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Original Article

Overexpression of STAT3/pSTAT3 was associated with poor prognosis in gastric cancer: a meta-analysis

Shaozhong He[1,2,5*], Guixiang Liao[2,3*], Yungen Liu[1], Liling Huang[4], Mafei Kang[5], Longhua Chen[2]

[1]Department of Oncology, The People's Hospital of Ganzhou, Ganzhou, China; [2]Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, 1838 North Guangzhou Avenue, Guangzhou, China; [3]Department of Radiation Oncology, The People's Hospital of Shen Zhen, Jinan University, China; [4]Institute of Biochemistry and Clinical Biochemistry, Catholic University of Rome, Largo F. Vito, Rome, Italy; [5]Department of Oncology, The Affiliated Hospital of Guilin Medical College Guilin, China. [*]Equal contributors.

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Abstract: Signal transducer and activator of transcription 3 (STAT3) and phospho-STAT3 (pSTAT3) play important roles in the development of gastric cancer. STAT3 is often associated with cell survival, proliferation, and transformation. The prognostic value of STAT3/pSTAT3 in patients with gastric cancer remains controversial in numerous published studies. The aim of this study was to summarize recent findings relevant to the prognostic role of STAT3 and pSTAT3 in patients with gastric cancer. A meta-analysis was performed by searching Web of Knowledge, EMBASE, and PubMed to identify studies on the prognostic impact of STAT3/pSTAT3 in gastric cancers in August 2014. In all, 10 studies were included in the analysis. Data were collected for comparing survival rates in patients with high STAT3 levels compared to those with low levels. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Sensitivity analysis was conducted, and publication bias was evaluated. Eventually, 1667 cases of gastric cancer were subjected to the final analysis. Among patients with gastric cancer, poor survival was predicted by higher expressions of STAT3 (HR=2.30; 95% CI=1.13-4.68; P=0.02) and pSTAT3 (HR=1.75; 95% CI=1.17-2.61; P=0.006). Moreover, overexpression of STAT3 was associated with poor tumor stage. Additionally, our analysis did not show any statistically significant effect of publication bias regarding STAT3 or pSTAT3. The results of this meta-analysis demonstrated that overexpression of STAT3 and pSTAT3 was associated with poor prognosis in gastric cancer.

Keywords: Gastric cancer, signal transducer and activator of transcription 3, prognosis, meta-analysis

Introduction

Gastric cancer is the fourth most common cancer worldwide and the second most lethal neoplasm overall [1]. Despite progress in multimodality therapy, the five-year survival rate remains low. Therefore, identification of factors that affect patient survival is critical for novel therapy development.

Signal transducer and activator of transcription 3 (STAT3) plays an important role in many pathophysiologic processes, such as differentiation, proliferation, survival, inflammation, angiogenesis, and immune function [2-4]. As an oncogenic transcriptional factor, the role of STAT3 in tumorigenesis has been demonstrated in various human cancers, including breast, pancreatic, prostate, nasopharyngeal, and gastric cancers [5-7]. STAT3 is the most important member of the STAT family. It can be activated via phosphorylation by many cytokines and growth factor receptors [8], such as EGFR, c-Met, and the IL-6 receptor. The activated STAT3 complex then translocates into the nucleus, where it initiates transcription of STAT3 target genes (including cyclin D1, Bcl-xL, survivin, and VEGF) [9]. STAT3 is transiently phosphorylated in normal cells. However, persistent STAT3 phosphorylation is observed in various cancer cells [10].

Recent evidence indicates that STAT3 is aberrantly active in gastric cancers and gastric cancer cell lines [11, 12]. However, the prognostic value of STAT3 or phospho-STAT3 (pSTAT3) in gastric cancer is controversial. Several studies have reported that STAT3 activation is associ-

