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ORIGINAL ARTICLE

Prognostic and Clinicopathological Significance of Long Noncoding RNA GHET1 in Human Solid Tumors: a Meta-Analysis

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SUMMARY

Background: **Gastric carcinoma high expressed transcript 1 (GHET1) is a long noncoding RNA (lncRNA) that is aberrantly upregulated in numerous cancers. Here we carried out a systematical meta-analysis to investigate the potential prognostic and clinicopathologic significance of lncRNA GHET1 expression in multiple types of malignant tumors.**

Methods: **A systematic document retrieval of the online databases Embase, PubMed, and CNKI for studies relevant to the connection between lncRNA GHET1 level and clinical result of tumors was conducted (up to May 8, 2019). The aggregated odds rates (ORs)/hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were calculated to assess the relationship.**

Results: **Nine hundred twenty carcinoma patients were enrolled from 12 studies in the present study. The results revealed that increased GHET1 expression was obviously related to worse overall survival (OS) (pooled HR = 2.75, 95% CI: 2.18 - 3.45, p < 0.001). Subgroup analysis results indicated that high GHET1 levels present a stronger connection with poor OS in digestive system cancers. In addition, cancer patients with high GHET1 levels are likely to have distant metastasis (DM) (OR = 12.5, 95% CI: 2.31 - 66.67, p = 0.003), lymph node metastasis (LNM) (OR = 4.29, 95% CI: 2.930 - 6.29, p < 0.001), and advanced clinical staging OR = 4.6, 95% CI: 3.33 - 6.34, p < 0.001), but GHET1 expression was not correlated with gender (p = 0.586), age (p = 0.332), tumor differentiation (p = 0.550), or tumor size (p = 0.084).**

Conclusions: **Overexpression of GHET1 may be a convincing adverse prognostic factor that contributes to the clinical decision-making procedure of cancer treatment.**

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long noncoding RNA, GHET1, cancers, prognosis, meta-analysis

INTRODUCTION

Gastric cancer high expressed transcript 1 (GHET1) is a recently identified long non-coding RNA (lncRNA) transcript with the length of 1913 nt, coded by the GHET1 gene and situated on chromosome at position 7q36.1 [1,2]. lncRNA GHET1 was initially reported to over-express in gastric carcinoma and was linked to poor prognosis, invasion, and tumor size. It promotes

gastric carcinoma cell growth by enhancing c-Myc mRNA stability and expression [1]. Knockdown of lncRNA GHET1 stimulates gastric cancer cell apoptosis and inhibits cell proliferation and invasion as well as migration [3]. Besides, up-regulation of lncRNA GHET1 promotes gastric cancer cells developing multidrug resistance to chemotherapy drugs [4]. All in all, these results show that lncRNA GHET1 plays a pivotal role in regulating the development and drug resistance of gastric cancer.

For the last 5 years, lncRNA GHET1 has been received considerable interest because it was determined to be deregulated in various tumors, including gastric cancer (GC) [1,3-5], bladder cancer (BC) [6], breast cancer (BRC) [7], hepatocellular carcinoma (HC) [8-10], esophageal squamous cell carcinoma (ESCC) [11], colorectal cancer (CC) [12], non-small cell lung cancer (NSCLC) [13,14], pancreatic carcinoma (PC) [2], head and neck cancer (HNC) [15], cervical cancer (CC) [16], and so on. Studies also continue to demonstrate that highly expressed GHET1 is generally related to unfavorable prognosis of cancer patients and facilitates tumor cell proliferation, migration, invasion, metastasis and reduces cell apoptosis [1-4,9,12,17]. By interacting with many biomolecules, such as ATF1 [10], IGF2BP1, and c-Myc mRNA [1], GHET1 regulates gene expression and influences key regulatory pathways for cell growth. Furthermore, receiver operating characteristic (ROC) curve analysis revealed that GHET1 level is a good marker with high specificity and sensitivity for diagnosing ESCC [11]. These discoveries are consistent with GHET1 which serves as a common oncogenic lncRNA and prognosis molecular biomarker.

However, due to the deficiencies related to the study of methodology and sample size, individual research is often insufficient and/or inaccurate. Therefore, further investigation of the clinical value of GHET1 in diverse tumors is of great significance. Thereupon, we systematically searched the corresponding studies and then carried out this work to assess the prognostic significance of lncRNA GHET1 for cancer patients. It is designed to evaluate the capacity of GHET1 more accurately as a molecular marker to predict metastasis and prognosis for neoplasms.

