Original Article
Prognostic significance of STAT3/phosphorylated-STAT3 in tumor: a meta-analysis of literatures

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Abstract: Purpose: The prognostic value of the expression of STAT3/phosphorylated-STAT3 on survival for cancer patients remains controversial. We performed a meta-analysis of the published literature in this field to identify its impact. Methods: We conducted a meta-analysis of 26 studies (n=3877 patients) that evaluated the relationship between the prognostic value and the expression of STAT3/phosphorylated-STAT3 in 15 different kinds of carcinomas. Studies evaluated the correlation between STAT3/phosphorylated-STAT3, which detected mostly by immunohistochemistry and western blot, and clinical staging, overall survival (OS) and disease free survival (DFS) were included. The impact of STAT3 and phosphorylated-STAT3 was analyzed separately. Results: A total of 26 studies (14 for STAT3 and 16 for phosphorylated-STAT3), comprising 3877 patients, were included for meta-analysis. The expression of STAT3 was strongly associated with a poor impact on overall survival (OS) in all eligible studies [hazard ratio (HR)=2.91, (95% confidence interval (CI), 1.91-4.42)], while a significant association was shown between the expression of phosphorylated-STAT3 and patients' outcome [HR=1.53, (95% CI, 0.86-2.70)]. No significant effect was shown between the expression of STAT3/phosphorylated-STAT3 and clinical staging, neither with DFS. Conclusion: High expression of STAT3 seems to be associated with poor OS in patients with carcinomas, while phosphorylated-STAT3 does not.

Keywords: Meta-analysis, STAT3/phosphorylated-STAT3, prognosis, tumor

Introduction

Previous studies have shown several potential complex signal transduction systems involved in the process of malignant transformation. The signal transducers and activators of transcription (STAT) protein family has been reported to play vital roles in several oncogenic processes including proliferation, survival, differentiation and angiogenesis [1]. As an important member of STAT family, it is activated by phosphorylation on tyrosine residue in the cytoplasm, after which it translocates into the nucleus to regulate gene expression [2, 4]. A large number of studies have focused on the prognostic significance of STAT3 expression in different human carcinomas. However, the formation is still limited.

Phosphorylated-STAT3 (p-STAT3) is the activated form of STAT3 with the ability to be detected in the process of oncogenesis. It dimerizes and translocates into the nucleus, where its occupation of specific DNA-binding sites resulting in the increased transcription of several molecules that are involved directly related to survival, proliferation, self-renewal, and invasion. However, the activation of STAT3 signaling pathway is temporary and in tight control under physical circumstances. If STAT3 is continuously activated to promote the transcription of downstream target genes, malignant transformation will ultimately take place [5]. We cannot figure out the differences between these two indicators in the process of oncogenesis. Therefore, in this study, we performed an analy-

sis of STAT3 and p-STAT3. The meta-analysis is as follows.

Materials and methods

Identification and eligibility of relevant studies

We carried out our meta-analysis according to a predetermined written protocol. To be eligible for our meta-analysis, studies had to deal with expression of STAT3/p-STAT3 factors in different tumors, evaluated the prognostic effect of the expression and survival, and be published in English or Chinese languages. We searched on Pubmed (MEDLINE) 1950-present and EMBASE, with common search terms "Transcription Factor STAT3", "APRF Transcription Factor", "IL6-Response Factor", "Signal Transducer and Activator of Transcription 3", "STAT3 Protein", "Acute-Phase Response Factor", and "Neoplasm", "Neoplasms", "Tumors", "Tumor", "Cancer", "Cancers", and "prognosis", "prognostic", "outcome". The deadline of the eligible articles was August 2013. Reference list from primary identified studies were also searched to prevent missing any studies by the internet searching.

Inclusion criteria for primary studies were as follows: (1) proven clinical diagnosis of different tumors, (2) immunohistochemistry or western blot was applied as a evaluating method for STAT3/p-STAT3, (3) STAT3 detected in the cytoplasm and p-STAT3 in the nuclear were considered suitable positive, and (4) correlation of STAT3/p-STAT3 expression with OS, DFS and TNM staging. Exclusion criteria include: (1) animal experiment, (2) reported the value of STAT3/p-STAT3 other than prognosis, (3) without exploitable survival statistics, (4) evaluate other cell surface markers relate to STAT3/p-STAT3. Full articles were retrieved for further assessment if the eligibility was unclear from the abstracts. Any disagreements were resolved by elaborate discussions. Eligible studies were then carefully examined to ensure the reliability.

Definitions and standardization

We used regular rules to standardize as much as possible the definition of STAT3 positive. The majority of the eligible studies used 10% as a cutoff value [6-13], so we defined STAT3 positive as positive cell stain in at least 10% of tumor cells. As to standard methods used in some articles, we contacted the author for their suggested cutoff value. When it was not retrieved, we just accepted the cutoff value as at least 10% as the majority. Also, as STAT3 and p-STAT3 were not the same form, so we considered them as two different subjects and did the analysis separately.

Data extraction and quality evaluation

Data were carefully extracted from the eligible original studies using a standard information collection form, with the following information: first author, year of publication, nationality of first author, tumor type, number of patients, TNM stage, median age of patients, median follow up year of patients, method of evaluation, antibody used, cutoff value and analysis methods. For different articles based on a same study, we just collected the recently published one or the one with sufficient data for analysis. The Newcastle-Ottawa Scale (NOS) recommended by the Cochrane Collaboration was used, and eight criteria were established to evaluate the quality of the included case-control studies and cohort studies [48]. Such being the case, studies could receive a score of 0-9 points, based on the three criteria of subject selection, comparability between groups and measurement of exposure factors. The main outcomes are shown in **Table 1**.

Statistical analyses

Eligible studies were first divided into 2 groups for analysis: those detected the expression of STAT3 and others with p-STAT3 expression. Then we performed further statistic analysis in each of the two groups regarding OS, DFS, and TNM stage. The result of the study was labeled 'positive' when a high expression of STAT3/p-STAT3 predicted a poor patient survival, and labeled 'negative' when a high STAT3/p-STAT3 predicted a good patient survival, and labeled 'intermediate' when no significant relationship between the expression of STAT3/p-STAT3 and survival.

