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CSK may be a potential prognostic biomarker reflecting the immune status of gastric cancer

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Abstract. – OBJECTIVE: C-terminal Src kinase (CSK), a sarcoma (Src) homologous family kinase, is one of the most important negative regulators. It acts as a tumor suppressor by inhibiting the activity of Src family tyrosine kinases. Paradoxically, CSK is highly expressed in a variety of common tumors. Therefore, we report the expression profile of CSK in pan-cancer patients, focusing on the prognostic value, immune infiltration pattern, and biological function of CSK in gastric cancer.

MATERIALS AND METHODS: We used the TCGA database to analyze CSK expression, clinical relevance, prognostic significance, assessment of the tumor immune microenvironment, and GO and Kegg enrichment analysis based on co-expressed genes using a bioinformatics approach.

RESULTS: CSK is a protective factor in gastric cancer, and its expression correlates with the level of immune cell infiltration and immune checkpoint molecules.

CONCLUSIONS: Our findings suggest that CSK is an independent prognostic factor in gastric cancer and may predict molecular targeting and immunotherapy and provide ideas for its therapeutic strategy.

Key Words:
CSK, Cancer, Immune status, Prognostic, Biomarker, Molecular targeting.

Introduction

Gastric cancer (GC) is the fifth most prevalent cancer worldwide and the third leading cause of cancer-related deaths[1,2]. Over 95% of gastric cancers are of adenocarcinoma nature[3]. The prognosis for gastric cancer remains poor, as it is diagnosed at an advanced stage. The 5-year survival rate for GC remains below 30%, while the survival rate for metastatic GC remains below 2 years[4]. The use of molecular targeted therapy and immunotherapy in patients with locally advanced, recurrent, or metastatic cancers has produced encouraging results in clinical trials. However, the poor prognosis of GC patients and the limitations of immunotherapy urge us to look for new prognostic and immunotherapeutic biological markers.

CSK encodes a protein that is a non-receptor tyrosine-protein kinase with important roles in the regulation of cell growth, differentiation, migration, and immune responses. It is involved in a variety of pathways, including the regulation of sarcoma (Src) family kinases (SFK). This protein inhibits the kinase activity of Src family tyrosine kinases by phosphorylating the C-terminal tyrosine residue of SFK, resulting in conformational inactivation. CSK is recruited to the plasma membrane by binding to transmembrane or bridging proteins located near the plasma membrane and inhibits signaling to various surface receptors, including the T-cell receptor (TCR) and B-cell receptor (BCR), by phosphorylating and maintaining the inactivation of residues of SFK. It also plays an important role in T cell activation by binding to the protein encoded by the protein type 22 tyrosine phosphatase non-receptor (PTPN22) gene.

Literature has shown that CSK exhibits oncogenic effects through negative regulation of SFK. However, CSK expression was increased in gastric cancer tissues compared to normal gastric tissues, so we conducted this study to further investigate the relationship between CSK and gastric cancer. The results suggest that CSK may be an independent prognostic indicator and a protective factor in gastric cancer, which is closely linked to the tumor immune microenvironment.

Materials and Methods

Data Sources

RNA-sequencing expression data and corresponding clinical information were download-

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ed from the UCSC XENA (https://xenabrowser.net/datapages/) and the TCGA-STAD (https://portal.gdc.cancer.gov/)[5]. The differential expression between tumor and normal tissues was tested by the Wilcoxon Rank Sum Test and visualized through boxplots and scatter plots. The prognostic statistics were obtained from the research by Liu et al[6]. Markers of the mentioned immune cells are from an article on immunity[7].

Gene Expression Difference and Survival Analysis

The Log-rank test was used to compare the overall survival (OS), disease-specific survival (DSS), and progress-free interval (PFI) survival differences between these groups.

Construction and Validation of Nomogram

The pinpointed independent aspects correlated with GC prognosis were used to construct a nomogram that predicted the probability of 1-, 3-, and 5-year survival in patients with GC. A nomogram was generated by R Studio (Solvusoft Corporation Co. Ltd, Los Angeles, CA, USA) with the survival and RMS package (R software version 4.2.1, Vienna, Austria). Harrell's concordance index (C-index) was used to quantify the predictive accuracy, which ranges from 0.5 (no predictive power) to 1 (perfect prediction). Furthermore, calibration plots were generated to examine the performance characteristics of the predictive nomogram.

UALCAN Database

UALCAN (http://ualcan.path.uab.edu/) is a comprehensive web resource for analyzing cancer OMICS data, including 33 TCGA cancer types, which was used to investigate the relationship between CSK and clinical features of STAD patients[8,9].

LinkedOmics

LinkedOmics (http://www.linkedomics.org/) is a publicly available portal that includes multi-omics data from all 32 TCGA cancer types and 10 Clinical Proteomics Tumor Analysis Consortium (CPTAC) cancer cohorts[10]. The web application has three analytical modules: LinkFinder, LinkInterpreter, and LinkCompare. CSK co-expression was analyzed utilizing the Pearson correlation coefficient by LinkFinder and visualized with volcano plots and heat maps.

TIMER

TIMER database (http://timer.cistrome.org/) is a comprehensive computational tool that conveniently explores and visualizes tumor immunological and genomics data. We used the sCNA module to compare immune infiltration distribution by the sCNA status of CSK across gastric cancer estimates the sCNA information from copy number segmentation profiles at the gene level, including "deep deletion", "arm-level deletion", "diploid/normal", "arm-level gain", and "high amplification" defined by GISTIC2.0[11,12].

