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Expression characteristics of the yes-associated protein in breast cancer
A meta-analysis

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Abstract

Background: The yes-associated protein (YAP) gene plays an important role in many malignant tumors, but its clinical significance in breast cancer remains unclear. This study aimed to explore the significance of YAP expression in breast cancer using meta-analysis.

Methods: Seven databases will be searched to collect the case–control studies published on the association between YAP expression and clinical pathogenic features in breast cancer until December 2021: PubMed, EMBASE, Web of Science, China National Knowledge Infrastructure, Chinese Scientific Journal Database, Wan Fang Database, and the Chinese Biomedical Literature Database. To perform meta-analysis, STATA 14.0 and RevMan5 software were used with odds ratio (OR) and 95% confidence interval (95% CI) as the effect index, and publication bias and sensitivity analysis were subsequently tested.

Results: Form a total of 10 articles used in this study, 8 studies consisted of nontriple negative breast cancer (non-TNBC) and the other 2 of TNBC. Meta-analysis indicated a positive expression rate of YAP in non-TNBC tissues that was lower than in normal breast tissue (OR = 0.15, 95% CI = 0.10–0.21, $P < .001$). In contrast, the positive rate of YAP expression in TNBC was significantly higher than that in normal breast tissue (OR = 18.23, 95% CI = 8.20–40.52, $P < .001$). Furthermore, the positive expression rate was higher in the patients with lymph node metastasis, higher tumor node metastasis stage and histologic grade, and larger diameter in TNBC. However, there was no statistical difference in the positive expression rate of YAP between non-TNBC patients and lymph node metastasis, tumor node metastasis stage, histologic grade, and tumor size.

Conclusions: YAP may participate in the occurrence and development of non-TNBC as a tumor suppressor gene; however, it may also be a carcinogenic factor in TNBC and may be a potential therapeutic target for TNBC.

Abbreviations: 95% CI = 95% confidence interval, ER = estrogen receptor, IHC = immunohistochemistry, non-TNBC = nontriple negative breast cancer, OR = odds ratio, PR = progesterone receptor, TNBC = triple negative breast cancer, TNM = tumor node metastasis, WBP = WW domain binding protein-1, YAP = yes-associated protein.

Keywords: breast cancer, case–control, meta-analysis, triple negative breast cancer, YAP, yes-associated protein

1. Introduction

Breast cancer is the leading cause of cancer-related death in women. According to the latest statistics from the Global Cancer Statistics 2020, female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases (11.7%), followed by lung cancer (11.4%), making it the number 1 malignant tumor-causing cancer globally.[1] Although multiple therapeutic modalities are available to treat breast cancer, mortality is still unacceptably high, especially for triple-negative breast cancer (TNBC). Owing to its easy metastasis,

"cold" tumor immune microenvironment, and lack of targeted therapies, TNBC has a poor prognosis. Chemoimmunotherapy is considered the most effective and holds the most potential as treatment for TNBC; however, it also faces a series of challenges, such as low TNBC selectivity, pronounced systemic toxicity, and limited immunogenic cell death (ICD) induction.[2] For TNBC, novel biomarkers need to be researched to accurately identify high-risk patients and predict disease prognosis. Genes that are abnormally expressed during tumor progression and metastasis may be used as biomarkers and therapeutic targets to provide a theoretical basis for clinical assessment.

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The Hippo signaling pathway is a central regulator of organ size and tissue homeostasis and was first discovered in Drosophila.[3] Hippo kinases and adaptor proteins mediate the phosphorylation and inactivation of yes-associated protein (YAP) and TAZ, 2 closely related transcriptional coactivators. Pervasive activation and expression of YAP/TAZ has been observed in many human tumors and is closely associated with the acquisition of malignant traits, including resistance to anticancer therapies, distant dissemination, and maintenance of cancer stem cells.[4] Overexpression of YAP or its nuclear localization is correlated with poor prognosis in various cancers, such as lung, colorectal, ovarian, and liver cancers.[5] YAP is a 65-kDa proline-rich phosphoprotein and acts as the core downstream effector molecule of the tumor suppressor pathway called the Hippo pathway, containing a "WW domain."[6] The 2 identified putative ligands of the WW domain were named WW domain binding protein-1 (WBP-1) and WW domain binding protein-2 (WBP-2).[7] Case–control studies have demonstrated YAP as a tumor suppressor, showing decreased expression or deletion of YAP in non-TNBC compared to that in normal breast tissue[6,8,9] in contrast, other case–control studies showed that YAP expression level was exceptionally higher in TNBC than that in normal breast tissues.[10,11] Cell experimental research have shown that YAP promotes breast cancer cell proliferation and survival, and its overexpression enhances breast cancer formation and growth in vivo.[12,13] It has found that WBP-2 specifically interacted with progesterone receptor (PR) and estrogen receptor (ER), and enhanced the transactivation functions of PR and ER,[14] and YAP expression also inversely correlated with the Her-2 and Ki67 levels.[15] In summary, YAP expression might be absolutely associated with expression status of ER, PR, and Her-2. Therefore, this meta-analysis was performed to evaluate the potential relationship between YAP expression and TNBC and non-TNBC, respectively.

