Prognostic and clinicopathological significance of YAP in Colorectal carcinoma: A systematic review and meta-analysis

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Research article

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Abstract

Background: YAP is a protein encoded by the YAP gene in humans. Numerous studied showed that YAP expressed in colorecal carcinoma (CRC) and has a association with poor clinical outcomes. However, the association between YAP expression level with prognostic and clinicopathological features in CRC patients remains unclear. Therefore, we performed a meta-analysis to investigate the prognostics effect of YAP expression on CRC patients.

Methods: A systematic search of the PubMed, Web of Science, Cochrane Library and Embase databases was conducted based on predefined selection criteria in April 26, 2020. The correlation between YAP expression level and survival outcomes or clinicopathological characteristic was analyzed by hazard ratios (HR) or odds ratios (OR) at 95% confdence intervals (CI).

Results: 12 studies were included, with a total of 2286 CRC patients,in our meta-analysis.

the results show the relationship between YAP expression level with overall survival (OS) in CRC patients HR (2.02, 95%CI 1.67-2.44 $I2$ =19.7% P= 0.25) . In addition to clinicpathological features, CRC patients with overexpression of YAP were tend to advanced TNM stage(OR:2.99, 95%CI 2.11-4.25, I2=0.0%, P=0.699), lymph node metastasis(OR:3.73, 95% CI 2.63-5.30, I2=4.8%, P=0.386), distant metastasis(OR:3.03, 95% CI 1.21-7.56, I2=65.3%, P=0.021), tumor invasion depth HR (2.82 95%CI 1.65-4.83 I2=0.0%, p=0.413), but have no associated with sex, tumor size, tumor location and tumor differentiation.

Conclusion: The results of this meta-analysis show that high expression of YAP tended to have a worse progosis and have great influence on clinicpathological features. which means YAP may serve as a promising indicator in the prediction of prognosis and clinicopathological features in CRC patients.

Background

Colorectal carcinoma (CRC) represents one of the most prevalent malignancies and one of the leading causes of cancer-related deaths in the world[1]. Risk factors associated with CRC include obesity, age, excessive alcohol consumption, genetic mutations and chronic intestinal inflammation. The treatment of CRC is mainly surgical operation and chemotherapy. Surgical resection of CRC has a good effect in early stage, but is not suitable for advanced patients. Chemotherapy is the most important treatment for metastatic CRC , but drug resistance has become the biggest challenge to the CRC patients . In recent years, molecular targeted therapy of CRC has made great progress. Currently, EGFR and VEGF targeted antibodies have been

included in the treatment strategies of metastatic colorectal cancer [2] . However, the 5-year survival rate of CRC is still poor, so it is urgent to find an ideal biological target for effective treatment of CRC.

The hippo pathway is a conservative anticancer pathway that regulates organ size, tissue homeostasis, specific stem cell proliferation in Tephritidae and mammals[3] . Mst1/2, sav1 kinase and effector lats1/2 represent the core components of the Hippo pathway, and YAP is the main downstream effector of the Hippo signaling pathway[4]. A number of studies have shown that YAP is highly expressed in CRC, and is highly correlated with the formation, progression, and metastasis of CRC[5]. Therefore, we predict that YAP may be one of the ideal biological targets for the treatment of CRC.

YAP, also known as the yes-associated protein 1, is a transcriptional coactivators highly activated in human malignancies. YAP can shuttle from cytoplasm to the nucleus. In cytoplasm, kinases Lats1 and Lats2(LATS1 / 2) phosphorylates YAP and promote its binding to 14-3-3 proteins, thereby YAP was degraded by ubiquitin-ligase. while in nucleus ,they can distinguish cognate cis-regulatory elements by interacting with TEA domain family members (TEAD) or other transcription factors to control the target gene's transcription[6] . Sustained activation of YAP enhance several of the key characteristic of cancer cells, including cancer stem cells attributes, proliferation, chemoresistance and metastasis. It is worth to mention that the ability to tumorigenesis , chemoresistance, metastasis and expand undifferentiated cell populations are all connection with reprogram CSC regulated by YAP[7]. As such, YAP is appealing therapeutic targets in cancer and regenerative medicine.

There was a meta-analysis suggests that YAP associated with the prognosis of gastrointestinal tumor [8]. however this meta-analysis only enrolled 4 studies about the relationship of YAP and CRC and clinicopathological characteristics were not performed in this meta-analysis. Recent work indicates that, YAP are essential for initiation or growth of colorectal tumors. Considering the inconsistent data among published studies . We conducted the meta-analysis, to clarify the association of YAP between the outcome and clilicopathological features in CRC patients . In the end, We predicted that YAP might be one of the ideal biological targets for the treatment of CRC.

