

Clinical value of *Xenopus* kinesin-like protein 2 as a prognostic marker in patients with digestive system cancers: a systematic review and meta-analysis

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Abstract: *Xenopus* kinesin-like protein 2 (TPX2) is a microtubule-associated protein that plays an important role in spindle assembly and dynamics. However, the clinical and prognostic value of TPX2 in the digestive system cancers remains unclear. The objective of this review was to evaluate the association of TPX2 expression with disease-free survival (DFS), overall survival (OS), and clinicopathological features of digestive system cancers. The software Stata 12.0 was used to analyze the outcomes, including OS, disease-free survival (DFS), and clinicopathological characteristics. A total of 10 eligible studies with 906 patients were included. Elevated TPX2 expression was significantly associated with poor DFS (pooled hazard ratio [HR] =2.48, 95% confidence interval [CI]: 1.96–3.13) and OS (pooled HR =2.66, 95% CI: 2.04–3.48) of digestive system malignancies. Subgroup analyses showed that cancer type, sample size, study quality, and laboratory detection methods did not alter the significant prognostic value of TPX2. Additionally, TPX2 expression was found to be an independent predictive factor for DFS (HR =2.31, 95% CI: 1.78–3.01). TPX2 expression might be associated with TNM stage and pathological grade in digestive system cancer. In conclusion, TPX2 is an independent prognostic factor for survival of patients with digestive system cancer. Furthermore, its overexpression is associated with TNM stage and pathological grade in digestive system cancer.

Keywords: digestive system neoplasm, TPX2, meta-analysis, prognosis

Introduction

Digestive system cancers, one of the most common malignancies, have overtaken cardiovascular disease and infectious diseases as a major cause of morbidity and mortality in the world.^{1–3} They cause approximately 2.9 million deaths per year.⁴ Although novel targeted therapies for terminal cancer patients are emerging, the application range is still limited.⁵ Therefore, it is of great importance to identify applicable prognostic biomarkers to improve the unfavorable prognosis.

Xenopus kinesin-like protein 2 (TPX2), a 100 kDa protein, was first described by Heidebrecht et al in 1997.⁶ Human TPX2, a microtubule-associated protein located in chromosome 20q11.2,^{7,8} was reported to play an important role in spindle assembly and dynamics.^{9,10} In addition, TPX2 was found to participate in the regulation of cell mitosis or meiosis.^{11,12} Overexpression of TPX2 could cause DNA aneuploidy and polyploidy.^{13,14} The aberrant expression of TPX2 could inhibit normal mitosis and lead to carcinogenesis. Thus, TPX2 expression might have great potential for a more precise evaluation of progression of malignancy.

Among numerous independent studies, the clinical predictive value of TPX2 in patients with cancer, especially digestive system cancer, remains controversial.

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A recently published work by Liu et al revealed a significant relationship of positive TPX2 to cancer stage III/IV and cancer grade of differentiation.¹⁵ Huang et al also showed that TPX2 level was positively associated with (TNM) tumor stage and Edmondson-Steiner grading.¹⁶ In obvious contrast, TPX2 expression was not correlated with TNM stage, cancer grade of differentiation, and tumor capsule according to the study by Liang et al.¹⁷ No correlation between TPX2 expression and tumor staging, grading, or TNM stage was indicated.¹⁸

The conflicting results lead to an unresolved issue on the relationship of TPX2 expression with clinical outcomes of cancer patients. Therefore, we performed the meta-analysis to evaluate the association of TPX2 expression with disease-free survival (DFS), overall survival (OS), and clinicopathological features of digestive system cancers.

Methods

Literature search strategy

The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and guidelines.¹⁹ Details of the preferred reporting items for systematic reviews and meta-analyses statement criteria used are available in Table S1. A comprehensive literature search from electronic databases PubMed, EMBASE, Cochrane library, CBM, and Chinese CNKI was performed (up to July 2016). Search keywords were (“TPX2” or “Xklp2” or “Xenopus kinesin-like protein 2”) and (“tumor” or “malignancy” or “neoplasia” or “cancer” or “carcinoma”) and “prognosis” or “survival” or “outcome” or “mortality”. Reference lists in the included studies were also searched manually to identify potential studies.

Selection criteria

Inclusion criteria

- (1) Cohort studies and case-control studies.
- (2) Studies investigating any type of digestive system cancers.
- (3) Studies providing data for the estimation of the hazard ratio (HR) for OS or DFS with 95% confidence intervals (CIs) included.
- (4) Studies where the association between TPX2 and clinical prognosis was clarified.
- (5) Studies of TPX2 overexpression based on primary cancer tissues.
- (6) The most samples and most informative studies when the duplicate studies were published.

Exclusion criteria

- (1) Studies irrelevant to digestive system cancers.

- (2) Studies which assessed patients with metastatic cancers other than primary cancer.
- (3) Data that were incomplete or could not be combined.
- (4) Case reports, comments, letters, meeting abstract, systematic reviews, and meta-analysis.

Data extraction

Data extraction tables were set up to enter data from each study, including first author, publication year, country of origin, type of tumor, TNM stage, number of patients recruited, cut-off value, TPX2 expression and detection method, preoperative treatment, outcome measures, follow-up time, survival analysis, and HRs with the corresponding 95% CIs (Table 1). Two authors (QW and GW) independently assessed the quality of the studies, and a consensus decision was made regarding any discrepancies by a third investigator (XLH).

Under the condition that the total number of events and the corresponding *p*-values were not reported in text, several survival rates at specified times from Kaplan–Meier survival curves were extracted using the Engauge Digitizer version 4.1. The extracted survival rates at specified times were input into the calculation spreadsheet developed by Tierney et al²⁰ to reconstruct the survival curve and produce the HRs with their 95% CIs.

Quality assessment

Study quality in this meta-analysis was assessed using the Quality Scale for Biological Prognostic Factors reported previously.²¹ QW and GW independently assessed the quality of each study according to the quality scale (Table S2).²¹ The quality scale was focused on four aspects: scientific design, laboratory methodology, generalizability, and result analysis. The overall maximum points were 40. The global scores were presented as percentages, ranging from 0% to 100%. Studies with higher proportion values were considered high quality. Any discrepancies on the eligibility of studies were resolved by a third reviewer (XLH) until the two original reviewers reached consensus.

Statistical analysis

Statistical analysis was performed by STATA version 12.1 (StataCorp LP, College Station, TX, USA). Heterogeneity was detected using the I^2 statistic (25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively). In this analysis, $I^2 < 50\%$ indicated low heterogeneity, and $I^2 > 50\%$ indicated substantial heterogeneity. Both fixed- and random-effect models were assessed for the pooled estimates.

