

Glucose Transporter-1 Cooperating with AKT Signaling Promote Gastric Cancer Progression

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Objective: High expression of GLUT1 has been observed in numerous solid cancers, facilitating glucose consumption for supporting tumor cell survival. The altered metabolic activity is regulated by series of signaling pathways, including AKT signaling that acts as a key role in glucose metabolism and shows close correlation with the malignant transformation. In this study, we aimed to elucidate the effect of GLUT1 on gastric cancer (GC) and to explore the relation between GLUT1 and AKT signaling.

Materials and Methods: GLUT1, p-AKT, and p-S6k1 expression were investigated by immunohistochemistry and semi-quantitative analysis in 57 paired-GC samples. The relationship of GLUT1 with clinical indexes in GC tissues was investigated. The effects of GLUT1 on the prognosis of GC patients and the underlying mechanism involved were studied by subgroup analysis.

Results: In GC tissues, an obvious increase in GLUT1 expression was observed when compared with that of normal tissues ($P < 0.001$). Advanced clinicopathological factors (tumor size $P = 0.019$, invasion depth $P = 0.002$, lymph node metastasis $P < 0.001$, differentiation $P = 0.024$, neural invasion $P = 0.003$, and TNM staging $P = 0.001$) correlated with high GLUT1 levels. GLUT1 was an independent risk factor resulting in poor prognosis ($P = 0.002$, HR=5.132). GLUT1 increased the activation ratio of p-AKT ($P < 0.01$) and p-S6K1 ($P < 0.001$) in GC. The expression of p-S6K1 and GLUT1 was positively correlated. ($P = 0.001$, $R = 0.173$). The survival probability of GC patients with GLUT1(+)/p-S6K1(+) was worse when compared to that of GLUT1(+)/p-S6K1(-) or GLUT1(-)/p-S6K1(+) ($P < 0.001$).

Conclusion: High expression of GLUT1 facilitated GC progression, leading to poor prognosis. Overexpression of GLUT1 activated AKT-S6K1 axis, resulting in adverse outcomes of GC. GLUT1 is novel indicator of GC prognosis and GLUT1 targeted metabolic treatment that has potential therapeutic value.

Keywords: AKT, gastric cancer, GLUT1, S6K1

Introduction

Gastric cancer (GC) is the common gastrointestinal malignancy, and accounts for 8.2% of cancer-related deaths worldwide.¹

The prognosis of GC patients remains unsatisfactory, because of the low diagnostic rate of early GC. Many patients were preliminary diagnosed at advanced or metastatic stages. Intensive surgical efforts could improve the survival; however, chemotherapy is still indispensable in the treatment of GC. However, drug resistance during chemotherapy limits treatment efficacy.^{2,3}

Cancer cells display enhanced glucose metabolism and prefer to generate ATP via glycolysis instead of oxidative phosphorylation even in the presence of oxygen.⁴ The characteristic metabolic phenotype is known as aerobic glycolysis.⁵

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The glucose transporter (GLUT) family includes various homologous membrane proteins that transport glucose from the extracellular environment to the cytosol. Among the GLUT family, GLUT1 is the most widely expressed, and functions in basal glucose uptake.⁶ Elevated expression of GLUT1 is commonly observed in various types of malignancies.^{7–10} In GC, GLUT1 overexpression has been associated with higher stages of disease and inferior prognosis.^{10,12} Moreover, it has been found that GLUT1 promotes cell proliferation and metastasis in GC cells.¹³ Thus, GLUT1 may be a potential target for GC therapy. However, the underlying mechanism of action of how GLUT1 impacts cellular functions in GC remains unknown.

As one of the most commonly activated signaling pathways in cancer, the threonine-protein kinase (AKT) signaling pathway is crucial for a cellular activity, such as cell proliferation, survival, and differentiation, which is mainly mediated by ribosomal protein S6 kinase 1 (S6K1) downstream of AKT.^{14,15} Previous studies reported that AKT signaling plays a regulatory role in the surface expression of GLUT1.^{16,17} In addition, in a recent study, it was revealed that silencing of GLUT1 inhibited cell proliferation and promoted apoptosis by inactivating the AKT signaling pathway in GC cells.¹⁸ Although upregulation of the AKT signaling pathway has been frequently observed in GC, the effects of GLUT1 expression on AKT signaling has not yet been elucidated. In this study, we aimed to explore the mechanism of action between GLUT1 and AKT-S6K1 axis in GC, to identify a novel therapeutic target for GC treatment.

Materials and Methods

Patients and Tissue Specimens

A total of 57 patients were included in this study. All patients were diagnosed as having GC in the first affiliated Hospital of Soochow University (Suzhou, China) between 2008 and 2012 without artificial selection. Tissue samples from these patients including GC tissues and normal tissues were detected with immunohistochemistry (IHC).