Methods

Literature collection

Electronic databases PubMed, Cochrane Library, Web of science, Embase databases were searched on April 26, 2020, covering a time period from 1995 until 2020. The following search terms were used:"YAP" or "YAP1" or "yes associated protein 1" or “yes associated protein” and "colorectal neoplasms" or "colorectal carcinoma" or "colorectal cancer" or "colorectal tumor " . The pubmed search term is that: ((((((((((((((colorectal neoplasms) OR colorectal neoplasm) OR neoplasm, colorectal) OR colorectal carcinoma) OR carcinoma, colorectal) OR colorectal carcinomas) OR colorectal cancer) OR cancer, colorectal) OR cancers, colorectal) OR colorectal cancers) OR colorectal tumors) OR colorectal tumor) OR tumor, colorectal) OR tumors, colorectal) OR neoplasms, colorectal)) AND ((((yes associated protein 1) OR YAP1) OR yes associated protein) OR YAP). All eligible manuscripts and their references were retrieved for data extraction and analysis.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) All included patients were diagnosed with colorectal neoplasms by histopathology; (2) The expression of YAP was detected by immunohistochemistry or QPCR ; (3) The correlation between YAP and survival prognosis was investigated. (4) Provide sufficient data to calculate the odds ratio (OR), risk ratio (HR) and corresponding 95% confidence interval (CI); (5)The correlation between the YAP expression level and the clinicopathological characteristic and at least one pathological feature was investigated, such as TNM stage, lymph node metastasis, distant metastasis, tumor invasion depth, Sex, tumor location, tumor size and differentiation;(6) Articles published in English.

Exclusion criteria:(1)non-human studies, reviews, editorials, expert opinions, letters and case reports; (2) duplication of publications; (3)Non-English published papers ; (4) no research with valuable data.

Data extraction and quality assessmet

Two researchers, Lu dai, xiao jin, independently extracted information from the eligible publications. The following data included the first author's name, year of publication, country, time of sample collection, age, sample size, endpoint(OS), assay method and cut-off value to define the expression of the YAP. For the clinicopathological features, sex, TNM, tumor invasion depth, lymph node metastasis, distant metastasis, tumor size, tumor differentiation and tumor location were extracted. quality of the enrolled studies was assessed individually by two authors, based on the Newcastle-Ottawa Scale(NOS), when a score greater than 5, we though the record as a high quality document,which the scores varied from 0 to 9.

Statistical analysis

All the statistical data were calculated by stata 15.1 sofeware. Engauge Digitizer 10.0 was used to extracted the survival data from a Kaplan-Meier curve. Pooled HRs and 95%CIs were calculated to assess the relationship of YAP ecpression level with Overall survival in colorectal carcinoma patients. If HR>1, and 95%CI did not contain 1, it implied that patients with high YAP expression had a worse prognosis. The association between YAP expression and clilicopathological features was assessed by pooled odds ratios (ORs) with 95% CI. The heterogeneity among our records was performed by Chi-squared test and I2 statistics . we defined the existence of heterogeneity as I2>50% and p<0.05. The randoms-effect model was chosen when the heterogeneity existed, otherwise, we used the fixed-effct model. Subgroup analysis stratified by HR obtained measurement, NOS score and sample capacity were conducted to analyze source of heterogeneity. Both Begg's and Egger's tests were performed to examine the publication bias of our records. Meanwhile , sensitivity analysis was employed to assess the reliability of the results, p values<0.05 meant statistically significant.

Results

Search results and study characteristis

976 articles were identified by searching the PubMed, Embase, Web of science and Cochrane library. We excluded 941 articles after screening the titles and abstracts. Then we included 12 studies after reviewing 43 Full-text articles in detail[9-20]. A flowchart of the retrieval process is shown in Fig.1. Among the included studies, all of them reported the correlation of YAP expression with OS, 10 records evaluated the relationship between YAP and clinicopathological signification in patiens with CRC. 7 studies provided Hazard ratio(HR) statistic in the original literature, and others were determined from the Kaplan-Meier curve by using Engauge Digitizer 10.0 sofeware. There were 2286 patients with sample size ranging between 66 and 903. Most of studies were from china except one from Korea. A summary of the main characteristics of the included studies is shown in Table 1. Immunohistochemical techniques and qRT-PCR were used to defined for YAP expression levels. All patients were divided into two groups: high and low YAP expression group. The relationship between high expression of YAP and clinicopathological features in CRC patients is shown in the table 2 , whereas the low expression of YAP is shown in the table3.

Association of YAP and OS

In the meta-analysis of OS, 12 studies with a total of 973 patients were included. The forest results are shown in fig.2. The pooled hazard ratio (HR) evaluated for OS was (2.02,95%CI 1.67-2.44 P=0.05) in CRC patients(Fig.2a). A fixed-effects was used for no no heterogeneity (I2=19.7% P= 0.25). The pooled results suggested that high YAP expression could be a reliable biomarker to predicate the endpoint in CRC patients.

Next we proceeded with subgroup analyses stratified by HR obtained measurements, NOS score and sample capacity. When it came to the HR obtained measurements, pooled HR was (1.69 95%CI 1.18-2.44) for the records with indirect method subgroup with no heterogeneity (I2=0.0%,P=0.857) and direct method subgroup (HR:2.05 ,95%CI 1.72-2.44 , I2=47.9% P=0.073) (Fig2b). The combined HR for high and low NOS score were HR 2.20 (95%CI 1.65-2.93 I2=0.0% P=0.453) and HR 1.89 (95%CI 1.57-2.29 I2=38.0% P=0.153) (Fig.2c). In addition , the high expression YAP predicted a worse OS in studies with sample capacity > 100 HR (2.06 95%CI 1.74-2.44, I2=39.6% P=0.115) while there was no significant difference between YAS overexpression and OS in records with size < 100 (HR=1.48 95%CI 0.95-2.31 , I2 0.0%, P=0.968) (Fig.2d)