Statistical Analysis

The data were analyzed by SPSS 21.0 (IBM Corp., Armonk, NY, USA). $p<0.05$ was considered statistically different.

Results

The Expression Characteristics of CSK in Pan-Cancer and GC Tissues

According to data analysis, there is a significant difference in the expression of CSK in most cancers. The results showed that CSK was statistically significantly over-expressed in matched and unmatched samples of STAD ($p < 0.05$). Our analysis revealed that CSK expression was closely related to the patient's clinical characteristics. Although CSK expression is elevated in gastric cancer tissues, it gradually decreases during its progression, such as tumor grade, nodal metastasis status, and cancer stages, and is differentially expressed by gender, age, and histological subtypes (Figure 1).

The abbreviations for 33 cancers are as follows: adrenocortical carcinoma (ACC); bladder urothelial carcinoma (BLCA); breast invasive carcinoma (BRCA); cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC); cholangiocarcinoma (CHOL); colon adenocarcinoma (COAD); lymphoid neoplasm diffuse large B-cell lymphoma (DLBC); esophageal carcinoma (ESCA); glioblastoma multiforme (GBM); head and neck squamous cell carcinoma (HNSC); kidney Chromophobe (KICH); kidney renal clear cell carcinoma (KIRC); kidney renal papillary cell carcinoma (KIRP); acute myeloid leukemia (LAML); brain lower grade glioma (LGG); liver hepatocellular carcinoma (LIHC); lung adenocarcinoma (LUAD); mesothelioma (MESO); ovarian serous cystadenocarcinoma (OV); pancreatic adenocarcinoma (PAAD); pheochromocytoma and paraganglioma (PCPG); prostate adenocarcinoma (PRAD); rectum adenocarcinoma

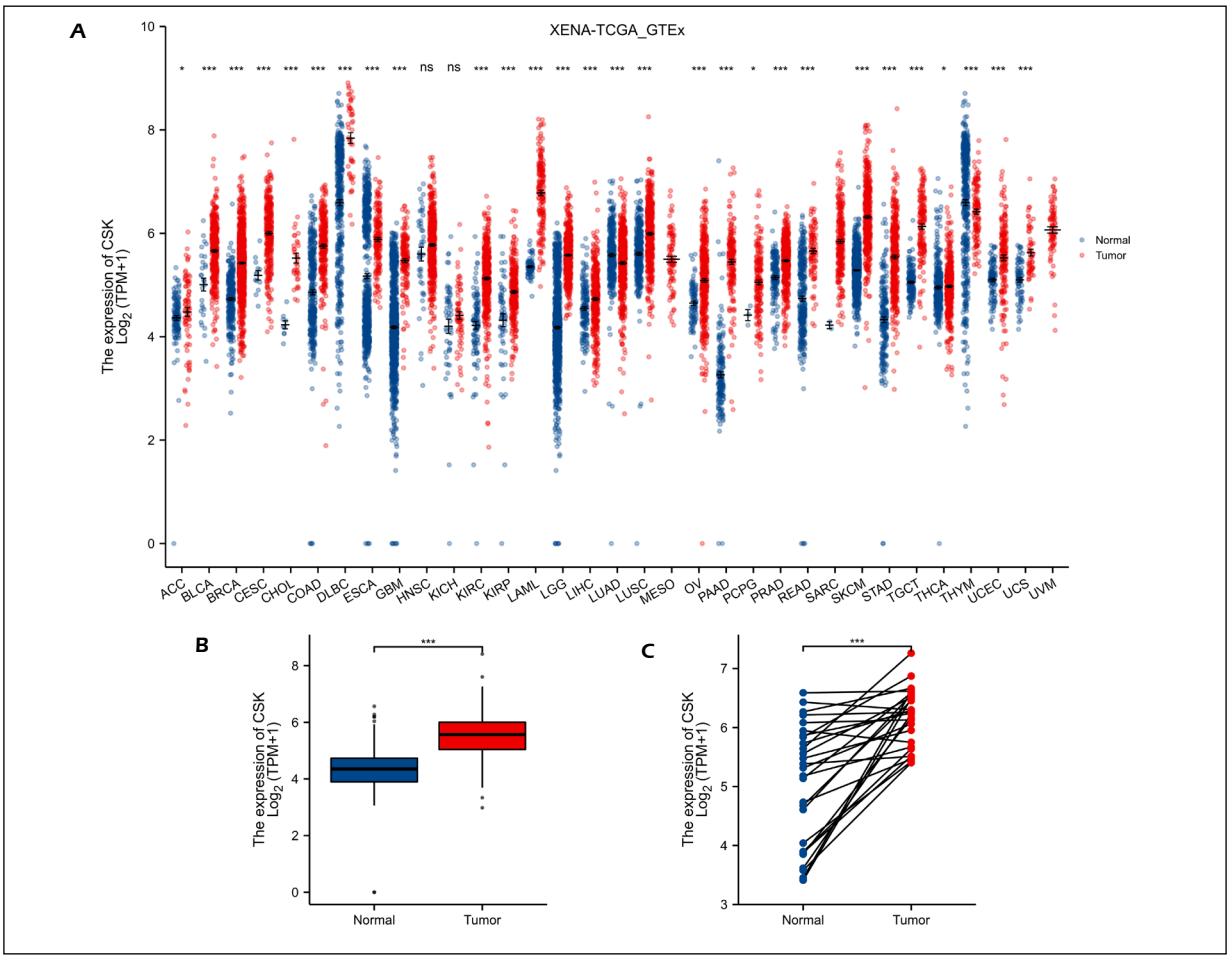

Figure 1. Differential expression of CSK in different tumors and related to a patient's clinical characteristics, **A**, Differential expression of CSK of Pan-cancer compared with normal tissues in the TCGA and GTEx database. **B-C**, Differential expression of CSK in paired and unpaired samples of STAD. ns, $p \geq 0.05$; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

