Cancer Management and Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Prognostic role and clinical significance of trophoblast cell surface antigen 2 in various carcinomas

This article was published in the following Dove Press journal:
Cancer Management and Research

Peng Xu*
Yang Zhao*
Kang Liu*
Shuai Lin
Xinghan Liu
Meng Wang
Pengtao Yang
Tian Tian
Yu-yao Zhu
Zhijun Dai

Department of Oncology, The Second Affiliated Hospital, Xi'an Jiaotong University, Xi'an, China

*These authors contributed equally to this work

Introduction: Trophoblast cell surface antigen 2 (TROP2) has been linked to disease prognosis in various human cancers and plays a critical role in tumor development, progression, and metastasis. A number of relevant studies have been published on this topic. A meta-analysis of the latest literature to evaluate the value of TROP2 as a predictive prognosticator of cancer was performed.

Methods: Several online databases were searched, and relevant articles were retrieved. Overall and subcategory meta-analyses were performed, and results were collated.

Results: Twenty-seven articles, including 29 studies, were included, involving 4,852 cancer patients, and results showed that the above-baseline expression of TROP2 was significantly associated with poorer overall survival (OS) (pooled hazard ratio [HR]: 1.84, 95% confidence interval [CI]: 1.45–2.35), disease-free survival (DFS) (pooled HR: 2.77, 95% CI: 1.73–4.42), and progression-free survival (PFS) (pooled HR: 1.71, 95% CI: 1.25–2.35). The following clinical characteristics were also significantly linked with TROP2 overexpression: moderate/poor differentiation (pooled HR: 3.03, 95% CI: 1.99–4.63), distant metastasis (pooled HR: 2.46, 95% CI: 1.05–5.75), lymph node metastasis (pooled HR: 2.47, 95%: CI 1.72–3.56), and advanced TNM stage (pooled HR: 2.02, 95% CI: 1.38–2.95).

Conclusion: TROP2 overexpression was predictive of poor prognosis in human cancers and may be an independent prognostic predictive biomarker. Further studies should be performed to confirm the significance of TROP2 in clinical practice.

Keywords: TROP2, carcinomas, prognosis, meta-analysis

Introduction

Cancer is a major disease burden worldwide, with high morbidity and mortality rates compounded by the economic burden of maintaining patient quality-of-life and lengthening survival period.[1,2] To date, many predictive biomarkers with excellent prognostic utility have been discovered for various cancers. Targeted molecular therapy and cancer immunotherapy have been introduced to improve disease management.[3–6] One such biomarker is a cell surface protein known as trophoblast cell surface antigen 2 (TROP2),[7] also called "tacstd2", "m1s1 protein", "tumor-associated calcium signal transducer 2", "tumor-associated antigen ga733-1", "ga733-1 antigen", "membrane component 1 surface marker 1", "epithelial glycoprotein 1", and "gastrointestinal antigen 733-1".[8] This protein shows relatively low expression in normal epithelial cells and is overexpressed in various types of human cancers.[9–23] Overexpression of TROP2 in cancer has been linked to disease aggression and shorter overall survival (OS).

Correspondence: Zhijun Dai
Department of Oncology, The Second Affiliated Hospital, Xi'an Jiaotong University, No. 157 West 5 Road, Xi'an 710004, Shaanxi Province, China
Tel +86 029 8767 9513
Email dzj0911@126.com

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/CMAR.S147033

Several clinical studies have demonstrated that therapies targeting TROP2-benefited cancer patients by inhibiting TROP2 expression[24–33] and have explored this protein as a potential predictor of cancer prognosis. However, due to small sample size, the results were not categorically conclusive.[13,15,23,34–46] The first meta-analysis about TROP2 was published 1 year ago,[47] which indicated that TROP2 overexpression was associated with poor survival in human solid tumors. Some new relevant studies have been published since then, therefore, we performed this meta-analysis to systematically review and gather more powerful evidence to verify the relationship between TROP2 overexpression and clinical characteristics/prognosis in patients with a variety of human cancers.

Methods

Search strategy

Articles related to TROP2 and carcinomas were retrieved from online databases: Embase, PubMed, ISI Web of Science, China National Knowledge Infrastructure (CNKI), and WanFang Data Knowledge Service Platform (WanFang Data). The Medical Subject Headings (MeSH) search terms were as follows: "tacstd2" or "m1s1 protein" or "tumor-associated calcium signal transducer 2" or "trop2" or "tumor-associated antigen ga733-1" or "ga733-1 antigen" or "trop-2" or "trophoblast cell surface antigen 2" or "membrane component 1 surface marker 1" or "epithelial glycoprotein 1" or "gastrointestinal antigen 733-1" and "cancer" or "tumor" or "carcinoma" or "neoplasm". We additionally retrieved references cited in the articles and included them in the study. The last search was performed on September 23, 2017.

Selection criteria

Studies that 1) investigated the relationship between TROP2 and patient prognosis; 2) provided available data to obtain or calculate risk ratio (RR) or hazard ratio (HR) for survival and 95% confidence interval (CI); and 3) had clear statement about TROP2 expression state as "high" and "low" or "positive" and "negative" were included in this meta-analysis.

Exclusion criteria were (1) published letters, editorials, abstracts, reviews, case reports and expert opinions; (2) experiments not performed on patients; and (3) articles without the HRs and 95% CI or K–M survival curves about patients' prognostic outcomes.

Data extraction

The following data were extracted from each publication: first author, year of publication, country, tumor type, clinical stage, sample size, age of patients, analysis method, follow-up period, outcome, parameter cutoff values, survival analysis, estimates such as HRs or RRs concerning the overexpression of TROP2 in terms of OS, disease-free survival (DFS)/progression-free survival (PFS), disease recurrence (DR), and patient clinical characteristics. The HRs or RRs and their 95% CIs were extracted from the original papers directly if available (23 articles, 25 studies). Otherwise, relevant data such as sample number in test groups, log-rank statistics, and p value were used to calculate the variable (3 studies[48–50]). Alternatively, the approximate HRs (1 study[15]) were calculated according to the Zhou ZR's statistical method from the Kaplan–Meier survival curves.[51] The Engauge Digitizer version 4.1 was used for this analysis.

Statistical analysis

The extracted HRs/RRs were summarized as pooled HR and 95% CI values, using Stata, version 12.0. The fixed-effects model was used at first to calculate the heterogeneity and construct forest plots. For inconsistency tests, $I^2 > 50\%$ and $p < 0.05$ were considered statistically significant. Larger values of I^2 indicated higher heterogeneity. The fixed-effects model was subsequently used when heterogeneity was not significant (<50%).[52] We conducted subgroup analysis and sensitivity analysis to compensate for statistical heterogeneity. Graphical funnel plots were generated, and Begg's test and Egger's test were performed to assess the extent of publication bias by visual inspection or by quantitative evaluation.[53,54]

Results

Study selection and characteristics

As shown in Figure 1, a total of 1,155 articles were identified initially. After excluding 515 duplicates, titles/abstracts of 640 studies were reviewed. Of these, 167 articles were not related to the research objective, 435 articles were not performed on patients and 3 were systematic reviews. Thirty-five articles were reviewed further. Three articles were not available to get full text, and five papers did not provide applicable data for meta-analysis. We handpicked the remaining 27 articles eligible for this meta-analysis. The studies by Inamura estimated the roles of TROP2 in cancer prognosis among 3 different lung cancer subtypes (adenocarcinoma, squamous cell carcinoma, and high-grade neuroendocrine tumor), and thus it was regarded as 3 independent studies.[55] The main characteristics of these studies are presented in Table 1. All included studies were published from 2006 to 2017. There were 17 studies from China, 5 from Japan, 3 from Austria, 3 from Italy, and 1 from South Korea. A total

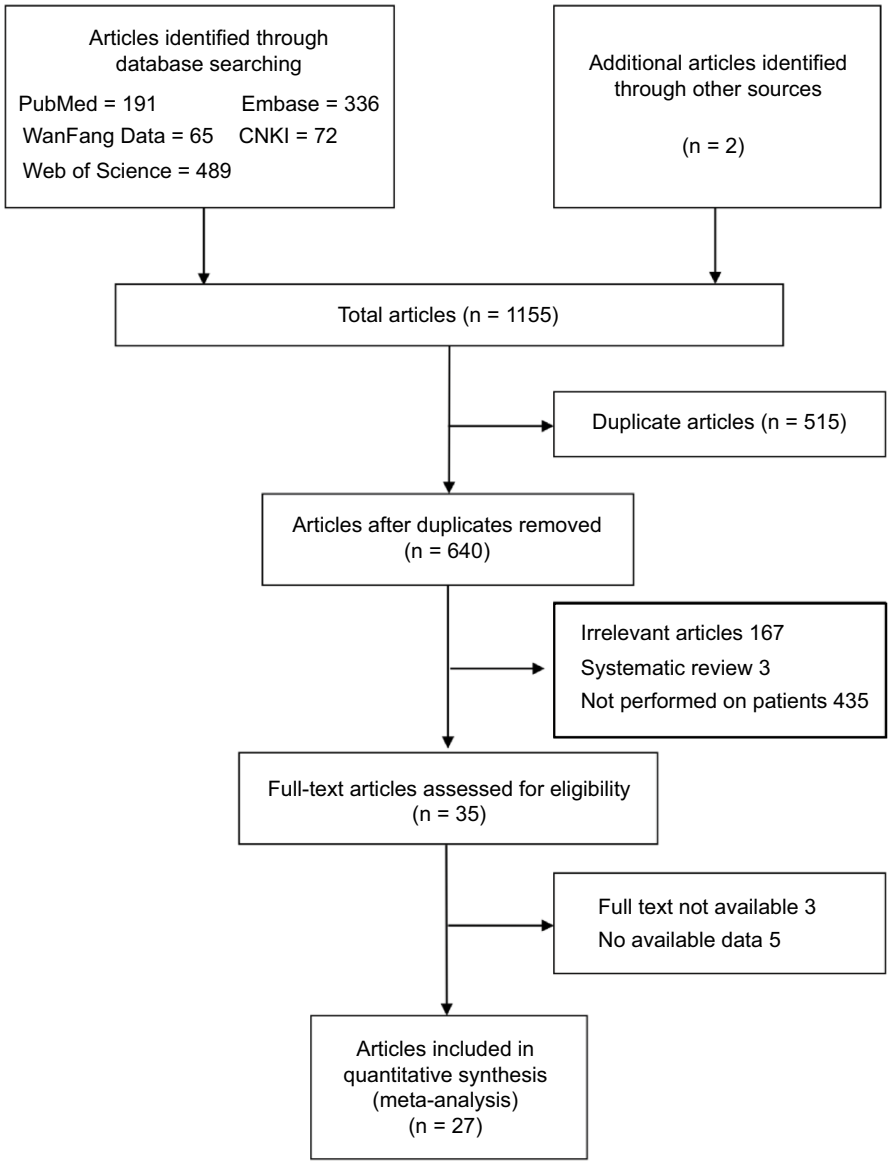


Figure 1 Flow diagram of study selection.

of 4,852 patients were enrolled (sample size: maximum: 702, minimum: 47, and mean: 167), and 16 carcinoma types were analyzed, including lung cancer (6, different subtypes), colorectal cancer (4), bladder cancer (2), breast cancer (2), gallbladder cancer (2), gastric cancer (2), ovarian carcinoma (2), cervical cancer (1), endometrioid endometrial carcinoma (1), extranodal natural killer (NK)/T cell lymphoma/nasal type (1), hilar cholangiocarcinoma (1), laryngeal squamous cell carcinoma (1), nasopharyngeal carcinoma (1), pancreatic cancer (1), pituitary adenomas (1), and squamous cell carcinoma of oral cavity (1). A total of 47 HRs/RRs were extracted from 29 studies, including 26 for OS, 6 for DFS,[15,34,35,41,44,56] 5 for PFS,[13,34,35,39,57] 4 for DR,[38,49,57,58] 3 for CSS,[55] and 1 for DFS/PFS.[59] Study quality was evaluated by using the Newcastle–Ottawa Scale (NOS), and the quality scores ranged from 6 to 9, suggesting high methodological quality.

