

Original Article

Golgi phosphoprotein3 overexpression is associated with poor survival in patients with solid tumors: a meta-analysis

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Abstract: Golgi phosphoprotein3 (GOLPH3) is known as an oncoprotein and may be a prognostic biomarker in various tumors. Here we performed a meta-analysis on the association of GOLPH3 expression and survival in solid tumors. All eligible studies were identified in Embase, PubMed and Web of Science Databases up to November 2014. Data about overall survival (OS), and disease-free survival (DFS) were extracted and pooled hazard ratios (HRs) of GOLPH3 for survival were calculated by using a random-effect model. Heterogeneity and publication bias were also assessed. A total of 15 eligible studies which comprised of 2529 cases were included in this global analysis: 14 were dealing with overall survival (OS) and 6 were with disease-free survival (DFS). We found that GOLPH3 overexpression was associated with shorter OS (HR 2.487, 95% CI 1.897-3.258, $P < 0.001$) and DFS (HR 1.911, 95% CI 1.245-2.932, $P = 0.003$) in general carcinomas. Importantly, subgroup analysis suggested that overexpression of GOLPH3 correlated with shorter OS in urogenital system cancers (HR 4.258, 95% CI 1.81-4.91, $P < 0.001$). Moreover, publication bias was not significant ($P > 0.05$). In conclusion, the present meta-analysis showed that overexpression of GOLPH3 predicts poor prognosis in solid tumors.

Keywords: Golgi phosphoprotein3, solid tumors, meta-analysis, prognosis

Introduction

Golgi phosphoprotein3 (GOLPH3), also known as GPP34, GMx33, MIDAS, or yeast Vps74p, was originally identified by proteomic analyses of Golgi proteins localized to the trans-Golgi network [1, 2]. The nucleotide sequence of GOLPH3 is highly conserved from yeast to human. It is localized on chromosome 5p13 and encodes a membrane protein with a molecular mass of 34 kDa. GOLPH3 was found to localize in the cytoplasmic face of trans-Golgi, and also other parts of cell, including cytosolic pool, endosomal compartments and plasma membrane [2]. It was reported that GOLPH3 plays an important role in maintaining Golgi function and protein sorting pathways by binding to phosphatidylinositol 4-phosphate (PtdIns (4) P), MYO18A and F-actin [3, 4]. Recently, GOLPH3 has been identified as a first-in-class

Golgi oncoprotein frequently targeted for copy number gain/amplification on chromosome 5p13 and is capable of modulating the response to a clinical drug, rapamycin in various cancers [5]. Observations suggested that GOLPH3 promote tumorigenesis and cell proliferation, motility, and metastasis via regulating several downstream molecules such as PI3K-AKT-mTOR pathway [5, 6], Rho A [7], FOXO1 [8], sialylation [9] and YB1 [10]. Subsequent investigations have documented that GOLPH3 was frequently overexpressed in many types of human tumors, such as gliomas [11, 12], hepatocellular carcinoma [13, 14], renal cell carcinoma [15], non-small cell lung cancer [16, 17], pancreatic ductal adenocarcinoma [18], bladder cancer [19], colorectal cancer [20], ovarian carcinoma [21, 22], gastric cancer [23], breast cancer [8], prostate cancer [24], esophageal cancer [25] and oral tongue cancer [26]. More importantly, over-

expression of GOLPH3 has been reported to be associated with tumorigenesis and progression in most of these tumors. However, the prognostic value of GOLPH3 overexpression across different solid tumors remains inconsistent. Some researchers found GOLPH3 overexpression predicted worse survival whereas others did not agree. Therefore, we performed this meta-analysis to evaluate the prognostic value of GOLPH3 overexpression in general solid tumors. The aim of this study was to evaluate the prognostic significance of GOLPH3 in solid tumors, thereby developing better therapeutic strategies.

Materials and methods

Search strategy

A comprehensive literature search of PubMed, Embase and Web of Science databases covering all papers was performed up to November 19, 2014. The following search terms and their combinations was used: "GOLPH3", "Golgi phosphoprotein 3", "cancer", "neoplasms", "carcinoma", "tumor". All eligible studies were retrieved and their references were used to identify other additional suitable studies.

