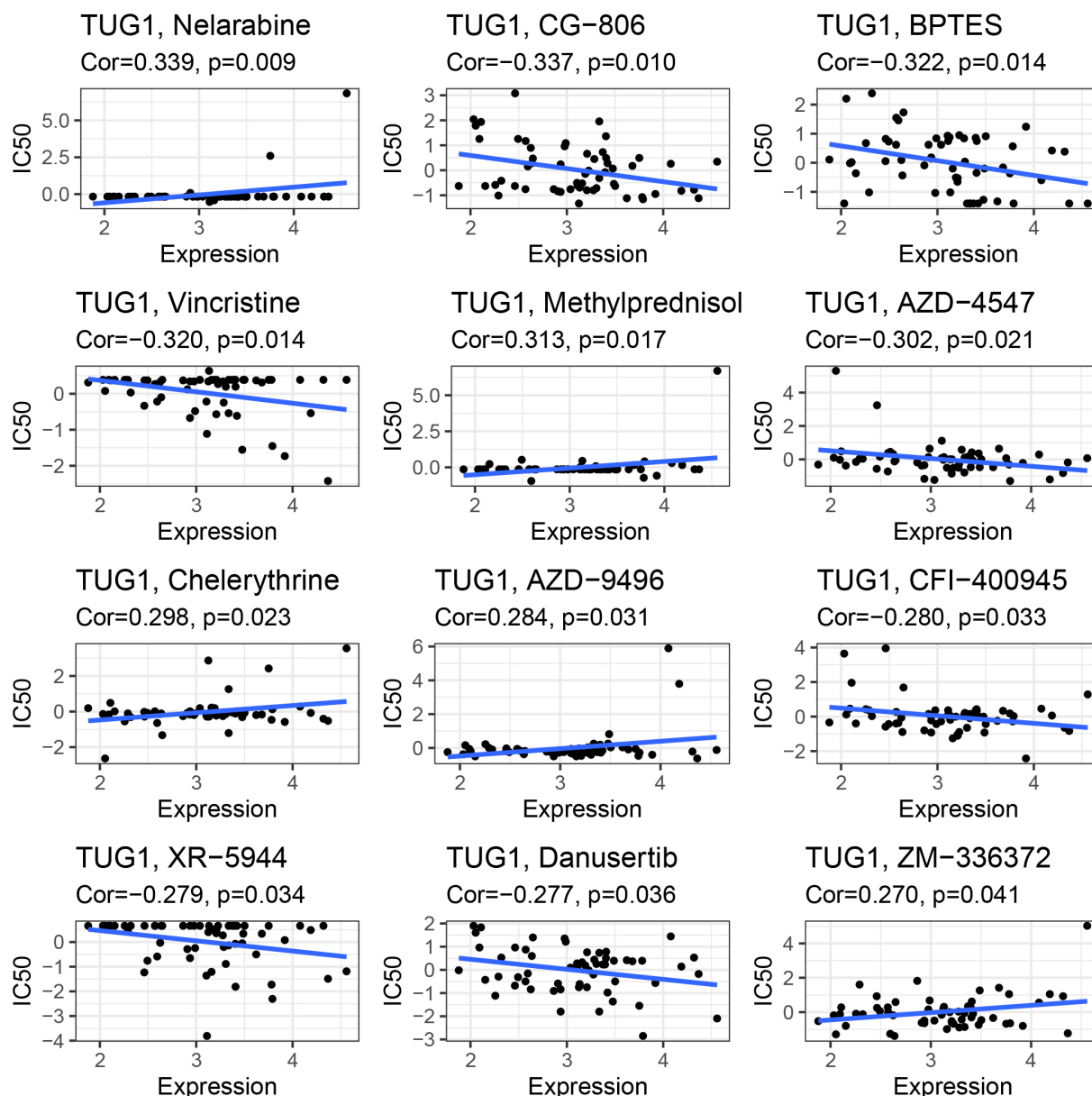


Fig. 12. Drug sensitivity analysis of *TUG1*. The association between *TUG1* expression and Vincristine, Nelarabine, Chelerythrine, Fluorouracil, Geldanamycin analog, and Vinblastine.

ious tumor types and corresponding normal tissues were explored using data from the TCGA database, revealing differential expression of *TUG1* in 12 tumors. Subsequent pairwise analysis with adjacent normal tissues unveiled differential expression in 11 cancers. Integration of TCGA and GTEx further confirmed dysregulation of *TUG1* in 21 cancers.