(READ); sarcoma (SARC); skin cutaneous melanoma (SKCM); testicular germ cell tumors (TGCT); thyroid carcinoma (THCA); thymoma (THYM); uterine corpus endometrial carcinoma (UCEC); uterine carcinosarcoma (UCS); uveal melanoma (UVM) (Figure 2).

Prognostic Potential of CSK in STAD

The explorations suggested that enhanced CSK expression is linked with good patient prognosis (Figure 3). Using the Survminer package (R software version 4.2.1, Vienna, Austria) and survival package (R software version 4.2.1, Vienna, Austria), we examined the connection of CSK expression with prognosis data, which revealed that upward CSK expression was statistically significant in relation to excellent overall survival (OS), disease-specific survival (DSS), and progress-free interval (PFI) in STAD patients ($p < 0.05$) (Figure 3A-3C). Multivariate Cox regression analysis was executed to determine independent aspects affecting the OS of GC identity for the sake of eliminating the influence of other variables on the OS of GC. In univariate analysis, gender, age, TNM grade, pathological stage, histological type, residual tumor, primary therapy outcome, and CSK expression were strongly associated with OS of STAD ($p < 0.05$). Basis multivariate research, CSK expression [hazard ratio (HR)=0.594, 95% confidence interval (95% CI) = (0.383-0.921), $p = 0.02$] was identified as an independent prognostic factor in patients with STAD (Table I), and the Nomogramto predict 1-, 3-, and 5-years' OS probability was constructed on the basis of five prognostic factors including it. The C-index of this nomogram was 0.740 (0.716-0.763), indicating that the prediction was in good consistency with the actual survival (Figures 3 and 4).