Selection criteria

Studies met the following criteria were collected to conduct this meta-analysis: (1) solid cancers were all histopathological diagnosed; (2) the expression of GOLPH3 was evaluated by immunohistochemistry; (3) all studies about GOLPH3 in overall survival (OS) or disease free survival (DFS) of solid tumor were included; (4) studies were published in English; (5) contain sufficient information allowing for estimation of hazard ratios (HRs) with their 95% confidence interval (95% CI) of OS/DFS. (6) if overlapping data were published in different reports by the same investigator, only the most complete one was included.

Data extraction

Data was carefully extracted from each eligible study independently by two investigators (Yuqi Su and Yang Zhao) using predefined data abstraction forms. For each study, the following information were extracted: author, year of publication, country, number of patients, tumor stage, GOLPH3 assessment method, cutoff

value of overexpression of GOLPH3, follow-up period, prognostic outcomes of interest, analytical method, and HR with its 95% CI. Data were extracted directly from the Kaplan-Meier curves using the methods developed by Parmar if the prognostic value was just demonstrated with Kaplan-Meier curve in some articles [27]. Disagreements were resolved by iteration, discussion, and consensus between the two authors.

Quality assessment

The studies methodology quality was assessed and scored by two independent authors (Changqie Pan and Yaqi Jiang) according to the Newcastle-Ottawa Scale the quality scale [28]. This scale assesses the selection of cases, comparability of populations and ascertainment of exposure to risks. Each of these categories has a maximum score of four stars except the second category in which a maximum of two stars can be allotted. Each study was given a score ranging from 0 to 9 after consultation of any discrepancies between the two authors.

Statistical analysis

The impact of GOLPH3 overexpression on survival in solid tumors was estimated by HR and its 95% CI. When HRs was described in original studies, we used crude values directly. Otherwise, the values were calculated from Kaplan-Meier curves. Statistical heterogeneity between studies was quantified using Cochran's Q test and Higgins I-squared statistic. Heterogeneity was defined as $P < 0.1$ or $I^2 > 50\%$. In the absence of statistically significant heterogeneity, a fixed effects model was selected to combine the data. Otherwise, a random effects model was used. The sensitivity analysis was used to verify the robustness of our meta-analysis. Therefore, every single study was deleted, and the pooled HR and 95% CI as well as the tests for heterogeneity of the remaining studies were calculated. Publication bias was assessed by using Begg's funnel plot test and Egger's test. Subgroup analysis was conducted by stratifying on HR estimate and tumor type. For all analyses, a two-sided P value less than 0.05 was considered as statistically significant. All analyses were performed with Stata analysis software (version 12.0; Stata Corporation, College Station, TX).

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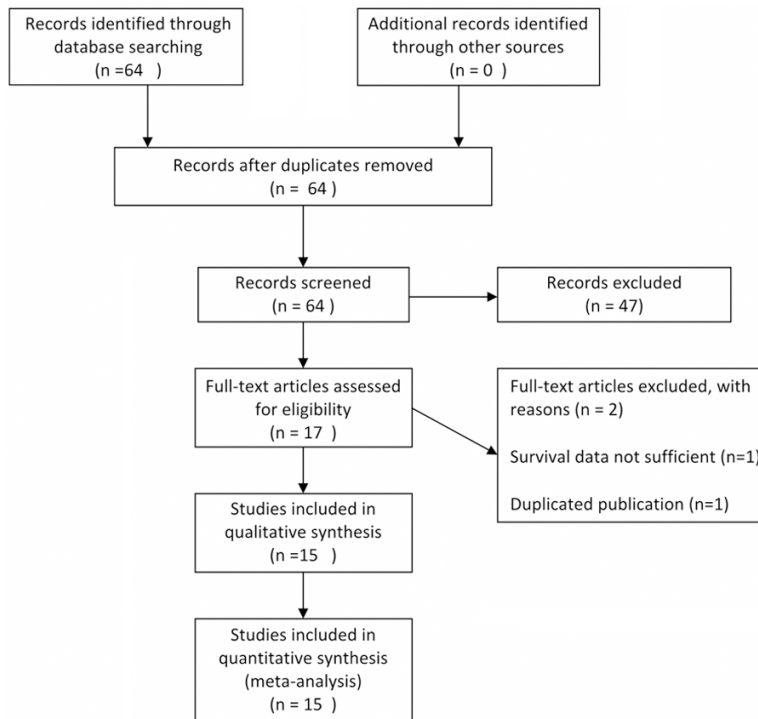