Inclusion criteria: (a) Diagnosed as gastric adenocarcinoma by postoperative pathological analysis. No prior history of cancer; (b) Have not undergone any type of preoperative therapy, including neoadjuvant chemotherapy, radiotherapy, or other therapy; (c) Agreed to be followed up with unabridged clinical data; (d) Patients were informed about the details of the study and signed informed consent. The diagnosis criteria of clinical stages and pathological features of GC was consistent

with the criteria of the American Joint Commission on Cancer. Conduction of this study complied with the human subject regulations of the Soochow University and the Code of Ethics of the World Medical Association (Declaration of Helsinki). The study passed the review of the Research Ethics Committee of The First Affiliated Hospital of the Soochow University (Soochow, China).¹⁹

Immunohistochemistry

GLUT1, p-AKT, and p-S6K1 expression in tissue samples was determined by IHC. After excision, tissue samples were immediately fixed in formalin. Then, samples were paraffin-embedded, and cut into 5- μ m sections. IHC was performed as described in our previous study.¹⁹

The immunoreactive scores (IRSS) were the product of the scores of positively-stained cells and staining intensity. (percentage of positive cells: 0, <5%; 1, 5%-25%; 2, 25%-50%; 3, 50%-75%; 4, >75%; staining intensity: 0, negative; 1, weak; 2, moderate; 3, strong).

The IRSSs were classified by grade: negative (0–1), weakly positive (2–3), moderately positive (4–7) and strongly positive (8–12). For further studies, tissues were divided into negative (0–4) and positive (5–12). IHC staining was independently evaluated by two pathologists.

Statistical Analysis

Continuous variables are expressed as the mean \pm SD. The Student's *t*-test was applied for evaluating the difference in IHC scores between groups. Chi-square (χ^2) test or Fisher's exact test were performed for evaluating the effect of GLUT1 expression with the clinicopathologic index.

Patient's survival was evaluated by Kaplan-Meier survival analysis and compared by the Log rank test. Univariate analysis with Cox proportional hazard model revealed several significant risk factors. Then, significant risk factors underwent multivariate survival analysis. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 22.0 software (SPSS Inc, Chicago, IL, USA) and GraphPad prism 8. R program (version 3.6.1 for Windows) was used for cluster analysis and nomogram construction. Figures were created using Microsoft PowerPoint.

Results

Increased Expression of GLUT1 in Gastric Cancer

Diverse studies reported that anomalous GLUT1 expression was correlated with cancer development.^{20–25} GLUT1

expression in paired GC tissue samples was evaluated by IHC, and the IRS was introduced for semiquantitative analysis, estimating GLUT1 expression (Figure 1A). We found significantly increased GLUT1 expression in GC tissues when compared with para-cancerous tissues (Figure 1B). In addition, GLUT1 was also differentially expressed in cancer tissues as demarcated by tumor invasion depth, lymph node metastasis, and TNM staging (Figure 1B–E). We showed that GLUT1 expression was increased by deeper invasion (Figure 1C), lymph node metastasis (Figure 1D) and advanced TNM staging tissues (Figure 1E). Taken together, the above-mentioned results showed that high GLUT1 levels correlated with GC progression.

GLUT1 Promotes Cancer Progression in Gastric Cancer

Subsequently, the relationship between GLUT1 expression and clinicopathological parameters was investigated (Table 1). We found a higher GLUT1 positive ratio in GC tumors with a massive tumor size ($P=0.019$), advanced invasion depth ($P=0.002$), lymph node metastasis ($P<0.001$), poor differentiation ($P=0.024$), neural invasion ($P=0.003$), and an advanced TNM stage ($P=0.001$). However, no significant correlation was observed between GLUT1 expression and other parameters, including gender, age, and venous invasion ($P>0.05$). Given the elevated GLUT1 expression in GC tissues with advanced

clinicopathological parameters, we hypothesized that GLUT1 could facilitate the development of GC.

High GLUT1 Expression Results in Poor Prognosis in Gastric Cancer Patients

To extend our results, the influence of GLUT1 on overall survival (OS) of GC patients was examined. GC patients were divided to subgroups according to their GLUT1 expression level and OS curves were created analyzed. We found a significant decrease in survival of the group with GLUT1 positive results when compared with that of the GLUT1 negative group ($P<0.001$, Figure 2A).¹⁰

Subsequently, patients were discriminated with lymph node metastasis (LNM) (-), LNM (+), TNM I-II, and TNM III-IV and OS of patients in each group was evaluated according to GLUT1 expression. The results further confirmed that high GLUT1 expression contributed to poor prognosis of GC patients regardless of LNM ($P<0.001$, Figure 2B) or without LNM ($P=0.016$, Figure 2C) and classified into TNM I-II stage ($P<0.001$, Figure 2D). However, GLUT1 expression had no effect on the OS of GC patients with TNM III-IV stage ($P=0.212$, Figure 2E).