MATERIALS AND METHODS

Literature collection

The articles regarding GHET1 expression were methodically retrieved from the electronic databases of Embase, PubMed, and CNKI. The latest search was updated on May 8, 2019. Literature search keywords and means were as follows: “gastric carcinoma high expressed transcript 1 OR GHET1 OR lncRNA-GHET1 OR gastric carcinoma proliferation enhancing transcript 1”. The strategy has been adjusted in different databases.

Study inclusion and exclusion

In the present meta-analysis, inclusion standards of all included articles were as follows: (1) studies reporting the connection between GHET1 expression and patient prognosis; (2) the carcinoma patients had to be divided into two groups based on the level of GHET1; (3) sufficient data or survival curve were provided to obtain ORs, HRs, and corresponding 95% confidence intervals (CIs); and (4) reporting related clinical parameters, like tumor stage, tumor size, lymph node metastasis (LNM), and distant metastasis (DM). Articles were excluded if they meet the following conditions: (1) duplicate documents; (2) reviews, editorials, case reports, conference abstracts, expert views, etc. (3) studies with insufficient or usable data.

Data collection

Data from each original study was collected independently by two researchers (Liping Zeng and Dan Gao). Any disagreements were resolved by the third party (Na Li). The following data from each individual study were extracted: first author, country of the population enrolled, publication date, tumor stage, tumor type, detection means of GHET1, standard for high GHET1 expression, number of patients, follow-up time, overall survival (OS), clinicopathological parameters, HRs and their 95% CIs. If the HRs with 95% CIs were not directly shown in the publications, original data was requested from the correspondence authors, or the necessary information was gathered from the Kaplan-Meier plots, and the Engauge Digitizer software was used to calculate the HRs and their 95% CIs as previously described [18,19].

Online cross-validation

Gene Expression Profiling Interactive Analysis (GEPIA) [20], using the data from The Cancer Genome Atlas (TCGA), was used to validate the association between lncRNA GHET1 level and survival situation in tumor patients.

Statistical analysis

All extracted data were pooled into a meta-analysis utilizing STATA 12.0 software (Stata, College Station, TX, USA). Pooled HRs with the corresponding 95% CIs were utilized to analyze the intensity of the correlation between lncRNA GHET1 level and patient prognosis in various solid tumors. Pooled ORs and their corresponding 95% CIs were used to explore the correlation between GHET1 and clinicopathological characteristics. The heterogeneity of pooled results was checked by applying I^2 and Q test. The calculated result of I^2 more than 0.5 indicating that obviously heterogeneity was existed. The random effect model was utilized to estimate the integrated HRs or ORs when apparent heterogeneity was found among included studies (I^2 more than 0.5). Otherwise, the fixed effect model was used (I^2 less than 0.5). A “Begg's funnel plot” was utilized to determine possible publication bias. A sensibility analysis was car-

Table 1. The main clinical characteristics of the include studies in this meta-analysis.

Studies	Region	Cancer types	Sample size	Detection method	Cutoff	Survival analysis	Follow-up (months)
Li 2014	China	BC	80	qRT-PCR	median	OS	~60
Yang 2014	China	GC	42	qRT-PCR	median	OS	~40
Xia 2016	China	GC	35	qRT-PCR	median	-	-
Li 2017	China	HC	179	qRT-PCR	mean	OS/DFS	~60
Liu 2017	China	ESCC	55	qRT-PCR	median	-	-
Zhou 2017	China	PC	64	qRT-PCR	fold change	-	-
Guan 2018	China	NSCLC	52	qRT-PCR	median	OS	~60
Jin 2018	China	HC	68	qRT-PCR	mean	OS	~60
Liu 2018	China	HNC	86	qRT-PCR	median	OS	over 60
Shen 2018	China	NSCLC	105	qRT-PCR	mean	OS/PFS	over 60
Song 2018	China	BRC	60	qRT-PCR	median	OS	~60
Wang 2019	China	CC	94	qRT-PCR	ROC curve	OS	over 108

BC - bladder cancer, CC - cervical cancer, GC - gastric carcinoma, HC - hepatocellular carcinoma, ESCC - esophageal squamous cell carcinoma, PC - pancreatic cancer, NSCLC - non-small cell lung cancer, HNC - head and neck cancer, BRC - breast cancer, OS - overall survival, PFS - progression-free survival, DFS - disease free survival.

ried out to assess the robustness of the pooled OS. All p-values less than 0.05 were considered statistically significant.

