

Prognostic significance of TAZ expression in various cancers: a meta-analysis

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Background: The overexpression of transcriptional coactivator with PDZ-binding motif (TAZ), a Hippo pathway effector, was detected in a variety of cancers. However, controversies remain in published studies on the prognostic value of TAZ expression in cancer. We performed a meta-analysis to demonstrate the prognostic significance of TAZ in overall survival (OS) and its association with clinicopathologic characteristics.

Methods: A systematic literature search was performed by using PubMed, EMBASE, and Web of Science databases for eligible studies investigating the association between TAZ and survival. After extracting data, we used hazard ratio (HR), odds ratio (OR) and 95% confidence intervals (95% CIs) for association evaluation, I^2 for heterogeneity across studies, and Egger's test and Begg's funnel plot for publication bias assessment.

Results: A total of 15 studies including 2,881 patients were analyzed. Pooled results showed that a high TAZ was significantly associated with poor OS (HR =1.82, 95% CI =1.58–2.11; $I^2=33%$; $P=0.11$). Subgroup analysis indicated significant correlation between TAZ overexpression and OS in patients stratified by ethnicity, sample size, sample source, and staining location. Furthermore, TAZ overexpression was associated with worse OS in hepatocellular carcinoma (HR =2.26, 95% CI =1.43–3.57; $P=0.49$) and gastrointestinal cancers (HR =2.00, 95% CI =1.54–2.58; $P=0.97$), but not in non-small-cell lung cancer (HR =1.71, 95% CI =0.93–3.14; $P=0.08$). TAZ overexpression was also found to be significantly associated with some clinicopathologic characteristics, including TNM stage (OR =2.56, 95% CI =1.60–4.11; $P=0.52$), tumor differentiation (OR =3.08, 95% CI =1.25–7.63; $P=0.01$), and lymph node metastasis (OR =2.53, 95% CI =1.81–3.53; $P=0.58$).

Conclusion: TAZ overexpression is not only a predictive factor of poor prognosis but also associated with advanced TNM stage, poor tumor differentiation, and lymph node metastasis.

Keywords: Hippo pathway, TAZ, cancer, prognosis, meta-analysis, overall survival

Introduction

Transcriptional coactivator with PDZ-binding motif (TAZ; also known by gene name WW domain-containing transcription regulator 1, WWTR1) functions as a key effector in Hippo pathway cascade, which controls the balance between proliferation and apoptosis and regulates organ size through interaction with various transcription factors, particularly TEA domain family members.¹ It has been well-documented that TAZ is involved in many cellular progresses, such as induction of proliferation, migration and increased metastatic potential, and inhibition of apoptosis, among others.^{2,3} Highly expressed TAZ has been observed in a broad range of cancers. Moreover, poor prognostic outcomes seem to be associated with high TAZ expression.⁴ However, the results are controversial. Some studies also revealed no significant association between TAZ and survival outcomes.⁵ We conducted this meta-analysis to address limitations

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of single study, as well as to find the precise significance of TAZ expression in the prognosis of various cancers.

Methods

Search strategy and selection criteria

A comprehensive search in online PubMed, EMBASE, and Web of Science databases was conducted to identify all relevant articles focusing on the association between TAZ expression and cancer prognosis published up to December 1, 2015. We used the following keywords and their combinations to search the databases: “TAZ”, “transcriptional co-activator with PDZ-binding motif”, “WWTR1”, “Hippo”, “cancer”, “carcinoma”, “neoplasm”, “tumor”, “survival”, “prognostic”, and “outcome”. References were also retrieved to find additional eligible studies.

Studies were included in our analysis if they met the following inclusion criteria: 1) the relationship between TAZ expression and prognosis of patients with various cancers was studied; 2) the association between clinicopathologic features and TAZ expression was described; 3) TAZ-positive expression was quantified by immunohistochemistry or other adequate methods; 4) subjects were categorized into high TAZ (or TAZ-positive) group and low TAZ (or TAZ-negative) group for survival analysis; 5) hazard ratio (HR) with 95% confidence intervals (CIs) was reported, or the reported data were sufficient for calculation; 6) when several studies involved the same population, only the most recent or the most comprehensive one was included; and 7) the article was published in English. Studies were excluded if they met any of the following exclusion criteria: 1) systemic review, laboratory study, case report, comment, or letter; 2) published in a language other than English; 3) provided no information on survival outcomes or survival curves; and 4) nonhuman experiments. Two authors (JF and PR) independently evaluated titles and abstracts of the articles to decide whether the full text should be further reviewed. In case of any disagreement, consensus would be reached after discussion. If this failed, the article would be excluded.

