

Gelsolin Can Be a Prognostic Biomarker and Correlated with Immune Infiltrates in Gastric Cancer

Yingmei Wu^{1,2,*}Junhui Zheng^{1,2,*}Yanhua Yan^{1,2}Jiduo Liu³Yingchun Zhou³

¹Guangzhou University of Chinese Medicine, Guangzhou, 510000, People's Republic of China; ²Lingnan Medical Research Center, Guangzhou University of Chinese Medicine, Guangzhou, 510000, People's Republic of China;

³Department of Clinical Laboratory, The First Affiliated Hospital, Guangzhou University of Chinese Medicine, Guangzhou, 510000, People's Republic of China

*These authors contributed equally to this work

Background: Gelsolin (GSN) is the most widely expressed actin-severing protein in humans, which could regulate cell morphology, differentiation, movement and apoptosis. This study aims to explore the GSN as a prognostic biomarker of stomach adenocarcinoma (STAD).

Methods: In this study, we used several online databases to comprehensively analyze the role of GSN in STAD. Oncomine and HPA databases were used to explore the GSN expression in various cancer, especially in gastric cancer. Then, UALCAN database was used to evaluate the relationship between GSN expression and promoter methylation in clinical characteristics. Finally, we used TIMER to analyze the correlation between GSN expression and immune infiltrates in gastric cancer.

Results: GSN was down-regulated in gastric cancer, and decreased expression of GSN was related to worse survival. The GSN expression was significantly related to tumor purity in STAD and significantly correlated with infiltrating level of various immune cells, especially the dendritic cells.

Conclusion: Our study proposes that GSN can be served as the biomarker of disease and neoantigen for STAD treatment, which can improve the deficiency of disease-specific targeted therapies currently exist.

Keywords: gelsolin, gastric cancer, prognosis, immune cell infiltration

Introduction

Gastric cancer (GC) remains an important cause of cancer-related incidence and mortality, with over one million new cases and close to 800,000 deaths in 2018. Therefore, it has been supposed to the fifth most frequently diagnosed cancer and the third-leading cause of cancer death.¹ It is estimated that there were 1,033,701 new cases of GC (representing 5.7% of all cancer cases diagnosed) and 782,685 deaths related to GC in 2018 around the world.² Furthermore, GC was the fourth most commonly diagnosed cancer type in men and the seventh-most commonly diagnosed cancer type in women.³ Although a recent global study indicated that compared to incidence, the mortality rates of GC have decreased more rapidly because of socioeconomic development, diagnosis improvement and treatment facilities amelioration.⁴ However, the mortality rate of GC is still high because of the difficulty in detection and asymptomatic in early stage.⁵

The early diagnosis plays a key role in curing GC while the unobvious symptom and the difficulties lying in the early diagnosis largely affect the effect of the

Correspondence: Yingchun Zhou; Jiduo Liu
Department of Clinical Laboratory,
The First Affiliated Hospital, Guangzhou
University of Chinese Medicine,
Guangzhou, 510000, People's Republic of China
Email yingchunbaby@126.com;
13668996592@163.com

treatment. Thus, the five-years survival rate of GC ranges between 20% and 40% in most countries.^{6,7} Meanwhile, because of the genetic complexity and heterogeneity, the traditional therapy, whether chemotherapy or anti-human epidermal growth factor receptor-2 (HER-2) therapy,⁸ having much to desire.

Gelsolin (GSN) belongs to the actin-binding proteins, a family which can mediate multiple cellular functions like cell motility, apoptosis, morphogenesis, and actin cytoskeletal remodeling. The most extensive features of gelsolin are its actin filament severing, capping, uncapping, and nucleating activities.^{9,10} Previous literature has addressed the role of GSN in cancer, many of this suggested that GSN functions as both tumor suppressor gene and oncogene. In other words, GSN will probably become a new mark in diagnoses and target in therapies.⁶ However, there were some reports that the therapeutic applicability of GSN depends on the cancer subtype. In Ras-induced tumors, it was shown that mutated GSN can suppress tumor growth.¹¹ And research has suggested that high GSN expression under conditions such as heart disease, aging, and stress, all those characters are lethal for heart disease.¹² In addition, previous studies show that the expression of GSN in colorectal cancer cells was necessary for invasion.¹³ Another report observed that the total GSN expression affects cell proliferation and viability by vitro techniques in head and neck squamous cell carcinoma.¹⁴ Recently, some case reports even found that a patient encounters renal gelsolin amyloidosis with the p. Asp174Asn mutation in the GSN gene, another with the phenotype of amyloidosis of the Finnish type because of GSN variant.^{15,16}

In this study, we used several online datasets to analyze GSN expression and its relevance to prognosis in patients with GC, as well as the correlation with immune infiltration in the tumor microenvironment. Therefore, we proposed that GSN can be considered as a potential biomarker of GC occurrence and progression. Further, due to the limited number of disease-specific targeted therapies, GSN may be a promising neoantigen for STAD treatment.