Relationship between the expression of TROP2 and patients' OS

Our analysis revealed a positive link between TROP2 overexpression and OS (pooled HR: 1.84, 95% CI: 1.45–2.35), with heterogeneity ($I^2 = 67.3\%$; $p = 0.000$), indicating that higher level of TROP2 expression could predict shorter OS outcomes (Figure 2 and Table 2). In subgroup analysis according to geographical location, HRs were greater than 1.0 in the population from China, Austria, with low heterogeneity, in agreement with previous studies (China: $I^2 = 43.0\%$, $p = 0.044$; Austria: $I^2 = 0.0\%$, $p = 0.762$) (Figure 2). While HRs of Japan and

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

Author	Year	Tumor type	Country	Sample size	Age of the patients (years, median and range)	Clinical stage of tumor	Method	Cutoff value	Follow-up (months) (median and range)	Outcome	Survival analysis	NOS
Ambrogi et al[49]	2014	Breast cancer	Italy	702	NA	TNM $T_{1-3}N_xM_0$	IHC	Low ≤ 5% High > 86%	96	OS DR	Univariate analysis Multivariate analysis	6
Bignotti et al[34]	2010	Ovarian carcinoma	Italy	104	55 (47–69)	FIGO stage WHO	IHC	Low = score 0–2 High = score 3	28.5 (7.3–77.7)	OS DFS PFS	Univariate analysis Multivariate analysis	8
Bignotti et al[35]	2012	Endometrioid endometrial carcinoma	Italy	103	NA	FIGO stage WHO	IHC	Low = score 0–2 High = score 3	48.7 (6.1–124.9)	OS DFS PFS	Univariate analysis Multivariate analysis	7
Chen et al[36]	2014	Gallbladder cancer	China	93	NA	TNM I–IV	IHC	Low = score 0–3 High = score 4–9	NA	OS	Univariate analysis Multivariate analysis	8
Chen et al[37]	2013	Extranodal NK/T cell lymphoma/nasal type	China	90	50.3 (25–71)	Ann Arbor Stage I–IV	IHC	Low = score 0–3 High = score 4–9	NA	OS	Multivariate analysis	8
Chen et al[59]	2014	Pituitary adenomas	China	72		NA	IHC	Low TIS ≤ 4 High TIS = 5–9	NA	DFS/PFS	Multivariate analysis	6
Fang et al[38]	2009	Colon cancer	China	620	59 (15–86)	TNM I–IV	IHC	Immunoreactivity rating of II or III; moderate/strong	52 (1–130)	OS DR	Multivariate analysis	9
Fong et al[39]	2008	Pancreatic cancer	Austria	197	65 (37–91)	TNM I–IV	IHC	Low = score 0–4 High = score 5–12	9 (1–68)	OS PFS	Multivariate analysis	7
Fong et al[40]	2008	Squamous cell carcinoma of oral cavity	Austria	90	63.4 (25–85)	TNM I–IV	IHC	Low = score 0–4 High = score 5–12	23.8 (1–245)	OS	Univariate analysis Multivariate analysis	8
Guan et al[41]	2015	Nasopharyngeal carcinoma	China	58	45 (24–72)	TNM I–IV	IHC	Low = score 0–1.5 High = score 2–3	96 (1–161)	OS DFS	Univariate analysis Multivariate analysis	8
Inamura[55]	2017	Lung cancer ADC	Japan	270	NA	The 7th edition of the AJCC-TNM staging system	IHC	No/low: In intensity 1 < 50% and intensity 2 < 10% High: intensity 1 ≥ 50% or intensity 2 ≥ 10%	13.0 (9.1–15.5) years	CSS OS	Univariate analysis Multivariate analysis	8
Inamura[55]	2017	Lung cancer SqCC	Japan	201	NA	The 7th edition of the AJCC-TNM staging system	IHC	No/low: in intensity 1 < 50% and intensity 2 < 10% High: intensity 1 ≥ 50% or intensity 2 ≥ 11%	5.0 (3.1–6.3) years	CSS OS	Univariate analysis Multivariate analysis	8
Inamura[55]	2017	Lung cancer HGNET	Japan	115	NA	The 7th edition of the AJCC-TNM staging system	IHC	No/low: in intensity 1 < 50% and intensity 2 < 10% High: intensity 1 ≥ 50% or intensity 2 ≥ 12%	5.8 (3.1–8.2) years	CSS OS	Univariate analysis Multivariate analysis	8
Jiang et al[48]	2013	Lung cancer NSCLC	China	87	(58.6 ± 9.8)	TNM III_b IV	IHC	Low = score 0–3 High = score 4–9	15.197 (13.688–16.706)	OS	Multivariate analysis	6

Kobayashi et al[43]	2010	Lung cancer ADC	Japan	130	60.7 (38–82)	Noguchi Classification A–F	IHC	Low = score 0–4 High = score 5–12	NA	OS	Multivariate analysis	8
Li[60]	2017	Gallbladder cancer	China	88	NA	TNM I–IV	IHC	Low = score 0–3 High = score 4–12	36.75	OS	Univariate analysis Multivariate analysis	6
Lin et al[50]	2013	Breast cancer	China	82	NA	TNM I–IV	IHC	Intensity scores: low: 0–2, high: 3–6	NA	OS	Univariate analysis Multivariate analysis	7
Liu et al[13]	2013	Cervical cancer	China	160	43.6 ± 11.5	FIGO stage	IHC	Low = score 0 High = score 1–9	60 (9.6–82.5)	OS PFS	Univariate analysis Multivariate analysis	9
Mühlmann et al[44]	2008	Gastric carcinoma	Austrian	104	67 (30–94)	TNM I–IV	IHC	Low = score 0–4 High = score 5–12	Intestinal-type carcinoma 52 (1–163); diffuse-type carcinoma 16 (1–54)	OS DFS	Univariate analysis Multivariate analysis	9
Ning[45]	2012	Hilar cholangiocarcinoma	China	70	59 (39–79)	TNM I–IV	IHC QRT-PCR	Low = score 0–4 High = score 5–12	37 (5–115)	OS	Univariate analysis Multivariate analysis	9
Ohmachi et al[46]	2006	Colorectal cancer	Japan	74	High 66.6 ± 3.8 Low 67.5 ± 2.8	NA	QRT-PCR (74) IHC (34)	>95% of the expression values of the normal samples	NA	OS	Univariate analysis Multivariate analysis	7
Pak et al[15]	2012	Lung cancer: NSCLC (ADC and SqCC)	South Korea	164	63.4 (42–81)	TNM I–IV	IHC	Low = score 0–4 High = score 5–12	39.4 (1–123)	OS DFS	Multivariate analysis	7
Wu[61]	2012	Laryngeal squamous cell carcinoma	China	109	60.8 (29–87)	TNM I–IV	IHC QRT-PCR	Low = score 0 High = score 1–9	35.1 (42.9 ± 29.9)	OS	Univariate analysis Multivariate analysis	9
Xu[62]	2009	Colon cancer	China	80	High 58.9 ± 11.2 Low 57.0 ± 11.0	TNM II III	QRT-PCR	The median of the expression level of colorectal carcinoma	38.5 (7–71)	OS	Univariate analysis Multivariate analysis	6
Xu et al[56]	2016	Ovarian carcinoma	China	128	52.6 (25–82)	FIGO stage WHO	IHC	Low = score 0–4 High = score 5–12	NA	OS DFS	Univariate analysis Multivariate analysis	8
Yuan et al[58]	2015	Bladder cancer	China	112	Team A (34–91) Team B (49–84)	TNM I–IV	IHC	Low = score 0–4 High = score 5–9	NA	DR	Univariate analysis Multivariate analysis	7
Zhang et al[57]	2017	Bladder cancer NMIBC	China	102	66.1 (41–88)	TNM Ta T1	IHC	Low IS ≤ 1 High IS = 2–9 IS:staining index	47 (6–103)	DR PFS	Univariate analysis Multivariate analysis	8
Zhao[63]	2016	Colon cancer	China	47	35-90 (61.6 ± 9.8)	Dukes stage A–D	IHC	Low = score 0–3 High = score 4–9	NA	OS	Univariate analysis Multivariate analysis	7
Zhao[64]	2015	Gastric cancer	China	600	NA	TNM I–IV	IHC QRT-PCR	Low = score 0–130 High = score 131–300	NA	OS	Univariate analysis Multivariate analysis	6

Note: TIS = PS × IS.

Abbreviations: NOS, Newcastle–Ottawa Scale; FIGO, International Federation of Gynecology and Obstetrics; WHO, World Health Organization; AJCC, The American Joint Committee on Cancer; ADC, adenocarcinoma; CSS, cancer-specific survival; DR, disease recurrence; IHC, immunohistochemistry; HGNET, high-grade neuroendocrine tumor; DFS, disease-free survival; QRT-PCR, quantitative real-time–polymerase chain reaction; SqCC, squamous cell carcinoma; NSCLC, non-small-cell lung cancer; NMIBC, non-muscle invasive bladder cancer; NA, not available; OS, overall survival; PFS, progression-free survival; TIS, total immunostaining score; PS, proportion score; IS, intensity score.