Association of YAP expression with tumor clinicopathological features

In this meta-analysis, 6 studies were identified the relationship between TNM and YAP in CRC, 4 studies about tumor invasion depth, 6 records about lymph node metastasis and 5 records about distant metastasis . The main results are listed in the Fig3. High expression of YAP was associated with advanced TNM stage (OR 2.99 , 95%CI 2.11-4.25, I2=0.0%, P=0.699), Lymph node metastasis (OR 3.73, 95%CI 2.63-5.30, I2=4.8%, P=0.386), distant metastasis (OR 3.03, 95%CI 1.21-7.56, I2=65.3%, P=0.021) but had no association with tumor invasion depth (OR:1.91 ,95%CI 0.75-4.83 , I2=70.3%, P=0.018). The results show heterogeneity across the included studies about tumor invasion depth. However, after removing the study by Fang et al, the OR(2.82 95%CI 1.65-4.83 I2=0.0%, p=0.413) has a significant. We though YAP expression still had a significant impact on tumor invasion depth. Our results demostrated

that CRC patients with high expression of YAP tended to have distant metastasis , lymph node metastasis , advanced TNM stage and deep tumor invasion depth and having a worse outcome in clinic features.

With respect to the other parameters (sex, tumor size, tumor differentiation, tumor location), we could not find a significant association as shown in Fig.4. High expression of YAP was associated with sex (male vs female) (OR 0.89 ,95%CI 0.68-1.17 , I2= 17.4%, p= 0.288), tumor size(≥3cm vs <3cm) (OR 1.27 ,95%CI 0.87-1.83 , I2= 28.8%, p= 0.219), Tumor differentiation(poorly vs moderately and well) (OR 1.21 ,95%CI 0.45-3.82 , I2= 78.3%, p= 0.001), Tumor location(colon vs rectum) (OR 0.85 ,95%CI 0.54-1.33 , I2= 2%, p= 0.395).

Publication bias

In this meta-analysis, we used Begg's funnel plots and Egger's test to assess the publication bias between YAP expression levels and OS in colorectal carcinoma patients. Begg's test indicated no obvious evidence for publication bias(Fig.5). In addition, a similar result was abtained in Egger's test (p=0921). However, we did't check the publication bias between YAP and clilicopathological features due to the limited number of included records.

Sensitivity analysis

Sensitivity analysis was used to assess the reliability and stability of our results by removing any separate study(Fig.6). This indicated that the result of this meta-analysis were reliable.

Discussion

YAP at the roots of colorectal carcinoma. There are many signals regulated YAP activity in cancers. YAP was the main effectors of the Hippo signaling pathway and it can be regulated by the MST1/2-LAT1/2[21]. Recent studies suggests that PI3K-AKT signaling inhibits the Hippo pathway to promote YAP activation[22]. Furthermore gene amplifications[23], chromosomal translocations[24] and mutation[25] have been observed at the YAP loci in human cancer. When YAP activated, it can promote the proliferation of tumor cells, inhibit apoptosis, and reprogram tumor stem cells to accelerate the tumorigenesis and metastasis in CRC[26].

A modern view of "cancer: wounds that do not heal." show the relationship between cancer and inflammation . YAP plays a crucial role in wound healing and tissue regeneration . CRC is one of the most commonly diagnosed cancers closely associated with inflammation[27]. By interacting with other transcription factors, YAP regulates the expression of inflammation-related factors to promote the transformation of inflammation into malignant tumors[26]. For example, in hippo mutant mice, elevated YAP levels did not trigger the onset of early colorectal cancer, but occurred after intestinal injury[28]. This also explains why patients with severe ulcerative colitis have a significantly increased risk of colorectal cancer. For advanced CRC patients, the overall survival period is only 15-19 months, and chemoresistance

is a major limitation for survival and management of CRC patients. Recently, YAP appears to confer resistance to chemotherapeutics such as 5FU in CRC. A study shown that YES1 silencing induced the depletion of nuclear YAP levels. Which YAP activity can be though to a potential mechanism involved in the control of the balance of cell quiescence and proliferation , demonstrating that YAP play an importance role in drug resistance and the c-Yes/YAP signaling pathway and YAP should be considered as a potential therapeutic target to kill drug-resistant quiescent cancer cells[29]. Another study shown that YAP conferred drug resistance through increasing COX-2 transcription expression by intacting TEAD binding sites in the COX-2 promoter[30]. YAP is a regulator of COX-2 expression and targeting YAP-COX-2 may be a attractive therapeutic targets to treat drug-resistant colorectal cancers. About 90% of the patients with colorectal cancer (CRC) were abnormally activated by Wnt/β-catenin signaling pathway, resulting in the continuous accumulation of β-catenin in the nucleus[31]. Evidence shows that the YAP is interconnected with the WNT pathway to promote CRC progression. Azzolin L et,al had proved that YAP is a key mediator between WNT and Hippo pathways. Activated WNT signaling pathway stabilizes YAP, promoting YAP nuclear accumulation, and nuclear YAP collaborated with β-catenin to activate WNT downstream target genes to drive intestinal stem cell and tumor cell proliferation[32]. Other signaling pathways such as transforming growth factor-β(TGF-β), G protein-coupled receptors (GPCRs) signaling pathway also showed interconnected with YAP. Unfortunately, although YAP has been shown to be associated with a variety of signaling pathways, the specific regulatory mechanisms need to be further studied.