RESULTS

Study features

By searching PubMed, Embase, and the China National Knowledge Infrastructure (CNKI), we retrieved 45 potentially relevant papers. After removing duplicates, 28 records were retained. Following the title and abstract screening, 15 full text publications were included. Subsequently, 3 of them were excluded because they did not provide sufficient data. Finally, 12 studies met the eligibility criteria, including nine on prognosis [1,5-9, 13-15] and eleven on clinicopathological features [1,2, 6-9,11,13-15,21] were included in the present meta-analysis. The flow chart of the selection procedure for the included studies is shown in Figure 1. All twelve studies came from China, comprised 826 patients, and addressed 8 different cancer types: non-small cell lung cancer (NSCLC), bladder cancer (BC), breast cancer (BRC), esophageal squamous cell carcinoma (ESCC), hepatocellular carcinoma (HC), gastric carcinoma (GC), head and neck cancer (HNC), as well as pancreatic cancer (PC). In all cases, lncRNA GHET1 expression was determined by qRT-PCR and separated by inconsistent "cutoff" values. The main clinical data of the eleven studies included in this work are generalized in Table 1.

Relationship between GHET1 and prognosis

A total of 9 articles reported the OS of 7 types of cancer accorded to different GHET1 expression in 766 tumor patients. Since no obvious heterogeneity was found among all included studies (I^2 = 0.0%, p = 0.647), the fixed-effects model was applied to determine the merged HR. The incorporated outcome (HR = 2.75, 95% CI: 2.18 - 3.45, p < 0.001) showed that increased GHET1 level predicts a worse OS than patients with low GHET1 level (Figure 2). The online cross-validation based on GEPIA indicated patients with over-expression of GHET1 significantly tended to have shorter OS compared to patients with low GHET1 expression (HR = 1.20, p < 0.001) (Figure 3). We also conducted a subgroup analysis for OS according to sample size, cancer type, and cutoff methods. As shown in Table 2, high GHET1 expression shows closer connection with poor OS in digestive system cancers, HCC, and sample size less than 100.

Association between GHET1 expression and clinicopathological parameters

To further understand the clinical significance of GHET1 expression level in cancer patients, we aggregated the clinicopathological data from all qualified studies. As the results show in Table 3, elevated expression level of GHET1 was significantly related to distant metastasis (DM) (OR = 12.5, 95% CI: 2.31 - 66.67, p = 0.003; fixed-effects model), and lymph node metastasis (LNM) (OR = 4.29, 95% CI: 2.930 - 6.29, p < 0.001;

Table 2. Pooled HR of OS in light of subgroup analysis.

Categories	Subgroups	Patient number	HR (95% CI)	p-value	Heterogeneity	
					I^2 (%)	P_h
All		766	2.75 (2.18, 3.45)	< 0.001	0.0	0.647
Cancer type	1) respiratory system cancers	157	2.24 (1.49, 3.36)	< 0.001	0.0	0.469
	digestive system cancers	289	3.39 (2.10, 5.48)	< 0.001	32.5	0.227
	reproductive system cancers	154	3.14 (2.05, 4.82)	< 0.001	0.0	0.664
	others	166	2.42 (1.38, 4.24)	0.002	0.0	0.833
	2) HC	247	3.54 (1.32,9.52)	0.012	66.2	0.085
	NSCLC	157	2.24 (1.49, 3.36)	< 0.001	0.0	0.469
	others	362	2.92 (2.12, 4.01)	< 0.001	0.0	0.926
Sample size	≥ 100	284	1.98 (1.18, 3.31)	0.009	0.0	0.717
	< 100	482	2.98 (2.31, 3.85)	< 0.001	0.0	0.688
Cutoff	median value	410	2.66 (1.98, 3.57)	< 0.001	0.0	0.963
	mean value	262	2.77 (1.39, 5.52)	0.004	58.3	0.091

Table 3. Pooled ORs for the relationship between GHET1 expression and clinical pathology factors.