The univariate analysis showed several risk factors, including tumor size, invasion depth, lymph node metastasis, venous invasion, neural invasion, TNM stage, and GLUT1 expression, which related with poor prognosis (Table 2). In

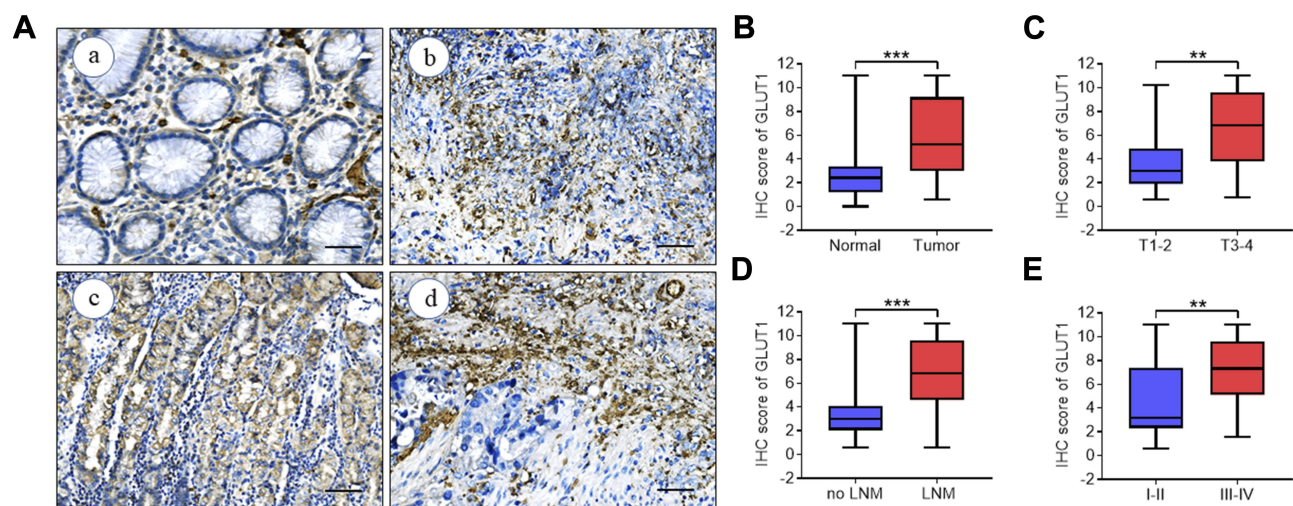


Figure 1 GLUT1 expression in GC tissues. (A) Representative immunohistochemistry (IHC) staining of GLUT1 in GC and adjacent normal tissues (scale bar = 100 μ m), (a) negative (b) weak (c) positive (d) strongly positive). (B–E) Nonparametric *t* test of IHC scores between (B) normal and tumor tissues, (C) T1-2 and T3-4, (D) no LNM and LNM and (E) TNM I-II and TNM III-IV (** $P<0.01$; *** $P<0.001$).

Abbreviations: T, tumor grading; LNM, lymph node metastasis; TNM, TNM staging.

Table 1 Association Between GLUT1 Expression and Clinicopathological Factors in 57 Patients with GC

	GLUT1		
	Negative	Positive	P
Gender			
Male	19	21	0.976
Female	8	9	
Age (years)			
≤60	13	11	0.381
>60	14	19	
Size (cm)			
≤5	23	17	0.019
>5	4	13	
Depth of invasion			
T1-2	15	5	0.002
T3-4	12	25	
Lymph node metastasis			
Negative	19	5	<0.001***
Positive	8	25	
Degree of differentiation			
Well	9	19	0.024
Poor	18	11	
Venous invasion			
Negative	20	18	0.260
Positive	7	12	
Neural invasion			
Negative	24	16	0.003
Positive	3	14	
TNM staging			
I-II	22	11	0.001
III-IV	5	19	

Note: ***P<0.001.

Abbreviations: GC, gastric cancer; TNM, tumor-lymph node-metastasis.

addition, multivariate analyses indicated that GLUT1 was an independent prognostic factor of survival (Table 2).

Subgroup Analysis of GLUT1 Expression with Prognostic Factors

As shown in Figure 3, GC patients with overexpressed GLUT1 had a worse prognosis when compared to patients with low GLUT1 levels regardless of age, gender, tumor size, invasion depth, lymph node metastasis, differentiation, venous invasion, neural invasion, and TNM staging (Figure 3).

In addition, high GLUT1 levels markedly reduced OS of GC patients with a tumor size <5cm (P<0.001),

negative neural invasion (P<0.001), and TNM I-II stage (P<0.001). However, no significant differences were observed in the respective matched group containing GC patients with a tumor size ≥5cm (P=0.283), positive neural invasion (P=0.153), and TNM III-IV stage (P=0.245), which could be attributed to a more advanced GC stage. The above-mentioned results confirmed that high expression of GLUT1 could be a poor prognosis index for GC, especially for early stage GC patients.