Figure 1. Flow chart of search strategy.

Results

Study characteristics

Firstly, a total of sixty-four literatures about GOLPH3 in solid tumors were identified from a primary literature search in Embase, PubMed and Web of Science databases. Then 47 studies were excluded after carefully review of the titles and abstracts, because of inconsistency with the topic. Of the seventeen candidate studies, two were excluded for including duplicate data [29] or lacking survival data [19]. Finally, we enrolled 15 studies in our meta-analysis (**Figure 1**), and the patients characteristics in the studies were summarized in **Table 1**. It is obvious that all studies came from China. Of this studies, two were about liver cancer, two were about ovarian cancer, two were about lung cancer, and one each was about gastric cancer, pancreatic cancer, colorectal cancer, esophageal cancer, breast cancer, renal cancer, prostate cancer, glioblastoma and oral tongue cancer. GOLPH3 expression was evaluated by immunohistochemistry (IHC) in all 15 studies within our meta-analysis. A total of 2529 cases were included in those studies, ranging from 75 to 259 patients per study. As for the end point,

fourteen studies were dealing with OS, six studies were with DFS, and two studies were with PFS. The cutoff value for GOLPH3 overexpression in the 15 studies were defined by the use of complex score (CS) combining intensity and percentage of GOLPH3 expression [12-18, 20-22, 25, 26]; whereas the remaining two only used the percentage of GOLPH3 expression [23, 24]. These enrolled studies obtained scores ranging from 6 to 8 of high quality by using Newcastle-Ottawa Scale (**Table 1**).

Meta-analysis results

The main results between GOLPH3 expression and survival were listed in (**Table 2**). Firstly, we evaluated the correlation between expression

levels of GOLPH3 and OS, and heterogeneity was found among this studies ($I^2 = 80.6$, $P < 0.001$). Hence, a random model was applied to calculate the pooled HR and its 95% CI. The combined analysis of 14 studies showed that GOLPH3 overexpression was significantly correlated with shorter OS in solid tumors (HR 2.487, 95% CI 1.897-3.258, $P < 0.001$) (**Figure 2**). In addition, subgroup analysis by tumor type revealed that GOLPH3 overexpression was significantly associated with shorter OS in digestion system cancers (HR 1.932, 95% CI 1.299 = 2.874, $P = 0.001$), and urogenital system cancers (HR 4.258, 95% CI 1.81-4.91, $P < 0.001$). Meanwhile, subgroup analysis by HR estimate showed that the combined HR estimate for OS under survival curves was 2.436 (95% CI 1.893-3.134, $P < 0.001$), while for multivariate analysis was 2.553 (95% CI 1.720-3.787, $P < 0.001$).

There were 6 studies reported correlations between GOLPH3 expression and DFS. A random effects model was used to combine the pooled HR and its 95% CI because of the heterogeneity observed among the studies ($I^2 = 76.9$, $P = 0.001$). Meta-analysis of these studies showed that GOLPH3 overexpression was

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Table 1. Main characteristic and results of the included studies

