Systematic Review and Meta-Analysis

Medicine®

OPEN

Prognostic and clinical value of Targeting protein for Xenopus kinesin-like protein 2 in patients with gastrointestinal tract cancers

A meta-analysis

Wanwei Liu, MMed*, Jiwei Xu, MMed, Caiyun Zhang, MB

Abstract

Background: Accumulating studies have indicated that Targeting protein for Xenopus kinesin-like protein 2 (TPX2) was overexpressed in various types of human cancers. However, the prognostic and clinical value of TPX2 in gastrointestinal (GI) tract cancers was not well-understood. This study was aimed to comprehensively explore the prognostic and clinical significance of TPX2 in GI tract cancers.

Methods: Eligible studies were systematically retrieved in PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI) and Wanfang database. The eligible studies were collected to evaluate the association of TPX2 with prognosis and clinicopathological features, with the pooling hazard ratio (HR) and odds ratio (OR) with 95% confidence interval (CI).

Result: The meta-analysis suggested that overexpression of TPX2 protein was significantly correlated with poor overall survival (OS) (HR: 2.20, 95% CI: 1.60–2.80, $P < .001$) in GI tract cancers, the subgroup meta-analysis also confirmed the prognostic value of TPX2 protein. Furthermore, clinical significances of TPX2 protein in gastric cancer were discussed.

Conclusion: Upregulated TPX2 protein was correlated with poor clinical outcomes, suggesting that TPX2 protein can serve as a promising predictive biomarker in patients with GI tract cancers.

Abbreviations: CIs = confidence intervals, CC = colon cancer, DSS = disease-specific survival, GC = gastric cancer, GI = Gastrointestinal , HR = hazard ratio, MFS = metastasis-free survival, OS = overall survival, RFI = relapse-free interval, TPX2 = Targeting protein for Xenopus kinesin-like protein 2.

Keywords: gastrointestinal tract cancer, prognosis, protein expression, TPX2

1. Introduction

Gastrointestinal (GI) tract cancers refer to malignancies of the GI tract, including esophagus cancer, stomach cancer, small and large intestine cancer. Those result in a large proportion of the all-cancer incidence and mortality worldwide.[1,2] The outcome of patients with those cancers remained unsatisfactory, although great advances have been made in treatment and diagnosis.[3–5] There is still no effective and accessible prognostic biomarker that available in clinical applications for GI tract cancer. Thus, prognosis predictor is significant and urgently required for patients with this kind of cancer.

Targeting protein for Xenopus kinesin-like protein 2 (TPX2) was known as a microtubule-associated protein, which played a pivotal role in mitotic spindle formation and chromosome segregation process.[6,7] TPX2 gene was recently identified as a candidate oncogene localized at 20q11.2.[8] Many studies have shown that TPX2 was implicated in tumor development, and the abnormal expression of TPX2 has been reported in various malignancies, such as lung cancer, thyroid carcinoma, and clear cell renal carcinoma.[9–15] The roles of TPX2 in GI tract cancers have attracted much attention. Increased expression of TPX2 was correlated with the tumor progression and poor prognosis in GI tract cancers,[16–21] suggesting its potential value as a promising biomarker for prognostic evaluation. However, there has been no consensus on the prognostic and clinical value of TPX2 protein in GI tract cancers, and no systematic study has been conducted to investigate the prognostic and clinical value of TPX2 protein so far. Therefore, this present meta-analysis was performed to make a synthetic evaluation of TPX2's prognostic and clinical value in GI tract cancers. In addition, the clinicopathological value of TPX2 protein was further analyzed in gastric cancer (GC).

2. Materials and methods

The ethical approval was not necessary for our study, for the article type of this paper is a meta-analysis. And informed consent was also unnecessary.

Editor: Kou Yi.

The authors declared no conflicts of interest.

Supplemental Digital Content is available for this article.

Department of Hepatobiliary Surgery, Meizhou People's Hospital (Huangtang Hospital), Meizhou, Guangdong Province, P. R. China.

* Correspondence: Wanwei Liu, Department of Hepatobiliary Surgery, Meizhou People's Hospital (Huangtang Hospital), Huangtang Road 63, Meijiang District, Meizhou 514031, Guangdong Province, P. R. China (e-mail: wanweiliu9008@163.com).