The survival result in each individual study was estimated by HRs with 95% confidence interval values. We first extracted HRs and their 95% CI from the original articles. If the data were not available, we used the method described by Parmer et al [13] to calculated HRs. This meth-

Table 1. Basic characteristics of eligible studies

First Author	Year	Country	Tumor Type	No.of patient (M/F)	Stage I/II (III/IV)	Median age (y)	Median follow-up (m)	Method	Antibody	Cut-off (positive)	Analysis	NOS
Andreas W.	2002	Austria	Breast cancer	73 (0/73)	Sep-63	56	81.6	W-B	R-P-A	NR	OS/RFS	8
Mingzhen Y.	2010	China	Breast cancer	367 (0/367)	212/155	52.8	43.3	IHC/W-B	R-P-A/Tyr705	≥10%	DFS	6
Amir S.	2013	Israel	Breast cancer	375 (0/375)	188/138	50	>5	IHC	R-P-A	≥10%	OS	6
Yujuan C.	2013	China	Breast cancer	140 (0/140)	108/32	48.79	54	IHC	R-P-A	>25%	OS	7
Sung-Im D.	2008	Korea	Osteosarcoma	47 (25/22)	Aug-35	25	76.9	IHC/RT-PCR	Try705	>10%	Survival curve	7
Yucai W.	2010	China	Osteosarcoma	76 (25/51)	NR	NR	NR	IHC/PT-PCR/W-B	R-P-A	≥5%	OS/DFS	7
Keinosuke R.	2010	USA	Osteosarcoma	51 (38/13)	NR	20.2	137.6	IHC/I-B	NR	≥10%	Survival curve	6
Weida G.	2005	USA	Gastric cancer	86 (56/30)	42/44	62	25.7	IHC/W-B	G-P-A	≥10%	OS	8
Yuichi Y.	2006	Japan	Gastric cancer	111 (63/48)	NR	68.9	NR	IHC/I-B	G-P-A	>10%	Survival curve	7
Sungmin W.	2011	Korea	Gastric cancer	103 (36/67)	168/117	54.5	51	IHC	Tyr705	>1%	Survival curve	7
Yanfei J.	2013	China	Gastric cancer	48 (34/14)	22/26	NR	NR	IHC/W-B	R-P-A	NR	Survival curve	6
Bin Z.	2010	China	Hepatocellular carcinoma	196 (136/60)	100/96	48.1±12.6	NR	IHC	M-M-A	NR	OS	4
Wenyong W.	2011	China	Hepatocellular carcinoma	113 (93/20)	86/27	NR	NR	IHC/RT-PCR	Tyr705	>25%	OS	6
Eric B.H.	2005	USA	NSCLC	176 (97/79)	NR	69	37	IHC	Tyr705	NR	OS/DFS	8
Mei Z.	2011	China	NSCLC	68 (38/30)	27/41	59.44	NR	IHC/W-B	R-P-A/Tyr705	≥20%	OS	7
Chang K-C.	2005	Taiwan, China	Thymic epithelial tumor	118 (65/53)	49/58	52.7	>9	IHC	NR	≥10%	Survival curve	5
Chao L.	2013	China	Thymic epithelial tumor	80 (47/33)	43/33	46.5	61.5	IHC	NR	>10%	OS	5
Mustafa B.	2012	USA	Acute myeloid leukemia	63 (32/31)	NR	64	40	W-B	Y705/C-20	NR	OS/DFS	8
Christina B.	2011	Greece	Astrocytomas	97 (60/37)	20/77	59	13	IHC	R-M-A	>5%	Survival curve	7
Teppei M.	2011	USA	Colorectal cancers	724 (266/458)	384/301	NR	129	IHC	R-P-A	NR	OS	8
Chel-Hun C.	2009	Korea	Cervical carcinoma	29 (0/29)	20he9	47	NR	IHC	G-P-A	>51%	DFS	6
Sibastian-F S.	2012	Austria	Esophagealcarcimoma	324 (252/72)	101/78	63+10	NR	IHC	R-M-A	NR	OS/DFS	5
Yanyang T.	2010	China	Gliomas	96 (61/35)	18/78	50.9	42	IHC/W-B	A-M-IgG	≥5%	Survival curve	5
Yan Z.	2012	China	LSCC	163	112/51	NR	60	IHC	A-STAT3	≥10%	OS	5
Chih-cheng C.	2009	Taiwan, China	Pharyngeal cancer	95	15/80	53	Till death	IHC	NR	>10%	OS/OR	6
Lijuan Z.	2013	China	Wilma' tumor	58 (20/38)	44/14	31 months	NR	IHC	R-P-A	≥51%	OS/DFS	7

*W-B: Western blot; IHC: Immunohistochemistry; NR: Not reported; OS: Over survival; DFS: Disease free survival; NSCLC: None small cell lung cancer; LSCC: lingual squamous cell carcinoma; R-P-A: Rabbit poly antigen; G-P-A: Goat polycolonal antigen; M-M-A: Mouse monoclonal antigen.
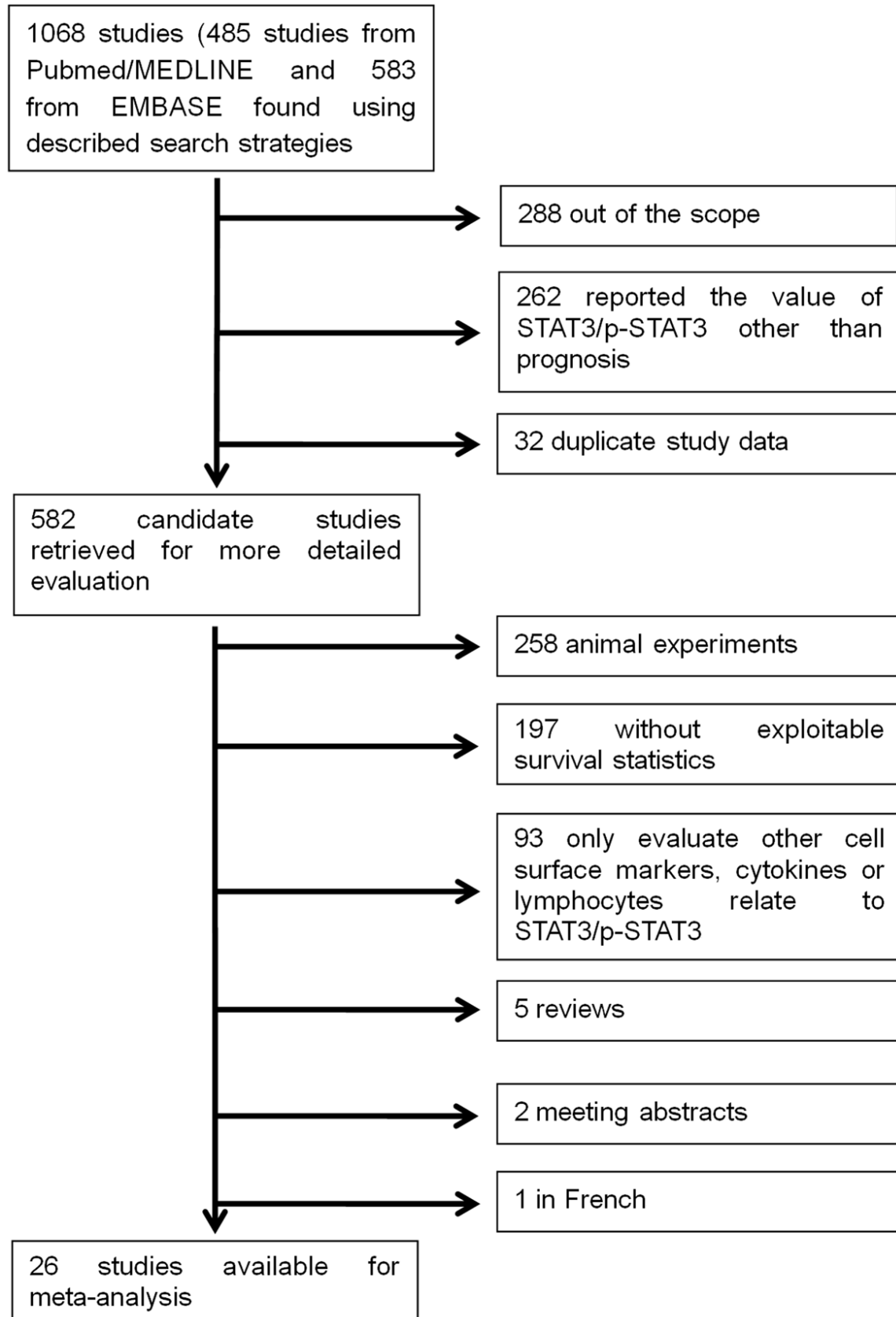
Figure 1. Flow chart of the literature search and selection of included studies.