Study	Year	Tumor type	Patient source	Number of patients	Stage	Method	Cut-off	GPLPH3 expression%	Median (range) follow-up (month)	Multivariate/uni-variate	Outcome	HR (95%)	Result	Assessment of study quality
Zhang	2014	Lung	China	145	I-III	IHC	CS	71.7	37 (6-72)	Multivariate	DFS	3.58 (1.83-7.01)	Unfavorable	7
Zhang	2014	Pancreatic	China	109	I-IV	IHC	CS	72.50	8.3 (0.67-63.5)	Multivariate	OS	2.733 (1.578-4.732)	Unfavorable	7
Xue	2014	Renal	China	218	I-IV	IHC	CS	53.21	45.4 (3-94)	Multivariate	OS	5.341 (2.496-11.428)	Unfavorable	8
				196				48.47	45.4 (3-94)	Multivariate	RFS	4.416 (2.193-8.894)	Unfavorable	
Wang	2014	Colorectal	China	130	II-IV	IHC	CS	43.10	62 (6.2-131.2)	Multivariate	OS	0.557 (0.292-1.062)	Favorable	8
									62 (6.2-131.2)	Multivariate	DFS	0.468 (0.222-0.987)	Favorable	
Ma	2014	Ovarian	China	175	I-IV	IHC	CS	45.30	22.7 (8-51)	Multivariate	OS	3.60 (1.14-11.33)	Unfavorable	7
Ma	2014	Ovarian	China	135	I-IV	IHC	CS	71.90	45 (4-89)	Multivariate	OS	5.667 (2.831-11.34)	Unfavorable	
Lu	2014	Lung	China	116	NR	IHC	CS	58.62	60	Multivariate	OS	1.899 (1.021-3.532)	Unfavorable	7
										Surv curve	DFS	2.03 (1.27-3.24)	Unfavorable	8
										Multivariate	PFS	1.833 (1.034-3.251)	Unfavorable	7
Hu	2014	Liver	China	167	NR	IHC	CS	64.70	19.1 (1.1-64.5)	Multivariate	OS	1.81 (1.14-2.87)	Unfavorable	
										Multivariate	DFS	1.84 (1.16-2.93)	Unfavorable	
Dai	2014	Liver	China	A, 217; B, 173	I-IV	IHC	CS	A, 53.50; B, 52.00	NR	Multivariate	OS	A, 2.517 (1.459-4.344)	Unfavorable	6
										Multivariate	OS	B, 2.156 (1.100-4.224)	Unfavorable	
Hu	2013	Gastric	China	123	I-IV	IHC	30%	55.30	NR	Multivariate	OS	1.876 (1.082-3.543)	Unfavorable	7
Zhou	2012	Glioblastoma multiforme	China	97	NR	IHC	CS	41.20	NR	Multivariate	OS	1.934 (1.201-3.115)	Unfavorable	6
										Multivariate	PFS	2.041 (1.279-3.255)	Unfavorable	6
Zeng	2012	Breast	China	258	I-IV	IHC	CS	51.60	NR	Multivariate	OS	5.834 (3.531-9.638)	Unfavorable	
Wang	2012	Esophageal	China	155	I-IV	IHC	CS	49.00	32.17 (1-77)	Multivariate	OS	3.344 (1.816-6.157)	Unfavorable	7
Li	2012	Oral tongue	China	179	I-IV	IHC	CS	68.20	60	Surv curve	OS	2.10 (1.3-3.37)	Unfavorable	6
										Surv curve	DFS	2.04 (1.25-3.35)	Unfavorable	7
Hua	2012	Prostate	China	232	NR	IHC	10%	42.24	38.5 (10-91)	Surv curve	OS	2.52 (1.77-3.59)	Unfavorable	7
										Surv curve	DFS	2.90 (2.05-4.10)	Unfavorable	

NOTE: GOLPH3 Golgi phosphoprotein3, IHC immunohistochemistry, Surv curve, survival curve, HR hazard ratios, CI confidence interval, OS overall survival, DFS disease-free survival, RFS relapse-free survival, PFS Progression-free survival, CS complex score combining intensity and percentage, NR, not report.