Moreover, serum levels of *TUG1* were compared between patients with invasive ductal carcinoma of the breast and healthy individuals, revealing higher expression of *TUG1* in breast cancer patients. Additionally, elevated serum *TUG1* levels were observed in patients with early-stage tumors compared to those with advanced stages [17]. In colon cancer tissues, *TUG1* was significantly upregu-

lated, and its increased expression was associated with tumor differentiation. Notably, the AUC values of *TUG1* in diagnosing colon cancer exceeded 0.8 [18].

Furthermore, in hepatocellular carcinoma (HCC), *TUG1* exhibited prominent distribution in the cytoplasm and nucleus. Its expression was elevated in HCC compared to normal liver tissue. Mechanistically, *TUG1* was observed to recruit *USF1* transcription factors, leading to increased *ROMO1* expression and promotion of HCC growth [19]. *TUG1* expression was low in non-small cell lung cancer (NSCLC), and further decreased as NSCLC progressed to a later stage [20]. Li *et al.* [21] demonstrated that upregulation of *TUG1* was associated with lymph node or distant metastasis in lung adenocarcinoma, promoting tumor

growth through modulation of the *miR-138-5p-HIF1A* axis. Although no studies have specifically investigated *TUG1* expression in KIHc, our study revealed significantly decreased *TUG1* expression in KIHc compared to normal tissues, warranting further investigation.

The correlation between *TUG1* and methylation, TMB, and MSI was explored. DNA methylation is a significant epigenetic mechanism regulating gene expression, with aberrant methylation patterns closely linked to cancer development [22]. TMB is a promising immunotherapy response and prognosis biomarker, indicating improved ORR, DCB, OS, and PFS [23]. MSI is also a crucial biomarker for diagnosis, disease prognosis, and prediction of immunotherapy and kinase inhibitor responsiveness, possibly for specific biological drug therapies [24]. PD-L1 expression, TMB and MSI, and immune cell infiltration are validated predictors for guiding immunotherapy in cancer patients [25]. Our study revealed associations between *TUG1* methylation and 17 tumor types. *TUG1* expression correlated with TMB in 12 cancers and MSI in 11 cancers. Specifically, *TUG1* expression positively correlated with TMB in ACC, STAD, READ, PAAD, OV, LUAD, LAML, HNSC, BRCA, and BLCA, suggesting that higher *TUG1* expression is associated with increased tumor mutation burden. Conversely, *TUG1* expression was negatively correlated with TMB in THCA and KIRC. Additionally, *TUG1* expression was positively correlated with MSI in UCEC, STAD, SARC, READ, LUSC, LUAD, LAML, and CHOL, while a negative correlation was observed in HNSC, DLBC, and BRCA. These findings suggest that *TUG1* may influence tumorigenesis through methylation, participate in genetic alterations, and serve as a prognostic biomarker for various cancers.

Meta-analysis revealed that increased *TUG1* expression was associated with poor prognosis in gastrointestinal tumors, urologic tumors, gynecologic tumors, hematologic tumors, and osteosarcomas. Conversely, elevated *TUG1* expression in respiratory tract tumors was associated with favorable prognosis. However, no significant association was observed between high *TUG1* expression and OS in patients with head and neck tumors or melanoma [26]. Given the pathological and clinical significance of *TUG1* in various tumors, its potential utility as a diagnostic marker for cancer was investigated. Consequently, the association between *TUG1* expression and OS, DSS, DFI, and PFI in 33 cancers was analyzed.