Medicine (2018) 97:46(e13303)

Received: 30 January 2018 / Accepted: 25 October 2018

http://dx.doi.org/10.1097/MD.0000000000013303

2.1. Publication retrieval

A comprehensive literature retrieval was conducted in several databases including PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI) and Wanfang database. Those studies assessing TPX2 protein expression and clinical outcomes in GI tract cancers up to July 1, 2017, were collected. The search strategy included the following terms through MeSH headings, keywords, and text words: "TPX2" or "Targeting protein for Xenopus kinesin-like protein 2" or "target protein for Xklp2 protein" or "DIL-2 protein" or "C20orf2 protein" combined with "cancer" or "carcinoma" or "neoplasm" or "tumor". The references cited in the relevant articles were also manually reviewed for possible inclusion. There was no language limitation in this process.

2.2. Study selection

The inclusion criteria for eligible articles were listed as follows:

1) studies that reported TPX2 protein expression in primary GI tract cancer tissues;
2) studies analyzing the relationship between TPX2 expression level and prognosis;
3) survival outcomes with hazard ratio (HR) and corresponding 95% confidence interval (CI) were available or could be calculated from original studies;
4) patients were divided into 2 groups according the TPX2 protein expression levels.

Studies were excluded if they were:

1) reviews, letters or conference abstracts,
2) non-GI tract cancers research,
3) studies with insufficient data for calculating the HR and 95% CI.

2.3. Data extraction

The data from each eligible study was independently extracted by two authors with predefined item forms. Accordingly, the following data and information were collected: first author's surname, publication year, study country or region, cancer type, sample size, expression pattern, cancer stage, the criterion of over-expression, detection method, follow-up time, outcome measures, and analysis type. In addition, the relevant clinicopathological features in GC were also extracted.

If a study reported HRs and 95% CIs in univariate and multivariate analyses, the latter were preferentially selected, if a study only provided Kaplan–Meier curve, the HRs and 95% CIs were estimated via Engauge Digitizer version 4.1.

Study quality was assessed with the Newcastle-Ottawa Scale (NOS) (Supplementary information, http://links.lww.com/MD/C644), including 3 main categories: selection, comparability, and outcome ascertainment. The studies with scores great than 6 were defined as high quality. In this meta-analysis, the quality scores of all included studies were varied from 6 to 8, with a mean value of 7.2.

2.4. Statistical analysis

The Stata statistical software version 12.0 was applied to analyze the relationship between TPX2 protein expression and prognosis, the RevMan5.3 software was applied to calculate the association between TPX2 protein expression and clinicopathological features in GC.

Statistical heterogeneity of combined HR or OR was assessed with Cochrane Q test and Higgins I^2 metrics. If there was significant heterogeneity across studies ($I^2 > 50\%$ or/and $P_Q < .05$), the random-effect model (DerSimonian and Laird method) would be applied to pool the results. If there was no obvious heterogeneity, the fixed-effect model (Mantel–Haenszel method) was selected. Sensitivity analysis was applied to evaluate the stability of the results. The publication bias was assessed with the Begg and Egger test. All statistical tests were 2-sided, and statistical significance was defined as a P value less than .05.

3. Results

3.1. Study characteristics

A total of 6 eligible publications were screened based on study selection criteria (Fig. 1) and included in this meta-analysis.[16–21] The characteristics of these enrolled studies were summarized (Table 1). The 6 studies have involved 871 patients, with the median sample-size of 145.2 and ranged from 61 to 290. The studies were published from 2013 to 2017. Among those 6 publications, there were 4 different kinds of GI tract cancers, including 3 GC,[16–18] 1 adenocarcinoma of the esophagogastric junction (AEG),[19] 1 esophageal squamous cell carcinoma (ESCC)[20] and 1 colon cancer (CC).[21] Among those studies, 5 articles were written in English and 1 study was written in Chinese, they were all came from Asian countries (China and Japan). The survival outcomes included overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), metastasis-free survival (MFS), relapse-free survival (RFS), and relapse-free interval (RFI). Multivariate Cox analysis was performed to evaluate the prognostic role of TPX2 protein in all included studies. Immunohistochemistry (IHC) staining was applied to test the TPX2 protein in cancer tissues. The percentage of over-expression in the cohort population varied in different cancer types and ranged from 41.67% to 73.77%.

3.2. Results of the meta-analysis

3.2.1. TPX2 protein and OS in GI tract cancers. A total of 5 studies[17–21] with 581 cases focused on evaluating the association between TPX2 protein and OS in GI tract cancers. The overall results showed a statistically significant association of TPX2 expression and OS (HR: 2.20, 95% CI: 1.60–2.80, $P < .001$, fixed-effect model) (Fig. 2). TPX2 over-expression was significantly associated with poor OS in patients with GI tract cancers, the expression of TPX2 protein could act as a negative independent prognostic factor for OS of patients with GI tract cancers.