2. Materials and Methods

2.1. Literature search strategy

A search was conducted using PubMed, EMBASE, Web of Science, Chinese National Knowledge Infrastructure, Chinese Scientific Journal Database (VIP), Wan Fang Database, and the Chinese Biomedical Literature Database (CBM) for articles on YAP expression in breast cancer. Relevant studies were identified using the following terms: "Breast Neoplasm" or "breast tumor" or "Breast cancer" and "YAP" or "YAP1." The article languages were limited to English and Chinese. All searched studies were retrieved and references were reviewed to identify additional eligible studies. Authors were emailed in cases where studies did not contain sufficient data. We manually searched the databases to ensure that all available studies were included in this meta-analysis.

2.2. Inclusion and exclusion criteria

To ensure that the studies in the literature were comparable and consistent, the inclusion criteria of this study were as follows: A case–control study on the clinical significance of YAP expression in breast cancer; Patients who were pathologically diagnosed with breast cancer and received surgical therapies; The Newcastle–Ottawa scale score of the article should be ≥6; Should the data from multiple studies be the same or have an overlap, the literature with the largest amount of data or the latest date of publication will be included; Finally, immunohistochemistry (IHC) was performed for detection. The exclusion criteria were as follows: Literature formats such as expert opinions, reviews, meeting abstracts, letters, case reports, and animal trials; The study had no clear control group; Incomplete data presented in the study.

2.3. Data extraction and quality assessment

The full texts of candidate articles were reviewed by 2 independent investigators according to the predetermined inclusion and exclusion criteria, and the data were extracted and sorted. The following information was extracted from each included study: name of the first author, publication year, country, sample size, number of patients with positive YAP expression, source of the control group, tumor node metastasis (TNM) stage, lymph node metastasis, and tumor size.

The quality of the included studies was assessed using the Newcastle–Ottawa scale.[16] A scale (1–10) was established to determine article relevance for the incorporation into the meta-analysis. Studies with a score of <6 were considered "low-quality" and were excluded.

2.4. Statistical analysis

Meta-analysis was performed using STATA 14.0 (College Station, TX) and RevMan5. YAP expression between breast cancer and normal control tissues as well as any correlation with clinicopathological features in breast cancer were estimated using odds ratios (ORs) with 95% confidence intervals (95% CIs), and $P < .05$ was considered statistically significant. Study heterogeneity was investigated using the chi-square and Q test and was quantified using I^2. P values < 0.05 and I^2 values exceeding 50% indicated significant heterogeneity. Using a fixed effects model (Mantel–Haenszel model), ORs were pooled. Otherwise, a random-effects model (DerSimonian and Laird model) was used. Sensitivity analyses were used to assess the stability of the results, and a sensitivity analysis was performed by removing a specific study from the meta-analysis. Begg funnel plots were used to evaluate publication bias, and 2 reviewers independently analyzed the data and obtained the same conclusion.

3. Results

3.1. Characteristics of the included studies

As shown in Figure 1, 702 records were initially retrieved from PubMed, EMBASE, Web of Science, Chinese National Knowledge Infrastructure, VIP, Wan Fang, and CBM. After 206 duplicate publications were removed, 496 records remained. Then, 42 articles were reviewed with full texts for eligibility after excluding 446 inconsistent records and 8 reviews or systematic evaluation by reading the topics and abstracts. Finally, 10 case–control studies[6,9–11,17–22] were included in this meta-analysis after careful reading of the full text, which included 1028 patients and 392 normal controls. The basic information and literature quality evaluations of the included studies are shown in Table 1.

