

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

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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).

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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 study¹⁵) 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

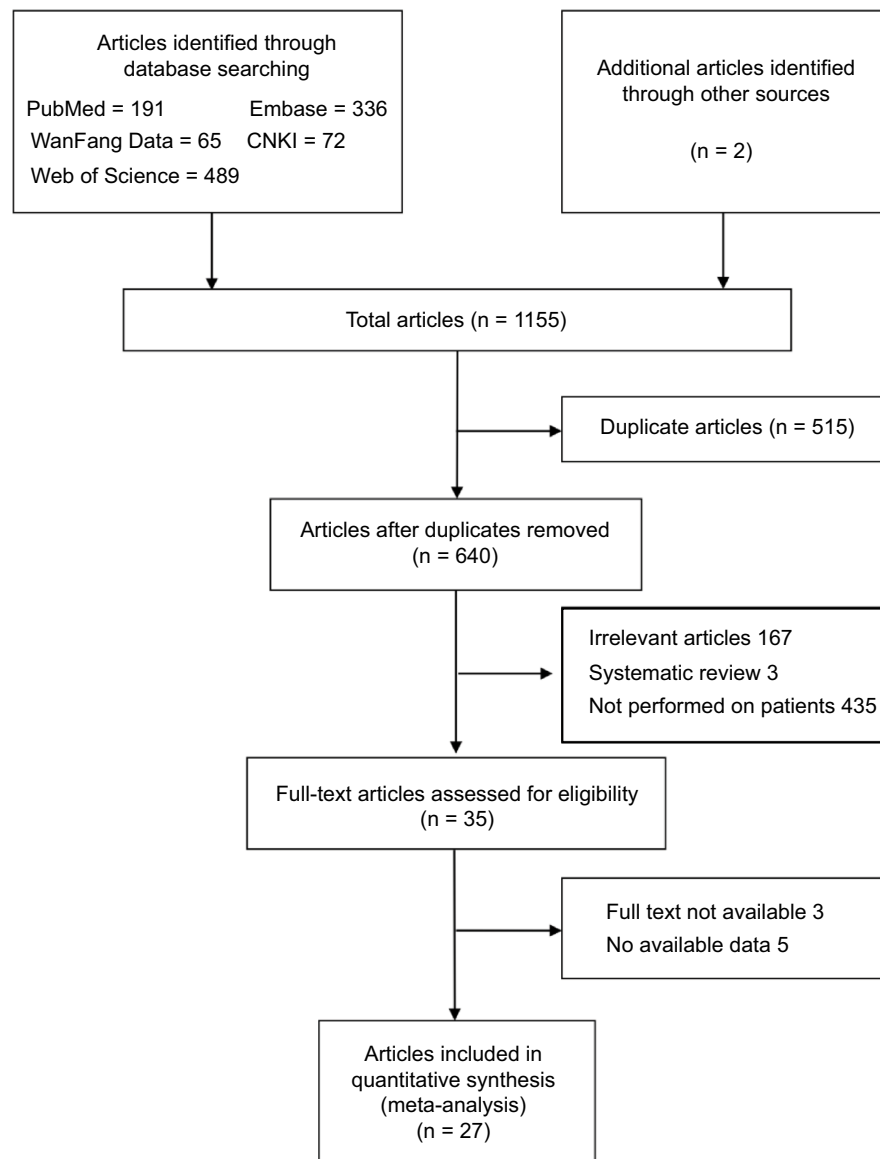


Figure 1 Flow diagram of study selection.

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
Ambroggi et al ⁴⁹	2014	Breast cancer	Italy	702	NA	TNM T ₁₋₃ N ₁ M ₀	IHC	Low ≤ 5% High > 86%	96	OS	Univariate analysis Multivariate analysis	6
Bignotti et al ⁵⁴	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	Univariate analysis Multivariate analysis	8
Bignotti et al ⁵⁵	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	Univariate analysis Multivariate analysis	7
Chen et al ⁵⁶	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 ⁵⁷	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	NA	IHC	Low TIS ≤ 4 High TIS = 5–9	NA	DFS/PFS	Multivariate analysis	6
Fang et al ⁵⁸	2009	Colon cancer	China	620	59 (15–86)	TNM I–IV	IHC	Immunoreactivity rating of II or III; moderate/strong	52 (1–130)	OS	Multivariate analysis	9
Fong et al ⁵⁹	2008	Pancreatic cancer	Austria	197	65 (37–91)	TNM I–IV	IHC	Low = score 0–4 High = score 5–12	9 (1–68)	OS	Multivariate analysis	7
Fong et al ⁶⁰	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	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% or High: intensity 1 ≥ 50% or intensity 2 ≥ 10%	13.0 (9.1–15.5) years	CSS	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% or High: intensity 1 ≥ 50% or intensity 2 ≥ 11%	5.0 (3.1–6.3) years	CSS	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% or High: intensity 1 ≥ 50% or intensity 2 ≥ 12%	5.8 (3.1–8.2) years	CSS	Univariate analysis Multivariate analysis	8
Jiang et al ⁴⁸	2013	Lung cancer NSCLC	China	87	(58.6 ± 9.8)	TNM III ₀ 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 ⁶⁰	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	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 ⁶⁵	2012	Hilar cholangiocarcinoma	China	70	59 (39–79)	TNM I–IV	IHC	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	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 III	QRT-PCR QRT-PCR	The median of the expression level of colorectal carcinoma	38.5 (7–71)	OS	Univariate analysis Multivariate analysis	6
Xu et al ⁶⁶	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 ⁶⁸	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 ⁶⁷	2017	Bladder cancer NMIBC	China	102	66.1 (41–88)	TNM Ta T1	IHC	Low IS ≤ 1 High IS = 2–9	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	IS: staining index 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	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.