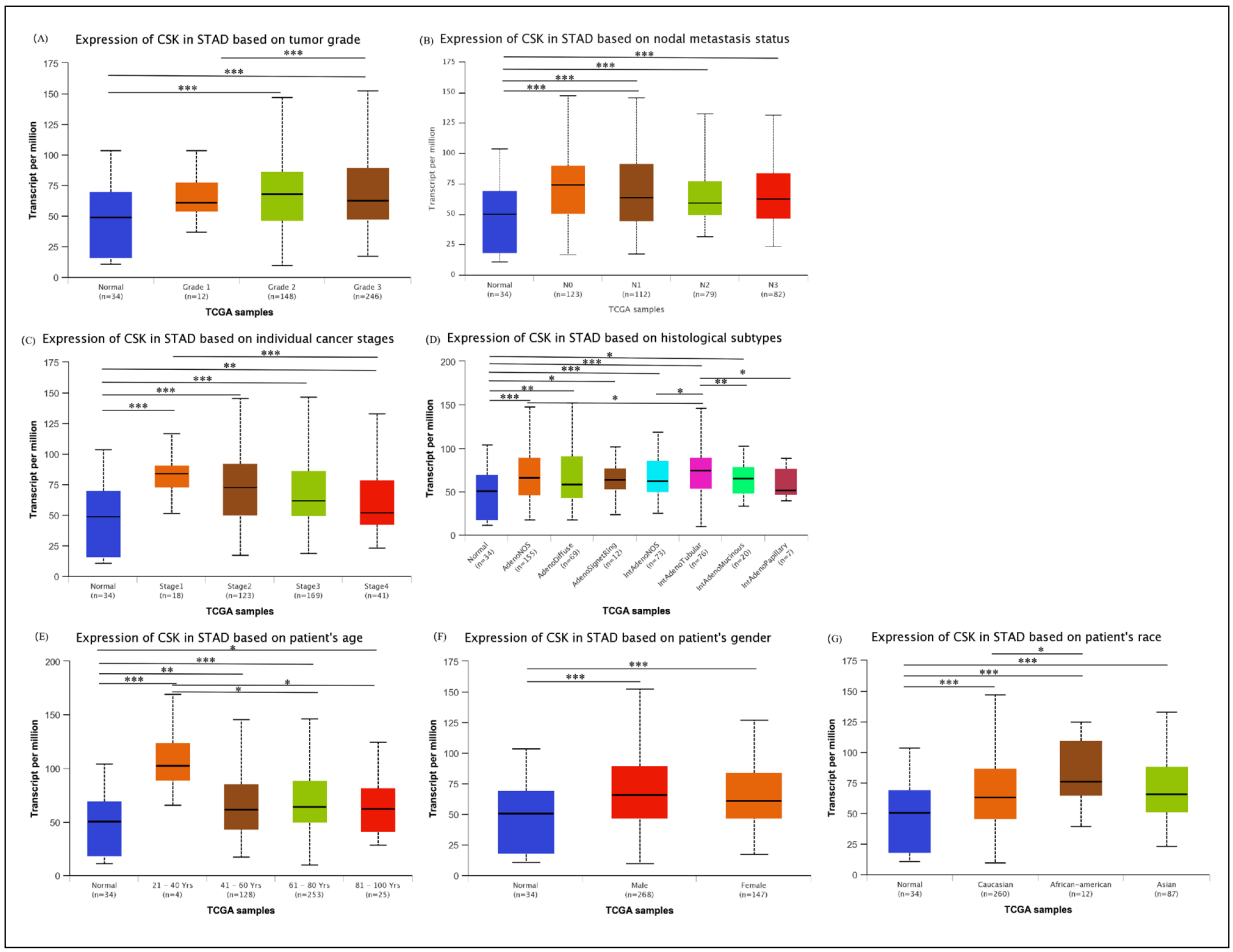

Figure 2. CSK expression related to a patient's clinical characteristics Box plot showing the relationship of tumor grade (**A**), nodal metastasis status (**B**), cancer stages (**C**), histological subtypes (**D**), age (**E**), gender (**F**), and race (**G**) with CSK expressions in stomach tumor. Significance marker: ns, $p \geq 0.05$; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

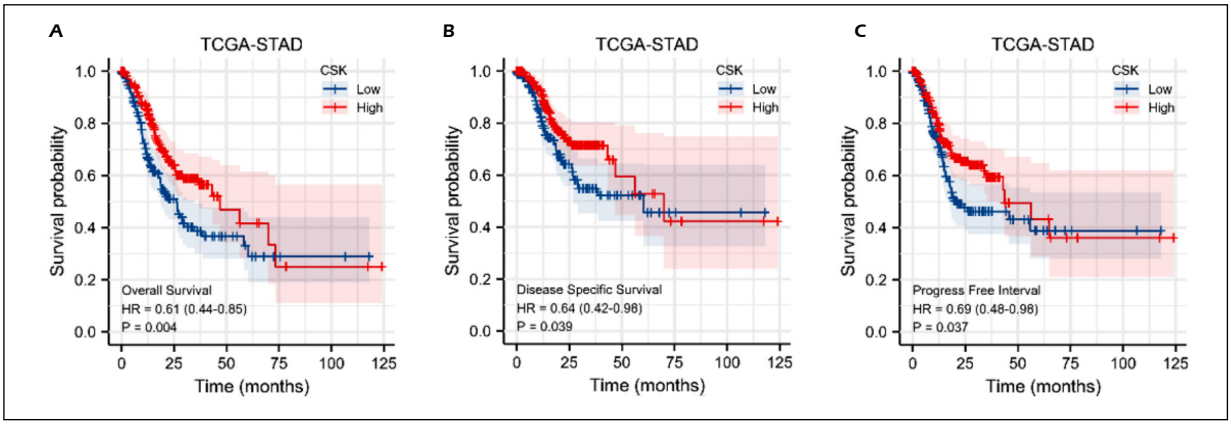

Figure 3. Survival analysis of SATD patients with higher and lower CSKexpression. Kaplan-Meier analysis of the correlation between CSK expression and the Overall Survival (**A**), Disease Specific Survival (**B**) and Progress Free Interval of patients with STAD (**C**).

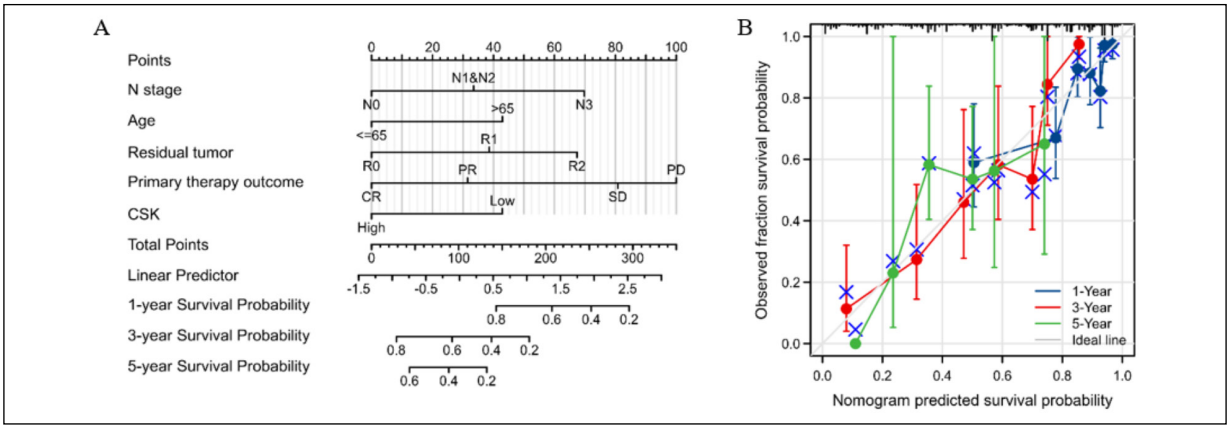

Figure 4. Establishment and evaluation of the prognostic nomogram model. **A**, Nomogram was established to predict OS of glioma patients. **B**, Calibration curves were used to compare nomogram prediction and actual observation.