Table 1. Definitions of 18 items of study reporting quality

Study design
1. Objectives or prespecified hypothesis: state the study objectives, prespecified hypothesis or study protocol
2. Sample size: state a statistical sample size or power calculation
3. Follow-up description: state the follow-up period or the median follow-up time
4. Population source: state health care setting from which patients were recruited
5. Population selection criteria: state inclusion or exclusion
6. Population characteristics: state the population characteristics (e.g., age, gender, and disease stage)
7. Number of patients included in each stage of the analysis and reason for dropout: description of number of patients at different stage, including the number of patients who participate in the study, who met the inclusion criteria, and who followed up and reason for dropout
Assay method
1. Sample handling: state the method of storage
2. Assay method: state the type of assay method used to measure Stat3/p-Stat3
3. Manufacturer: state the name of company which makes the assay for Stat3/p-Stat3
4. Cut off point determination: state methods used for cut-off point determination
Confounders
1. Conventional risk factors: state the conventional risk factors (e.g., age, gender, depth of tumor, lymph node metastasis) relating with the Stat3/p-Stat3 expression
2. Other biomarkers (e.g., p53, PCNA, VEGF, and microvessel density): state other biologic marker relating with the disease
Outcome
1. Clinical endpoint: define the clinical endpoint
2. Validation: state the outcome events checked by independent source (e.g., medical records, outpatient visits, by letter, and by telephone)
Analysis
1. Univariate estimate: report the effect of Stat3/p-Stat3 on outcome
2. Multivariate estimate: adjusted for risk factors or other biomarkers (list above)
3. Missing value: state the number of patients with missing value for Stat3/p-Stat3 or confounders and how to deal with it

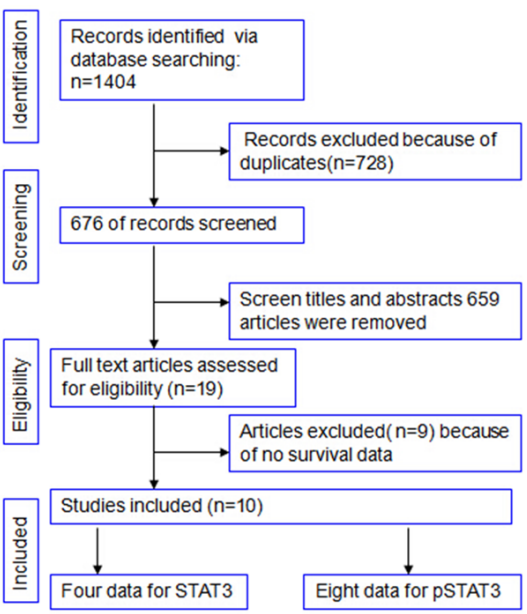

Figure 1. Flow diagram of study selection.

ated with poor prognosis for gastric cancer patients [13, 14]. On the contrary, another study found no significant relationship between STAT3 activation and patient survival [15]. Thus, we conducted this meta-analysis to explore the biological significance of STAT3/pSTAT3 in gastric cancer.

Materials and methods

Literature search

We searched the PubMed, EMBASE, and ISI Web of Knowledge databases in August 2014, for all eligible studies. The search was conducted using the following search terms: "STAT3" OR "signal transducer and activator of transcription 3", and "gastric OR stomach" and "cancer OR carcinoma". In an effort to broaden the search, reference lists from identified primary studies were then searched carefully to include some eligible studies that would have been missed by electronic searches alone.

Study selection

Titles and abstracts of all candidate papers were screened by two reviewers (G Liao and S He). Papers that could not be categorized based on titles and abstracts alone were retrieved for full-text review. Two reviewers screened and checked these papers individually according to the inclusion criteria. Disagreements between reviewers were resolved through consensus with a third reviewer (L Chen).

Inclusion criteria for the primary studies were as follows: (i) Diagnosis of gastric cancer in

Table 2. Basic characteristics of included studies evaluating survival in gastric cancer patients