3.2. Differential expression of YAP in breast cancer and controls

Following the identification of suitable articles, we used 10 publications, including 8 studies on non-TNBC and the other 2 on TNBC. No heterogeneity among the studies was found ($I^2 = 42\%$ $< 50\%$, $P = .1$ and $I^2 = 0\%$ $< 50\%$, $P = .41$). Therefore, the fixed effects were included in the meta-analysis. The meta-analysis demonstrated that the positive rate of YAP expression in non-TNBC was much lower than that in normal breast tissue (OR $= 0.15$, 95% CI $= 0.10$–0.21, $P < .001$). In contrast, the positive rate of YAP expression in TNBC was much higher than that in normal breast tissue (OR $= 18.23$, 95% CI $= 8.20$–40.52, $P < .001$), showing significant differences between the 2 subgroups, suggesting that YAP expression might strongly depend on the expression of ER, PR, and Her-2 in breast cancer (Fig. 2).
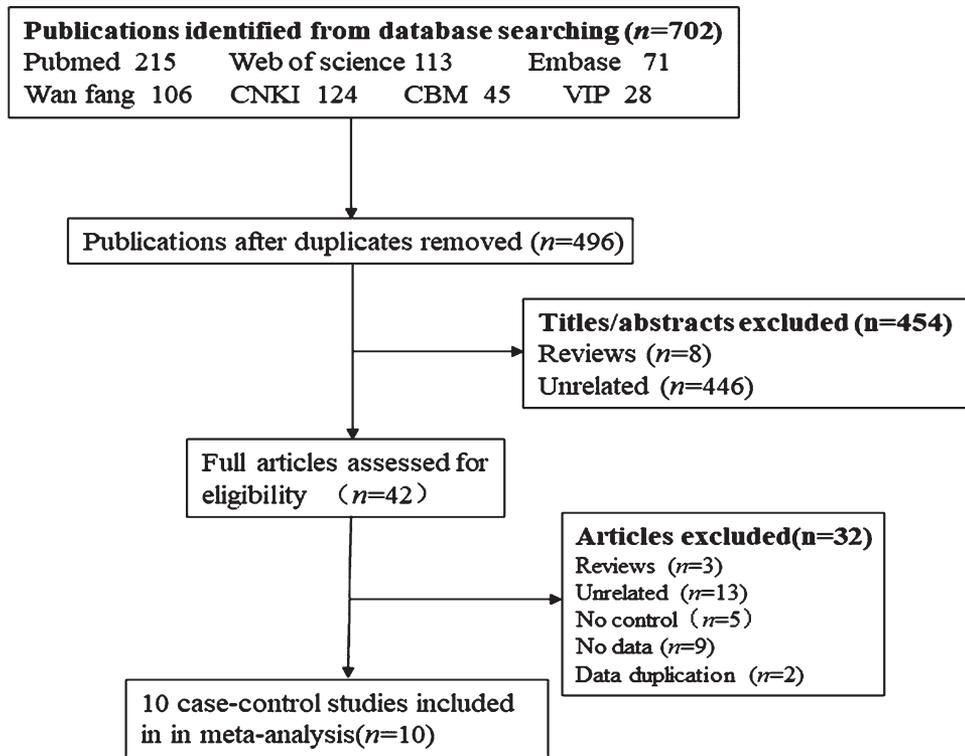
Figure 1. Flowchart of literature retrieval.

Table 1

Basic information and literature quality evaluation table of included studies.

Study	Country	Method	Source of control	Breast cancer Positive	Breast cancer Total	Control Positive	Control Total	NOS score
Liu et al[17]	China	IHC	Paracancerous tissue	20	60	25	26	7
Li et al[18]	China	IHC	Paracancerous tissue	61	133	38	47	7
Liang et al[19]	China	IHC	Paracancerous tissue	28	94	62	83	7
Ren et al[20]	China	IHC	Paracancerous tissue	39	97	27	32	7
Jaramillo et al[9]	Mexico	IHC	Normal breast tissue	9	105	3	17	8
Tufail et al[6]	America	IHC	Normal breast tissue	102	226	33	40	7
Michel et al[21]	Mexico	IHC	Normal breast tissue	56	76	39	44	7
Yuan et al[22]	China	IHC	Normal breast tissue	49	134	20	20	7
Bo et al[11]	China	IHC	Paracancerous tissue	52	73	10	73	7
Liu al[10]	China	IHC	Paracancerous tissue	22	30	0	10	7

IHC = immunohistochemistry.

3.3. Association of YAP expression with clinicopathological parameters in breast cancer patients

Based on the information provided by the included studies, we explored the relationship between YAP expression and lymph node metastasis (lymph node metastasis vs no lymph node metastasis), TNM stage (I/II vs IV/III), tumor size (≤2 cm vs >2 cm), and histologic grade (I/II vs III). The results revealed a significant difference between the non-TNBC and TNBC patients. In TNBC, the positive expression rate was higher in patients with lymph node metastasis (Fig. 3), higher TNM stage (Fig. 4), histologic grade (Fig. 5), and larger tumor diameter (Fig. 6). However, no significant association was observed between YAP expression and any of these parameters in the non-TNBC (Table 2).

3.4. Sensitivity analysis and publication bias

The RevMan5 sensitivity analysis was performed by excluding each study individually, which in turn signified that the results

of our meta-analysis were stable (Table 3). In non-TNBC, we used STATA 14.0 to conduct Begg funnel plot and Egger test to identify potential publication bias. As a result, the Begg funnel plot was symmetrical (Fig. 7A), and the P values for the Begg test and the Egger test were 0.536 and 0.267, respectively, which indicated that no significant publication bias existed. In TNBC, the Begg funnel plot (Fig. 7B) was nearly symmetrical, and the P value of the Begg test was 1, which also revealed that no significant publication bias existed.