Materials and Methods

Oncomine and HPA Database Analysis

Oncomine (<https://www.oncomine.org/resource/login.html>)¹⁷ and the human protein atlas (<https://www.proteinatlas.org/>)¹⁸, are the databases we always used to identify the gene expression in diverse cancers. The threshold in Oncomine database is

as follows: *P*-value of 0.001, fold change of 1.5, and gene ranking of all.

TIMER Database Analysis

The expression of GSN in various cancers and the relevance to the expression of GSN and the abundance of immune invasion were analyzed by the TIMER (<https://cistrome.shinyapps.io/timer/>)¹⁹, an online database that can analyze immune infiltrates in various cancers, comprehensively, systematically and respectively. GSN expression and tumor infiltrating immune cell gene markers by the related modules.

UALCAN Database Analysis

In order to study healthy tissue as well as tumor in different stage, grade and other clinicopathological characteristics, we used UALCAN (<http://ualcan.path.uab.edu>)²⁰ to drawn 9 box plots. UALCAN is a database that includes 31 cancer types from the Cancer Genome Atlas (TCGA) clinical data.

Kaplan-Meier Plotter Database Analysis

Prognosis is usually comprised of overall survival (OS), First progression (FS), and post progression survival (PPS), we use Kaplan–Meier (<https://kmplot.com/>)²¹ to construct survival curve and analyze correlative data. All data provide the hazard ratio (HR) value with 95% confidence intervals and log-rank *P*-values.

Cell Culture and Quantitative Real-Time Polymerase Chain Reactions (qRT-PCR)

Human gastric cancer cells and human normal gastric epithelial cell line GES-1 were acquired from the American Type Culture Collection (ATCC, Manassas, VA, USA). We placed the cells in RPMI-1640 Medium (Gibco, USA, No.8121571) supplemented with 10% fetal bovine serum (Gibco, USA, No.25200–056), cultivated it in 5% CO₂ incubator at 37°C. We adopted the third generation of cell after revived the same batch of frozen cells, in order to ensure the stability of cell characteristics. TRIzol reagent (Life Technologies, USA, No.252604) lyses cells, then collect total RNA to reverse transcription (Evo M-MLVRT Premix Accurate Biotechnology, China, No. AG11706) and quantitative real-time PCR (qRT-PCR) analysis use SYBR Green (Accurate Biotechnology, No. AG11701) for quantification. The primers used in our study were as follows: GSN forward primer, 5'-GGTGTGGCATCAGGATTCAAG-3'; GSN reverse

primer, 3'-TTTCATACCGATTGCTGTTGGA-5'; GAPDH forward primer, 5'-GGACCTGACCTGCCGTCTAG-3'; GAPDH reverse primer, 3'-GTAGCCCAGGATGCCCTTGA-5' (Genaray Biotech Co, Shanghai).

Statistical Analysis

The cut-off value of GSN expression is medium among the statistics. P-value, fold change, and mRNA were used to analyze gene expression in the Oncomine database, and the Kaplan Meier plots database act as tool to draw survival curves, all data calculated by HR and P-values from a Log rank test. In TIMER, we choose Spearman correlation analysis to evaluate. $P < 0.05$ was considered statistically significant. The GSN expression was calculated based on $2^{-\Delta\Delta Ct}$ method with GAPDH as an internal reference.