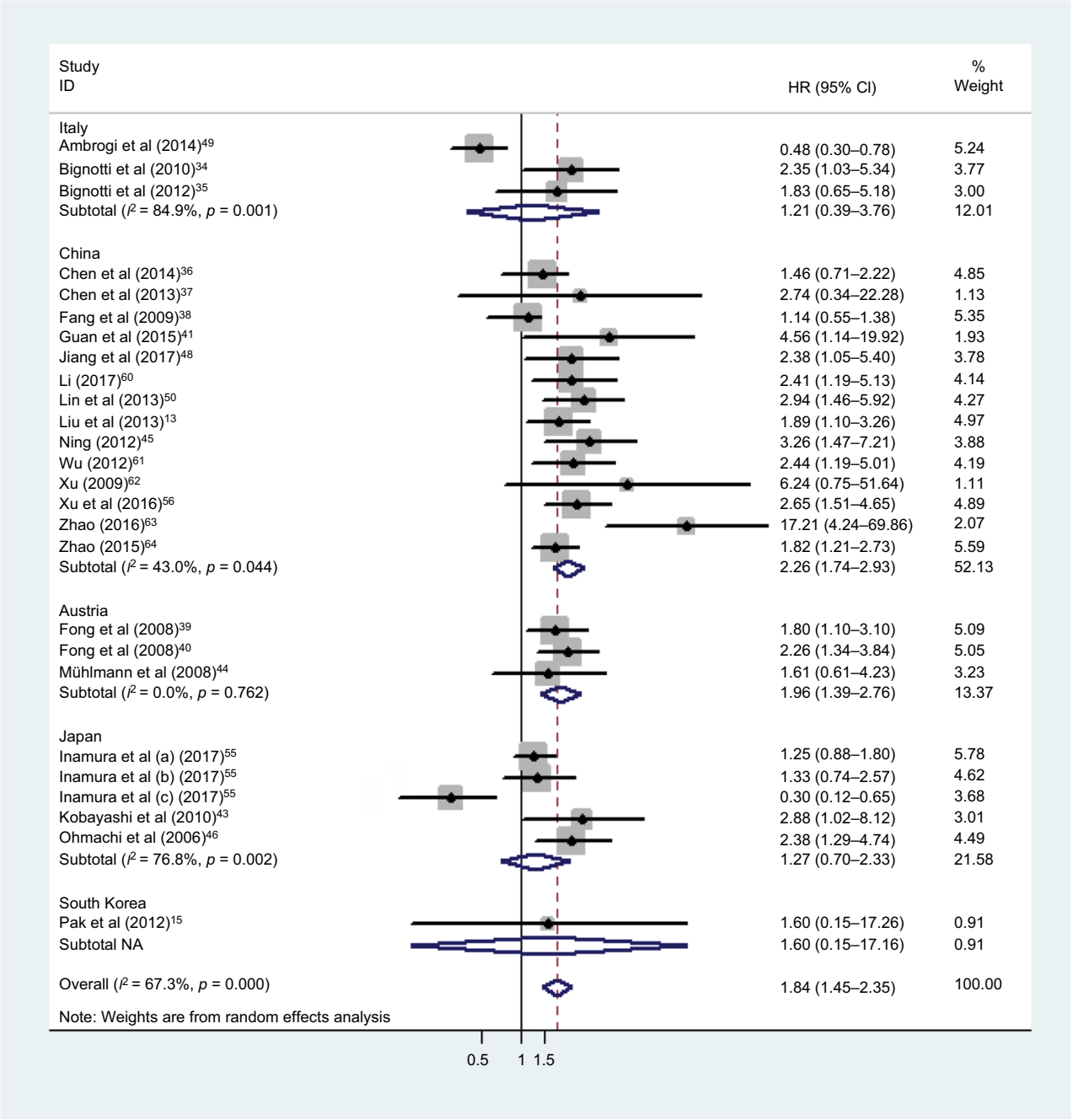


Figure 2 Overall analysis and subgroup analysis about patients' overall survival.
Notes: The segments represent the 95% CI of each study. The diamonds represent the overall effect sizes, and the diamond widths represent the overall 95% CIs.
Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable.

Italy were not statistically significant (Figure 2), the results of the sensitivity analysis showed that the association between TROP2 and OS was stable, and the studies by Ambrogi et al,[49] Inamura et al[55] affected results greatly (Figure 3). After excluding these 2 studies (Ambrogi and Inamura (c)) one by one, the heterogeneity decreased significantly (without Ambrogi: I^2 = 51.8%, p = 0.002; without Ambrogi and Inamura (c): I^2 = 28.1%, p = 0.100) (Figure 4A and B). The publication bias evaluation is shown in Figure 5 (Egger's test: p = 0.048; Begg's test: p = 0.217). According to Shi's conclusions,[65] we thought that there is no significant publication bias.

Relationship between TROP2 expression and patient outcomes

There were 6 studies, 5 studies, 4 studies, 3 studies, and one related to the association between TROP2 expression and DFS, PFS, DR, CSS, and DFS/PFS, respectively. We found that the overexpression of TROP2 was a potential negative

Table 2 Results of meta-analysis

Overall survival	Number of studies	Number of patients	Pooled HR (95% CI)	*I*-squared (I^2)	Chi-squared heterogeneity test (P)	Analysis model
Overall	26	4566	**1.84 (1.45–2.35)**	67.3%	**0.000**	Random
Subgroup						
Austria	3	391	**1.96 (1.39–2.76)**	0.0%	0.762	Random
China	14	2312	**2.26 (1.74–2.93)**	43.0%	**0.044**	Random
Italy	3	909	1.21 (0.39–3.76)	84.9%	**0.001**	Random
Japan	5	790	1.27 (0.70–2.33	76.8%	**0.002**	Random
South Korea	1	164	–	–	–	–
Without Ambrogi[49]	25	3864	**1.94 (1.58–2.39)**	51.8%	**0.002**	Random
Without Ambrogi[49] and Inamura (c)[55]	24	3749	**2.00 (1.68–2.36)**	28.1%	0.100	Random
Outcomes						
DFS	6	661	**2.77 (1.73–4.42)**	20.8%	0.277	Random
PFS	5	666	**1.71 (1.25–2.35)**	0.0%	0.809	Random
DR	4	1536	1.44 (0.59–3.52)	86.7%	**0.000**	Random
CSS	3	586	0.65 (0.24–1.76)	75.7%	**0.016**	Random
DFS/PFS	1	72	–	–	–	–
Characteristics						
Age: (elderly/nonelderly)	20	2783	0.94 (0.79–1.11)	0.0%	0.778	Fixed
Differentiation: (moderate + poor/well)	16	2237	**3.03 (1.99–4.63)**	61.2%	**0.001**	Random
Distant metastasis: (present/absent)	5	970	**2.46 (1.05–5.75)**	52.7%	0.076	Random
Lymph node metastasis: (present/absent)	17	2081	**2.47 (1.72–3.56)**	59.9%	**0.001**	Random
TNM stage: (III + IV/I + II)	15	2243	**2.02 (1.38–2.95)**	59.9%	**0.002**	Random
Sex: (male/female)	19	2627	1.08 (0.90–1.29)	0.0%	0.659	Fixed

Note: Bold values indicate statistical significance.
Abbreviations: CI, confidence interval; TNM, The TNM Classification of Malignant Tumours; CSS, cancer-specific survival; DR, disease recurrence; DFS, disease-free survival; HR, hazard ratio; PFS, progression-free survival.

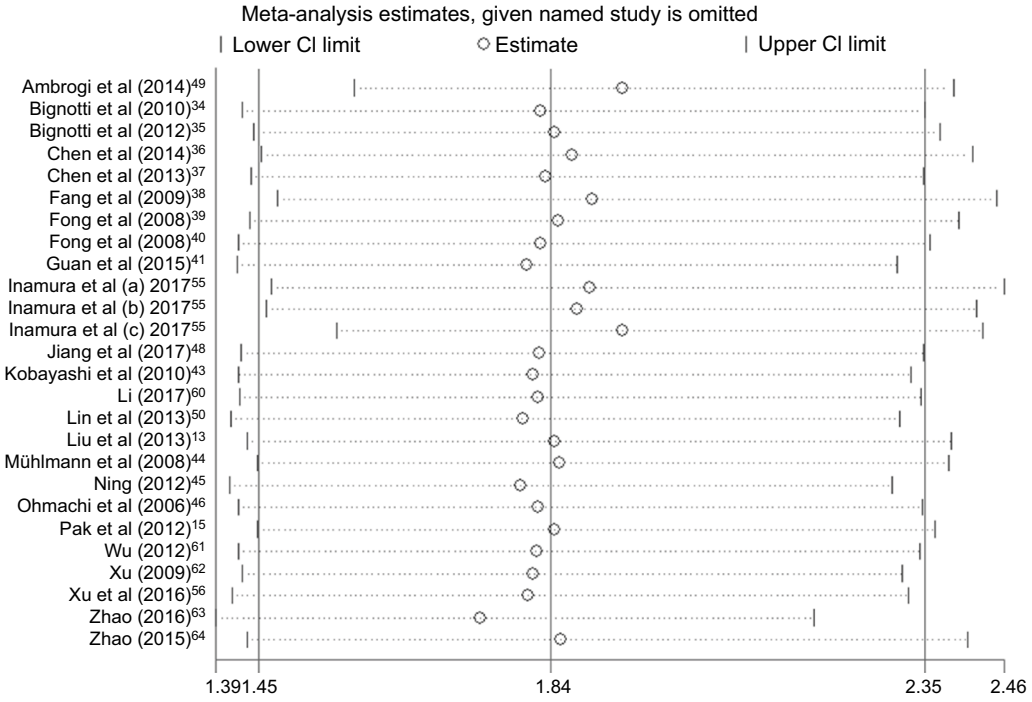


Figure 3 Sensitivity analysis to assess the effect of each study of the meta-analysis about the overall survival (random model).
Abbreviation: CI, confidence interval.

prognostic factor for DFS (pooled HR: 2.77, 95% CI: 1.73–4.42) and PFS (pooled HR: 1.71, 95% CI: 1.25–2.35), with low heterogeneity between studies (DFS: I^2 =20.8%, p = 0.277; PFS: I^2 =0.0%, p = 0.809; random model) (Figure 6A). The association between TROP2 and DR or CSS was not significant (DR: pooled HR: 1.44, 95% CI: 0.59–3.52; I^2 =86.7%, p = 0.000; CSS: pooled HR: 0.65, 95% CI: 0.24–1.76; I^2 =75.7%, p = 0.016; random model)

