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REVIEW – CLINICAL ONCOLOGY

The prognostic value of pSTAT3 in gastric cancer: a meta-analysis

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Abstract
Introduction The prognostic value of pSTAT3 in gastric cancer has been assessed for years while the results remain controversial and heterogeneous. Therefore, we conducted this meta-analysis to determine the prognostic effect of pSTAT3 in gastric cancer patients.
Methods We searched PubMed, Embase and Web of Science and eight studies comprising 1314 gastric cancer patients were included in our meta-analysis. Hazard ratios (HRs) with 95 % confidence interval (95 % CI) were extracted to perform meta-analysis on the overall survival. Subgroup analysis according to study location, publication year, number of patients and quality score of studies were also investigated.
Results Our results revealed that pSTAT3-positive patients had a significant increase in mortality risk as compared to pSTAT3-negative patients in the random-effects model (combined HR 1.87, 95 % CI 1.28–2.74). However, our result showed no statistically significant association between pSTAT3 and clinicopathological characteristics (TMN stage, lymph node metastasis, grade of differentiation, Lauren classification and distant metastasis) of gastric cancer.
Conclusion In conclusion, our meta-analysis suggests that positive expression of pSTAT3 is associated with poor prognosis in gastric cancer patients.

Keywords pSTAT3 · Gastric cancer · Prognosis · Meta-analysis

Background

Gastric cancer is the fifth most common cancer over the world, and the fatality rate is 75 %. It is also the third leading cause of death in both sexes (723,000 deaths), accounting for 8.8 % of the total deaths from cancer (Fock 2014). However, it has been reported that the incidence of gastric cancer has been decreasing in most industrialized countries over the past three decades. In spite of this favorable trend, a large geographical variability in both incidence and mortality rates still persists (Zilberstein et al. 2012). The burden of the disease is higher in less developed countries, where 70 % of the cases occur.

The STAT proteins, composed of seven members, are a family of transcription factors which regulate expression of genes involved in both normal and pathological cellular processes(Deng et al. 2010).They are normally inactive within the cytoplasm of cells and become activated by tyrosine phosphorylation in response to cytokines and growth factors(Yakata et al. 2007). Among STAT family members, STAT3 is of particular interest due to its constitutive phosphorylation (pSTAT3) in a large proportion of human cancers and its ability to induce neoplastic transformation (Buettner et al. 2002). Actually, STAT3 can be activated by growth factor receptors, including epidermal growth factor receptor (EGFR), fibroblast growth factor receptor and so on(Yu et al. 2007). Upon activation by upstream receptor tyrosine kinases, of which EGFR plays a dominant role(Alvarez et al. 2006), STAT3 is phosphorylated (pSTAT3) and acts as a transcriptional factor by binding to promoter regions of its target genes that regulate cell cycle progression, apoptosis, angiogenesis,

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tumor invasion and metastasis (Kanda et al. 2004). Either EGFR blockade or EGFR inhibitors can decrease STAT3 activation (Kluge et al. 2009). Moreover, several studies have demonstrated that STAT3 pathway activation is associated with aggressiveness of tumors, drug resistance and thus poor prognosis Gritsko et al. 2006). The constitutive activation of STAT3 signaling is thought to induce tumorigenesis by up-regulations of apoptosis inhibitors such as Bcl-XL, Mcl-1, survivin and cell cycle regulators such as cyclin D1 and c-Myc and angiogenesis inducers including vascular endothelial growth factor(VEGF) (Buettner et al. 2002; Jing et al. 2005).

It has been found that the expression of STAT3 has prognostic value in various cancers, including gastric cancer. In clinical samples, constitutive activation of STAT3 positively correlated with a poor prognosis for patients with prostate cancer (Mora et al. 2002), serous ovarian cancer (Meinhold-Heerlein et al. 2005) or breast cancer (Sheen-Chen et al. 2008). On the contrary, constitutive activation of STAT3 showed a positive association with a good prognosis for patients with head and neck cancer (Nagpal et al. 2002) or oral squamous cell cancers (Shah et al. 2006). However, the prognostic value of pSTAT3 for gastric cancer patients remains controversial. Several studies showed that the positive expression of pSTAT3 correlate with the poor prognosis for gastric cancer patients (Deng et al. 2010, 2013; Yakata et al. 2007; Inokuchi et al. 2011; Lee et al. 2009; Song et al. 2014; Xiong et al. 2012). In contrast, in another study, no significant correlation between them was noted (Choi et al. 2006). Besides, Woo et al. (2011) reported that positive expression of pSTAT3 significantly correlated with better prognosis. Thus, we conducted a meta-analysis of all available cohort studies to determine the role of pSTAT3 protein, the active form of STAT3, in the prognosis of gastric cancer patients.

