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STAT1 as a potential diagnostic biomarker for gastric cancer

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Abstract

Introduction: Gastric cancer is a major contributor to cancer-related mortality across the globe. The discovery of novel molecular biomarkers is critical for achieving early diagnosis and developing targeted therapeutic strategies for this disease. The role of *STAT1* in gastric cancer has not been fully elucidated.

Objective: This research was designed to analyze the expression profile of *STAT1* in gastric cancer and explore its feasibility as a diagnostic biomarker.

Methods: We screened differentially expressed genes (DEGs) between gastric cancer specimens and normal controls using GSE63089 and GSE2685. Common upregulated DEGs were identified using Venn diagram analysis and further evaluated in GSE49515. STAT1 expression was examined using the Gene Expression Profiling Interactive Analysis (GEPIA) database and validated in clinical gastric cancer samples and paired adjacent normal tissues. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic value of STAT1.

Results: A total of 8,058 DEGs were detected in GSE63089 and 2,139 DEGs in GSE2685. Venn diagram analysis revealed that 94 common upregulated DEGs were shared between the two datasets. Analysis of GSE49515 identified *STAT1* as the only consistently upregulated gene among these common DEGs. Bioinformatics analysis confirmed that *STAT1* levels were notably higher in gastric cancer, especially in diffuse-type samples, than in normal samples. Validation using clinical samples confirmed significant upregulation of *STAT1* in gastric cancer blood samples compared with normal controls. ROC curve analysis showed an area under the curve of 0.8645, indicating favorable diagnostic performance.

Conclusion: These findings indicate that *STAT1* has potential as a diagnostic biomarker for gastric cancer.

Keywords: STAT1; Gastric cancer; Biomarker; Diagnosis; Blood

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1. Introduction

Gastric cancer is the fifth most common malignancy and the fourth leading cause of cancer-related death globally, with over one million new cases diagnosed annually.[1] Despite advances in surgical techniques, chemotherapy, and targeted therapy, the prognosis of gastric cancer patients remains poor, primarily due to late-stage diagnosis and tumor heterogeneity.[2] The five-year survival rate for metastatic gastric cancer is less

than 10%, whereas early-stage gastric cancer can achieve an excellent survival rate following curative resection.[3] This stark contrast highlights that early and accurate detection is the most effective strategy to improve survival and reduce mortality. However, conventional diagnostic approaches, including gastroscopy, serum tumor markers such as carcinoembryonic antigen, CA19-9, and CA72-4, and imaging examinations, have limitations in sensitivity, specificity, or patient compliance. Gastroscopy is invasive and unsuitable for large-scale screening, while traditional serum markers often show unsatisfactory accuracy for early gastric cancer. Therefore, the identification of sensitive and specific molecular biomarkers for early detection is of paramount importance in improving patient outcomes.

Signal transducer and activator of transcription 1 (STAT1) is a core member of the STAT protein family, which is widely distributed in various tissues and cells of the human body and participates in the regulation of multiple critical cellular physiological processes.[4] STAT1 acts as a key signal transduction molecule that mediates cellular responses to various cytokines, growth factors, and interferon signals, playing an irreplaceable role in maintaining normal cellular functions. When stimulated by interferons (IFNs), interleukins, and other extracellular ligands, STAT1 undergoes tyrosine phosphorylation modification, forms homologous or heterologous dimers, and rapidly translocates from the cytoplasm to the nucleus, thereby regulating the transcriptional expression of downstream target genes involved in immune response activation, cell cycle progression, cell proliferation and apoptosis, cell differentiation, and inflammatory response regulation.[5] The Janus kinase (JAK)–STAT signaling pathway represents one of the most evolutionarily conserved cytokine signaling cascades, with STAT1 serving as the principal transcription factor mediating type I and type II IFN responses.[6] Upon ligand binding to cell surface receptors, JAKs (JAK1, JAK2, and TYK2) undergo autophosphorylation and subsequently phosphorylate STAT1 at critical tyrosine residues, enabling its nuclear translocation and DNA binding activity. This canonical signaling axis is tightly regulated by multiple negative feedback mechanisms, including suppressor of cytokine signaling proteins and protein tyrosine phosphatases, which collectively maintain the homeostatic balance of immune and inflammatory responses.

A large number of previous studies have confirmed that STAT1 exerts a tumor suppressor effect in many malignant tumors, including ovarian cancer, osteosarcoma, lung cancer, breast cancer, and colorectal cancer. In these tumor types, STAT1 mainly inhibits tumor cell proliferation, promotes tumor cell apoptosis, enhances the anti-tumor immune response, and suppresses tumor invasion and metastasis through multiple signaling pathways, thereby exerting a negative regulatory effect on tumor occurrence and development.[7-9] For example, interleukin (IL)-27 exerts potent anti-tumor and anti-metastatic activities through STAT1-dependent signaling pathways. Upon binding to its receptor complex (WSX-1 and gp130), IL-27 induces phosphorylation of multiple STAT proteins, including STAT1, STAT2, STAT3, STAT4, and STAT5. Notably, STAT1 activation is indispensable for IL-27-induced T-bet expression, which drives Th1 immune responses by transactivating the IFN-γ gene and upregulating IL-12Rβ2.[10] Thus, IL-27 functions as a powerful angiogenesis inhibitor through STAT1-dependent, IFN-γ-independent mechanisms, selectively utilizing antiangiogenic effector pathways against tumors with low immunogenicity and poor major histocompatibility complex class I expression. Furthermore, IL-27's anti-tumor efficacy in non-small cell lung cancer is mediated primarily through STAT1-dependent mechanisms, including induction of mesenchymal-to-epithelial transition, arrest of migration, and inhibition of angiogenesis.[11] The identification of STAT1 as the dominant effector pathway, coupled with its role in restraining oncogenic STAT3 activity, positions IL-27 as a promising therapeutic candidate for lung cancer, particularly given the limitations of IL-12 therapy due to excessive toxicity.