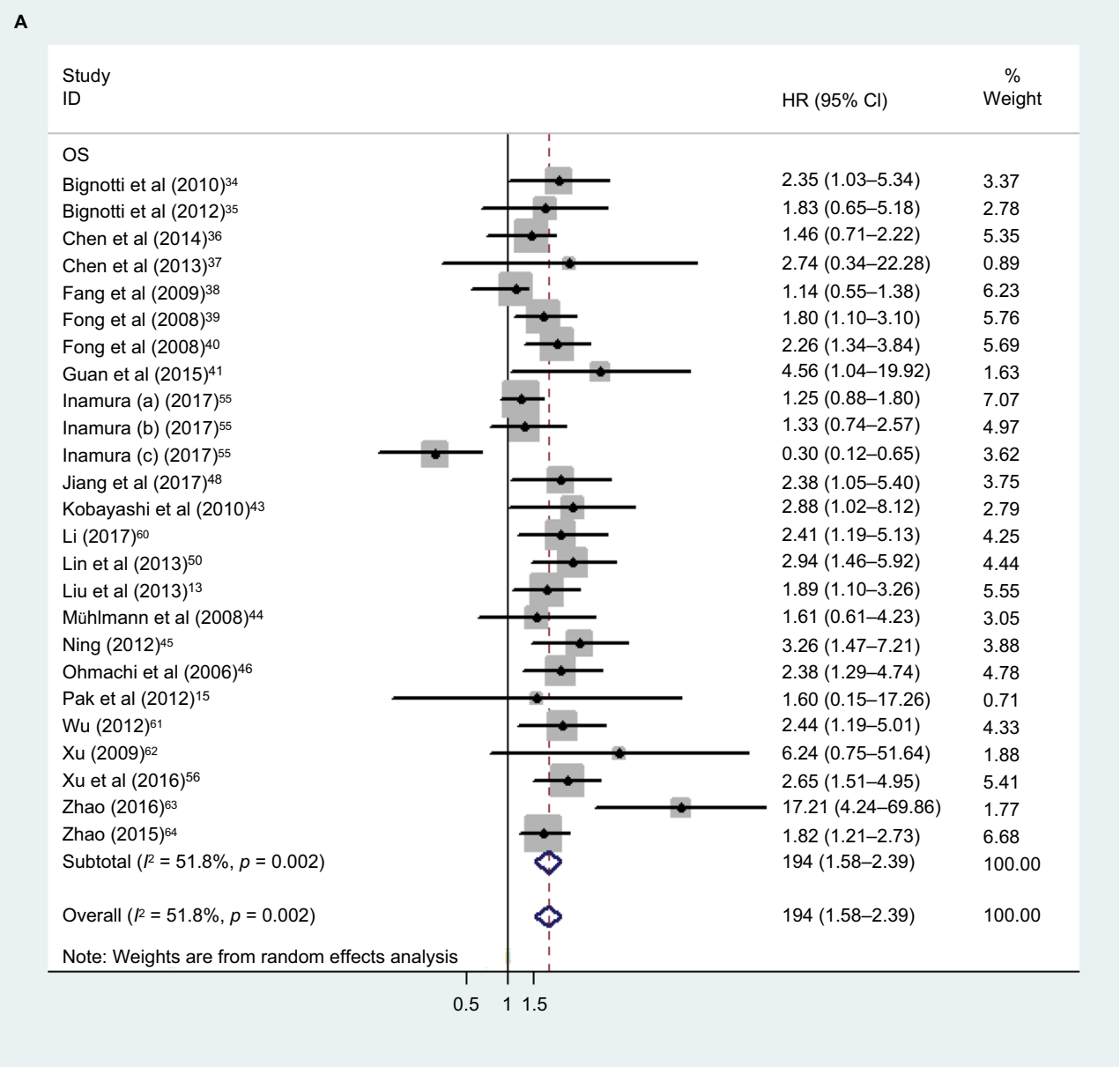


Figure 4 (*Continued*)

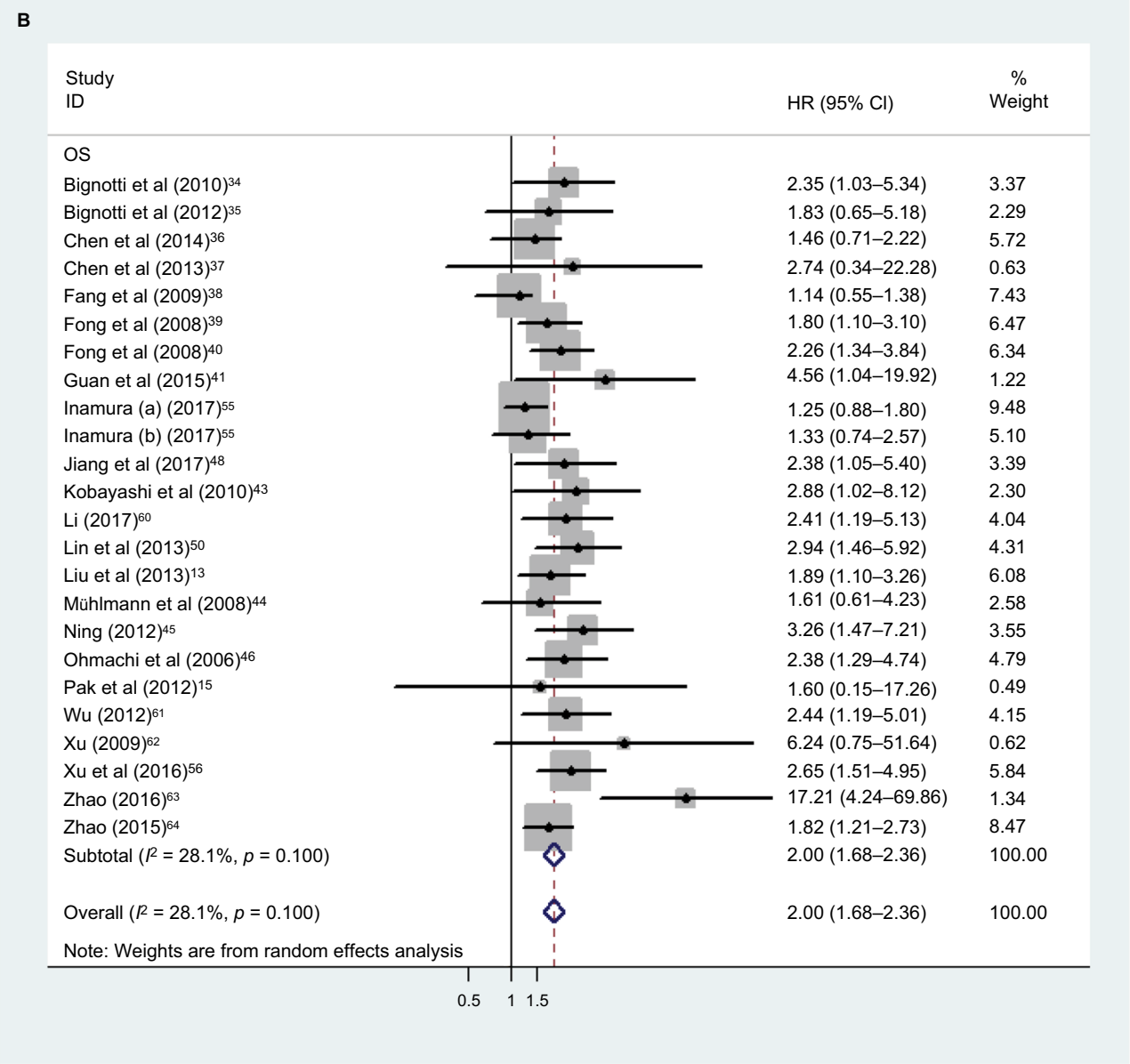


Figure 4 Overall analysis of the correlation between TROP2 expression and patients' OS after excluding the significant studies which held opposite views.
Notes: (**A**) Without Ambrogi[49] and (**B**) without Ambrogi[49] and Inamura (c).[55]
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

(Figure 6A). The publication bias analyses were performed, and no significant publication bias was found (Egger's test: $p = 0.297$; Begg's test $p = 0.624$) (Figure 6B).

Relationship between TROP2 overexpression and clinical characteristics

Table 3 shows the patient clinical characteristics, including sex, age, lymph node metastasis, distant metastasis, TNM stage, and differentiation. Our results (Table 2) showed that TROP2 overexpression correlated with moderate/poor differentiation (pooled HR: 3.03, 95% CI: 1.99–4.63), distant metastasis (pooled HR: 2.46, 95% CI: 1.05–5.75), lymph node metastasis (pooled HR: 2.47, 95%: CI 1.72–3.56), and advanced TNM stage (pooled HR: 2.02, 95% CI: 1.38–2.95) (Figure 7A–D), with a certain heterogeneity (all: $I^2 = 52.7$–61.2%, $p = 0.001$–0.076). The sex and age of patients were not significantly linked to the expression level of TROP2 (sex: pooled HR: 1.08, 95% CI: 0.90–1.29; age: pooled HR: 0.94, 95% CI: 0.79–1.11).

Discussion

This meta-analysis contained data from 4,852 participants, evaluated in 27 articles (29 studies). Overall analysis and subgroup analysis were performed. The results clearly showed

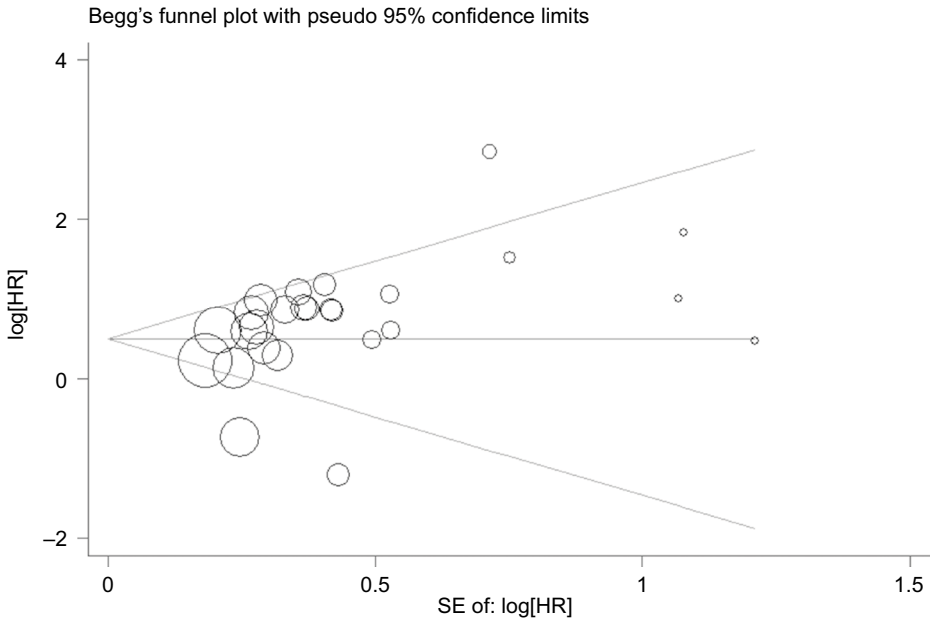


Figure 5 Begg's funnel plot for the studies involved in meta-analysis about the overall survival.
Abbreviations: HR, hazard ratio; SE, standard error.

that overexpression of TROP2 is significantly associated with poor OS, DFS, PFS, as well as the following clinical characteristics: moderate/poor tumor differentiation, lymph node metastasis, the presence of distant metastasis, and advanced TNM stage. Although some significant heterogeneity was found, the association between TROP2 and cancers was stable, just as sensitivity analysis and publication bias evaluation showed. We found that the studies by Ambrogi et al[49] and Inamura et al[55] put forward opposite views from the other studies, then we checked them carefully and no obvious error or defect was found. That is why we made this meta-analysis due to the urgent need of further studies with larger sample sizes.