Methods

Identification and eligibility of relevant studies

We searched PubMed, Embase and Web of Science to identify studies that assessed the prognostic value of pSTAT3 expression in gastric cancer patients using immunohistochemistry. The search ended in October 18, 2014, and no lower date limit was used. The following keywords and MeSH terms were used in searching: "gastric cancer," "gastric carcinoma," "gastric neoplasms," "stat3," "pstat3," "Signal transducer and activator of transcription 3," " phospho-STAT3," "prognosis," "prognostic" and "survival." For the full-text reading and final evaluation, we only performed the studies published in English language. We also searched the bibliographies cited in an identified article manually to find other applicable studies.

The studies must conform with the following criteria to be eligible: (1) the studies must evaluate the correlation between the expression of pSTAT and the overall survival of gastric cancer patients; (2) the patients diagnosed with gastric cancer must be confirmed by histopathologic examinations; (3) the expression of pSTAT3 in cancer cells must be tested by immunohistochemistry; (4) the studies must provide sufficient information for us to estimate their HRs and the 95 % CI; and (5) the articles must be fully published in English. If the study could not meet the inclusion criteria, it would be excluded. When the results reported in identified studies have the possible overlap (e.g., same authors, institutions), only the most recent or the most complete study was involved in the analysis.

Data extraction

Two investigators systematically extracted the most relevant data from each study including the first author's surname, geographical location, language of publication, sample size, the source of the subjects, publication year of the article, study type, protein expression levels, tumor characteristics and protein detection method.

Methodological assessment

To evaluate the study methodology, two investigators read each publication independently and scored them using the Newcastle–Ottawa Scale (NOS) criteria (Stang 2010). The NOS criteria evaluate three aspects of the study: (1) subject selection: 0–4; (2) comparability of subject: 0–2; and (3) clinical outcome: 0–3. NOS scores ranged from 0 to 9, and a score ≥ 7 indicates good quality.

Statistical analysis

To value the impact of pSTAT3 on survival, we calculated the HR of each study. The most accurate approach is to get the HR and 95 % CI directly from the paper, or calculating them using the parameters offered in the manuscript. If the study did not provide a HR but reported the data in the form of the survival curve, survival rates at certain specified times were extracted from them for the reconstruction of the HR estimate and its variance, with the assumption that the rate of patients censored was constant during the follow-up (Parmar MK et al. 1998).

The individual HR estimates were pooled into a summary HR using the method reported by Yusuf et al. (1985), which consists of using a fixed-effects model with the assumption of the homogeneity of the individual HRs. This assumption was tested by performing Cochran's Q-statistic and I^2 tests for heterogeneity (Zintzaras and Ioannidis 2005). If Q-test shows a $p < 0.05$ or I^2 test exhibits >50 % which indicates significant heterogeneity, the random-effect model was conducted; otherwise, the fixed-effects model was used. We also conducted meta-regression and subgroup analysis by stratifying on study location, publication year, number of patients and quality

score. For the pooled analysis of the correlation between positive expression of pSTAT3 and clinicopathological features (TMN stage, lymph node metastasis, grade of differentiation, Lauren classification and distant metastasis), odds ratios (ORs) and their 95 % CIs were combined to estimate the effect. If the HR or OR > 1 implied a worse prognosis for the group with positive pSTAT3 expression and would be considered to be statistically significant if the 95 % CI did not overlap 1.

To evaluate the influence of single studies on the overall estimate, we performed a sensitivity analysis. In addition, funnel plots and Egger's linear regression test were applied to investigate publication bias (Peters et al. 2006). Analysis was performed with STATA version 10.0.