We also conducted subgroup meta-analysis to assess the prognostic value of TPX2 protein in GI tract cancers (Table 2). The results showed that TPX2 protein might be a prognostic indicator of OS for patients with GC (HR: 2.68, 95% CI: 1.53–3.84, $P < .001$). Furthermore, the combined HR values >1 were also observed in subgroup meta-analysis stratified by sample size and follow-up time (Table 2).

3.2.2. TPX2 protein and MFS in GI tract cancers. Only 2 studies[19,21] including 264 patients investigated the association between TPX2 protein and MFS. The pooled results showed a strong trend, but no significant difference was observed between TPX2 protein expression level and MFS in GI tract cancers (HR: 3.25; 95% CI: 0.99–5.51), and there was no significant heterogeneity across studies ($I^2 = 0.0\%$, $P_Q = .697$; fixed-effect model) (Fig. 3).

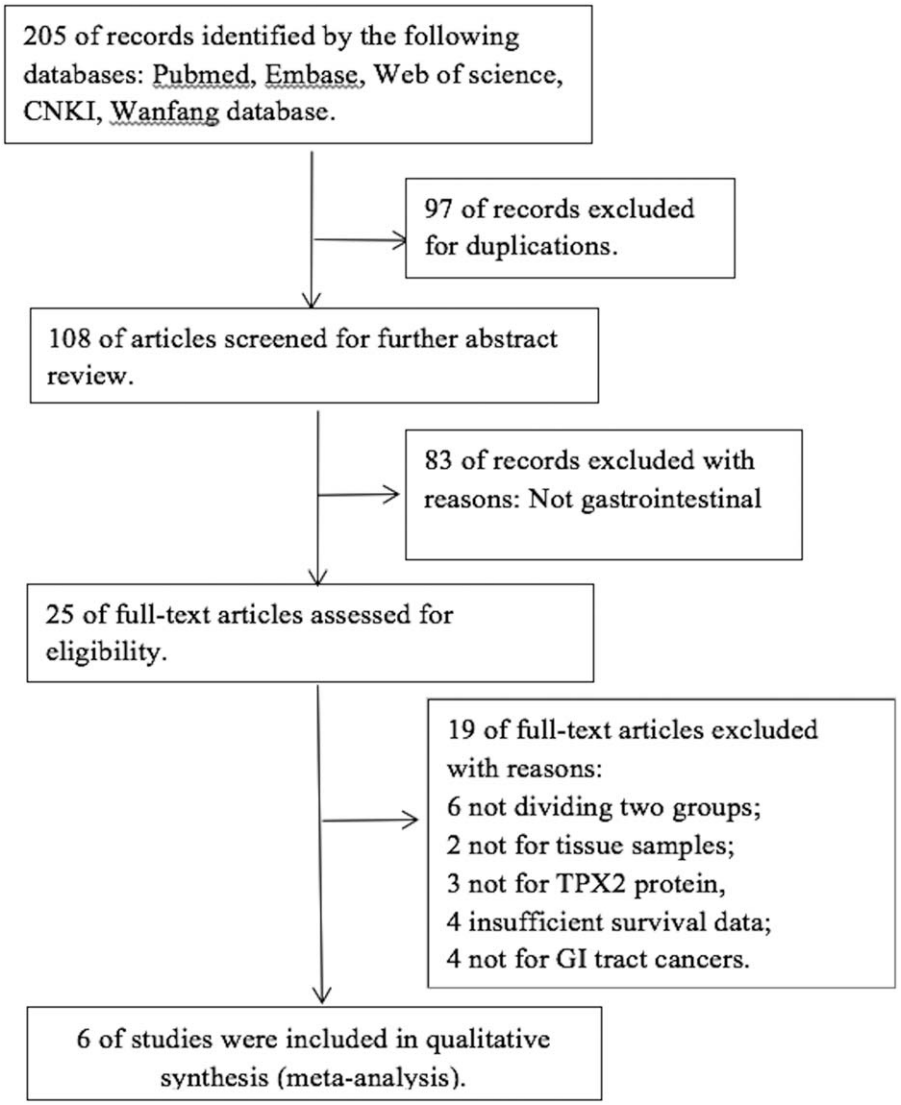

Figure 1. The steps for screening eligible articles.

3.2.3. TPX2 over-expression and clinicopathological factors in GC. There were only 3 studies[16–18] exploring the relationship between TPX2 level and clinicopathological features of GC. 3 studies were assessed the correlation between TPX2 expression and gender, lymph node metastasis (LNM) and tumor stage. Two studies were reported the association between TPX2 expression and depth of invasion and distant metastasis (DM) (Table 3).