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Table 2. Main meta-analysis results

Analysis	N	Patients	HR (95% CI)	P value	Heterogeneity		
					Chi ²	I ² (%)	P value
Overall survival (OS)	14	2384	2.487 (1.897 3.258)	< 0.001	47.52	70.50	< 0.001
HR estimate							
Multivariate analysis	11	1864	2.553 (1.720 3.787)	< 0.001	46.79	0.786	0
Survival curves	3	520	2.436 (1.893 3.134)	< 0.001	0.58	0	0.749
Tumor type							
Digestion system cancers	6	1074	1.932 (1.299 2.874)	0.001	19.96	69.9	0.003
Urogenital system cancers	5	918	4.258 (2.746 6.603)	< 0.001	10.03	60.1	0.04
Other cancers	3	392	1.988 (1.479 2.673)	< 0.001	0.08	0	0.959
Disease-free survival (DFS)	6	969	1.911 (1.245 2.932)	0.003	21.65	76.9	0.001

N, number of studies; HR, hazard ratio; CI, confidence interval.

associated with shorter DFS (HR 1.911, 95% CI 1.245-2.932, $P = 0.003$, **Figure 3**). In consideration of that just a small part of studies reported DFS, we gave up the further subgroup analysis.

Sensitivity analysis

To further evaluate the robustness of our results, we performed a one-way sensitivity analysis. Therefore, every single study was omitted for each round of analysis, and the pooled HR and 95% CI of the remaining studies were calculated. We found that none of the studies had impact on our pooled HR (data not shown), indicating that our results were robust.

Publication bias

Begg's funnel and Egger's test were performed to assess the publication bias of the literatures in this meta-analysis. As shown in **Figure 4**, the shape of the Funnel plots did not reveal obvious evidence of asymmetry. The Egger's test also showed no significant evidence for publication bias for OS ($P = 0.707$) and DFS ($P = 0.218$).

Discussion

In this study, we meta-analyzed the prognostic value of GOLPH3 in solid cancers. The results showed that overexpression of GOLPH3 indeed predicts poor prognosis in different solid tumors.

GOLPH3 is one member of the Golgi family. Growing evidences demonstrated that GOLPH3 protein plays a critical role in supporting cell

physiological function, such as Golgi architecture maintenance vesicular trafficking [30], protein glycosylation [31, 32], receptor sorting [33] and mitochondrial functions [34]. Recently, more attention was attracted to GOLPH3, since it was identified as an oncogene [5]. As shown by Scott [5], GOLPH3 is frequently targeted for amplification in various malignant tumors, such as lung, melanoma, breast, ovarian, prostate, and pancreatic cancer. GOLPH3 involved in tumorigenesis via regulation of mTOR signaling [5, 6], mTOR is a serine/threonine protein kinase known to integrate different kinds of upstream signals that include energy stress sensing and amino acid to regulate cell proliferation, growth, and survival [35, 36]. In addition, studies also indicated that GOLPH3 may also promote breast cancer proliferation and tumorigenicity via inhibition of the FOXO1 transcription factor and activation of AKT signaling pathway [8]. Importantly, Zhou et al. [7] reported that GOLPH3 was involved in the regulation of RhoA expression and cell migration in glioma cells. Isaji T et al. [9] showed that GOLPH3 could promote cell migration via sialylation. Moreover, Zhang et al. [10] found that GOLPH3 downregulation significantly suppressed YB1 expression, as well as mTOR activity. Further study revealed that GOLPH3 may be also involved in activation of the NF- κ B signaling pathway [14]. All the results demonstrated that GOLPH3 may play an important role in the tumorigenesis and tumor progression.

The overexpression of GOLPH3 with regard to the prognosis was still controversial. Zeng et al. [8] reported the relationship between GOLPH3 expression and survival of breast cancer firstly, showing that breast cancer patients with high