Results

Study selection and characteristics

As shown in Fig. 1, we identified 335 articles using the search strategy in PubMed, Web of science and Embase as described above. We reviewed the titles and abstracts of all 335 articles and excluded 84 articles. Then, we systematically reviewed the full texts and another 236 articles were further excluded. Another three studies were also excluded due to the lack of data integrity, and four studies were excluded due to the lack of comparability. After selection, a total of eight publications were finally enrolled for analysis of the prognostic value of pSTAT3 expression in gastric cancer.

The clinical features of these eight included studies are summarized in Table 1. All these studies evaluated patients from East Asia, including four from China, two from Korea and two from Japan. The eight studies comprised 1314 patients, with sample sizes ranging from 60 to 303 patients. Two of these studies enrolled less than 100 patients, and three studies included more than 200 patients. The information on Lauren classification was available in six studies comprising 992 patients. Among these patients, there are 377 patients with intestinal type (38.0 %), 607 with diffuse type (61.2 %) and eight with mixed type (0.8 %). The NOS scores of all included studies were ≥5.

Study results report and meta-analysis

The forest plot of the individual HR estimates and results from the meta-analysis are shown in Fig. 2. Overall,

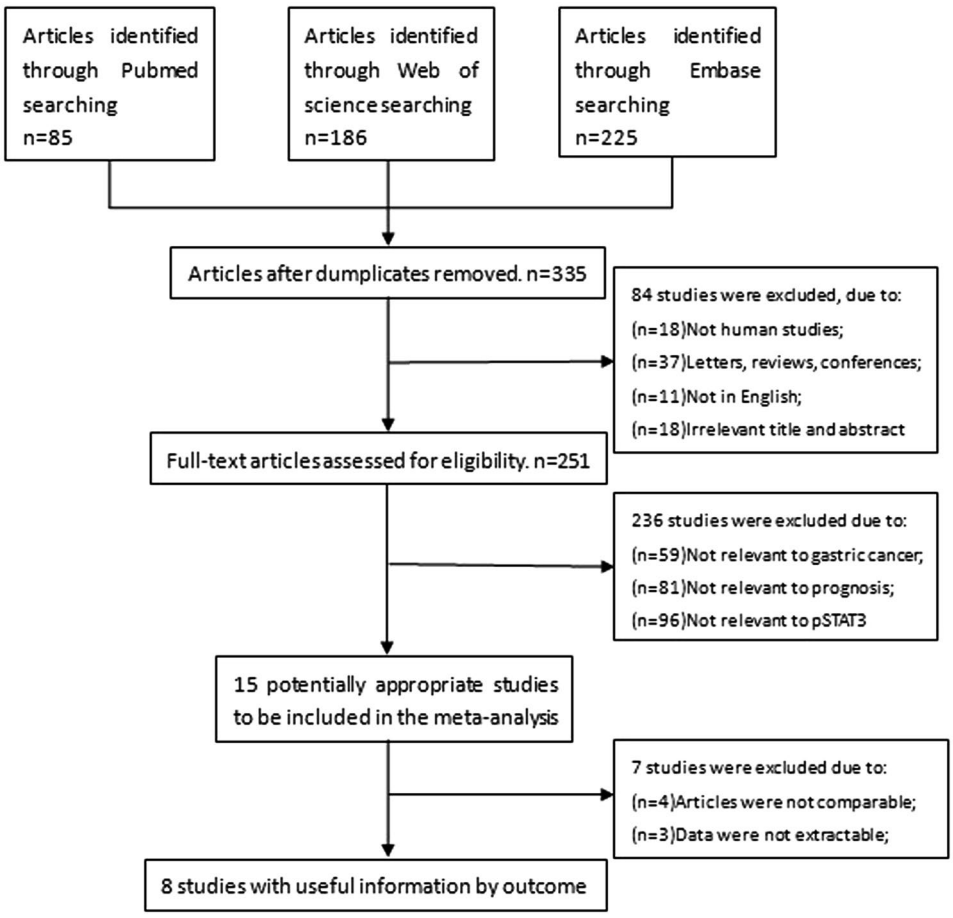

Fig. 1 Flow chart shows study selection procedure

Table 1 Main features and methodological assessment of the included studies

References	Study location	No. of patients	Gender (M/F)	Lauren classification			pSTAT3		NOS score
				Intestinal	Diffuse	Mixed	Positive	Negative	
Woo et al. (2011)	Korea	285	193/92	109	171	5	101	179	8
Inokuchi et al. (2011)	Japan	126	88/38	48	78	0	52	74	7
Yakata et al. (2007)	Japan	111	63/48	63	48	0	55	56	7
Song et al. (2014)	China	60	46/14	–	–	–	35	25	8
Deng et al. (2013)	China	114	76/38	37	75	2	89	25	7
Xiong et al. (2012)	China	262	176/86	–	–	–	136	126	5
Deng et al. (2010)	China	53	37/16	25	28	0	26	27	8
Lee et al. (2009)	Korea	303	206/97	95	207	1	79	224	6