Data extraction and quality assessment

Two reviewers (JF and PR) extracted the required information from all eligible studies independently. Documented information included name of the first author, year of publication, country of origin, number of patients, age of patients, cancer type, TAZ measuring method, and HRs and their 95% CIs for survival. If both univariate and multivariate analyses were performed, HRs from multivariate analyses

were extracted. For studies providing HRs, we extracted data directly; otherwise, the HRs and CIs were calculated with Tierney's methods.⁶

Study quality was assessed using the Newcastle–Ottawa quality assessment scale by two independent investigators. Only studies that scored >5 were included while others were excluded in order to ensure the quality of this meta-analysis. Any disagreement was resolved by discussion. Table S1 summarizes the by-item quality scores of each study.

Statistical analysis

Pooled HRs with 95% CIs were calculated to quantify the predictive value of TAZ level on overall survival (OS). An HR >1.0 indicated poor prognosis. Pooled odds ratios (ORs) with 95% CIs were also calculated to describe the association between TAZ expression and clinicopathologic features. Heterogeneity analysis was performed using chi-square test and expressed in I^2 index. Heterogeneity was considered as significant when P -value was <0.1 in chi-square test and/or an I^2 measure was >50%, and then a random-effects model would be applied; otherwise, a fixed-effects model was applied. A sensitivity analysis was performed by sequential omission of individual studies. Potential publication bias was assessed using Begg's funnel plot and Egger's linear regression. Meta-analysis was performed using Review Manager 5 (version: 5.2, Cochrane Informatics and Knowledge Management Department; <http://tech.cochrane.org/revman/download>) and STATA (version 12.0, Stata-Corp LP, College Station, TX, USA). Particularly, Egger's test and sensitivity analysis were performed with STATA. A P -value <0.05 was considered as significant.

Results

Eligible studies

The flow chart for literature search is shown in Figure 1. In brief, 341 articles were identified by primary search strategy. After title and abstract screening, 34 reviews and 270 original studies were excluded because of irrelevance to TAZ or cancer prognosis, or they were animal studies, duplicated, or not in the English language. The full texts of 37 articles were reviewed for more details and an additional 23 studies were excluded for insufficiency of survival data. Finally, 14 articles^{5,7–19} meeting the inclusion criteria were included. The study by Yuen et al included survival analyses for two different cohorts.¹² Thus, a total of 15 studies including 2,881 patients were analyzed in this meta-analysis. All the eligible studies were published from 2012 to 2015, of which

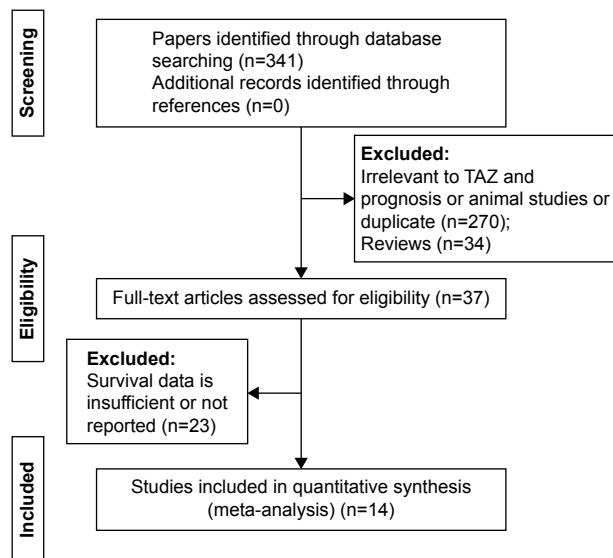


Figure 1 Flow diagram of the inclusion and exclusion of studies.

12 were conducted in Asia and two otherwise. Cancer types enrolled in these studies included non-small-cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), colon carcinoma, colorectal carcinoma, oral squamous cell carcinoma, tongue squamous cell carcinoma, adenocarcinoma of the esophagogastric junction, breast cancer (BC), glioblastoma multiforme, and retinoblastoma. Formalin-fixed and paraffin-embedded sample processing method was applied in nine studies, while the other six studies used tissue microarray. Immunohistochemistry was used to detect TAZ expression in all studies. TAZ expression was tested by nuclear staining in two studies or by both nuclear and cytoplasmic stainings (for overall TAZ expression) in 13 studies. Furthermore, the association between TAZ and OS was analyzed in 13 studies; disease-free survival (DFS) in the study by Wang et al;¹³ and OS and progression-free survival (PFS) in the study by Zhang et al.¹⁹ The main characteristics of the enrolled studies are summarized in Table 1.