In this meta-analysis, we focus on the relationship between YAP expression level and the prognosis or clinicopathology of CRC patients from 12 included studies. when the records came to OS or DFS, We only choose the OS duo to the limitation of the studies about the DFS. Our results demonstrated that increased YAP level was significantly correlated with poor survival rates in CRC. As for subgroup, The pooled HRs and their corresponding 95% CIs showed similar outcome regardless of the alteration in NOS score and HR obtained measurements. However, there was a difference result between the large and small sample size. In the large sample capacity subgroup , YAP overexpression showed a positive relationship with CRC survival, while in the small sample capacity subgroup the pooled HRs showed a negative relationship between YAP and CRC survival. This difference between the large size and small size subgroup may be caused by the limitation of the sample or the reliability of our data.

Then we aseessed the relationship between the YAP level with clilicipathological features. We founded that YAP overexpression has a great significant associated with TNM, lymph node metastasis, distant metastasis and tumor invasion depth, suggesting that high level expression of YAP tended to have a advanced cancer stage. There was no publication bias which assessed by Begg’s funnel plots and Egger’s test of OS in our results. Sensitivity analysis indicated that the result of our meta-analysis were reliable. Collectively, the above findings supported that YAP was a potential independent factor involved in colorectal tumorigenensis and tumor progression.

This meta-analysis existed several limitations. First, most of the included records originated from China, making it more suitable for the Asian population context. More studies are needed to assess the clinical

value of YAP in different ethnicities. Second , the eligible records and the size of the enrolled patients were comparatively smaller, which reducing the accuracy of our study. More studies of large sample size needed to verify the prognostic value of YAP overexpression on CRC. Third IHC was the main method to evaluate YAP status at the protein level. There following issues may be responsible for the wide difference: (1). no widely accepted scoring system; (2). pathologist subjective perceptions; (3). difference antibodies, size of sample and experimental designs. In the end, we extracted the HR data from Kaplan-Meier survival curves may have influenced the reliability of the data.

Conclusion

Despite these limitations, our meta-analysis preliminarily indicates that YAP overexpression may be an ideal predictor of poor overall survival and advanced clinic features. YAP could be a potential biomarker to predict prognosis for CRC patients. However, further well-designed and larger sample size studies are needed to explore the role of YAP in CRC or other cancers.

Abbreviations

YAP: yes-associated protein ; HRs: hazard ratios; ORs: odds ratios; CIs: confidence intervals; OS: overall survival; DFS: disease-free survival NOS: Newcastle-Ottawa Scale; CRC: colorectal carcinoma; ; qRT-PCR: quantitative reverse transcription-polymerase chain reaction; IHC: Immunohistochemical ; TGF-β: transforming growth factor-β; GPCRs: G protein-coupled receptors

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data are included in this article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LD and XJ collected and analyzed the data, wrote the paper; JW and YM performed quality assessment and analyzed the data. XZ and ZL conceived and designed this study. All authors reviewed the paper. All authors read and approved the final manuscript.