4. Discussion

The Hippo signaling pathway functions as a switch to control the activity of a downstream effector nuclear transcriptional module that regulates cell proliferation and survival. When the Hippo signaling pathway is "open," that is, the upstream signal is introduced into the activated core kinase cascade reaction chain, the protein kinase MST1/2 is first phosphorylated, which
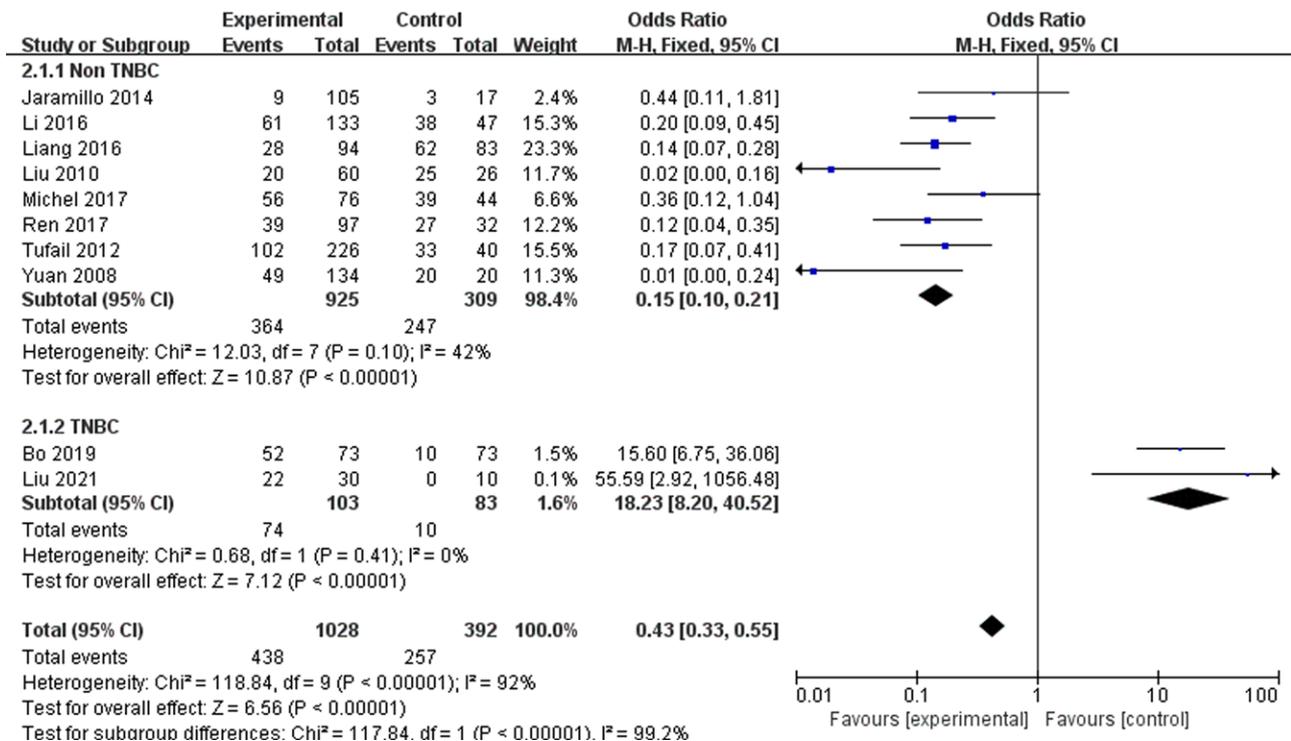
Figure 2. Forest plot of YAP expression in breast cancer and normal breast tissue. YAP = yes-associated protein.
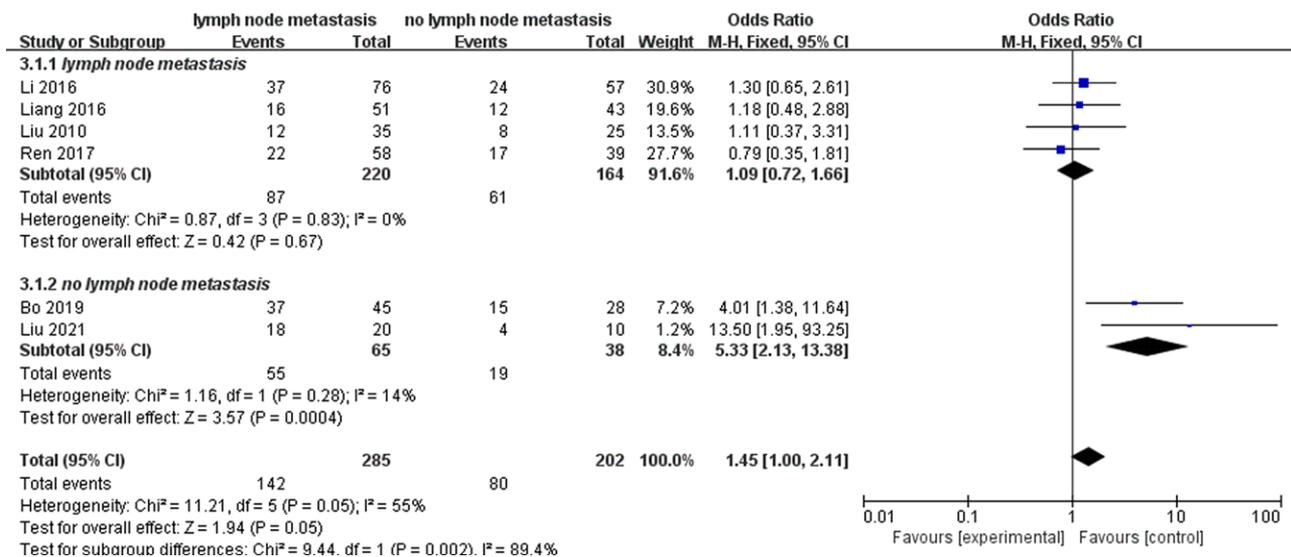
Figure 3. Forest plot of YAP expression in breast cancer with or without lymph node metastasis. YAP = yes-associated protein.