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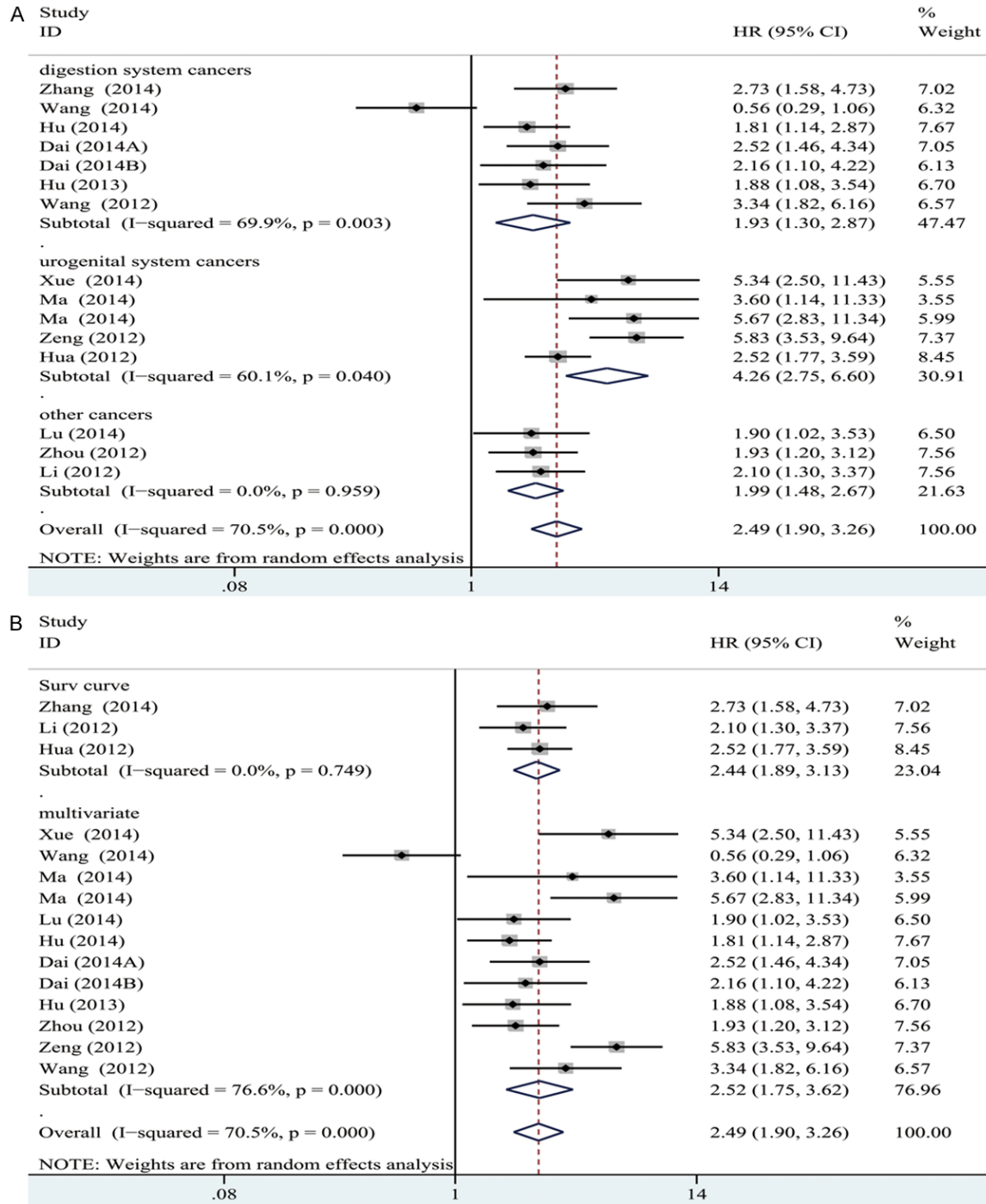


Figure 2. Forest plot of hazard ratio for the association of GOLPH3 overexpression and overall survival. A. Subgroup analysis by tumor type. B. Subgroup analysis by HR estimate. Random-effect model was used.

levels of GOLPH3 presented a relative shorter OS than those with low levels of GOLPH3. Moreover, other studies also reported that overexpression of GOLPH3 was associated with poor prognosis in several types of solid tumors [12-19, 21-26]. However, Wang et al.

demonstrate that the GOLPH3 overexpression was significantly associated with prolonged DFS and OS in colorectal cancer patients [20]. Therefore, we performed this meta-analysis to definite the prognostic significance of GOLPH3 in solid tumors.