Results of meta-analysis

HRs for OS were available in 14 studies involving 2,713 patients, but only one study reported data on the relationship between TAZ and DFS or PFS. As shown in Figure 2, pooled OS data suggested an increased risk of death in patients with higher TAZ expression (HR =1.82, 95% CI =1.58–2.11, $I^2=33%$, $P=0.11$). There was no significant heterogeneity in these studies.

Subgroup analyses for OS were conducted by covariates, such as ethnicity, sample size, sample source, staining

location, and cancer types. Results of the subgroup analysis for prognosis value of TAZ in different cancer types are shown in Table 2. Subgroup analyses by ethnicity showed a significant association between high TAZ expression and poor OS in both Asian (HR =1.474, 95% CI =1.203–1.807; $P=0.729$) and non-Asian patients (HR =1.474, 95% CI =1.203–1.807; $P=0.729$). The results of subgroup analyses by sample size showed that combined HRs were 2.09 (95% CI =1.65–2.64) for studies with <200 cases and 1.69 (95% CI =1.42–2.02) for those with >200 cases. This result indicated that high TAZ expression remained an unfavorable prognostic factor regardless of sample size. Regarding sample source, the results showed that high TAZ expression indicated a poor prognosis in studies using formalin-fixed and paraffin-embedded samples (HR =2.03, 95% CI =1.58–2.62; $P=0.16$) and tissue microarray samples (HR =1.73, 95% CI =1.46–2.06; $P=0.16$). Subgroup analyses by staining location found that positive overall (nuclear and cytoplasmic) TAZ expression (HR =1.91, 95% CI =1.54–2.38; $P=0.06$) and positive nuclear TAZ expression (HR =2.11, 95% CI =1.26–3.55; $P=0.91$) both indicated poor OS. In subgroup analysis by cancer types, overexpression of TAZ was correlated with poor OS in HCC (HR =2.26, 95% CI =1.43–3.57; $P=0.49$), gastrointestinal cancer (HR =2.00, 95% CI =1.54–2.58; $P=0.97$), and BC (HR =2.11, 95% CI =1.26–3.55; $P=0.91$). But in NSCLC, “1” was within the 95% CI (HR =1.71, 95% CI =0.93–3.14; $P=0.08$), which indicated that positive TAZ expression may not be a prognostic predictor for OS in NSCLC.

Furthermore, we also analyzed the relationship between TAZ expression and clinicopathologic features. As shown in Figure 3, expression of TAZ was found to be associated with more advanced TNM stage (OR =2.56, 95% CI =1.60–4.11; $P=0.52$), poor tumor differentiation (OR =3.08, 95% CI =1.25–7.63; $P=0.01$), and lymph node metastasis (OR =2.53, 95% CI =1.81–3.53; $P=0.58$), but not with tumor size (HR =1.27, 95% CI =0.26–6.268; $P=0.005$).

Publication bias and sensitivity analysis

Begg’s funnel plot and Egger’s test were performed to evaluate the publication bias of the enrolled studies. As shown in Figure 4, the shape of the funnel plots was of no obvious asymmetry. And the P -value for OS from Egger’s test was 0.343, further confirming the nonexistence of significant publication bias. Meanwhile, the sensitivity analysis for contribution of each individual study on the pooled HRs for OS was performed by sequentially omitting individual studies, and found that no individual study significantly influenced

Table 1 Main characteristics of the eligible studies included in the meta-analysis