This meta-analysis has both strengths and limitations. A larger sample size compared to a previous study[47] (27 vs 16 articles, 4,852 vs 2,569 patients) powered the study effectively and increased the reliability of the results. However, most of the included papers are retrospective observational studies without control groups. In addition, there were inconsistencies among studies in defining important terms such as: "the overexpression of TROP2", "the TNM stage", "differentiation", and "the cut-off value for age". Another limitation of this study is that, in some cases, values were indirectly obtained from survival curves or were calculated using related data, probably resulting in some bias because of analytical errors. Furthermore, a wide range of the publication dates meant that other biases may have been introduced due to gradual improvements in detection techniques, surgical efficacy, safety, and medical treatment over time. These limitations were unavoidable and could only be addressed by performing more studies with larger sample sizes.

Currently, the mechanism of TROP2 signaling and its function remain uncertain. The proposed mechanisms of TROP2 action are as follows: regulating calcium levels via protein kinase C (PKC) mitogenic signaling pathway, modulating extracellular regulated protein kinases (ERK) signaling, decreasing cell adhesion to fibronectin via integrin pathway, regulating gene expression via intramembrane proteolysis, causing neuregulin 1 (NRG1) release, and activating the epidermal growth factor family receptor, ErbB3.[8] Studies in zebrafish and mice have elucidated the role of TROP2 in the development of lung, intestines, and kidney.[66,67] These studies have revealed the role of TROP2 in promoting cell proliferation and organ development. A number of clinical studies overwhelmingly confirmed a strong association between TROP2 expression levels and tumor proliferation, aggressiveness, invasiveness, and metastasis, so they pointed out that TROP2 can be used as a biomarker for clinical diagnosis and to predict prognosis.[9,31,35,37,39,42,46,68] Furthermore, recombinant antibodies against TROP2 have been used to treat cancers by inhibiting TROP2 expression or by destroying cancer cells directly. Results from such studies have confirmed the efficacy of TROP2 targeted therapies.[24–33] However, normal-born TROP2-knockout mice can survive and grow to adulthood, which means that TROP2 may not be vital for organ and body development, or that its function can be taken over by other proteins.[69] In addition, one study has shown that tumorigenesis may result as a consequence of defective TROP2.[70]

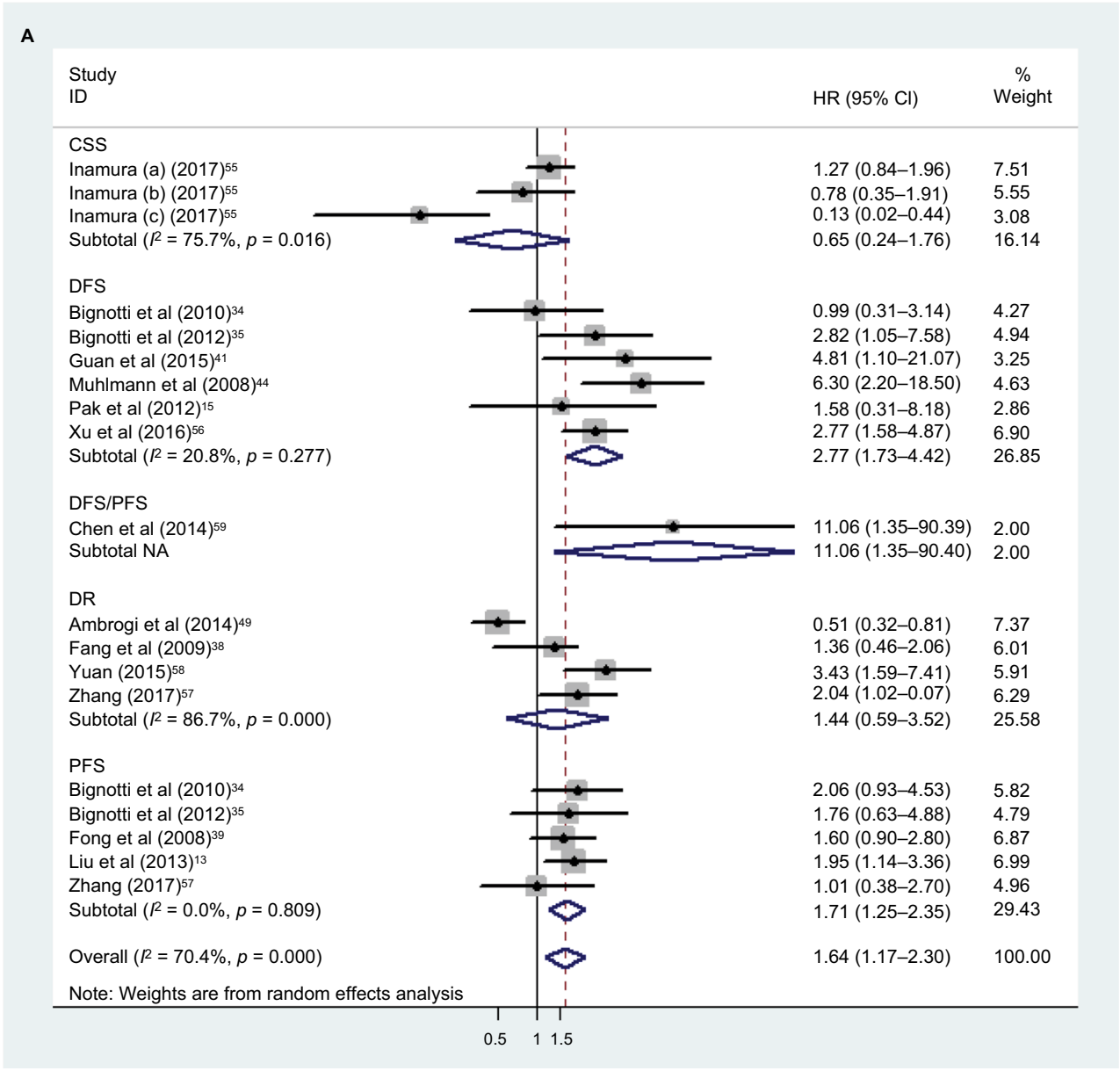


Figure 6 (*Continued*)

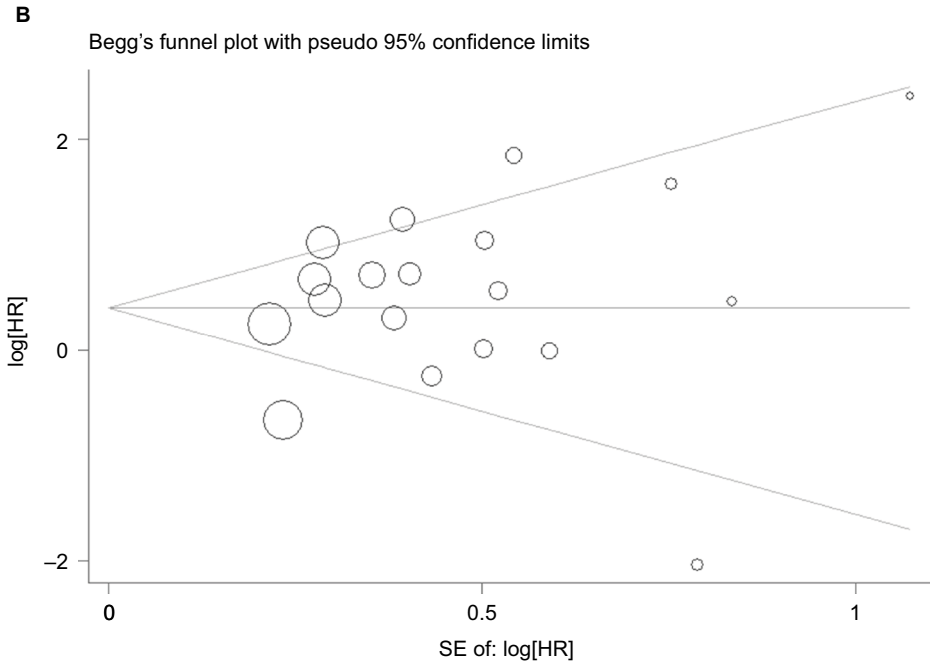


Figure 6 The meta-analysis and Begg's funnel plot of the correlation between TROP2 expression and patients' DFS/PFS/CSS/DR.
Notes: (**A**) The correlation between TROP2 expression and patients' DFS/PFS/CSS/DR. (**B**) Begg's funnel plot for the studies involved in meta-analysis about DFS/PFS/CSS/DR (random model).
Abbreviations: CSS, cancer-specific survival; DR, disease recurrence; DFS, disease-free survival; PFS, progression-free survival; TROP2, trophoblast cell surface antigen 2; NA, not applicable.

