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Review Article

Potential Role of Glucose Transporter-1 Expression in Gastric Cancer: A Meta-Analysis and Systematic Review

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Abstract

Background: Glucose transporter-1 (GLUT-1) has been differentially expressed in various malignancies including gastric cancer (GC). Several previous meta-analyses of GLUT-1 have some significant limitations, such as researching the association between GLUT-1 and various cancer types with no specificity, not studying clinicopathological parameters with GLUT-1, existing conspicuous heterogeneity and so forth. Therefore, we performed a meta-analysis to evaluate the association between GLUT-1 expression and survival of gastric cancer patients, as well as clinicopathological characteristics.

Methods: We systematically searched PubMed, Embase, Web of Science and China National Knowledge Infrastructure for relevant studies in accordance with the applicable criteria up to Aug 2017. Hazard ratios (HRs) and odds ratios (ORs) with their 95% confidence intervals (CIs) were used as the effective measures.

Results: A total of 13 studies involving 1972 patients were included in this meta-analysis. The results demonstrated that there was a significant association between GLUT-1 expression and overall survival (OS) (HR=1.45, 95% CI=1.13-1.87) or disease-free survival (DFS) (HR=2.18, 95% CI=1.46-3.25). Moreover, GLUT-1 expression was significantly correlated with worse tumor nodes metastases (TNM) stage (OR=0.34, 95% CI=0.28-0.43), presence of lymph node metastasis (OR=2.88, 95% CI=1.34-6.19), intestinal type of Lauren classification (OR=3.84, 95% CI=2.57-5.74) and invasion of serosa (OR=0.25, 95% CI=0.18-0.35).

Conclusion: Our meta-analysis showed that GLUT-1 was significantly correlated with poor OS and DFS in gastric cancer. Additionally, GLUT-1 was also a potential prognostic indicator of aggressive clinicopathological parameters in gastric cancer.

Keywords: Gastric cancer; Glucose transporter-1; Meta-analysis; Prognosis

Introduction

Gastric cancer (GC) is the fourth most prevalent cancer and third leading cause of cancer-related death worldwide. There has been an estimated 28,000 new cases and 10,960 deaths occurred in the United States in 2017. In general, the incidence rates are highest in Eastern Asia, particularly in Korea, Mongolia, Japan and China (1, 2). Although the clinical prognosis for GC has been improved by the development of early detection and adjuvant chemo-radiotherapy, the 5-yr overall survival rate (OS) for GC patients is still less than 25% worldwide (3). Therefore, it is important to identify effective biomarkers for prognosis of GC and provide clinical treatment strategies for patients.

In most cancer cells, the rate of glucose uptake is significantly elevated, and oxidative phosphorylation in mitochondria is often decreased compared to normal cells (4). It is known that the Warburg effect was put forward by Otto Warburg in the 1920s (5). Glucose transporter-1 (GLUT-1) is the first identified member of facilitative glucose transporters, which belongs to the solute carrier 2A family, allowing the energy-independent transport of glucose across the hydrophobic cell membrane and down its concentration gradient (6). Previously, GLUT-1 has been reported to be associated with various cancers, including pancreatic (7), colorectal (8), breast (9), endometrial (10) and neuroblastic cancers (11). Many studies reported that GLUT-1 expression was connected with clinicopathologic characteristics of GC, but no meta-analysis has been conducted to investigate the correlation between GLUT-1 expression with the survival and clinical features of GC patients. However, some meta-analyses (12-17) had researched the relationship between GLUT-1 and other various type of cancers and all of them existed some significant problems.

Therefore, we performed the current meta-analysis to investigate the survival and clinical role of GLUT-1 expression in GC.

Methods

Information source and search strategy

The meta-analysis was carried out in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (18). A systematic search was performed in PubMed, Web of Science, Embase and China National Knowledge Infrastructure (CNKI) up to Aug 31th, 2017. The following terms were applied to search for relevant researches in the databases: ("glucose transporter 1" or "GLUT-1" or "SLC2A1") and ("gastric cancer" or "gastric carcinoma" or "stomach neoplasms").