Classification	Sample size	OR (95% CI)	p-value	Heterogeneity		
				I^2	P_h	Model
Gender (male vs. female)	686	0.92 (0.66, 1.26)	0.586	0.0%	0.862	fixed effects
Age (≤ 60 vs. > 60)	402	0.81 (0.54, 1.23)	0.332	0.0%	0.936	fixed effects
Clinical stage (I/II vs. III/IV)	714	4.60 (3.33, 6.34)	< 0.001	0.0%	0.552	fixed effects
Lymph node metastasis (yes vs. no)	529	4.29 (2.93, 6.29)	< 0.001	14.6%	0.315	fixed effects
Distant metastasis (yes vs. no)	200	12.5 (2.31, 66.67)	0.003	0.0%	0.827	fixed effects
Differentiation (low/undiff vs. middle/high)	597	0.88 (0.38, 2.01)	0.550	77.9%	0.000	random effects
Tumor size (< 5 cm vs. ≥ 5 cm)	423	1.97 (0.91, 4.23)	0.084	68.2%	0.013	random effects

fixed-effects model). The pooled results show that cancer patients overexpressing GHET1 were more prone to have DM and LNM than those with low GHET1 level. Furthermore, we also found a positive relationship between GHET1 expression level and advanced clinical stage (OR = 4.6, 95% CI: 3.33 - 6.34, p < 0.001; fixed effect model). However, high GHET1 expression did not associate significantly with age (OR = 0.81, 95% CI: 0.54 - 1.23, p = 0.332), gender (OR = 0.92, 95% CI: 0.66 - 1.26, p = 0.586), tumor size (OR = 1.97, 95% CI: 0.91 - 4.23, p = 0.084), or tumor differentiation (OR = 0.88, 95% CI: 0.38 - 2.01, p = 0.550) (Table 3). In view of the inadequate information, we were unable to define the relationship between high GHET1 expression and other clinical pathology parameters.

Evaluation of publication bias

The publication bias for OS was assessed by Begg's test analysis. The result of the funnel plot was asymmetric, indicating that there may be a bias in publications (Figure 4), but the Begg's test demonstrated no significant publication bias during these studies ($Pr > |z| = 0.602$).

Influence analysis

In order to detect the robustness of merged outcomes in our present study, an influence analysis was executed by successively omitting every individual study from the pooled analysis. As the result shows in Figure 5, the relationship between expressed level of GHET1 and overall survival was not significantly affected by excluding any single study, indicating that the outcomes were comparatively robust.

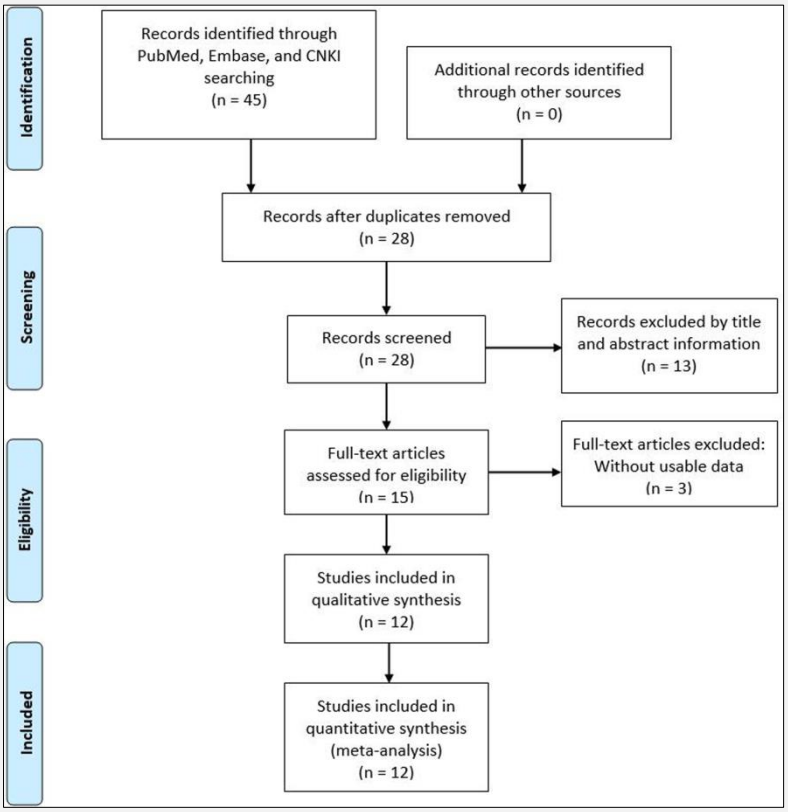

Figure 1. Flow chart of literature retrieval and selection.