in turn activates LATS1/2 and MOB1 with the help of protein SAV1. Phosphorylated LATS1/2 and MOB1 combine to form the LATS1/2-MOB1 complex, which further promotes the phosphorylation of TAZ and YAP, which bind to 14-3-3 proteins in the cytoplasm and are ubiquitinated and modified by ubiquitin-dependent proteasome (SCFβ-TrCP) degradation, thereby inhibiting cell proliferation and differentiation.[23–25] When the Hippo signaling pathway is "closed," that is, when the core kinase cascade reaction chain does not receive the activation signal, the nonphosphorylated YAP/TAZ nuclear translocation combines with the transcription factor TEAD1-4 to form a transcription complex, which activates the downstream target genes, such as CTGF, IGFBP3, and AXL, to promote cell proliferation, differentiation, and inhibit apoptosis.[23,25] These 2 aspects of

regulation restrict each other in normal cells so that the growth and differentiation of cells are strictly limited. The YAP is a major downstream effector of Hippo signaling, and members of the Hippo signaling pathway can act as transcriptional coactivators to promote the expression of target genes involved in proliferation and survival.[26] The YAP and TAZ are commonly required during embryonic development as well as under nonhomeostatic conditions, such as during wound healing, regeneration, and cancer development, where tissues undergo high rates of proliferation.[27] Thus, in normal tissues, YAP/TAZ are constantly regulated by multiple negative regulators and activated only under conditions of regenerative or malignant growth. Remarkably, YAP/TAZ are essential for the initiation of cancer and growth of most solid tumors. Their activation induces
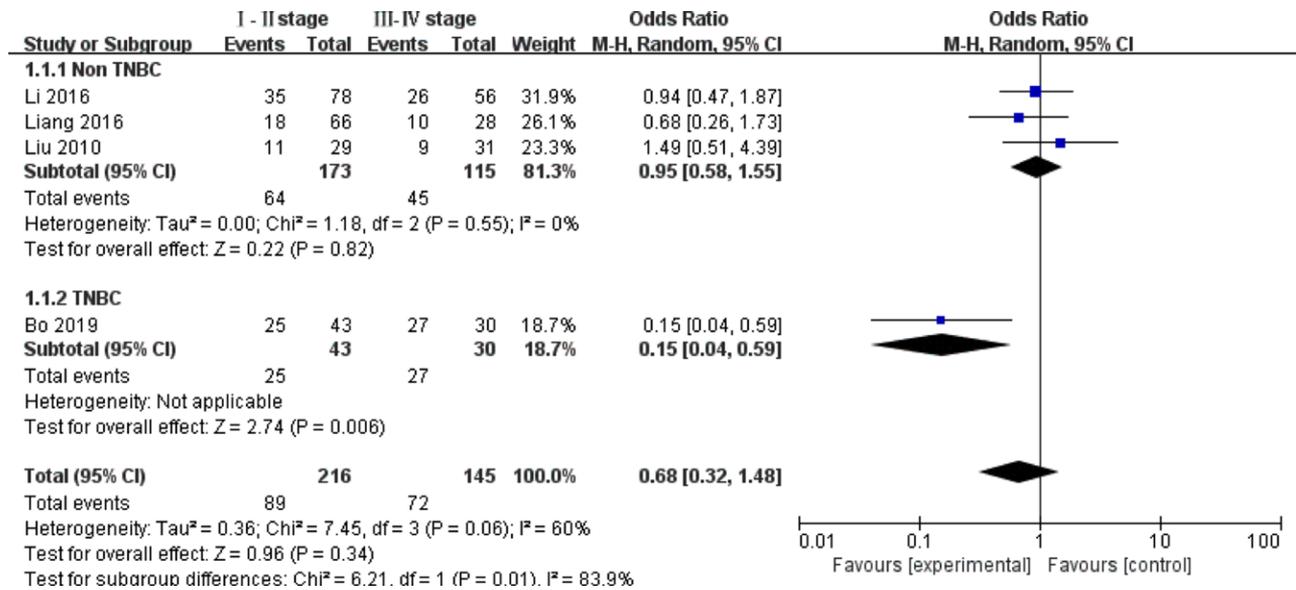
Figure 4. Forest plot of YAP expression in different clinical stages of breast cancer. YAP = yes-associated protein.
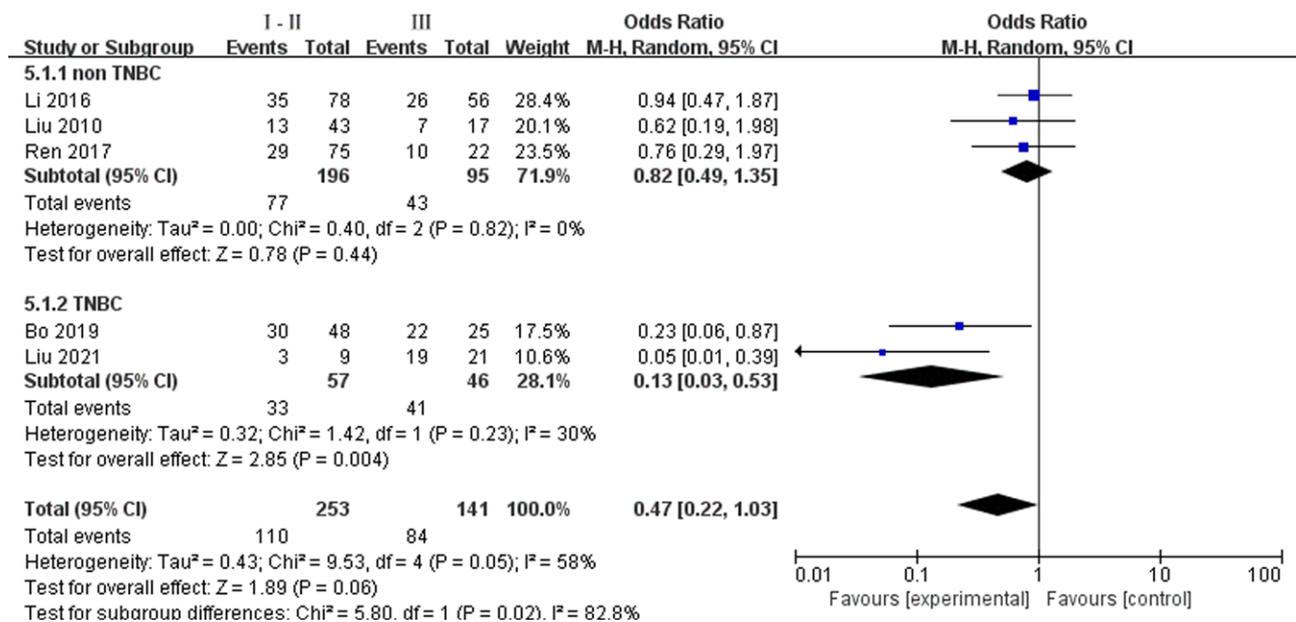
Figure 5. Forest plot of YAP expression in different histologic grade of breast cancer. YAP = yes-associated protein.