Inclusion and exclusion criteria

The inclusion criteria in this meta-analysis were as follows: 1) human-based studies; 2) studies reporting the correlation between GLUT-1 expression and survival outcomes or clinical features; 3) studies where the diagnosis of GC was conformed via pathology reports; 4) studies measuring GLUT-1 expression via immunohistochemistry (IHC); 5) studies published as full-text articles in English or Chinese; 6) studies where the hazard ratios (HRs) and 95% confidence intervals (CI) were reported or could be acquired by communicating with the author. If the studies met the following selection criteria, they would be excluded based on the following exclusion criteria: 1) meeting abstracts, case reports, reviews, meta-analysis and animal studies; 2) studies lacking necessary data for calculation; 3) studies not using IHC to detect GLUT-1.

Data extraction and quality assessment

Two independent investigators (TJX and ZY) extracted the information and decided on the basic characteristics and variables to include through discussion. The following data were collected: first author's name, year of publication, study country, numbers of cases, age, sex, GLUT-1 detection methods, treatment methods, clinicopathological parameters, multivariate analysis data for OS and univariate analysis data for disease-free survival (DFS). The Newcastle-Ottawa Scale (NOS) (19) was applied to assess the quality of each included study. The NOS criteria included three aspects: 1) selection (4 stars), 2) comparability (2 stars), 3) outcome (3 stars). Scores based on NOS of 1-3, 4-6 and 7-9 were defined as low-, intermediate-, and high-quality studies, respectively. All disagreements were discussed and resolved with consensus.

Statistical analysis

The meta-analysis was performed by using Stata/SE 14.0 (Stata Corp, TX). Hazard ratios (HRs) and 95% CIs were used to assess the relationship between the GLUT-1 expression, OS, and DFS in GC patients. Heterogeneity was evaluated by Chi-squared and I-squared tests. If the $I^2 < 50\%$, the fixed-effect model was applied, which meant no significant heterogeneity. Oth-

erwise, the random-effect model was used. Odds ratios (ORs) and 95% CI were utilized to estimate the relevance of GLUT-1 and clinical features. Publication bias was assessed by Begg's test and Egger's test. $P<0.05$ was regarded as statistically significant.

Results

Studies selection and characteristics

Overall, 181 records were identified by searching the databases as described in the methods. After discarding duplicated records, 126 records were left for further screening, of which 102 records were removed by title/abstract inspection. In the remaining 24 records, 12 studies were excluded due to being a meeting abstract/review/case report (n=8), lacking necessary data (n=2) and no full text (n=1) after assessment by full-text reading. Consequently, 13 studies (20-32) published from 2000 to 2017 were included in the meta-analysis. The search and selection process is described in Fig. 1. These studies included 1972 participants, and all studies used immunohistochemistry (IHC) to detect GLUT-1. Among the studies, three (21, 27, 30) including 960 patients, compared GLUT-1 and OS, and one (32), including 215 patients, compared GLUT-1 of DFS. Newcastle-Ottawa Scale scores ranged from 6 to 8, with an average of 6.85. The basic characteristics of included studies are demonstrated in Table 1.