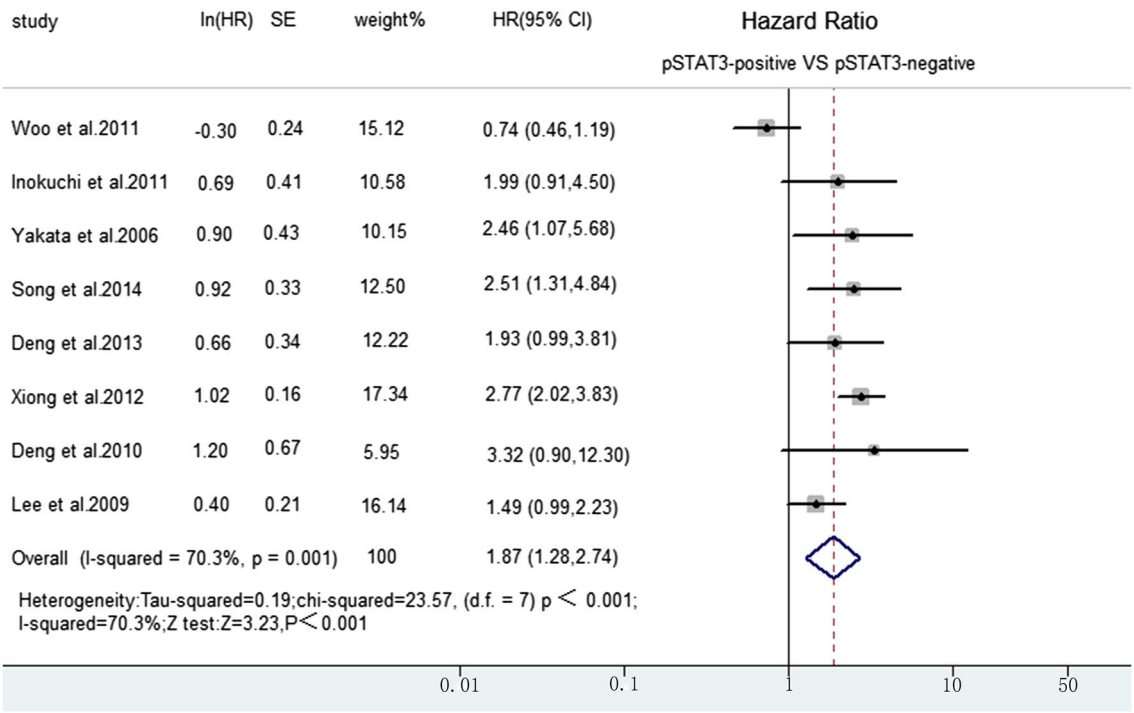

Fig. 2 Meta-analysis of effects of pSTAT3 on overall survival of patients with gastric cancer. Results are presented as individual and pooled hazard ratio (HR) and 95 % confidence interval (CI)

pSTAT3-positive patients indicates a significant increase in mortality risk as compared to pSTAT3-negative patients in the random-effects model (combined HR 1.87, 95 % CI 1.28–2.74), as a significant degree of heterogeneity (I^2 = 70.3 %, p = 0.001) was presented. Meta-regression analysis and subgroup analysis by study location, publication year, number of patients and quality score were also performed (Table 2). The results showed that a significant relation between pSTAT3 positive and OS was exhibited in both China (HR = 2.61, 95 % CI 2.01–3.38) and Japan (HR = 2.20, 95 % CI 1.24–3.93), while the result in Korea indicated no statistical significance (HR = 1.06, 95 % CI 0.54–2.11). Other factors including publication year, number of the patients and NOS scores did not change the significant prognostic impact of positive pSTAT3 expression. However, subgroup analysis and meta-regression analysis failed to reveal the source of heterogeneity.