Results

The Expression Levels of GSN in Various Types of Human Cancer

We used three independent databases to analyze GSN expression between tumors and normal tissues. Firstly, the Oncomine database shows that GSN expression was down-

regulated in bladder, breast, colorectal, esophageal, gastric, head and neck, lung, myeloma, ovarian, and prostate cancer compared to the normal tissues (Figure 1A). Meanwhile, we use TIMER to analyze the expression of GSN in pan-cancers between the tumor and adjacent normal tissues. GSN expression was significantly lower in BLCA (bladder urothelial carcinoma), BRCA (breast invasive carcinoma) and COAD (colon adenocarcinoma), ESCA (esophageal carcinoma), KICH (kidney chromophobe), KIRP (kidney renal papillary cell carcinoma), LIHC (liver hepatocellular carcinoma), LUA (lung adenocarcinoma), STAD (stomach adenocarcinoma), and UCEC (uterine corpus endometrial carcinoma) (Figure 1B). Further analysis from HPA website displays the GSN protein expression in different cancers. The results showed that the GSN protein is moderately expressed in STAD among various cancers (Figure 1C).

Relationship Between GSN Expression and Clinical Characteristics in GC Patients

We assessed whether GSN expression was associated with clinicopathological factors in patients with GC (Figure 2A). The results in GEPIA database are in excellent agreement

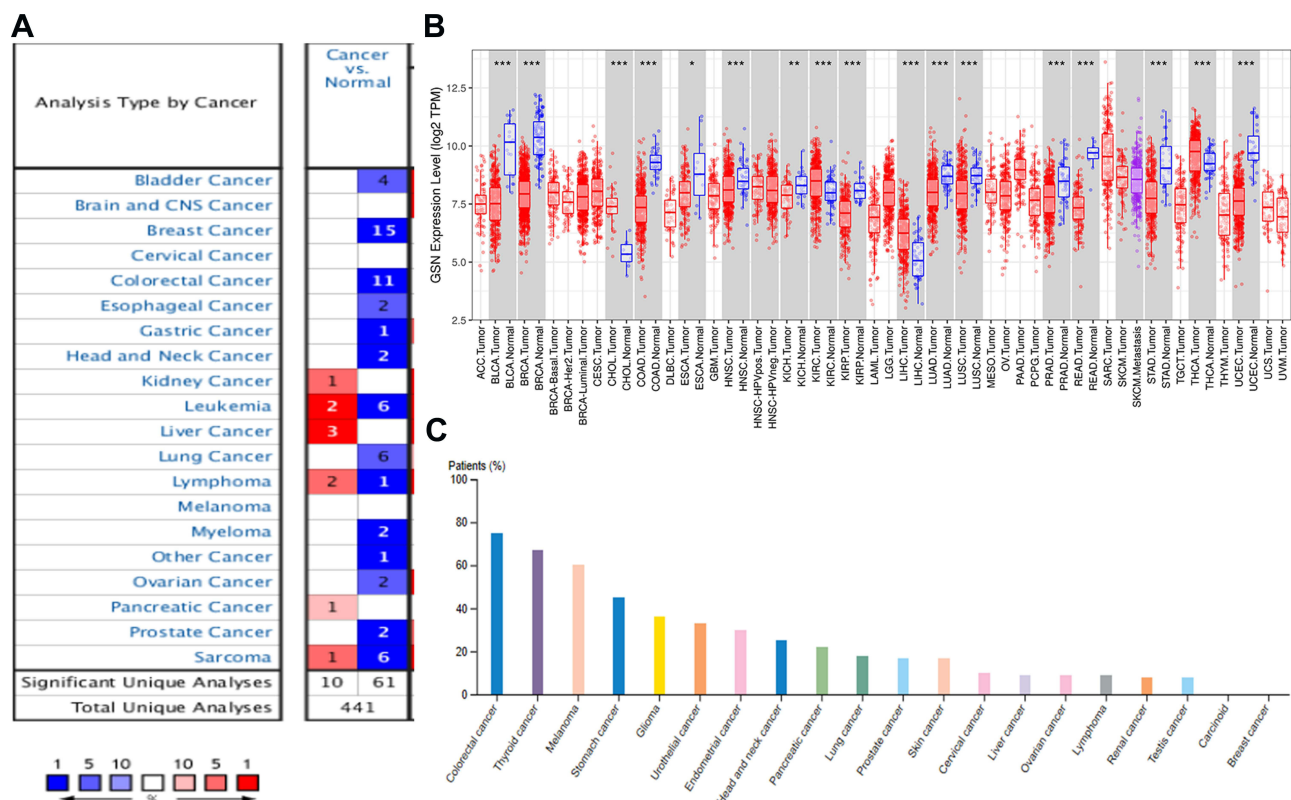


Figure 1 The expression levels of GSN in various types of human cancer. (A–C), the results are from Oncomine, TIMER, and HPA. P-value significant codes: 0 ≤ *** ≤ 0.001 ≤ ** ≤ 0.01 ≤ * ≤ 0.05.