However, in recent years, accumulating evidence has shown that *STAT1* may exhibit context-dependent oncogenic properties in specific tumor types and cellular microenvironments, including hematological malignancies such as chronic lymphocytic leukemia and multiple myeloma, as well as some solid tumors such as nasopharyngeal carcinoma and non-small cell lung cancer.[12,13] In these tumors, abnormal activation or overexpression of *STAT1* can promote tumor cell survival, proliferation, invasion, metastasis, and chemotherapy resistance, showing a dual regulatory role in tumorigenesis. The oncogenic functions of *STAT1* appear to be closely associated with sustained, chronic activation rather than transient physiological signaling, thereby establishing pro-survival gene expression programs that favor tumor progression. In lung adenocarcinoma, identifying the Oct4/STAT1/Mcl-1 axis as a pro-survival pathway highlights *STAT1* as a potential therapeutic target.[14] Fludarabine, repurposed as a STAT1 inhibitor, demonstrates efficacy in suppressing tumor growth and sensitizing cancer cells to cisplatin, suggesting that combination strategies targeting this axis may improve outcomes for patients with poor prognosis in lung adenocarcinoma. In colorectal cancer, STAT1 drives oncogenic lipid biosynthesis in mutant *KRAS* colorectal cancer by transcriptionally upregulating

sterol regulatory element-binding protein-1/2 through S727 phosphorylation-dependent binding, establishing a feedforward loop with Yes-associated protein 1–TEA domain transcription factor 4 that sustains mevalonate pathway activation, accelerates tumor growth, and confers resistance to chemotherapy and targeted therapies.[15]

The dual regulatory role of *STAT1* in tumorigenesis can be attributed to several underlying mechanisms. First, the duration and intensity of STAT1 activation determine its functional outcomes, with transient activation typically associated with anti-tumor effects and sustained activation with pro-tumor effects. Second, the cellular context and microenvironment significantly influence *STAT1* function, as the availability of co-activators, co-repressors, and competing transcription factors can modulate *STAT1*-mediated gene expression programs. Third, post-translational modifications beyond tyrosine phosphorylation, including serine phosphorylation, acetylation, methylation, and ubiquitination, can alter STAT1 stability, localization, and transcriptional activity, thereby shifting its functional balance toward either tumor suppression or promotion. Fourth, the interaction of STAT1 with other signaling pathways, such as nuclear factor kappa B, phosphoinositide 3-kinase/protein kinase B, and mitogen-activated protein kinase cascades, can create complex regulatory networks that either synergize with or antagonize STAT1 functions in a context-dependent manner.

At present, the biological function and clinical significance of *STAT1* in gastric cancer remain controversial and have not been fully elucidated. Previous relevant studies have reported inconsistent and even contradictory results regarding *STAT1* expression level, subcellular localization, and its correlation with clinicopathological features and prognosis of gastric cancer patients.[16,17] Some studies have suggested that *STAT1* is lowly expressed in gastric cancer tissues and is associated with poor prognosis, acting as a tumor suppressor; while other studies have found that *STAT1* is highly expressed in gastric cancer and promotes tumor progression through regulating immune escape and chemotherapy resistance. These conflicting conclusions may be related to differences in research sample sources, sample sizes, detection methods, and tumor heterogeneity. Therefore, it is urgent to conduct a comprehensive, systematic, and multidimensional investigation of *STAT1* expression patterns in gastric cancer by integrating multiple independent public databases and clinical sample validation to clarify its clinical value and potential as a diagnostic biomarker. The integration of bioinformatics approaches with experimental validation is a robust strategy for identifying reliable biomarkers, as it enables cross-validation across diverse patient cohorts and analytical platforms, thereby minimizing the biases inherent in single-dataset or single-center studies.

Given these conflicting reports, we performed a comprehensive bioinformatics analysis of two independent Gene Expression Omnibus (GEO) datasets (GSE63089 and GSE2685) to screen differentially expressed genes (DEGs) between gastric cancer and normal tissues (Figure 1). The overlapping DEGs between these two datasets were further evaluated in the GSE49515 dataset, which identified *STAT1* as the only consistently upregulated candidate gene. We then validated *STAT1* expression using the Gene Expression Profiling Interactive Analysis (GEPIA) dataset and clinical samples and assessed its diagnostic performance via receiver operating characteristic (ROC)

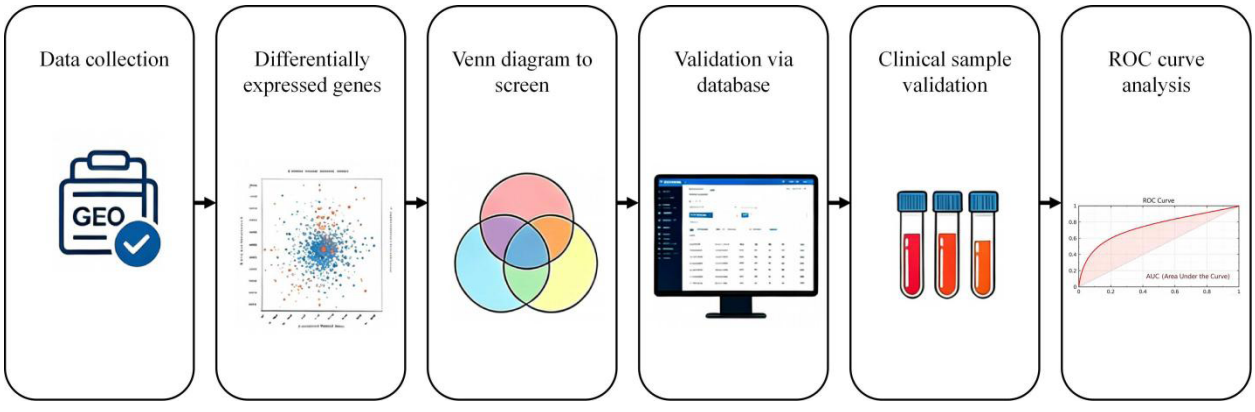

Figure 1. Study design for the identification and validation of *STAT1* as a diagnostic biomarker for gastric cancer
Abbreviations: ROC: Receiver operating characteristic curve.

curve analysis.