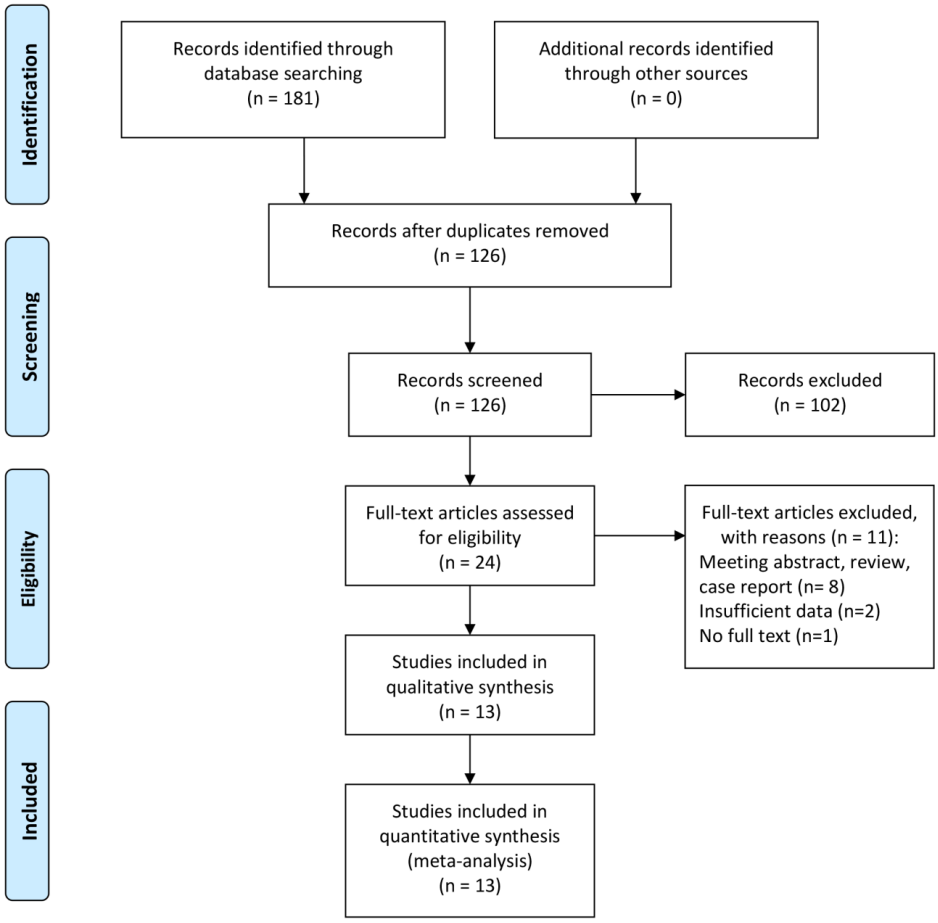

Fig. 1: Flow diagram for articles included in this meta-analysis

GLUT-1 and overall survival

The connection between the expression of GLUT-1 and OS were reported in 3 studies (21, 27, 30), which included a total of 960 participants. Due to no significant heterogeneity (I-squared=0.0%, *P*=0.765), a fixed-effects model was used (Table 2). The results showed that there was a significant correlation between GLUT-1 and OS in GC (Hazard ratio [HR] =1.45, 95% confidence interval [CI] =1.13-1.87, *P*=0.004; Table 2, Fig. 2A).

Table 1: Basic information of included studies in this meta-analysis

Study	*Year*	*Country*	*No. of patient*	*Sex (M/F)*	*Age median (range)*	*Method*	*NOS score*	*Estimate (95% CI)*
Kim	2000	Korea	65	NR	56(26-79)	IHC, RT-PCR	6	Lymph node metastasis: 0.670(0.119-3.764) Lauren classification: 9.000(1.758-46.087)
Kawa-mura	2001	Japan	617	374/243	60.5(27-88)	IHC	7	Depth of invasion: 0.350(0.041-3.015) OS: 1.410(1.039-1.914) TNM stage: 0.294(0.202-2.426) Lymph node metastasis: 16.479(10.967-24.761)
Li	2008	China	52	30/22	60.06(27-88)	IHC	6	Depth of invasion: 0.237(0.163-0.345) TNM stage: 0.249(0.065-0.957)
Wei	2009	China	79	NR	NR	IHC	8	Lymph node metastasis: 12.375(2.862-53.510) Sex: 1.232(0.348-4.359) Differentiation: 4.018(1.044-15.457) TNM stage: 0.242(0.084-0.698)
Zhang	2010	China	120	88/32	57(31-82)	IHC	6	Lymph node metastasis: 2.033(0.510-8.101) Differentiation: 0.596(0.208-1.705) TNM stage: 0.278(0.123-0.624)
Alakus	2010	Germany	35	28/7	58.7(32-87)	IHC	6	Lymph node metastasis: 3.045(1.366-6.789) Differentiation: 1.892(0.864-4.142) Lauren classification: 16.500(1.767-154.071)
Chen	2012	China	120	87/33	63.5(39-82)	IHC	6	Differentiation: 0.152(0.027-0.850) TNM stage: 0.298(0.136-0.657) Lymph node metastasis: 6.370(2.242-18.099) Sex: 0.867(0.381-1.971) Differentiation: 4.193(1.934-9.091)
Jung	2013	Korea	193	123/70	NR	IHC	8	Age: 1.034(0.503-2.129) Depth of invasion: 0.289(0.127-0.656) OS: 1.262(0.577-2.758) TNM stage: 0.403(0.216-0.752) Lymph node metastasis: 2.176(1.216-3.892) Lauren classification: 2.246(1.186-4.252) Sex: 0.701(0.388-1.267) Differentiation: 0.675(0.378-1.204)
Berlth	2015	Germany	124	93/31	66.6(19-85)	IHC	8	Age: 0.458(0.254-0.827) TNM stage: 0.541(0.249-1.177) Lymph node metastasis: 2.547(1.151-5.637) Lauren classification: 3.238(1.493-7.022) Sex: 1.542(0.678-3.506) Differentiation: 0.822(0.404-1.671)
Liu	2016	China	120	NR	68.7(53-86)	IHC	6	TNM stage: 0.340(0.157-0.738) Lymph node metastasis: 2.314(1.046-5.120) Differentiation: 2.489(1.122-5.521)
Schlosser	2017	Germany	150	114/36	64(NR)	IHC	8	OS: 1.731(0.988-3.033) TNM stage: 0.712(0.320-1.583) Lymph node metastasis: 0.361(0.150-0.865) Lauren classification: 7.321(3.009-17.812)
Yang	2017	China	82	42/40	64(19-77)	IHC	6	TNM stage: 0.293(0.095-0.905) Lymph node metastasis: 3.409(1.154-10.069) Sex: 1.067(0.389-2.923) Differentiation: 3.200(1.036-9.887)
Sun	2017	China	215	135/80	NR	IHC	8	DFS: 2.18(1.46-3.26)