The overall results shwed that there was significant association between TPX2 expression and depth of invasion (OR: 2.55, 95% CI: 1.66–3.93, fixed-effect model), LNM (OR: 2.67, 95% CI:

Table 1

Main characteristics of all studies included in the meta-analysis.

First author, Year	Cancer type	Country	Sample size	Over-expression (N, %)	Tumor stage	Follow-up	Criterion of over-expression	Detection method	Outcome measures	Multivariate analysis
Tomii et al, 2017[16]	GC	Japan	290	123 (42.41%)	I-IV	≥ 5 years	≥5% of tumor cells stained	IHC	DSS, RFI	Yes
Liang et al, 2016[17]	GC	China	115	54 (46.96%)	I-IV	< 5 years	overall staining index (2–9)	IHC	OS	Yes
Shao et al, 2016[18]	GC	China	106	71 (66.98%)	I-IV	≥ 5 years	final score more than zero	IHC	OS	Yes
Shen et al, 2016[19]	AEG	China	61	45 (73.77%)	I-III	< 5 years	nuclear staining of the tumor cells > 20%	IHC	OS, MFS	Yes
Hsu et al, 2014[20]	ESCC	China	96	40 (41.67%)	I-IV	≥ 5 years	≥median IHC score	IHC	OS, DFS	Yes
Wei et al, 2013[21]	CC	China	203	124 (61.08%)	I-IV	≥ 5 years	sum of staining score index (3–6)	IHC	OS, MFS	Yes

AEG = adenocarcinoma of the esophagogastric junction, CC = colon cancer, DFS = disease-free survival, DSS = disease-specific survival, ESCC = esophageal squamous cell carcinoma, GC = gastric cancer, IHC = immunohistochemistry, MFS = metastasis-free survival, OS = overall survival, RFI = relapse-free interval.

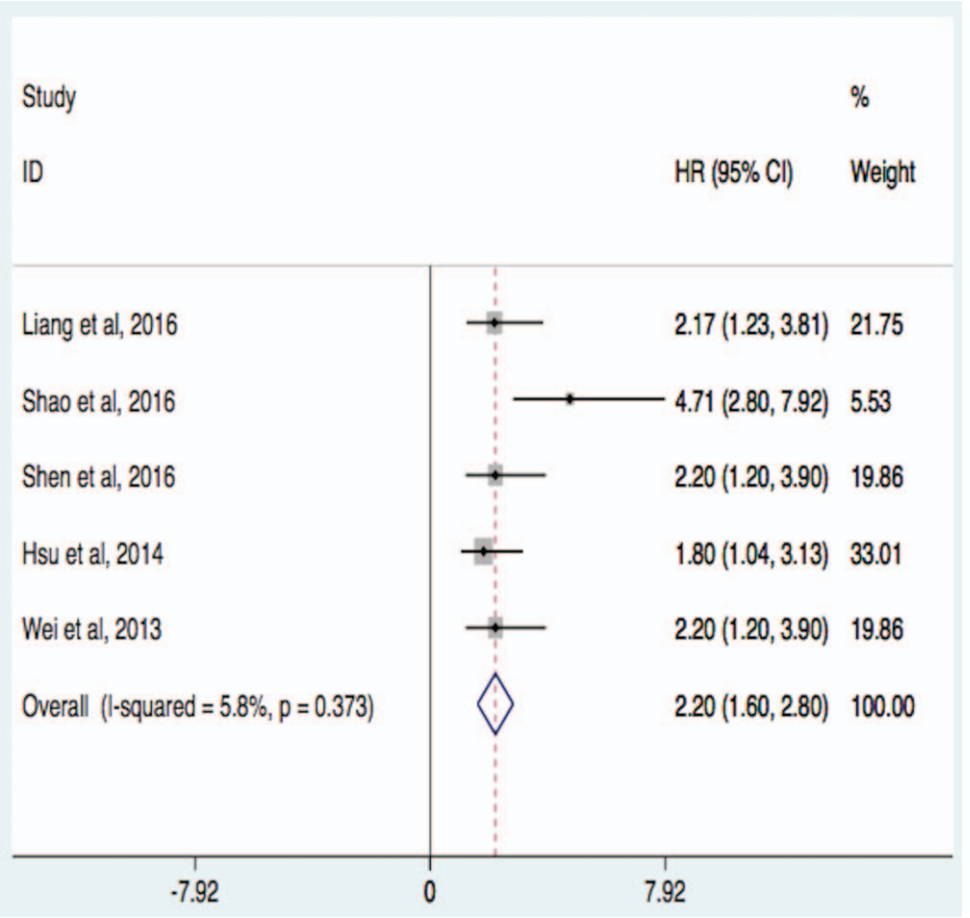

Figure 2. Meta-analysis of the pooled HRs of OS of patients with TPX2 over-expression in GI tract cancers. GI tract = gastrointestinal tract, HR = hazard ratio, OS = overall survival.