2. Materials and methods

2.1. Data acquisition and processing

Three publicly available GEO datasets (GSE63089, GSE2685, and GSE49515) were downloaded from the GEO database (https://www.ncbi.nlm.nih.gov/geo/). The GSE63089 and GSE2685 datasets were derived from the GPL5175 platform (Affymetrix Human Exon 1.0 ST Array) and the GPL80 platform (Affymetrix Human Full Length HuGeneFL Array), respectively, both of which include gene expression data from gastric cancer and normal gastric tissues. The GSE49515 dataset was based on the GPL570 platform (Affymetrix Human Genome U133 Plus 2.0 Array) and contained gene expression profiles of peripheral blood from healthy individuals and pathologically confirmed gastric cancer patients. The GSE183635 dataset was based on the Illumina NovaSeq 6000 platform and contained transcriptomic profiles of tumor blood RNA and non-cancer controls. Differential expression analysis between tumor and normal tissues was performed for each GEO dataset using the GEO2R online analysis. Genes exhibiting an adjusted p-value < 0.05 were considered significantly differentially expressed. Volcano plots were generated to visualize the distribution of DEGs, with the x-axis representing $\log_2$-transformed mean expression ($\log_2$Exp) and the y-axis representing $\log_2$-transformed fold change ($\log_2$FC). Upregulated genes were defined as $\log_2FC > 0$ with adjusted $p < 0.05$ (marked in red), downregulated genes as $\log_2FC < 0$ with adjusted $p < 0.05$ (marked in blue), and genes with non-significant difference were marked in gray. The volcano plots provide a comprehensive visual representation of the magnitude and statistical significance of gene expression changes, enabling the identification of candidate genes with both substantial fold changes and high statistical confidence.

The data from GEPIA (https://gepia.cancer-pku.cn/) were also used to analyze *STAT1* expression in gastric cancer and normal samples. GEPIA is an interactive web application that analyzes RNA sequencing expression data from 9,736 tumors and 8,587 normal samples across 33 cancer types from The Cancer Genome Atlas (TCGA) and Genotype–Tissue Expression (GTEx) projects.[18] The platform provides comprehensive gene expression profiling, survival analysis, and differential expression analysis capabilities, making it an invaluable resource for validating bioinformatics findings across large-scale cohorts. For *STAT1* expression analysis in gastric cancer, we utilized the stomach adenocarcinoma (STAD) dataset within GEPIA, which contains 408 tumor samples and 211 normal samples, to generate cumulative distribution plots and perform statistical comparisons between tumor and normal tissues. Tumor Immune Estimation Resource (TIMER2.0) is also an interactive web server.[19] This resource is particularly valuable for evaluating gene expression differences and immune cell compositions across tumor and normal tissues in large-scale cohorts. For *STAT1* expression analysis, we utilized TIMER2.0 to examine its expression profile across multiple human gastrointestinal tumor types

2.2. Venn diagram analysis

To focus on the most biologically relevant alterations, we refined our DEG criteria by requiring $\log_2FC > 1$ and adjusted $p < 0.05$. Venn diagrams were constructed to identify overlapping DEGs between the GSE63089 and GSE2685 datasets using the VennDiagram tool (https://www.bic.ac.cn/test/venn/). The total number of analyzed genes in each dataset and the number of common DEGs were determined. The intersection of DEGs across independent datasets represents a robust strategy for identifying consistently altered genes, as it minimizes dataset-specific artifacts and technical biases while highlighting biologically significant molecular alterations. Genes that appear in the intersection of multiple independent datasets are more likely to represent genuine cancer-related changes rather than random fluctuations or platform-specific effects.

2.3. Clinical sample collection and validation

Gastric cancer blood and normal health samples were collected at the First Affiliated Hospital of Xi'an Medical University. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Medical University and was conducted in accordance with the principles of the Declaration of Helsinki. Patient enrollment characteristics are summarized in Table 1. The inclusion criteria for gastric cancer patients were: (i) histopathologically confirmed primary gastric adenocarcinoma; (ii) no prior chemotherapy, radiotherapy, or surgical treatment; (iii) no concurrent malignancies or autoimmune diseases; and (iv) availability of complete clinical and pathological information. Healthy controls were recruited from individuals undergoing routine physical examination at the same hospital, with no history of malignancy, chronic inflammatory diseases, or autoimmune disorders.

For RNA extraction from whole blood, the samples were collected in ethylenediaminetetraacetic acid tubes. Blood samples were processed within two hours of collection and centrifuged at 1,500×g for 15 min at 4 °C. Blood was isolated using Ficoll–Paque density gradient centrifugation. Then, we isolated total RNA using the QIAamp RNA Blood Mini Kit according to the manufacturer's instructions (Qiagen,

Germany). The QIAamp RNA Blood Mini Kit employs silica membrane technology for efficient purification of total RNA from stabilized blood samples, with a typical yield of 3–8 μg RNA per 1.5 mL of blood and an A260/A280 ratio of 1.9–2.1 indicating high purity. Complementary DNA was synthesized using the PrimeScript RT Master Mix (Takara, China). Quantitative real-time polymerase chain reaction (qRT-PCR) was performed using SYBR Green Master Mix (Applied Biosystems, United States) on an ABI 7500 Real-Time PCR System (Applied Biosystems, United States) under the following conditions: 95 °C for 10 min; 40 cycles of 95 °C for 15 s, 60 °C for 60 s; followed by a melt curve analysis (95 °C for 15 s, 60 °C for 1 min, 95 °C for 15 s). All reactions were performed in triplicate. The SYBR Green detection method provides sensitive and specific quantification of PCR products by intercalating the fluorescent dye into double-stranded DNA, with melt curve analysis performed after *amplification* to verify product specificity. The relative expression of *STAT1* was normalized to GAPDH and calculated using the $2^{-\Delta\Delta Ct}$ method. *GAPDH* expression stability was confirmed across all samples (Ct variation < 0.5 cycles). The primer sequences are shown in Table 2.

2.4. Statistical analysis

All statistical analyses were conducted using GraphPad Prism 9.0. The Student's *t*-test was used to compare *STAT1* expression between two groups, and one-way analysis of variance followed by Tukey's post-hoc test was used for multiple group comparisons. ROC curve analysis by the Wilson/Brown method was conducted to assess the diagnostic value of *STAT1*, and the area under the curve (AUC) was calculated. A p-value < 0.05 was deemed statistically significant.

