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Association of Elevated Yes-Associated Protein Expression with Gastric Cancer and Its Clinicopathological Features: A Meta-Analysis

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Abstract

Objectives: To evaluate the difference of YAP-positive expression between GC and adjacent tissues, as well as the association of elevated YAP expression with clinicopathological features of GC. **Methods:** PubMed, Embase, Web of Science databases and the Chinese National Knowledge Infrastructure (CNKI) were searched from inception up to December 2018. The pooled ORs and corresponding 95% CIs were used to assess the strength of association. The heterogeneity among eligible studies was evaluated by the Q-test and I^2 values. The sensitivity analysis was performed by sequential omission of individual studies. Moreover, Begg's test and Egger's test were used to evaluate publication bias. **Results:** A total of 2229 patients from 16 studies were included in this meta-analysis. The results showed that positive YAP expression was closely correlated with GC but not adjacent non-tumor tissue (OR = 8.08, 95% CI = 4.41 - 14.80). Additionally, YAP overexpression was found to be associated with more advanced TNM stage (OR = 2.68, 95% CI = 1.61 - 4.48), deeper invasion depth (OR = 2.05, 95% CI = 1.32 - 3.19), and lymph node metastasis (OR = 1.95, 95% CI = 1.29 - 2.96). No significant correlation was observed between YAP overexpression and degree of differentiation (OR = 1.17, 95% CI = 0.63 - 2.16), as well as gender of patients (OR = 1.12, 95% CI = 0.91 - 1.37) or tumor size (OR = 1.11, 95% CI = 0.82 - 1.49) of gastric cancer. **Conclusions:** This meta-analysis demonstrated that YAP might be a promising diagnostic marker and even a therapeutic target for gastric cancer.

Keywords

Yes-Associated Protein, Gastric Cancer, Clinicopathological Feature, Meta-Analysis

*These authors contributed equally to this work.

1. Introduction

Gastric cancer (GC) is one of the most common malignant tumors in the digestive system. It has become the third leading cause of cancer death worldwide. Over 70% of GC cases occur in developing countries, and roughly half of the world's total occurs in eastern Asia (chiefly in China) [1]. Most GC patients present with advanced tumor due to the inconspicuous symptoms of early onset GC and the limited diagnostic conditions, making the sufferers lose the optimal opportunity for radical cure [2]. For these patients, systemic treatments, such as chemotherapy, are the main treatment option. Although great progress has been made for advanced GC chemotherapy in recent years, mortality is still unacceptably high. Therefore, searching for ideal diagnostic biomarkers and novel therapeutic targets remains critical for the treatment of GC.

Hippo signaling pathway is an evolutionarily conserved regulator for organ size control and tissue growth. Accumulating literature suggests that dysregulation of Hippo pathway leads to proliferation and anti-apoptosis associated with increased cancer risk [3] [4] [5]. As a pivotal downstream effector of Hippo signal cascade, Yes-associated protein (YAP) was considered as an oncoprotein, and its overexpression and accumulation in the nucleus were closely related to the poor clinical outcomes of various tumors including gastric cancer [6] [7]. Moreover, YAP was even reported as a potential target for GC therapy [8]. Nevertheless, the published clinical studies showed the data were still controversial, and the opposite role of YAP in GC was also reported [9]. Therefore, we conducted this meta-analysis to comprehensively assess the relationship between YAP overexpression and gastric cancer.

2. Methods

2.1. Search Strategy

We performed a systematic literature search in PubMed, Embase, Web of Science databases and the Chinese National Knowledge Infrastructure (CNKI) from inception up to December 2018. Relevant studies were identified using a combination of the following terms: "YAP" or "Yes-associated protein" or "Yes protein" or "Hippo" and "gastric cancer" or "gastric carcinoma" or "gastric neoplasm" or "stomach cancer" or "GC". To availably identify relevant studies, we also manually searched for references cited in the eligible articles. When two studies had partial overlaps, both studies should be considered.

2.2. Inclusion and Exclusion Criteria

The eligible literature in this study fulfill the following inclusion criteria: 1) patients were diagnosed as gastric cancer; 2) YAP expression was quantified by immunohistochemistry or other adequate methods; 3) sufferers were categorized into high YAP (or YAP-positive) and low YAP (or YAP-negative) groups; 4) the association between YAP expression and clinicopathological features was described, or YAP expression in human tumor and adjacent tissues was detected;

5) the search was restricted to human studies published in English or Chinese. Studies were excluded if they met any of the following exclusion criteria: a) reviews, case reports, comments, conference abstracts, letters, or laboratory studies; b) published in a language other than English or Chinese; c) insufficient data available to estimate the association.