Abbreviations: IHC, immunohistochemistry; RT-PCR, reverse transcription polymerase chain reaction; NR, not report; OS, overall survival; DFS, disease-free survival; NOS, Newcastle-Ottawa Scale

Table 2: Results of correlation of GLUT-1 expression with OS, DFS and clinicopathological parameters

Outcome	*No. of studies*	*Estimate (95% CI)*	P value	Heterogeneity	
				I^2 (%)	P_h
OS	3	1.45(1.13-1.87)	0.004	0	0.765
DFS	1	2.18(1.46-3.46)	<0.001	-	-
Clinicopathological parameters					
TNM stage (I + II vs. III+ IV)	9	0.33(0.26-0.42)	<0.001	0	0.746
Lymph node metastasis (yes vs. no)	10	2.91(1.25-6.77)	0.013	89.9	<0.001
Lauren classification (intestinal vs. diffuse)	4	5.39(2.18-13.35)	<0.001	59.6	0.060
Sex (male vs. female)	4	0.84(0.56-1.27)	0.407	0	0.817
Differentiation (poor vs. moderate/well)	8	1.52(0.78-2.99)	0.220	76.3	<0.001
Age (<60 vs. ≥60)	2	0.67(0.30-1.48)	0.324	65.9	0.087
Depth of invasion (no serosa vs. serosa)	3	0.25(0.18-0.35)	<0.001	0	0.866

Abbreviations: CI, confidence interval; OS, overall survival; DFS, disease-free survival

GLUT-1 and disease-free survival

There was only one study (32) with 215 patients reporting the GLUT-1 expression and DFS. The HR was 2.18, 95% CI=1.46-3.26 and *P*<0.001 (Table 2). There was no need to make the forest plot because this is the only one study. According to the result, there was a significant association between GLUT-1 expression and DFS in GC.

GLUT-1 and clinicopathological parameters

Twelve studies (20-31) reported the association between GLUT-1 and clinical features. A total of seven clinicopathological features were investigated, including TNM stage (I + II vs. III+ IV), lymph node metastasis (yes vs. no), Lauren classification (intestinal vs. diffuse), sex (male vs. female), differentiation (poor vs. moderate/well), age (<60 vs. ≥60) and depth of invasion (no serosa vs. serosa). The results (Table 2) illustrated that GLUT-1 expression had significant correlations with worse TNM stage (n=10, OR=0.34, 95% CI=0.28-0.43, *P*<0.001; Fig. 2B), presence of lymph node metastasis (n=11, OR=2.88, 95% CI=1.34-6.19, *P*=0.007; Fig. 2C), intestinal type of Lauren classification (n=5, OR=3.84, 95% CI=2.57-5.74, *P*<0.001; Fig. 2D) and invasion of serosa (n=3, OR=0.25, 95% CI=0.18-0.35, *P*<0.001; Fig. 2H). However, the results (Table 2) demonstrated no significant correlations between GLUT-1 expression and other clinical features including sex (n=5, OR=0.95, 95% CI=0.66-1.37, *P*=0.785; Fig. 2E), differentiation (n=9, OR=1.41, 95% CI=0.78-2.57, *P*=0.255; Fig. 2F) and age (n=2, OR=0.67, 95% CI=0.30-1.48, *P*=0.324; Fig. 2G).