The Link Between CSK and Immune Cell Infiltration in STAD

We investigated the correlation between CSK expression and the degree of infiltration of different types of immune cells by the ssGSEA algorithm[13]. The analysis suggested a statistically significant higher degree of immune cells ($p < 0.05$), which were dendritic cells, B cells, natural killer CD56dim cells, CD8 T cells, cytotoxic cells, T follicular helper cells, T gamma delta, T helper 17 (Th17) cells, T helper 2 (Th2) cells, and regulatory T (Treg) cells infiltration, in the high expression group (Figure 5). The bar graphs reveal differences in the distribu-

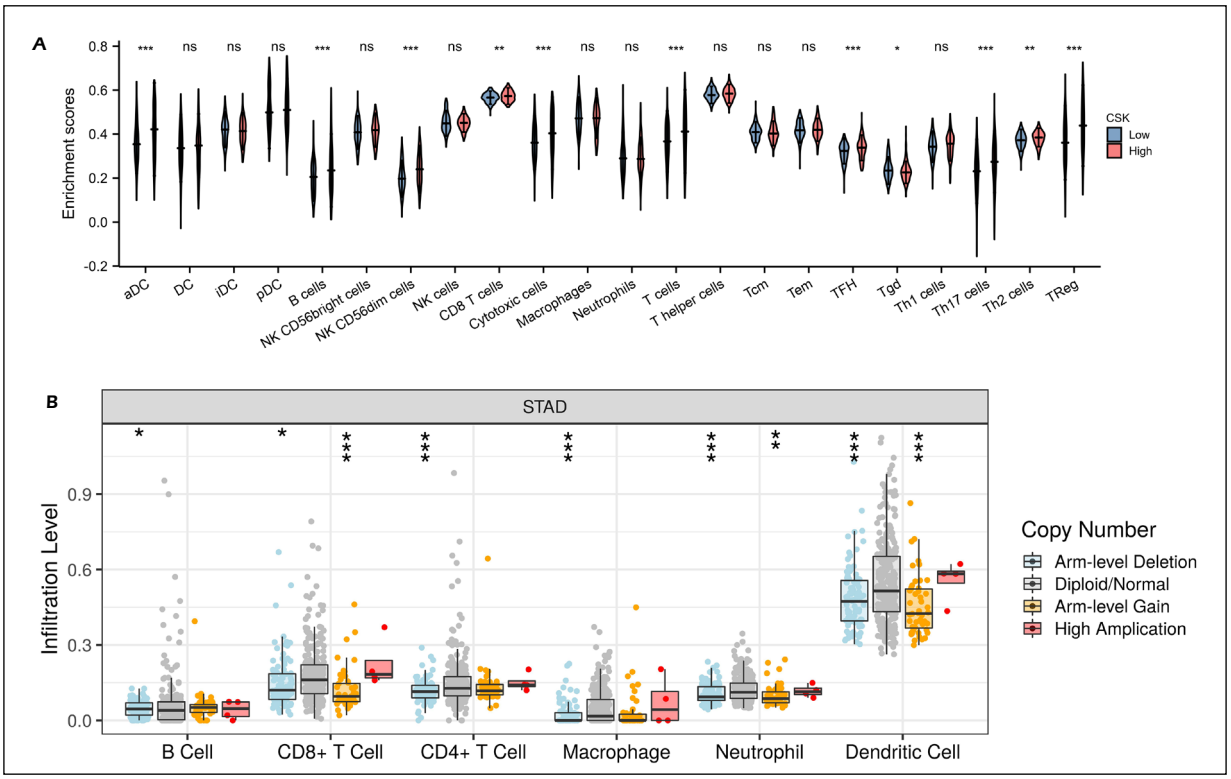

Figure 5. Correlations of CSK expression with immune infiltration level in STAD. **A**, Different kinds of TME cells infiltration abundance of high and low CSK expression. The line in the box represents the median value and the asterisk represents the *p*-value. **B**, The distributions of each immune subset at each copy number status in STAD. (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$).

tion of immune cell infiltration in different SCNA states. SCNAs are defined by GISTIC 2.0 (GenePattern software, Harvard University and MIT, Cambridge, Massachusetts, USA), including deep deletion (-2), arm-level deletion (-1), diploid/normal (0), arm-level gain (1), and high amplification (2). The result indicated that arm-level deletion inSTAD was positively associated with the infiltration ofB cells, CD8+ T cells, CD4+ T cells, neutrophils, macrophages, and myeloid dendritic cells ($p < 0.05$), which implied that SCNA of CSK may affect the level of immune cell infiltration.

Co-Expressed Genes of CSK

Seeking the biological meaning of CSK in STAD, we used the function module of LinkedOmics to examine the co-expression gene of CSK. Genes positively and negatively associated with CSK were obtained using Spearman correlation analysis, as shown in the volcano diagram. The top fifty significant genes positively or negatively associated with CSK are shown by the heat map. CSK expression showed a strong positive relationship with the expression levels of SH3BP1 (r = 0.643, $p = 6.37E-50$), FAM110PA (r = 0.561, $p = 7.89E-36$) and MESDC1 (TLNRD1) (r = 0.0.550, $p = 3.09E-34$), and strong negative associations with SERINC1 (r = -0.522, $p = 2.55E-30$), SCAMP1 (r = -0.511, $p = 4.91E-29$) and ITGB1 (r = -0.508, $p = 1.42E-28$). It deserves to be mentioned that the top 50 significantly positive genes showed a high probability of becoming high-risk markers in BLCA, and the overwhelming majority of genes had low HR in the top fifty negatively significant genes (Figure 6).