Table I Characteristics of the studies included in the meta-analysis (n=10)

First author	Year	Country	Tumor type	Sample type	Tumor stage	Sample size	Sample Cutoff value	Elevated TPX2 (n, %)	Laboratory method	PT	Sample storage	Outcome measures	Follow-up time (months)	Survival analysis	HR (95% CI)
Liang et al ²³	2016	China	GC	Tumor tissue	I-IV	115	Score ≥ 2	54, 47	IHC	NA	Frozen	OS	48	Univariate	OS: 2.84 (1.34–5.98)
Hsu et al ²⁴	2014	China	ESCC	Tumor tissue	I-IV	96	Score ≥ 2	87, 90.6	IHC	NA	Frozen	OS, DFS	96	Univariate	OS: 1.9 (1.04–3.48) DFS: 2.1 (1.19–3.71)
Liu et al ²⁵	2013	China	ESCC	Tumor tissue	NA	62	Nuclear staining above 10%	69, 74.1	IHC	No	FFPE	Lymphatic metastasis	NA	NA	NA
Wei et al ²⁶	2013	China	GRC	Tumor tissue	I-IV	203	Score ≥ 3	124, 61.0	IHC	No	FFPE	OS	100	Univariate, multivariate	OS: 2.2 (1.2–3.9)
Liu et al ¹⁵	2015	China	HCC	Tumor tissue	I-III	130	Score ≥ 2	96, 74.1	IHC	No	Frozen	OS, DFS	100	Univariate, multivariate	OS: 2.58 (1.52–4.37) DFS: 2.67 (1.68–4.23)
Huang et al ¹⁶	2014	China	HCC	Tumor tissue	I-IV	86	Nuclear staining above 10%	56, 65.1	IHC	No	NA	OS, DFS	60	Univariate, multivariate	OS: 3.7 (1.7–8.1) DFS: 2.2 (1.2–3.9)
Liang et al ¹⁸	2015	China	HCC	Tumor tissue	I-IV	50	Nuclear staining above 10%	28, 56.0	RT-PCR	NA	FFPE	DFS	42	Univariate	DFS: 3.45 (1.18–10.07)
Satow et al ²²	2010	Japan	HCC	Tumor tissue	NA	19	Nuclear staining above 10%	11, 57.8	RT-PCR	NA	FFPE	Metastasis	NA	NA	NA
Liang et al ¹⁷	2015	China	HCC	Tumor tissue	I-IV	100	Score ≥ 2	66, 66.0	IHC	No	Frozen	RFS	48	Univariate	RFS: 3.12 (1.52–4.56)
Zhang et al ²⁷	2012	China	PDA	Tumor tissue	I-IV	45	Score ≥ 2	25, 55.5	RT-PCR	NA	Frozen	DFS	60	Univariate, multivariate	DFS: 2.42 (1.27–4.61)

Abbreviations: CI, confidence interval; DFS, disease-free survival; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HR, hazard ratio; IHC, immunocytochemistry; FFPE, formalin-fixed paraffin-embedded; PDA, pancreatic ductal adenocarcinoma; NA, not available; OS, overall survival; PT, preoperative treatment; RFS, recurrence-free survival; TPX2, Xenopus kinesin-like protein 2.

Furthermore, cumulative meta-analysis was performed to show the trend in the estimated effect. Subgroup analyses were carried out on cancer type, sample size, quality score, and laboratory detection method. Sensitivity analysis was carried out by sequentially omitting individual study to guarantee the stability of the results. The odds ratios (ORs) with corresponding 95% CIs were used to assess the correlation between TPX2 expression and clinicopathological features. Egger's regression plot and Begg's test were used to evaluate the risk of publication bias.

Results

Study characteristics

The search strategy retrieved 174 potentially relevant studies. According to the inclusive criteria, 10 eligible studies with a total of 906 patients, conducted in two countries (nine

in China and one in Japan), were included in this meta-analysis.^{15–18,22–27} The flowchart of study selection is shown in Figure 1. Study characteristics of these studies are summarized in Table 1. Among the studies included, five focused on hepatocellular carcinoma (HCC), and two were about esophageal squamous cell carcinoma (ESCC), with single studies about gastric cancer, pancreatic cancer, and colon cancer. There were seven studies for DFS, five for OS, and one for recurrence-free survival (RFS). Expression of TPX2 was evaluated by immunocytochemistry (IHC) in seven studies, and reverse transcription polymerase chain reaction (RT-PCR) was adopted in the remaining three studies. The total positive rate of TPX2 was 63.7% (from 47% to 90.6%). The maximum and minimum sample sizes were 203 and 19, respectively. The quality assessment of the included studies is shown in Table 2.