Our result showed no statistically significant association between pSTAT3 and clinical parameters such as TMN stage (OR = 0.93, 95 % CI 0.29–2.93, random effect), lymph node metastasis (OR = 2.86, 95 % CI 0.71–11.56, random effect), grade of differentiation (OR = 1.36, 95 % CI 0.15–12.44, random effect), Lauren classification (OR = 1.01, 95 % CI 0.69–1.48, fixed effect) and distant metastasis (OR = 0.56, 95 % CI 0.03–10.27, random effect; Table 3).

Table 2 Stratified analysis of pooled hazard ratios of gastric cancer patients with positive pSTAT3 expression

Stratified analysis	No. of studies	No. of patients	Pooled HR (95 % CI)		Meta-regression *p* value	Heterogeneity	
			Fixed	Random		I^2 (%)	*p* value
Study location					1		
China	4	489	2.61 (2.01–3.38)	2.61 (2.01–3.38)		0	0.792
Korea	2	588	1.11 (0.82–1.51)	1.06 (0.54–2.11)		79.20	0.028
Japan	2	237	2.20 (1.24–3.93)	2.20 (1.24–3.93)		0	0.722
Publication year					1		
≥2010	6	900	1.96 (1.57–2.45)	1.91 (1.14–3.21)		77.10	0.001
<2010	2	414	1.64 (1.14–2.37)	1.67 (1.11–2.51)		10.30	0.291
No. of patients					0.865		
≥100	6	1201	1.79 (1.47–2.19)	1.72 (1.10–2.70)		77.20	0.001
<100	2	113	2.65 (1.48–4.77)	2.65 (1.48–4.76)		0	0.707
NOS scores					0.976		
≥7	6	749	1.53 (1.16–2.03)	1.81 (1.09–3.03)		65.80	0.012
<7	2	565	2.19 (1.70–2.81)	2.06 (1.12–3.78)		81.90	0.019

Table 3 Meta-analysis of positive pSTAT3 expression and clinicopathological features of gastric cancer

Stratification of gastric cancer	No. of studies	No. of patients	Poor OR (95 % CI)		Heterogeneity	
			Fixed	Random	I^2 (%)	*p* value
TMN stage	3	607	0.91 (0.64–1.29)	0.93 (0.29–2.93)	89.60	<0.0001
Lymph node metastasis	4	582	1.41 (0.98–2.02)	2.86 (0.71–11.56)	91.80	<0.0001
Grade of differentiation	2	322	0.72 (0.44–1.16)	1.36 (0.15–12.44)	92.40	<0.0001
Lauren classification	3	540	1.01 (0.69–1.48)	0.99 (0.63–1.58)	29.30	0.243
Distant metastasis	2	411	1.45 (0.69–3.03)	0.56 (0.03–10.27)	85.90	0.008

The sensitivity analysis indicated that the overall pooled HRs could not be significant influenced by omitting any single study (Fig. 3). The evaluation of publication bias by Egger tests ($p = 0.969 > t = 0.04$) showed that there were no publication bias for all studies.

Also, the shape of the funnel plot did not reveal obvious asymmetry (Fig. 4).

Discussion

This meta-analysis aimed to examine the association between positive pSTAT3 expression and OS and clinicopathological characteristics of gastric cancer. Combining the outcomes of 1314 patients from eight studies, our analysis revealed that positive pSTAT3 expression significantly predicted poor OS of gastric cancer patients (HR = 1.87, 95 % CI 1.28–2.74). Subgroup analysis showed that positive pSTAT3 expression correlated with poor prognosis in both China (HR = 2.61, 95 % CI 2.01–3.38) and Japan (HR = 2.20, 95 % CI 1.24–3.93), while the result in Korea indicated no statistical significance (HR = 1.06, 95 % CI 0.54–2.11). In addition, statistically significant correlations were not observed between pSTAT3 expression and clinicopathological features including TMN stage, lymph node metastasis, differentiation, distant metastasis and Lauren classification.