First author	Year	Country	Cases	HR	Survival analysis	Follow up time (month)	Technique	Cut-off value	Quality assessment
STAT3									
Chatrerje D	2008	USA	143	3.00 (1.82-4.95)	Univariate	34 (12-180)	IHC	≥4	13
Deng J	2010	China	53	4.44 (1.80-10.93)	Univariate	35 (4-85)	IHC	>3	15
Kim DY	2008	Korea	100	2.73 (0.83-9.05)	Univariate	NA	IHC	>10%	13
Xiong H	2012	China	305	0.66 (0.24-1.80)	Multivariate	39.7 (4-84)	IHC	≥5%	13
pSTAT3									
Deng J	2010	China	53	9.605 (3.11-29.69)	Multivariate	35 (4-85)	IHC	>3	15
Deng J	2013	China	114	2.49 (1.41-4.39)	Multivariate	38 (2-108)	IHC	>25%	15
Gong W	2005	USA	86	1.36 (0.79-2.36)	Multivariate	25.7	IHC	>3	15
Inokuchi M	2011	Japan	126	2.00 (0.91-4.5)	Multivariate	73 (2-135)	IHC	>10%	12
Lee J	2009	Korea	311	1.51 (1.03-2.21)	Multivariate	NA	IHC	≥1%	15
Woo S	2011	Korea	285	0.57 (0.36-0.91)	Univariate	51 (1-72)	IHC	>1%	15
Xiong H	2012	China	305	2.10 (1.53-2.89)	Multivariate	39.7 (4-84)	IHC	≥5%	13
Yakata Y	2006	Japan	111	1.63 (0.73-3.65)	Univariate	NA	IHC	>10%	11

NA, not available, STAT3, signal transducer and activator of transcription 3, pSTAT3, phospho-STAT3, IHC: immunohistochemistry.

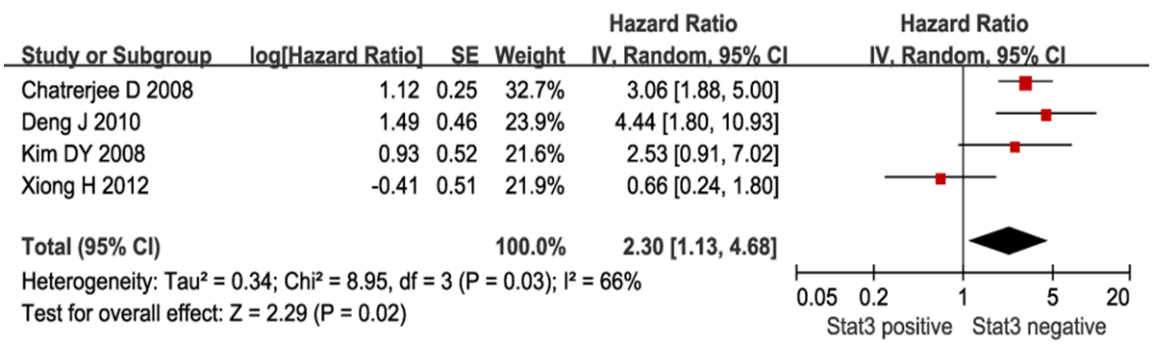

Figure 2. Meta-analysis of STAT3 expression and prognosis in patients with gastric cancer. Results are presented as individual and pooled HR, and 95% CI.

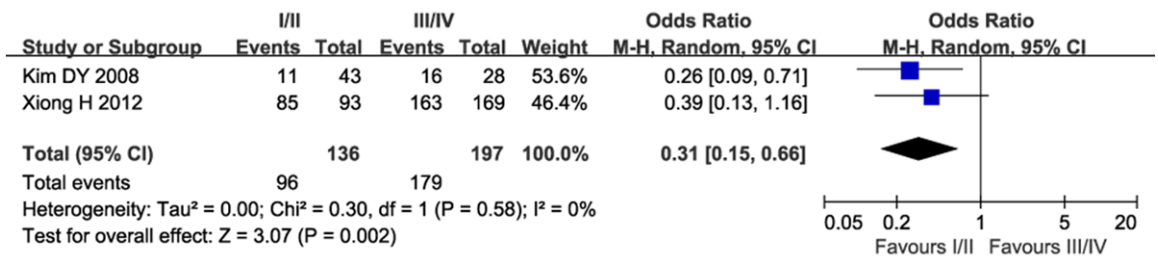

Figure 3. Meta-analysis of STAT3 expression and TNM stage in patients with gastric cancer.

humans was proven, (ii) STAT3 or pSTAT3 evaluation was performed, (iii) data reported was related to the survival of patients with gastric cancer, and (iv) if an author published the same group of cases in different journals, the most recent and completed study was included. In addition, the language was restricted to English. Reviews, letters to the editors, and meeting abstracts were excluded.