3. Results

3.1. Identification of differentially expressed genes in GEO datasets

Differential gene expression analysis was performed on the GSE63089 and GSE2685 datasets. In the GSE63089 dataset, a total of 8,058 DEGs were identified (adjusted $p < 0.05$), including both upregulated and downregulated genes

Table 1. Basic characteristics of patients with gastric cancer

Variable	Gastric cancer patients ($n = 55$)	Healthy controls ($n = 50$)
Gender		
Male	29	27
Female	26	23
Age		
≤60	22	21
>60	33	29
Stage		
I	11	-
II	21	--
III/IV	23	

Table 2. The sequences of primers for quantitative real-time polymerase chain reaction

Gene		Sequences	Amplicon size	Annealing temperature (°C)
STAT1	Foward	ATCAGGCTCAGTCGGGGAATA	186	62.2
	Reverse	TGGTCTCGTGTTCTCTGTTCT		60.4
GAPDH	Foward	ACAACTTTGGTATCGTGGAAGG	101	60.2
	Reverse	GCCATCACGCCACAGTTTC		61.7

(Figure 2A and 2C). Similarly, 2,139 DEGs were identified in the GSE2685 dataset (adjusted $p < 0.05$; Figure 2B and 2C). The differences in the number of DEGs between the two datasets may be attributed to variations in sample size, microarray platform sensitivity, tissue processing protocols, and patient demographic characteristics. To focus on potentially biologically relevant upregulation, DEGs with $|\log_2 FC| > 1$ were further screened using a stringent FC threshold to prioritize genes with substantial expression changes more likely to have functional consequences in tumor development and progression. Venn diagram analysis showed the distribution of DEGs in each dataset, and the intersection analysis revealed that 94 genes were identified as the common differentially expressed genes shared between the two independent datasets (Figure 2D). This intersection represents a conservative yet robust set of candidate genes that exhibit consistent expression changes across patient cohorts and analytical platforms, thereby reducing the likelihood of false positives from single-dataset analyses. The identification of 94 common DEGs from over 8,000 and 2,000 initial candidates highlights the stringency of our cross-validation approach and the importance of independent replication in biomarker discovery. The differential genes were evaluated in the GSE49515 dataset, and only the *STAT1* level was increased (Figure 2E). The unique identification of *STAT1* as the consistently upregulated gene across all three datasets underscores its potential significance as a robust diagnostic biomarker for gastric cancer, independent of sample source or analytical methodology.

3.2. Upregulation of *STAT1* in gastric cancer across multiple databases

To comprehensively characterize *STAT1* expression in gastric cancer, we analyzed its expression profile across the STAD dataset (GEPIA) and the two independent GEO datasets. The cumulative distribution plot from the GEPIA dataset demonstrated that *STAT1* expression was markedly higher in tumor samples than in normal samples, with the median expression value in the tumor group exceeding that of the normal group ($p < 0.05$; Figure 3A). The GEPIA analysis, based on large-scale TCGA and GTEx data, provides strong validation of our initial bioinformatics findings, as it encompasses hundreds of

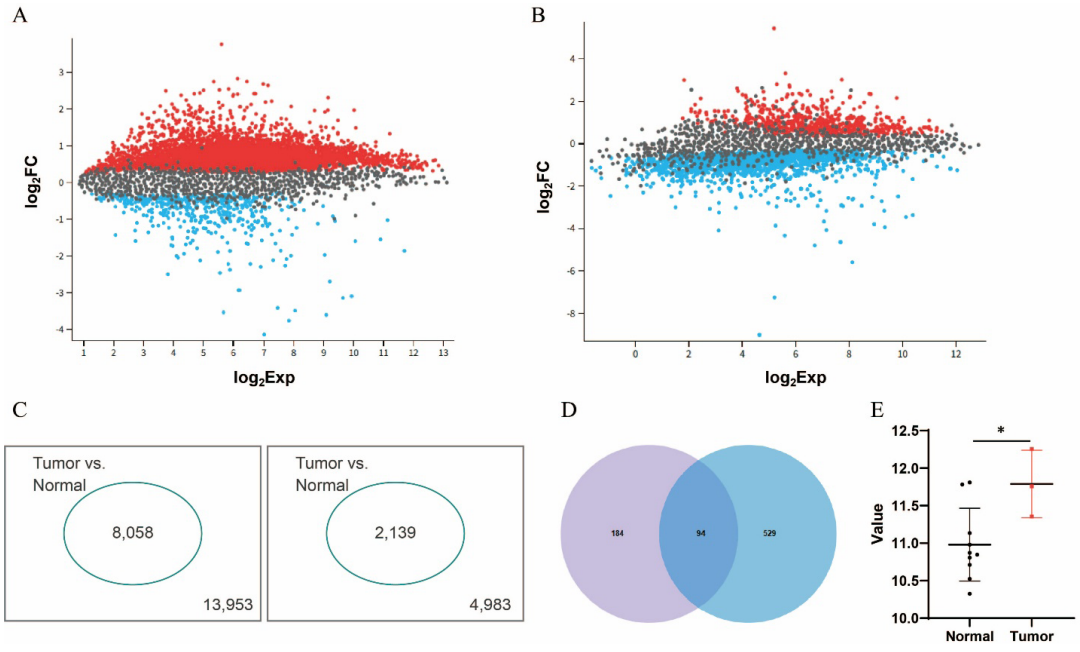

Figure 2. Differential gene expression analysis between tumor and normal samples in two GEO datasets. (A) Volcano plot of differentially expressed genes (DEGs) in the GSE63089 dataset. (B) Volcano plot of differentially expressed genes in the GSE2685 dataset. The x-axis represents $\log_2$-transformed mean expression ($\log_2$Exp), and the y-axis represents $\log_2$-transformed fold change ($\log_2$FC). Red dots indicate significantly upregulated genes ($\log_2 FC > 0$, adjusted $p < 0.05$), blue dots indicate significantly downregulated genes ($\log_2 FC < 0$, adjusted $p < 0.05$), and gray dots indicate non-significantly expressed genes. (C) Venn diagrams showing the number of differentially expressed genes identified in GSE63089 (left) and GSE2685 (right) datasets (tumor vs. normal, adjusted $p < 0.05$). The number of DEGs analyzed in each dataset is indicated in each circle. (D) Venn diagram showing the overlap of DEGs between the GSE63089 and GSE2685 datasets by defining $\log_2 FC > 1$. (E) The expression of *STAT1* in GSE49515. *$p < 0.05$, compared with the normal samples by *t*-test.