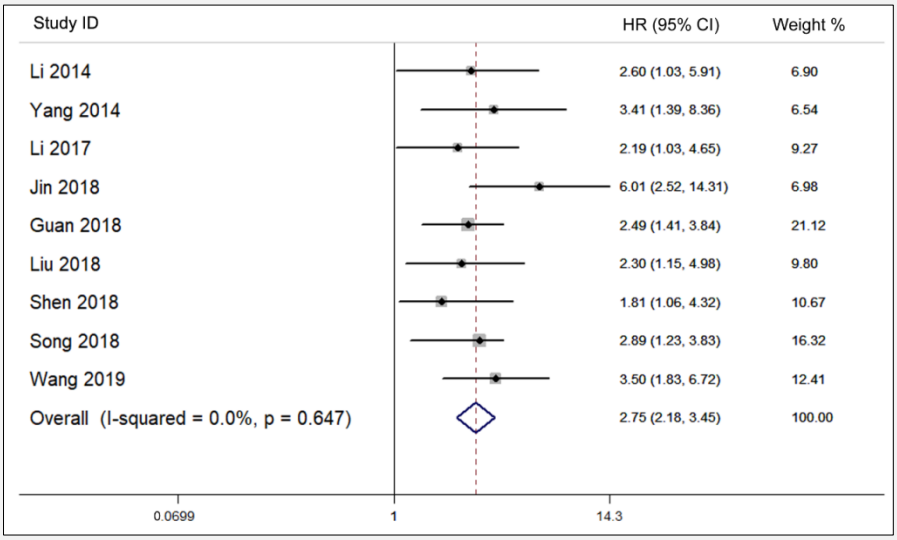

Figure 2. The association between GHET1 expression and OS in patients with cancer.

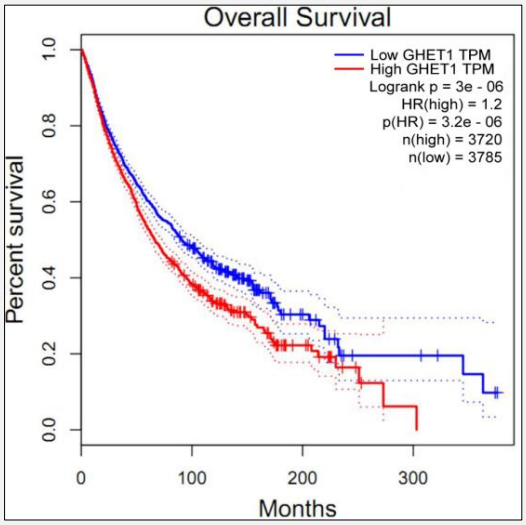

Figure 3. Online cross-validation of OS.

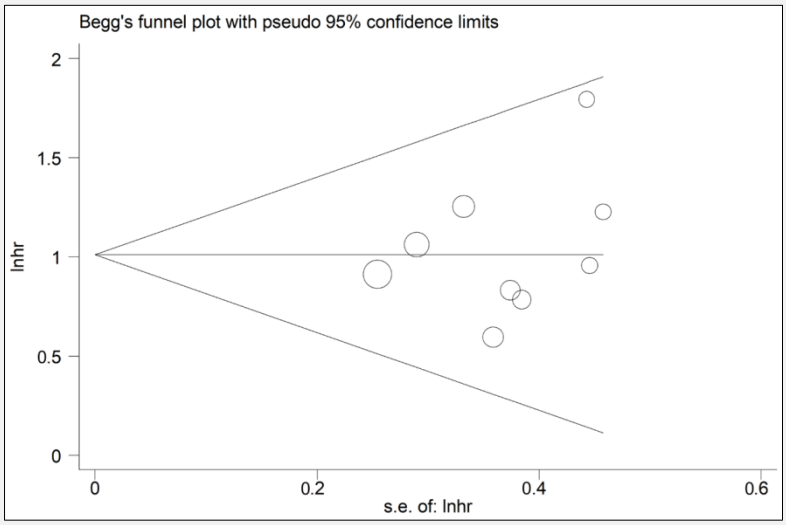

Figure 4. Begg's test of the eligible studies for publication bias.