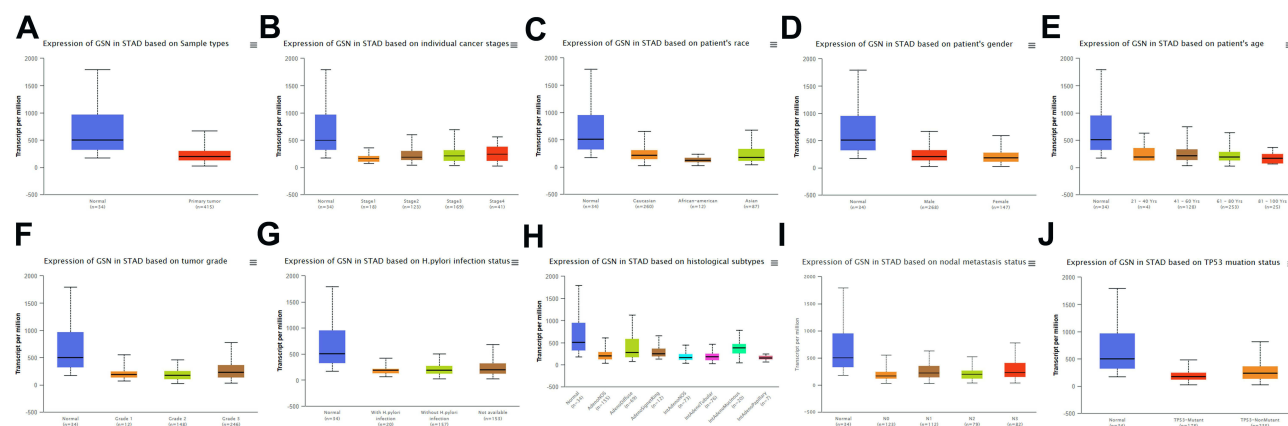


Figure 2 Relationship between GSN expression and clinical characteristics in GC patients. (A–J), expression of GSN on cancer stages, race, gender, age, tumor grade, *H. pylori* infection status, histological subtypes, metastasis, and TP53 mutation.

with the previous paper. The tumor stage (Stage 1, Stage 2, Stage 3 and Stage 4), race (Caucasian, African and Asian), gender (male and female), age (41–60, 61–80, and 81–100 years old), tumor grade (Grade 1, Grade 2 and Grade 3), *H. pylori* infection, histological (AdenoNos, AdenoDiffuse, AdenosignetRing, IntAdenoNos, IntAdenoMucinous, IntAdenopapillary), metastasis (N0, N1, N2, N3), and TP53 mutation (Figure 2B–J), all of the changes has made aspects of GSN.

Prognostic Potential of GSN in GC

To investigate the correlation between GSN expression and survival rates, the survival curve and the impact were analyzed by the Kaplan–Meier plotter. Notably, GSN expression significantly impacts prognosis in STAD. Higher GSN expression, and poorer prognosis. (OS, HR = 0.73 (0.59–0.91), $P = 0.0045$. FP, HR = 0.8 (0.66–0.91), $P = 0.018$. PPS, HR = 0.76 (0.6–0.96), $P =$

0.021) (Figure 3A–C). There are 2 gene symbols in Kaplan–Meier plotter, 200696_s_at and 214040_s_at, but the result of 200696_s_at is contrary to expectation, so we delete it. This may be due to insufficient data, possibly characteristic of mucosal immunity. Anyhow, the prognostic valuation of GSN will be plainly obvious. Then we show the correlation between GSN expression and some clinicopathological factors via Table 1, these results indicated that the abnormal GSN and low survival rates may be more common in female and the late stage.