Table 3 Relationship between TROP2 overexpression and clinical characteristics

Comparison basis	Sex (male vs female)				Age (elderly vs nonelderly)				Lymph node metastasis (present vs absent)				Distant metastasis (present vs absent)				TNM stage (III + IV vs I + II)				Differentiation (moderate + poor vs well)			
Study ID	a1	a0	b1	b0	a1	a0	b1	b0	a1	a0	b1	b0	a1	a0	b1	b0	a1	a0	b1	b0	a1	a0	b1	b0
Bignotti et al (2010)[34]	–	–	–	–	16	35	1	4	6	6	7	24	–	–	–	–	–	–	–	–	–	–	–	–
Bignotti et al (2012)[35]	–	–	–	–	13	54	12	39	5	10	16	63	–	–	–	–	–	–	–	–	–	–	–	–
Chen et al (2014)[36]	27	21	25	20	34	27	18	14	36	17	16	24	–	–	–	–	21	7	31	34	29	14	23	27
Fong et al (2008)[39]	60	51	49	37	62	51	47	37	70	41	31	34	17	8	61	56	34	12	68	66	93	64	7	17
Fong et al (2008)[40]	–	–	–	–	27	23	25	15	23	13	23	19					46	30	6	8	–	–	–	–
Guan et al (2015)[41]	28	14	11	5	20	9	19	10	29	8	10	11	7	5	32	14	27	12	12	7	–	–	–	–
Inamura (a) (2017)[55]	104	40	68	58	109	65	63	33	–	–	–	–	–	–	–	–	85	33	87	65	107	49	64	49
Inamura (b) (2017)[55]	131	44	19	7	136	44	14	7	–	–	–	–	–	–	–	–	64	20	86	31	131	49	16	1
Inamura (c) (2017)[55]	18	75	3	19	17	70	4	24	–	–	–	–	–	–	–	–	13	48	8	45	–	–	–	–
Jiang et al (2013)[48]	14	12	32	29	25	22	21	19	39	24	7	17	–	–	–	–	–	–	–	–	29	12	17	29
Kobayashi (2010)[43]	43	19	44	24	42	28	45	15	27	14	60	29	–	–	–	–	–	–	–	–	–	–	–	–
Li (2017)[60]	6	15	25	42	23	45	8	12	21	5	10	52	–	–	–	–	24	12	7	45	28	6	3	51
Lin et al (2013)[50]	–	–	–	–	–	–	–	–	22	1	22	37	11	1	33	37	14	0	30	38	39	24	5	14
Liu et al (2013)[13]	–	–	–	–	57	6	37	6	–	–	–	–	–	–	–	–	6	0	88	12	66	5	28	7

(*Continued*)

Table 3 (*Continued*)

	Sex (male vs female)				Age (elderly vs nonelderly)				Lymph node metastasis (present vs absent)				Distant metastasis (present vs absent)				TNM stage (III + IV vs I + II)				Differentiation (moderate + poor vs well)			
Mühlmann et al (2008)[44]	40	23	13	12	–	–	–	–	29	23	24	12	7	2	46	33					52	33	1	2
Ning et al (2013)[45]	26	18	17	9	22	14	21	13	–	–	–	–	–	–	–	–	18	17	24	11	22	6	21	21
Ohmachi et al (2006)[46]	14	30	12	18	–	–	–	–	14	17	12	31	–	–	–	–					20	30	6	18
Pak et al (2012)[15]	13	39	10	38	–	–	–	–	–	–	–	–	–	–	–	–	8	24	15	53	18	40	5	37
Wu (2012)[61]	95	12	2	0	59	5	38	7	18	1	79	11	–	–	–	–	39	5	58	7	57	1	40	11
Xu (2009)[62]	21	19	19	21	–	–	–	–	23	17	17	23	–	–	–	–	–	–	–	–	31	27	9	13
Xu et al (2016)[56]	–	–	–	–	44	34	31	19	28	12	39	40	–	–	–	–	–	–	–	–	–	–	–	–
Yuan (2015)[58]	26	41	5	11	19	24	12	28	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Zhang et al (2017)[57]	30	37	20	15	32	30	18	22	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Zhao (2016)[63]	48	4	27	3	41	2	34	5	41	1	34	6	–	–	–	–	43	1	32	6	54	4	21	3
Zhao (2015)[64]	280	148	118	54	168	98	230	104	271	102	127	100	34	4	364	198	203	60	195	142	325	149	29	28

Notes: a1: the number of TROP2 overexpression of each former group; a0: the number of normal/low expression of TROP2 of each former group; b1: the number of TROP2 overexpression of each later group; and b0: the number of normal/low expression of TROP2 of each later group.
Abbreviation: TNM, The TNM Classification of Malignant Tumours; TROP2, trophoblast cell surface antigen 2.

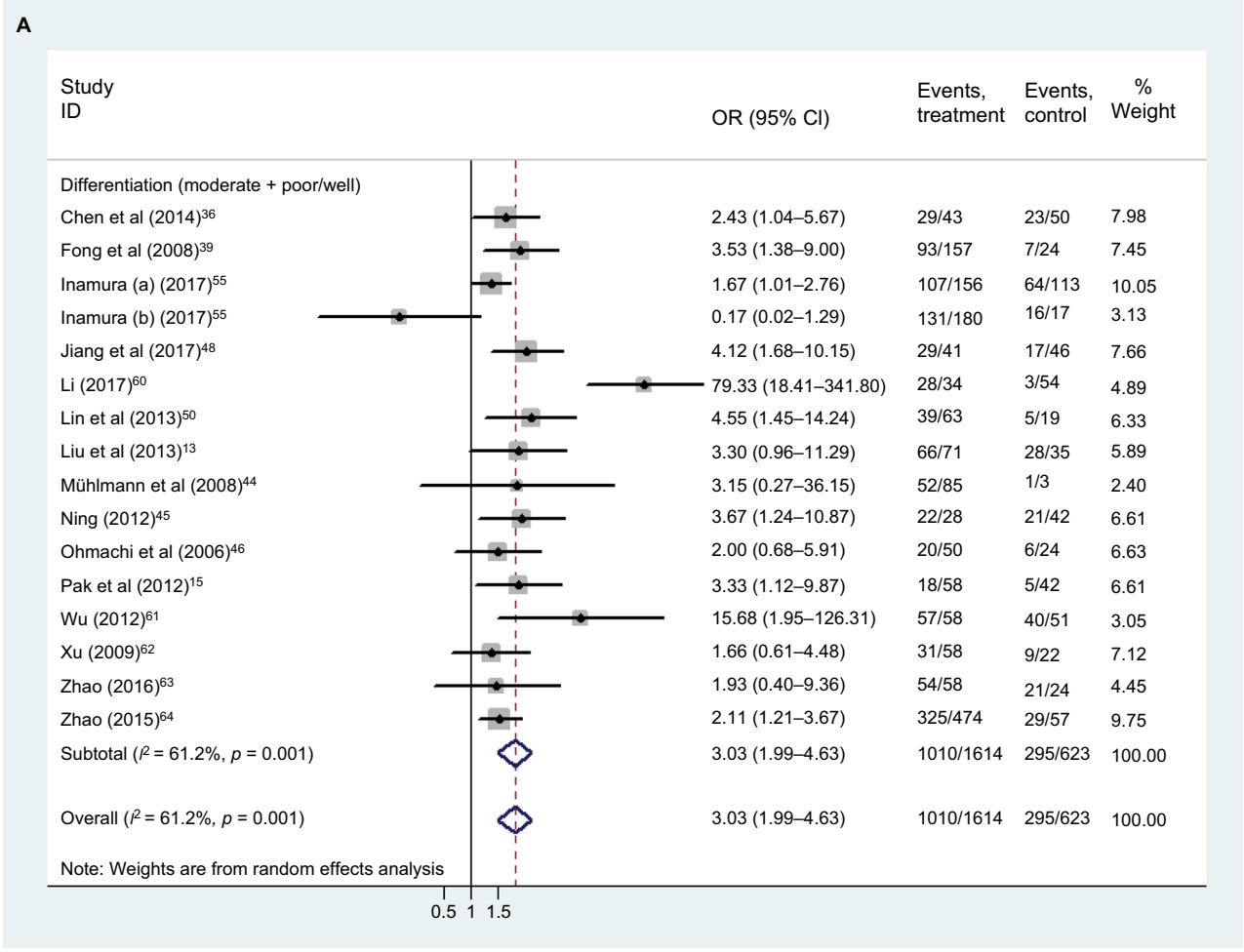
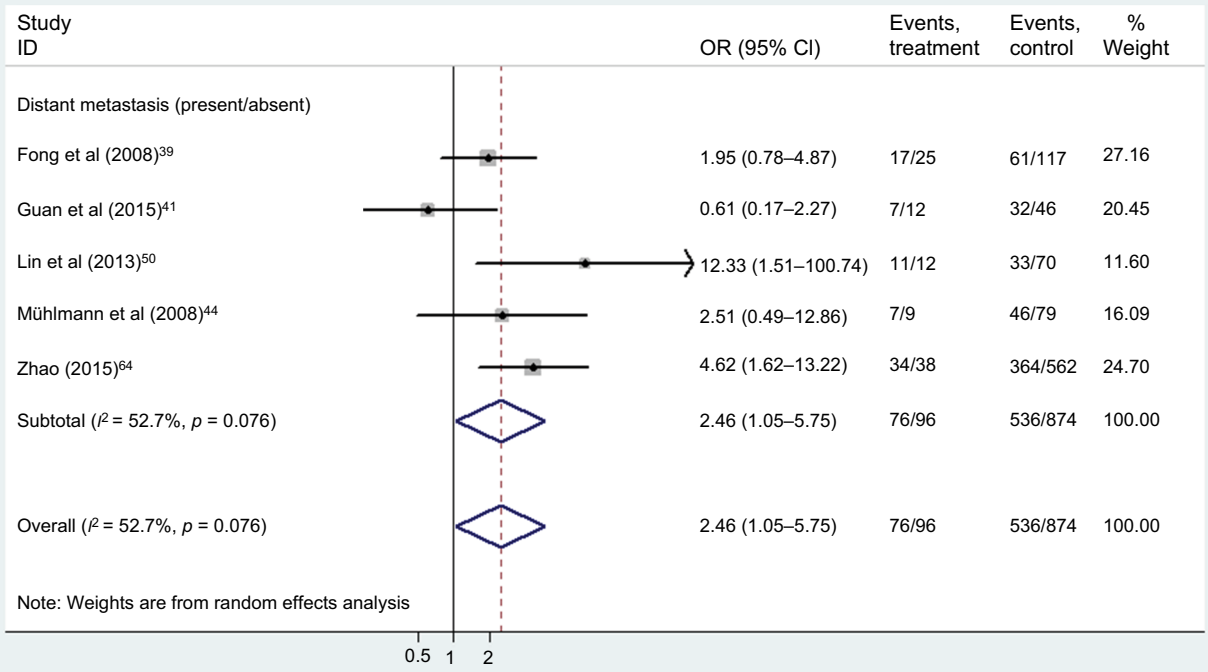


Figure 7 (*Continued*)