Table 2. Overall survival for STAT3/p-STAT3 expression

First Author	Year	Country	Tumor Type	HR (Hazard ratio)	95% CI	
STAT3 OS						
Andreas W.	2002	Austria	Breast cancer	1.56	0.66	3.73
Yujuan C.	2013	China	Breast cancer	3.05	0.032	0.595
Sung-Im D.	2008	Korea	Osteosarcoma	4.25	1.12	16.12
Yucai W.	2010	China	Osteosarcoma	2.244	1.763	3.116
Weida G.	2005	USA	Gastric cancer	2.28	0.99	4.58
Yanfei J.	2013	China	Gastric cancer	4.01	1.07	15.07
Chang K-C.	2005	Taiwan, China	Thymic epithelial tumor	1.48	0.42	5.24
Chao L.	2013	China	Thymic epithelial tumor	9.325	1.508	82.207
Mustafa B.	2012	USA	Acute myeloid leukemia	1.2	1.07	1.34
Yanyang T.	2010	China	Gliomas	2.36	1.37	10.98
Bin Z.	2010	China	Hepatocellular carcinoma	9.416	4.747	18.676
Yan Z.	2012	China	LSCC	4.83	2.37	9.88
Mei Z.	2011	China	NSCLC	4.85	0.96	24.53
Lijuan Z.	2013	China	Wilma' tumor	3.07	0.946	9.951
p-STAT3 OS						
First Author	Year	Country	Tumor Type	HR (Hazard ratio)	95% CI	
Amir S.	2013	Israel	Breast cancer	0.48	0.275	0.839
Yujuan C.	2013	China	Breast cancer	4.01	1.076	8.675
Yuichi Y.	2006	Japan	Gastric cancer	2.91	1.35	6.3
Sungmin W.	2011	Korea	Gastric cancer	0.37	0.22	0.64
Eric B.H.	2005	USA	NSCLC	0.68	0.37	1.23
Mei Z.	2011	China	NSCLC	1.937	0.639	5.875
Christina B.	2011	Greece	Astrocytomas	0.611	0.332	1.124
Teppei M.	2011	USA	Colorectal cancers	3.23	1.89	5.53
Sibastian-F S.	2012	Austria	Esophagealcarcimoma	2.146	1.476	3.119
Wenyong W.	2011	China	Hepatocellular carcinoma	14.9	3.19	69.6
Keinosuke R.	2010	USA	Osteosarcoma	7.27	1.94	27.2
Chang K-C.	2009	Taiwan, China	Pharyngeal cancer	0.5369	0.2713	1.0627

od would require published data from numbers of patients at risk and total number of events in each group. When data were only available in the form of figures, we interpreted Kaplan-Meier curves by Engauge Digitizer version 4.1 (free software downloaded from http://source-forge.net) and extracted survival data from each curve of OS, DFS and TNM stage, then we used the survival data to reconstructed HRs and their 95% CI. If the HR>1, we considered it a worse outcome with STAT3/p-STAT3 expression while statistical significance when 95% CI surpass 1 and $P<0.05$ the same time. Heterogeneity across the studies was evaluated with Cochrane Q test and the I^2 statistic. We regarded $P>0.10$ or $I^2<50\%$ as indicators of no heterogeneity using a fixed-effect model. Otherwise, $P\leq0.10$ or $I^2>50\%$ were regarded as indicators of heterogeneity using a random effect model [49]. We performed subgroup analysis regarding with tumor type, region, study methods as well in order to identify the sources heterogeneity across studies. The effect of publication bias on the outcomes was assessed by Begg's funnel plot and Egger's linear regression method. ($P < 0.05$ was considered statistically significant publication bias) [14]. Sensitivity analysis was conducted to evaluate the stability of the results by sequentially omitting one study at each turn with the metaninf algorithm in Stata. version 11.0 (Stata Corporation, College Station, TX, USA). $P<0.05$ was considered to be statistically significant. Meta-analyses were carried out by Stata version 11.0 (Stata Corporation, College Station, TX, USA).