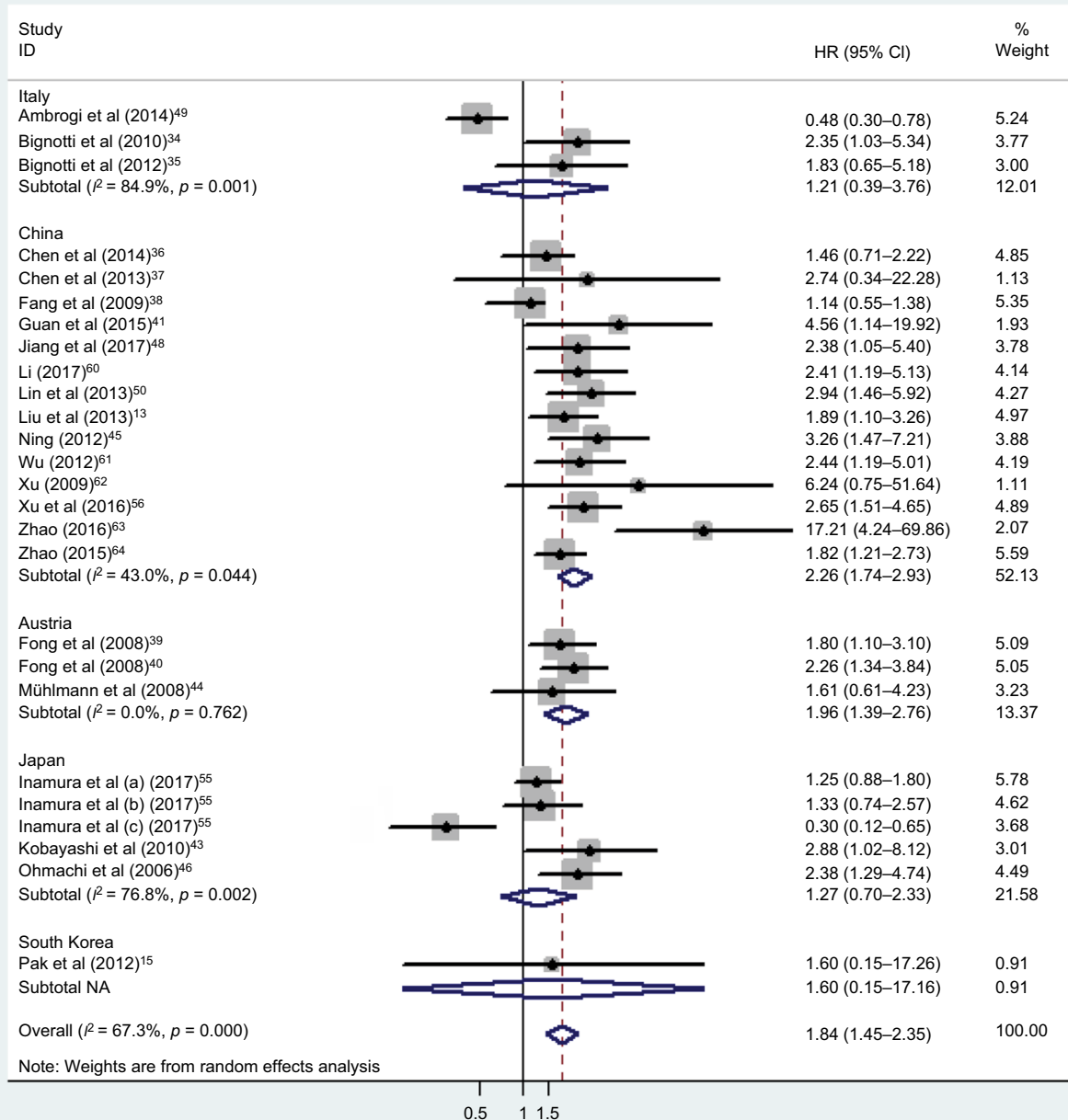


Figure 2 Overall analysis and subgroup analysis about patients' overall survival.

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 al⁵⁵ 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.