Data extraction

Two authors carefully reviewed all eligible studies and extracted the following data: first au-

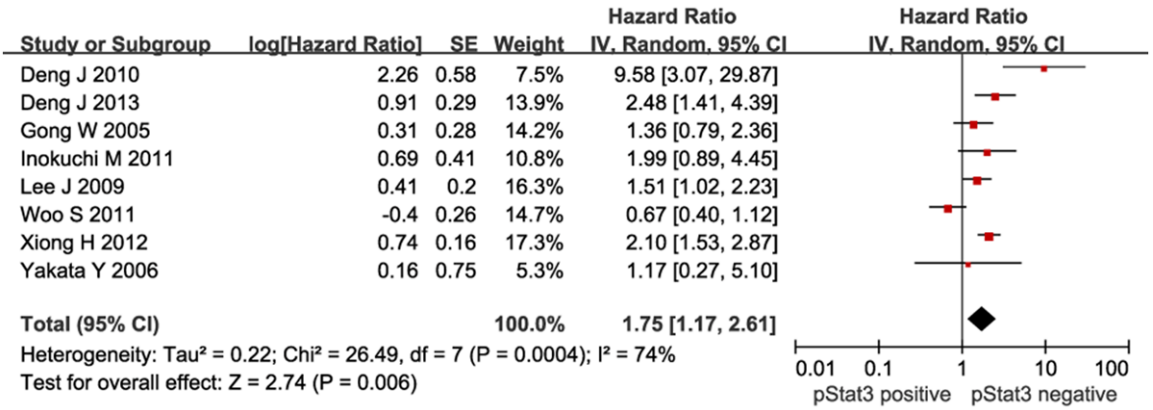

Figure 4. Meta-analysis of pSTAT3 expression and prognosis in patients with gastric cancer. Results are presented as individual and pooled HR, and 95% CI.

Table 3. Subgroup analyses and meta-regression the association between pSTAT3 and survival in gastric cancer

Subgroup	No. of studies	No. of patients	Pooled HR (Random)		Meta-regression	Heterogeneity	
			HR	95% CI	*P* value	I^2 (%)	*P* value
Country					0.579		
Asian country	7	1352	1.63	1.11-2.38		66	0.008
Non-Aisan country	2	229	2.06	0.93-4.56		79	0.03
Year					0.708		
<2010	5	731	1.86	1.27-2.70		43	0.13
>2010	4	830	1.61	0.88-2.94		82	0.0009
Survival analysis					0.687		
Multivariate	5	942	1.85	1.51-2.26		0	0.42
Univariate	4	619	1.58	0.62-4.01		84	0.0003
Number of patients					0.214		
<200	6	660	2.16	1.61-2.91		12	0.34
>200	3	901	1.32	0.72-2.42		86	0.0009
Antibody used					0.406		
Stat3	3	329	2.16	1.22-3.83		58	0.09
p-Stat3	6	1232	1.56	1.03-2.34		70	0.005
Quality score					0.118		
≤14	5	765	2.28	1.79-2.89		0	0.63
>14	4	796	1.35	0.82-2.23		75	0.007

thor, publication year and country, the number of patients evaluated, follow-up times, detection methods, cut-off values, and survival data. Any disagreements in the data extraction were resolved by discussion among authors.

Methodological assessment

Methodological assessment was conducted according to REMARK guidelines [16] for each eligible study by independent reviewers (G Liao and S He). The REMARK guidelines are widely used for evaluating the quality of studies on prognostic markers of cancers that were included in meta-analyses [17, 18]. Briefly, the scale contained 18 items (**Table 1**), and each item was scored according to an ordinal scale (possible values 1 and 0): 1 represented the complete description or partly matched description, whereas 0 represented no matched description. The total scored was ranged from 0 to 18.