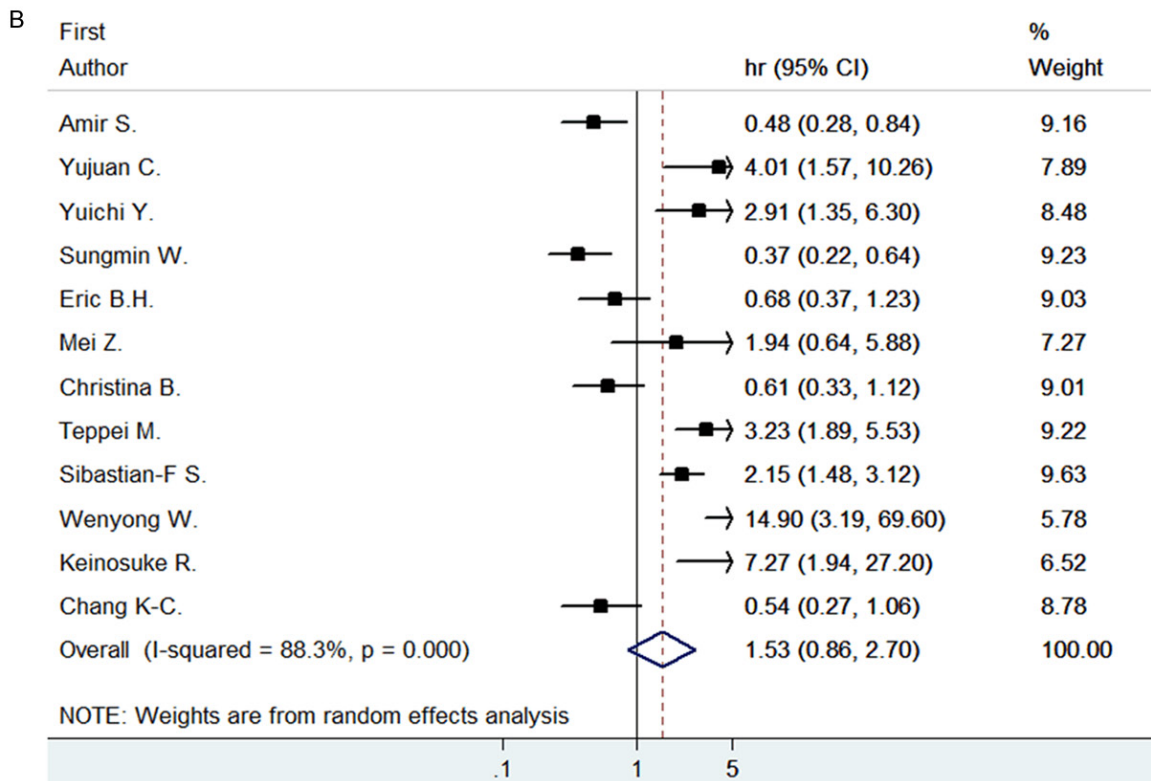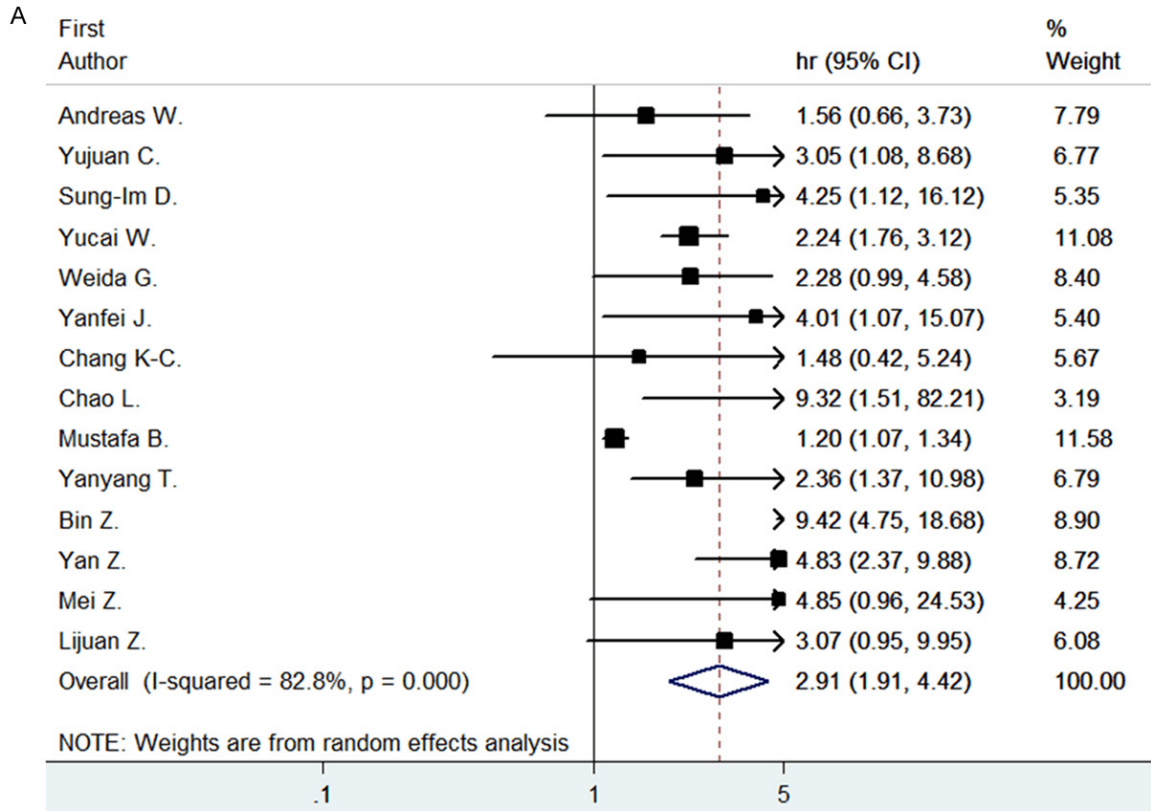# STAT3/phosphorylated-STAT3 in tumor

Figure 2. Forrest plots and meta-analysis of studies evaluating HR of high STAT3 (A) and p-STAT3 (B) counts as compared to low counts. Survival data is reported as oversurvival (OS).
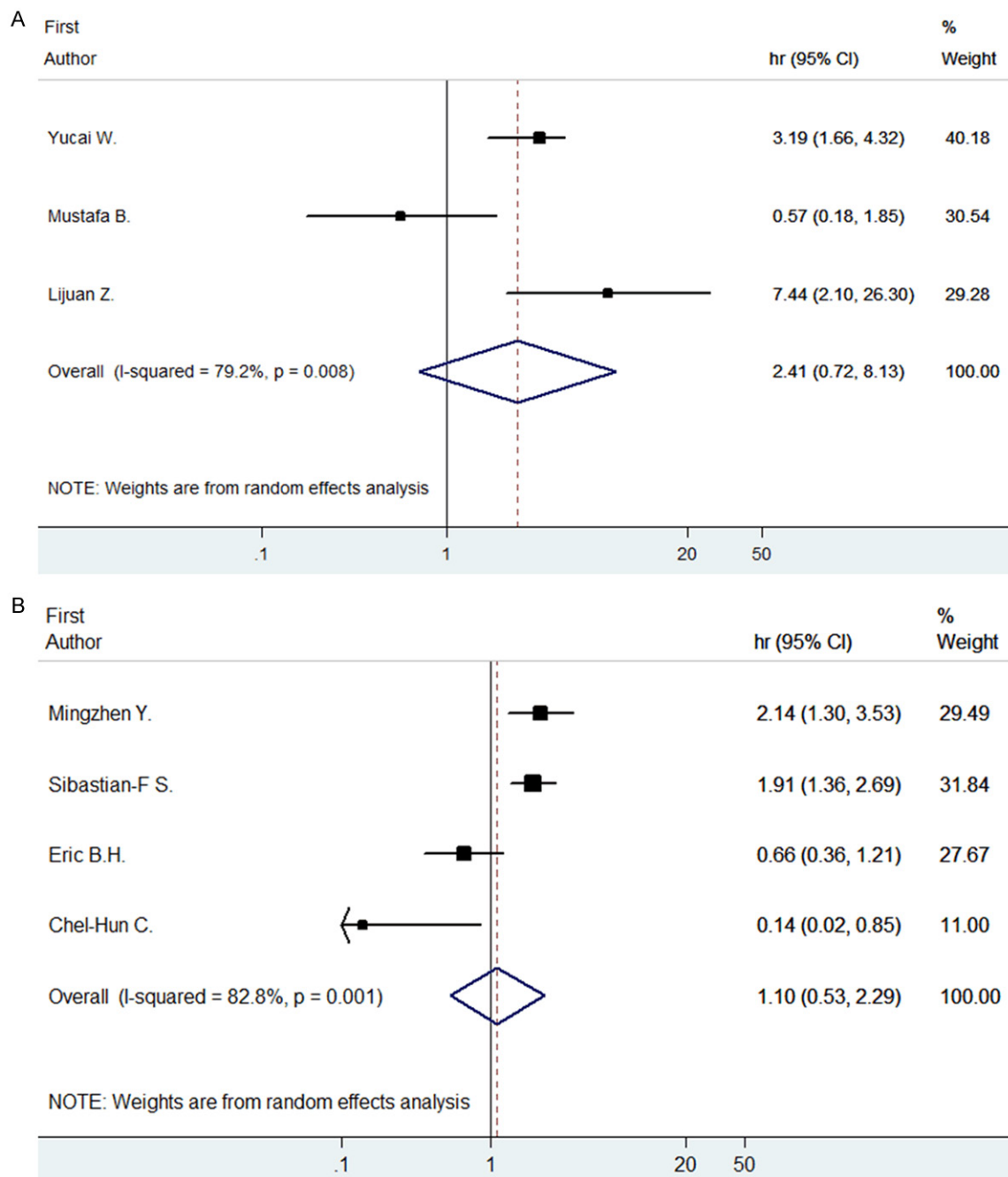
STAT3/phosphorylated-STAT3 in tumor