1.81–3.92, fixed-effect model), DM (OR: 4.52, 95% CI: 1.92–10.63, fixed-effect model), and tumor stage (OR: 2.67, 95% CI: 1.83–3.90, fixed-effect model) (Table 3). While TPX2 over-expression was not associated with gender (OR: 0.87, 95% CI: 0.59–1.29, fixed-effect model) in GC (Table 3).

3.2.4. Publication bias. No significant publication bias was found across- studies (Fig. 4). The test also showed a negative result ($P_{\text{Begg's test}} = 1.000$; $P_{\text{Egger's test}} = .154$).

3.2.5. Sensitivity analysis. The result for sensitivity analysis for OS was negative (Fig. 5) indicating stable results.

Table 2

Subgroup analysis of pooled HRs of OS of patients with TPX2 over-expression.

Stratified analysis	No. of studies	No. of patients	Pooled HR (95% CI)	*P* value	Heterogeneity	
					I^2 (%)	P_Q
[1] Cancer type						
GC[17,18]	2	221	2.68 (1.53–3.84)	<.001	66.8	.083
AEG[19]	1	61	2.20 (1.20–3.90)	.003	—	—
ESCC[20]	1	96	1.80 (1.04–3.13)	.037	—	—
CC[21]	1	203	2.20 (1.20–3.90)	.006	—	—
[2] Sample size						
≥ 100[17,18,21]	3	424	2.48 (1.60–3.36)	<.001	39.4	.192
< 100[19,20]	2	157	1.95 (1.12–2.78)	<.001	0.0	.648
[3] Follow-up time						
≥ 5 years[18,20,21]	3	405	2.21 (1.43–3.00)	<.001	52.9	.120
< 5 years[17,19]	2	176	2.18 (1.25–3.12)	<.001	0.0	.975

AEG = adenocarcinoma of the esophagogastric junction, CC = colon cancer, CI = confidence interval, ESCC = esophageal squamous cell carcinoma, GC = gastric cancer, HR = hazard ratio.

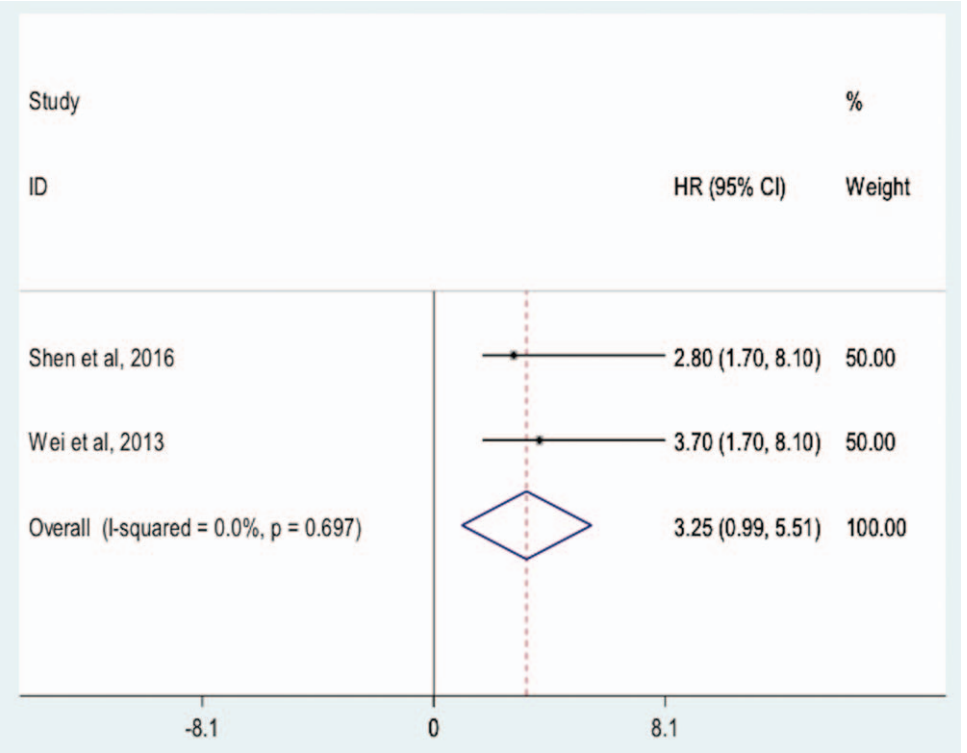

Figure 3. Meta-analysis of the pooled HRs of MFS of patients with TPX2 over-expression in GI tract cancers cancers. GI tract = gastrointestinal tract, HR = hazard ratio, MFS = metastasis-free survival, TPX2 = Targeting protein for Xenopus kinesin-like protein 2.