To elucidate the biological functions of CSK, we selected genes that were positively or negatively associated with CSK for analysis based on > 0.3 or r < -0.3 and $p < 0.05$. We also performed a GSEA pathway analysis (Figure 7)[14,15,]. The findings revealed that the orthologically-related genomes were mainly enriched in "co-stimulation by the CD28 family", "signaling by the B cell receptor (BCR)", "regulation of TP53 activity through acetylation", "TNF alpha signaling pathway" "PD-1 signaling", and "APC_Cmediated degradation of cell cycleproteins". The minimally related genomes were mainly enriched in "Focal adhesionPI3K AKT mTOR signaling pathway", "WNT signaling", "downstreamsignalingofactivatedFGFR2", "reactomedownstreamsignalingofactivatedFGFR1", "TGF beta signaling" and "epithelial to mesenchymal transition in cancer". In parallel, we performed the GO analysis. The positive group was predominantly enriched in "regulation of ERBB signaling pathway", "epidermal growth factor receptor signaling", "protein serine/threonine kinase activity", and "PD-L1expression and PD-1 checkpoint pathway in cancer". The negative group was predominantly enriched in the "transforming growth factor beta receptor signaling pathway," "cell leading edge," "VEGF signaling pathway," and "MAPK signaling pathway"(Figure 8).

Discussion

The results showed that CSK was differentially expressed in most of the 33 tumors and was significantly expressed in GC tissues. We then performed survival analysis as well as univariate and multifactorial regression analysis and found that CSK was instead an independent favorable prognostic factor. It is important to mention that GC patients with high CSK expression may have better histological type, higher tumor differentiation, and early tumor status by the analysis of clinical data characteristics.

Immunotherapy is considered to be a promising approach for the treatment of advanced or metastatic GC. Pembrolizumab/nivolumab treatment has been approved by the FDA for advanced gastric cancer[16,17]. However, so far, only some GC patients who received immunotherapy have benefited from it. In this study, we analyzed the association between the level of immune infiltration and CSK expression in stomach carcinoma. Our findings showed that CSK was positively associated with activated dendritic cells, early NK cells, B cells, and T cells. Treg cells, as an adverse prognostic factor, also infiltrated at similarly increased levels in the high-expression group[18]. Part of this inconsistent result may be due to the actual high proportion of anti-tumor immune cells compared to pro-tumor immune cells, which is a favorable factor in GC survival. Another part may be attributed to the accumulation of Th17 cells and Treg in the tumor microenvironment occurring in the early stages of the disease, followed by a gradual decrease in Th17 cell infiltration as the disease progresses and a dynamic change between Th17 and Treg cells[19]. Furthermore, our study revealed that changes in CSK copy number affected the level of tu-