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Authors' Information

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Figures

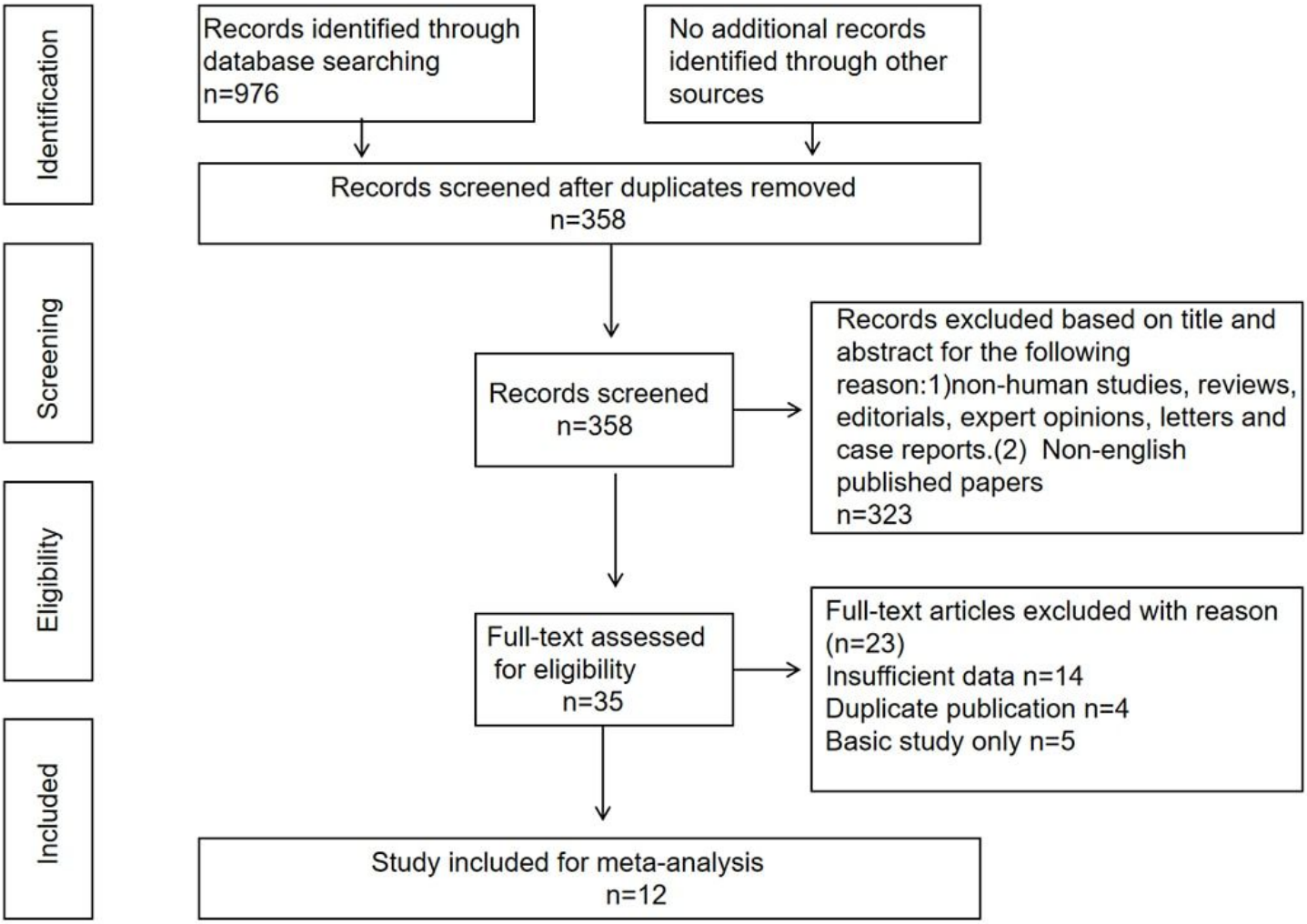

Figure 1

Flow diagram of the study search and selection process.

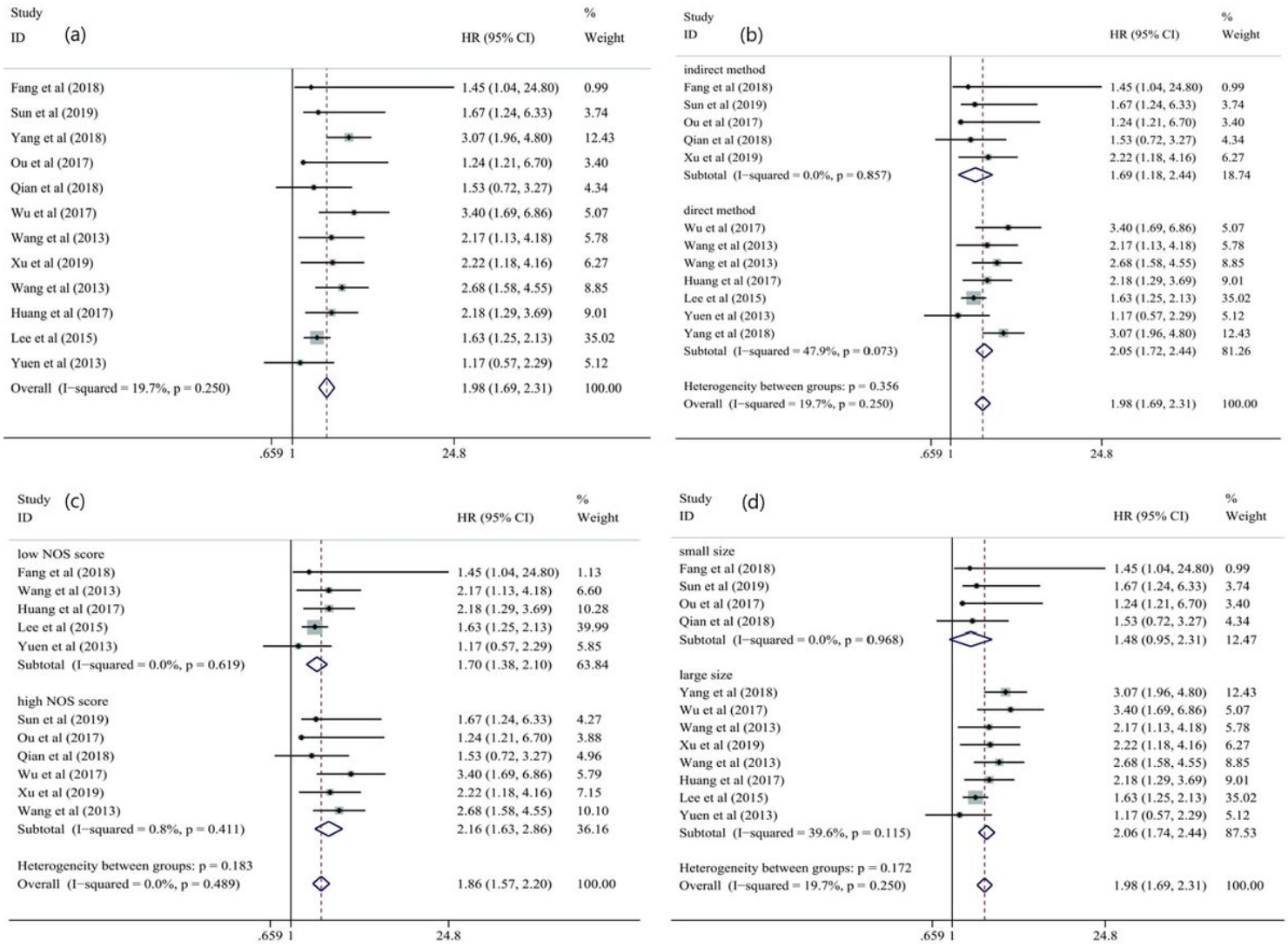

Figure 2

Forest plot for the association between YAP expression and OS (a); Forest plot for the subgroup analysis (b-d): (b): HR obtained measurements, (c): NOS score (d): sample capacity