Figure 3. Forrest plots and meta-analysis of studies evaluating HR of high STAT (A) and p-STAT3 (B) counts as compared to low counts. Survival data is reported as disease free survival (DFS).

Results

Studies selection and characteristics

A total of 1068 studies were selected from databases and we evaluated 582 candidate studies in full text. By further review, 556 articles were excluded for animal experiments, no exploitable survival statistics or so (**Figure 1**). Finally we selected 26 articles (n=3877) with STAT3/p-STAT3 measurements in patients with 15 types of tumor.

The characteristics of eligible articles were listed in **Table 1**. The median age of the patients was 50.2 years ranging from 2.5 to 69. The
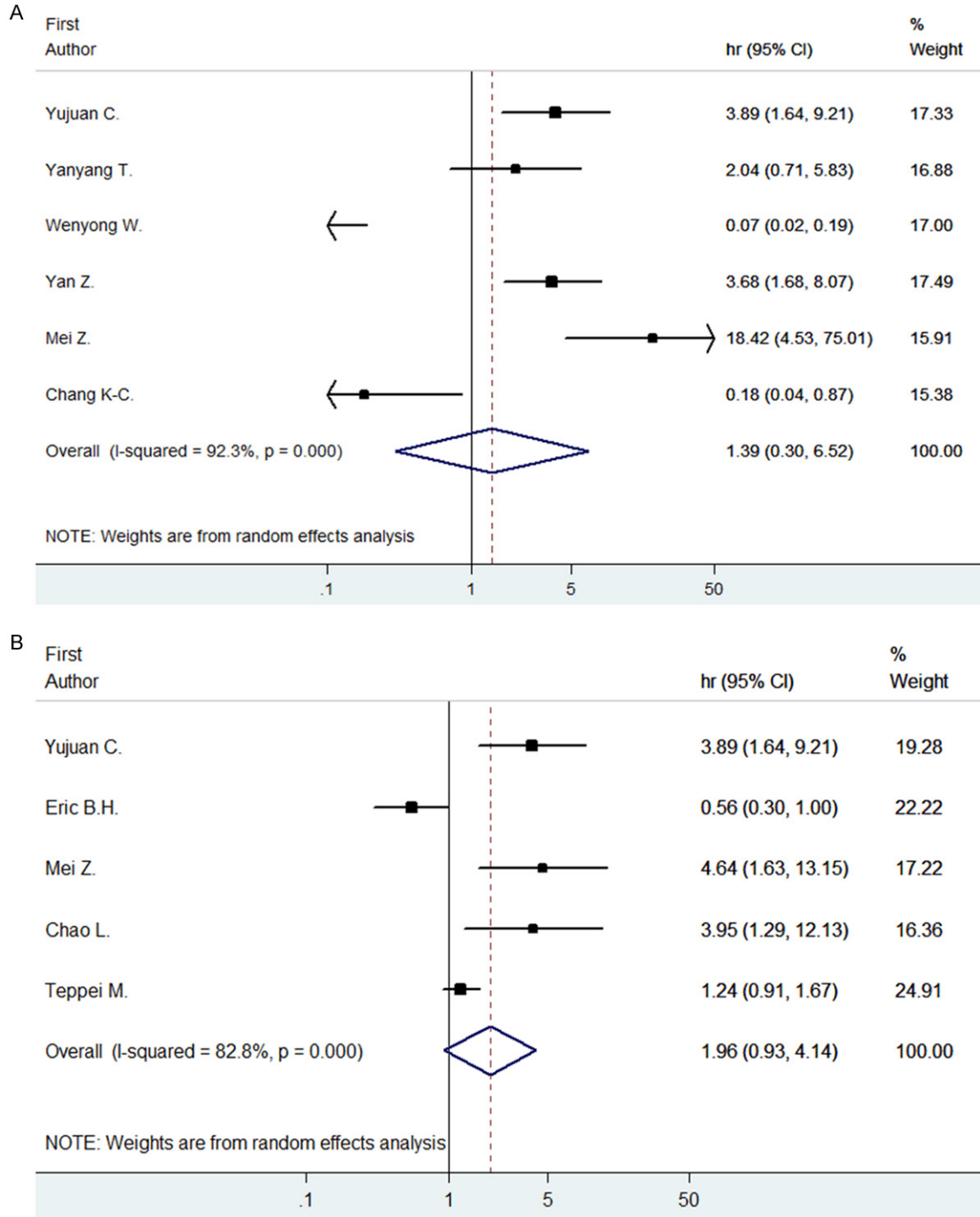
STAT3/phosphorylated-STAT3 in tumor

Figure 4. Forrest plots and meta-analysis of studies evaluating HR of high STAT (A) and p-STAT3 (B) counts as compared to low counts. Survival data is reported as clinical staging.