GSN Expression is Correlated with Immune Infiltration Level in GC

We explored the correlation between GSN expression and immune infiltration levels in STAD. The results showed that the GSN expression was significantly correlated with immune infiltration levels of various

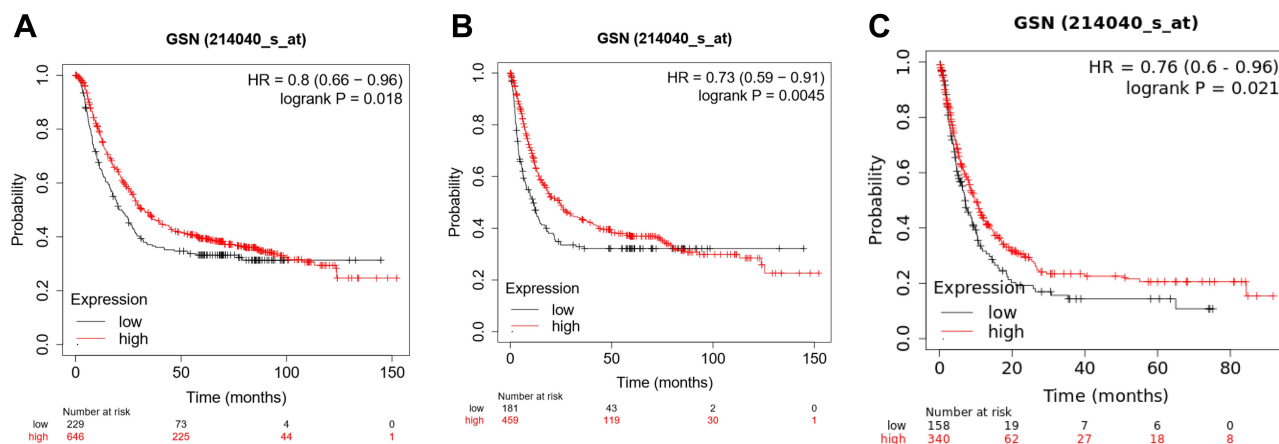


Figure 3 Prognostic potential of GSN in GC. (A), OS; (B), FP; (C), PPS.

Table I The Correlation Between GSN Expression and Prognosis in GC with Respect to Clinicopathological Factors

Clinicopathological	Overall Survival			Progression-Free Survival		
	N	Hazard Ratio	P-value	N	Hazard Ratio	P-value
SEX						
Female	244	1.58 (1.1–2.27)	0.013	201	1.29 (0.86–1.92)	0.21
Male	566	1.2 (0.96–1.49)	0.11	437		
STAGE						
I	67	1.92 (0.72–5.15)	0.19	60	3.14 (0.41–24.33)	0.25
2	140	2.11 (1.16–3.86)	0.013	131	1.44 (0.79–2.63)	0.23
3	305	1.41 (1.05–1.88)	0.021	186	1.26 (0.84–1.9)	0.26
4	148	1.88 (1.17–3.04)	0.0086	141	1.74 (1.06–2.84)	0.026
STAGE T						
2	241	1.45 (0.87–2.41)	0.15	239	1.32 (0.79–2.18)	0.29
3	204	1.55 (1.08–2.21)	0.015	204	1.54 (1.1–2.18)	0.013
4	38	2.41 (1–5.82)	0.045	39	2.29 (1.01–5.2)	0.043
STAGE N						
0	74	3.53 (1.04–11.94)	0.031	72	3.48 (1.03–11.79)	0.033
1	225	1.34 (0.89–2.02)	0.16	222	1.28 (0.87–1.89)	0.21
2	121	1.38 (0.85–2.25)	0.19	125	1.26 (0.79–2.02)	0.33
3	76	3.28 (1.46–7.4)	0.0026	76	2.64 (1.17–5.97)	0.016
1+2+3	422	1.48 (1.12–1.95)	0.0056	423	1.35 (1.05–1.74)	0.021
STAGE M						
0	444	1.47 (1.11–1.93)	0.0063	443	1.4 (1.07–1.82)	0.013
1	56	2.5 (1.14–5.49)	0.019	56	2.24 (1.01–4.97)	0.042
LAUREN CLASSIFICATION						
Intestinal	320	1.44 (1.05–1.99)	0.023	263	1.29 (0.85–1.94)	0.22
Diffuse	241	1.67 (1.17–2.4)	0.0048	231	1.78 (1.24–2.55)	0.0015
DIFFERENTIATION						
Poor	165	0.83 (0.56–1.24)	0.36	121	1.66 (0.93–2.98)	0.084

Abbreviation: N, number.

immune cells in STAD. Concretely, GSN was significantly correlated with infiltration level of B cell, CD8+ T cells, CD4+ T cells, macrophages, neutrophil and dendritic cells in TME (Figure 4A–C). Moreover, GSN was significantly correlated with tumor purity in STAD. Above all, the expression of GSN is associated with immune regulation disorder (Table 2).