Publication bias

Begg's test (33) and Egger's test (34) were used to evaluate possible publication bias. For OS, the *P* values for Begg's test and Egger's test were 1.000 and 0.916 (Fig. 3). For DFS, there was no need to carry out the Begg's test or Egger's test because there was only one study in DFS. For clinicopathological parameters, the *P* values of Begg's test and Egger's test were 0.721 and 0.748 for TNM stage, 0.755 and 0.093 for lymph node metastasis, 0.221 and 0.091 for Lauren classification, and 1.000 and 0.235 for depth of invasion, respectively. The results showed that there was no evidence of significant publication bias of the meta-analysis, therefore the results above were statistically reliable.

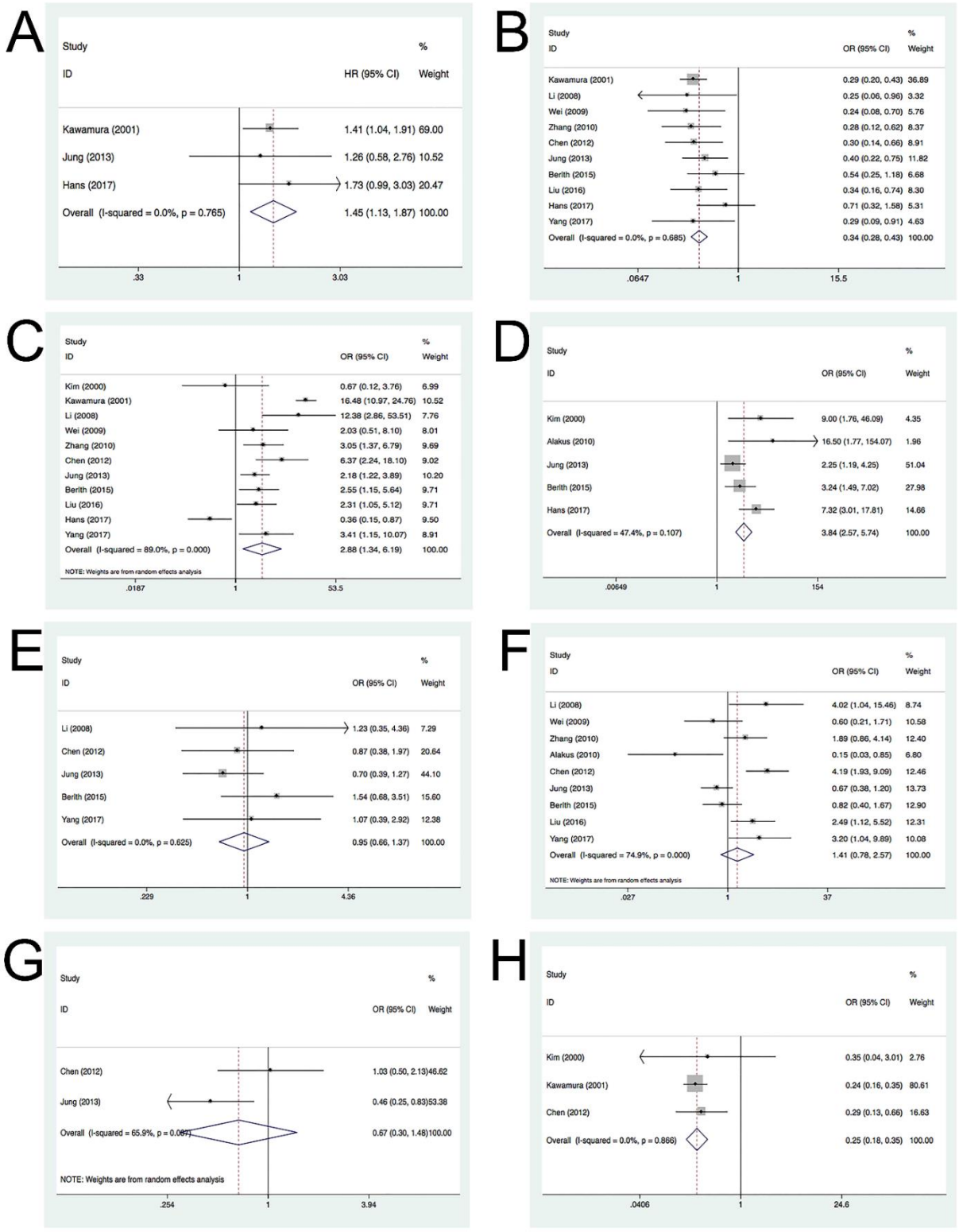