Overexpression of GLUT1 Activates AKT-S6K1 Axis in Gastric Cancer

Glucose metabolism is closely regulated by AKT signaling and S6K1 acts as one of the downstream components of AKT mediating protein transcription.²⁵ Activation of AKT-S6K1 axis promotes phosphorylation of AKT and S6K1.^{26,27} Therefore, we further explored the effects of GLUT1 on AKT-S6K1 in GC by evaluating p-AKT and p-S6K1 (Figure 4A and D). As shown in Figure 4, high expression of GLUT1 promoted the positive ratio of p-AKT (Figure 4B) and p-S6K1 (Figure 4E). Moreover, p-AKT and p-S6K1 were significantly overexpressed in GC tumors compared to normal tissues. Thus, we speculated that high GLUT1 expression promoted AKT-S6K1 axis activation, and that high level of p-AKT/p-S6K1 contributed to GC development (Figure 4C and F).

Cluster analysis revealed the significant difference in IHC scores of GLUT1 and p-AKT between GC tumors and normal tissues (Figure 5A). Normal tissue mainly collects in Cluster 1, whereas tumor tissue mainly collects in Cluster 2 (Figure 5B). Furthermore, correlation analysis showed a significant positive correlation between IHC scores of GLUT1 and p-S6K1 in GC tissues (Figure 5C). OS curves of GC patients in subgroups based on p-S6K1 and GLUT1 expression confirmed the influence of p-S6K1 on GC patients. Our data showed that GC patients with p-S6K1(+) had a reduced OS to p-S6K1(-) (Figure 5D). Although GC patients with GLUT1(+)/p-S6K1(+) showed a worse prognosis to anyone low (GLUT1(-)/p-S6K1(+) or GLUT1(+)/p-S6K1(-), Figure 5E), we observed a similar survival probability in GLUT1(+)/p-S6K1(-) and GLUT1(+)/p-S6K1(+) groups, thereby indicating that GLUT1 was the dominant factor resulting in a poor OS (Figure 5F). The above-mentioned variables were integrated in a nomogram, showing the prediction of the 3-year and 5-year survival probability (Figure 6). The nomogram confirmed the massive impetus of GLUT1(+)/p-S6K1(+)

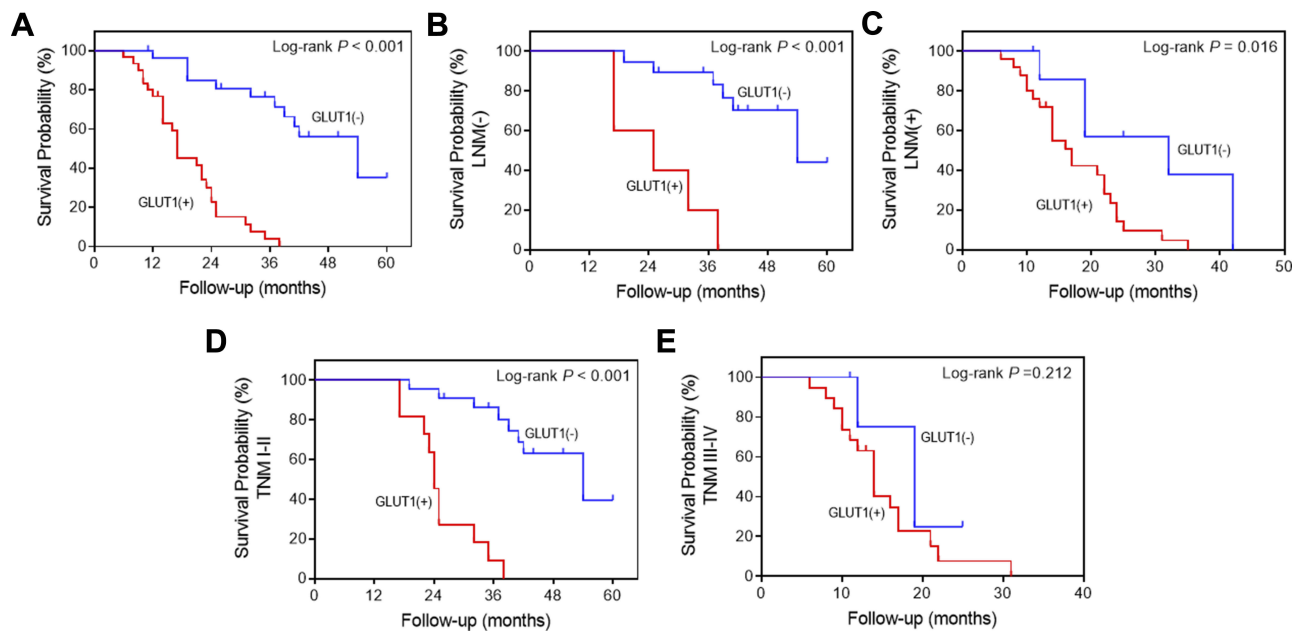


Figure 2 Kaplan-Meier survival analysis of postoperative GC patients. (A) Overall survival (OS) curves of 57 postoperative patients according to positive or negative GLUT1 expression. OS curves of postoperative patients in subgroups demarcated with lymph node metastasis (B), without lymph node metastasis (C), TNM I - II (D) or TNM III-IV (E) according to GLUT1 expression.

to poor prognosis, which was mainly GLUT1(+) mediated because of the analogous rank between GLUT1(+)/p-S6K1 (+) and GLUT1(+)/p-S6K1(-) (Figure 6).