GSN Expression in Different Gastric Cancer Cell Lines

Data results generated from the qRT-PCR analysis shows that GSN was down-regulated in several human gastric carcinoma cell lines. For Figure 5 expression, the BGC-823 was shown to be the lowest level, and after it the MKN-45 AGS and MGC-803. ($P < 0.01$). However, the specific reasons need further research.

Discussion

In this study, we describe the expression of GSN and its prognostic value in GC, and summarize the relevant knowledge about the immune features in gastric cancer. In short, GSN was down-regulated in GC tissues, and high expression GSN was related to longer survival. The GSN expression is related to tumor purity in STAD and significantly correlated with immune cell infiltration, especially the dendritic cells.

Understanding the mechanism of the gastric mucosal immunity in the development of gastric cancer may help us to search for new clinical diagnostic and therapeutic methods.²² In the human body, gastrointestinal mucosal is an important immune organ,²³ which can play its immune function in a layer-by-layer progressive mode through innate and adaptive immunity²⁴ and maintain the balance of microbe in an immune homeostasis mechanism.²⁵ However,

Table 2 Correlations Between GSN and Related Genes and Markers of Immune Cells

Description	Gene Markers	None		Purity	
		Cor	P-value	Cor	P-value
CD8+ T cell	CD8A	0.246	***	0.244	***
	CD8B	0.117	*	0.117	***
T cell	CD3D	0.179	***	0.17	***
	CD3E	0.22	***	0.217	***
B cell	CD2	0.192	***	0.185	***
	CD19	0.306	***	0.306	***
Monocyte	CD79A	0.303	***	0.29	***
	CD86	0.232	***	0.218	***
TAM	CD115 (CSF1R)	0.453	0e+00	0.439	***
	CCL2	0.363	***	0.345	***
M1 Macrophage	CD68	0.202	***	0.186	***
	IL10	0.295	***	0.282	***
M2 Macrophage	INOS (NOS2)	-0.091		-0.082	1.12e-01
	IRF5	0.343	***	0.337	***
Neutrophils	COX2(PTGS2)	0.093		0.071	1.67e-01
	CD163	0.34	***	0.324	***
Natural killer cell	VSIG4	0.355	***	0.355	***
	MS4A4A	0.356	***	0.34	***
Dendritic cell	CD66b (CEACAM8)	-0.018	7.18e-01	0	1.00e+00
	CD11b (ITGAM)	0.403	0e+00	0.391	***
Th1	CCR7	0.456	0e+00	0.462	***
	KIR2DL1	0.005	9.18e-01	0.015	7.66e-01
Th2	KIR2DL3	-0.062	2.08e-01	-0.073	1.55e-01
	KIR2DL4	-0.124	*	-0.13	*
Th17	KIR3DL1	0.047	3.43e-01	0.052	3.17e-01
	KIR3DL2	0.019	6.93e-01	0.03	5.57e-01
Tfh	KIR3DL3	-0.092		-0.064	2.14e-01
	KIR2DS4	-0.031	5.35e-01	-0.026	6.08e-01
Treg	HLA-DPB1	0.263	6e-08	0.251	7.56e-01
	HLA-DQB1	0.145	**	0.129	*
CD8+ T cell	HLA-DRA	0.154	**	0.141	**
	HLA-DPA1	0.0198	***	0.185	***
Th1	BDCA-1(CD1C)	0.515	***	0.54	***
	BDCA-4(NRP1)	0.542	0e+00	0.518	***
Th2	CD11c (ITGAX)	0.32	***	0.304	***
	T-bet (TBX21)	0.216	***	0.221	***
Th17	STAT4	0.268	***	0.27	***
	STAT1	0.012	8.11e-01	0.024	6.47e-01
Tfh	IFN- γ (IFNG)	-0.128	**	-0.124	**
	TNF- α (TNF)	0.08	1.05e-01	0.054	2.91e-01
Treg	GATA3	0.364	2.39e-14	0.376	***
	STAT6	0.319	2.87e-11	0.321	***
Th1	STAT5A	0.418	5.1e-19	0.415	***
	IL13	0.075	1.26e-01	0.089	
Th2	BCL6	0.549	4.65e-34	0.532	***
	IL21	0.027	5.8e-01	0.027	6.02e-01
Th17	STAT3	0.422	0e+00	0.406	***
	IL17A	-0.249	2.86e-07	-0.264	***
Treg	FOXP3	0.203	3.18e-05	0.198	***
	CCR8	0.277	9.61e-09	0.271	***
CD8+ T cell	STAT5B	0.563	0e+00	0.542	***
	TGF β (TGFB1)	0.598	1.32e-41	0.595	***

(Continued)

Table 2 (Continued).