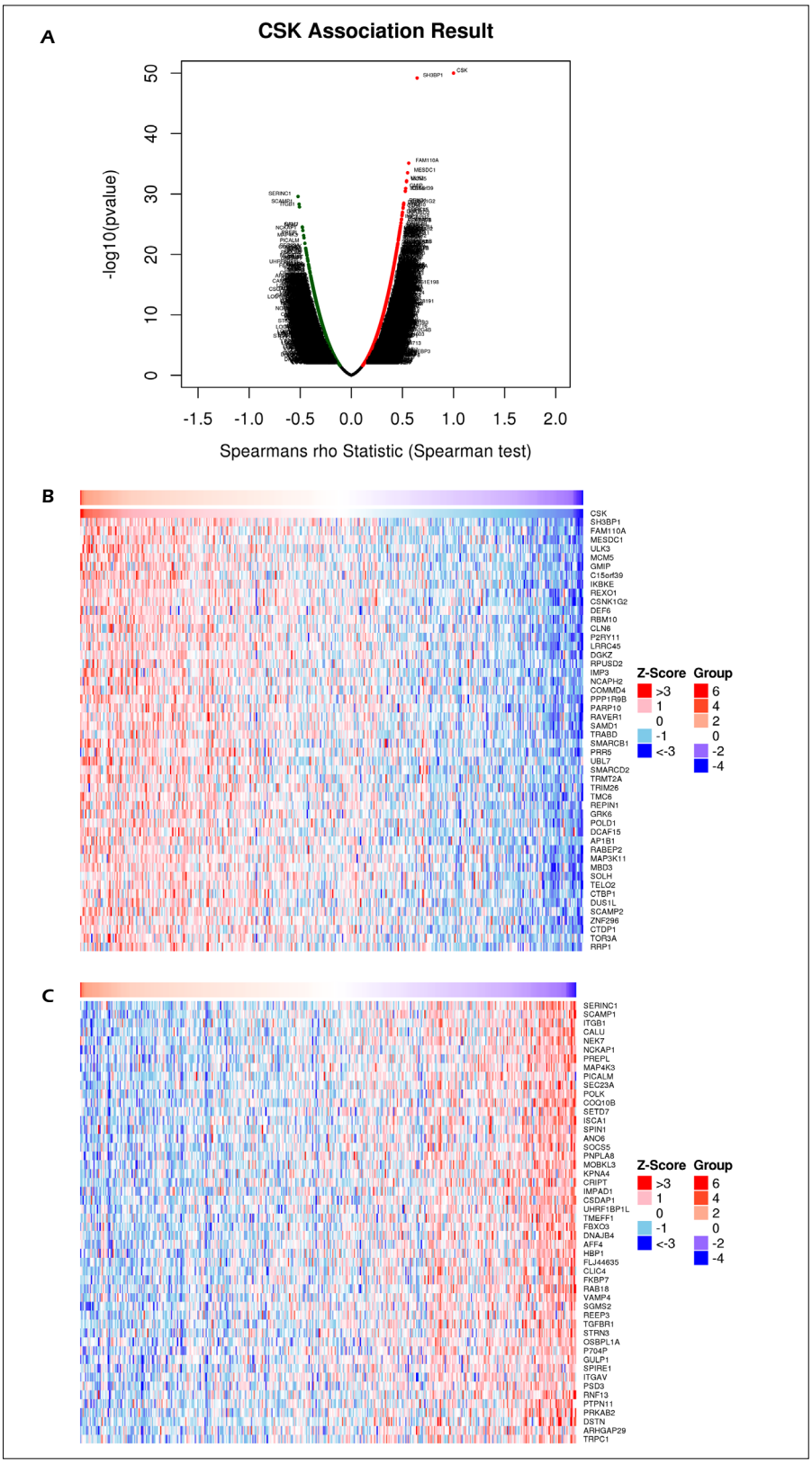

Figure 6. Co-expression genes of CSK in STAD analyzed by LinkedOmics database. **A**, Volcano map of CSK related genes. The red dot represents a positive correlation gene, and the green dot represents a negative correlation gene. **B**, Heat map of positive correlation gene expression. **C**, Heat map of negative correlation gene expression.

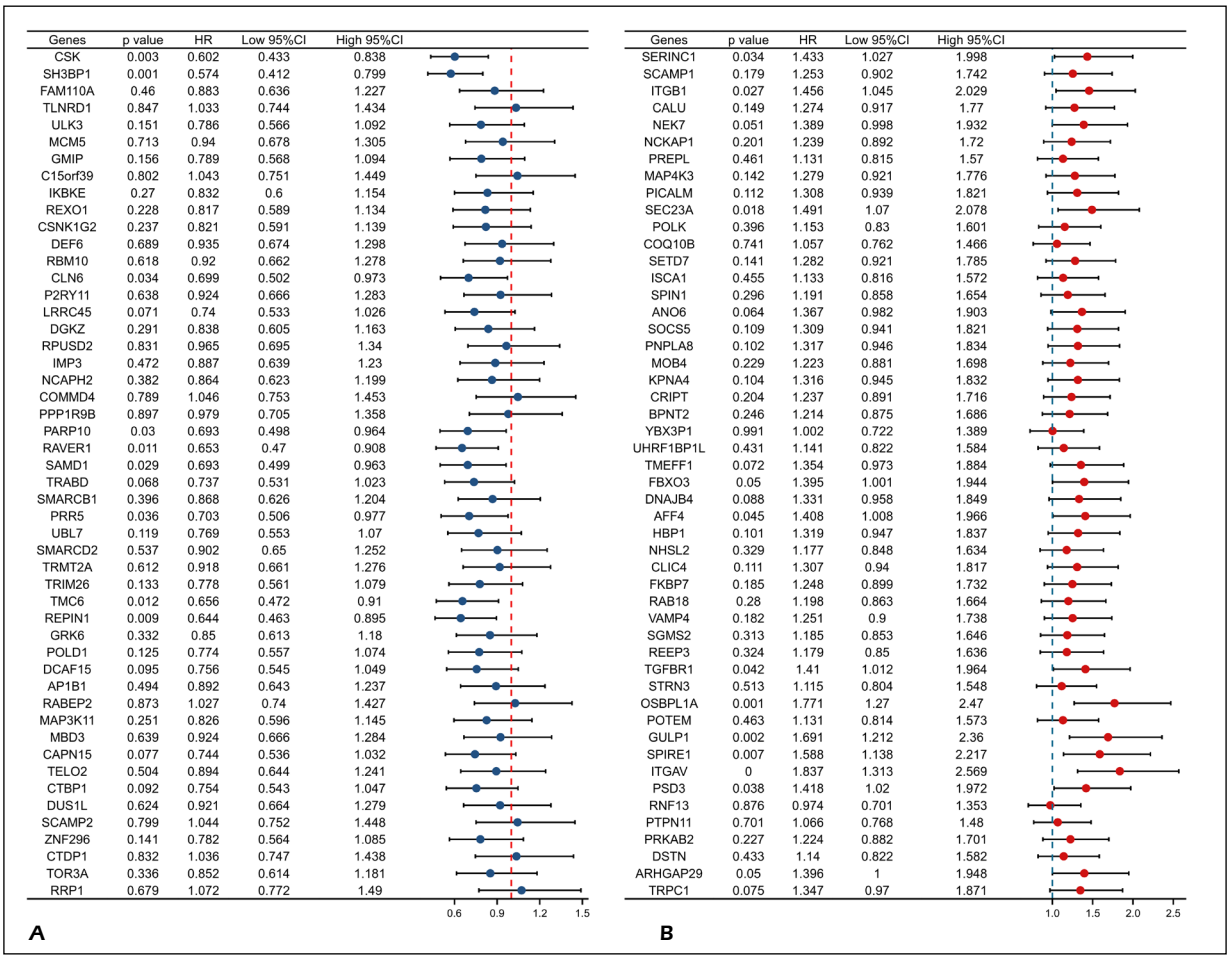

Figure 7. Risk analysis of the gene set. **A**, Hazard ratio scores for positively associated gene sets. **B**, Hazard ratio scores for negatively associated gene sets.

mor immune cell infiltration to some extent, as witnessed by the significantly lower score in the arm-level deletion group compared to the normal group. Finally, our GSEA analysis showed that the homogeneous gene set positively associated with CSK was enriched to some pathways that inhibit tumorigenesis progression, as listed in the above images, while the negatively associated gene set was enriched to some pathways that promote tumorigenesis progression. Moreover, the study also indicated that CSK-related genes were positively associated with ERBB and PD-1/PD-L1 pathways. This may be the reason why CSK-related genes are favorable prognostic factors, and indirectly suggests that CSK expression status may play an important role in predicting the effect of immunotherapy[20]. The relationship between CSK and immunity deserves deeper investigation and requires further mechanistic exploration and experimental validation.