2.3. Data Extraction

Required data were extracted by two investigators independently based on the inclusion criteria listed above. Any discrepancies in data extraction were evaluated by discussion to reach a consensus. The extracted data included the first author's name, year of publication, country of origin, distribution of gender and age in patients, number of patients, staining location, method of detection, YAP expression in gastric cancer and adjacent normal tissue, and clinicopathological features.

2.4. Assessment of Study Quality

Two investigators independently evaluated the quality of each study according to Newcastle-Ottawa Scale (NOS) [10]. The NOS includes three parameters of quality for studies: selection of the study population, comparability of subjects, and exposure assessment, with scores ranging from 0 to 9 (Additional file 1: **Table S1**). NOS scores > 5 was considered as high-quality studies.

2.5. Statistical Analysis

We implemented the meta-analysis based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Checklist (Additional file 2: **Table S2**). The odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were used to assess the association between YAP expression and gastric cancer or the clinicopathological features of gastric cancer. The heterogeneity among eligible studies was evaluated by the Q-test. *P*-value < 0.1 indicated that the heterogeneity was significant. I^2 values were also calculated to quantify the heterogeneity: $I^2 < 25\%$, $25\% < I^2 < 50\%$, $50\% < I^2 < 75\%$, and $I^2 > 75\%$, indicated no heterogeneity, moderate heterogeneity, large heterogeneity, and extreme heterogeneity, respectively. When *P*-value > 0.1 and $I^2 < 25\%$, the heterogeneity was considered not significant, and then the pooled OR and 95% CI were assessed by the fixed-effects model; otherwise, the random-effects model was performed [11]. The sensitivity analysis was carried out by sequential omission of individual studies to test the stability of meta-analysis results. Moreover, Begg's test and Egger's test were used to evaluate the publication bias; *P*-value < 0.05 indicated the presence of publication bias. All statistical analyses were performed using the software STATA version 12.0 (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Study Characteristics

The flow chart of the study selection process was presented in **Figure 1**. A total

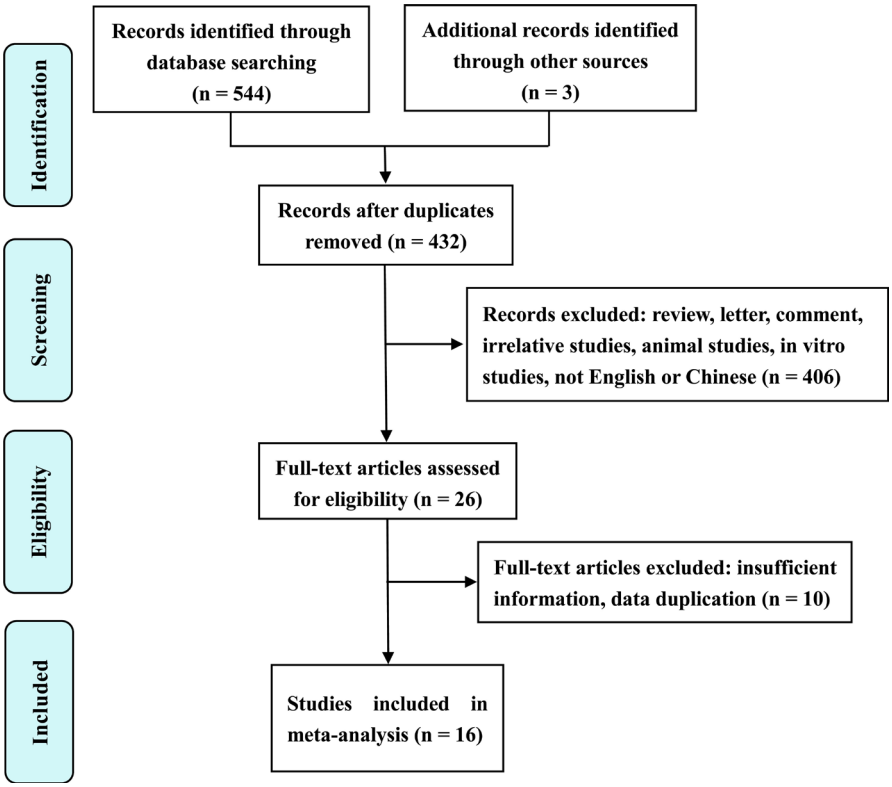

Figure 1. Flow chart of study selection.