Discussion

Although the treatment of GC has achieved significant progress, over 780,000 deaths are attributed to GC annually.²⁸ The most important factor is that most patients were initially diagnosed with advanced GC. For advanced GC, traditional adjuvant chemotherapy is essential, however drug resistance and side effects along with treatment

significantly restricted curative effects.^{29,30} Novel strategies for advanced GC patients are emerging, including metabolism-targeted cancer therapy, which showed extensive application value.³¹⁻³⁶

High level of glycolysis and glucose uptake is a significant hallmark in cancer and GLUT1 is the main rate limiting step of glucose uptake.^{37,38} Existing studies have proven that elevated GLUT1 expression is observed in most solid cancers.^{4,39-42}

In our study, we further demonstrated the aberrant expression of GLUT1 in GC tissues, resulting GC progression. In

Table 2 Results of Univariate and Multivariate Analyses of Patients' Survival in Gastric Cancer by Cox's Proportional Hazard Model

Factor	Univariate Analysis			Multivariate Analysis		
	HR	95.0% CI	p	HR	95.0% CI	p
Gender (Male/Female)	1.134	0.586–2.196	0.708			
Age (≤60 or >60 years)	1.208	0.644–2.267	0.555			
Size of cancer (≤5 or >5 cm)	5.709	2.743–11.885	<0.001***	2.236	0.898–5.569	0.084
Depth of invasion (T1-2/T3-4)	5.631	2.464–12.867	<0.001***	2.284	0.791–6.598	0.127
Lymph node metastasis (negative/positive)	6.772	3.065–14.962	<0.001***	2.753	0.944–8.031	0.064
Degree of differentiation (poor/well)	0.555	0.299–1.032	0.063			
Venous invasion (negative/positive)	2.758	1.466–5.190	0.002	2.099	1.012–4.355	0.046
Neural invasion (negative/positive)	2.085	1.072–4.054	0.030	0.972	0.472–2.002	0.938
TNM stage (I-II/III-IV)	9.650	4.247–21.929	0.001**	1.517	0.475–4.841	0.482
GLUT1 expression (low/high)	9.903	4.106–23.888	<0.001***	5.132	1.846–14.265	0.002