median follow-up time was 60.9 months from 13 to 137.6. Twenty four articles were evaluated in the level of STAT3/p-STAT3 expression by IHC staining while the other 2 by western blot. The total proportion of patients in TNM grade I/ II was 54.6%. The cut-off value was informed in 19 of the retrieved articles and over half of the articles provided the original HRs of OS or DFS or Stage. Twenty four out of 26 can do the meta-analysis OS, in which 14 articles were
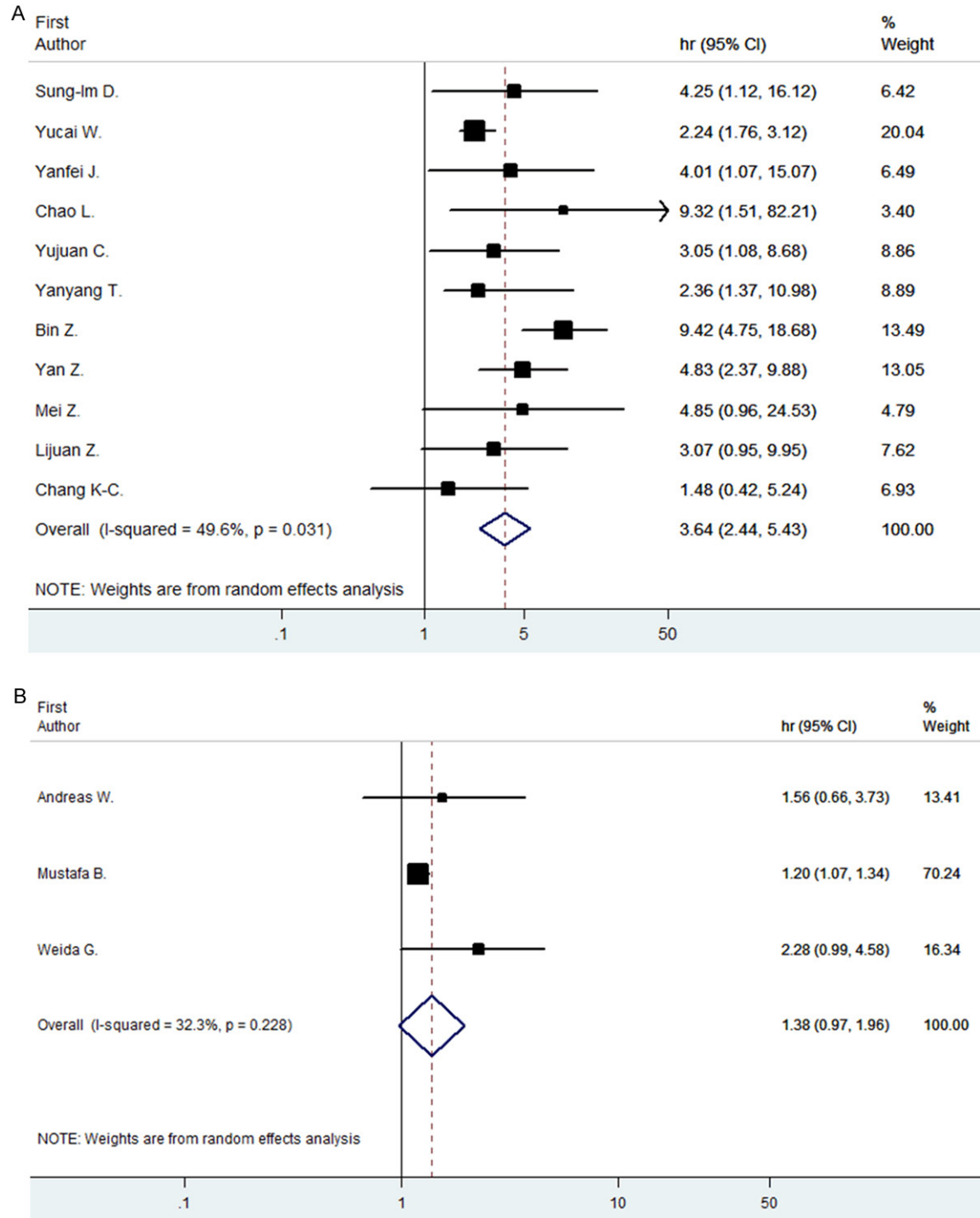
Figure 5. Subgroup analysis for OS by region. Forrest plots and meta-analysis of studies evaluating HR of high STAT3 in Asian country (A) and in Western country (B) compared to low counts.

evaluated the expression of STAT3 and 12 evaluated the expression of p-STAT3. Seven out of the 26 studies could be included into the meta-analysis of DFS while 11 could be included for staging analysis.

Among the total 26 articles, including 4 studies for breast cancer, 3 for osteosarcoma, 4 for gastric cancer, 2 for hepatocellular carcinoma, non-small-cell carcinoma, thymic epithelial tumor each. The remaining studies included
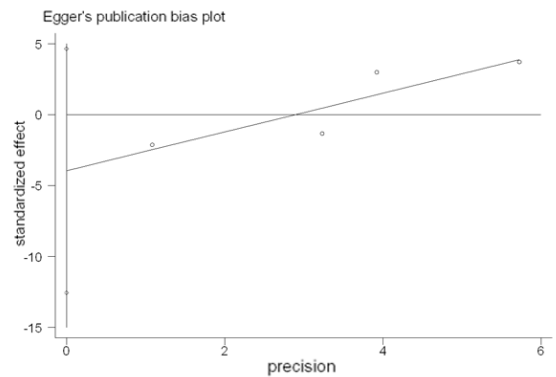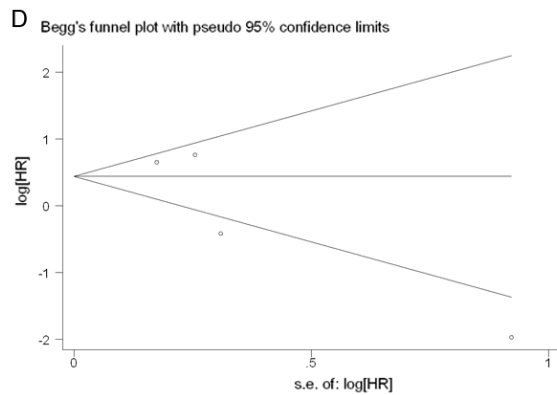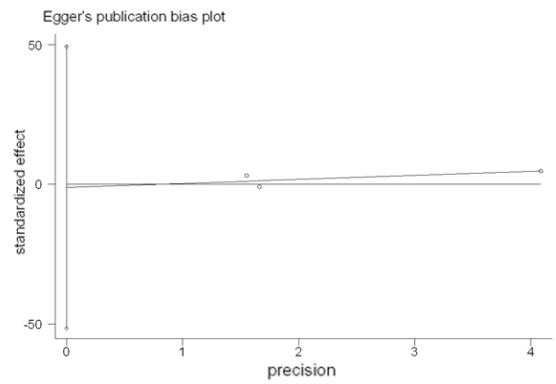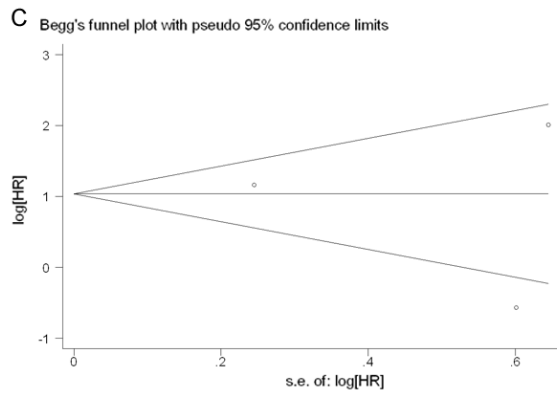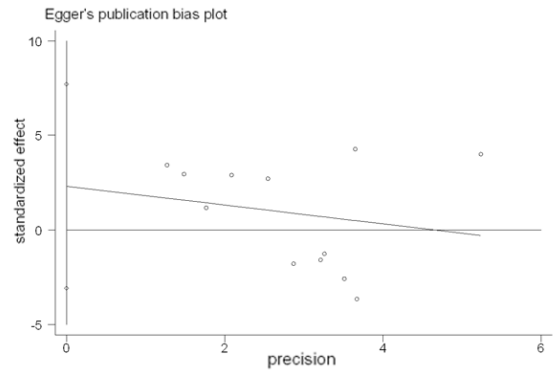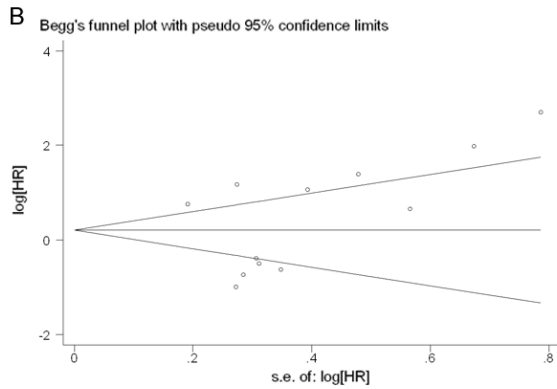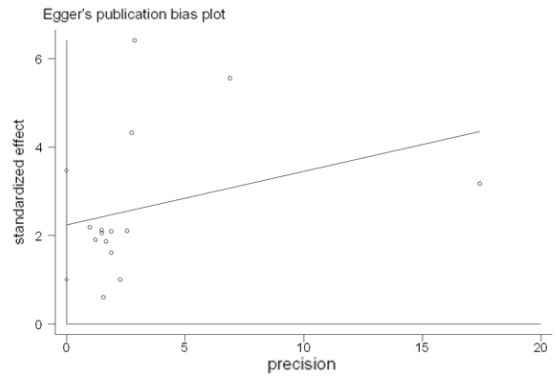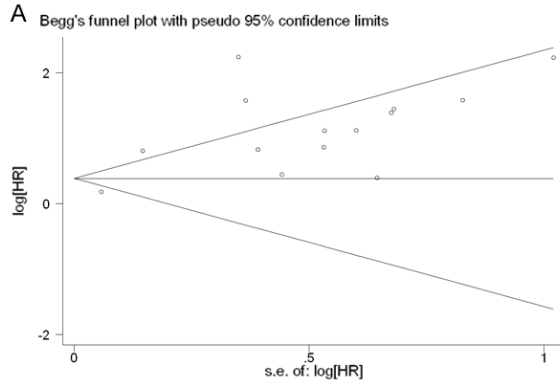
STAT3/phosphorylated-STAT3 in tumor