cancer stem cell attributes, proliferation, chemoresistance, and metastasis.[28] In multiple instances, expression of YAP/TAZ is sufficient for reprogramming mature differentiated cells into their corresponding less-differentiated progenitors, often resembling embryonic precursors, which can occur both in vivo and in vitro.[29,30] This led to the initial idea that YAP/TAZ is a general factor required for stem cell self-renewal. However, forced expression of YAP/TAZ in cells or tissues potently promotes proliferation, leading to organ overgrowth and almost invariably to the development of cancer.[28] IHC studies have shown that elevated expression and nuclear localization of YAP/TAZ correlate with malignant features and poor patient outcomes.

Abnormal expression of YAP has been noted in various types of cancer. The meta-analysis performed in this study confirmed that the expression of YAP in hepatocellular carcinoma (HCC) tissues may be higher than in cirrhotic liver samples and healthy livers,[31] Tschaharganeh et al[32] found that YAP activated the

Notch signaling pathway by upregulating jagged1 expression, thereby accelerating the proliferation of hepatoma cells. High expression levels of a gene signature for YAP activity have been found to be prognostic for bad outcome in 4 datasets of Colorectal carcinoma (CRC) patients and correlated with cetuximab resistance.[33] The YAP mRNA and protein levels are upregulated in a relevant portion of gastric adenocarcinomas (GAC), and YAP nuclear localization correlates with poor patient outcomes.[34] In datasets of breast cancer patients, elevated expression of gene signatures for YAP/TAZ activity correlates with high histological grades, enrichment of stem cell signatures, metastatic proclivities, and poor outcomes.[35,36] Expression detection of YAP in benign, borderline, and malignant breast phyllodes tumors, indicated increasing YAP expression level with the histologic grade of the phyllodes tumor (PT) in the stromal component of the human breast. Hence, YAP expression in phyllodes tumor was significantly related to tumor