Fig. 2: Forest plot for the relationship of GLUT-1 with OS and clinicopathological parameters. A. overall survival; B. TNM stage; C. lymph node metastasis; D. Lauren classification; E. sex; F. differentiation; G. age; H. depth of invasion

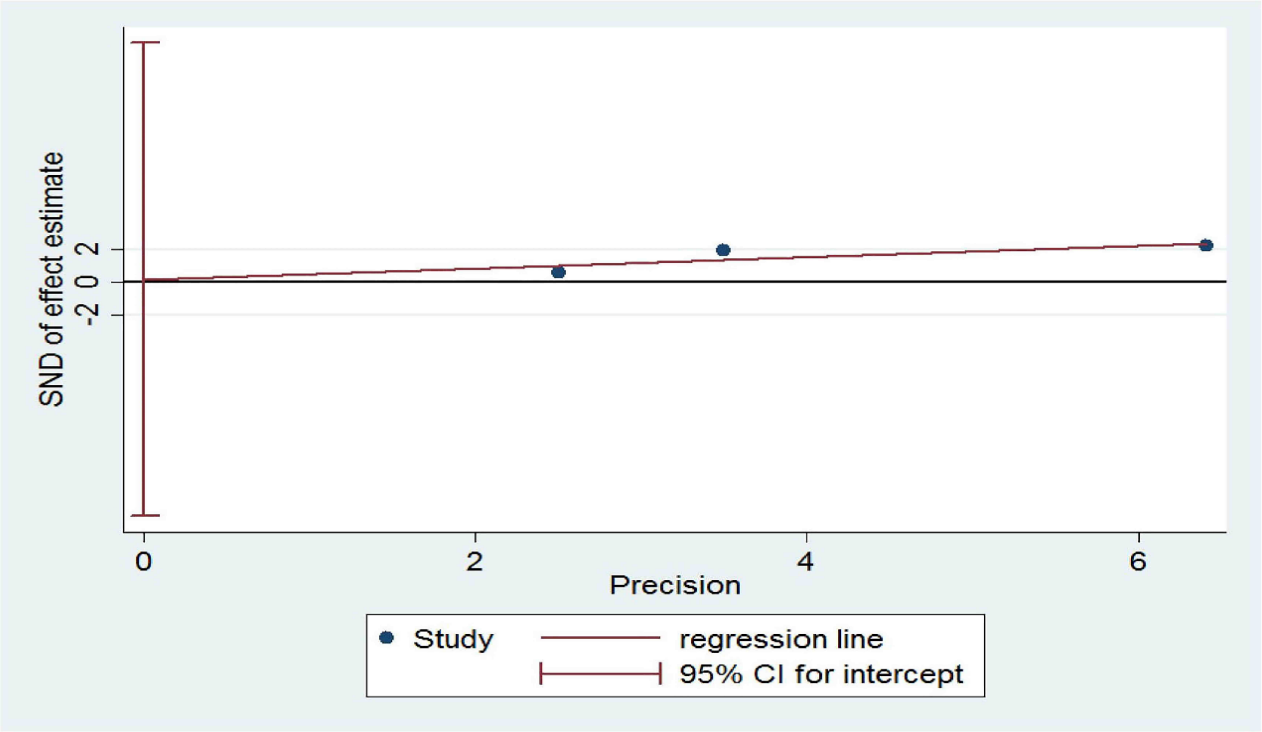

Fig. 3: Publication bias in the meta-analysis. Egger's test for OS

Discussion

The results of our meta-analysis demonstrated that GLUT-1 was associated with poor OS and DFS in GC. Moreover, GLUT-1 expression was significantly correlated with worse TNM stage, presence of lymph node metastasis, intestinal type of Lauren classification and invasion of serosa. These results suggested that GLUT-1 was a promising indicator for shorter OS, DFS and aggressive clinicopathological parameters.