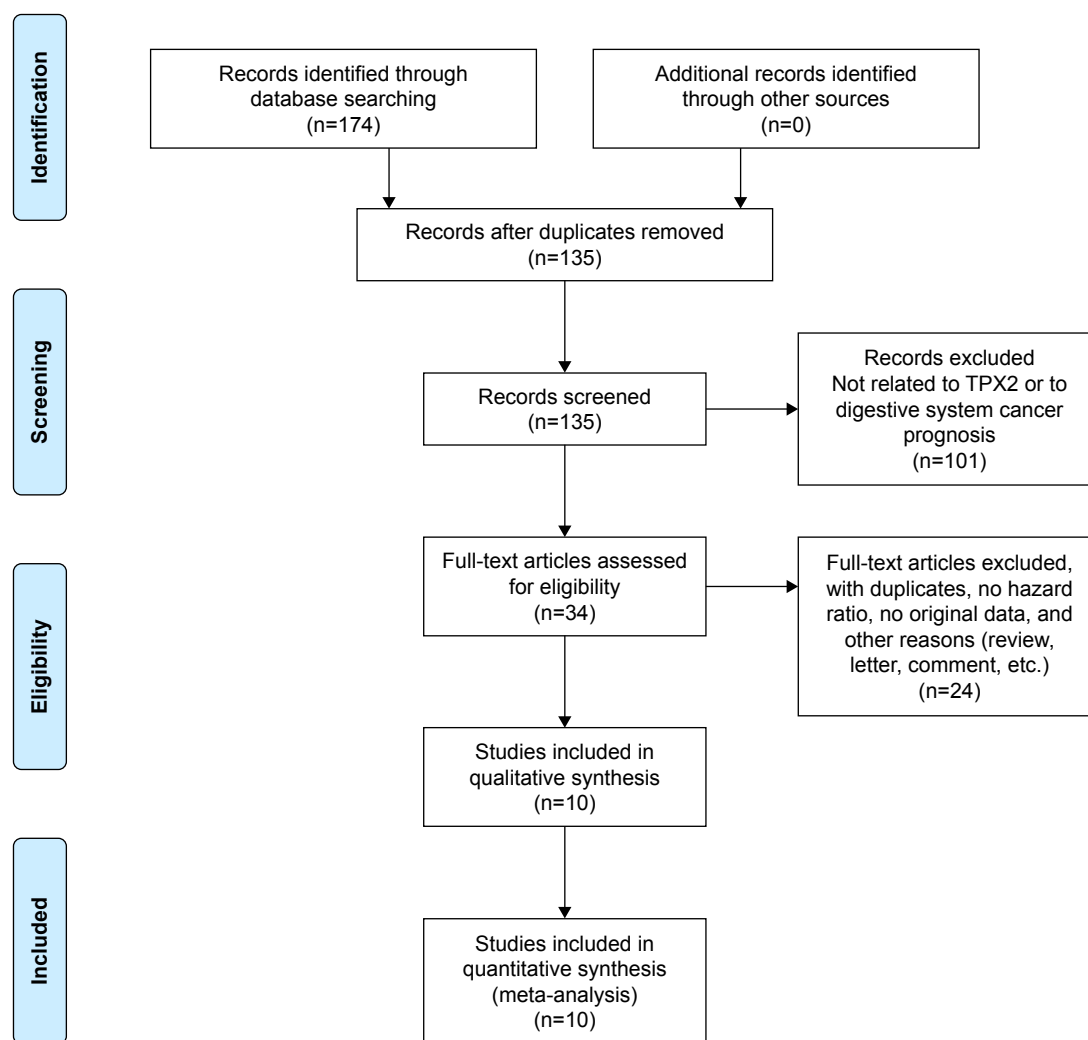


Figure 1 Flowchart of the process of identifying relevant studies.

Abbreviation: TPX2, Xenopus kinesin-like protein 2.

Table 2 Quality assessment of the included studies based on the quality scale for biological prognostic factors

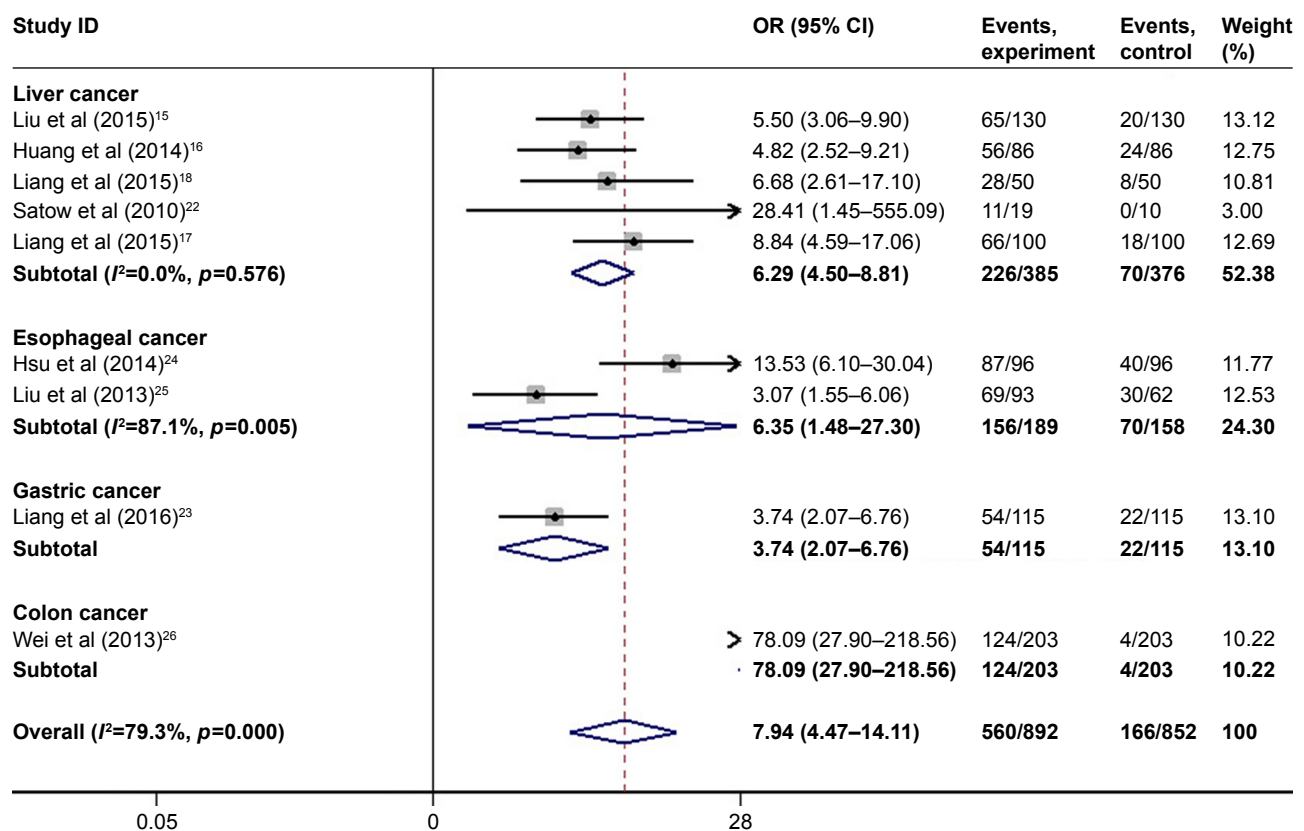
Study	Scientific design	Laboratory methodology	Generalizability	Results analysis	Global score (%)
Liu et al (2015) ¹⁵	9	11	10	7	93
Huang et al (2014) ¹⁶	8	8	10	6	80
Liang et al (2015) ¹⁸	8	11	10	7	90
Satow et al (2010) ²²	8	10	9	2	73
Liang et al (2015) ¹⁷	9	11	10	4	85
Liang et al (2016) ²³	9	10	9	6	85
Hsu et al (2014) ²⁴	8	10	10	4	80
Liu et al (2013) ²⁵	8	9	8	2	68
Wei et al (2013) ²⁶	9	10	9	4	80
Zhang et al (2012) ²⁷	8	9	8	4	73

Aberrant overexpression of TPX2 in digestive system cancers

Meta-analysis using a random-effects model indicated that TPX2 was highly expressed in digestive system cancers, including liver cancer (pooled HR =6.29, 95% CI: 4.50–8.81), esophageal cancer (pooled HR =6.35, 95% CI: 1.48–27.3), gastric cancer (pooled HR =3.74, 95% CI: 2.07–6.76), and colon cancer (pooled HR =78.09, 95% CI: 27.90–218.56) (Figure 2).

Prognostic value of TPX2 for DFS of digestive system cancers

Among the studies included, a total of seven with 725 subjects reported HRs for DFS. As shown in Figure 3, it was indicated that elevated TPX2 expression predicted a poor outcome for DFS of digestive system cancer patients (pooled HR =2.48, 95% CI: 1.96–3.13). In addition, a cumulative meta-analysis according to the time of publication was carried out. A stable trend of significant correlation between TPX2 overexpression

**Figure 2** Meta-analysis of aberrant overexpression of TPX2 in digestive system cancers.

Note: Weights are from random-effects analysis.