The studies included in this analysis were all from East Asia, and thus, we could not test whether there are different influences between Caucasians and Asians. Besides, two Korean articles included in our analysis hold opposite views, so the subgroup analysis of Korea would be more likely to have no statistical significance. But it does not influence the overall result of our analysis as the combining outcomes from all studies revealed that pSTAT3 expression is associated with poor prognosis in patients with gastric cancer (HR = 1.87, 95 % CI 1.28–2.74).

At present, the associations between the expression of pSTAT3 and tumor stage, lymph node metastasis or distant metastasis of gastric cancer patients remain controversial and heterogeneous. A few scholars (Sungmin Woo et al. 2011) consider that nuclear expression of pSTAT3 was more likely to be found in earlier-stage tumors and inversely correlated with lymphatic metastasis and distant metastasis.

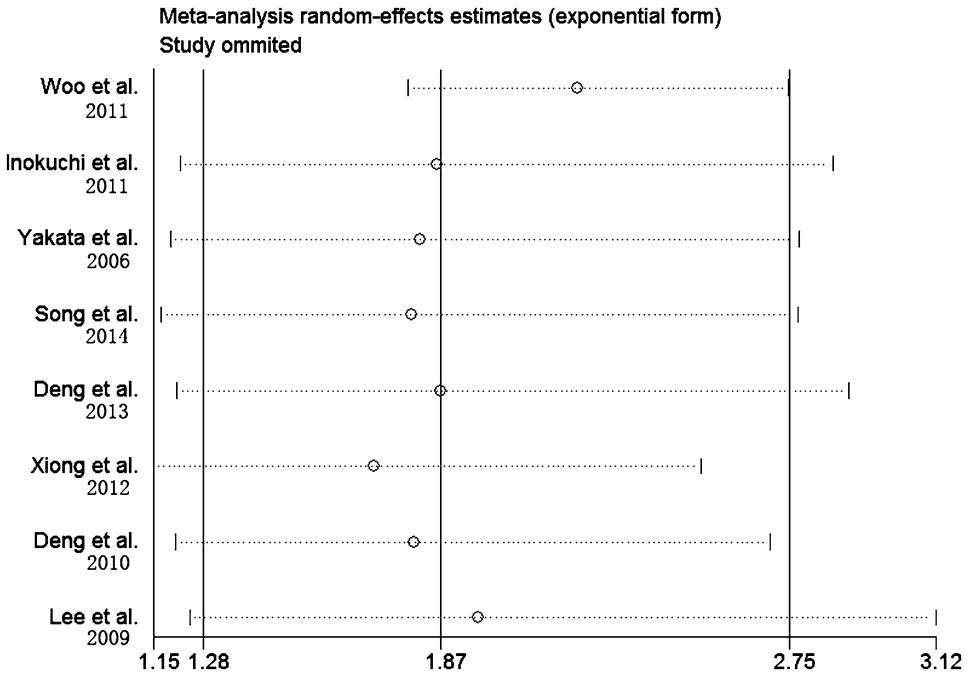

Fig. 3 Sensitivity analysis of the pooled hazard ratios coefficients on the relationships between pSTAT3 protein expression and prognosis of patients with gastric cancer