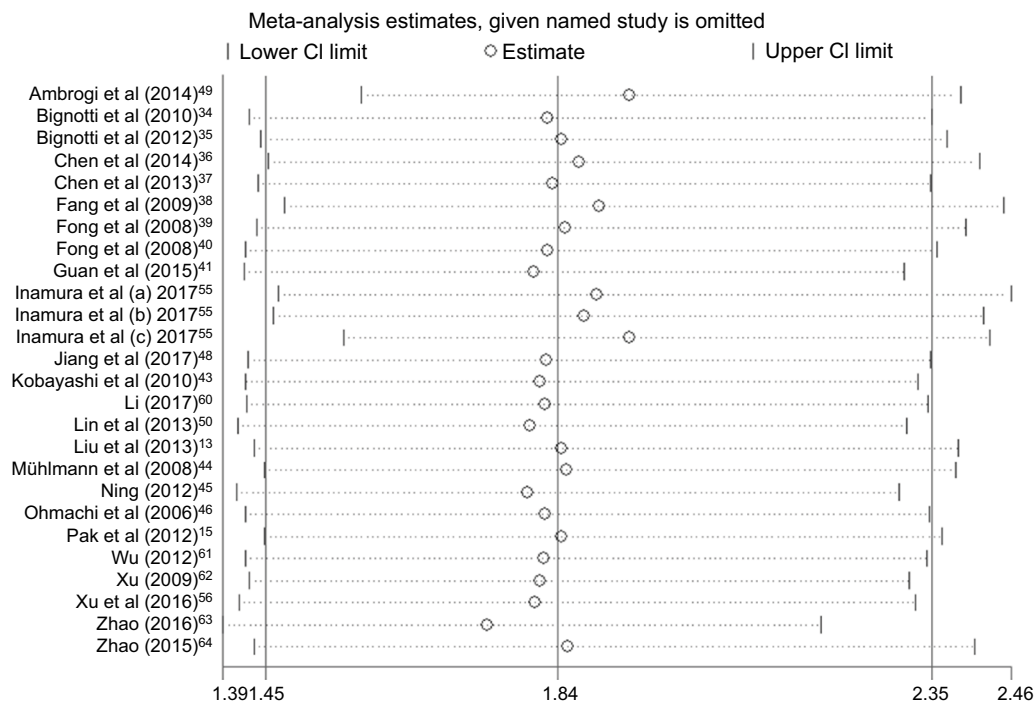


Figure 3 Sensitivity analysis to assess the effect of each study of the meta-analysis about the overall survival (random model).

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)

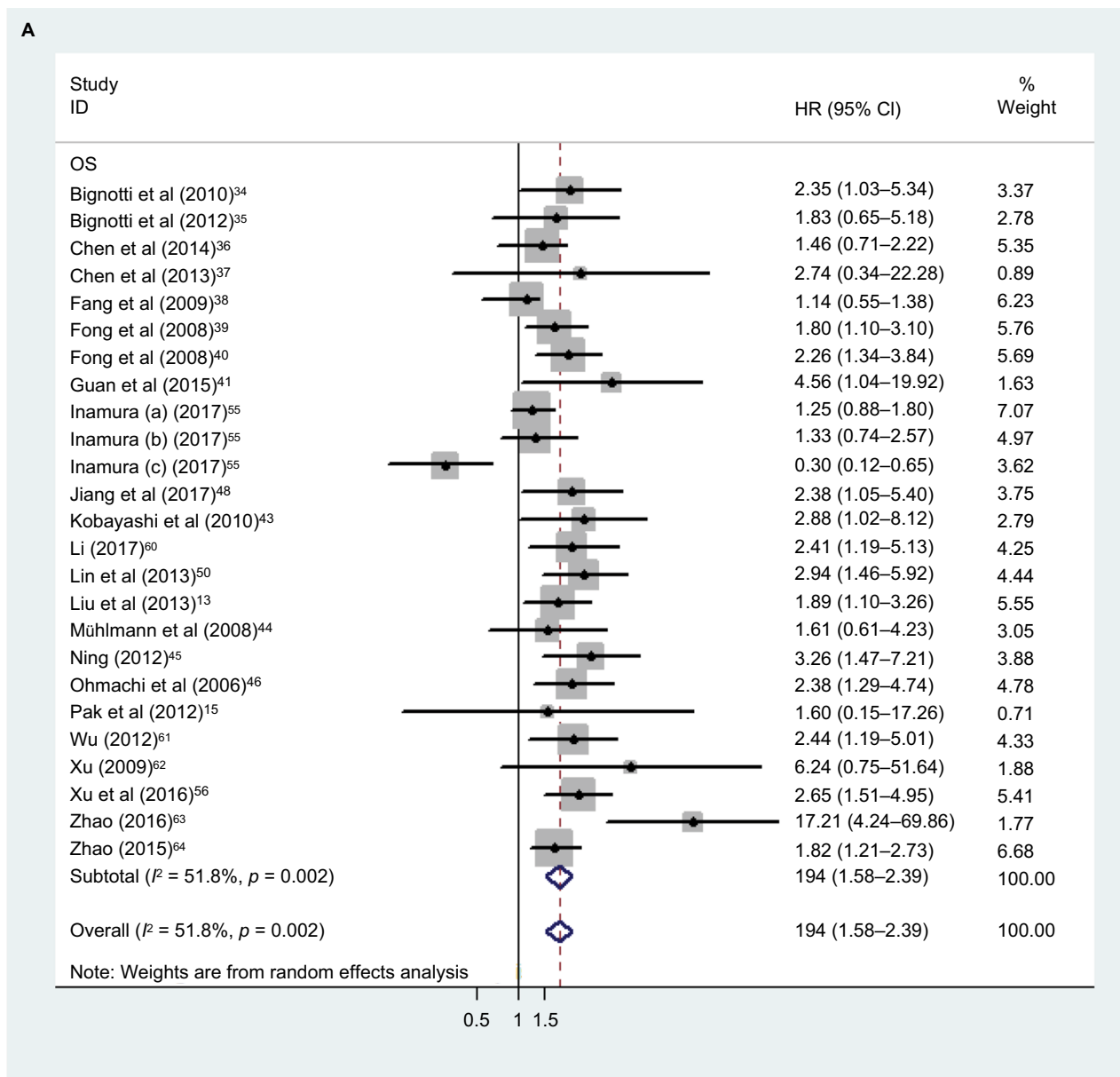


Figure 4 (Continued)