Abbreviations: TPX2, Xenopus kinesin-like protein 2; OR, odds ratios; CI, confidence interval.

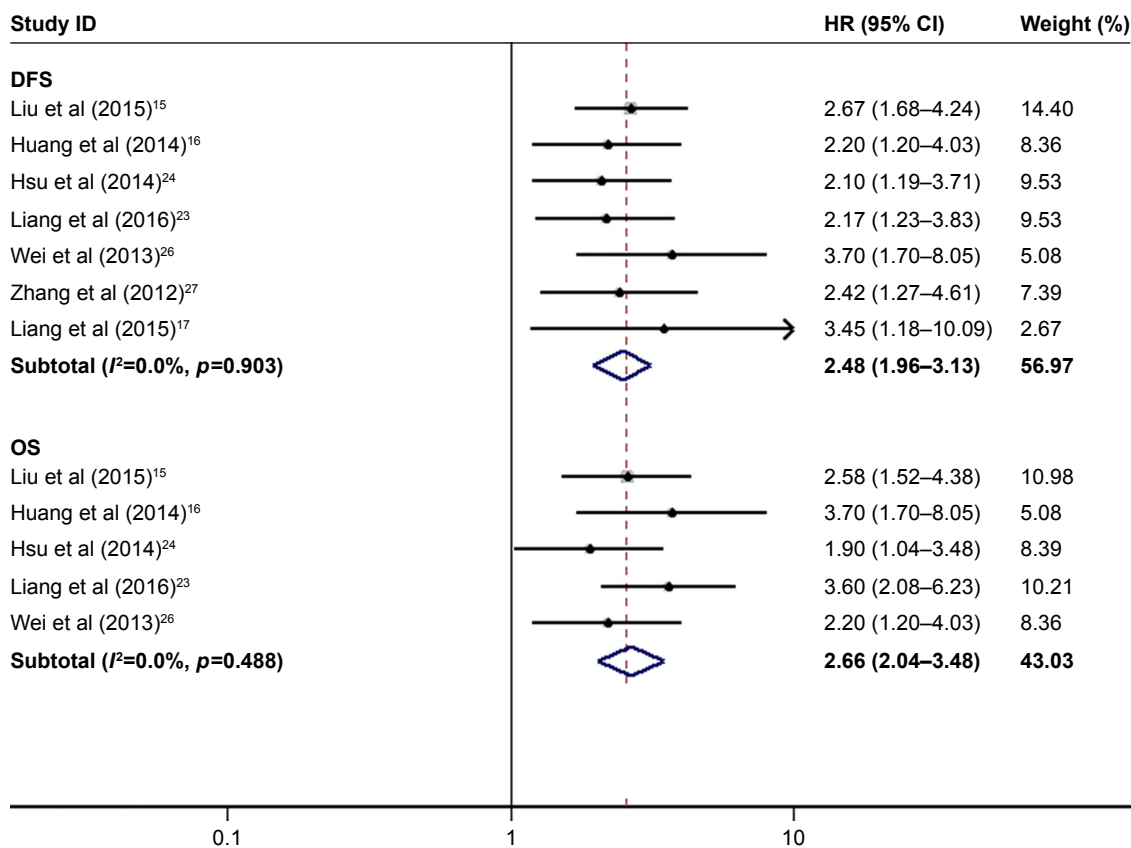


Figure 3 Meta-analysis of the pooled HRs of patients with elevated TPX2 expression.

Note: Weights are from random-effects analysis.

Abbreviations: TPX2, Xenopus kinesin-like protein 2; HR, hazard ratio; CI, confidence interval; DFS, disease-free survival; OS, overall survival.

and a poor DFS was confirmed as time accumulates with an increasingly narrow 95% CI (Figure S1). Although no inter-study heterogeneity was observed in the quantitative synthesis ($I^2=0.0\%$, $p=0.903$), subsequent analyses of subgroups were performed on the basis of cancer type (liver, esophageal, gastric, colon, and pancreatic), sample size (≥ 100 vs < 100), quality score ($\geq 85\%$ vs $< 85\%$), and laboratory detection method (RT-PCR vs IHC) (Figure 4). A significant correlation between TPX2 overexpression and a poor DFS was shown in patients with liver cancer (HR =2.57, 95% CI: 1.82–3.64), esophageal cancer (HR =2.10, 95% CI: 1.19–3.71), gastric cancer (HR =2.17, 95% CI: 1.23–3.83), colon cancer (HR =3.70, 95% CI: 1.70–8.05), and pancreatic cancer (HR =2.42, 95% CI: 1.27–4.61), indicating the expression level of TPX2 could be used to predict the DFS of various kinds of digestive system malignancies. In the analysis stratified by the size of the sample, TPX2 was found to be significantly associated with DFS of patients in studies with sample size > 100 (HR =2.64, 95% CI: 1.91–3.66) and sample size < 100 (HR =2.32, 95% CI: 1.66–3.23). There was a significant association of increased TPX2 expression with DFS of patients in studies with a quality score of $> 85\%$

(HR =2.54, 95% CI: 1.81–3.57) and $< 85\%$ (HR =2.42, 95% CI: 1.76–3.33). Stratified analysis on the laboratory detection method revealed a significant relationship of elevated TPX2 to DFS of patients in both RT-PCR subgroup (HR =2.66, 95% CI: 1.53–4.62) and IHC subgroup (HR =2.44, 95% CI: 1.89–3.15). In order to evaluate the robustness of the pooled results, we conducted sensitivity analysis by sequentially omitting one study. The leave-one-out sensitivity analysis implied that no individual study altered the pooled estimates significantly (Figure 5A), validating the stability of our results.