The outcomes revealed that *TUG1* expression was correlated with tumor stage in 12 cancers, especially in ACC and BLCA. Furthermore, *TUG1* was associated with the prognosis of various tumors and emerged as an independent risk factor for ACC and LGG. Elevated *TUG1* expression was associated with poor OS in ACC, whereas it exhibited a protective effect in LGG. These findings underscore the role of *TUG1* as a multi-cancer-associated gene with prognostic potential in cancer risk assessment.

The tumor microenvironment, comprising the extracellular matrix, blood vessels, infiltrating immune cells, and cancer-related fibroblasts, is crucial in creating a suitable condition for tumor progression [27]. Dysfunction of immune cells within this microenvironment is closely related to tumor progression and poor clinical outcomes. Numerous immunosuppressive factors in the tumor microenvironment suppress immune cell function, facilitating tumor progression and metastasis [28]. Immunotherapy has emerged as a rapidly evolving field in cancer treatment, revolutionizing conventional therapeutic approaches and demonstrating clinical efficacy across various cancer types. However, some patients fail to respond to immunotherapy, while others experience disease exacerbation post-treatment [29,30]. Consequently, there is a pressing need to identify novel targets and biomarkers to enhance the efficacy of immunotherapeutic interventions.

Our study revealed a negative correlation between *TUG1* expression and stromal scores in 15 cancer types and immune scores in 25 cancer types. Additionally, *TUG1* expression was associated with T cell CD4 memory quiescence, T cell CD8, NK cell activation, T cell regulation, and macrophage M0 across various cancers. Immune checkpoint inhibitors are effective immunotherapy exerting anti-tumor effects by blocking checkpoint pathways. Notably, our findings indicate that *TUG1* is associated with numerous immune checkpoint genes, including *CTLA4*, *LAG3*, and *CD276*, in most cancers. Thus, *TUG1* holds promise as a novel target for cancer immunotherapy.

Drug resistance remains a significant challenge in cancer research. Studies have demonstrated that targeting *TUG1* could enhance the efficacy of 5-FU and gemcitabine in pancreatic ductal adenocarcinoma while mitigating systemic adverse reactions to chemotherapy [31,32]. Conversely, *TUG1* overexpression has conferred resistance to cisplatin in tongue squamous cell carcinoma, esophageal squamous cell carcinoma, and methotrexate in colorectal cancer [33–35]. Our research suggests that elevated *TUG1* expression may correlate with resistance to chemotherapeutic agents such as Vincristine and daunorubicin.

Our study comprehensively analyzed the role of *TUG1* expression in pan-cancer from various perspectives. Multiple databases indicated that *TUG1* could serve as an essential gene for tumor prognosis. However, our study has several limitations. Firstly, there is no experiment to verify our results. Secondly, the diagnostic and prognostic value of *TUG1* across various tumors requires evaluation through clinical trials. Thirdly, although we utilized databases such as TCGA and GTEx for our analysis, numerous tumor databases exist, each potentially yielding different results. Thus, further investigations are warranted to elucidate the role of *TUG1* in the tumor microenvironment, immunotherapy, and drug resistance.

Conclusions

In conclusion, our findings reveal distinct expression patterns of *TUG1* across various cancer types. *TUG1* expression was significantly correlated with tumor prognosis and closely associated with tumor methylation, TMB, MSI, immune cell infiltration, immune checkpoint genes, and resistance of chemotherapeutic drugs. Based on these findings, *TUG1* emerges as a potential candidate for the prognosis and treatment of cancer patients.

Availability of Data and Materials

The original data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

Data analysis was performed by QYY, YFX, YWY and JWY. QYY and YFX wrote the manuscript. YFX, YXL and YQW designed the study. All authors have been involved in revising it critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was supported by Zhejiang Provincial Health Science and Technology Plan (YXL, No. 2021KY908), Hangzhou Agricultural and Social Development Research Project (QYY, No. 20201203B215).

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.23812/j.biol.regul.homeost.agents.20243806.418>

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