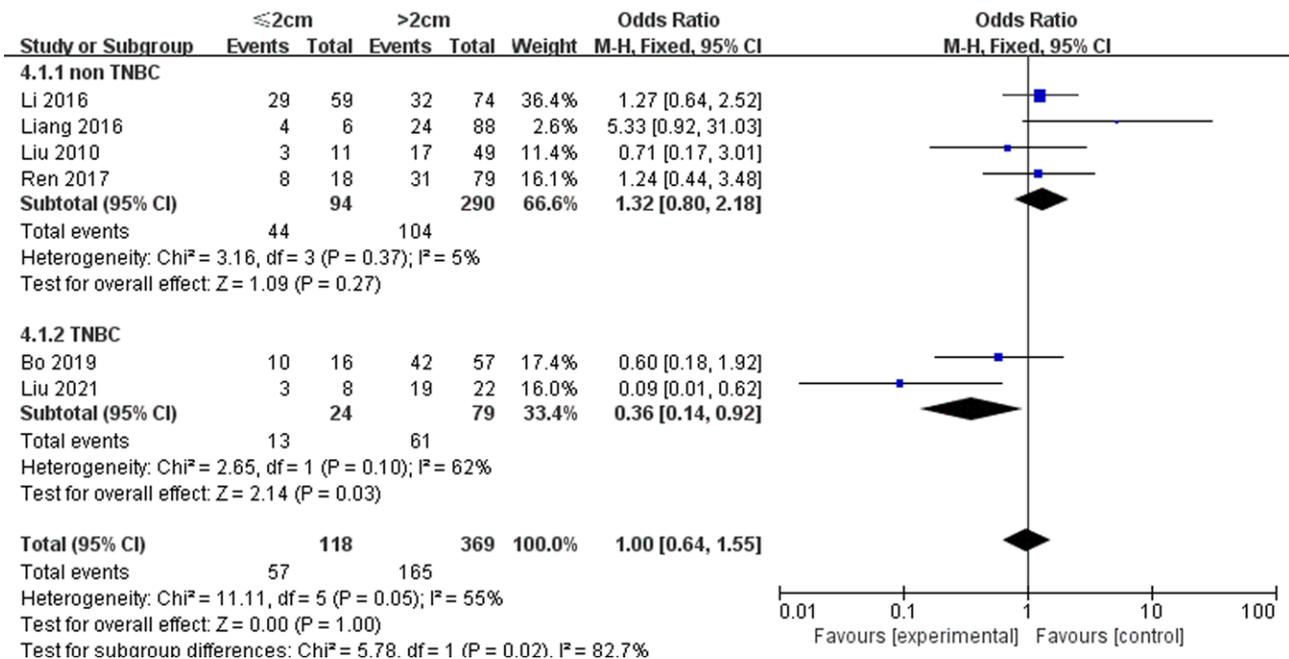
Figure 6. Forest plot of YAP expression in different sizes of breast cancer. YAP = yes-associated protein.

Table 2

Correlations of YAP expression with clinicopathological characteristics in resected breast cancer.

Analysis	Cancer type	No. of studies	OR (95% CI)	Log-rank P value	I²	P value
Overall	Non-TNBC	8	0.15 (0.10–0.21)	**<.00001**	42%	.1
	TNBC	2	18.23 (8.2–40.52)	**<.00001**	0%	.42
Lymph node metastasis (present vs absent)	Non-TNBC	4	1.09 (0.72–1.66)	.67	0%	.83
	TNBC	2	5.33 (2.13–13.38)	**.0004**	14%	.28
TNM stage (I/II vs IV/III)	Non-TNBC	3	0.95 (0.58–1.55)	.82	0%	.55
	TNBC	1	0.15 (0.04–0.59)	**.006**	–	–
Histologic grade (I/II vs III)	Non-TNBC	3	0.82 (0.49–1.35)	.44	0%	.82
	TNBC	2	0.13 (0.03–0.53)	**.004**	30%	.23
Tumor diameter (≤2 cm vs > 2 cm)	Non-TNBC	4	1.32 (0.80–2.18)	.27	5%	.37
	TNBC	2	0.36 (0.14–0.92)	**.03**	62%	.1

P values with statistical differences in bold.
95% CI = 95% confidence interval, OR = odds ratio, TNBC = triple negative breast cancer, TNM = tumor node metastasis, YAP = yes-associated protein.

Table 3

Results of sensitivity analysis.

Study	Heterogeneity test		Association test	
	I²	P value	OR (95% CI)	P value
Liu et al[17]	20%	.28	0.16 (0.11–0.23)	<.0001
Li et al[18]	50%	.06	0.14 (0.09–0.20)	<.0001
Liang et al[19]	50%	.06	0.15 (0.10–0.22)	<.0001
Ren et al[20]	49%	.06	0.15 (0.10–0.22)	<.0001
Jaramillo et al[9]	40%	.12	0.14 (0.10–0.20)	<.0001
Tufail et al[6]	51%	.06	0.14 (0.10–0.21)	<.0001
Michel et al[21]	39%	.13	0.13 (0.09–0.19)	<.0001
Yuan et al[22]	30%	.20	0.16 (0.12–0.23)	<.0001

95% CI = 95% confidence interval, OR = odds ratio.

progression and poor prognosis.[37] The mRNA level of YAP and its receptors is also elevated in breast cancer compared with that in normal breast tissues.[38] Some functional regions of YAP bind to Kruppel-like factor 5 (KLF5), a transcription factor that promotes breast cell proliferation and survival, thereby regulating cell proliferation.[12]