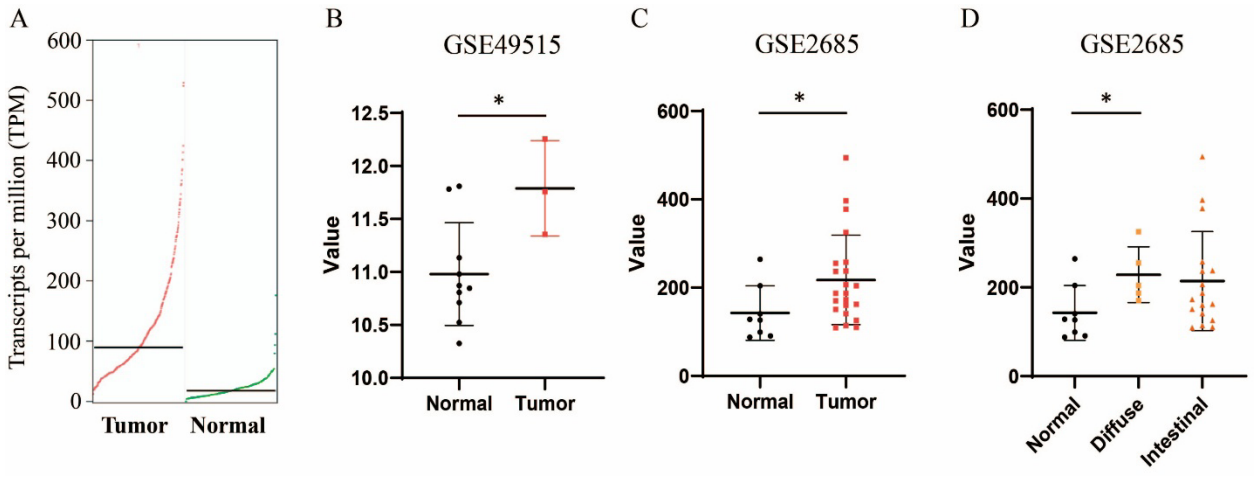

Figure 3. Expression analysis of *STAT1* in gastric cancer based on public databases. (A) Expression profile of *STAT1* across all samples in the GEPIA dataset. The cumulative distribution plot shows the expression levels of *STAT1* in tumor (red) and normal (green) samples. (B) Expression levels of *STAT1* in the GSE63089 dataset. (C) Expression levels of *STAT1* in the GSE2685 dataset. (D) Expression levels of *STAT1* across different histological subtypes of gastric cancer in the GSE2685 dataset. *STAT1* expression was compared among normal tissues, diffuse-type gastric cancer, and intestinal-type gastric cancer. *$p < 0.05$, compared with the normal samples by *t*-test.

samples and represents diverse patient populations. The consistent elevation of *STAT1* in gastric cancer across this comprehensive database supports the generalizability of our observation beyond the specific cohorts included in the GEO datasets.

Consistent with the GEPIA data, *STAT1* levels were significantly higher in gastric cancer tissues than in normal samples in both the GSE63089 dataset ($p < 0.05$; Figure 3B) and the GSE2685 dataset ($p < 0.05$; Figure 3C). The concordance of *STAT1* upregulation across three independent datasets—two tissue-based GEO datasets and one large-scale TCGA/GTEx database—provides compelling evidence for the robustness and reproducibility of this molecular alteration in gastric cancer. Furthermore, analysis of different histological subtypes in the GSE2685 dataset revealed that *STAT1* expression was significantly elevated in diffuse-type gastric cancer compared to normal tissues ($p < 0.05$; Figure 3D). This finding is particularly noteworthy given the distinct molecular and clinical characteristics of diffuse-type gastric cancer, which is typically more aggressive, less responsive to conventional chemotherapy, and associated with worse prognosis compared to intestinal-type gastric cancer. The specific high expression of *STAT1* in diffuse-type gastric cancer suggests that this biomarker may have particular utility in identifying high-risk patient subgroups that require more aggressive therapeutic intervention and intensive surveillance. Moreover, we examined *STAT1* expression across human gastrointestinal tumors via TIMER2.0. Pan-cancer analysis revealed that *STAT1* mRNA expression was significantly higher in tumor tissues than in adjacent normal tissues across esophageal carcinoma (ESCA) and STAD ($p < 0.001$; Figure 4A). Transcriptomic analysis of the blood GSE183635 dataset identified 8,183 significantly dysregulated genes between ESCA and healthy normal controls (adjusted $p < 0.05$; Figure 4B and 3C). In this cohort, *STAT1* expression did not differ significantly between tumor and control samples ($p = 0.99$; Figure 4D).

3.3. Diagnostic value of *STAT1* in gastric cancer

To validate the bioinformatics findings, we performed qRT-PCR analysis of *STAT1* expression in clinical gastric cancer blood and normal health samples. The results confirmed that *STAT1* was significantly upregulated in tumor samples compared to normal ones ($p < 0.05$; Figure 5A). The validation of *STAT1* upregulation in peripheral blood samples is of particular clinical significance, as it demonstrates the feasibility of detecting this biomarker via minimally invasive liquid biopsy. Liquid biopsy-based biomarkers offer substantial advantages over traditional tissue biopsy, including reduced patient discomfort, lower risk of complications, the ability to perform serial monitoring, and the potential for large-scale population screening.