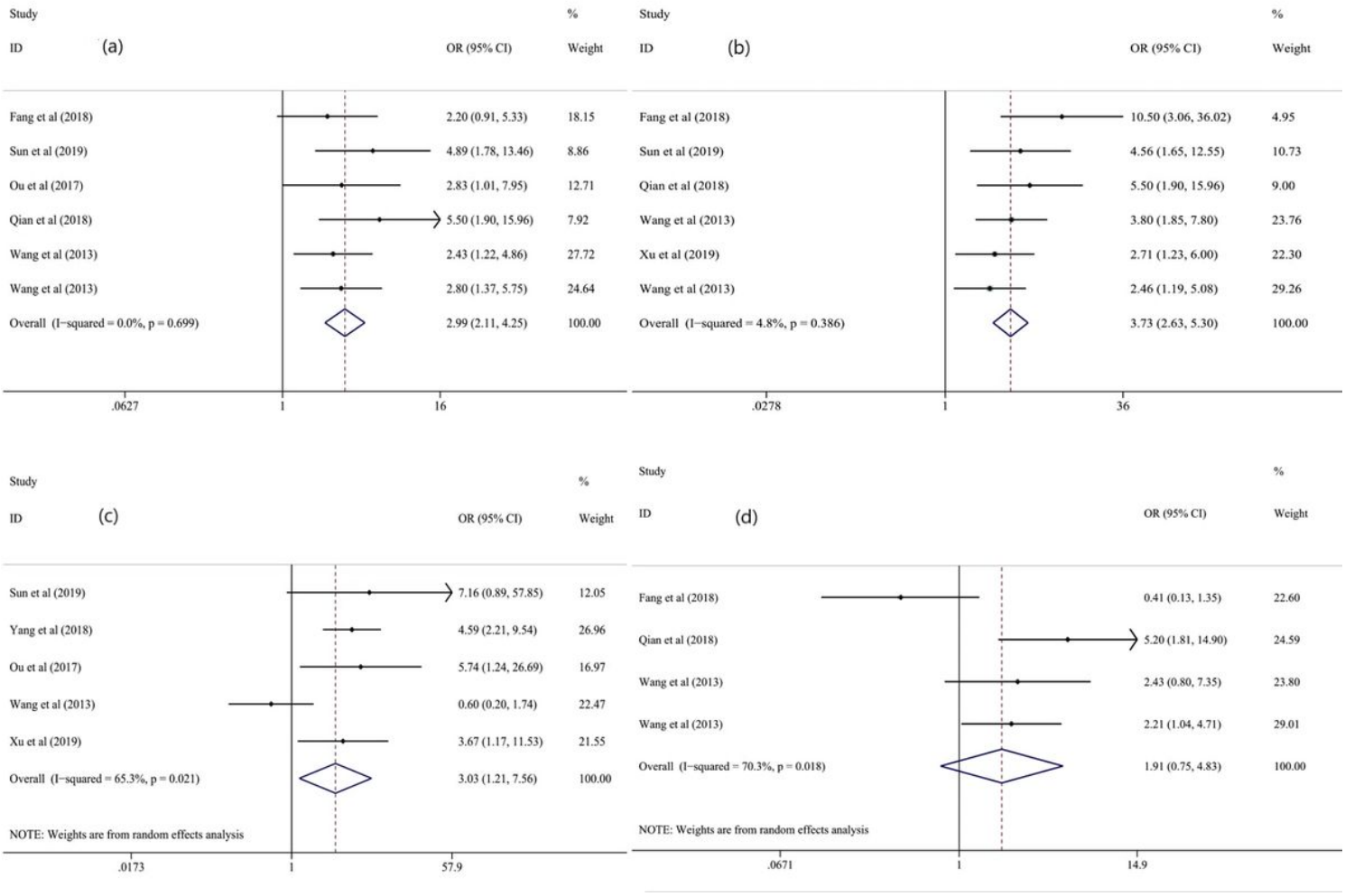

Figure 3

Forest plot for the association between YAP expression and clinicopathological parameters. (a): TNM stage; (b): lymph node metastasis; (c): distant metastasis; (d): tumor invasion depth.