The current meta-analysis of this study, however, indicated contradictory results between non-TNBC and TNBC by summarizing 10 case–control studies. These controversial outcomes showed that YAP might act as a tumor suppressor in non-TNBC (OR = 0.15 [0.10–0.21], P < .0001) but as a carcinogenic gene in TNBC (OR = 18.23 [8.2–40.52], P < .0001). Furthermore, there were no significant correlations between YAP expression and any clinicopathological characteristics in non-TNBC; however, the expression of YAP was significantly higher in TNBC with lymph node metastasis (5.33 [2.13–13.38], P = .0004), higher TNM stage (0.15 [0.04–0.59], P = .006), higher histologic grade (0.13 [0.03–0.53], P = .004), and larger tumor diameter (0.36 [0.14–0.92], P = .03). The YAP has been characterized as a coactivator of ER and PR receptors, and its expression level is significantly related to the status of ER and PR. Additionally, the positive rate of the YAP in breast cancer tissues with negative expression of ER and PR was significantly higher than that of breast cancer tissues with positive expression of both,[6,15] and YAP expression was also inversely correlated with Her-2 and Ki67 levels and
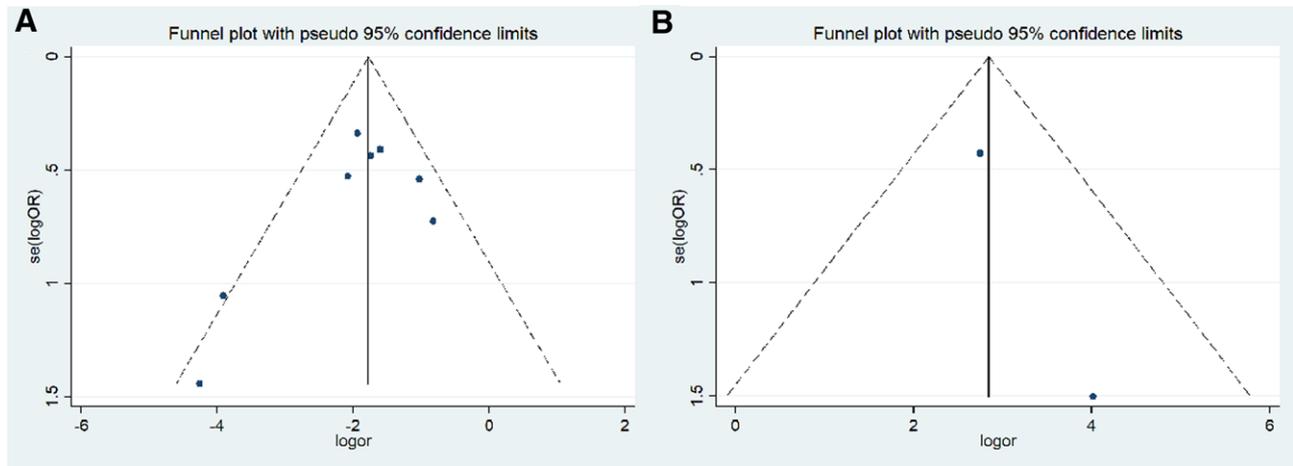
Figure 7. Funnel plot of YAP expression in breast cancer and normal breast tissue: (A) non-TNBC and (B) TNBC. TNBC = triple negative breast cancer, YAP = yes-associated protein.

lymph node metastasis.[15] Furthermore, TAZ mRNA and protein expression have been reported to be preferentially higher in TNBC than in other breast cancer subclasses.[39,40] The combined expression of the YAP in TNBC cells and the surrounding stroma seems to be associated with a decreased likelihood of achieving pathological complete response (pCR). Conversely, the combined expression of TAZ and YAP was associated with shorter disease-free survival in multivariate analysis, conferring poor survival outcomes.[41] Overall, our current study revealed that the YAP could become a new target for the treatment of TNBC, but its low expression or deletion might have a protective effect in non-TNBC.

Using the I^2 tests, Egger tests, and construction of a Begg funnel plots, the results indicated that there was no heterogeneity or publication bias, so the pooled effect size OR was credible. However, this study has certain limitations: Although a comprehensive search was carried out, the included literature was small; the sample size was insufficient; and the amount of data on TNM stage, histological grade, tumor size, and lymph node metastasis were insufficient, which may have caused aggregated results to deviate; All included studies used IHC to qualitatively detect the expression level of YAP protein in tissues, which is greatly affected by experimental conditions, reagents, and technical problems of the operators; YAP exists in 2 forms, phosphorylated and nonphosphorylated and the 2 phosphorylation states are dynamically shuttling in the cytoplasm and nucleus, but the included studies did not distinguish between them; Since there are only a few studies on the difference in YAP expression in different histological types of breast cancer, our meta-analysis failed to report the relationship between YAP expression and the histological type of breast cancer; Finally, the included studies did not report the relationship between YAP expression and the prognosis or survival rate of breast cancer, thus, this meta-analysis failed to report the correlation between YAP expression and related outcome indicators of prognosis.

In conclusion, our meta-analysis is the first study to systematically estimate the great distinction in YAP expression between TNBC and non-TNBC, and it may become a controversial topic in the study of breast cancer. The YAP may be a potential therapeutic target for TNBC. However, further large-scale clinical case–control studies are needed to confirm this finding.

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Author contributions

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