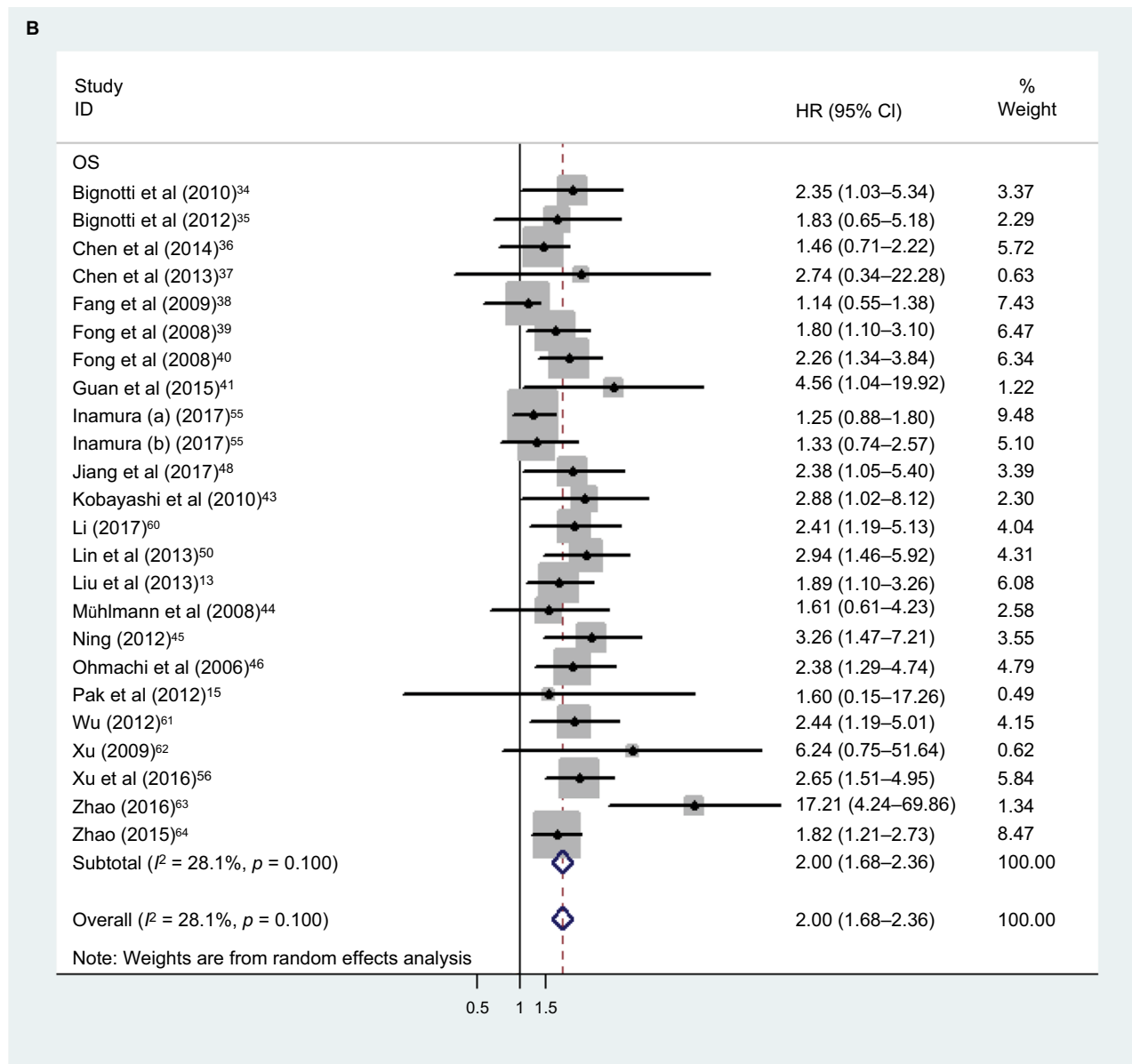


Figure 4 Overall analysis of the correlation between TROP2 expression and patients' OS after excluding the significant studies which held opposite views.

Notes: (A) Without Ambrogio⁴⁹ and (B) without Ambrogio⁴⁹ 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

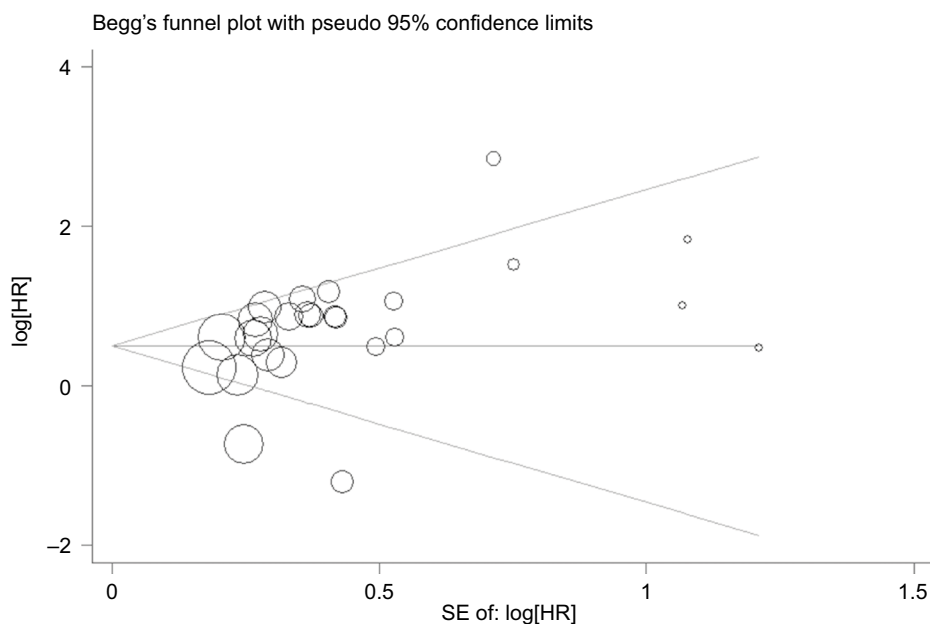


Figure 5 Begg's funnel plot for the studies involved in meta-analysis about the overall survival.
Abbreviations: HR, hazard ratio; SE, standard error.