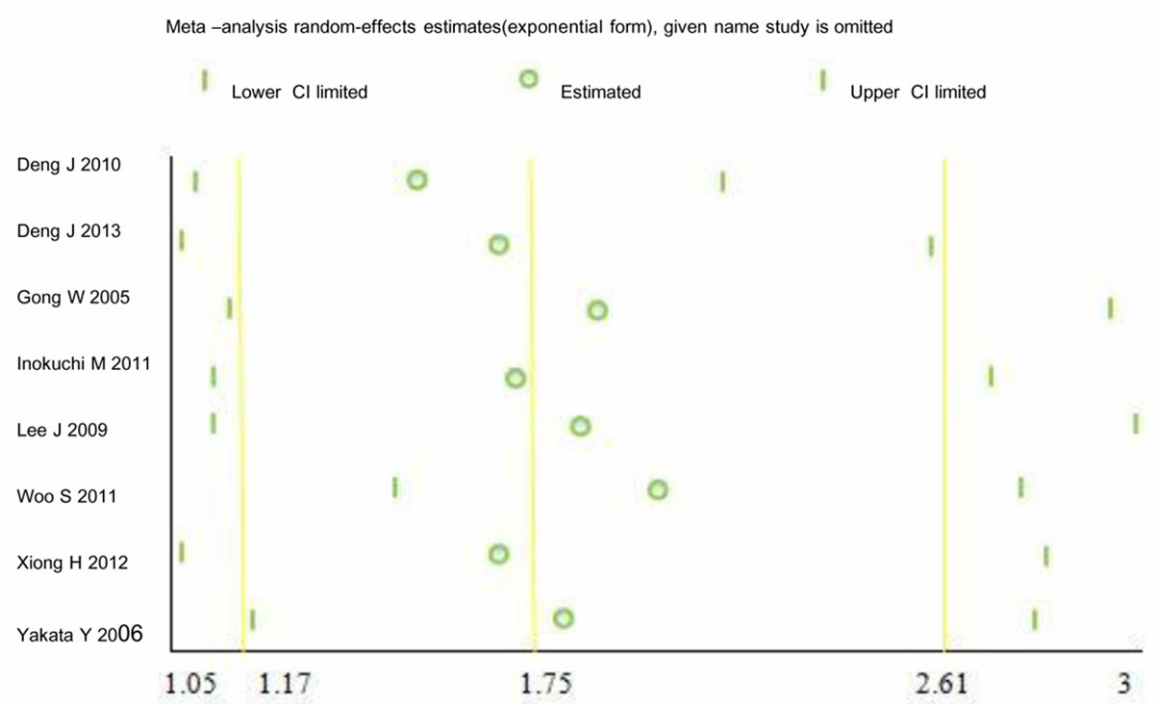

Figure 5. Sensitivity analysis results.

Statistical analyses

Hazard ratios (HRs) and 95% confidence intervals (CIs) were applied to estimate the association between STAT3/pSTAT3 expression and survival (including disease specific survival and overall survival) in patients with gastric cancer. The most accurate results were found in studies that reported the exact HR values and its 95% CIs. However, for some of the studies that did not report HR and 95% CIs directly in the study, mathematical HR approximation was estimated using Parmar's methods [19]. If the available survival data were only in the form of figures, we read Kaplan-Meier curves by using Engauge Digitizer version 4.1 (free software down-loaded from http://sourceforge.net) and extracted survival rates to calculate the HR and standard error (SE). Odds ratio was applied for evaluating the relationship between STAT3 expression and tumor stage.

The meta-analysis was conducted by Review Manager Software (version 5.2, The Nordic Cochrane Centre, Copenhagen, Denmark). Statistical heterogeneity was evaluated by Cochrane's Q test (Chi squared test; χ^2) and by measuring inconsistency (I^2) [20, 21]. I^2>50% represents significant heterogeneity. Given that data were gathered from distinctly different populations with potential heterogeneity [22], a random effects model was adopted for the pooled analysis of HRs with 95% CIs. In addition, risk of publication bias was assessed using a funnel plot for overall survival, and the exact statistical value was assessed by using a method reported by Egger M [23]. Sensitivity analysis was performed by sequential omission of any single study. *P* values of less than 0.05 were considered statistically significant.