4. Discussion

TPX2, as an emerging candidate oncogene, was overexpressed in different types of human tumors.[22] It was reported to be abnormally expression in GI tract cancers, upregulation of TPX2 was further found to be associated with aggressive tumor biology and unfavorable prognosis in GI tract cancers. These findings indicated that TPX2 might be a candidate prognostic marker for GI tract cancers.

Our meta-analysis showed that TPX2 protein could serve as a promising biomarker for prognostication in GI tract cancers. High expression of TPX2 protein was significantly associated with unfavorable prognosis in GI tract cancers. From the pooled results, we found that patients with elevated level of TPX2 protein had a poorer OS when compared with low TPX2 protein expression patient. Subgroup meta-analysis was further conducted to confirm the prognostic value of TPX2 protein in GI tract cancers. Furthermore, the patients with high TPX2 protein expression tended to have worse MFS. The clinical significances of TPX2 protein in GC were also confirmed in this meta-analysis. Those results indicated that TPX2 protein might play an important role in the development and progression of GI tract cancers, which suggested the clinical significance of TPX2 as a promising prognostic marker in GI tract cancers.

The cellular functions and mechanisms of TPX2 in GI cancer have been elucidated in previous studies. A study by Liu et al[23] showed that TPX2 might contribute to tumor cell invasion through activating AKT signaling and subsequently increasing MMP2 and MMP9 in HCC.[24] Takahashi et al[25] reported that the AURKA/TPX2 axis could drive colon tumorigenesis cooperatively with MYC and identified inhibiting AURKA/TPX2 axis could be a novel synthetic lethal therapeutic approach for MYC-driven cancers. TPX2 played an important role in promoting tumorigenesis and metastasis of human CC.[21]

To the best of our knowledge, this was the first meta-analysis giving a comprehensive evaluation of prognostic value of TPX2

Table 3

Meta-analysis of TPX2 over-expression and clinicopathological features in gastric cancer.

Stratified analysis	No. of studies	No. of patients	Pooled OR (95% CI)	*P*-value	Heterogeneity		
					I^2 (%)	P_Q	Model
Gender (male vs. female)[16–18]	3	511	0.87 (0.59–1.29)	.50	0	.70	Fixed effects
Depth of invasion (T3–4 vs.T1–2)[16,18]	2	396	2.55 (1.66–3.93)	<.0001	1	.31	Fixed effects
Lymph node metastasis (yes vs. no)[16–18]	3	511	2.67 (1.81–3.92)	<.00001	0	.87	Fixed effects
Distant metastasis (yes vs. no)[17,18]	2	221	4.52 (1.92–10.63)	.0005	0	.71	Fixed effects
Tumor stage (III+IV vs. I+II)[16–18]	3	511	2.67 (1.83–3.90)	<.00001	0	.37	Fixed effects

CI = confidence interval, OR = odds ratio.