DISCUSSION

Malignant neoplasm is still a serious public health problem all over the world [22,23]. In recent years, aberrantly expressed lncRNAs have been demonstrated to be closely correlated with cancer pathogenesis, development, and prognosis [24-27]. Among all cancer-related lncRNAs, GHET1, as an outstanding non-protein coding RNA gene, is significantly upregulated in a large number of neoplasm types. Moreover, high GHET1 expression is related to unfavorable clinical prognosis in cancer patients [6-9,11,14]. It has been reported that down-regulating GHET1 expression can inhibit cell proliferation, migration, invasion activities, and cell cy-

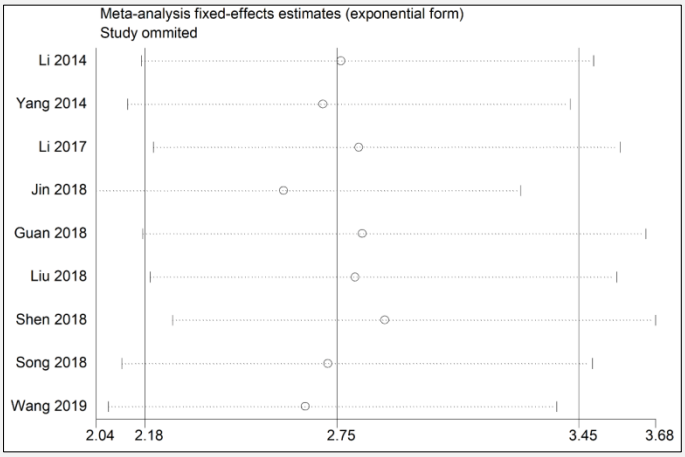

Figure 5. Sensitivity analysis for GHET1 and OS.

cle arrest [3,12]. Further mechanistic research found that knockdown of GHET1 inhibits tumor cell survival through the regulation of pathways including LATS1/YAP [13] and epithelial-mesenchymal-transition [6,7]. On the other hand, overexpression of GHET1 contributes to the occurrence and development of cancers by down-regulating the expression of genes such as Bax [4], KLF2 [8], Cyclin D1 [9], vimentin, and N-cadherin [7,11], and increasing the expression of genes involving E-cadherin [7,11], c-Myc [1], Bcl-2, MDR1, and MRP1 [4]. In addition, GHET1 activated by H3K27 acetylation promotes cell tumorigenesis and progression by regulating ATF1 in hepatocellular carcinoma cells [10]. In the present study, we executed a comprehensive meta-analysis to explore the relationship between GHET1 expression and clinical results in various tumor patients. A total of 11 studies met our selection criteria for inclusion. Our meta-analysis provided evidence that increased GHET1 expression could be a promising prognostic indicator for cancer patients. First, the pooled HR values and the online cross-validation based on TCGA represented that GHET1 overexpression was associated with unfavorable OS, suggesting that GHET1 might act as a potential independent predictive factor of OS in cancer patients.

Besides, two studies have reported that high GHET1 expression shows significantly shorter disease free survival (DFS) and progression-free survival (PFS) of HC patients [9] and NSCLC patients [14], respectively. Second, increased GHET1 level was significantly related to LNM and DM. It is suggested that the patients with high GHET1 level have elevated risk of developed DM as well as LNM. Third, according to the aggregated outcomes, we found that high GHET1 level was positively related to advanced clinical stage. However, there are limited studies on the specific role of GHET1 expression during tumorigenesis, the conclusion of the present study should be further confirmed.

Although GHET1 was found to be obviously related to the prognosis of tumor patients, several limitations call for cautious interpretation of the results for the current study. For example, only 11 studies were included in this analysis and all cohorts came from China. Then, our results need to be validated with clinical data from more ethnic groups. Additionally, the cut-of value of low and high GHET1 expression was not consistent across these studies, even though most of them were set as median. Moreover, some of the HRs and their corresponding 95% CIs were calculated through survival plots, it may not be precise enough. Furthermore, positive results are always published, and negative results are always ignored, so our results may overestimate the prognostic value of GHET1 in carcinoma to some extent. Finally, many other factors may affect the prognostic outcome, such as treatment methods, mental state, and age. Therefore, more studies are needed to verify the current results.

CONCLUSION

Our study found that high GHET1 expression is an independent risk factor for poor clinical prognosis in a variety of tumors. Furthermore, the expression of GHET1 was linked with clinicopathological parameters, including distant metastasis, lymph node metastasis, and clinical stage. Nevertheless, larger-size, multi-center, and higher-quality studies are warranted to confirm our results.

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Declaration of Interest:
The authors declare no competing financial interests.

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