of 432 relevant publications were retrieved after the initial database searches. According to the inclusion and exclusion criteria, data from 16 studies including 2229 patients were included in this meta-analysis [9] [12]-[26]. As shown in **Table 1**, the eligible studies were published between 2009 and 2018, and sample sizes ranged from 53 to 302. 12 studies (75.00%) reported on Chinese, 3 studies (18.75%) on Koreans, and only 1 study (6.25%) on Japanese. YAP expression was detected by immunohistochemistry in all eligible studies, among them, formalin-fixed and paraffin-embedded (FFPE) samples were used for immunohistochemical staining in 8 studies, while the other 8 studies used tissue microarray (TMA). Of the eligible publications, 13 studies reported nuclear and cytoplasmic staining of YAP (overall YAP expression), and 3 studies detected YAP expression only by nuclear staining. Additionally, the quality of each eligible study was assessed according to the NOS, and all articles were of high quality (NOS score > 5).

3.2. The Difference of YAP-Positive Expression between GC and Adjacent Tissues

YAP expression in GC and adjacent non-tumor tissues was detected simultaneously in 8 studies [12] [15] [16] [17] [21] [22] [24] [26]. As depicted in **Table 2**, the eight studies included 925 GC samples (case) and 728 paracancerous samples (control). YAP-positive rate in GC was much higher than that in normal tissues (OR = 8.08, 95% CI = 4.41 - 14.80). Moreover, the results of meta-analysis showed that 95% confidence intervals of combined study, as well as each independent

Table 1. Characteristics of the studies included in the meta-analysis.

Author	Year	Country	Gender (male/female)	Age (year)	Patient number (negative/positive)	Staining location	Method of detection	NOS	Ref.
Da CL	2009	China	66/32	≥60, 54 <60, 44	98 (51/47)	YAP expression	TMA	7	[12]
Song M	2012	South Korea	140/83	≥65, 68 <65, 155	223 (162/61)	YAP nuclear expression	FFPE tissues	6	[13]
Zhang J	2012	China	39/14	≥70, 20 <70, 33	53 (33/20)	YAP expression	TMA	6	[14]
Luo H	2013	China	40/16	Median: 66.1 ± 3.7 (range: 60 - 73)	56 (16/40)	YAP expression	FFPE tissues	7	[15]
Hu X	2014	China	64/150	>61, 103 ≤61, 111	214 (67/147)	YAP expression	TMA	7	[16]
Suh JH	2015	South Korea	-	Median: 64.6 (range: 39 - 88)	116 (66/50)	YAP expression	TMA	7	[9]
Huang S	2017	China	87/33	>57.5, 60 <57.5, 60	120 (16/104)	YAP nuclear expression	FFPE tissues	7	[17]
Sun D	2017	China	216/86	>55, 192 ≤55, 110	302 (64/238)	YAP expression	TMA	7	[18]
Nambara S	2017	Japan	68/33	≥65, 54 <65, 47	101 (35/66)	YAP expression	FFPE tissues	6	[19]
Hong SA	2017	South Korea	118/48	≥62.5, 83 <62.5, 83	166 (85/81)	YAP expression	TMA	6	[20]
Yu B	2017	China	73/25	≥60, 68 <60, 30	98 (22/76)	YAP nuclear expression	TMA	7	[21]
Fan JH	2017	China	53/34	≥58, 52 <58, 35	87 (50/37)	YAP expression	FFPE tissues	7	[22]
Fu Y	2018	China	84/76	Median: 58 ± 3	160 (55/105)	YAP expression	FFPE tissues	6	[23]
Bao SS	2018	China	82/35	≥60, 66 <60, 51	117 (28/89)	YAP expression	FFPE tissues	7	[24]
Han XY	2018	China	129/54	≥60, 107 <60, 76	183 (46/137)	YAP expression	FFPE tissues	6	[25]
Xiao L	2018	China	99/36	>60, 48 ≤60, 87	135 (68/67)	YAP expression	TMA	7	[26]

Abbreviations: YAP, Yes-associated protein; TMA, tissue microarray; FFPE, formalin-fixed and paraffin-embedded; NOS, Newcastle-Ottawa Scale.

Table 2. YAP expression in gastric cancer and adjacent non-tumor tissue.

Author	Year	Case	Control	Case		Control	
				YAP (+)	YAP (−)	YAP (+)	YAP (−)
Da CL	2009	98	98	47	51	13	85
Luo H	2013	56	56	40	16	8	48
Hu X	2014	214	167	147	67	32	135
Huang S	2017	120	30	104	16	20	10
Yu B	2017	98	98	22	76	0	98
Fan JH	2017	87	27	50	37	5	22
Bao SS	2018	117	117	89	28	12	105
Xiao L	2018	135	135	67	68	33	102

study, exceeded "1", indicating that positive YAP expression was correlated with gastric cancer but not adjacent non-tumor tissue (Figure 2(a)).