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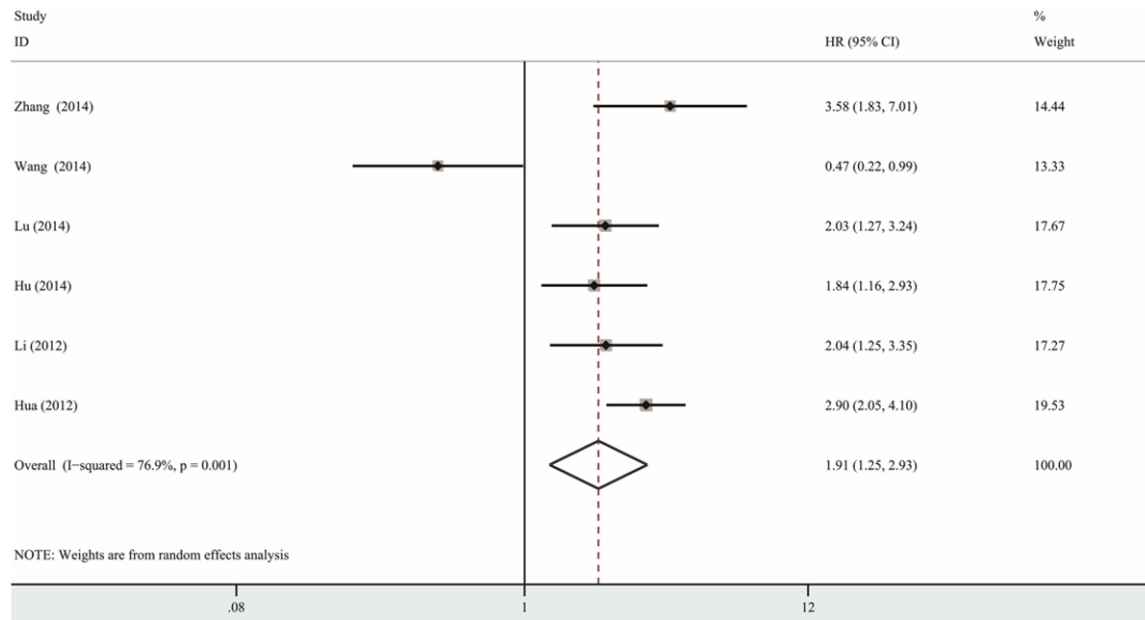


Figure 3. Forest plot of hazard ratio for the association of GOLPH3 overexpression and disease-free survival.

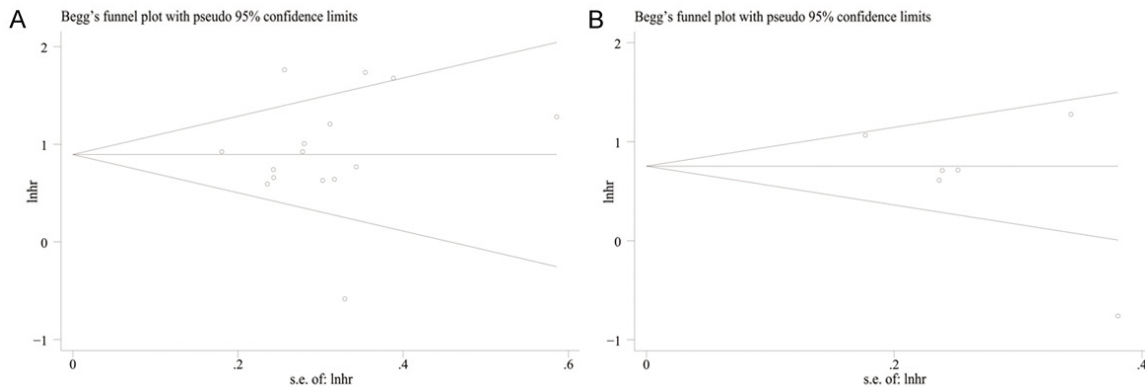


Figure 4. Begg's funnel plots of publication bias. A. Meta-analysis of the association between GOLPH3 overexpression with overall survival (Begg's test $P = 0.276$, Egger's test 0.707 95% CI (-3.63 5.20)). B. Meta-analysis of the association between GOLPH3 overexpression with disease-free survival (Begg's test $P = 0.707$, Egger's test 0.218 95% CI (-13.34 4.14)).