Prognostic value of TPX2 for OS and RFS of digestive system cancers

Five studies comprising 630 individuals reported OS according to the expression level of TPX2, and one study consisting of 100 patients reported HRs and corresponding 95% CIs for RFS. As shown in Figure 3, upregulated TPX2 expression was tightly associated with poor clinical outcome for OS (pooled HR =2.66, 95% CI: 2.04–3.48) of digestive system tumors. We also conducted sensitivity analysis by sequentially omitting one study. The results showed that no

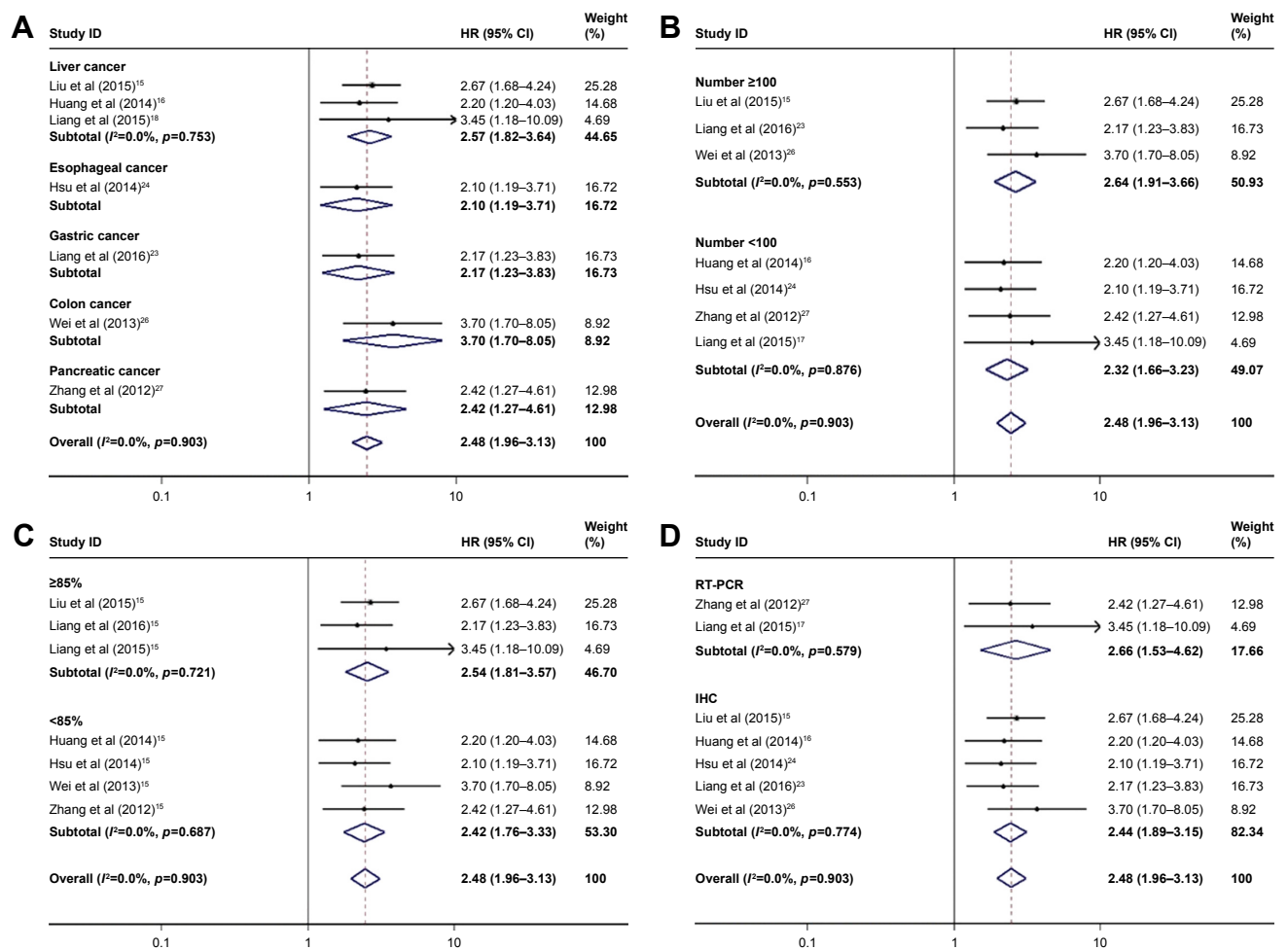


Figure 4 Subgroup analyses were performed by the factors of cancer type (A), sample size (B), quality score (C), and laboratory detection method (D). **Note:** Weights are from random-effects analysis. **Abbreviations:** HR, hazard ratio; CI, confidence interval.

individual study altered the pooled estimates significantly (Figure 5B), validating the stability of our results. In addition, a cumulative meta-analysis according to the time of publication was carried out. A stable trend of significant correlation between TPX2 overexpression and a poor OS was confirmed as time accumulates with an increasingly narrow 95% CI (Figure S2). Similarly, TPX2 overexpression was associated with a poor RFS (HR =3.12, 95% CI: 1.52–4.56) in patients with HCC.

Independent prognostic value of TPX2 in digestive system cancers

Cox multivariate analyses were performed in five studies, and the role of TPX2 as an independent predictive factor for OS of patients with digestive system cancer was investigated. The pooled results showed that TPX2 expression was an independent prognostic factor for OS of patients with digestive system cancers (pooled HR =2.31, 95% CI: 1.78–3.01),

and there was no heterogeneity among the studies ($I^2=0.0\%$, $p=0.660$) (Figure 6).

Association between TPX2 and clinicopathological characteristics of digestive system cancers

A total of eight studies assessed the relationship between TPX2 expression and clinicopathological characteristics of digestive system cancers, including five about HCC, and three studies about ESCC, gastric cancer, and colorectal cancer, respectively. The pooled estimates showed that TPX2 expression was closely correlated with pathological grade (pooled HR =3.438, 95% CI: 2.040–5.794) and TNM stage (pooled HR =2.690, 95% CI: 1.540–4.699) in HCC, but was not related to most of the clinicopathological features, including age, gender, tumor size, hepatitis B surface antigen (HBsAg) status, alpha-fetoprotein (AFP), liver cirrhosis, tumor number, tumor encapsulation, and vascular invasion.