Author	Cancer types	Year	Country	Age (year)	Follow-up time (month)	Patient number (TAZ-negative/-positive)	Staining location	Method of detection	Method of HR estimation	HR (95% CI)	Outcome
Xie et al ¹¹	NSCLC	2012	People's Republic of China	<65 101 ≥65 80	Range 8–73 Median 62.1	181 (60/121)	Nucleus and cytoplasm	FFPE tissues	Reported	2.54 (1.30–4.941)	OS
Noguchi et al ⁷	NSCLC	2014	Japan	≤70 233 >70 112	>120	355 (249/96)	Nucleus and cytoplasm	Microarray	Reported	1.34 (1.01–1.76)	OS
Guo et al ¹⁰	HCC	2015	People's Republic of China	<55 95 ≥55 85	>60	180 (66/114)	Nucleus and cytoplasm	FFPE tissues	Data extrapolated	1.93 (1.51–3.70)	OS
Xiao et al ⁹	HCC	2015	People's Republic of China	≤50 23 >50 60	>60	83 (29/54)	Nucleus and cytoplasm	FFPE tissues	Data extrapolated	2.89 (1.81–4.38)	OS
Han et al ⁵	HCC	2014	People's Republic of China	<55 23 ≥55 16	Median 19.5	39 (13/26)	Nucleus and cytoplasm	FFPE tissues	Reported	1.962 (0.514–7.499)	OS
Yuen et al ¹²	Colon cancer	2013	People's Republic of China	–	–	226 (111/115)	Nucleus and cytoplasm	Microarray	Reported	2.062 (1.472–3.116)	OS
Wang et al ¹³	CRC	2013	Singapore	<60 85 ≥60 83	Range 1–56 Median 43	232 (116/116) 168 (71/97)	Nucleus and cytoplasm	Microarray	Reported	1.998 (1.245–3.205)	OS
Li et al ¹⁴	OSCC	2015	People's Republic of China	–	>100	111 (55/56)	Nucleus and cytoplasm	FFPE tissues	Reported	1.544 (0.999–2.451)	DFS
Díaz-Martín et al ⁸	BC	2015	Spain	–	Median 53.7	–	Nucleus and cytoplasm	Microarray	Reported	2.218 (1.205–4.084)	OS
Bartucci et al ¹⁵	BC	2015	Italy	–	Median 90	99 (54/45)	Nucleus	FFPE tissues	Reported	2.06 (1.01–4.20)	OS
Wei et al ¹⁶	TSCC	2013	People's Republic of China	≤60 35 >60 17	Range 2–101 Mean 42.3	52 (22/30)	Nucleus and cytoplasm	FFPE tissues	Reported	4.351 (1.477–12.819)	OS
Tian et al ¹⁷	GBM	2015	People's Republic of China	–	–	504 (252/252)	Nucleus and cytoplasm	Microarray	Reported	1.870 (1.216–2.877)	OS
Sun et al ¹⁸	AEG	2014	People's Republic of China	<60 48 ≥60 87	Range 1–81 Median 35	135 (80/55)	Nucleus and cytoplasm	FFPE tissues	Reported	1.879 (1.079–3.218)	OS
Zhang et al ¹⁹	Retinoblastoma	2015	People's Republic of China	<5 39 ≥5 4	>50	43 (15/28)	Nucleus and cytoplasm	FFPE tissues	Reported	0.226 (0.051–0.994) 0.144 (0.037–0.559)	OS PFS

Abbreviations: AEG, adenocarcinoma of the esophagogastric junction; BC, breast cancer; CI, confidence interval; CRC, colorectal carcinoma; DFS, disease-free survival; FFPE, formalin-fixed and paraffin-embedded; GBM, glioblastoma multiforme; HCC, hepatocellular carcinoma; HR, hazard ratio; NSCLC, non-small-cell lung cancer; OS, overall survival; OSCC, oral squamous cell carcinoma; PFS, progression-free survival; TSCC, tongue squamous cell carcinoma.