To evaluate the diagnostic performance of blood *STAT1* as a biomarker for gastric cancer, ROC curve analysis was performed. As shown in Table 3, blood *STAT1* demonstrated a sensitivity of 67.27% (95% confidence interval [CI]:

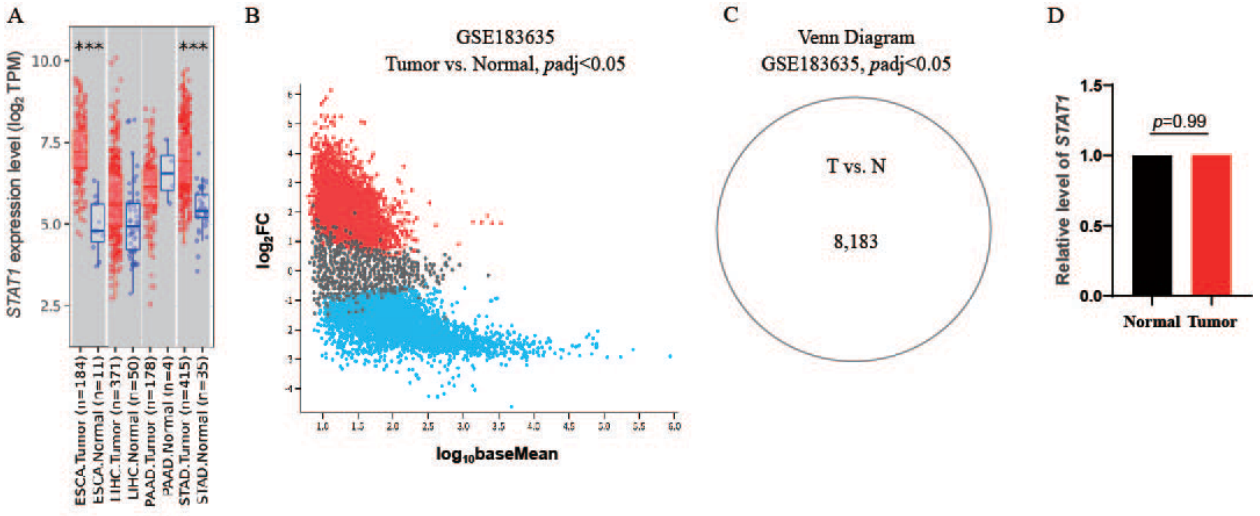

Figure 4. *STAT1* expression profile and transcriptomic analysis of tumor vs. normal tissues in the GSE183635 cohort. (A) *STAT1* expression (log_2-transformed transcripts per million [TPM]) in tumor (red) and adjacent normal (blue) tissues across multiple cancer types (ESCA, LIHC, PAAD, STAD). ***$p < 0.001$. (B) Volcano plot of differentially expressed genes (DEGs) between ESCA and healthy normal controls in GSE183635 ($padj < 0.05$). Red: upregulated genes; blue: downregulated genes; gray: non-significant genes. (C) Venn diagram showing the total number of DEGs ($n = 8,183$) identified at $padj < 0.05$. (D) Relative *STAT1* expression in tumor vs. normal tissues from GSE183635 ($p = 0.99$).
Abbreviations: ESCA: Esophageal carcinoma; LIHC: Liver hepatocellular carcinoma; PAAD: Pancreatic adenocarcinoma; STAD: Stomach adenocarcinoma.

0.541–0.7819) and a specificity of 96.00% (95% CI: 0.8654–0.9929) for distinguishing gastric cancer patients from healthy controls. The AUC was 0.8645 (95% CI: 0.7960–0.9331) (Figure 5B), indicating good diagnostic accuracy of blood STAT1 as a potential biomarker for detecting gastric cancer. An AUC value exceeding 0.85 is generally considered excellent diagnostic performance, and a 95% CI excluding 0.5 indicates statistical significance. The high specificity (96%) is particularly valuable in a screening context, as it minimizes false-positive results and reduces the burden of unnecessary confirmatory procedures. The diagnostic performance of *STAT1* observed in this study is comparable to existing biomarkers for gastric cancer.

4. Discussion

Gastric cancer is a heterogeneous disease with complex molecular mechanisms underlying its initiation and progression.[20,21] The molecular heterogeneity of gastric cancer is reflected in its diverse histological subtypes, genomic alterations, and clinical behaviors, which collectively contribute to the challenges in early detection and effective treatment. Despite significant advances in understanding the molecular landscape of gastric cancer, effective biomarkers for early detection remain limited.[22,23] Current diagnostic approaches rely heavily on endoscopic examination, which is invasive, expensive, and not suitable for large-scale population screening. Consequently, there is an urgent need for non-invasive, blood-based biomarkers that can facilitate early detection, monitor treatment response, and predict recurrence in gastric cancer patients.

In the present study, we identified *STAT1* as a consistently upregulated gene in gastric cancer through integrative analysis of two independent GEO datasets. This finding was further validated using the GEPIA STAD database and confirmed in clinical samples. Moreover, our ROC curve analysis demonstrated that *STAT1* possesses good diagnostic accuracy in distinguishing gastric cancer from normal samples. The multi-level validation strategy employed in our study—spanning bioinformatics screening across independent public databases, large-scale TCGA/GTEx validation, and independent clinical sample verification—provides robust evidence supporting *STAT1* as a potential diagnostic biomarker for gastric cancer.

Signal transducer and activator of transcription 1 is

Table 3. Diagnostic value of blood *STAT1* for gastric cancer

Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
67.27 (0.541–0.7819)	96.00 (0.8654–0.9929)	0.8645 (0.7960–0.9331)

Abbreviations: AUC: Area under the curve; CI: Confidence interval.