Results

The primary search retrieved 1404 studies; 148, 657, and 617 articles were retrieved from PubMed, EMBASE, and Web of Knowledge, respectively. First, 728 duplicated studies were removed by Endnote software; then, the remaining 676 studies were assessed by reading their titles and abstracts. At this stage, studies that did not meet the criteria for our meta-analysis were excluded. Thus, 19 papers were identified for full-text evaluation. After carefully reading the entire papers, nine studies were excluded because they did not evaluate STAT3 expression on survival or survival data could not obtain in the study. Finally, 10 studies that met our inclusion criteria were

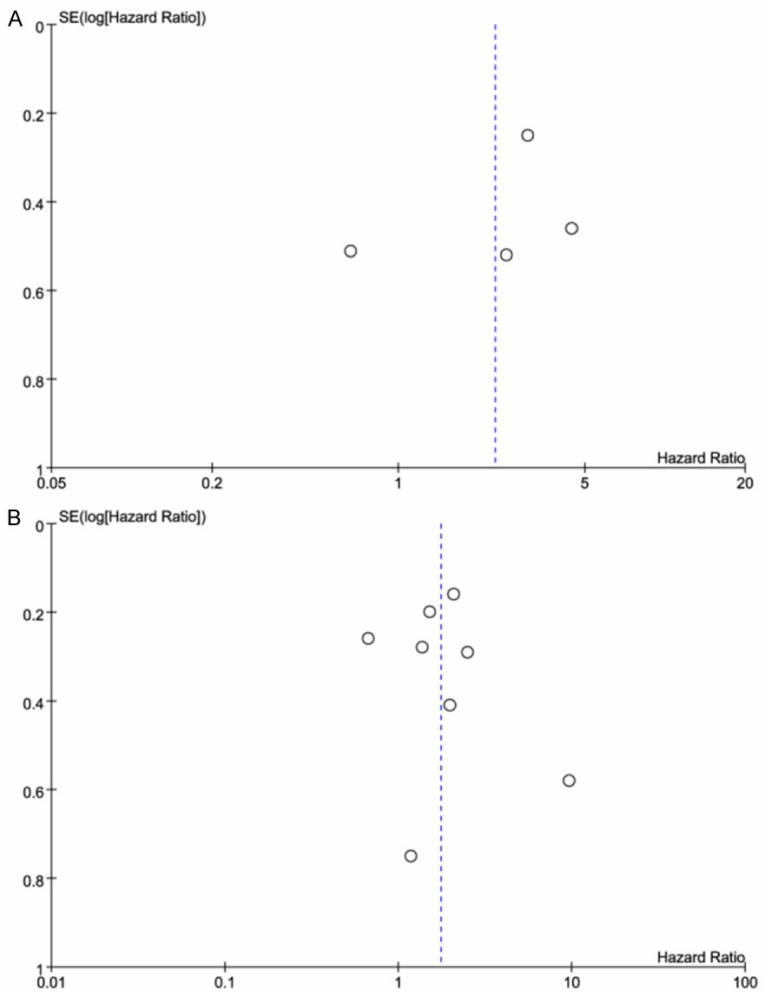

Figure 6. Funnel plot of the HR for publication bias, A. For STAT3; B. For pSTAT3.

included in our meta-analysis [13, 14, 24-31]. These included four studies that analyzed STAT3 as a prognostic marker and eight studies that analyzed pSTAT3 as a prognostic marker. The selection chart is listed in **Figure 1**. The major baseline characteristics of the included studies and quality assessments are reported in **Table 2**. The details of each study quality assessment are provided in Table S1. Quality scores ranged from 11 to 15, with a median value of 13.7. All of the included studies mentioned study objectives, sample sizes, population sources, population characteristics, assay methods, the antibody manufacturers, cut-off values, clinical endpoints, and univariate survival analyses. However, fewer studies provided information on number of patients included in each stage of the analysis and reason for dropout, confounders of other biological markers, and missing values.

All of the studies were published from 2005 to 2013. The sample size ranged from 53 to 311 cases, with most studies (8/10) reporting more than 100 cases. All of the included studies detected STAT3 and pSTAT3 expression by immunohistochemistry.

Meta-analysis of STAT3 expression in gastric cancer

Pooled analyses of the four studies that evaluated STAT3 expression in gastric cancer was shown in **Figure 2**. The results indicate that STAT3 overexpression was positively associated with poor survival in patients with gastric cancer (HR=2.30; 95% CI=1.13-4.68; P=0.02). Of note, the heterogeneity was statistically significant (χ^2=8.95; P=0.03; I^2=66%).

In order to evaluate the effect of STAT3 expression on the clinical characteristics of gastric cancer, we next studied the relationship between STAT3 expression and tumor node metastasis (TNM) stage. As shown in **Figure 3**, STAT3 overexpression correlated with higher TNM stage (Odds ratio =0.31; 95% CI=0.15-0.66; P=0.002).