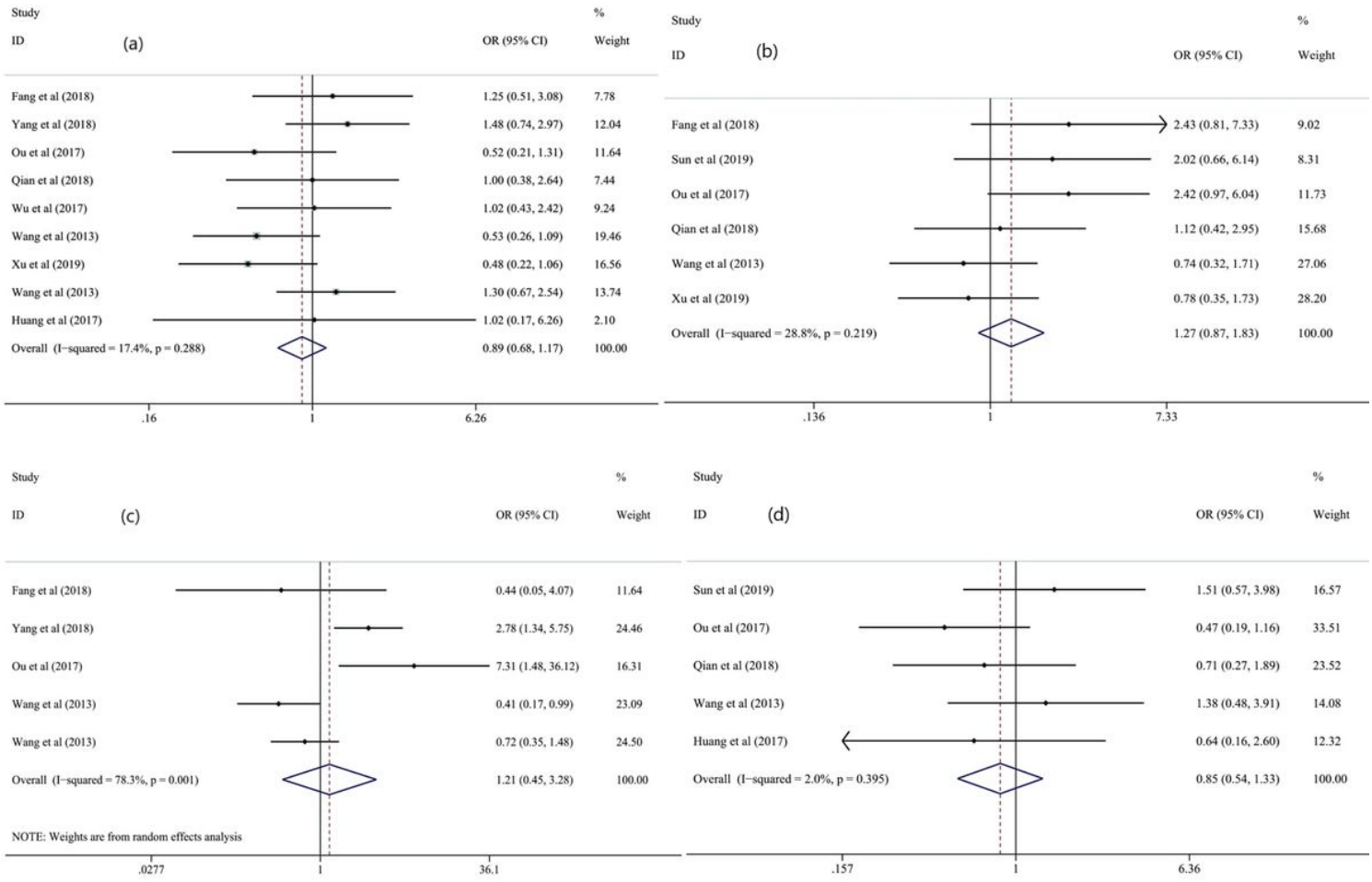

Figure 4

Forest plot for the association between YAP expression and clinicopathological parameters. (a): sex; (b): tumor size; (c): tumor differentiation; (d): tumor location.