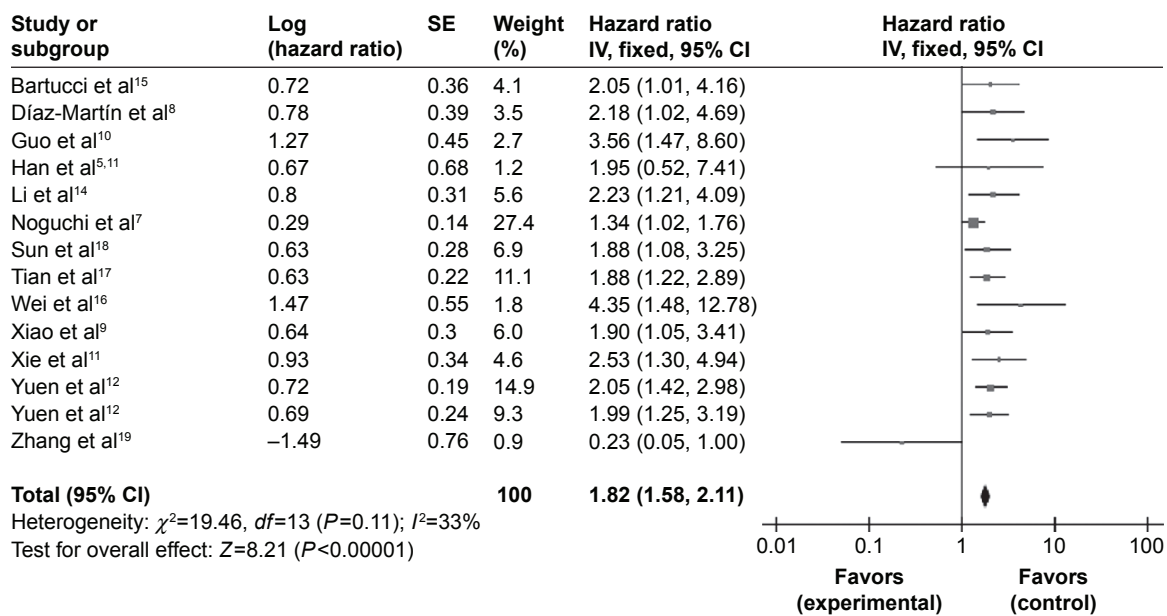


Figure 2 Forest plot for the association of TAZ expression with overall survival in various cancer types.

Abbreviations: CI, confidence interval; df , degrees of freedom; SE, standard error.

the overall HR, as shown in Figure 5. This confirmed the credibility of this meta-analysis.

Discussion

Cancer is a major global public health problem and is the second leading cause of death in the US with an estimation of 1,700,000 new cases and 600,000 deaths in 2016.²⁰

The more we identify and understand the mechanisms of cancer development and contributing factors of survival outcomes, the more valuable information can be provided to facilitate clinical decision making, optimize treatment and, ultimately, improve survival of cancer patients.

TAZ, structurally homologous to yes-associated protein, functions as a transcriptional coactivator and major

Table 2 Subgroup analysis of TAZ on overall survival in cancer patients

Variable	No of studies	Model	Pooled HR (95% CI)	Heterogeneity	
				I^2 (%)	P -value
Ethnicity					
Asian	12	Random	1.91 (1.54–2.38)	42.00	0.06
Non-Asian	2	Fixed	2.11 (1.26–3.55)	0.00	0.91
Sample size					
>200	5	Fixed	1.69 (1.42–2.02)	20.00	0.29
<200	9	Fixed	2.09 (1.65–2.64)	36.00	0.13
Sample source					
TMA	6	Fixed	1.73 (1.46–2.06)	36.00	0.16
FFPE	8	Fixed	2.03 (1.58–2.62)	34.00	0.16
Staining location					
Nucleus	2	Fixed	2.11 (1.26–3.55)	0.00	0.91
Nucleus and cytoplasm	12	Random	1.91 (1.54–2.38)	42.00	0.06
Cancer types					
NSCLC	2	Random	1.71 (0.93–3.14)	67.00	0.08
HCC	3	Fixed	2.26 (1.43–3.57)	0.00	0.49
Digestive system cancer	3	Fixed	2.00 (1.54–2.58)	0.00	0.97
BC	2	Fixed	2.11 (1.26–3.55)	0.00	0.91
Other	4	Random	1.92 (1.39–2.67)	71.00	0.02

Notes: Random-effects model was used when P -value for heterogeneity test <0.1 ; otherwise, fixed-effects model was used.

Abbreviations: BC, breast cancer; CI, confidence interval; FFPE, formalin-fixed and paraffin-embedded; HCC, hepatocellular carcinoma; HR, hazard ratio; NSCLC, non-small-cell lung cancer; TMA, tissue microarray.