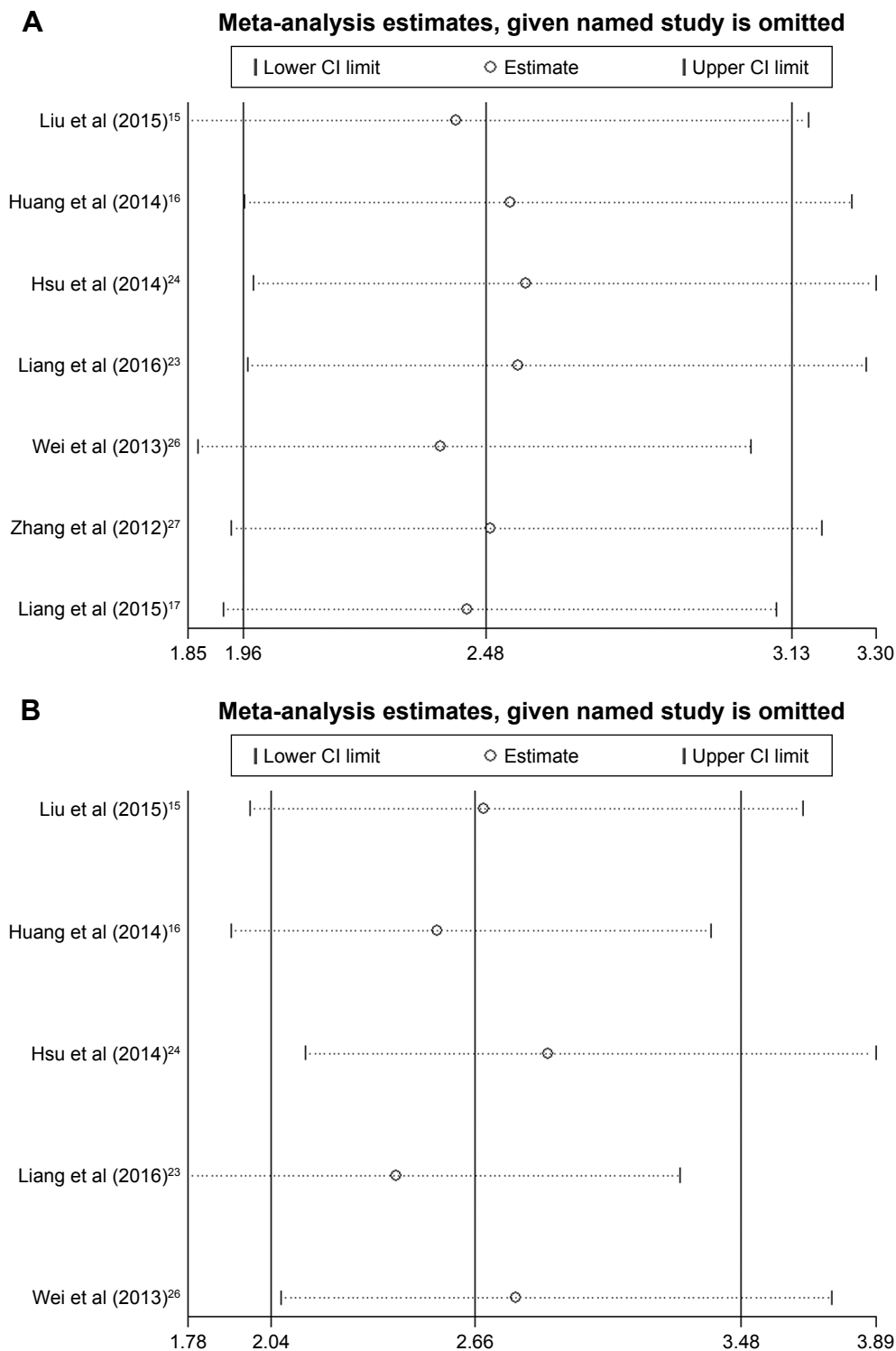


Figure 5 Sensitivity analysis of the effect of the individual study on the pooled HRs for the correlation between TPX2 and disease-free survival (**A**) and overall survival (**B**) in patients with digestive system cancer.

Abbreviations: TPX2, Xenopus kinesin-like protein 2; HR, hazard ratio; CI, confidence interval.

A significant relationship between TPX2 expression and lymph node metastasis (pooled HR =2.341, 95% CI: 1.478–3.709), distant metastasis (pooled HR =3.964, 95% CI: 1.987–7.906), and TNM stage (pooled HR =2.515,

95% CI: 1.332–4.746) was observed in three other cancers, including ESCC, gastric cancer (GC), and colorectal cancer. As shown in Table 3, there was no statistically significant publication bias across all the groups.

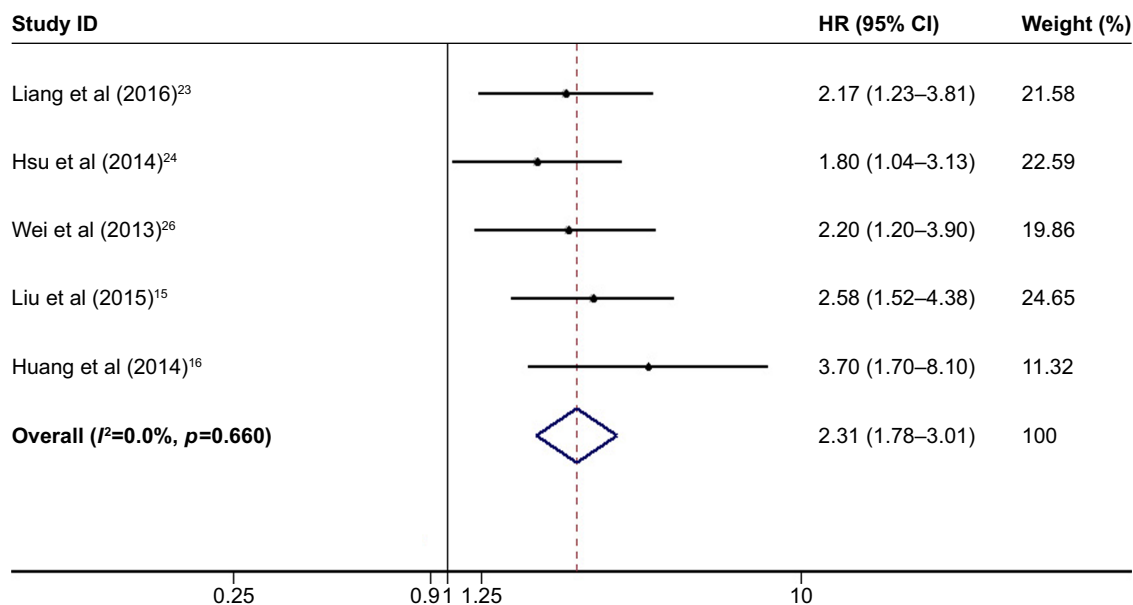


Figure 6 Meta-analysis of the independent role of TPX2 in overall survival of cancer patients.

Note: Weights are from random-effects analysis.

Abbreviations: TPX2, Xenopus kinesin-like protein 2; HR, hazard ratio; CI, confidence interval.

Publication bias

Egger's regression plot and Begg's test were performed to assess the potential bias in the available literature. Egger's test revealed no evidence of potential publication bias for DFS ($p=0.232$) and OS ($p=0.785$). In addition, Begg's test also indicated that there was no potential publication bias for DFS ($p=0.23$) and OS (1.000) (Figure S3).

Discussion

This study explored the prognostic role of TPX2, an important regulatory molecule involved in spindle assembly and dynamics, in various types of digestive system malignancies. We used a comprehensive and detailed search strategy combined with predetermined inclusion and exclusion criteria, providing convincing evidence that the expression level of TPX2 is predictive of poor survival in digestive system cancers.