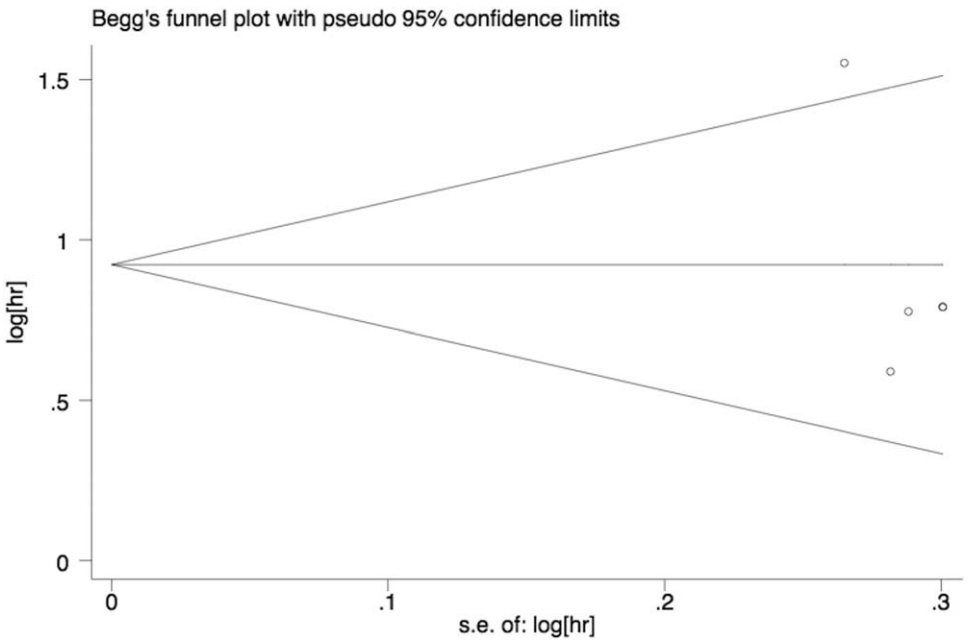

Figure 4. Publication bias test for OS. OS = overall survival.

protein in GI tract cancers. However, the result should be treated cautiously as there were several limitations in the present study. First, the sample size and number of studies included were relatively small. Especially, there were only 2 studies for MFS, 1 study for DSS, 1 study for RFI. The prognostic value of TPX2 protein in GI tract cancers was still needed to explore. Second, studies included in this meta-analysis were all from Asian countries, this might limit the application of the conclusions. Third, the cut-off values were not the same in those researches because it was hard to unify the standard across studies.

In conclusion, this study demonstrated that TPX2 protein could be applied for improving prognosis evaluation of GI tract cancers. Although only 6 studies were included, all the studies were retrieved and screened with strict criteria. In addition, the scattered results from individual studies could be comprehensively summarized. Certainly, prospective multi-center and well-designed studies

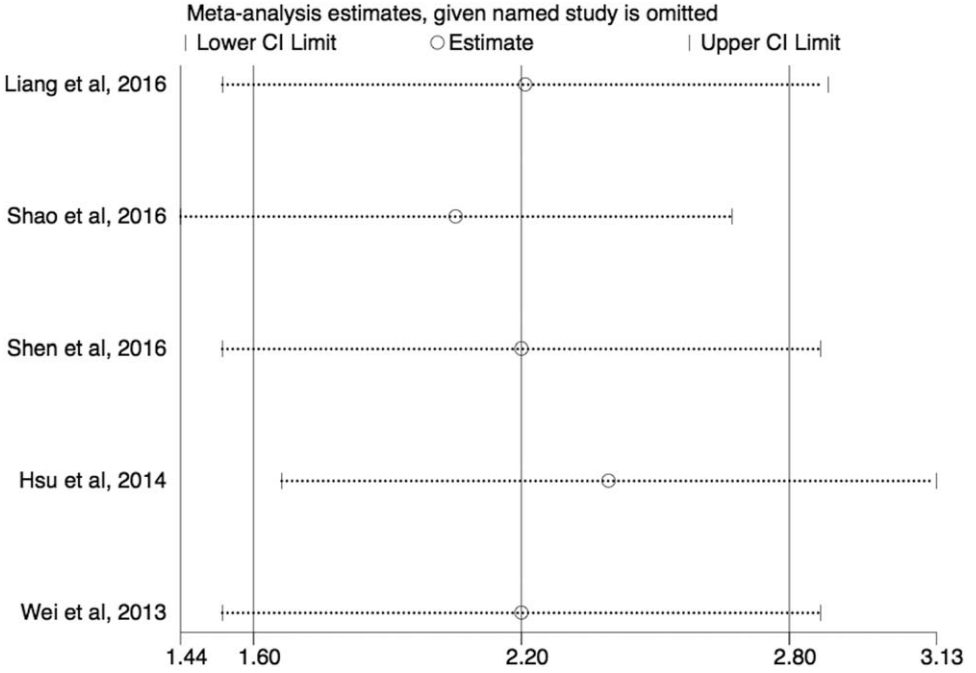

Figure 5. Sensitivity analysis for OS. OS = overall survival.

are warranted to confirm the prognosis value of TPX2 protein in GI tract cancers. We believed this conclusion would support and guide the further conduct of large-scale and multi-center clinical trial. In addition, the conclusion would provide guidance for further fundamental and clinical studies in other populations.

Author contributions

Conceptualization: Wanwei Liu.
Data curation: Wanwei Liu.
Formal analysis: Wanwei Liu.
Funding acquisition: Wanwei Liu.
Investigation: Wanwei Liu.
Methodology: Jiwei Xu.
Project administration: Jiwei Xu.
Resources: Caiyun Zhang.
Software: Caiyun Zhang.
Supervision: Wanwei Liu.
Validation: Wanwei Liu.
Visualization: Wanwei Liu.
Writing – original draft: Wanwei Liu.
Writing – review & editing: Wanwei Liu.