3.3. Association of YAP Overexpression with GC Clinicopathological Features

The main results of meta-analysis and heterogeneity test for the association study of YAP overexpression with gastric cancer clinicopathological features were summarised in Table 3. The elevated YAP expression was correlated with more advanced TNM stage (OR = 2.68, 95% CI = 1.61 - 4.48) (Figure 3(a)), deeper invasion depth (OR = 2.05, 95% CI = 1.32 - 3.19) (Figure 3(b)), and lymph node metastasis (OR = 1.95, 95% CI = 1.29 - 2.96) Figure 3(c)) in gastric cancer. Moreover, no significant correlation was observed between YAP overexpression and degree of differentiation (OR = 1.17, 95% CI = 0.63 - 2.16) (Figure 3(d)), as well as gender of patients (OR = 1.12, 95% CI = 0.91 - 1.37) (Figure S1(a)) or tumor size (OR = 1.11, 95% CI = 0.82-1.49) (Figure S1(b)) of gastric cancer.

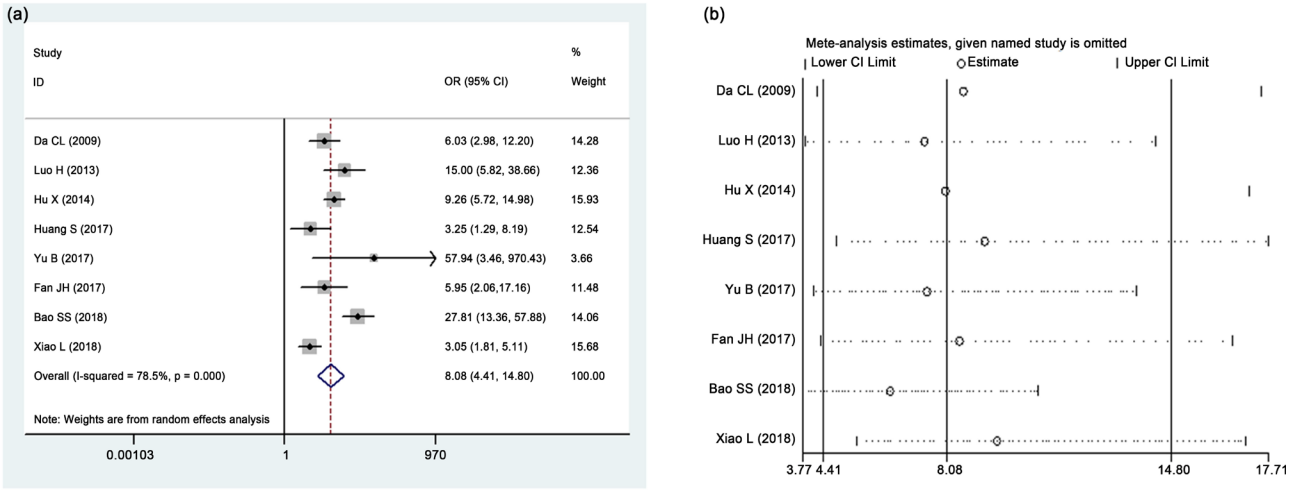

Figure 2. The difference of YAP-positive expression between gastric cancer and adjacent tissues. (a) Forest plot for the association between YAP-positive expression and gastric cancer; (b) Sensitivity analysis for the association between YAP-positive expression and gastric cancer.

Table 3. The correlation of YAP overexpression with GC clinicopathological features.

Variable	No. studies	Model	OR (95% CI)	Heterogeneity		Begg's test	Egger's test
				I^2 (%)	*P*-value (Q-test)		
Gender[a]	14	Fixed	1.12 (0.91, 1.37)	12.9	0.312	0.661	0.285
Tumor size[b]	8	Fixed	1.11 (0.82, 1.49)	39.6	0.115	0.902	0.139
TNM stage[c]	12	Random	2.68 (1.61, 4.48)	78.4	0.000	0.086	0.160
Invasion depth[d]	8	Random	2.05 (1.32, 3.19)	54.0	0.033	0.174	0.500
Lymph node metastasis[e]	14	Random	1.95 (1.29, 2.96)	71.8	0.000	0.443	0.847
Degree of differentiation[f]	11	Random	1.17 (0.63, 2.16)	82.3	0.000	0.436	0.521

Notes: [a]Male/female; [b]>5 cm/<5 cm; [c]III + IV/I + II; [d]T3 + T4/T1 + T2; [e]Yes/No; [f]Low differentiation/middle and high differentiation.