Figure 6. Begg's funnel graph and Egger's test for assessment of potential publication bias in studies of STAT3/p-STAT3 in patients with tumors. A. OS for STAT3. B. OS for p-STAT3. C. DFS for STAT3. D. DFS for p-STAT3. E. Stage for STAT3. F. Stage for p-STAT3. The funnel graph plots log HR against the standard error of the log HR.

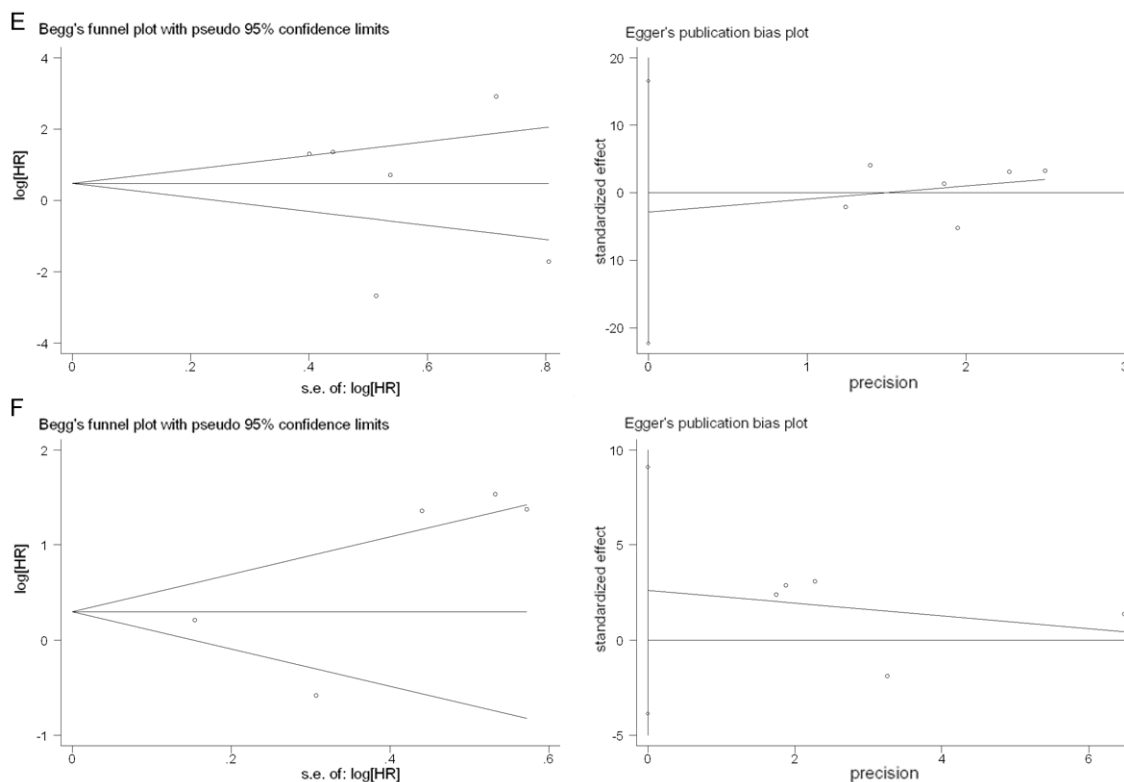acute myeloid leukemia (N=1), astrocytomas (N=1), colorectal cancers (N=1), cervical carcinoma (N=1), esophageal-carcinoma (N=1), gliomas (N=1), lingual squamous cell carcinoma (N=1), pharyngeal cancer (N=1), and Wilms' tumor (N=1).

All of the total 26 articles were with considerable NOS scores (≥4) that could ensure convincing results.

Data synthesis in two groups: overall survival of STAT3 and p-STAT3

The genotype of STAT3 is evaluated in two different types, STAT3 and p-STAT3, of which they show different results on overall survivals. Statistics for each HR of overall survival are listed in **Table 2**. Heterogeneity analysis showed P=0.000, I^2=75.36, so we conducted the random model. The overall HR for STAT3 is 2.91, (95% CI: 1.91-4.42), while for p-STAT3 is 1.53 (95% CI: 0.86-2.70), which indicate statistical significant only in the OS of STAT3 (**Figure 2**).

Data synthesis: disease free survival of STAT3 and p-STAT3

The numbers of articles included in the analysis of DFS on STAT3 were 3 and p-STAT3 were 4, because we could not get the exact data from some articles. The overall HR for OS is 2.41 (95% CI: 0.72-8.13) in STAT3 and 1.10 (95% CI: 0.53-2.29) in p-STAT3 analysis, which indicated no statistical significance between the expression of STAT3/p-STAT3 and DFS (**Figure 3**).