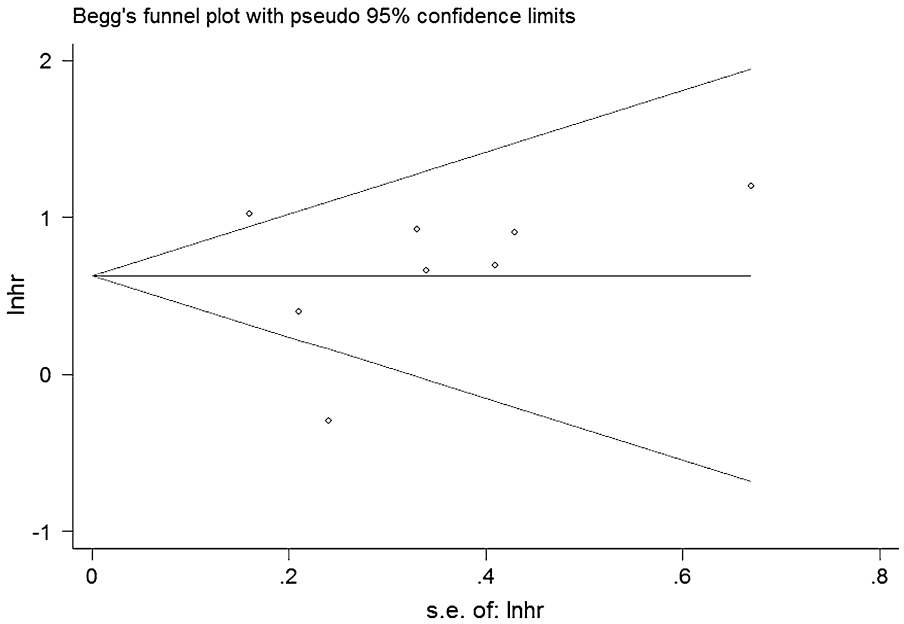

Fig. 4 Funnel plot of publication biases on the relationships between pSTAT3 protein expression and prognosis of patients with gastric cancer

In the study of Choi et al. (2006), there was no significant difference in clinicopathological parameters, such as tumor stage and lymph node metastasis between the pSTAT3-positive and pSTAT3-negative group. Nevertheless, some scholars hold different views. Compelling evidence supports the fact that STAT3 activation plays a critical role in every step of metastasis including cell proliferation and survival, invasion, migration and angiogenesis (Kamran et al. 2013).

In our analysis, five (Yakata et al. 2007; Song et al. 2014; Inokuchi et al. 2011; Deng et al. 2010, 2013) of eight articles suggest that the expression of pSTAT3 correlated with the presence of lymph node metastasis. However, the overall result of this analysis showed no statistically significant association between pSTAT3 expression and tumor stage, lymph node metastasis or distant metastasis.

The most likely reason is the small sample size. In our study, the number of the articles that can be used to extract the data to access the association between pSTAT3 expression and tumor stage, lymph node metastasis and distant metastasis is only 3, 4 and 2, respectively. Due to the small

Table 4 Summary of the prognostic value of the target genes of STAT3 in gastric cancer patients

Gene	Upregulated by STAT3?	Downregulated by STAT3?	Prognostic value in gastric cancer patients	References
IL-6	√		Inferior prognosis	Ikeguchi et al. (2009)
IL-10	√		Inferior prognosis	Ikeguchi et al. (2009)
IL-1β	√		Inferior prognosis	Resende et al. (2015)
COX2	√		Inferior prognosis	Shi et al. (2003)
IL-17	√		Inferior prognosis	Iida et al. (2011)
IL-21	√		Inferior prognosis	Iida et al. (2011)
TWIST1	√		Inferior prognosis	Sung et al. (2011)
BCL-X	√		Inferior prognosis	Kwon et al. (2012)
MCL1	√		Inferior prognosis	Lee et al. (2015)
CCND1	√		Inferior prognosis	Ma et al. (2015)
VEGF	√		Inferior prognosis	Chen et al. (2014a, b, c)
Myc	√		Inferior prognosis	Chen et al. (2015)
HIF-1a	√		Inferior prognosis	Chen et al. (2014a, b, c)
BIRC5	√		Inferior prognosis	Chen et al. (2014a, b, c)
MMP9	√		Inferior prognosis	Chen et al. (2014a, b, c)
MMP2	√		Inferior prognosis	Wang et al. (2014)
ICAM	√		Inferior prognosis	Alexiou et al. (2003)
p35		√	Unclear	[a]
IFN-β		√	Unclear	[a]
MCP1		√	Unclear	[a]

[a] There is a lack of relevant articles to elucidate the prognostic value of these proteins of gastric cancer patients

sample size, the results from our meta-analysis probably do not achieve a sufficient statistical power to state the association between pSTAT3 expression and clinicopathological features of gastric cancer patients.