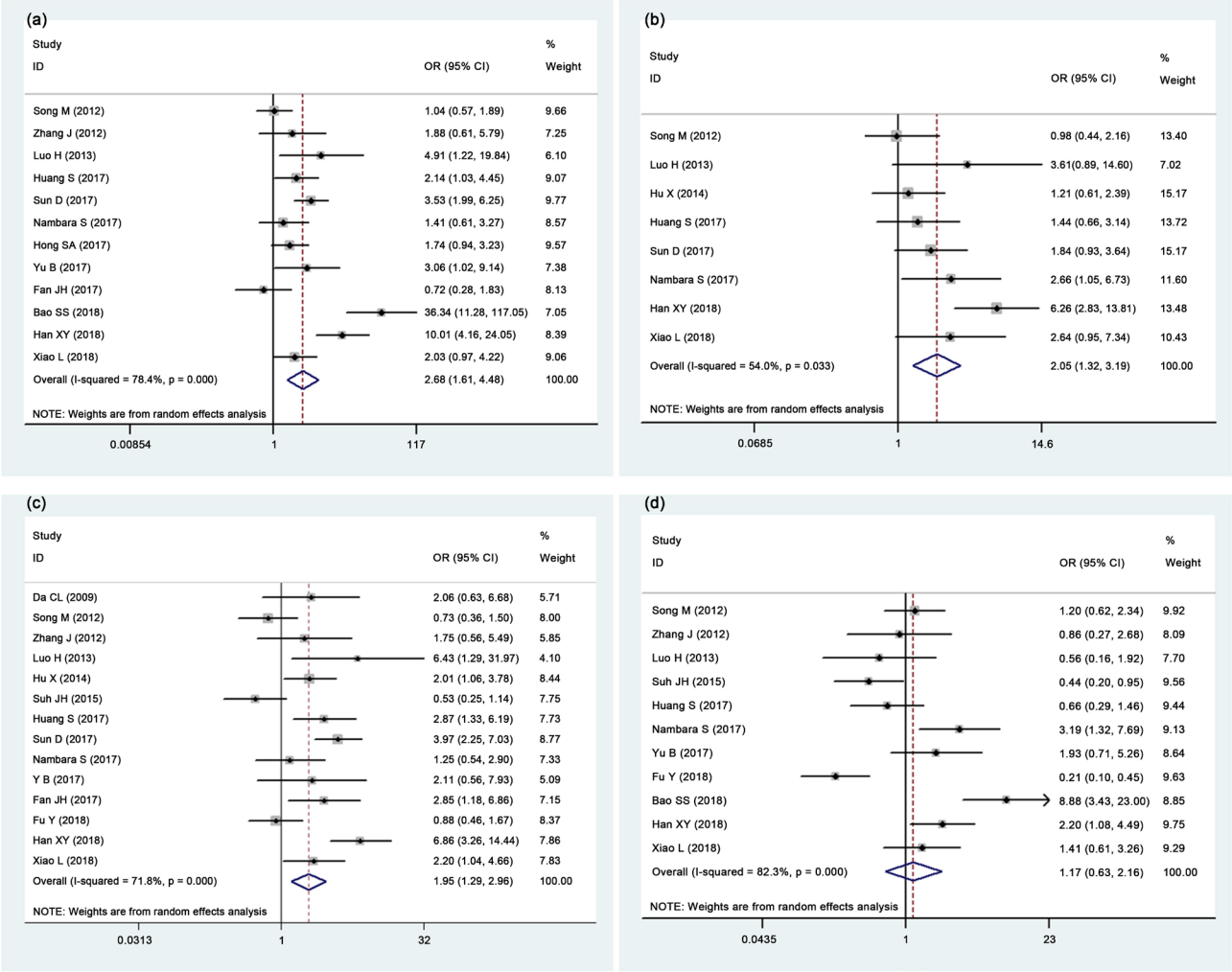

Figure 3. The association of elevated YAP expression with clinicopathological features of GC. Forest plots for the association between elevated YAP expression and (a) TNM stage, (b) invasion depth, (c) lymph node metastasis, or (d) degree of differentiation in GC.

3.4. Sensitivity Analysis

We conducted sensitivity analysis by sequential omission of individual studies to probe the change in the odds ratio and 95% confidence interval of meta-analysis. As shown in **Figure 2(b)**, **Figures 4(a)-(d)** and **Figure S1(c)** & **Figure S1(d)**, no significant difference was observed when any of the studies was excluded in all correlation assessments, indicating the reliability and stability of the meta-analysis.