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 al⁴⁹ and Inamura et al⁵⁵ 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 study⁴⁷ (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

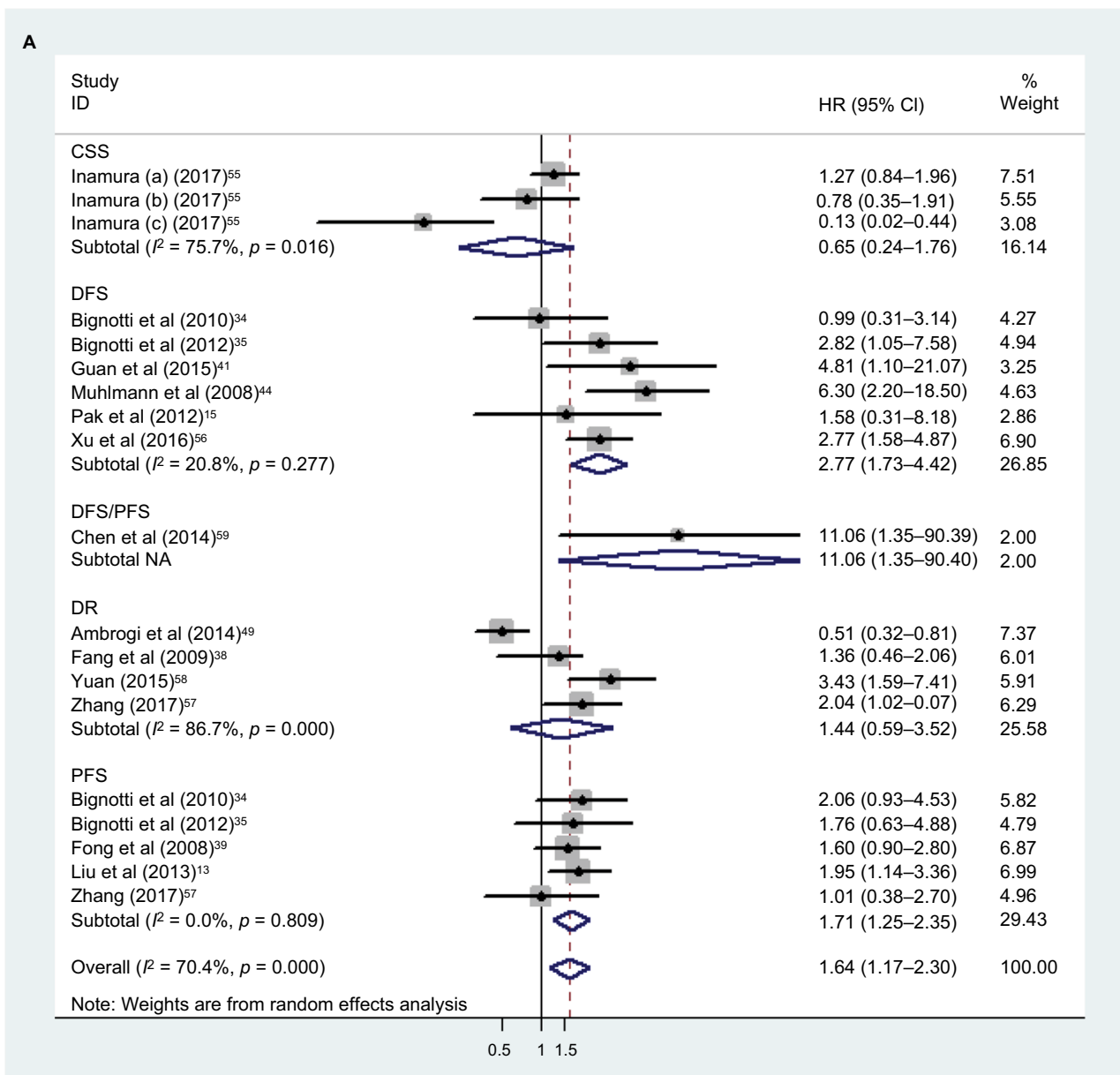


Figure 6 (Continued)