References

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10–29.
[2] Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
[3] Litwin MS, Tan HJ. The diagnosis and treatment of prostate cancer: a review. JAMA 2017;317:2532–42.
[4] Udomprasert A, Kangsamaksin T. DNA origami applications in cancer therapy. Cancer Sci 2017;108:1535–43.
[5] Quader S, Kataoka K. Nanomaterial-enabled cancer therapy. Mol Ther 2017;25:1501–13.
[6] Wittmann T, Boleti H, Antony C, et al. Localization of the kinesin-like protein Xklp2 to spindle poles requires a leucine zipper, a microtubule-associated protein, and dynein. J Cell Biol 1998;143:673–85.
[7] Wittmann T, Wilm M, Karsenti E, et al. TPX2, a novel xenopus MAP involved in spindle pole organization. J Cell Biol 2000;149:1405–18.
[8] Heidebrecht HJ, Buck F, Steinmann J, et al. p100: a novel proliferation-associated nuclear protein specifically restricted to cell cycle phases S, G2, and M. Blood 1997;90:226–33.
[9] Schneider MA, Christopoulos P, Muley T, et al. AURKA, DLGAP5, TPX2, KIF11 and CKAP5: five specific mitosis-associated genes correlate with poor prognosis for non-small cell lung cancer patients. Int J Oncol 2017;50:365–72.
[10] Chen QI, Cao B, Nan N, et al. TPX2 in human clear cell renal carcinoma: expression, function and prognostic significance. Oncol Lett 2016;11: 3515–21.
[11] Yang X, Liu G, Xiao H, et al. TPX2 overexpression in medullary thyroid carcinoma mediates TT cell proliferation. Pathol Oncol Res 2014;20: 641–8.
[12] Hsu CW, Chen YC, Su HH, et al. Targeting TPX2 suppresses the tumorigenesis of hepatocellular carcinoma cells resulting in arrested mitotic phase progression and increased genomic instability. J Cancer 2017;8:1378–94.
[13] Liu Q, Tu K, Zhang H, et al. TPX2 as a novel prognostic biomarker for hepatocellular carcinoma. Hepatol Res 2015;45:906–18.
[14] Liang B, Jia C, Huang Y, et al. TPX2 level correlates with hepatocellular carcinoma cell proliferation, apoptosis, and EMT. Dig Dis Sci 2015;60:2360–72.
[15] Huang Y, Guo W, Kan H. TPX2 is a prognostic marker and contributes to growth and metastasis of human hepatocellular carcinoma. Int J Mol Sci 2014;15:18148–61.
[16] Tomii C, Inokuchi M, Takagi Y, et al. TPX2 expression is associated with poor survival in gastric cancer. World J Surg Oncol 2017;15:14.
[17] Liang B, Zheng W, Fang L, et al. Overexpressed targeting protein for Xklp2 (TPX2) serves as a promising prognostic marker and therapeutic target for gastric cancer. Cancer Biol Ther 2016;17:824–32.
[18] Shao C, Duan C, Wang J, et al. Expression of microtubule-associated protein TPX2 in human gastric carcinoma and its prognostic significance. Cancer Cell Int 2016;16:79.
[19] Shen L, Xu YM, Ding SG, et al. Expression of TPX2 and its relationship with invasion and metastasis in esophageal gastric junction adenocarcinoma. Chin J Clin (Electronic Ed) 2016;10:1505–10.
[20] Hsu PK, Chen HY, Yeh YC, et al. TPX2 expression is associated with cell proliferation and patient outcome in esophageal squamous cell carcinoma. J Gastroenterol 2014;49:1231–40.
[21] Wei P, Zhang N, Xu Y, et al. TPX2 is a novel prognostic marker for the growth and metastasis of colon cancer. J Transl Med 2013;11:313.
[22] Neumayer G, Belzil C, Gruss OJ, et al. TPX2: of spindle assembly, DNA damage response, and cancer. Cell Mol Life Sci 2014;71:3027–47.
[23] Liu Q, Yang P, Tu K, et al. TPX2 knockdown suppressed hepatocellular carcinoma cell invasion via inactivating AKT signaling and inhibiting MMP2 and MMP9 expression. Chin J Cancer Res 2014;26:410–7.
[24] Aref AM, Hoa NT, Ge L, et al. HCA519/TPX2: a potential T-cell tumor-associated antigen for human hepatocellular carcinoma. Onco Targets Ther 2014;7:1061–70.
[25] Takahashi Y, Sheridan P, Niida A, et al. The AURKA/TPX2 axis drives colon tumorigenesis cooperatively with MYC. Ann Oncol 2015;26: 935–42.