Limitations

Yet, this study has some limitations: (1) The causes of differential expression of CSK in normal and tumor tissues of the stomach were not explored in detail, given the lack of accessible data; (2) Further experiments are needed to validate the mechanisms by which CSK regulates immune infiltration in the tumor microenvironment of gastric cancer; (3) The relationship between differential expression of CSK and prognosis of gastric cancer. The precise regulatory and control regimes between the differential expression of CSK and the prognosis of gastric cancer need to be further verified through well-designed experiments.

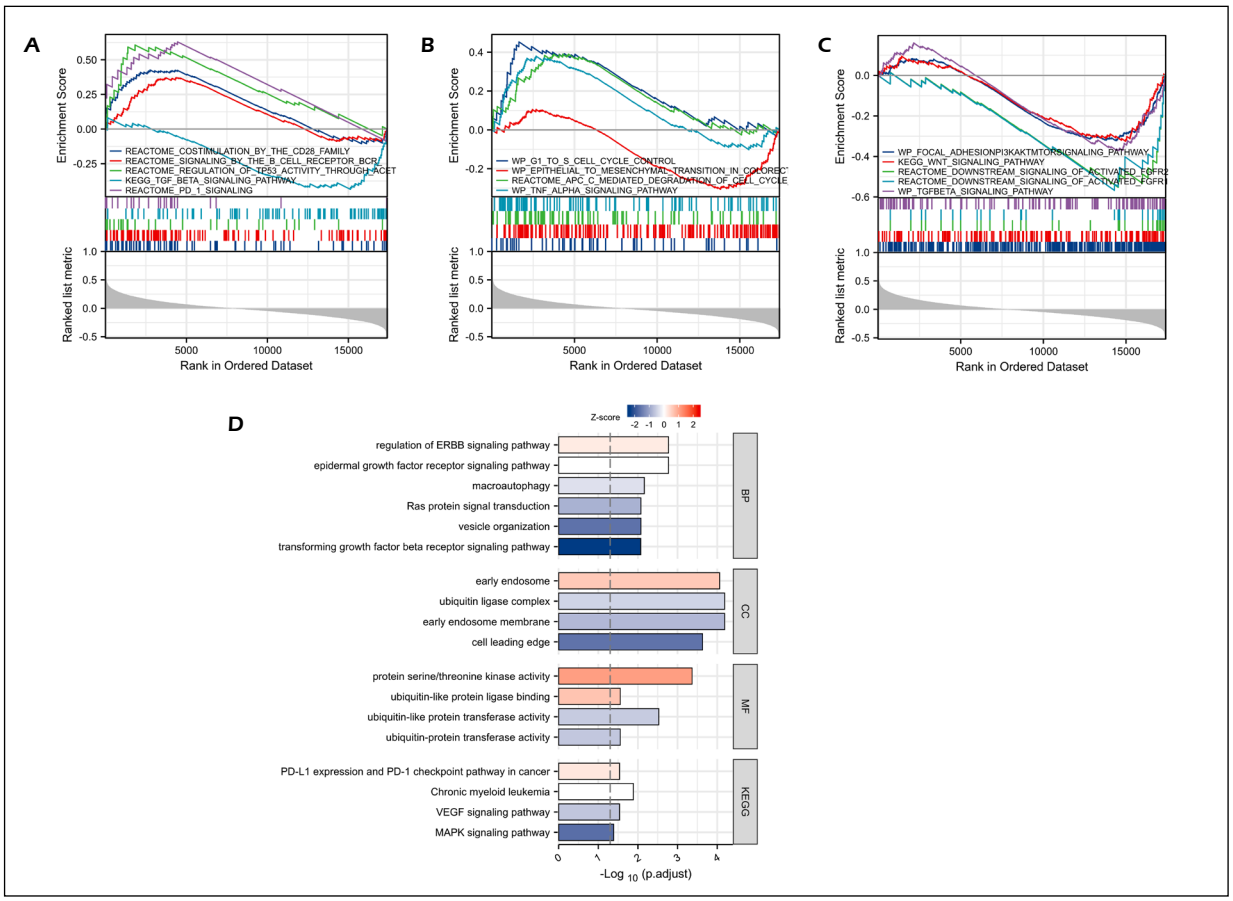

Figure 8. GSEA analysis results. **A-C**, Enrichment of the gene sets in the representative pathways by GSEA function analysis. **D**, GO analysis of relevant gene sets in terms of biological processes, cellular composition, and molecular function.

Conclusions

Upregulated CSK is associated with a better survival situation in gastric cancer. Furthermore, CSK may serve as a potential proportional prognostic biomarker and relate to the level of immune infiltration in gastric cancer.

Conflict of Interest

The authors declare that the study was conducted without any commercial or financial relationship that could be interpreted as a potential conflict of interest.

Informed Consent

Not applicable.

Ethics Approval

Not applicable.

ORCID ID

Jian Huan: 0009-0009-1159-7037

Authors' Contribution

Xia Yan: conceptualization, methodology, software, validation, formal analysis, data curation, writing - original draft. Jian Huan: writing - review and editing.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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