In the canonical STAT3 signaling pathway, activation of cell surface receptors by growth factors and cytokines induces the phosphorylation of specific tyrosine residues in STAT3 and then pSTAT3 form stable homodimers or heterodimers with other pSTAT proteins. The pSTAT3 dimers translocate to the nucleus, where they bind to specific DNA response elements in the promoter regions of responsive target genes to regulate their transcription (Germain and Frank 2007; Johnston and Grandis 2011; Yu et al. 2009). As a transcription factor, the final effectors of STAT3 are its downstream molecules, and those are the target genes of STAT3. Many STAT3-regulated genes encode cytokines and growth factors involved in the regulation of a variety of critical functions, including cell differentiation, proliferation, apoptosis, angiogenesis, metastasis and immune responses, which play important roles in the development, progression and maintenance of cancer (Yu et al. 2009; Frank 2007; Germain and Frank 2007; Regis et al. 2008) (Table 4). Nearly all the proteins encoded by target genes which are upregulated by STAT3 were proved to be poor prognostic markers of gastric cancer patients, while the prognostic value of the proteins downregulated by STAT3 of gastric cancer patients remains unclear (Table 4) For example, IL-6, IL-1β, macrophage colony-stimulating factor, prostaglandins and cyclooxygenase 2 (COX2, which is required for the production of prostaglandins), which are crucial for inducing and maintaining a cancer-promoting inflammatory environment, were proved to be regulated by STAT3 (Yu et al. 2009). Importantly, in tumor cells, STAT3 is a transcription factor for numerous genes encoding cytokines, chemokines and growth factors, the associated receptors of which in turn activate STAT3 in stromal cells, thereby propagating a stable feed-forward loop between tumor cells and non-transformed stromal cells to promote inflammatory responses that further support tumor growth and survival (Yu and Jove 2004; Zhong et al. 1994; Dalwadi et al. 2005).

In this analysis, the test for heterogeneity of included studies was significant ($I^2 = 70.3\ \%$, $p = 0.001$). Although we employed subgroup analysis, meta-regression analysis and sensitivity analysis, all the methods failed to clarify the source of heterogeneity.

All of the included studies evaluated the expression of pSTAT3 in cancer cells by immunohistochemistry method. However, the studies did not use the same primary antibody, and the dilutions of the antibodies were also different, leading to a potential bias because the sensitivity of the immunohistochemistry may rely on the antibody

concentration. Furthermore, because of the fact that an optimal threshold has not been defined, the cutoff defining a gastric cancer with positive pSTAT3 expression is arbitrary, which also might produce heterogeneity.

The methodological quality of the studies was also a potential source of heterogeneity. We evaluated the quality of the included studies by Newcastle–Ottawa Scale (NOS) criteria (Stang 2010). By comparing the quality scores of the studies in which pSTAT3 was a significant prognostic factor and of those in which it was not, differences suggesting biases induced by the methodology of studies might be identified. Nevertheless, the comparison of the quality scores of the two groups indicated no statistically significant difference. Furthermore, meta-regression and subgroup analysis indicated that quality score did not affect the significant association between positive pSTAT3 expression and poor OS of gastric cancer patients. All the quality scores of included studies were mostly >5, and six studies' scores were >7, indicating that the results of the present study were more convincible.

Moreover, the approach of extrapolating the HRs maybe another potential source of bias. In our analysis, HRs of the included studies were directly reported in only two studies, while we had to extrapolate the HRs from the survival curves of other six articles, assuming that censored observations were identically distributed. The estimated HR might thus be less reliable than when obtained directly from published statistics. However, we compared our estimated HRs with the results reported in papers and did not identify any major deviation.

The Egger's test showed that there was no publication bias for all studies. However, in this review, we only selected the studies published in English language, due to the reason that other languages were often not available for both the authors and readers. As we all know, studies which did not report statistically significant results are less often published, and they are often reported in a more brief way, leading to the difficulty of retrieving the data. This selection might favor the positive studies that are more frequently published in English language, whereas those negative ones tend to be more frequently published in native languages (Egger et al. 1997). Furthermore, our review only included fully published studies. Unpublished studies and conference abstracts were not selected because the data that were able to be used for the conduction of methodology assessment and meta-analysis were only available in full articles.

Although our study has many limitations, we performed a highly sensitive study search strategy of electronic databases and the selection process of the eligible articles was based on strict inclusion and exclusion criteria. More importantly, rigorous statistical analysis of data provided a basis for pooling of information from individual studies.

To sum up, this meta-analysis indicates that positive expression of pSTAT3 protein may potentially be associated with poor prognosis in gastric cancer patients. Thus, pSTAT3 expression level may be utilized as an independent prognostic marker for gastric cancer patients. However, due to the limitations acknowledged above, more researches with larger sample size are still in need to provide a more representative and convincing statistical analysis.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts to disclose.

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