GLUT-1, a member of the GLUT family, is ubiquitously expressed, normally in endothelial and epithelial-like barriers of the brain, eye, peripheral nerve, placenta and lactating mammary gland (35). Several signaling pathways were suggested to be involved in the stimulation of GLUT-1 expression to promote cancer cell proliferation, such as hypoxia-inducible factor-1 (HIF-1) signaling pathway (36). HIF-1 was suspected to be activated by the upstream receptor tyrosine kinase system (37), which also activated the phosphatidylinositol 3-kinase (38) and mitogen-activated protein kinase pathways (39). Additionally, the increased downstream mTOR activity stabilized the HIF-1 under normoxic conditions, which mediated the GLUT-1 expression (40). In the previous study, HIF-1 expression was also associated with poor survival in GC patients (41).

Various malignancies were reported to be associated with GLUT-1 overexpression in previous studies (7-11). Our summary focused on the same field in GC. Our meta-analysis illustrated that GLUT-1 expression was a significant indicator for OS and DFS in GC. Moreover, there were correlations between GLUT-1 and advanced tumor biological behaviors, such as TNM stage, lymph node metastasis and depth of invasion, all of which indicated poor prognosis. Potential clinical benefits of GLUT-1 targeted therapy may be achieved in the adjuvant treatment for GC patients with worse TNM stage and/or lymph node metastasis. In addition, the intestine type tumors,

which had better prognosis than the diffuse type, had closer correlation with GLUT-1 expression. Meanwhile, further studies are needed to focus on the relationship between GLUT-1 expression and tumor growth or distant metastasis.

Compared with previous meta-analyses (12-17) of GLUT-1, our study had many strongly significant advantages as follows. Our research described the relationship between GLUT-1 and only one single specific cancer type, as well as the influence of GLUT-1 on seven clinicopathological parameters, and we include Chinese studies, which could reduce the publication bias. Unlike the following four meta-analyses (12, 14, 16, 17), all of them described the correlation of between GLUT-1 and various types of cancer with no specificity due to various cancer characteristics. Additionally, they did not study the clinicopathological parameters, and excluded Chinese studies. The association between GLUT-1 expression and only four parameters was described, which failed in persuasiveness (16). A study had significant heterogeneity between GLUT-1 and OS, as well as no funnel plot graphs or Begg's test or Egger's test to illustrate the publication bias (12). Different and inconsistent analysis models were used to calculate the pooled HRs, which could cause remarkable bias (17). A research (14) had conspicuous heterogeneity of 3-yr and 5-yr survival, as well as several subgroup analyses (14). Besides, significant publication bias was shown in this article according to the Begg's test. Moreover, our study described the different single type of cancer from both following meta-analyses. The association between GLUT-1 and pancreatic cancer was described but included a limited sample size of 538 cases, much less than our study and had noteworthy heterogeneity of OS (13). The relationship between GLUT-1 and colorectal cancer was described, however, the study had remarkable heterogeneity of OS and most of the subgroup analyses (15).

Several limitations in this meta-analysis should be taken into account. First, the number of OS and DFS was too small to calculate the accurate estimation of the relationship between GLUT-1 expression and OS/DFS. Second, the study (32) of DFS used univariate analysis to assess the relationship between GLUT-1 expression and DFS. The others were all performed using multivariate analysis. Although Begg's test and Egger's test suggested no significant publication bias, selection bias potentially existed owing to the limited sample size.

Conclusion

GLUT-1 was significantly correlated with poor OS and DFS in GC. In addition, GLUT-1 was also a potential prognostic indicator of aggressive clinicopathological parameters in GC, which may facilitate therapeutic approaches to GC patients.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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