Notes: **P<0.01; ***P<0.001

Abbreviations: GC, gastric cancer; TNM, tumor-lymph node-metastasis

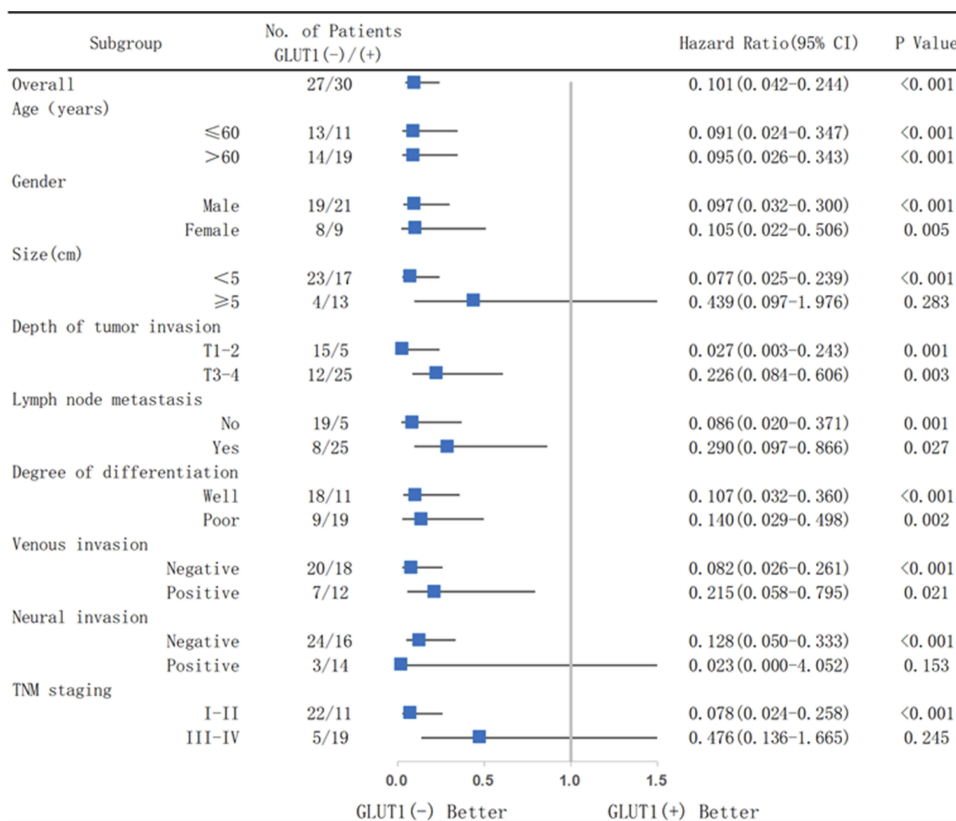


Figure 3 Analysis of the effects on survival of GC patients in subgroups according to GLUT1 expression. Patients were divided into groups by age, gender, tumor size, depth of tumor invasion, lymph node metastasis, degree of differentiation, venous invasion, neural invasion, and TNM staging.

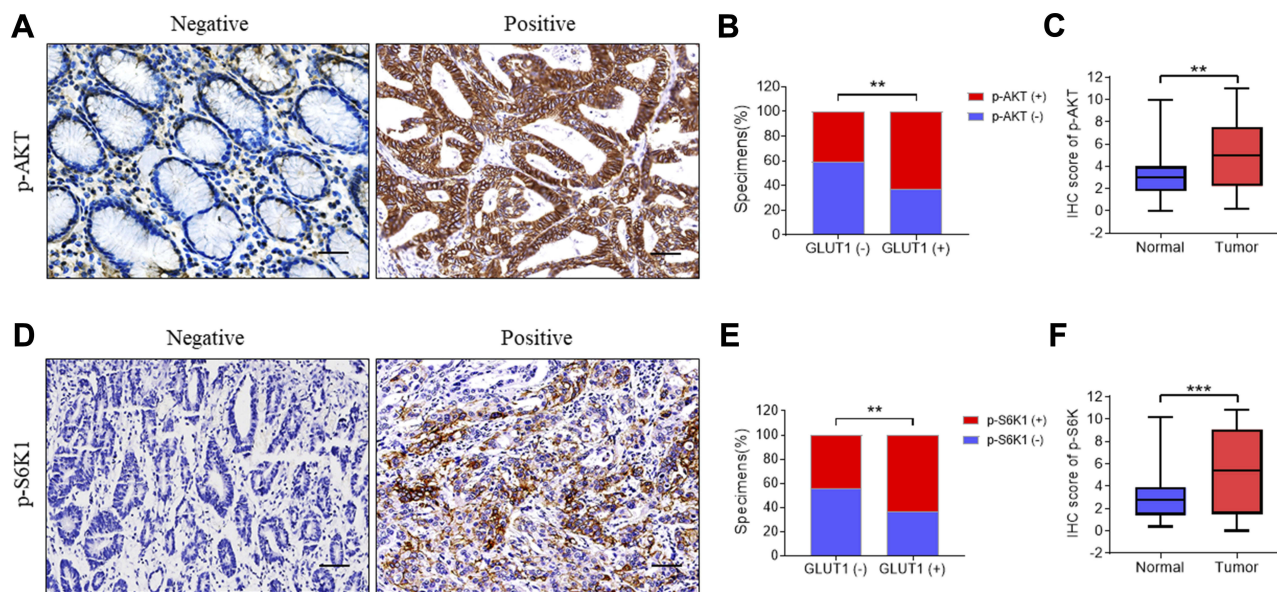


Figure 4 Immunohistochemistry of p-AKT and p-S6K1 correlated with GLUT1 expression in GC tissues. Expression of (A) p-AKT and (D) p-S6K1 were evaluated in gastric cancer (GC) tissues by immunohistochemistry (IHC) (scale bar=100µm). Expression analysis of (C) p-AKT and (F) p-S6K1 in normal and GC tissues. Proportion analysis of (B) p-AKT (-)/p-AKT (+), (E) p-S6K1 (-)/p-S6K1 (+) in GLUT1 (-)/(+) tissues. (**, $P<0.01$; ***, $P<0.001$; —, negative; +, positive).

addition, high GLUT1 expression closely correlated with advanced clinicopathological parameters, including tumor size, invasion depth, lymph node metastasis, neural invasion,

and TNM staging. However, poorly differentiated tumors seemed to have a reduced positive ratio of GLUT1 when compared to that of well differentiated tumors.