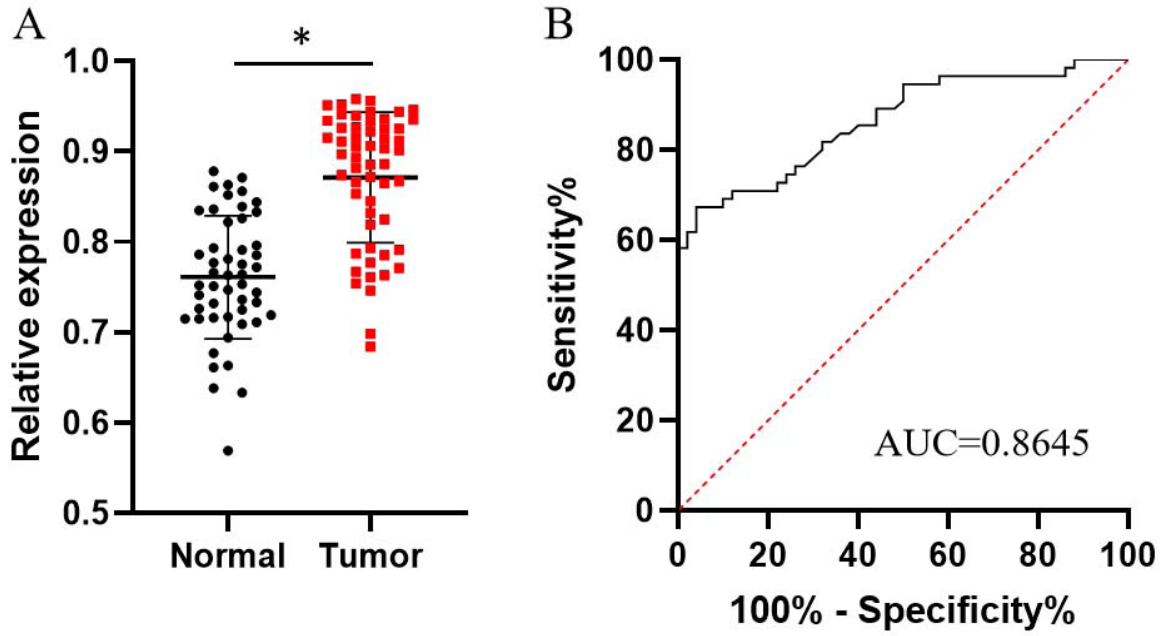

Figure 5. Validation of *STAT1* expression in gastric cancer blood samples and its diagnostic value. (A) Relative expression levels of *STAT1* in gastric cancer blood samples compared to healthy normal controls. *$p < 0.05$, compared with the normal samples by *t*-test. (B) Receiver operating characteristic (ROC) curve analysis of *STAT1* expression for distinguishing gastric cancer from normal samples. The area under the curve (AUC) was 0.8645. The red dashed line represents the reference line (AUC = 0.5).

a key transcription factor in the JAK–STAT signaling pathway, which is mainly activated by type I (IFN-α/β) and type II (IFN-γ) IFNs.[24] Upon phosphorylation at Tyr701, *STAT1* forms homodimers or heterodimers with *STAT2*, rapidly translocates to the nucleus, and specifically binds to the promoter region of IFN-stimulated genes, thereby regulating the transcriptional expression of downstream target genes.[25] The canonical IFN–γ/STAT1 signaling cascade plays a pivotal role in anti-tumor immunity by promoting the expression of major histocompatibility complex molecules, facilitating antigen presentation, and enhancing the cytotoxic activity of natural killer cells and $CD8^+$ T lymphocytes. For a long time, *STAT1* has been widely regarded as a tumor suppressor because it can promote tumor cell apoptosis and inhibit tumor cell proliferation, enhance anti-tumor immune response, and block tumor cell cycle progression.[26] For instance, *STAT1* deficiency in experimental mice results in increased susceptibility to chemically induced tumors, and reduced *STAT1* expression has been associated with poor prognosis in breast cancer.[27,28]

However, as research has deepened, it has been found that the role of STAT1 in tumors is not simply that of a tumor suppressor but exhibits a dual regulatory effect that is tissue-specific and microenvironment-dependent. In some hematological malignancies, persistent activation of *STAT1* has been reported in chronic lymphocytic leukemia and multiple myeloma, contributing to tumor cell survival and inhibition of apoptosis.[29,30] In solid tumors such as nasopharyngeal carcinoma and non-small cell lung cancer, *STAT1* has been reported to promote tumor progression through mechanisms involving immune evasion and epithelial-mesenchymal transition.[31,32] However, some studies also reported a tumor suppressor role in lung cancer and melanoma.[33,34] This apparent paradox can be reconciled by considering the duration, intensity, and cellular context of *STAT1* activation. Transient, physiologically regulated *STAT1* activation typically mediates anti-tumor effects through proper immune surveillance and controlled cell cycle regulation, whereas sustained, aberrant *STAT1* activation may drive oncogenic gene expression programs that promote cell survival, proliferation, and immune evasion.

The results of this study showed that *STAT1* was significantly upregulated in gastric cancer tissues and peripheral blood, which was consistent with the pro-tumor effect of *STAT1* in some solid tumors, suggesting that *STAT1* may be associated with the occurrence and development

of gastric cancer. Based on previous studies, we speculate that several molecular mechanisms underlie the role of *STAT1* in gastric cancer. First, persistent activation of *STAT1* signaling can upregulate the expression of programmed death-ligand 1 (PD-L1) in tumor cells and tumor-associated macrophages, constructing an immunosuppressive tumor microenvironment, inhibiting the activation and infiltration of cytotoxic T lymphocytes, and enabling tumor cells to evade the surveillance and clearance of the body's immune system.[35-37] The IFN-γ/STAT1/IFN regulatory factor 1axis has been identified as a critical regulator of PD-L1 expression in various malignancies, and the upregulation of PD-L1 through this pathway represents a key mechanism of adaptive immune resistance in gastric cancer. Second, *STAT1* can interact with classical signaling pathways, such as nuclear factor kappa B and phosphoinositide 3-kinase/protein kinase B, forming a positive feedback regulatory loop that enhances the proliferation, migration, and invasion of gastric cancer cells.[38,39] Third, *STAT1* is involved in regulating chemotherapy resistance in gastric cancer cells, and its overexpression can reduce their sensitivity to chemotherapeutic agents such as cisplatin and paclitaxel, leading to treatment failure.[40,41] The *STAT1*-mediated upregulation of anti-apoptotic proteins and DNA repair enzymes may contribute to the development of chemoresistance, while *STAT1*-dependent activation of drug efflux pumps could further compromise treatment efficacy.