Meta-analysis of pSTAT3 expression in gastric cancer

Increased levels of pSTAT3 was associated with a significant increase of mortality risk as compared to low pSTAT3 levels in the random effects model (HR=1.75; 95% CI=1.17-2.61; P=0.006), although significant heterogeneity (χ^2=26.49; P=0.0004; I^2=74%) was present in **Figure 4**.

To investigate the cause of the heterogeneity, meta-regression and subgroup analyses were performed to evaluate the following factors: study country, publication year, survival analysis, quality score, and number of patients. The results showed that none of these factors sig-

nificantly influenced the heterogeneity (**Table 3**). We performed a leave-one-out sensitivity analyses by excluding one study at a time and recalculating HR and 95% CI values. The results of this analysis confirmed that pSTAT3 over expression was association with mortality risk (**Figure 5**). Moreover, by excluding the study reported by Woo S [28], increased pSTAT3 indicated poor survival (HR=2.00; 95% CI=1.45-2.75; P<0.0001), and there was no significant heterogeneity among the remaining studies (χ^2=12.17; P=0.06; I^2=51%).

Publication bias

For STAT3, a funnel plot of the HR showed no obvious publication bias (**Figure 6A**) and the assessment of publication bias by Egger's tests showed no significance (P=0.541) for studies included in the analysis of survival. For pSTAT3, there was visual symmetry in the funnel plot graph (**Figure 6B**), and Egger's tests showed no statistical significance of publication bias (P=0.726).

Discussion

STAT3 proteins are involved in various cellular processes and are major effectors of cytokine and chemokine receptor signaling. Moreover, STAT3 proteins are key modulators of a variety of human cancers [32], regulating cell proliferation, apoptosis, survival, metastasis, and angiogenesis [33]. In normal cells, STAT3 phosphorylation occurs only transiently [34]. By contrast, almost 70% of human cancers display persistent STAT3 phosphorylation. Phosphorylated STAT3 initiates transcription of multiple cancer-associated genes, such as Cyclin D1, Bcl-xl, survivin, IL-6, and MMP-9. As such, STAT3 is a molecular hub for diverse signaling pathways, and is considered as a novel molecular target for cancer drugs [35]. A previous meta-analysis reported that over expression of STAT3 or pSTAT3 is associated with poor prognosis in patients with non-small-cell lung cancer [36]. However, STAT3/pSTAT3 as a prognostic marker of overall survival in patients with gastric cancer needs to be fully explored.

This meta-analysis was conducted to elucidate the prognostic role of STAT3/pSTAT3 expression in patients with gastric cancer. Our study combined results from four individual studies that indicated STAT3 was significantly associated with poor survival in patients with gastric cancer (HR=1.73; 95% CI=1.25-2.39; P=0.0009). Our study also analyzed results from eight individual studies that demonstrated pSTAT3 was associated with an unfavorable prognosis in patients with gastric cancer (HR=1.75; 95% CI=1.17-2.61; P=0.006). To our knowledge, this is the first meta-analysis to investigate STAT3/pSTAT3 as a prognostic marker in gastric cancer.

To gain further insights into the role of STAT3/pSTAT3 as a biological marker, we next investigated the association of STAT3/pSTAT3 expression with TNM stage, a classification currently used for the prognostic judgment for patients affected with solid cancers. TNM staging is regarded as the most reliable factor to predict the prognosis of gastric cancer. With appropriate treatment, up to 90% of gastric cancer patients will reach the 5-year survival mark [37]. On the contrary, in cases of advanced gastric cancer, the response to treatment rates and survival rates are poor. Specially, lymph node status and lymph node resection are both effective prognostic factors [38, 39]. Our study suggested that high expression of STAT3, but not pSTAT3, significantly correlated with TNM. Due to the limited number of studies, the correlation is required to be further investigated.

The prognosis of gastric cancer is also affected by the race of patients. In Western countries, the incidence of gastric cancer is declining; however, patients who are diagnosed with gastric cancer are presenting with advanced TNM stages and have a poor prognosis. In contrast, in Japan, where the incidence of gastric cancer is still high, the percentage of cases diagnosed at the stage of "early gastric cancer" has greatly increased, and thus, the prognosis has also improved [40]. One study reported that in patients with gastric cancer, when grouped by ethnicity, Asians have improved survival compared to other ethnic categories (Caucasian, African-origin, American Indians, or others) [41].