In total, 10 studies comprising 906 patients were included in the meta-analysis. Our pooled results showed that TPX2 might be utilized as an unfavorable and negative prognostic marker for digestive system cancer. We found that TPX2 overexpression is negatively correlated with OS, DFS, and RFS in patients with digestive system cancer. Moreover, the result of cumulative meta-analysis confirmed the stable trend of significant association between TPX2 and DFS and OS as time-accumulated. Stratified analyses were performed, and significant results pertaining to the relationship of TPX2 to a poor DFS were yielded in all subgroups on the basis of

cancer type, sample size, quality of study, and laboratory detection method. Next, sensitivity analysis showed that no single study altered the pooled estimates significantly. Furthermore, the pooled results showed that TPX2 expression was an independent prognostic factor for DFS of patients with digestive system cancers. In addition, TPX2 expression was closely correlated with pathological grade and TNM stage in HCC. A significant relationship between TPX2 expression and lymph node metastasis, distant metastasis, and TNM stage was observed in ESCC, GC, and colorectal cancer. Besides, no statistically significant inter-study heterogeneity was found in our meta-analysis.

In addition to gastrointestinal cancer, TPX2 has also been reported to be highly expressed in other non-gastrointestinal cancers, such as bladder cancer,²⁸ brain cancer,²⁹ lung cancer,^{30,31} oral cancer,³² ovarian cancer,³³ and salivary gland cancer.³⁴ However, the mechanism by which TPX2 promotes cancer progression has not been fully elucidated so far. Martens-de Kemp et al³⁵ identified 71 target genes by genome-wide siRNA screens, in which TPX2 was shown to be essential for tumor cell survival. Furthermore, in vivo and in vitro, silencing of *TPX2* gene could reduce the tumorigenicity of cancer cells.²⁶ Liu et al¹⁵ found that TPX2 could upregulate the expression of matrix metalloproteinase 2 (MMP2) by activation of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway in HCC. In addition to PI3K/Akt signaling pathway, TPX2 may partially activate the Ras/Raf/MEK/ERK signaling pathway to promote tumor proliferation.²⁶

Table 3 Results of meta-analysis of increased TPX2 expression and clinicopathological features of three types of cancer

Clinicopathological features	No of studies	No of patients	Fixed-effects model		Random-effects model		Heterogeneity		Begg's test		Egger's test	
			Pooled OR (95% CI)	p-value	Pooled OR (95% CI)	p-value	I ² (%)	p-value	z	p-value	t (bias)	p-value
HCC												
Age (>45 vs ≤45) (years)	3	286	1.366 (0.800–2.334)	0.253	1.266 (0.571–2.807)	0.561	46.9%	0.152	–1.57	0.296	–2.32	0.259
Gender (male vs female)	3	286	0.719 (0.393–1.315)	0.809	0.719 (0.392–1.317)	0.285	0.0%	0.809	1.57	0.296	0.247	0.247
Tumor size (>5 cm vs ≤5 cm)	3	286	0.804 (0.476–1.355)	0.412	0.758 (0.390–1.474)	0.414	28.5%	0.247	–1.57	0.296	–2.76	0.222
Pathological grade (III–IV vs I–II)	3	286	3.440 (2.042–5.796)	<0.001	3.438 (2.040–5.794)	<0.001	0.0%	0.900	–0.52	1.000	–1.32	0.412
HBsAg status (positive vs negative)	3	286	1.396 (0.785–2.483)	0.256	1.391 (0.778–2.486)	0.266	0.0%	0.656	–0.52	1.000	–0.81	0.567
AFP (positive vs negative)	3	286	1.049 (0.649–1.697)	0.844	1.052 (0.648–1.708)	0.837	0.0%	0.524	–0.52	1.000	–0.42	0.745
Liver cirrhosis (yes vs no)	3	286	0.976 (0.596–1.600)	0.924	0.978 (0.595–1.607)	0.930	0.0%	0.618	–0.52	1.000	–0.38	0.769
Tumor number (multiple vs single)	3	286	1.542 (0.890–2.670)	0.122	1.514 (0.592–3.868)	0.387	62.7%	0.069	0.52	1.000	–0.01	0.992
Tumor encapsulation (incomplete vs complete)	2	200	0.767 (0.416–1.413)	0.394	0.767 (0.416–1.413)	0.394	0.0%	0.931	1.00	1.000	–	–
Vascular invasion (yes vs no)	2	216	2.363 (1.217–4.589)	0.011	2.349 (0.872–6.332)	0.091	53.7%	0.141	–1.00	1.000	–	–
TNM stage (III–IV vs I–II)	3	286	2.796 (1.615–4.841)	<0.001	2.690 (1.540–4.699)	0.001	0.0%	0.436	1.57	0.296	0.99	0.502
Other digestive system cancers (ESCC, GC, and CRC)												
Age (>55 vs ≤55)	2	318	1.067 (0.679–1.677)	0.778	1.074 (0.662–1.744)	0.772	11.5%	0.288	1.00	1.000	–	–
Gender (male vs female)	3	414	0.770 (0.495–1.198)	0.246	0.753 (0.454–1.249)	0.273	13.8%	0.313	–1.57	0.296	–5.71	0.110
Lymph node metastasis (present vs absent)	3	414	2.374 (1.562–3.608)	<0.001	2.341 (1.478–3.709)	<0.001	14.0%	0.313	–0.52	1.000	–0.99	0.502
Distant metastasis (present vs absent)	3	414	3.945 (1.974–7.884)	<0.001	3.964 (1.987–7.906)	<0.001	0.0%	0.722	–1.57	0.296	–20.83	0.031
Poor/undifferentiated vs Well/moderated	3	414	1.949 (1.158–3.281)	0.012	1.928 (1.139–3.262)	0.014	0.0%	0.421	1.57	0.296	16.30	0.039
Stage (III/IV vs I/II)	3	414	2.560 (1.702–3.851)	<0.001	2.515 (1.332–4.746)	0.004	55.0%	0.109	0.52	1.000	–0.17	0.892

Notes: p-value in bold indicates statistical significance. “–” p-value cannot be calculated.

Abbreviations: TPX2, Xenopus kinesin-like protein 2; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; TNM, tumor node and metastasis; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; CRC, colorectal cancer; AFP, alpha-fetoprotein.

It has been known previously that the upregulation of TPX2 in cancer cells can promote epithelial-to-mesenchymal transition (EMT) by regulating the expression of EMT-related proteins. Depletion of TPX2 can lead to the upregulation of E-cadherin proteins that inhibit tumor metastasis and the downregulation of N-cadherin, β -catenin, Slug, MMP-9 and MMP-2 proteins that promote tumor metastasis.²⁶ Moreover, TPX2 plays an important role in regulating cell cycle and proliferation. Wei et al found that silencing TPX2 through siRNA transfection significantly inhibited the cell cycle progression at G1 arrest.²⁶ Collectively, previous studies indicate that TPX2 overexpression is associated with a tumor's proliferation, apoptosis, EMT, and invasiveness. However, further research is still needed.