Recent studies have provided additional insights into the mechanisms by which *STAT1* promotes gastric cancer progression. Sphingosine kinase 1 has been shown to facilitate gastric cancer progression via *STAT1* gene methylation-mediated mechanisms, in which overexpression of sphingosine kinase 1 increases *STAT1* promoter methylation and subsequent *STAT1* downregulation, paradoxically promoting tumor growth through complex feedback mechanisms.[42] This finding highlights the epigenetic regulation of *STAT1* in gastric cancer and suggests that DNA methylation patterns may serve as additional biomarkers for patient stratification. Furthermore, the IFN-γ/STAT1 pathway has been characterized as a "double-edged sword" in gastrointestinal tumors, capable of both promoting and inhibiting tumor progression depending on the activation of different downstream effectors and the cellular context.[43] Understanding these context-dependent effects is essential for developing targeted therapeutic strategies.

In terms of clinical application value, the results of this study showed that the AUC of peripheral blood *STAT1* in the diagnosis of gastric cancer was 0.8645, with high specificity (96.00%) and favorable sensitivity (67.27%), indicating that peripheral blood *STAT1* has good diagnostic performance and can be used as a non-invasive auxiliary diagnostic biomarker for gastric cancer. Compared with traditional invasive diagnostic methods, peripheral blood detection offers the advantages of simple operation, minimal invasiveness, good patient compliance, and repeatability, making it suitable for large-scale population screening and postoperative follow-up monitoring.[44-46] The implementation of blood-based biomarker screening programs could potentially identify high-risk individuals for subsequent confirmatory endoscopic examination, thereby improving the efficiency and cost-effectiveness of gastric cancer screening initiatives.

In addition, this study found that *STAT1* was specifically highly expressed in diffuse-type gastric cancer, which has important clinical value for the subtype classification and individualized treatment of gastric cancer. Diffuse-type gastric cancer is more malignant, more prone to metastasis, and has a worse prognosis than intestinal-type gastric cancer. The high expression of *STAT1* in diffuse-type gastric cancer can serve as a new molecular marker for the early identification of this high-risk subtype, helping clinicians formulate more targeted treatment strategies. The Lauren classification system, while widely used, does not always accurately predict patient outcomes; integrating molecular biomarkers such as *STAT1* could enhance risk stratification and guide treatment decisions. For instance, patients with diffuse-type gastric cancer and high *STAT1* expression might benefit from more aggressive neoadjuvant chemotherapy regimens, closer surveillance protocols, or enrollment in clinical trials evaluating *STAT1*-targeted therapies.

Our study has several strengths. First, the study design is rigorous and reliable, using two independent GEO datasets for initial screening, an independent dataset for external verification, and clinical samples for experimental validation, which greatly improves the credibility and repeatability of the results. The use of multiple independent datasets minimizes the impact of cohort-specific biases and technical artifacts, while the progression from tissue-based discovery to blood-based validation demonstrates the translational potential of our findings. Second, multi-level validation from tissue to peripheral blood samples confirms that *STAT1* can be used as a non-invasive diagnostic biomarker, expanding its clinical application scenario. The ability to detect *STAT1* alterations in peripheral blood mononuclear cells opens avenues for liquid biopsy-based screening and monitoring approaches that are more acceptable to patients and feasible for large-scale implementation. Third, the study

explores the expression difference of *STAT1* in different histological subtypes of gastric cancer, providing a new idea for subtype-specific diagnosis of gastric cancer.

Nevertheless, this study has some limitations that warrant attention in future research. First, the sample size of clinical validation is relatively small, and a larger sample size and multi-center clinical validation are needed to further confirm the diagnostic value of *STAT1*. Second, this study focuses only on the diagnostic value of *STAT1* and does not explore its correlation with clinicopathological features such as tumor stage, lymph node metastasis, distant metastasis, and the prognosis of gastric cancer patients, nor its predictive value for treatment efficacy. Third, the specific molecular mechanism by which *STAT1* regulates the biological behavior of gastric cancer cells has not been studied in depth, and *in vitro* cell experiments and *in vivo* animal models are needed to clarify its function and regulatory network. Fourth, the potential of *STAT1* as a therapeutic target for gastric cancer has not been explored, and the development of STAT1-targeted small-molecule inhibitors or monoclonal antibodies may provide a new strategy for targeted therapy. Finally, gastric cancer screening and early detection are also influenced by risk factor awareness, particularly *Helicobacter pylori* infection status and screening attitudes.[47]

The emerging field of *STAT*-targeted therapeutics offers promising avenues for future investigation. Small-molecule inhibitors targeting JAK kinases, which act upstream of *STAT1*, have shown clinical efficacy in hematological malignancies and are being explored for solid tumors.[48,49] Similarly, sanguinarine, as an *EphB4* inhibitor, attenuates tumor proliferation and migration.[50] However, the broad impact of JAK inhibition on multiple STAT family members and cytokine signaling pathways may limit its specificity and increase toxicity. More selective approaches, such as STAT1-specific peptidomimetics that disrupt STAT1 dimerization or nuclear translocation, or antisense oligonucleotides that selectively reduce STAT1 expression, could provide more targeted therapeutic options with improved safety profiles. Additionally, identifying STAT1-specific post-translational modifications or interacting proteins that modulate its functions could reveal novel druggable targets for gastric cancer treatment.

5. Conclusion

In conclusion, our integrative bioinformatics analysis using GEO2R and clinical validation demonstrates that *STAT1* is significantly upregulated in gastric cancer across multiple independent datasets. *STAT1* exhibits good diagnostic accuracy in distinguishing gastric cancer from normal samples, suggesting its potential as a novel biomarker for detecting gastric cancer. These findings provide a foundation for future mechanistic studies investigating the role of *STAT1* in gastric carcinogenesis and its potential clinical applications in diagnosis and targeted therapy.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

Conceptualization: Fengjie Guo
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Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Medical University (approval no. XYYFY2025LSKY-046). Written informed consent was obtained from all participants.

Consent for publication

All participants provided verbal consent for their data to be published.

Availability of data

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

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