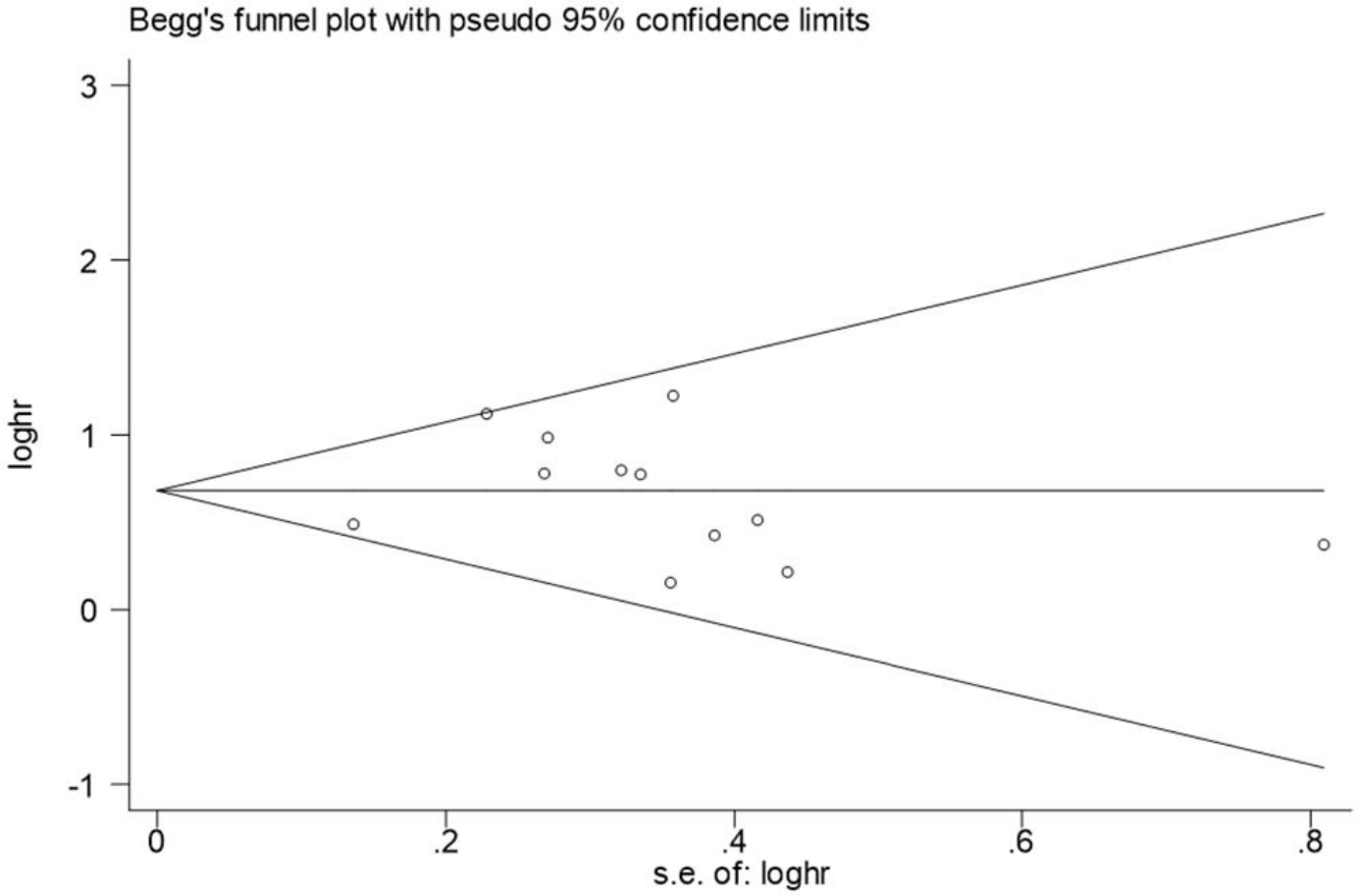

Figure 5

Funnel plot analysis of potential publication bias for OS.

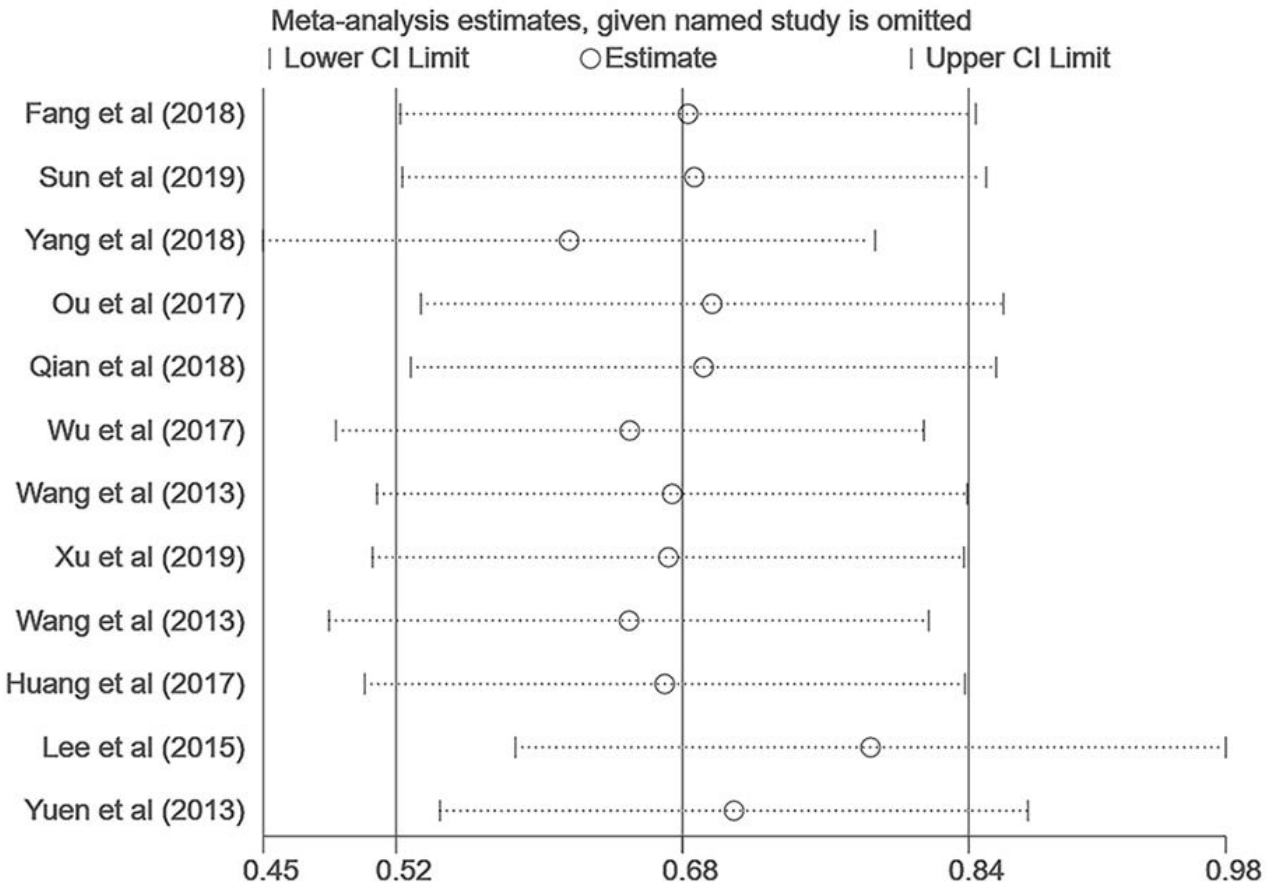

Figure 6

Sensitivity analysis of the relationship between YAP expression and OS.