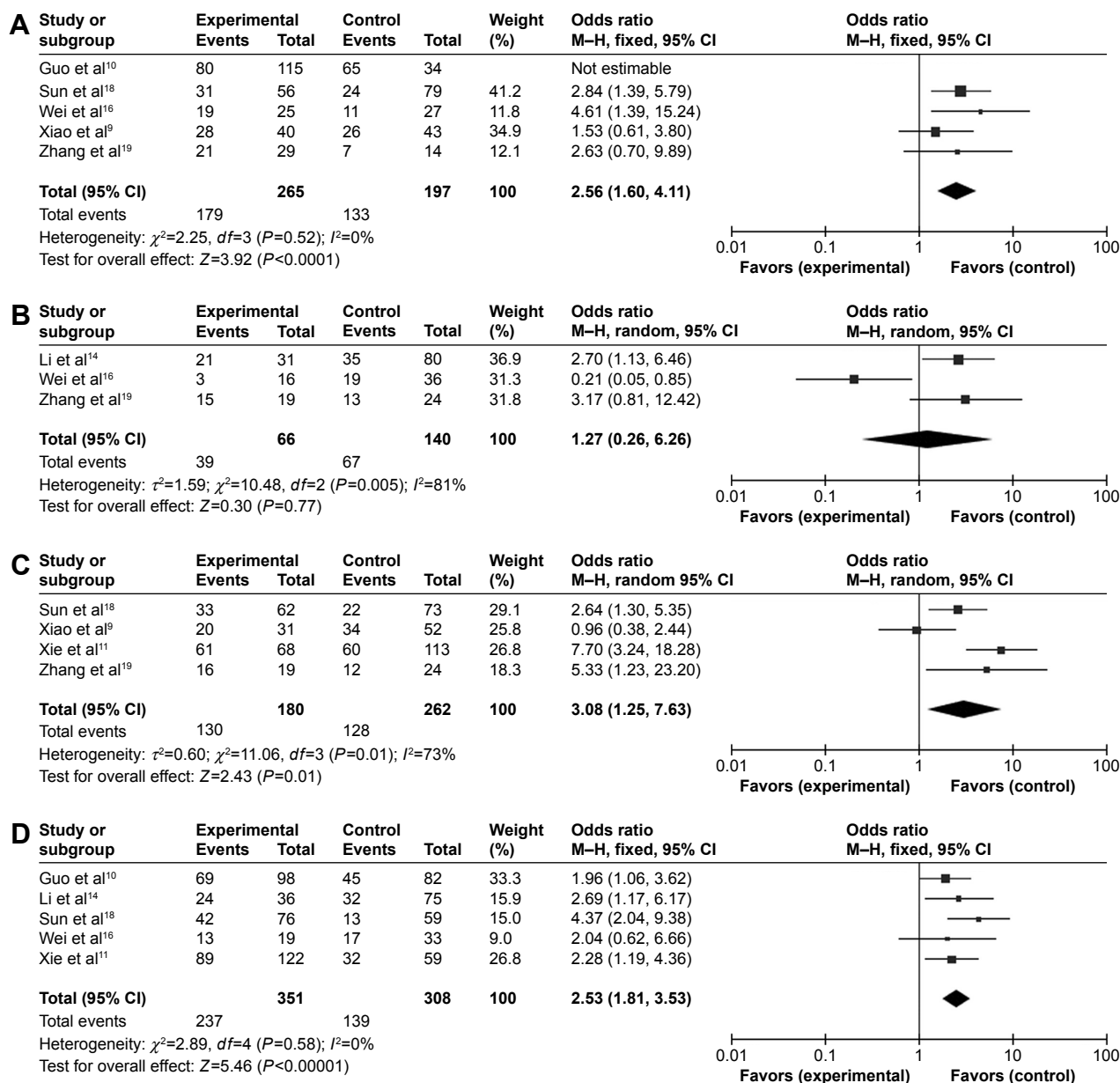


Figure 3 Forest plots of OR.

Notes: (A) OR for the relation between TAZ expression and TNM stage; (B) OR for the relation between TAZ expression and tumor size; (C) OR for the relation between TAZ expression and tumor differentiation; and (D) OR for the relation between TAZ expression and lymph node metastasis.

Abbreviations: CI, confidence interval; df , degrees of freedom; M-H, Mantel-Haenszel; OR, odds ratio.

effector of Hippo pathway cascade. Generally, this kinase cascade causes cytoplasmic retention of phosphorylated TAZ by 14-3-3 when it is activated. Otherwise, TAZ will be translocated into the nucleus where it interacts with TEA domain family members and drives the transcription process.²¹ Immunohistochemical analysis in a number of cancers showed that TAZ activation is highly related to cancer progression.⁴ Importantly, TAZ is involved in the acquisition of some cancer cell phenotypes by means of maintaining stem cell differentiation and self-renewal, and so on.^{22,23} It also contributes to the epithelial to

mesenchymal transition²⁴ and the inhibition of senescence.²⁵ Therefore, TAZ may serve as a promising biomarker for cancer patients. In addition, TAZ has been proved to be responsible for resistance to Taxol in human BC cells²⁶ and a higher recurrence rate in colon cancer.²⁷ These data substantiate that TAZ may be a novel marker in cancer prognosis.