3.5. Publication Bias

Begg–Mazumdar adjusted rank correlation test and Egger's regression test were performed to assess the publication bias. The results showed that the shape of Begg's funnel plots appeared to be symmetrical (data not shown). Meanwhile, the *P*-values were all greater than 0.05 in both Begg's test and Egger's test (**Table 3**). These results suggested the absence of significant publication bias in the overall meta-analysis.

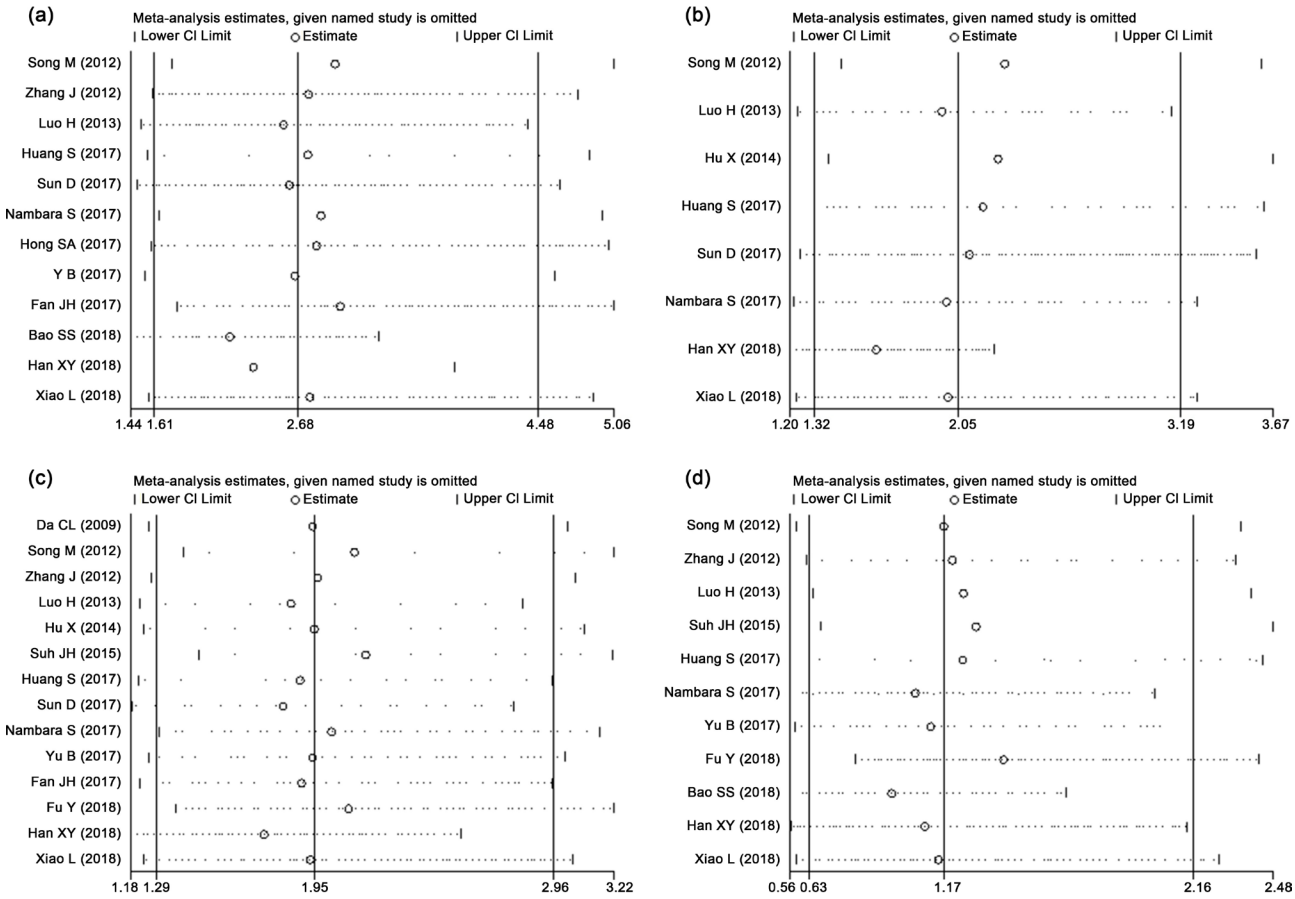

Figure 4. Sensitivity analysis for the association of elevated YAP expression with clinicopathological features of GC. Sensitivity analysis for the association between elevated YAP expression and (a) TNM stage, (b) invasion depth, (c) lymph node metastasis, or (d) degree of differentiation in GC.