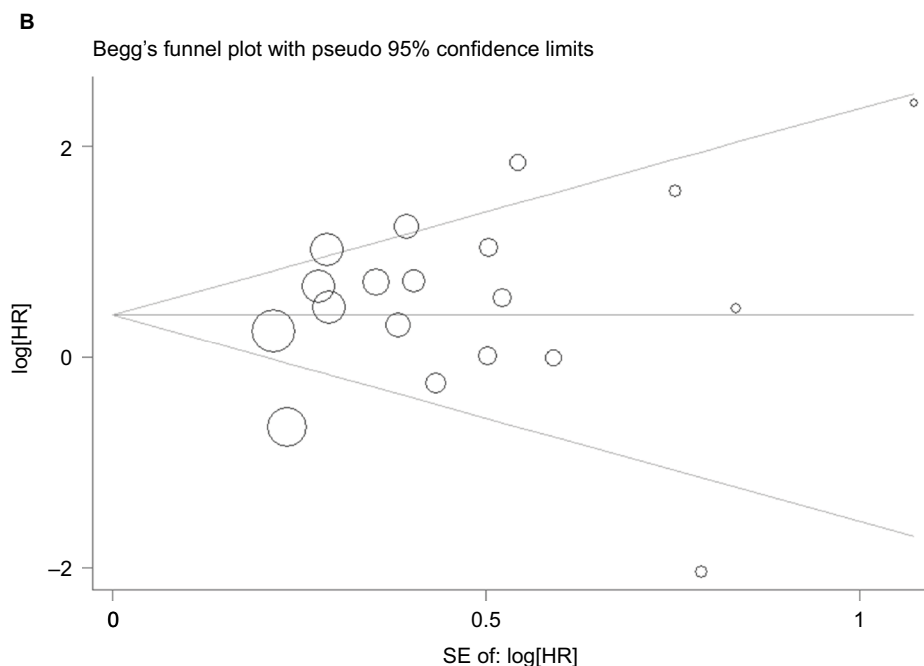


Figure 6 The meta-analysis and Begg's funnel plot of the correlation between TROP2 expression and patients' DFS/PFS/CSS/DR. **Notes:** (A) The correlation between TROP2 expression and patients' DFS/PFS/CSS/DR. (B) Begg's funnel plot for the studies involved in meta-analysis about DFS/PFS/CSS/DR (random 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)			
	a1	a0	b1	b0	a1	a0	b1	b0	a1	a0	b1	b0	a1	a0	b1	b0	a1	a0	b1	b0	a1	a0	b1	b0
Study ID																								
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

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.

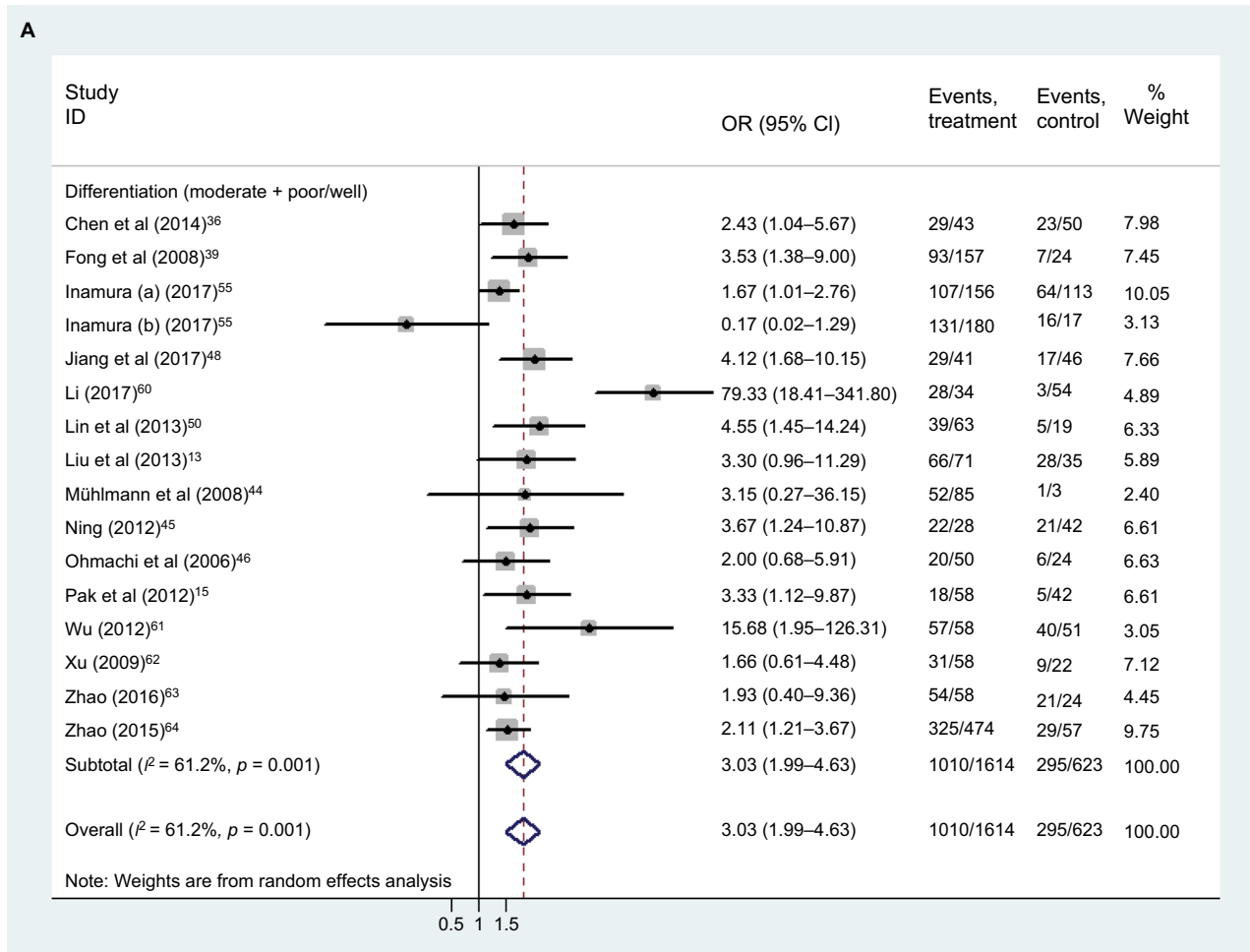


Figure 7 (Continued)