The evidence collected in the present meta-analysis indicated a statistically significant relationship between TAZ overexpression and poor OS (pooled HR =1.82, 95% CI =1.58–2.11). Intriguingly, results of subgroup

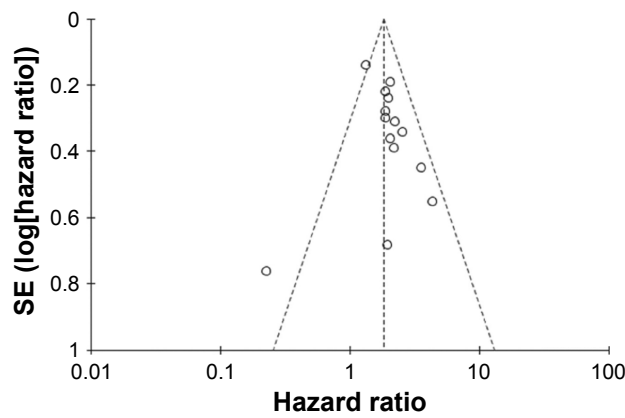


Figure 4 Funnel plot for the TAZ expression with overall survival in cancer patients. **Note:** Funnel plot analysis showed no publication bias among the 14 studies included. **Abbreviation:** SE, standard error.

analyses showed that positive TAZ was significantly correlated with OS in patients regardless of ethnicity, sample source, sample size, or staining location, which further confirmed the prognostic role of TAZ in OS. We also analyzed the combined HRs of different cancer types. Although there were only two or three studies for each cancer type, reliable and consistent conclusions were drawn that higher expression of TAZ indicated worse prognosis in patients with HCC ($P=0\%$), gastrointestinal cancers ($P=0\%$), and BC ($P=0\%$). While in NSCLC, 95% CI contained “1”, meaning the expression of TAZ did not appear to have an overall influence on survival in NSCLC patients. But, we should be extra cautious when interpreting this result, as only two studies for NSCLC were included and therefore the results might

be of less power. Further studies are needed to verify our conclusions. In this study, we also assessed the association between TAZ expression and clinicopathologic features in various cancer patients. High TAZ expression was found to be associated with more advanced TNM stage, poor tumor differentiation, and lymphatic metastasis.

This is the first meta-analysis on the association between TAZ expression and survival, but there are still some limitations despite the attempt to make it as comprehensive as possible. First, this meta-analysis only included a limited number of studies covering some, not all, cancer types, and some of the studies did not provide sufficient data for DFS/PFS analysis. As a consequence, the relationship between TAZ and patient outcomes still requires further investigation. Second, we extracted data from Kaplan–Meier curve in some studies due to unavailability of raw data, which may lead to less reliable results. Reanalysis might be performed if we can get the raw data of these studies. Third, many enrolled articles did not describe clinicopathologic features, which may result in biases. Another bias may exist due to language screening process, as positive results tend to be reported in articles written in native languages.²⁸ Moreover, all of the included studies were retrospective, which may have also introduced reporting bias. Therefore, our findings should be interpreted with caution.

In conclusion, this meta-analysis suggested that high expression of TAZ was significantly related to poor OS, more advanced TNM stage, poor tumor differentiation,