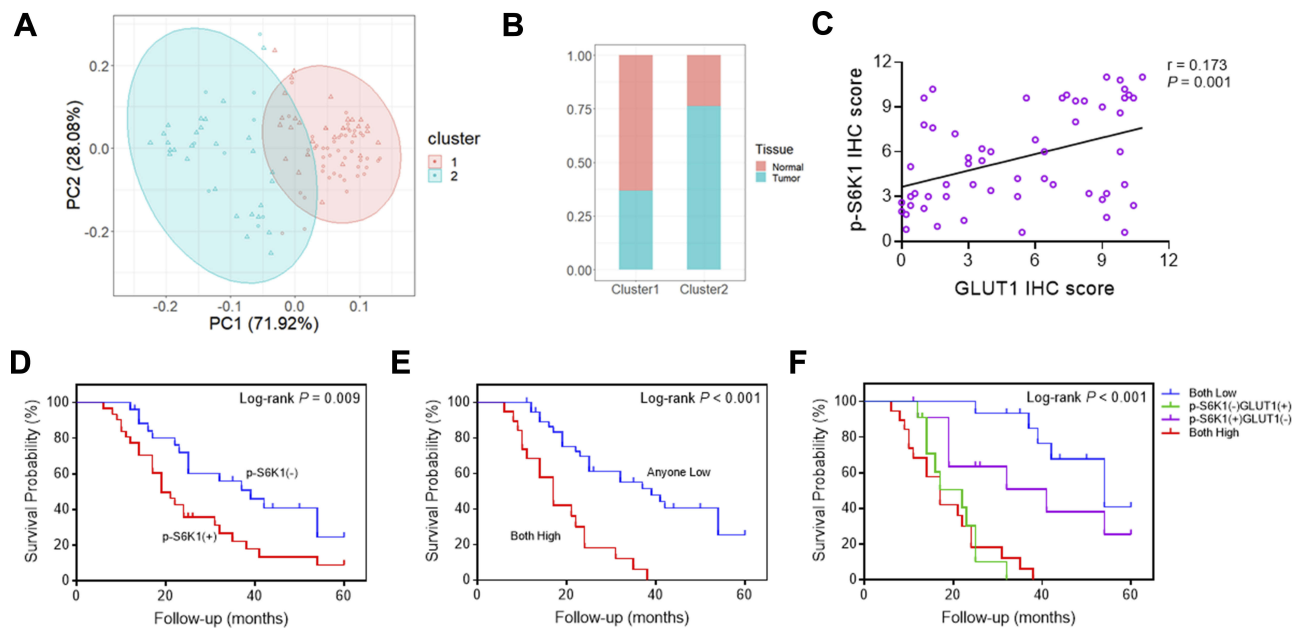


Figure 5 Correlation between GLUT1 and S6K1 expression in gastric cancer tissues. **(A)** Stratification of 57 pairs gastric cancer (GC) tissues and normal tissues into cluster 1 (RED) and cluster 2 (green) according to GLUT1 and S6K1 immunohistochemistry (IHC) staging scores. **(B)** The percentage of normal and tumor tissues in each cluster. **(C)** Correlation analysis of p-S6K1 and GLUT1 IHC score in GC tissues ($p=0.001$, $R=0.173$). **(D)** OS curves of GC patients according to negative or positive p-S6K1 expression. **(E)** OS curves of GC patients with GLUT1(+)/p-S6K1(+) or GLUT1(-)/p-S6K1(+) and GLUT1(+)/p-S6K1(-). **(F)** OS curves of GC patients with p-S6K1(-)/GLUT1(-), p-S6K1(-)/GLUT1(+), p-S6K1(+)/GLUT1(-) and p-S6K1(+)/GLUT1(+). (—, negative; +, positive).