As mentioned above, GOLPH3 might be a potential therapeutic target for novel anticancer drugs. Some researchers had demonstrated that silencing GOLPH3 expression by RNAi technologies significantly suppressed carcinoma cell proliferation, migration in vitro [8, 9, 12, 14, 15, 37, 38] and also reduced tumor growth in xenograft model mice [8, 14, 15]. However, to date, there are no GOLPH3-targeting antibodies or antagonists reported. So it is quite helpful for patients if GOLPH3 antibodies or antagonists was identified and developed.

To our best knowledge, this is the first meta-analysis to demonstrate the prognostic role of

GOLPH3 expression in a variety of solid carcinomas. This meta-analysis has several important implications. Firstly, our results showed that overexpression of GOLPH3 were associated with worse outcome, including OS and DFS. On the basis of these findings, we conclude that GOLPH3 may be used as a prognostic predictor, as well as a therapeutic target, in solid tumors. Secondly, subgroup analysis suggested that higher expression of GOLPH3 correlated with worse OS in urogenital system cancers. Thirdly, in consideration of that GOLPH3-overexpressing xenograft tumors were reported to be more sensitive to rapamycin treatment than GOLPH3-underexpressing ones, we spec-

ulated that GOLPH3 may be a promising markers for predicting clinical outcome of rapamycin treatment, as well as its analogs (such as temsirolimus and everolimus), in solid tumors.

Although the sensitivity analysis showed that the robustness of our results, our findings should be still interpreted with caution. In this meta-analysis, the heterogeneity of the studies included was significant. We used random-effect models and subgroup analyses based on tumor type and HR evaluation to pool the data, but none of the source of heterogeneity was identified. Although the sources of significant heterogeneity were uncertain, there are several potential causes. Firstly, the patients involved in the studies had different baseline characteristics, such as age, tumor type, grade or stage, the treatment they received, follow-up duration and of follow-up loss, which may contributed to the heterogeneous results. Secondly, although all studies in this meta-analysis used immunohistochemical staining for evaluating GOLPH3 expression, the results of this method were affected by many factors, such as storage time, different and dilution of primary antibodies, determination of cutoff values and other relevant factors. All of these factors could account for part of the heterogeneity. Thirdly, HRs estimated from survival curves seemed to be less reliable than that published directly, although subgroup analysis did not identify major deviation, so data extracted from the survival curves without reporting the HR value was also a potential source of this heterogeneity.

However, our meta-analysis has some limitations. Firstly, although no obvious publication bias was detected using Egger's test in this study, potential bias might still have occurred. This might due to the fact that positive results were more likely to be published compared to the negative results. Thus the association between GOLPH3 expression and poor survival should be exaggerated. Secondly, we included articles only written in English, thus, the language bias might exist. Thirdly, all studies included came from China, indicating possible ethnicity bias. Fourthly, there was neither a well-standardized technique for assessment of GOLPH3 expressions nor a clear line dividing high and low expression. So a widely accepted and validated method for GOLPH3 testing is needed.

In conclusion, our meta-analysis showed that GOLPH3 overexpression was significantly associated with shorter overall survival and disease-free survival in different tumor types. Therefore, GOLPH3 may be a potential biomarker for predicting prognosis of patients with solid tumors and helpful in identifying a subgroup of patients that may benefit from rapamycin or its analogs therapy. More importantly, strategies against this protein may be an effective therapeutic approach. However, our findings should be confirmed in further studies due to the limitations in this meta-analysis.

Disclosure of conflict of interest

None.

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