The identification of prognostic factors is critical to distinguish high-risk patients who are good candidates for individualized treatment. Our findings suggested that TPX2 might potentially act as a clinical biomarker, and might also be a molecular target for cancer therapy. Recently, Kilchmann et al³⁶ reported the discovery of a selective inhibitor of Aurora A. The inhibitor locks Aurora A in an inactive conformation and disrupts the function of TPX2. Chowdhury et al³⁷ discovered that TPX2 might serve as a biomarker for identifying a subpopulation of patients who are sensitive to Aurora A-inhibitor treatment. Therefore, increasing studies will focus on TPX2 as a novel antitumor therapeutic approach in the future.

There were some limitations in our meta-analysis. First, all of the included patients were Asian, decreasing the applicability of the results across different ethnicities. Therefore, additional well-designed studies with patients of different ethnic backgrounds are highly needed to give more reliable results. Second, the cutoff value of TPX2 expression varied across different studies and a consensus value was rather difficult to reach. Third, in some studies, estimated HRs with corresponding 95% CIs were calculated by Kaplan–Meier survival curves. Fourth, the number of studies enrolled in our analysis was relatively small. Finally, biological subtypes of a given tumor were not assessed because the distinction between different subtypes was not available for most of the studies.

Conclusion

In conclusion, this meta-analysis showed that TPX2 might be an independent prognostic factor for survival of patients with digestive system cancer. Furthermore, TPX2 expression might be associated with TNM stage and pathological grade in digestive system cancer. Additional well-designed studies

with larger and more diverse populations are highly needed to validate our current data.

Acknowledgments

We thank Fengfang Xiao for critically reviewing the manuscript.

Author contributions

QW conceived the study, assessed the quality of the studies, and drafted the manuscript. GW and ZYL searched the literature, assessed the quality of the studies, performed the statistical analysis, and drafted the manuscript. CXL and XLH participated in the statistical analysis and drafted the manuscript. All authors read and approved the final manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 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.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3–4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3–4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	4–5
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe the method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe the methods used for assessing the 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.	6
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	6

Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NA, not available.

Table S2 Quality assessment of the included studies based on the quality scale for biological prognostic factors

Study	Scientific design	Laboratory methodology	Generalizability	Results analysis	Global score (%)
Liu et al (2015) ¹	9	11	10	7	93
Huang et al (2014) ²	8	8	10	6	80
Liang et al (2015) ³	8	11	10	7	90
Satow et al (2010) ⁴	8	10	9	2	73
Liang et al (2015) ⁵	9	11	10	4	85
Liang et al (2016) ⁶	9	10	9	6	85
Hsu et al (2014) ⁷	8	10	10	4	80
Liu et al (2013) ⁸	8	9	8	2	68
Wei et al (2013) ⁹	9	10	9	4	80
Zhang et al (2012) ¹⁰	8	9	8	4	73

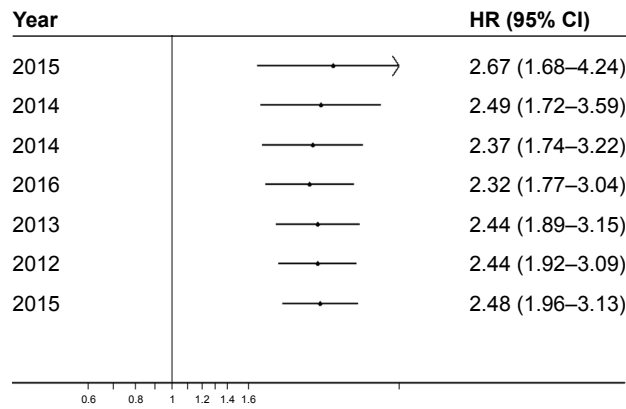


Figure S1 Cumulative meta-analysis of the correlation between TPX2 overexpression and DFS according to the time of publication.
Abbreviations: TPX2, Xenopus kinesin-like protein 2; HR, hazard ratio; CI, confidence interval.

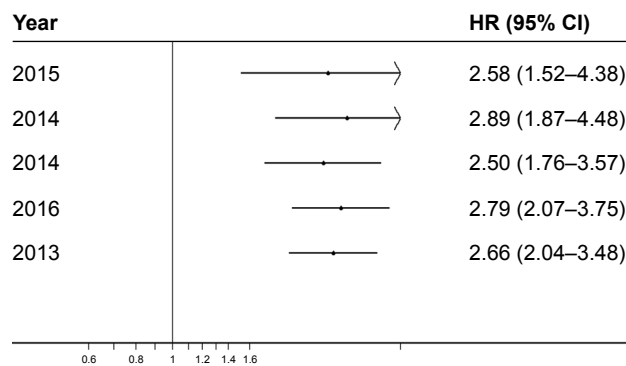


Figure S2 Cumulative meta-analysis of the correlation between TPX2 overexpression and OS according to the time of publication.
Abbreviations: TPX2, Xenopus kinesin-like protein 2; OS, overall survival; HR, hazard ratio; CI, confidence interval.

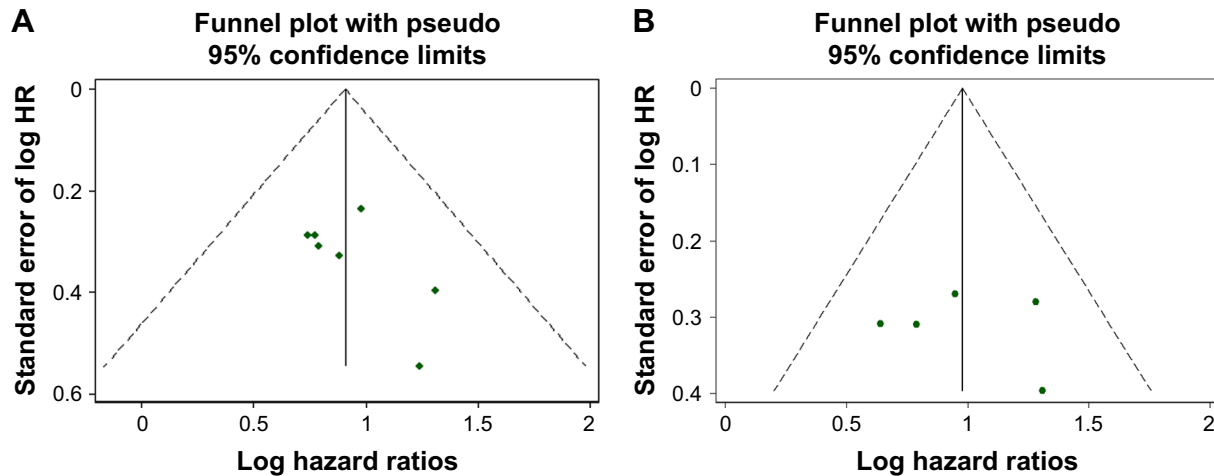


Figure S3 Funnel plot for publication bias of studies for DFS (A) and OS (B).
Abbreviations: DFS, disease-free survival; OS, overall survival; HR, hazard ratio.

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