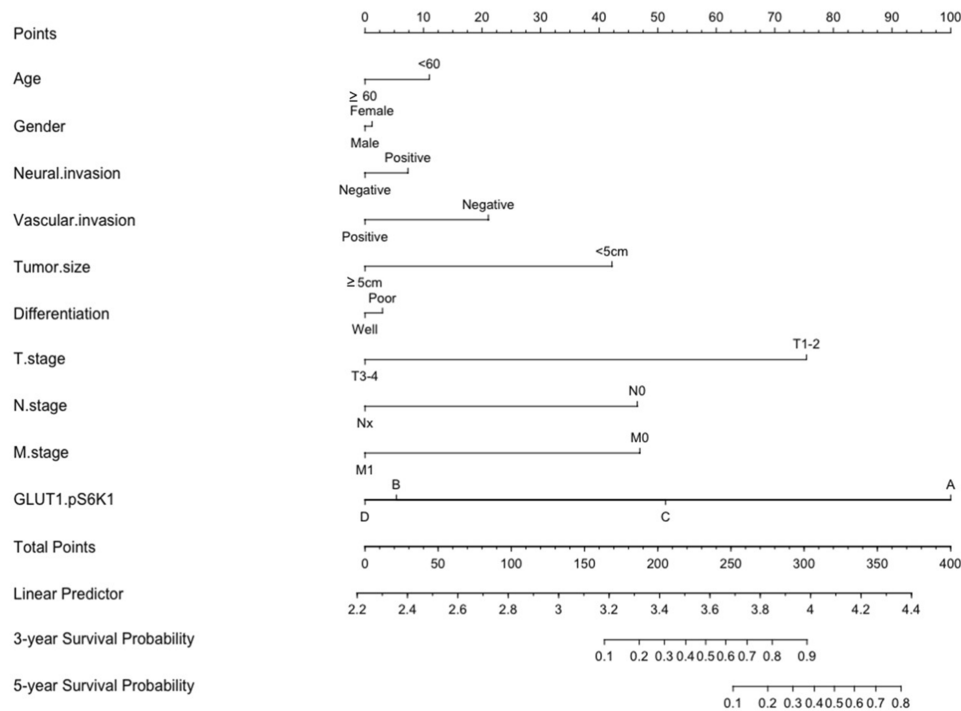


Figure 6 Nomogram for the predication of survival probability of gastric cancer patients. A total of 10 variables were involved, the points of every variable correspond to the scale in the first row. The summary of variable points projected on the TOTAL POINTS scale corresponds to the 3/5-year survival probability scale. (The scale of GLUT1.pS6K1: A= p-S6K1(-)/GLUT1(-); B= GLUT1(+)/p-S6K1(-); C= p-S6K1(+)/GLUT1(-); D= p-S6K1(+)/GLUT1(+)).

Although our survival analysis confirmed that increased GLUT1 expression shortened the survival time of GC patients, which was in line with previous studies,¹²

our subgroup analysis showed that the downtrend of survival probability of early GC patients without lymph node metastasis or TNM staging I - II was more apparent when

compared with that of advanced GC patients, resulting from GLUT1 overexpression. Thus, our results indicated that high GLUT1 expression in the early GC stage could be meaningful for therapeutic intervention. Multivariate analyses showed that GLUT1 was an independent prognostic factor for survival of GC. Taken together, the above-mentioned results revealed a critical role of GLUT1 in GC development.

In general, glucose metabolism is closely mediated by AKT signaling in response to insulin receptor stimulation, which promotes glucose transporter expression and translocation from the cytoplasm to the plasma membrane.^{42,43} It has been established that AKT is vital in the transformation of the Warburg effect in cancer cells.⁴⁴ Moreover, overactivated AKT signaling is commonly found in cancer, which facilitates cancer cell proliferation and survival.⁴⁵ S6K1 acts as the core effector protein downstream of AKT, mediating protein transcription and positively correlates with the activity of AKT signaling.^{46,47} However, whether activation of AKT signaling results in aberrant GLUT1 expression in GC still needs to be elucidated.

Here, we explored the interaction between GLUT1 and AKT-S6K1 in situ of GC tissues rather than in vivo or animal models as shown in other studies.⁴⁸ We showed that p-AKT and p-S6K1 expression were significantly increased in tumor tissues when compared to normal tissues. In addition, high GLUT1 levels promoted p-AKT/p-S6K1 expression in GC tumor tissues. We hypothesized that the activation of AKT-S6K1 axis attributed to high glucose levels in the cytoplasm, thereby activating glucose consumption and biosynthesis mediated by AKT signaling.²⁶ Furthermore, an apparent positive association between GLUT1 and p-S6K1 indicated that the AKT-S6K1 axis plays a role in the effect of GLUT1 on GC.^{46,49–51}

Subgroup survival analysis of GC patients based on p-S6K1 and GLUT1 expression showed that GLUT1 overexpression could be the governing factor upstream of AKT-S6K1. Because GC patients with p-S6K1(+) had worse prognosis than those with p-S6K1(-), GLUT1(+)/p-S6K1(+) also showed a lower survival probability to patients who showed a low negative expression of GLUT1 or p-S6K1. However, a survival probability of GLUT1(+)/p-S6K1(-) group was similar to GLUT1(+)/p-S6K1(+). The nomogram also showed a close rank between GLUT1(+)/p-S6K1(-) and GLUT1(+)/p-S6K1(+). The results indicated that high GLUT1 expression was the major risk of poor prognosis, which was independent of p-AKT and p-S6K1 expression. Therefore, we confirmed high expression of GLUT1 as

a representative indicator for a poor prognosis of GC as a supplement to related studies.^{10,12,52}

Instead of serving as the downstream of AKT-S6K1 axis activation, overexpressed GLUT1 acted as the upstream of AKT-S6K1 and promoted the activation of AKT signaling. However, the retroaction of AKT signaling on GLUT1 should be investigated and considered. In addition, the single center nature of the retrospective study with a limited sample capacity impaired the power of the study. We will address the above-mentioned limitations in our subsequent study.

In summary, we revealed that the anomalous increase of GLUT1 acted as an independent risk factor in GC tissues, contributing to advanced clinicopathological parameters and poor prognosis. Early stage GC was more sensitive to high GLUT1 expression and related to poor progression. GLUT1 was the dominant factor cooperating with AKT-S6K1 axis, thereby promoting GC progression.⁵³ Thus, GLUT1 was found to be a representative metabolic-associated prognostic index and estimable target for GC therapy especially for early stage patients.

Acknowledgments

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Disclosure

The authors declare no conflicts of interest in this work.

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