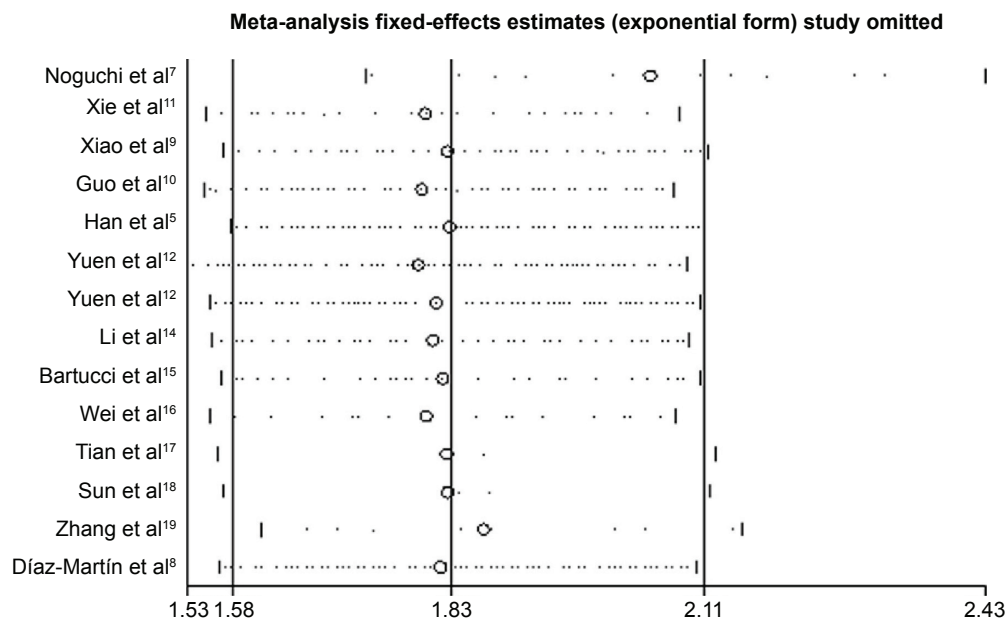


Figure 5 Sensitivity analysis by stepwise omission of one study at a time for overall survival. **Note:** The sensitivity analysis showed that no individual study significantly influenced the combined hazard ratio.

and lymph node metastasis in cancer patients. But the data were insufficient to determine the role of TAZ in DFS/PFS. To fully understand the clinical utility of TAZ in the prognosis of cancer patients, more well-designed prospective studies based on a larger sample size or larger-scale clinical investigations are awaited.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Newcastle–Ottawa quality assessment scale (cohort studies)

	Selection			Comparability		Outcome		Score
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	
a. Truly representative of the average (describe) in the community ☆	a. Community controls ☆	a. Secure record (eg, surgical records) ☆	a. Yes (endpoint) ☆	a. Study controls for (select the most important factor) ☆	a. Independent blind assessment ☆	a. Yes (select an adequate follow-up period for outcome of interest) ☆	a. Complete follow-up – all subjects accounted for ☆	
b. Somewhat representative of the average in the community ☆	b. Drawn from a different source	b. Structured interview	b. No	b. Study controls for any additional factor. (This criteria could be modified to indicate specific control for a second important factor.) ☆	b. Record linkage ☆	b. No	b. Subjects lost to follow-up – unlikely to introduce bias – small number lost – >80% (select an adequate %) follow-up, or description provided of those lost) ☆	
c. Selected group of users, for example, nurses, volunteers	c. No description of the nonexposed cohort	c. Written self-report			c. Self-report		c. Follow-up rate <80% (select an adequate %) and no description of those lost	
d. No description of the derivation of the cohort	d. No description of the cohort	d. No description			d. No description		d. No statement	
Noguchi et al ¹	☆	☆	☆	☆	b☆	☆	☆	6
Xiao et al ²	☆	☆	☆	☆	b☆	☆	☆	7
Guo et al ³	☆	☆	☆	☆	b☆	☆	☆	6
Han et al ⁴	☆	☆	☆	☆	b☆	☆	☆	7
Yuen et al ⁵	☆	☆	☆	☆	b☆	☆	☆	6
Wang et al ⁶	☆	☆	☆	☆	b☆	☆	☆	7
Li et al ⁷	☆	☆	☆	☆	b☆	☆	☆	6
Bartucci et al ⁸	☆	☆	☆	☆	b☆	☆	☆	6
Wei et al ⁹	☆	☆	☆	☆	b☆	☆	☆	7
Tian et al ¹⁰	☆	☆	☆	☆	b☆	☆	☆	6
Sun et al ¹¹	☆	☆	☆	☆	b☆	☆	☆	7
Zhang et al ¹²	☆	☆	☆	☆	b☆	☆	☆	7
Xie et al ¹⁴	☆	☆	☆	☆	b☆	☆	☆	7
Díaz-Martín et al ¹⁵	☆	☆	☆	☆	b☆	☆	☆	7

Notes: A study can be awarded a maximum of one star for each numbered item within the “selection” and “outcome” categories. A maximum of two stars can be given for “comparability”.

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