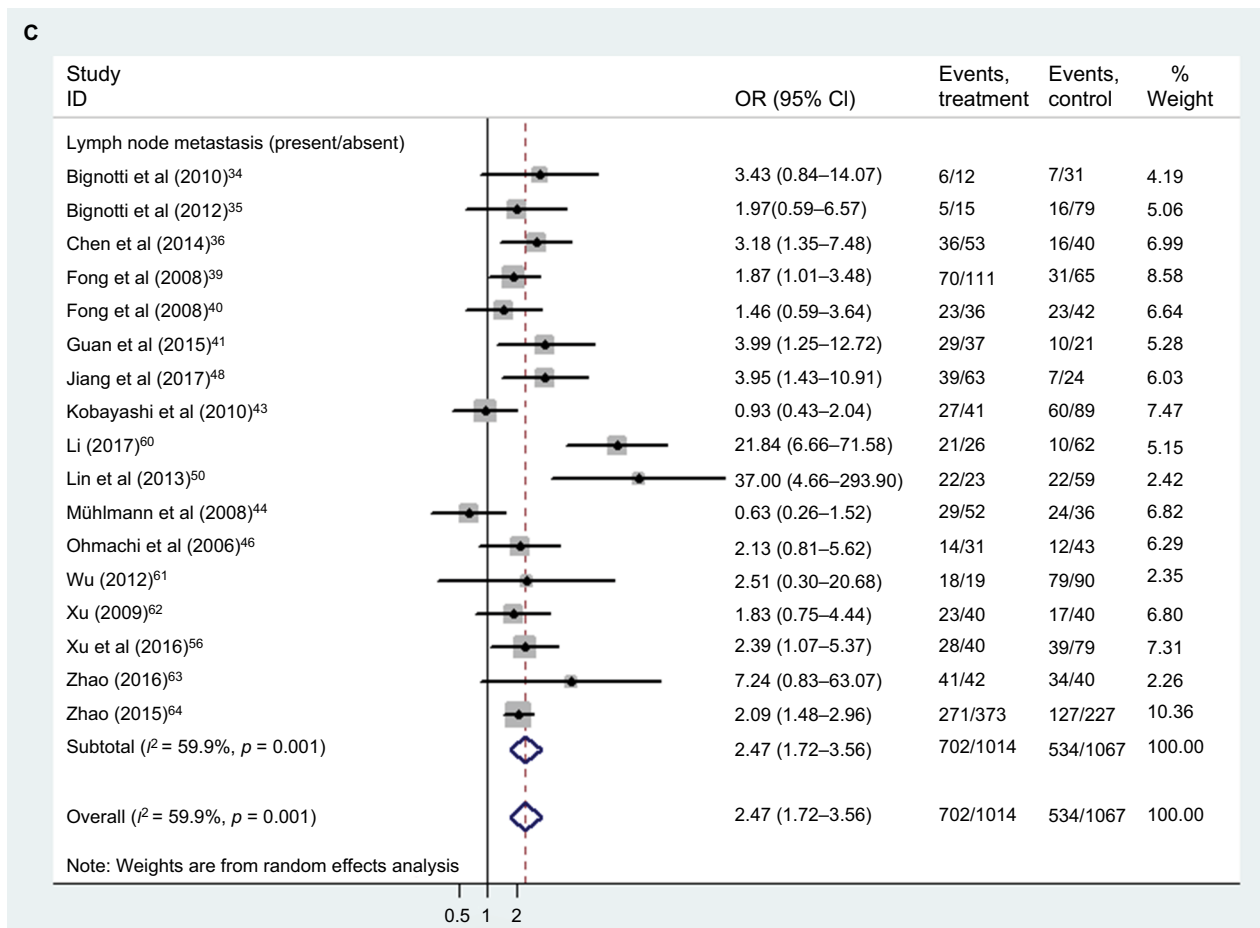
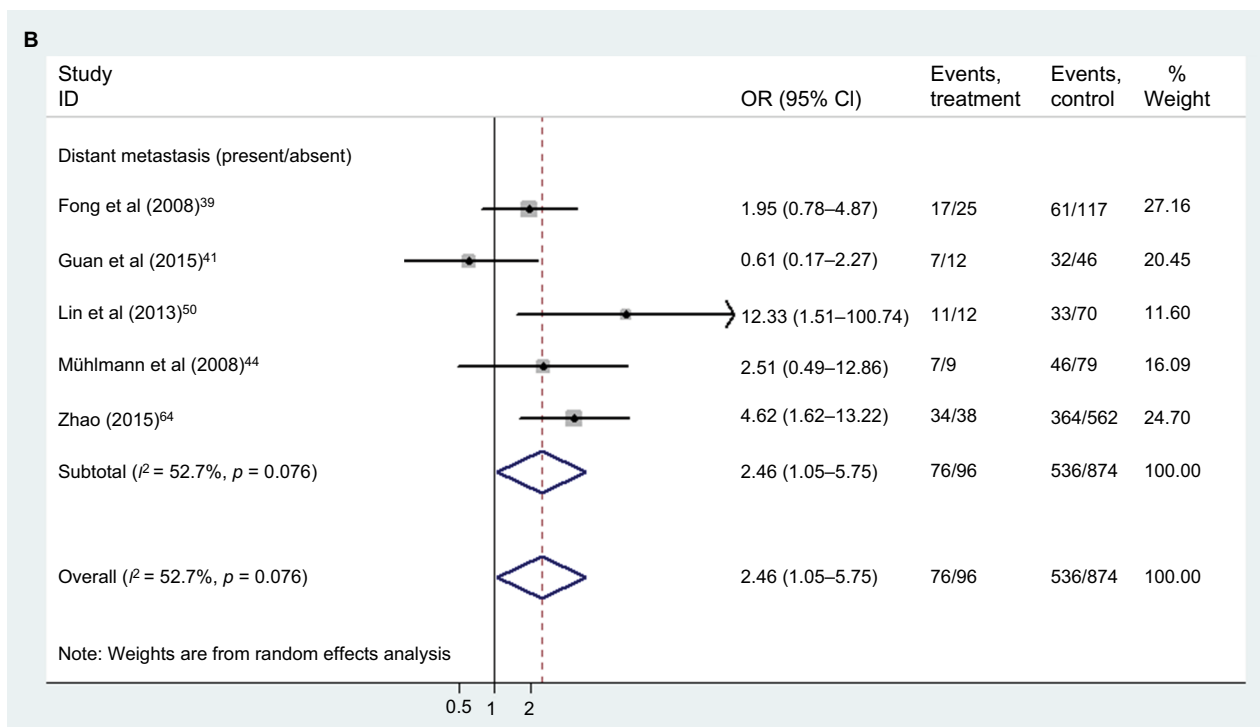