Description	Gene Markers	None		Purity	
		Cor	P-value	Cor	P-value
T cell exhaustion	PD-1 (PDCD1)	0.195	6.76e-05	0.195	***
	CTLA4	0.061	2.16e-01	0.049	3.41e-01
	LAG3	0.07	1.53e-01	0.071	1.66e-01
	TIM-3 (HAVCR2)	0.241	7.2e-07	0.233	***
	GZMB	-0.125	*	-0.144	**

Note: P-value significant codes: 0≤***≤0.001≤**≤0.01≤*≤0.05.

a target with broad implications and developing novel therapeutic strategy.

Conclusions

In conclusion, our result is consistent with those reported that GSN may be a prognostic biomarker in gastric cancer, and the value of GSN in immune infiltrates is potential. Although all data just from online databases analysis and qRT-PCR results, the evidence still have highly authoritative and quite match expectations. That is, the expression of GSN was exactly downregulate and this change was closely related to various prognostic value in GC, especially the relevant knowledge

about the immune features. In that respect, we really believe GSN can open-up huge possibilities in gastric cancer.

Abbreviations

GSN, gelsolin; GC, gastric cancer; STAD, stomach adenocarcinoma; OS, overall survival; FP, first progression; PPS, post progression survival; TAM, tumor-associated-macrophage; TME, tumor microenvironment; DCs, dendritic cells; APC, antigen presenting cells.

Data Sharing Statement

The datasets set generated and/or analyzed during the current study are available in the TIMER (<https://cistrome.shinyapps.io/timer/>) and the human protein atlas (<https://www.proteinatlas.org/>) and Oncomine (<https://www.oncomine.org/resource/login.html>) repository.

Ethics Approval and Informed Consent

All data for this study are derived from publicly available databases, and the Institutional Review Board of The First Affiliated Hospital, Guangzhou University of Chinese Medicine has provided the confirmation and waived the need for ethical approval.

Consent for Publication

All authors have made significant contributions to the concept and design, data acquisition or data analysis and interpretation; participated in drafting articles or critically revised important knowledge content; finally approved the version to be published; and agreed to be responsible for all aspects of the work.

Author Contributions

All authors participated in the research design, acquisition and data analysis, writing and revising the manuscript, and

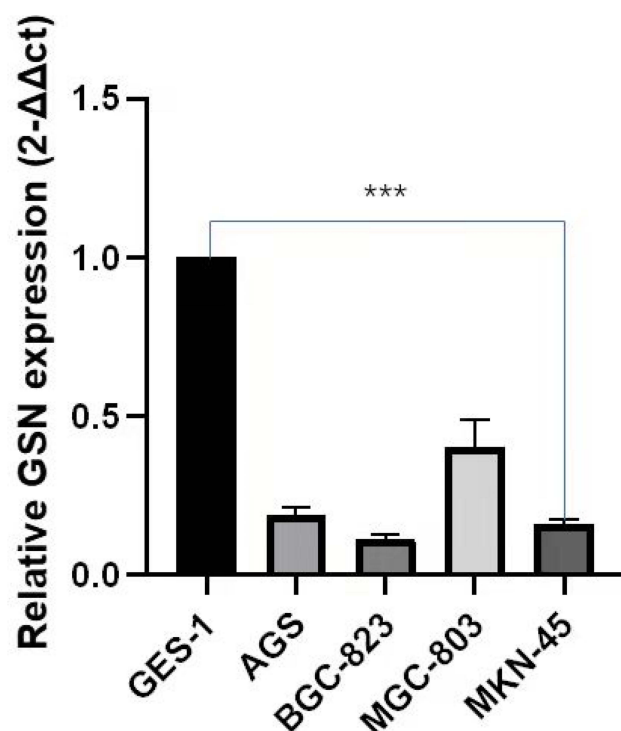


Figure 5 qRT-PCR of GSN expression in STAD cell lines and human normal gastric epithelial cell line GES-1. P-value significant codes: p≤***≤0.001.

reached a consensus on the journal to which the article was submitted, approved the final version for publication, and agreed to be responsible for all the content of the article.

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Disclosure

The authors report no conflicts of interest related to this paper.

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