B



C

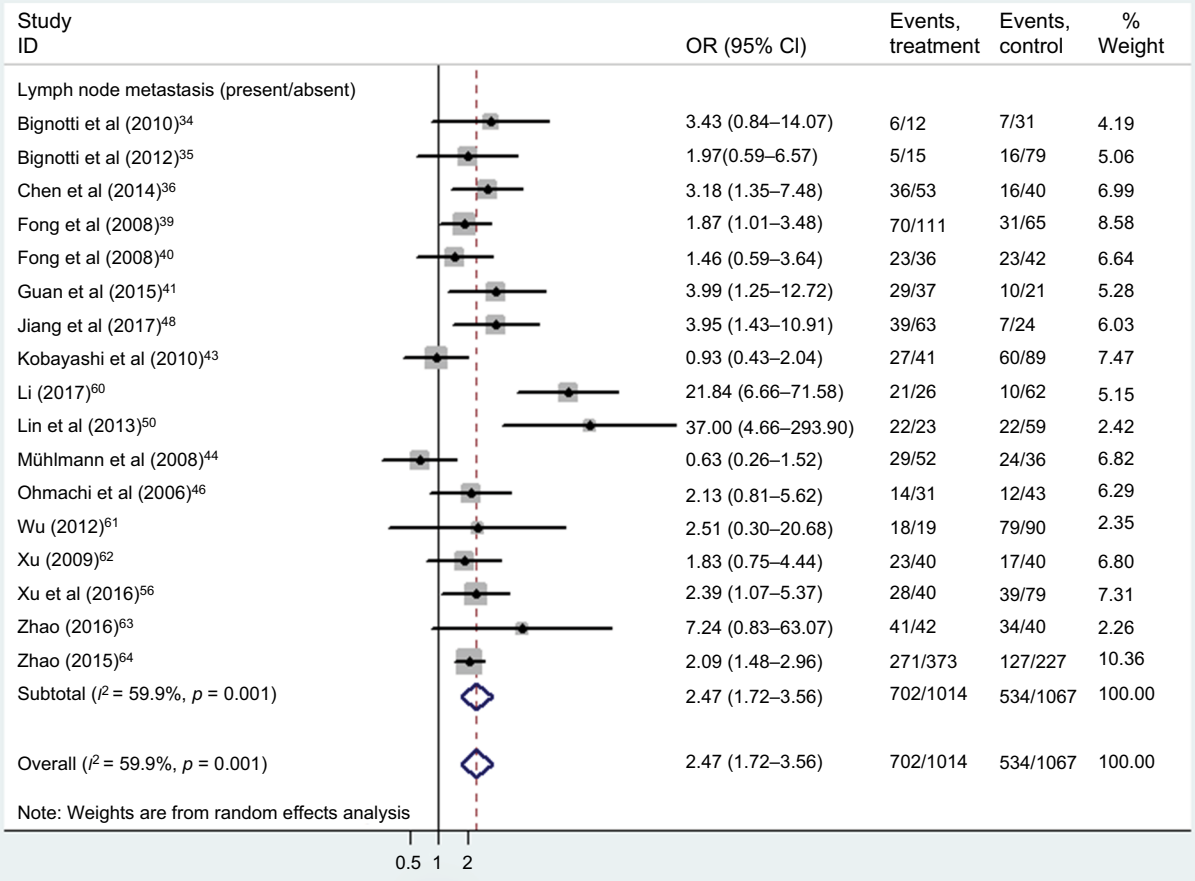


Figure 7 (*Continued*)

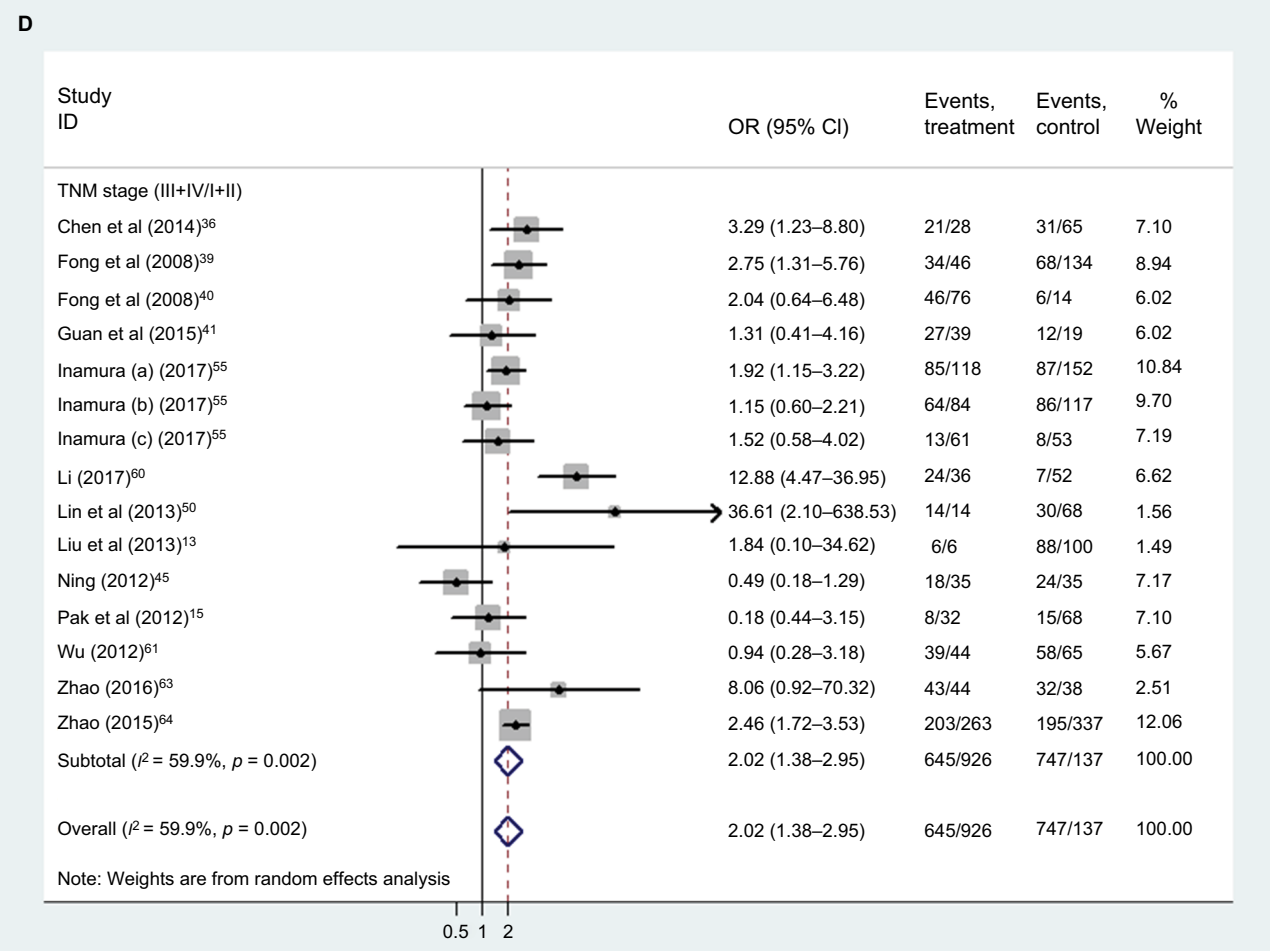


Figure 7 The correlation between TROP2 expression and carcinoma patients' clinicopathologic features.
Notes: **(A)** Differentiation (moderate/poor vs well); **(B)** distant metastasis (present vs absent); **(C)** lymph node metastasis (present vs absent); and **(D)** TNM stage (III + IV vs I + II).
Abbreviations: CI, confidence interval; OR, odds ratio; TNM, The TNM Classification of Malignant Tumours; TROP2, trophoblast cell surface antigen 2.

Conclusion

Thus, the function and the mechanisms of action of TROP2 are not clear yet, while the relationship between TROP2 and cell proliferation is complex, possibly determined by tissue type and context.[8,55] Further research studies with larger sample sizes should be conducted to learn and confirm its role in cancer occurrence, development, and mechanism of action. In conclusion, the expression of TROP2 is associated with cancer disease, maybe a potential diagnostic indicator and prognostic biomarker.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87–108.
2. Wang C, Zhang J, Cai M, et al. DBGC: A Database of Human Gastric Cancer. *PLoS One*. 2015;10(11):e0142591.
3. Weitz J, Koch M, Debus J, Hohler T, Galle PR, Buchler MW. Colorectal cancer. *Lancet*. 2005;365(9454):153–165.
4. McWilliams RR, Erlichman C. Novel therapeutics in colorectal cancer. *Dis Colon Rectum*. 2005;48(8):1632–1650.
5. Wu DH, Liu L, Chen LH. Antitumor effects and radiosensitization of cytosine deaminase and thymidine kinase fusion suicide gene on colorectal carcinoma cells. *World J Gastroenterol*. 2005;11(20):3051–3055.
6. Aggarwal S, Chu E. Current therapies for advanced colorectal cancer. *Oncology (Williston Park, NY)*. 2005;19(5):589–595.
7. Lipinski M, Parks DR, Rouse RV, Herzenberg LA. Human trophoblast cell-surface antigens defined by monoclonal antibodies. *Proc Natl Acadof Sci U S A*. 1981;78(8):5147–5150.
8. McDougall AR, Tolcos M, Hooper SB, Cole TJ, Wallace MJ. Trop2: from development to disease. *Dev Dyn*. 2015;244(2):99–109.
9. Cubas R, Zhang S, Li M, Chen C, Yao Q. Trop2 expression contributes to tumor pathogenesis by activating the ERK MAPK pathway. *Mol Cancer*. 2010;9:253.
10. Fornaro M, Arciprete RD, Stella M, et al. Cloning of the gene encoding TROP-2, a cell-surface glycoprotein expressed by human carcinomas. *Int J Cancer*. 1995;62(5):610–618.