Figure 7 (Continued)

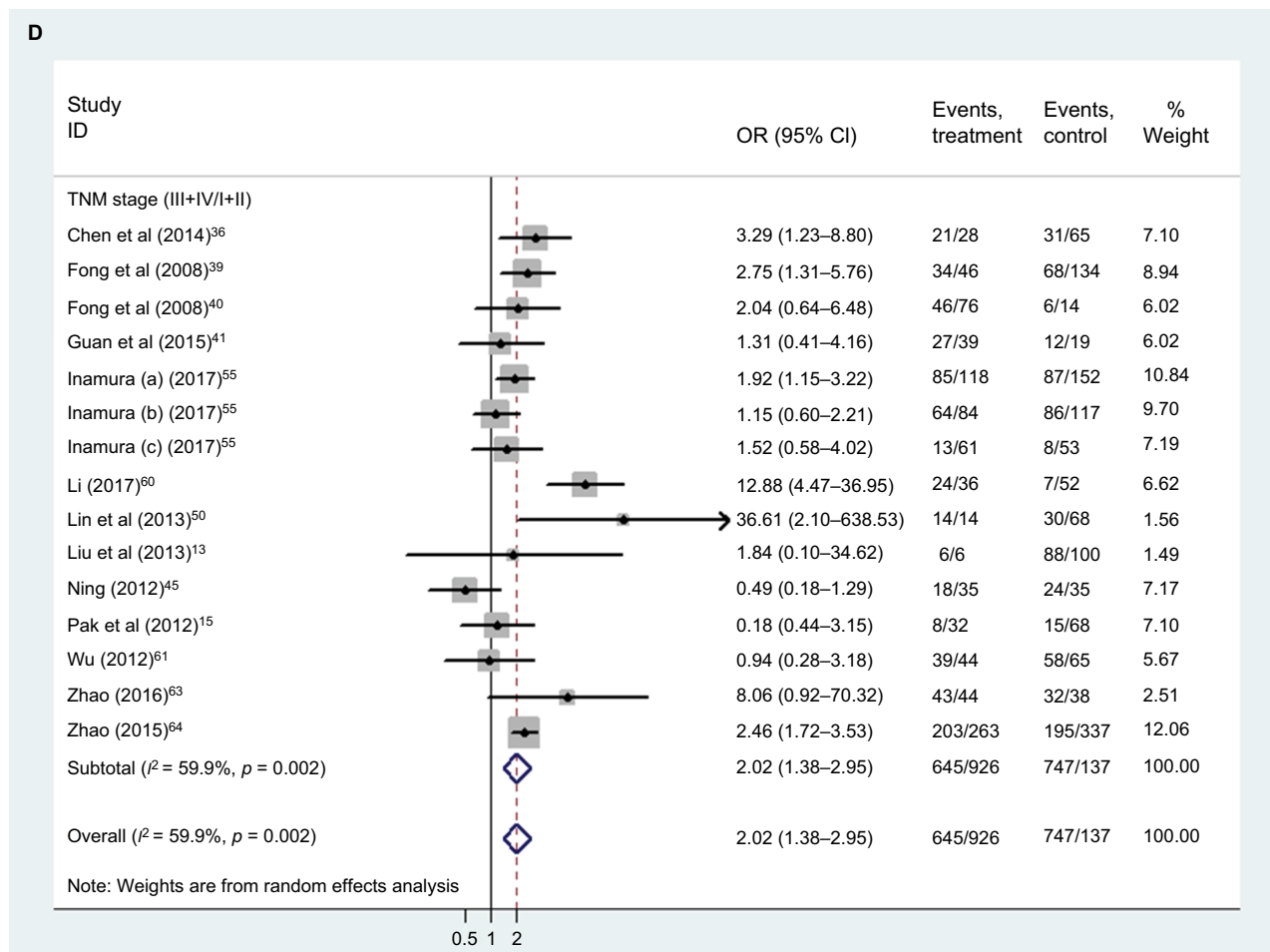


Figure 7 The correlation between TROP2 expression and carcinoma patients' clinicopathologic features.

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.

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