Data synthesis: clinical stage of STAT3 and p-STAT3

We conducted a meta-analysis to evaluate the clinical stage significance of STAT3/p-STAT3, including 11 out of 26 articles (6 for STAT3 and 5 for p-STAT3). The overall HR for STAT3 is 1.39 (95% CI: 0.30-6.52), indicating an insignificant impact on clinical stage while the overall HR for p-STAT3 is 1.96 (95% CI: 0.93-4.14), which indicated no significant result as well (**Figure 4**).

Subgroup analysis

As to identify the heterogeneity of the studies, we first aimed to perform subgroup analysis according to tumor type, but regrettably the data we had was not enough to do this job because we could not mix the HR of STAT3 and p-STAT3 together. So we performed subgroup analysis regard with study method and region, and only found heterogeneity with region in OS of STAT3. The overall HR for OS of STAT3 is 3.64 (95% CI: 2.44-5.43) in Asian countries such as China, Japan and Krea, while in west countries the data is 1.38 (95% CI: 0.97-1.96). These data indicate an significant difference in Asian countries while not in Western countries (**Figure 5**).

Evaluation of publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias in all eligible studies. Begg's funnel plot did not reveal any evidence of significant asymmetry in the OS meta-analysis of STAT3 (*P*=0.622), p-STAT3 (*P*=0.217), DFS meta-analysis of STAT3 (*P*=0.602), p-STAT3 (*P*=0.174), staging meta-analysis of STAT3 (*P*=0.573), and p-STAT3 (*P*=0.624). Egger's test also showed no significant relevance in OS for p-STAT3 (*P*=0.362); DFS for STAT3 (*P*=0.822), p-STAT3 (*P*=0.186); staging for STAT3 (*P*=0.702), p-STAT3 (*P*=0.289). While in OS for STAT3 (*P*=0.002), the Egger's test indicated a different result comparing to the Begg's funnel plot (**Figure 6**).

Sensitivity analysis

Sensitivity analysis was performed based on OS of STAT3 and p-STAT3 and the results demonstrated the robustness of analysis (Data not shown).

Discussion

At present, our study showed insignificant HRs with DFS and clinical stage. However we found that high STAT3 expression level, as detected by immunohistochemistry or western blot, was significantly associated with poor overall survival in different kinds of tumors.

As potential bias exists between studies on STAT3 and p-STAT3, relevant analysis were performed respectively. The patients' OS of STAT3

was significant, with a HR=2.91 (95% CI: 1.91-4.42) while p-STAT3 with a HR=1.53 (95% CI: 0.86-2.70), which indicated insignificant prognostic effects on tumors. We then compared the two factors and several different key factors.

As we mentioned above, the articles we included covered 15 kinds of tumors. The ones we analyzed for STAT3 were breast cancer [15, 16], osteosarcoma [8, 17], gastric cancer [9, 18], thymic epithelial tumor [12, 19], acute myeloid leukemia [20], glioma [21], hepatocellular carcinoma [22], LSCC [23], NSCLC [24], and Wilms' tumor [25]. And the ones for p-STAT3 were breast cancer [7, 16], gastric cancer [10, 11], NSCLC [24, 26], astrocytoma [27], colorectal cancer [28], esophageal carcinoma [29], hepatocellular carcinoma [30], osteosarcoma [31], and pharyngeal cancer [32]. Through the types of tumors we discovered, only four of them were the same (breast cancer, gastric cancer, NSCLC and hepotocellular carcinoma). By comparison, we found that both STAT3 and p-STAT3 expression in NSCLC both played a poor role in patients' OS. This result was in line with Y.H Xu and S. Lu in their meta- analysis with NSCLC only [33]. And in gastric cancer we found that both STAT3 and p-STAT3 expression showed bad outcome in patients' OS as well. While in breast cancer, STAT3 and p-STAT3 seemed to play a controversial role, even subtypes of tumors do influence the outcomes. Thus we suggested that more same type of tumors and subtype of one tumor studies studied to find out the final precise results.

In addition, the factors that have co-influence with STAT3 and p-STAT3 were not the same [34-37]. Aberrantly active STAT3 promotes uncontrolled growth and survival through dysregulating the expression of downstream targeted genes including survivin, Bcl-xL, Bcl-2, Mcl-1, c-Myc and cyclin D1 et al [38, 39]. And the factors co-effect p-STAT3 including SOCS3, EGFR, IL-6 and IL-8 et al [6, 26, 27, 32]. Take IL-6 and SOCS3 for example, it has been shown that STAT3 rapidly induced transcriptional activation of the STAT3 gene through an IL-6 response element located in the STAT3 gene promoter. This finding suggests the existence of autoregulatory mechanisms in the IL-6 signal-transducing system at the level of the signal transducing transcription factor. Thus, an increase in SOCS3

can block IL-6 signal transduction, causing a decrease in STAT3 protein expression [40]. What's more, the degradation of STAT3 has been shown to be involved with the ubiquitin (Ub)-proteosome pathway. This pathway is responsible for selective degradation of short-lived cellular proteins and is critical for the regulation of many cellular processes [41]. As the interaction between factors were not revealed as much as we need, we cannot come to a conclusion that whether the factors influenced STAT3 expression had the same effects on the p-STAT3 expression or not. We then suggested the mechanism of STAT3/p-STAT3 influencing factors been conducted actively.

In the Begg's funnel plot, the p value for OS of STAT3 is 0.622, while Egger's test is 0.002. The two numbers showed opposite results for the publication bias in the analysis. Begg's funnel plot is the most common used method in testing publication bias in meta-analysis [42], but it still has limitations, unless there are more eligible articles [43-45]. Since the number of original articles was limited, this method would be restrictive. So we used Egger's test [14] for a supplementary detection, finding contradictions. When the number of articles for analysis was 14, we considered the Egger's results suitable [14, 44, 46], which revealed an apparent asymmetry that suggested the presence of a potential publication bias. Therefore we suggested the relevant articles been reliable enough not only in types but in numbers and quantities.

Moreover, variability in definitions, outcomes, measurements, experimental procedure, and even antibody concentration may contribute to heterogeneity between studies [47]. Even though we made efforts to minimize the confounding bias, such as subgroup analysis and sensitivity analysis, the factors controlled were not so much and still differed between studies. We recommended the following criteria in the future study: (1) precisely describe the factors evaluation including cut-off value staining and antibody concentration; (2) the including patients be in an age that not so spread; (3) the follow-up years should define at a same level. Our study still discovered a difference in the cut-off values, for some of the studies set the value at 20%, while others at 10% or even using their own-defined score systems. We just chose the majorities as a final result. Although the using of standardized cut-off value in different studies did not differ greatly for OS in the total population analysis, conclusions need to be reached more cautiously.

In conclusion, we come to a conclusion that STAT3 factors have poor effect on the prognosis of many types of tumors while p-STAT3 do not. As discussed above, the clinical use should be of further concerned and measured more carefully. We anticipate more studies being reliable, revealing more clearly consequences, and leading to develop new therapeutic strategies against certain type of tumors.

Acknowledgements

Disclosure of conflict of interest

None.

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