Due to the important role of STAT3 in cancer, STAT3 has been validated as an anti-cancer target in several studies [42], and many studies have shown inhibition of STAT3 activation can be effective for cancer prevention and treatment [43, 44]. A previous study indicated that combined use of NF-κB and STAT3 inhibitors

may enhance the efficacy of the anti-metastatic treatment of gastric cancer [45]. Another study demonstrated that STAT3 inhibition leads to profound sensitization to both chemotherapy and radiotherapy in a cancer mouse model [46].

We should consider the following limitations in this meta-analysis. First, this meta-analysis did not address heterogeneity issues, and a notable heterogeneity was revealed amongst these studies. However, in terms of pSTAT3, when we conducted a sensitivity analysis by omitting the study reported by Woo S [28], no statistically significant heterogeneity was noted among the remaining studies (χ^2=12.17; P=0.06; I^2=51%). Furthermore, to identify potential sources of heterogeneity among the pSTAT3 data, meta-regression and subgroup analyses were conducted. The results of meta-regression revealed that study location, year of publication, quality score, and number of patients had no significant correlation to heterogeneity (**Table 3**). Therefore, these results suggested that the study reported by Woo S [28] contributed significantly to the heterogeneity. Since there were only four studies regarding STAT3 as a prognostic marker in gastric cancer, we did not perform subgroup analysis and meta-regression analysis for STAT3.

Second, most included studies were of a retrospective nature; the patients were selected randomly only in one study [25]. This fact could contribute to possible publication bias. However, our statistical test indicated no significant publication bias amongst the studies. To date, high-quality double-blind randomized controlled trials to evaluate the relationship between STAT3 and patient survival have not been reported. Future studies with well-designed should assess the prognostic role of STAT3 in gastric cancer.

Third, the included studies in our meta-analysis are all published in English that might contribute to the possibility of language bias. In addition, we excluded unpublished studies and conference abstracts because they did not have sufficient information. Those unpublished studies might have more frequently refuted our hypotheses.

Fourth, although we found a positive correlation between STAT3 expression and TNM stage, the definition of TNM stage was in accordance with different version of edition and the number of studies was limited; thus, future studies should pay attention to these issues. Finally, according to the quality assessment, few studies had included the number of patients in each stage, few had missing value, as well as had confounders of other biological markers; thus, future studies should account for these biases.

In summary, our data suggest that STAT3 or pSTAT3 could be a valuable prognostic marker in gastric cancer, with higher STAT3 protein expression significantly associating with higher TNM stage and increased pSTAT3 associating with increased mortality risk. Owing to the limited scope of the study, future studies should be performed with prospective, well-designed, randomized controlled trials to fully elaborate the prognostic value of STAT3/pSTAT3 in gastric cancer.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Longhua Chen, Department of Radiation Oncology, Nanfang Hospital, 1838 North Guangzhou Avenue, Guangzhou 510515, China. Fax: 86-20-61642136; E-mail: chenlhnfy@163.com; Dr. Mafei Kang, Department of Oncology, The Affiliated Hospital of Guilin Medical College Guilin, China. E-mail: kangmafei@sina.com.cn

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Table S1. Quality assessment details of each included study according to REMARK guidelines

Study	Scale items																		Quality score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Chaterjee D	1	1	1	1	1	1	0	1	1	1	1	0	0	1	1	1	0	0	13
Deng J 2013	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	0	15
Gong W	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	0	15
Kim DY	1	1	0	1	0	1	1	1	1	1	1	1	0	1	1	1	0	0	13
InoKuki M	1	1	1	1	0	1	0	0	1	1	1	1	0	1	0	1	1	0	12
Lee J	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	15
Woo S	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0	1	15
Xiong H	1	1	1	1	0	1	0	0	1	1	1	1	1	1	0	1	1	0	13
Yakata Y	1	1	0	1	0	1	0	1	1	1	1	1	0	1	0	1	0	0	11
Deng J 2010	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	0	15