11. Guerra E, Trerotola M, Dell' Arciprete R, et al. A bicistronic CYCLIN D1-TROP2 mRNA chimera demonstrates a novel oncogenic mechanism in human cancer. *Cancer Res*. 2008;68(19):8113–8121.
12. Ju X, Jiao X, Ertel A, et al. v-Src Oncogene Induces Trop2 Proteolytic Activation via Cyclin D1. *Cancer Res*. 2016;76(22):6723–6734.
13. Liu T, Liu Y, Bao X, Tian J, Liu Y, Yang X. Overexpression of TROP2 predicts poor prognosis of patients with cervical cancer and promotes the proliferation and invasion of cervical cancer cells by regulating ERK signaling pathway. *PLoS One*. 2013;8(9):e75864.
14. Nakanishi H, Taccioli C, Palatini J, et al. Loss of miR-125b-1 contributes to head and neck cancer development by dysregulating TACSTD2 and MAPK pathway. *Oncogene*. 2014;33(6):702–712.
15. Pak MG, Shin DH, Lee CH, Lee MK. Significance of EpCAM and TROP2 expression in non-small cell lung cancer. *World J Surg Oncol*. 2012;10:53.
16. Ripani E, Sacchetti A, Corda D, Alberti S. Human TROP-2 is a tumor-associated calcium signal transducer. *Int J Cancer*. 1998;76(5):671–676.
17. Sawanyawisuth K, Tantapotinan N, Wongkham C, et al. Suppression of trophoblast cell surface antigen 2 enhances proliferation and migration in liver fluke-associated cholangiocarcinoma. *Ann Hepatol*. 2016;15(1):71–81.
18. Stoyanova T, Goldstein AS, Cai H, Drake JM, Huang J, Witte ON. Regulated proteolysis of Trop2 drives epithelial hyperplasia and stem cell self-renewal via beta-catenin signaling. *Genes Dev*. 2012;26(20):2271–2285.
19. Trerotola M, Cantanelli P, Guerra E, et al. Upregulation of Trop-2 quantitatively stimulates human cancer growth. *Oncogene*. 2013;32(2):2 22–233.
20. Trerotola M, Ganguly KK, Fazli L, et al. Trop-2 is up-regulated in invasive prostate cancer and displaces FAK from focal contacts. *Oncotarget*. 2015;6(16):14318–14328.
21. Wang XD, Wang Q, Chen XL, et al. Trop2 inhibition suppresses the proliferation and invasion of laryngeal carcinoma cells via the extracellular signal-regulated kinase/mitogen-activated protein kinase pathway. *Mol Med Rep*. 2015;12(1):865–870.
22. Wanger TM, Dewitt S, Collins A, Maitland NJ, Poghosyan Z, Knauper V. Differential regulation of TROP2 release by PKC isoforms through vesicles and ADAM17. *Cell Signal*. 2015;27(7):1325–1335.
23. Yang J, Zhu Z, Wang H, Li F, Du X, Ma RZ. Trop2 regulates the proliferation and differentiation of murine compact-bone derived MSCs. *Int J Oncol*. 2013;43(3):859–867.
24. Wang H, Liu Q, Tang X, et al. Eukaryotic expression of human anti-TROP2 antibody IgG and its inhibitory effect on cell proliferation of pancreatic cancer. *J Nanjing Med Univ Nat Sci Ed*. 2014;34(7):863–869,882.
25. van Rij CM, Frielink C, Sharkey RM, et al. FDG-PET and pretargeted immunoPET of prostate cancer with an anti-TROP2 x anti-HSG bispecific antibody in a nude mouse model. *Eur J Nucl Med Mol Imaging*. 2012;39:S194-S195.
26. van Rij CM, Frielink C, Goldenberg DM, et al. Pretargeted Radioimmunotherapy of Prostate Cancer with an Anti-TROP-2xAnti-HSG Bispecific Antibody and a (177)Lu-Labeled Peptide. *Cancer Biother Radiopharm*. 2014;29(8):323–329.
27. van Rij CM, Frielink C, Goldenberg DM, et al. Pretargeted immunoPET of prostate cancer with an anti-TROP-2 x anti-HSG bispecific antibody in mice with PC3 xenografts. *Mol Imaging Biol*. 2015;17(1):94–101.
28. Mao Y, Wang X, Zheng F, et al. The tumor-inhibitory effectiveness of a novel anti-Trop2 Fab conjugate in pancreatic cancer. *Oncotarget*. 2016;7(17):24810–24823.
29. Liu X, Li S, Yi F. Trop2 gene: a novel target for cervical cancer treatment. *J Cancer Res Clin Oncol*. 2014;140(8):1331–1341.
30. Liu T, Tian J, Chen Z, et al. Anti-TROP2 conjugated hollow gold nanospheres as a novel nanostructure for targeted photothermal destruction of cervical cancer cells. *Nanotechnology*. 2014;25(34):345103.
31. Lin H, Zhang H, Wang J, et al. A novel human Fab antibody for Trop2 inhibits breast cancer growth in vitro and in vivo. *Int J Cancer*. 2014;134(5):1239–1249.
32. Farivar TN, Najafipour R, Johari P. Nano - drug Delivery of Apoptosis Activator 2 to AGS Cells by Liposomes Conjugated with Anti-TROP2 Antibody. *N Am J Med Sci*. 2012;4(11):582–585.
33. Alberti S, Trerotola M, Dell' AR, et al. Selective killing of human cancer cells by targeting a fusion mRNA between CYCLIN D1 and TROP2. *J Clin Oncol*. 2009;27(15_suppl):e14569.
34. Bignotti E, Todeschini P, Calza S, et al. Trop-2 overexpression as an independent marker for poor overall survival in ovarian carcinoma patients. *Eur J Cancer*. 2010;46(5):944–953.
35. Bignotti E, Zanotti L, Calza S, et al. Trop-2 protein overexpression is an independent marker for predicting disease recurrence in endometrioid endometrial carcinoma. *BMC Clin Pathol*. 2012;12(1):22.
36. Chen M-B, Wu H-F, Zhan Y, et al. Prognostic value of TROP2 expression in patients with gallbladder cancer. *Tumor Biol*. 2014;35(11):11565–11569.
37. Chen R, Lu M, Wang J, et al. Increased expression of Trop2 correlates with poor survival in extranodal NK/T cell lymphoma, nasal type. *Virchows Archiv*. 2013;463(5):713.
38. Fang YJ, Lu ZH, Wang GQ, et al. Elevated expressions of MMP7, TROP2, and survivin are associated with survival, disease recurrence, and liver metastasis of colon cancer. *Int J Colorectal Dis*. 2009;24(8):875–884.
39. Fong D, Moser P, Krammel C, et al. High expression of TROP2 correlates with poor prognosis in pancreatic cancer. *Br J Cancer*. 2008;99(8):1290–1295.
40. Fong D, Spizzo G, Gostner JM, et al. TROP2: a novel prognostic marker in squamous cell carcinoma of the oral cavity. *Mod Pathol*. 2008;21(2):186–191.
41. Guan GF, Zhang DJ, Wen LJ, et al. Prognostic value of TROP2 in human nasopharyngeal carcinoma. *Int J Clin Exp Pathol*. 2015;8(9):10995–11004.
42. Hao W, Huiming Xu MS, Shu ZM, et al. Potential therapeutic target and independent prognostic marker of TROP2 in laryngeal squamous cell carcinoma. *Head Neck*. 2013;35(10):1373–1378.
43. Kobayashi H, Minami Y, Anami Y, et al. Expression of the GA733 gene family and its relationship to prognosis in pulmonary adenocarcinoma. *Virchows Archiv*. 2010;457(1):69–76.
44. Muhlmann G, Spizzo G, Gostner J, et al. TROP2 expression as prognostic marker for gastric carcinoma. *J Clin Pathol*. 2009;62(2):152–158.
45. Ning S, Guo S, Xie J, Xu Y, Lu X, Chen Y. TROP2 correlates with microvessel density and poor prognosis in hilar cholangiocarcinoma. *J Gastrointest Surg*. 2013;17(2):360–368.
46. Ohmachi T, Tanaka F, Mimori K, Inoue H, Yanaga K, Mori M. Clinical significance of TROP2 expression in colorectal cancer. *Clin Cancer Res*. 2006;12(10):3057–3063.
47. Zeng P, Chen MB, Zhou LN, Tang M, Liu CY, Lu PH. Impact of TROP2 expression on prognosis in solid tumors: A Systematic Review and Meta-analysis. *Sci Rep*. 2016;6:33658.
48. Jiang A, Gao X, Zhang D, Zhang L, Lu H. Expression and clinical significance of the Trop-2 gene in advanced non-small cell lung carcinoma. *Oncol Lett*. 2013;6(2):375–380.
49. Ambrogi F, Fornili M, Boracchi P, et al. Trop-2 Is a Determinant of Breast Cancer Survival. *PLos One*. 2014;9(5):e96993.
50. Lin H, Huang JF, Qiu JR, et al. Significantly upregulated TACSTD2 and Cyclin D1 correlate with poor prognosis of invasive ductal breast cancer. *Exp Mol Pathol*. 2013;94(1):73–78.
51. Zhou ZR, Zhang TS, Bo LI, Mao Z, Zeng XT, Liu SX. Extracting and transforming of appropriate data of Meta-analysis in survival curve. *Chin J Evid-Based Cardiovasc Med*. 2014;6(3):243–247.
52. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J*. 2003;327(7414):557–560.
53. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088–1101.
54. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.

55. Inamura K, Yokouchi Y, Kobayashi M, et al. Association of tumor TROP2 expression with prognosis varies among lung cancer subtypes. *Oncotarget*. 2017;8(17):28725–28735.
56. Xu N, Zhang Z, Zhu J, et al. Overexpression of trophoblast cell surface antigen 2 as an independent marker for a poor prognosis and as a potential therapeutic target in epithelial ovarian carcinoma. *Int J Exp Pathol*. 2016;97(2):150–158.
57. Zhang L, Yang G, Jiang H, et al. TROP2 is associated with the recurrence of patients with non-muscle invasive bladder cancer. *Int J Clin Exp Med*. 2017;10(1):1643–1650.
58. Yuan G. Expression and significance of TROP2 in the non-muscle-invasive bladder transitional cell Cancer [Master Thesis], Soochow University; 2015.
59. Chen X, Pang B, Liang Y, et al. Overexpression of EpCAM and Trop2 in pituitary adenomas. *Int J Clin Exp Pathol*. 2014;7(11):7907–7914.
60. Li XX, Teng SF, Xu K, et al. Expression of trophoblast cell-surface antigen 2, phosphorylated extracellular signal-regulated kinase 1/2, and cyclin D1 in gallbladder carcinoma tissue and related clinical significance. *J Clin Hepatol*. 2017;33(5):909–914.
61. Wu H, Xu H, Zhang S, et al. Potential therapeutic target and independent prognostic marker of TROP2 in laryngeal squamous cell carcinoma. *Head Neck*. 2013;35(10):1373–1378.
62. Xu KY, Gu J. Expression of TROP2 mRNA in left-sided and right-sided colon cancer and its clinical significance. *Zhonghua Wei Chang Wai Ke Za Zhi*. 2009;12(3):285–289. Chinese.
63. Zhao P, Chen J, Cao W, et al. The expression and clinical significance of TROP-2 protein in colon cancer. *Chongqing Med*. 2016;45(35):4963–4966.
64. Zhao W, Zhu H, Zhang S, et al. Trop2 is overexpressed in gastric cancer and predicts poor prognosis. *Oncotarget*. 2016;7(5):6136–6145.
65. Shi X. Comparison of the Power Difference of Egger's Test and Begg's Test and the Reason Analysis. *Acta Med Univ Sci Et Technologiae Huazhong*. 2009;38(1):91–93.
66. Tsukahara Y, Tanaka M, Miyajima A. TROP2 expressed in the trunk of the ureteric duct regulates branching morphogenesis during kidney development. *PLos One*. 2011;6(12):e28607.
67. Mustata RC, Vasile G, Fernandezvallone V, et al. Identification of Lgr5-independent spheroid-generating progenitors of the mouse fetal intestinal epithelium. *Cell Rep*. 2013;5(2):421.
68. Trerotola M, Alberti S, Languino LR. Trop2 modulates beta1 integrin-mediated adhesion and migration of prostate cancer cells. Proceedings of the American Association for Cancer Research Annual Meeting. 2010;51:1246–1246.
69. Wang J, Zhang K, Grabowska D, et al. Loss of Trop2 promotes carcinogenesis and features of epithelial to mesenchymal transition in squamous cell carcinoma. *Mol Cancer Res*. 2011;9(12):1686–1695.
70. Lin JC, Wu YY, Wu JY, et al. TROP2 is epigenetically inactivated and modulates IGF-1R signalling in lung adenocarcinoma. *EMBO Mol Med*. 2012;4(6):472–485