4. Discussion

Gastric cancer is characteristic of poor prognosis and high death rate, and there is still a great need to identify diagnostic markers as well as develop novel therapeutic strategies for GC therapy. Hippo pathway regulates tissue growth and organ size via YAP-TEAD complex. Inactivation of Hippo cascade leads to the elevated expression and nucleus accumulation of YAP, which is significantly associated with poor clinical outcomes of most cancers. Therefore, Hippo cascade acts as a tumor suppressor pathway, and YAP is considered to be an oncoprotein in multiple cancers including GC. There are many published clinical data supporting this conclusion. Zhang reported that YAP was strongly expressed in GC, and knockdown of YAP could inhibit the proliferation and metastasis of GC cells [27]. The similar results could also be observed in the study of Zhou and his colleagues [28]. Moreover, Yan showed that YAP acted as a tumor promoter in gastric cancer, and involved in the survival and migration of GC cells through the activation of the SIRT1/Mfn2/mitochondrial autophagy axis [29]. However, there are still inconsistent results published. Suh and colleagues supported that YAP functioned as a tumor suppressor in GC [9]. Zhang also indicated that there

was no significant correlation between YAP expression and clinicopathological characteristics in GC, and YAP was not a potential marker for diagnosis or prognosis of GC [14]. In this account, a meta-analysis including 16 studies was performed to comprehensively evaluate the relevance of elevated YAP expression with GC and its pathological parameters. The results of pooled data showed a significant correlation between positive YAP expression and GC, but not adjacent non-tumor tissue. Furthermore, the elevated YAP expression in GC was closely related to more advanced TNM stage, deeper invasion depth and lymph node metastasis.

The heterogeneity and several limitations of this meta-analysis should be acknowledged. First, all of the eligible studies in this meta-analysis were carried out in Asian population, therefore, it might be insufficient to provide support for other ethnic groups. Second, the evaluation criteria of positive YAP expression differed among included studies, which might influence the results of pooled data and contribute to the heterogeneity. Third, the data we extracted contain both YAP nuclear staining and overall YAP expression, the difference in staining location is also a potential heterogeneous source due to the expression characteristics of YAP in different cell states.

In conclusion, this meta-analysis demonstrated that YAP-positive expression in gastric cancer was significantly higher than that in adjacent non-tumor tissues. Additionally, the overexpression of YAP was closely correlated with more advanced TNM stage, deeper invasion depth and lymph node metastasis. Therefore, YAP may be a promising diagnostic marker and even a therapeutic target for GC. However, the results of this study should be interpreted cautiously due to the existence of heterogeneity and limitations. Hence, well-designed prospective studies based on larger sample sizes, as well as the corresponding basic research are still warranted to validate the present findings.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

Table S1. Newscastle-ottawa quality assessment scale.

Study	Selection				Comparability	Exposure			Score
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	☆
	a) Yes, with independent validation ☆	a) Consecutive or obviously representative series of cases ☆	a) Community controls ☆	a) No history of disease (endpoint) ☆	a) Study controls for_____ (Select the most important factor) ☆	a) Secure record (e.g. surgical records) ☆	a) Yes ☆	a) Same rate for both groups ☆	
	b) Yes, e.g. record linkage or based on self reports	b) Potential for selection biases or not stated	b) Hospital controls	b) No description of source	b) Study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor) ☆	b) Structured interview where blind to case/control status ☆	b) No	b) Non respondents described	
	c) No description		c) No description			c) Interview not blinded to case/control status		c) Rate different and no designation	
						d) Written self report or medical record only			
						e) No description			
Da CL	☆	☆	☆	☆	☆	☆	☆		7
Song M	☆	☆		☆	☆	☆	☆		6
Zhang J	☆	☆		☆	☆	☆	☆		6
Luo H	☆	☆	☆	☆	☆	☆	☆		7
Hu X	☆	☆	☆	☆	☆	☆	☆		7
Suh JH	☆	☆	☆	☆	☆	☆	☆		7
Huang S	☆	☆	☆	☆	☆	☆	☆		7
Sun D	☆	☆	☆	☆	☆	☆	☆		7
Nambara S	☆	☆		☆	☆	☆	☆		6
Hong SA	☆	☆	☆		☆	☆	☆		6
Yu B	☆	☆	☆	☆	☆	☆	☆		7
Fan JH	☆	☆	☆	☆	☆	☆	☆		7
Fu Y	☆	☆	☆		☆	☆	☆		6
Bao SS	☆	☆	☆	☆	☆	☆	☆		7
Han XY	☆	☆		☆	☆	☆	☆		6
Xiao L	☆	☆	☆	☆	☆	☆	☆		7

Table S2. PRISMA 2009 Checklist.

Section/Topic	#	Checklist Item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2 - 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2 - 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2 - 3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2
Study selection	9	State the process for selecting studies (*i.e.*, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2 - 3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2 - 3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3 - 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3 - 4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3 - 4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	4 Table 3

Continued

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3 Figure 3 & 4 3-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 2 Figure 2 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	3 - 4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	4 - 5
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	4
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	4 - 5
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	5

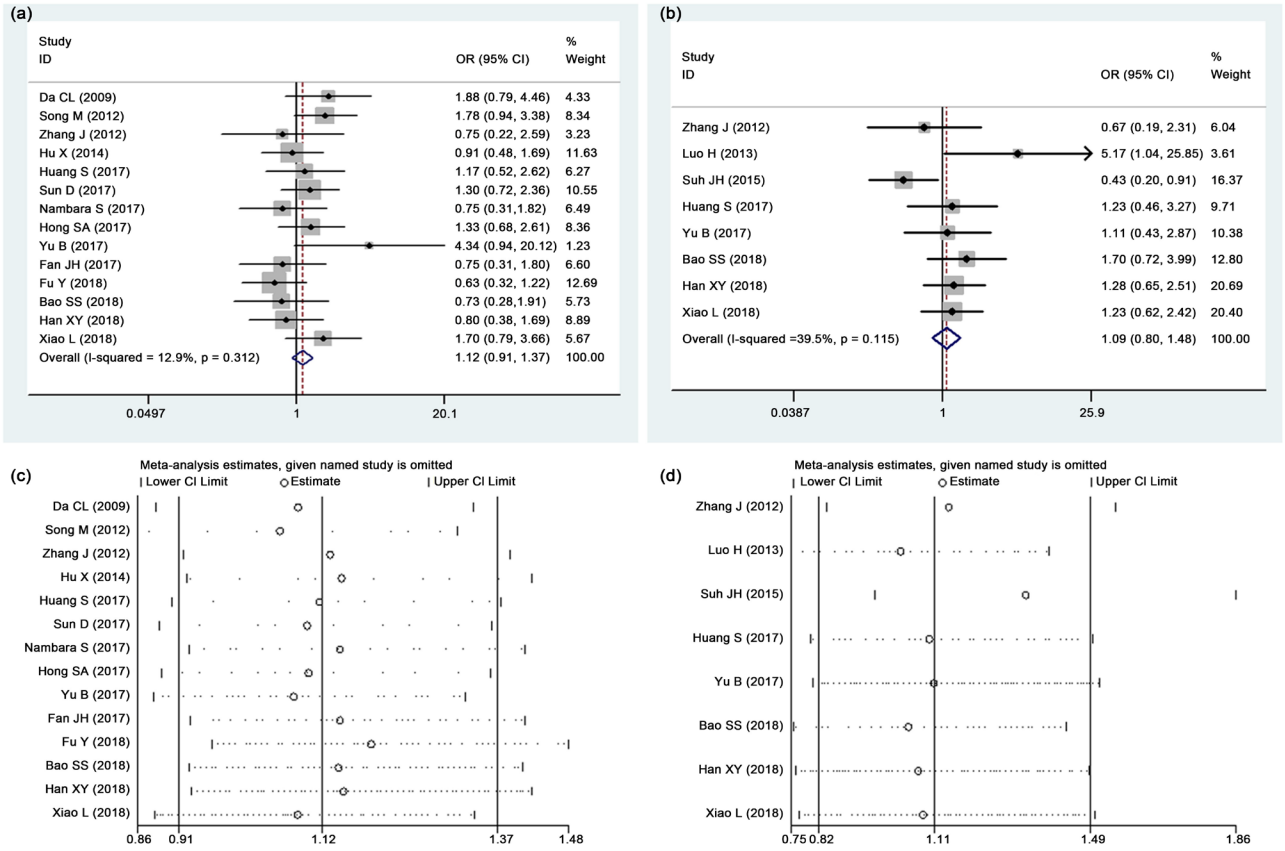

Figure S1. The association of elevated YAP expression with clinicopathological features of GC. Forest plots for the association between elevated YAP expression and (a) gender, or (b) tumor size in GC. Sensitivity analysis for the association between elevated YAP expression and (c) gender, or (d) tumor size in GC.